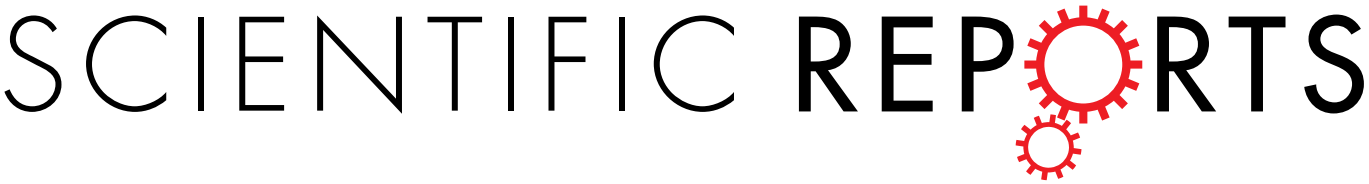

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Factors influencing immunologic response to hepatitis B vaccine in adults

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Hepatitis B was still a worldwide health problem. This study aimed to conducted a systematic review and meta-analysis to assess a more precise estimation of factors that influence the response to hepatitis B vaccine in adults. Our included studies examined seroprotection rates close to the end of vaccination schedules in healthy adult populations. This meta-analysis including 21053 adults in 37 articles showed that a significantly decreased response to hepatitis B vaccine appeared in adults (age $\geq$ 40) (RR:1.86, 95% CI:1.55–2.23), male adults (RR:1.40, 95% CI:1.22–1.61), BMI $\geq$ 25 adults (RR:1.56, 95% CI:1.12–2.17), smoker (RR:1.53, 95% CI:1.21–1.93), and adults with concomitant disease (RR:1.39, 95% CI:1.04–1.86). Meanwhile, we further found a decreased response to hepatitis B vaccine appeared in adults (age $\geq$ 30) (RR:1.77, 95% CI:1.48–2.10), and adults (age $\geq$ 60) (RR:1.30, 95% CI:1.01–1.68). However, there were no difference in response to hepatitis B vaccine both in alcoholic (RR:0.90, 95% CI:0.64–1.26) and 0-1-12 vs. 0-1-6 vaccination schedule (RR:1.39, 95% CI:0.41–4.67). Pooling of these studies recommended the sooner the better for adult hepatitis B vaccine strategy. More vaccine doses, supplemental/additional strengthening immunity should be emphasized on the susceptible population of increasing aged, male, BMI $\geq$ 25, smoking and concomitant disease. The conventional 0-1-6 vaccination schedule could be still worth to be recommended.

Hepatitis B as an acute and chronic communicable disease, has been a worldwide health problem estimated to lead to between 500,000 to 1.2 million deaths every year through causing chronic hepatitis, cirrhosis and hepatocellular carcinoma[1]. The prevalence of HBV infection varies significantly in different areas: prevalence of chronic infection with HBV estimates range between 0.1–0.7% in Western, Northern, and Central Europe, while those considerably higher in Eastern and Southern European countries, such as Italy (0.2–4.3%), Turkey (2.5–9%), and Romania (5.6%)[2,3]. In Alaska, 41% had anti-HBs levels of >10 mIU/ml 7 to 9 years after booster vaccination at birth[4], even 51% had this protective levels 30 years after receiving the primary series without subsequent doses in Alaska native persons[5]. In China, the HBsAg carrier rate was 8.75% in 1979, 9.75% in 1992, and 7.18% in 2006[6]; in Taiwan, the values are as high as 15–20% in adults[7]; and in the Middle East and North Africa region, the HBV infection estimates are various such as 9.8% in Egypt, 7.4% in Iran, 2.4% in Lebanon and 6.9% Libya from the prisoners; 50.7% in Iran, 8.6% in Israel, 2.8% in Lebanon, 4.5% in Libya, 2.6% in Palestine, 6.1% in Saudi Arabia from the injecting drug users[8]. In Gambia, 13.2% were found to carry HbsAg[9] and national infant HBV vaccination controlling chronic infection had 94% vaccine efficacy[10]. HBV can be transmitted in many ways, with sexual intercourse and mother-to-child transmission being the most common. Between 15% and 40% of those infected develop acute or chronic liver disease and liver failure, cirrhosis or hepatocellular carcinoma may result.

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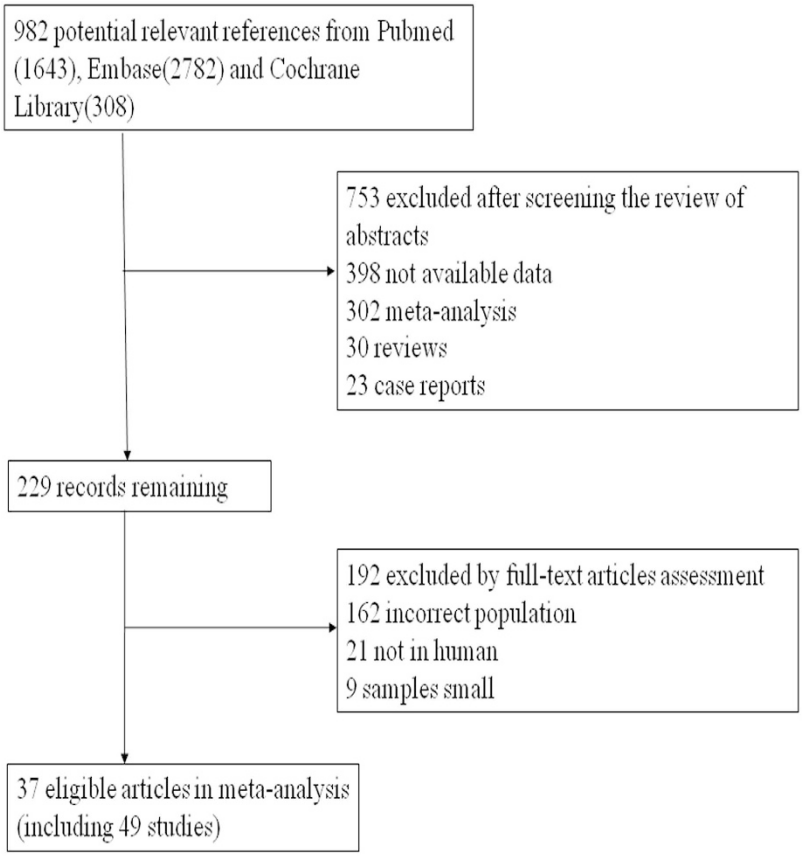

Figure 1. Flow diagram of the study selection process.

