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REVIEW

Suitable hepatitis B vaccine for adult immunization in China: a systematic review and meta-analysis

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ABSTRACT

Hepatitis B virus (HBV) infection remains an important public health problem in China, and adults need to be vaccinated. This systematic review and meta-analysis assessed the appropriate immunization of adults in China. Only randomized controlled trials (RCTs) were eligible, and seroprotection was defined as anti-HBs≥ 10 mIU/ml; 18,308 participants in 27 studies were included. Relative risk (RR) and random effects models were used. Twenty micrograms of HBV vaccine resulted in a better response than 10 μg (RR: 1.05, 95% confidence interval (CI): 1.02 to 1.08), and the 0-, 1-, and 6-month schedule was more effective than the 0-, 1-, and 2 – or 3-month schedule (RR: 0.98, 95% CI: 0.96 to 1.00). No significant differences were observed between 10 μg and 5 μg (RR: 1.05, 95% CI: 0.88 to 1.01); (yeast-derived hepatitis B vaccines) YDV and recombinant Chinese hamster ovary cell (CHO) hepatitis B vaccine (RR: 1.01, 95% CI: 0.98 to 1.04); domestic and imported (RR: 1.02, 95% CI: 0.99 to 1.05); or 0-, 1-, and 6-month and 0-, 1-, and 12-month schedules (RR: 1.02, 95% CI: 0.89 to 1.08). In conclusion, 20 μg of vaccine is recommended for adults in China, and the 0-, 1-, and 12-month immunization program schedule is also worth choosing when it is not possible to complete the 0-, 1-, and 6-month schedule.

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Introduction

Hepatitis B virus (HBV) is still an important worldwide public health problem. It is estimated that 257 million persons, or 3.5% of the population, are living with chronic HBV infection worldwide.[1] The prevalence of HBV infection varies significantly in different areas; China is a highly endemic area for HBV infection.[2]

Today, after decades of HBV mass vaccination, the HBsAg prevalence in children has decreased significantly, but there remains a large proportion of adults who are as yet unvaccinated.[3] In addition, Chen WG et al. analyzed 7119 newly discovered patients with chronic HBV infection and found that those aged 30–50 had the highest incidence; another report from the USA also showed that the highest proportion of new HBV infections occurs in the population aged 25 to 44.[4,5] The Advisory Committee on Immunization Practices (ACIP) recommends vaccination for all unvaccinated adults at risk for HBV infection, and Britain and Italy also have adopted vaccination programs for adults at high risk for HBV infection.[6–8] However, in China, adult hepatitis B vaccination has not been systematically performed, and the recommendation for adults from the national Centers for Disease Control follows the conventional immunization programs available for infants.[9] Therefore, the need for vaccination among adults in China should receive wide attention.

At present, the factors that influence the immune response can be divided into two types: personal factors, such as overweight, smoking, age, gender, and region, which are difficult to change in vaccination; and immunization program factors, such as dosage and immunization schedule, which can be adjusted for better immune effect.[9–42] In this study, we focused on immunization program factors. In the last decades, numerous emerging studies[9,14–40,43] in China have been conducted to explore the factors that influence immunologic response to hepatitis B vaccine in adults. However, it is still inconclusive which immunization programs are the most appropriate. Therefore, we conducted a systematic review and meta-analysis to assess a more appropriate immunization program for adults in China.

Results

Characteristics of eligible studies

As shown in the flow diagram (Figure 1), a total of 3180 potentially eligible articles were identified by searching the relevant databases and the references of eligible studies, and 3008 records were excluded after screening the titles and

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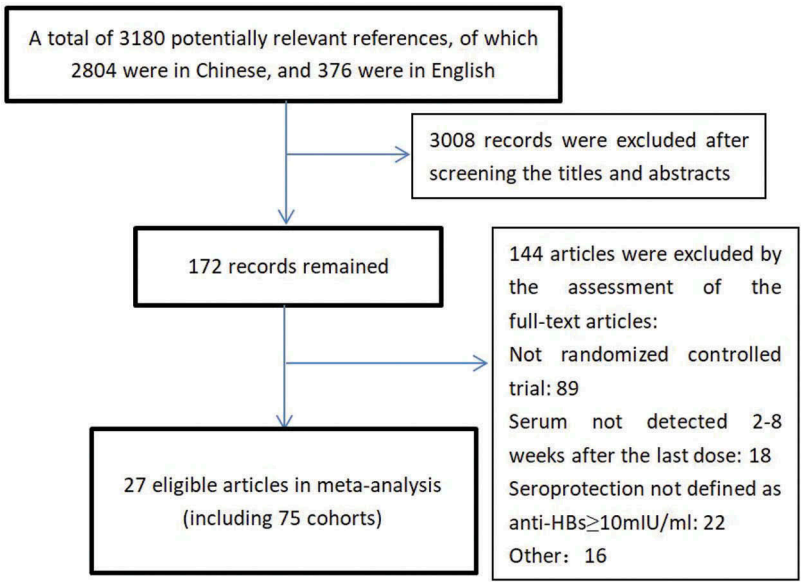

Figure 1. Flow diagram of the study selection process.

abstracts. After reviewing the full texts, 27 studies that included 75 cohorts were included in this study.[9,14–40] Of these 27 studies, 22 were published in Chinese, and 5 were published in English.