Many countries have gradually adopted the HBV vaccine in national immunization programs since the World Health Organization (WHO) recommended vaccination for children in 1990s. Most individuals with chronic hepatitis B are asymptomatic and therefore ignorant of their infection status but HBV vaccination, if used for primary prevention, can significantly lower the risk of infection. HBV vaccination triggers antibody response and antibody to hepatitis B surface antigen (anti-HBs) levels $\geq$10 IU/L are usually regarded as seroprotection for most vaccinees.

Vaccination efficacy among children has been widely studied, but there remains a large proportion of adult populations who are as yet unvaccinated. A previous meta-analysis in 2002 observed many factors influencing response to hepatitis B vaccine, especially a decrease response to recombinant HBV vaccine at higher ages[11], which suggested that earlier vaccination should be prioritized for prevention at the population level. However, in the last decade, numerous emerging reports, which focused on the seroprotection rate of hepatitis B vaccine in adults[12–48], are still inconclusive to immunize what adults are the most appropriate in order to increase the seroprotection rate. Factors influencing immunologic response to hepatitis B vaccine in adults have been inconsistently examined in existing studies. In this study, we conducted a systematic review and meta-analysis to update and assess a more precise estimation of factors that influence the response to HBV vaccine.

Material and Methods

Search strategy. To find all relevant publications that investigated the association between adult and hepatitis B vaccine and seroprotection, a systematic literature search was independently conducted by two individual investigators with the same method in PubMed, Embase and Cochrane Library using the keywords "hepatitis B vaccine", "HBV", "adult", "anti-HBs" were used. Data were collected from the full-published paper and no language or race restriction was used. Bibliographies of relevant review articles were also screened to supplement the electronic searches.

Inclusion criteria. Included studies met the following criteria (1) original research papers; (2) prospective or retrospective studies, including cohorts and trials; (3) sample size $\geq$10; (4) healthy subjects, pregnant women, participants with diabetes, chronic renal failure or other diseases but without congestive hepatopathy or infectious diseases; (5) mean sample population age $\geq$18 years; (6) populations are largely vaccine naive; (7) seroprotection (generally defined as antibody-HBs at a titer of $>$10 mIU/mL) is assessed at least one month after last recombinant vaccine dose in the majority of participants.

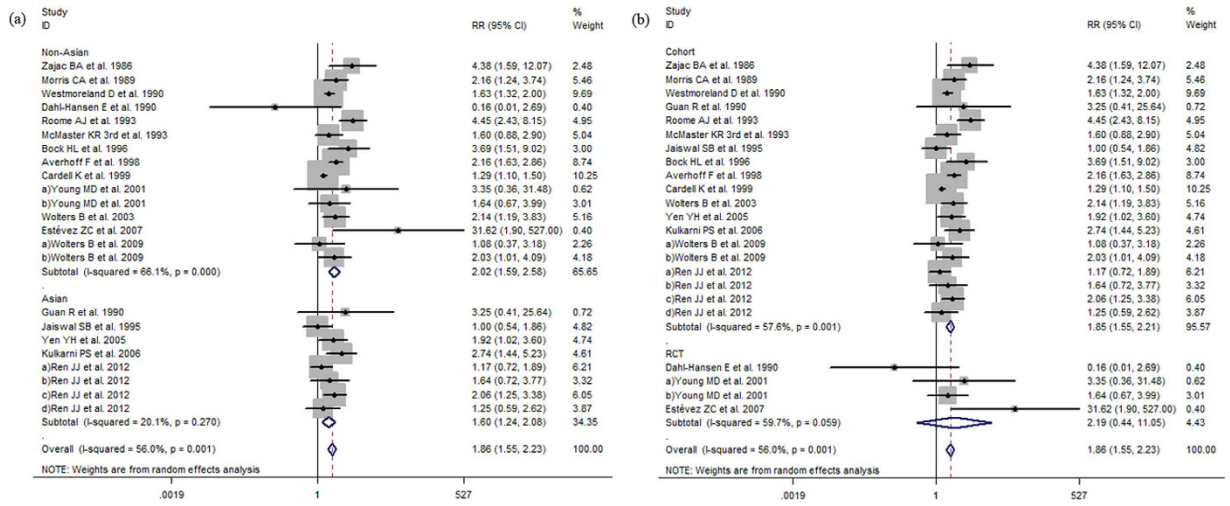

Figure 2. (**a**) The relative risks of response to HBV vaccine between adults age ≥40 and adults age <40. (**b**) The relative risks of response to HBV vaccine between adults age ≥40 and adults age <40. Comparing with adults age <40, the RRs show decreased response to HBV vaccine among adults age ≥40 in cohort and overall studies.

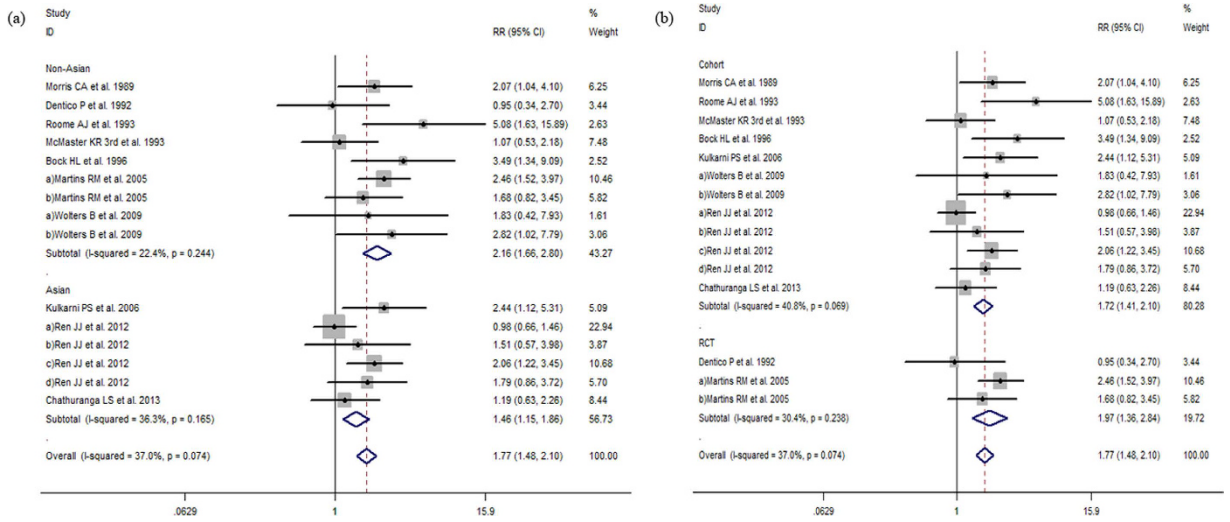

Figure 3. (**a**) The relative risks of response to HBV vaccine between adults age ≥30 and adults age <30. (**b**) The relative risks of response to HBV vaccine between adults age ≥30 and adults age <30 grouped by study design. Comparing with adults age <30, the RRs indicate reduced response to HBV vaccine among adults age ≥30 both in cohort and RCT studies.

Article screening. Citations were electronically downloaded into reference management software and duplicate citations were electronically/manually excluded. Where studies had multiple reports, the most recent or most complete article was retained. The remaining citations were screened independently by two reviewers using pre-defined criteria. Full-text versions of potentially relevant citations were obtained and again screened independently by two reviewers according to pre-defined criteria. Disagreement was resolved by the opinion of a third reviewer.

Data extraction and quality assessment. The data was independently extracted and then cross-checked by two investigators according to a standard format as follows: author, publication year, age, country, male/female participants, body mass index (BMI), vaccination schedule, time of immunological assessment after last vaccine dose, vaccine characteristics and injection pathwayIf necessary data were unavailable in articles, a request was sent to the author for relevant data. The definition of age strata varied among studies. We considered age ≥16 years as adult and age ≥40 years as a default definition of older age for study participants. We considered individuals with anti-HBs titers ≥10 IU/L to be seroprotective after completion of vaccination against HBV. In a few articles, those data are also available if the seroconversion was defined as anti-HBs titers ≥10 IU/L. The articles

Author	Year	Study design	Age (years)	Population characteristics	Country	Male/ Female	BMI	Schedule (months)	Follow-up (After last does of vaccine)	Vaccine detail	Injection pathway	Geometric mean titer (IU/L)	Seroprotection reached n/% (>=10 mIU/mL)
Zajac B. A. *et al.*	1986	Retrospective cohort	20–70	Healthy adults	USA	NA	NA	0-1-6	1–6 months	10 μg recombinant vaccine	IM	a) 300 IU/L (2.5 ug); b) 350 IU/L (5 ug); c) 1250 IU/L (10 ug); d) 1000 IU/L (20 ug)	a) 98% (2.5 ug); b) 89% (5 ug); c) 97% (10 ug); d) 87% (20 ug)
Jilg W. *et al.*	1989	Randomized trials	a) 24.7 ± 2.1 b) 24.4 ± 1.7 c) 24.6 ± 1.8	Healthy medical students	Germany	a) 12/17; b) 16/14; c) 16/14	NA	a) 0-1-2-12; b) 0-1-6; c) 0-1-12	12 months	10 μg recombinant vaccine	IM	a) 53 IU/I (0-1-2); b) 5846 IU/L (0-1-6); c) 19912 IU/L (0-1-12)	Seroconversion rate in all three groups was 100% after the third dose.
Morris C. A. *et al.*	1989	Retrospective cohort	19–60+	Health care volunteers	United Kingdom	79/136	NA	0-1-6	1–2 months	2 μg recombinant vaccine, Engerix-B	ID	NA	80.9%
Westmoreland D. *et al.*	1990	Retrospective cohort	17–71	Occupational risk of infection	United Kingdom	304/1016	NA	0-1-6	6–8 weeks	20 μg recombinant vaccine, Engerix-B	IM	NA	90.50%
Guan R. *et al.*	1990	Retrospective cohort	40 ± 7.7 range: 23–54	Chronic renal failure	Singapore	11/18	NA	0-1-2-6	6 months	40 μg recombinant vaccine, Engerix-B	IM	112 IU/L	69% (>2.1 IU/L, 79%)
Dahl-Hansen E. *et al.*	1990	Randomized trials	21–62	Healthy adults	Norway	30/109	NA	0-1-6	3 months	recombinant vaccine,20 μg Engerix-B and 10 μg Recombivax	IM	a) 189 IU/L (SKR 20 ug); b) 99 IU/L (MSD 10 ug)	100.0%
Dentico P. *et al.*	1992	Randomized trials	18–60	Volunteer employees	Italy	a) 43/57; b) 35/65	NA	0-1-6	1–42 months	a) 10 μg recombinant vaccine b) 20 μg recombinant vaccine	IM	a) 1252 IU/L (10 ug); b) 1340 IU/L (20 ug)	a) 87% (10 ug); b) 97% (20 ug)
Roome A. J. *et al.*	1993	Retrospective cohort	Mean: 39.3 range: 14–74	Healthy adults	USA	510/18	NA	0-1-6	1–6 months	recombinant vaccine, Recombivax HB	NA	235 IU/L	88.1%
McMaster K. R. 3rd *et al.*	1993	Retrospective cohort	NA	Most firefighters	USA	NA	NA	0-1-2-6	1–2 months	2 μg recombinant vaccine, Engerix-B	ID	NA	90.5%
Jaiswal S. B. *et al.*	1995	Retrospective cohort	NA	Chronic renal failure	India	29/11	NA	0-1-6	1 month	40 μg recombinant vaccine, Engerix-B	IM	NA	50.0%
Bock H. L. *et al.*	1996	Prospective cohort	28 ± 10.6	Health care staff and their relatives	Germany	176/704	NA	0-1-6	1 month	20 μg recombinant vaccine, Engerix-B	IM	1989 IU/L	97.8%
Averhoff F. *et al.*	1998	Retrospective cohort	41	Health care workers	USA	1335/416	NA	0-1-6	1 month	recombinant vaccine, 20 μg Engerix-B and 10 μg Recombivax	IM	<40 years of age: a) 2138 IU/L in Engerix-B, b) 1047 IU/L in Recombivax-HB; ≥40 years of age: a) 1000 IU/L in Engerix-B, b) 288 IU/L in Recombivax-HB	a) 90% in Engerix-B; b) 86% in Recombivax-HB