The characteristics of the included studies are shown in Table 1. All included studies were RCTs. The publication years of the included studies were concentrated between 2001 and 2017. All participants in these studies were older than 15 years, and most of them were aged between 16 and 50. Among these 75 cohorts, 21 used the CHO vaccine, 48 used YDVs made in China, and the rest used Engerix-B (an HBV vaccine made by GlaxoSmithKline). The standard 0-, 1-, and 6-month schedule was used in 53 cohorts; the 0-, 1-, and 2-month or the 0-, 1-, and 3-month schedules were used in 19 cohorts; and the other 3 cohorts used the 0-, 1-, and 12-month schedule. The positive rates of all cohorts included in the study ranged from 63.59% to 100%.

Meta-analysis results

A total of 18,307 participants from 27 studies were included, of whom 16,909 achieved an adequate immune response (anti-HBs≥ 10 mIU/ml).

Eleven studies[9,14–17,19,22,27,33,35,39] involving 4855 participants were included in the evaluation of the differences in response to vaccination with 20 μg and 10 μg; a total of 13 studies are listed in the forest plot because some studies had more than two cohorts. Compared with the 10-μg dose, the 20-μg dose resulted in a significantly more positive response to vaccination (relative risk [RR]: 1.05, 95% confidence interval [CI]: 1.02 to 1.08) (Figure 2A). A meta-analysis of 4 studies[14,22,26,28] involving 633 participants revealed no significant difference in the rates of response to vaccination between 5 μg and 10 μg of vaccine (RR: 1.05, 95% CI: 0.88 to 1.01) (Figure 2B).

Eight studies[14,20,21,27,29,32,34,39] involving 7289 participants used different vaccine production methods to define the experimental and control groups. The group receiving the CHO vaccine was defined as the experimental group, and the group receiving YDV was defined as the control group. There was no significant difference in the positive rate of response to vaccination found between the experimental and control groups (RR: 1.01, 95% CI: 0.98 to 1.04) (Figure 3A). In addition, the source of the vaccine as a factor affecting its immune effect was discussed in 5 studies.[17,21,27,30,39] The meta-analysis revealed that no significant difference was observed in immune efficacy between homemade or imported vaccines (RR: 1.02, 95% CI: 0.99 to 1.05) (Figure 3B).

A total of 5996 participants from 9 studies[14,23–25,31,36,37,40] received two different immune schedules; 3016 of those participants received a 0-, 1-, and 2-month or a 0-, 1-, and 3-month immune schedule, and the other 2980 participants received the normal 0-, 1-, and 6-month schedule. The meta-analysis revealed that the 0-, 1-, and 2-month or the 0-, 1-, and 3-month schedules had significantly lower positive immune response rates than the normal schedule (RR: 0.98, 95% CI: 0.96 to 1.00) (Figure 4A). In addition, we compared the differences in immune effects between the 0-, 1-, and 6-month and the 0-, 1-, and 12-month schedules,[23,37] and there was no significant difference in immune response observed between these two immune schedules (RR: 1.02, 95% CI: 0.89 to 1.08) (Figure 4B).

Sensitivity analysis and publication bias

A sensitivity analysis was conducted to estimate the reliability of the results. Generally, the results showed no significant change if any single study was excluded (**Figs S1-S4**), but significant sensitivity was found in the results between different immune programs (**Figs S5-S6**). In this study, we used funnel plots to observe publication bias, but studies with fewer than eight articles were excluded. Funnel plot asymmetry was assessed by Begg's test and revealed no significant publication bias was in the following groups (10 vs. 20 μg: $z = 1.28$, $p = 0.200$; YDV vs. CHO: $z = 0.89$, $p = 0.371$; domestic vs.

Table 1. Characteristics of the 27 studies included in the meta-analysis.