Continued

Author	Year	Study design	Age (years)	Population characteristics	Country	Male/ Female	BMI	Schedule (months)	Follow-up (After last does of vaccine)	Vaccine detail	Injection pathway	Geometric mean titer (IU/L)	Seroprotection reached n/% (>=10 mIU/mL)
Cardell K. *et al.*	1999	Prospective cohort	Mean: 36 range: 19–63	Health care workers	Sweden	239/1167	NA	0-1-6	2 months	2 μg recombinant vaccine, Engerix-B	ID	NA	68.3%
Ingardia C. J. *et al.*	1999	Retrospective cohort	23.8 ± 5.6 range: 15–40	Pregnant women	USA	0/80	27.7 ± 7.0 range: 18–56	0-1-6	11.1 ± 5.1 weeks	20 μg recombinant vaccine, Engerix-B	IM	NA	45.0%
Young M. D. *et al.*	2001	Randomized trials	a) 39.2 range: 18–65 b) 38.8 range: 18–65	Healthy adults	USA	a) 62/90;	NA	0-1-6	3–4 weeks	a) 20 ug recombinant vaccine; Hepacare; b) 20 ug recombinant vaccine; Engerix-B	IM	90% of vaccinees had titers ≥100 IU/L in both groups.	a) 98% in Hepacare;
						b) 60/91							b) 88% in Engerix-B
Wolters B. *et al.*	2003	Retrospective cohort	Mean: 54 range: 17–84	Older adults	Germany	51/53	NA	0-1-6	16.8 months (range 1–36 months)	20 μg recombinant vaccine, Twinrix	IM	NA	46.0%
Martins R. M. *et al.*	2004	Randomized trials	a) 20–30 b) 31–40	Healthy adults	Brazil	a) 364/114; b) 352/134	NA	0-1-6	28–100 days	a) 20 μg recombinant vaccine, Butang; b) 20 μg recombinant vaccine, Engerix-B	IM	a) Butang®, 351.1 in newborn infants, 3600.0 in children, 746.3 in adolescents, 453.5 in adults 20–30 years old, and 122.7 in adults 31–40 years old; b) Engerix-B, 1530.6 in newborn infants, 2753.1 in children, 1284.3 in adolescents, 1369.0 in adults 20–30 years old, and 686.2 in adults 31–40 years old	a) Butang, 93.7% in newborn infants, 100% in children, 95.1% in adolescents, 91.8% in adults 20–30 years old, and 79.8% in adults 31–40 years old; b) Engerix-B, 97.5% in newborn infants, 97.7% in children, 96% in adolescents, 95.5% in adults 20–30 years old, and 92.4% in adults 31–40 years old
Yen Y. H. *et al.*	2005	Retrospective cohort	Mean: 36.6 range: 25–70	Health care workers	China	50/200	NA	0-1-6	8 months	20 μg recombinant vaccine, Engerix-B	IM	5 of 8 responders were 10.5, 199.3, 396.9, 822.2 and 1000 IU/L, respectively.	86.4%
Panhotra B. R. *et al.*	2005	Retrospective cohort	34.6 ± 8.2 range: 21–60	Health care workers	Saudi Arabia	620/682	NA	0-1-6	3 months	20 μg recombinant vaccine, Engerix	IM	NA	92.2%
Kulkarni P. S. *et al.*	2006	Prospective cohort	33 ± 8.645	Healthy adults	India	766/22	22.4 ± 2.8	0-1-6	1 month	20 μg recombinant vaccine, Batch	IM	443 IU/L	96.0%
Estévez Z. C. *et al.*	2006	Randomized trials	20–64	Healthy adults	Cuba	167/293	NA	0-1-2	1 month	20 μg recombinant vaccine, Heberbiovac HB	IM	931.18 IU/L	97.0%
Locquet C. *et al.*	2007	Retrospective cohort	35 ± 10.4 range: 17–65	Women healthcare workers	France	0/880	23.4 ± 4.4	a) 0-1-2-12;	1–169 months	20 μg recombinant vaccine, Genhevac Pasteur/20 μg recombinant vaccine, Engerix GlaxoSmith-Kline	IM	NA	92.0%
								b) 0-1-6					

Continued

Author	Year	Study design	Age (years)	Population characteristics	Country	Male/ Female	BMI	Schedule (months)	Follow-up (After last does of vaccine)	Vaccine detail	Injection pathway	Geometric mean titer (IU/L)	Seroprotection reached n/% (>=10 mIU/mL)
Sabidó M. *et al.*	2007	Retrospective cohort	33 ± 10.51	Health care workers	Spain	437/1621	23.50 ± 3.76	0-1-6	1–6 months	17.4% plasma-derived vaccine, Hevac-B;	IM	NA	92.2%
										83.5% recombinant vaccine, Engerix-B			
Oliveira L. C. *et al.*	2007	Randomized trials	a) 46.6 ± 10.9(alcoholics); b) 37.8 ± 9.7(non-alcoholics)	Healthy adults	Portugal	60/0	NA	0-1-6	1 month	20 μg recombinant vaccine, Euvax-B	IM	a) 511 ± 448 IU/L (alcoholics); b) 696 ± 410 IU/L (non-alcoholics)	a) 50% (alcoholics); b) 52.5% (non-alcoholics)
Wolters B. *et al.*	2009	a) Prospective cohort b) Retrospective cohort	a) Mean: 38.9 range: 18–79 b) Mean: 39.9 range: 16–75	Healthy adults	German	a) 109/65 b) 133/115	a) 25.5 ± 4.8 b) 24.4 ± 3.8	0-1-6	1–2 months	Twinrix	NA	1430 IU/L	88.7%
Kevorkyan A. K. *et al.*	2011	Retrospective cohort	40.3 ± 2.6	Health care workers	Bulgaria	13/57	NA	0-1-6	1–2 months	20 μg recombinant vaccine, Hepavax Gen	NA	NA	92.8%
Sheffield J. S. *et al.*	2011	Prospective cohort	25.3 ± 5.2	Pregnant women	USA	0/168	a) 26(responder); b) 36(non-responder)	0-1-4	5–6 months	recombinant vaccine, Recombivax HB	IM	NA	90.0%
De Schryver A. *et al.*	2011	Randomized trials	a) 41.4 ± 10.4 b) 42.5 ± 9.8	Healthy volunteers	Belgium	310/61	a) 26.1 ± 5.0 b) 26.6 ± 4.6	a) 0-1-6; b) 0-1-12	1 month	20 μg recombinant vaccine, Twinrix	IM	a) 1900.6 IU/L (0-1-12); b) 749.0 IU/L (0-1-6)	a) 95.6% (0-1-12); b) 97.1% (0-1-6)
Tohme R. A. *et al.*	2011	Retrospective cohort	82.2 ± 14.2 range: 45–102	Older adults	USA	7/25	25.4 ± 4.6	0-1-4	80–90 days	20 μg recombinant vaccine, Engerix-B	IM	4.8 IU/L	33.3%
Ren J. J. *et al.*	2012	Retrospective cohort	a) 32.45 ± 0.66 b) 33.69 ± 0.70 c) 31.71 ± 0.69 d) 32.20 ± 1.07 range: 16–49	Healthy adults	China	a) 242/351; b) 182/283; c) 246/333; d) 101/134	NA	0-1-6	1 month	10 μg recombinant vaccine produced by 4 different manufacturers	IM	a) 177.28 IU/L (Kangtai); b) 473.23 IU/L (Dalian HTB); c) 246.13 IU/L (GeneTech BP); d) 332.20 IU/L (GlaxoSmith-Kline)	a) 81.67% (Kangtai); b) 95.05% (Dalian HTB); c) 89.64% (GeneTech BP); d) 86.81% (GlaxoSmith-Kline)
Williams R. E. *et al.*	2012	Retrospective cohort	Median: 79.5 range 45–101	Older adults	USA	39/47	NA	0-1-6	1–2 months	1 mldose recombinant vaccine, Twinrix	IM	NA	34.0%
Chathuranga L. S. *et al.*	2013	Retrospective cohort	NA	Health care workers	Sri Lanka	190/152	NA	NA	2 months-14 years	NA	NA	NA	92.1%
Bender T. J. *et al.*	2014	Retrospective cohort	Median: 60 range: 46–86	Adults with assisted living facilities	USA	17/10	NA	0-1-7	1–2 months	1 mldose recombinant vaccine, Twinrix	IM	91.7 IU/L	81.0%
Thomas R. J. *et al.*	2015	Retrospective cohort	16–50	Health care workers	India	148/306	NA	0-1-6	1 month	20 μg recombinant vaccine, GeneVac-B	IM	NA	98.9%
Nashibi R. *et al.**	2015	Retrospective cohort	31.9 ± 18.1 range: 20–55	Health care workers	Iran	43/196	a) 31.6 ± 7.5(responder); b) 33.4 ± 5.6(non-responder)	NA	1–6 months	NA	NA	NA	94.1%

Continued

Author	Year	Study design	Age (years)	Population characteristics	Country	Male/ Female	BMI	Schedule (months)	Follow-up (After last does of vaccine)	Vaccine detail	Injection pathway	Geometric mean titer (IU/L)	Seroprotection reached n/% (>=10 mIU/mL)
a) Yao J. *et al.*	2015	Randomized trials	a) 32.75 ± 7.93 b) 33.31 ± 7.71 c) 33.16 ± 8.00	Healthy adults	China	a) 354/519; b) 338/523; c) 259/445	NA	a) 0-1-3; b) 0-1-6; c) 0-1-12	12 months	10 ug recombinant vaccine	IM	a) 213.16 IU/L (0-1-3); b) 432.58 IU/L (0-1-6); c) 451.47 IU/L (0-1-12)	a) 100% (0-1-3); b) 99.9% (0-1-6); c) 97.9% (0-1-12)
b) Yao J. *et al.*	2015	Randomized trials	a) Median: 30.23 range: 20.01–39.76 b) Median: 29.42 range: 20.01–39.92 c) Median: 30.25 range: 20.10–39.98	Seronegative adults	China	a) 100/149; b) 111/118; c) 84/124	NA	a) 0-1-3; b) 0-1-6; c) 0-1-12	1 month	10 ug recombinant vaccine	IM	a) 61.19 IU/L (0-1-3); b) 214.04 IU/L (0-1-6); c) 345.78 IU/L (0-1-12)	a) 83.9% (0-1-3); b) 88.2% (0-1-6); c) 94.2% (0-1-12)

Table 1. Summary of studies investigating the response to hepatitis B vaccine in adults. NA: not available; IM: intramuscular; ID: intradermal. *This article was regarded cross-sectional as cohort study.

were divided into four quality levels such as high, moderate, low, and very low by GRADE evidence profile, which allocates original ranks of low score to observational studies and high score to RCTs[49].

Statistical analysis. In this meta-analysis, we calculated the relative risks (RRs) and 95% confidence intervals (CIs) by comparing the valid and invalid participators in the experimental group and control group of recruited articles. Statistical heterogeneity in the studies was examined by the Q statistic. We evaluated the heterogeneity in these studies by this method, $I^2 = 100\,\%*(\text{Q-df})/\text{Q}$. A fixed-effect model was used to analyze the data if there was no statistical difference of heterogeneity ($p \geq 0.05$). Otherwise, a random-effect model would be selected.

Subgroups analyses were defined in advance/defined according to the reported data, and studies or results were grouped according to age (older or younger than 40), sex, smoking status, alcoholism, vaccine administration (0-1-12/0-1-6 vaccination schedule), geographical location (Asians/Non-Asian). Sensitivity analysis was performed to estimate the stability of the model by removing each study in turn. Additionally, publication bias was assessed through the funnel plot and Egger's linear regression test[50]. All statistical analyses were conducted by Stata 12.0 software.

Results

Characteristics of eligible studies. We finally identified 21053 adults from 37 articles up to June 30, 2015 through electronic and manual searches (Fig. 1). Nine hundred and forty-six studies were excluded according to the mentioned criteria. The characteristics of included studies for this meta-analysis are presented in Table 1 and the majority of the studies were assessed as being of good quality (Table 2).

The studies were largely prospective cohort (n = 5), retrospective cohorts (n = 23), or randomized trials (n = 10). Studies varied considerably in size and were conducted among many countries. The three vaccine doses tended to be administered either at months 0, 1, 6 or 0, 1, 12 and recombinant vaccine doses ranged from 10 μg to 40 μg.

Meta-analysis results. *Heterogeneity test result and subgroup analysis.* The *Q*-tests of heterogeneity were marked in partial groups and then the pooled RRs were calculated by the random-effect models and fixed-effect models. Meta-analysis revealed that vaccine non-response rates were significantly greater in older participants (age ≥40 vs. <40 years, RR:1.86, 95% CI:1.55 to 2.23, $I^2 = 56\%$, $P = 0.001$; age ≥30 vs. <30 years, RR:1.77, 95% CI:1.48 to 2.10, $I^2 = 37\%$, $P = 0.074$; age ≥60 vs. age<60 years RR:1.30, 95% CI:1.01 to 1.68 $I^2 = 33.4\%$, $P = 0.199$). Non-response was also more likely among males (male adults vs. female adults, RR:1.40, 95% CI:1.22 to 1.61, $I^2 = 44.3\%$, $P = 0.005$); overweight participants (BMI ≥ 25 adults vs. <25, RR:1.56, 95% CI:1.12 to 2.17, $I^2 = 77.3\%$, $P < 0.001$); smokers (smoker vs. nonsmoker, RR:1. 53, 95% CI:1.21 to 1.93, $I^2 = 52.1\%$, $P = 0.01$) and those with concomitant disease compared to healthy participants (RR:1.39, 95% CI:1.04 to 1.86, $I^2 = 63.4\%$, $P = 0.002$) (Figs 2a, 3a, 4a,b,d and 5a,d). However, there were no differences in response to HBV by alcoholic status (alcoholic vs. nonalcoholic, RR:0.90, 95% CI:0.64 to 1.26, $I^2 = 0$, $P = 0.941$) or vaccination schedule (vaccine delivered at months 0-1-12 vs. 0-1-6, RR:1.39, 95% CI:0.41 to 4.67, $I^2 = 77.4\%$, $P = 0.004$).

Subgroup analysis by study location and age indicates that older adults (≥40 years) from non-Asian countries revealed that in contrast with Asians, specially non-Asians in older adults (age ≥ 40) may be slightly less response to hepatitis B vaccine than younger adults (age < 40) (RR:2.02, 95% CI:1.59–2.58; RR:1.60, 95% CI:1.24–2.08), consistent with the region result of older adults (age ≥ 30) (RR:2.16, 95% CI:1.66–2.80; RR:1.46, 95% CI:1.15–1.86). Particularly comparing with Asians, the male in non-Asians has a similar nonresponse to females (RR:1.42, 95% CI:1.18–1.71; RR:1.40, 95% CI:1.11–1.77).

When studies were subdivided by study design results were consistent and lower response was seen among studies with older participants and male participants and again, no difference was observed by alcoholic status (Figs 2b, 3b, 4c,d and 5a,b).

Comparator	Intervention	Illustrative comparative risks*(per 1000, 95% CI)		Relative risk of non-response (95% CI)	Number of Participants (studies)	Quality of the evidence (GRADE)
		Assumed risk with comparator	Corresponding risk with intervention			
Age < 40	Age ≥ 40	105	195 (163 to 233)	1.85 (1.55 to 2.21)	10233 (19 studies)	⊕⊕⊕⊕ high
Age < 30	Age ≥ 30	58	99 (81 to 121)	1.72 (1.41 to 2.1)	5372 (13 studies)	⊕⊕⊕⊖ moderate
Age < 60	Age ≥ 60	284	370 (287 to 478)	1.30 (1.01 to 1.68)	480 (5 studies)	⊕⊕⊕⊖ moderate
Female	Male	124	176 (149 to 209)	1.42 (1.2 to 1.68)	10118 (20 studies)	⊕⊕⊕⊕ high
BMI < 25	BMI ≥ 25	125	186 (134 to 255)	1.48 (1.07 to 2.03)	5807 (10 studies)	⊕⊕⊕⊖ moderate
Non-smoker	Smoker	132	195 (152 to 248)	1.47 (1.15 to 1.87)	6935 (13 studies)	⊕⊕⊕⊕ high
Non-alcoholic	Alcoholic	50	43 (29 to 63)	0.86 (0.58 to 1.26)	2381 (5 studies)	⊕⊕⊕⊖ moderate
Healthy	Concomitant diseases	100	140 (104 to 187)	1.39 (1.04 to 1.86)	4386 (12 studies)	⊕⊕⊕⊕ high
Vaccine at 0-1-6 months	Vaccine at 0-1-12 months	32	45 (12 to 192)	1.39 (0.41 to 4.67)	2433 (4 studies)	⊕⊖⊖⊖ very low

Table 2. The absolute and relative risk of non-response to HBV vaccine by subgroup and evidence quality grading*. GRADE: Grading of Recommendations, Assessment, Development and Evaluation. *The results presented in the Table 2 were built around the assumption of a consistent relative effect. The implications of this effect for populations were considered at different baseline risks. Based on the assumed risks, corresponding risks after an intervention were calculated using the meta-analytic risk ratio.

Sensitivity analysis and publication bias. Sensitivity analysis was conducted to estimate the stability of the results and indicated no significant change if any one study was excluded. Funnel plot asymmetry was assessed by means of Egger's linear regression test and showed that there was significant publication bias in the following groups: age of 40 years, gender and BMI (age40: $t = 2.54$, $P = 0.019$; sex: $t = 2.99$, $P = 0.006$; BMI: $t = 2.70$, $P = 0.025$).

Discussion

When stratified by demographic features, our study showed a lower response in older adults (especially age ≥ 40), male adults and overweight adults (BMI ≥ 25), smoker and adults with concomitant disease after completion of vaccination against hepatitis B.

Our study indicated that young adults have a higher seroprotection rate to hepatitis B vaccine than other age groups (age30: RR = 1.77; age40: RR = 1.86; age60: RR = 1.30). It means that the earlier adult vaccination was inoculated at an age, the better efficiency is. The lower responsiveness to hepatitis B vaccines in older adults might result from the waning immunity with age. In previous studies, it did not find a significant association between age and the immune response[43,44]. The reason may be that most adults in the study were under the age of 40 years. However, in an observational prospective study of 666 participants, the percentage of nonresponders elevated gradually with age[51]. Another study aligned with our findings also found that younger age and female gender were predictive of better response[52]. It indicated in our study that population in non-Asians were both better in age of 40 or 30 years (age30: RR = 2.16; age40: RR = 2.06). Surprisingly our result also showed that the response rate in the younger adults (age < 60) was better than those older (age ≥ 60), different from the previous study[44]. Some studies reported seroprotection rates of hepatitis B vaccine in older adults (aged ≥ 60 years) range from 30% to 80% and rely on these factors such as study population, vaccination plan, vaccination history and type of vaccine[40].

Besides age in our study, male gender both in Asians and non-Asians may be associated with nonresponse to hepatitis B vaccine. It may be owing to the opposite effects of sex hormone androgen and estrogen. This difference is experimentally repeated in animal models, which indicated to be activated by sex hormones in genetic regulation. Moreover, there are numerous immunological genes appearing on the X chromosome while few ones are mapped on the Y chromosome. Estrogen activates monocytes to secrete IL-10, which induces IgG and IgM secretion through B-cells in turn[53], while testosterone damages the production of IgG and IgM from B-lymphocytes, as well as restrains producing IL-6 from monocytes[54]. The hormones' joint effects on the epigenetic adjustment of genetic expression, and gene structure on the X chromosome differing between XX females and XY males, will partly account for vaccine response heterogeneity in gender[55]. Based on our results, future programme should be emphasized on males both Asians and non-Asians, who tend to have less response to hepatitis B vaccine.

BMI might influence the level of vaccine response[25]. The low response to vaccination of overweight on vaccine could be due to the main distribution of the vaccine in fat not in muscle. This could hinder absorption and enable denaturation of the vaccine antigen by enzymatic action[25]. Another possible interpretation is damaged proliferation and function of the antibody-secreting plasma cells.

The lower immunogenicity of hepatitis B vaccine was linked with smoking and male gender. In smokers, smoking can affect cells and humoral mediated immune responses in humans and animals. Nicotine restrains the antibody-forming cell response by damaging antigen-mediated pathway in T cells and intracellular calcium response. In addition, a high prevalence of HBV markers has been reported in alcoholics. Persistent alcohol intake could restrain immune responses especially in female[56]. But some studies also reported that difference

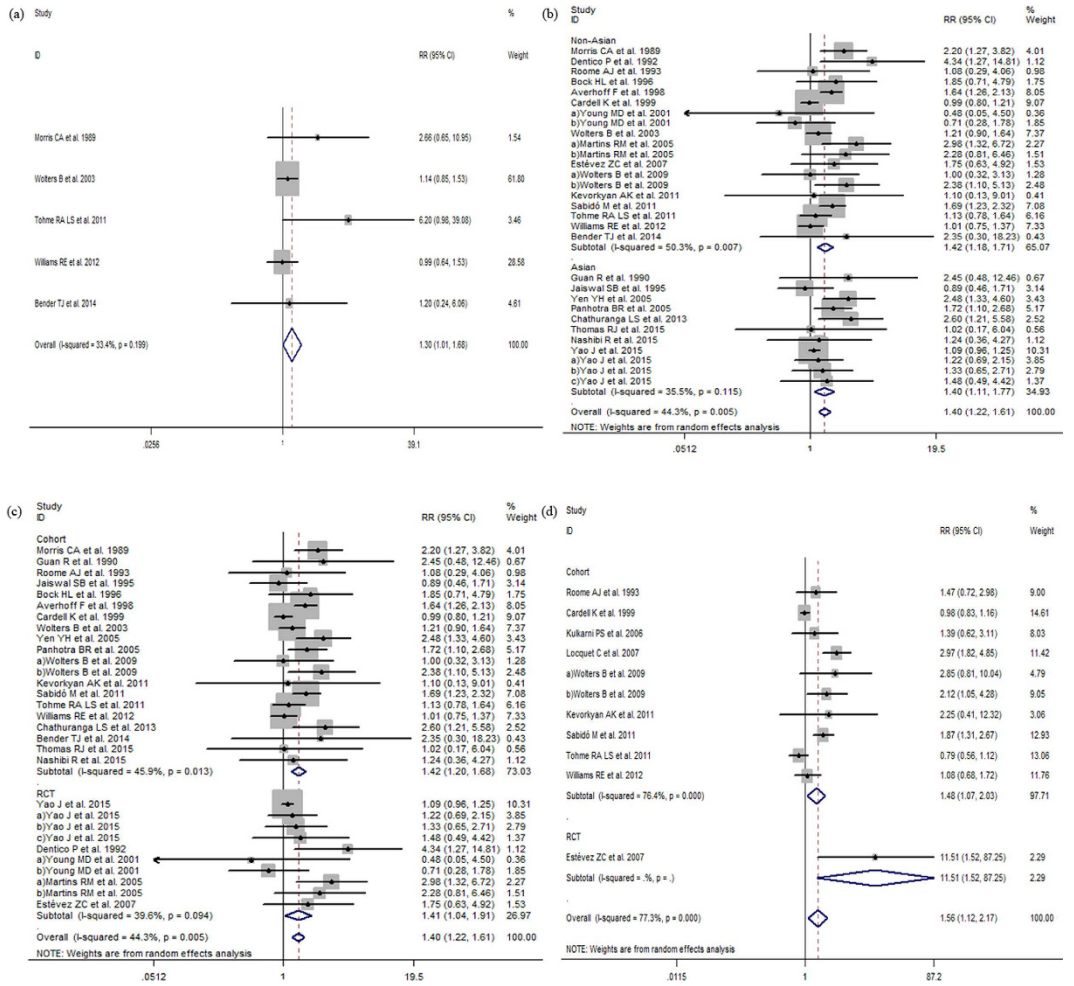

Figure 4. (**a**) The relative risks of response to HBV vaccine between adults age ≥60 and adults age <60. (**b**) The relative risks of response to HBV vaccine between male adults and female adults. (**c**) The relative risks of response to HBV vaccine between male adults and female adults grouped by study design. Comparing with female adults, The RRs suggest declined response to HBV vaccine among male adults both in cohort and RCT studies. (**d**) The relative risks of response to HBV vaccine between BMI ≥25 adults and BMI <25 adults.

was undetected between alcohol consumption and seroprotection of hepatitis B vaccination[31,38]. In this study, the inapparent association within alcoholic subgroup may result from the small sample size and drinking is not common in females.

Aside from those factors, patients with concomitant disease usually have a complicated and inconstant status due to diverse pathogenesis. Although some researches found no association between comorbidity and seroprotection[36,37], comorbidity may be a significant element decreasing the efficacy of hepatitis B vaccine from this analysis and others[23,27], which could bring immunity disturbance. However, the detailed mechanisms between the poor response to hepatitis B vaccine and adults suffering from concomitant disease are still incompletely understood.

What's more, the four reports regarding different vaccination schedules in adults such as 0-1-6 and 0-1-12 schedules are still controversial[13,39,47,48]. Three studies among them[13,39,47] observed no difference in seroconversion rates between these two schedules (as in these cases they were all nearly 100%), while another study[48] showed a higher seroconversion rate in individuals with the 0-1-12 schedule. Our meta analysis found no difference for seroconversion rate one month after the third injection both in 0-1-6 and 0-1-12 vaccination schedules. Thus in consideration of timing and vaccination compliance, the conventional 0-1-6 vaccination schedule could be still worth to be recommended.

Recently, emerging studies tended to suggest the genetic determinants of heterogeneity in response to the vaccines against hepatitis B. In twins study, 60% of the phenotypic variance was interpreted for the anti-HBs immune response by additive genetic while 40% by non-shared environmental effects[57]. Asians and non-Asians as study location may also play an important role in seroprotection efficiency of hepatitis B vaccine in adults. The percentage of nonresponders after hepatitis B vaccine remarkably varied in ethnic groups, which may result from the difference of environmental surroundings, the mutation rate and genetic variability, especially at the human leucocyte antigen

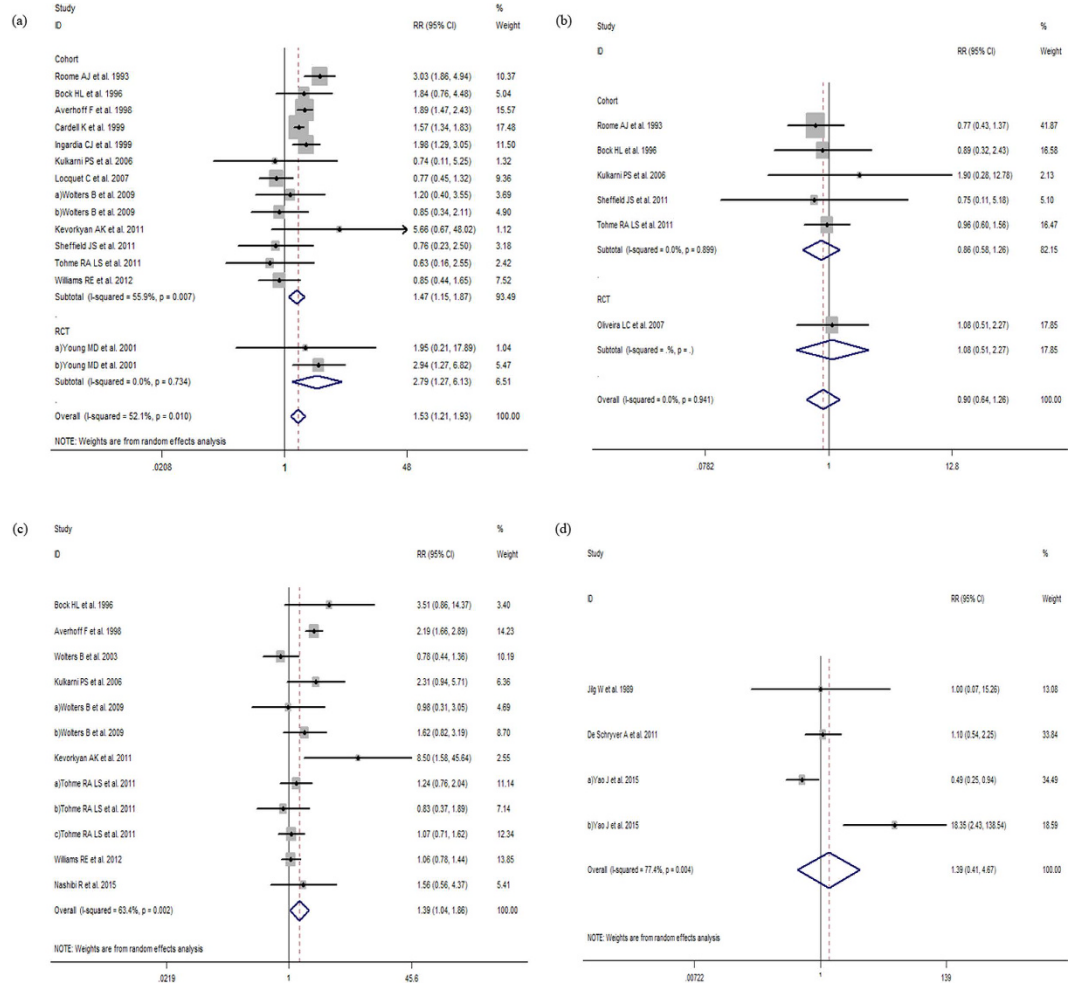

Figure 5. (**a**) The relative risks of response to HBV vaccine between smoker and nonsmoker. (**b**) The relative risks of response to HBV vaccine between alcoholic and nonalcoholic. (**c**) The relative risk of response to HBV vaccine between adults with concomitant disease and healthy adults. (**d**) The relative risk of response to HBV vaccine between 0-1-12 and 0-1-6 vaccination schedule.

(HLA) genetic region. However, it is also hard to accurately locate the variation affecting the HBV response in the HLA locus as a result of the long-range linkage disequilibrium in this area[58]. It needs further studies to explore.

In a word, the factors mentioned above suggested these factors consisting of elder adults, male, BMI ≥ 25, smoking and concomitant disease would be the significant variables reducing the immune response to hepatitis B vaccination. Those who are more likely to have non-response should be checked for seroprotection level and offered additional booster vaccinations. Thereby finding those without immunization and improving overall immunization rates across the population should be emphasized.

Our results should be interpreted in view of the following limitations. First, publication bias was identified among studies reporting rates by age groups, gender and BMI groups. Second, for the various subgroup analyses, sample size is diminished and therefore CIs are wide leading to less accurate estimates of response. Third, due to differences in lifestyle characteristics in different studies' population, significant heterogeneity was present in study, even among subgroup estimates. In addition, there were poor reporting in some included studies and limited inclusion in subgroup analyses such as BMI, smoking status, alcohol status and concomitant disease. What's more, several different vaccines were used in the different studies, which had different immunogenicity. Engerix B (with 20 μg HBsAg per dose) is more immunogenic than Recombivax (with 10 μg per dose), the difference being seen especially in older individuals. Twinrix is similar immunogenicity to Engerix-B. A multi-center study found that a S-PreS1/PreS2-vaccine (Hepacare) is also more immunogenic than Engerix B[2]. Despite limitations, in this work, we systematically sought out all published literature relevant to our research question and then carefully screened studies and extracted data in duplicate using protocols to ensure high quality and consistency in the extracted data. Missing data were sought from authors and studies results were statistically combined to provide robust estimates of the factors associated with poorer immunological response. To our knowledge, this is the first study to examine multiple factors associated with vaccine response and important differences have been found.

Conclusions

Taken together, this meta-analysis indicated that there were lower seroprotection rates to hepatitis B vaccine in the subgroups of increasing aged adults, male, BMI $\geq$ 25, smoking and concomitant disease, and more vaccine doses, supplemental/additional strengthening immunity should be focused on this specific population. No difference in seroconversion rates between 0-1-6 and 0-1-12 vaccination schedule was observed, but in consideration of timing and vaccination compliance, the vaccination 0-1-6 schedule could be still worth to be recommended. In order to obtain accurate effectiveness of hepatitis B vaccine in adults, more large-scale studies should be conducted in the future.

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Author Contributions

Study concept and design; S.Y., G.T., B.R., T.J. and L.L. Acquisition of data; S.Y., G.T., Y.C., C.D., M.D., C.Y., K.X., J.R., J.Y., Y.L., Q.C., P.C., T.X., C.W., B.W., B.R., T.J. and L.L. Analysis and interpretation of data; S.Y., G.T., C.M., Y.C. and C.D. Drafting of the manuscript; S.Y., G.T. and C.M. Critical revision of the manuscript for important intellectual content; S.Y., G.T. and C.M. Statistical analysis; S.Y., G.T., C.M., Y.C. and C.D. Obtained funding; S.Y., G.T., B.R., T.J. and L.L. Technical, or material support; Y.C., C.D., M.D., C.Y., K.X., J.R., J.Y., Y.L., Q.C., P.C., T.X., C.W. and B.W. Study supervision: B.R., T.J. and L.L.

Additional Information

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