NO	Author	Design	Year	Age	Gender	No	vaccine	dosage	schedule	population characteristics	Geometric mean titer (IU/L)	seroprotective rate anti-HBs ≥ 10 IU/L
1	Chen W. G. et al.	RCT	2001	18–20	NA	138	CHO	10 μg	0.1.6	seronegative students	NA	100.00%
						149	CHO	10 μg	0.1.2		NA	97.99%
2	Wang C. X. et al.	RCT	2002	18–55	38/55	93	YDV	5 μg	0.1.2	seronegative adults	18.88	68.82%
					35/71	106	YDV	10 μg	0.1.2		54.47	84.91%
3	Yuan Y. B. et al.	RCT	2003	20–60	NA	48	YDV	5 μg	0.1.6	seronegative	193.37	75.00%
						49	YDV	10 μg	0.1.6	teachers	315.58	91.84%
						47	YDV	20 μg	0.1.6		477.81	97.87%
4	Chen Y. Z. et al.	RCT	2005	15–60	NA	92	YDV	5 μg	0.1.2	seronegative adults	34.45	72.83%
						85	YDV	10 μg	0.1.2		41.16	77.65%
						91	YDV	5 μg	0.1.6		48.15	83.52%
						85	YDV	10 μg	0.1.6		67.91	89.41%
						159	CHO	10 μg	0.1.2		42.59	84.28%
						190	CHO	20 μg	0.1.2		77.90	90.53%
						170	CHO	10 μg	0.1.6		76.98	88.24%
						192	CHO	20 μg	0.1.6		123.82	97.40%
5	Li W. Q. et al.	RCT	2008	17–21	29/31	60	YDV	10 μg	0.1.6	seronegative students	NA	98.30%
					42/18	60	CHO	10 μg	0.1.6		NA	95.00%
					25/35	60	CHO	20 μg	0.1.6		NA	96.70%
					37/21	58	Engerix-B	20 μg	0.1.6		NA	96.50%
6	Dong M. H. et al.	RCT	2009	20–55	200/101	301	YDV	5 μg	0.1.6	seronegative adults	NA	94.40%
					231/101	332	YDV	10 μg	0.1.6		NA	94.60%
7	Ji X. L. et al.	RCT	2009	> 20	NA	238	CHO	10 μg	0.1.6	seronegative adults	NA	96.20%
						267	YDV	10 μg	0.1.6		NA	95.90%
8	Zhang W. et al.	RCT	2011	18–45	141/180	321	CHO	10 μg	0.1.6	seronegative adults	NA	88.80%
					129/192	321	CHO	20 μg	0.1.6		NA	95.30%
9	Liu C. C. et al.	RCT	2012	18–45	NA	114	CHO	10 μg	0.1.6	seronegative adults	134.57	89.47%
						108	CHO	20 μg	0.1.6		921.11	99.07%
10	Yu S. F. et al.	RCT	2012	16–49	NA	241	YDV	10 μg	0.1.3	seronegative adults	107.97	76.76%
						290	YDV	10 μg	0.1.6		306.90	86.21%
						240	YDV	10 μg	0.1.12		587.49	89.17%
11	Guo Y. H. et al.	RCT	2013	18–74	NA	140	CHO	20 μg	0.1.6	seronegative adults	1230.3	99.40%
						140	Engerix-B	20 μg	0.1.6		602.6	97.00%
12	Chen S. Y. et al.	RCT	2013	16–49	NA	190	YDV	10 μg	0.1.3	seronegative adults	94.96	88.95%
						191	YDV	10 μg	0.1.6		145.12	90.05%
13	Liu J. Y. et al.	RCT	2013	18–49	NA	2011	YDV	20 μg	0.1.6	seronegative adults	NA	85.78%
						2290	CHO	20 μg	0.1.6		NA	90.65%
14	Xu M. Q. et al.	RCT	2013	18–35	NA	60	YDV	10 μg	0.1.6	seronegative adults	NA	75.00%
						60	YDV	20 μg	0.1.6		NA	93.30%
						60	Engerix-B	20 μg	0.1.6		NA	95.00%
15	Xu F. et al.	RCT	2013	16–49	99/267	366	YDV	10 μg	0.1.3	seronegative adults	1863.60	98.36%
					88/174	262	YDV	10 μg	0.1.6		883.85	96.18%
					52/88	140	Engerix-B	20 μg	0.1.3		629.59	97.86%
					72/100	172	Engerix-B	20 μg	0.1.6		993.09	95.35%
16	Huang X. Y. et al.	RCT	2014	17–59	NA	65	YDV	10 μg	0.1.6	seronegative adults	202.99	89.04%
						72	CHO	10 μg	0.1.6		201.98	91.14%
17	Song J. P. et al.	RCT	2014	≥ 16	NA	591	YDV	20 μg	0.1.6	seronegative adults	575.40	99.15%
						254	YDV	10 μg	0.1.6		422.30	96.46%
18	Fu Q. P. et al.	RCT	2015	≥ 16	NA	479	YDV	10 μg	0.1.6	seronegative adults	718.86	98.96%
						523	YDV	20 μg	0.1.6		1112.34	98.66%
19	Zhou Y. et al.	RCT	2015	16–49	NA	217	CHO	20 μg	0.1.3	seronegative adults	31.99	63.59%
						218	CHO	20 μg	0.1.12		893.53	95.87%
20	Li J. et al.	RCT	2015	20–46	66/93	159	YDV	10 μg	0.1.3	seronegative adults	91.69	88.05%
					30/71	101	YDV	20 μg	0.1.3		290.23	94.06%
21	Zhang L. et al.	RCT	2015	18–49	59/59	118	YDV	20 μg	0.1.6	seronegative adults	88.14	88.14%
					65/68	133	CHO	20 μg	0.1.6		90.23	90.22%
22	Zhou B. Q. et al.	RCT	2015	16–49	NA	151	YDV	10 μg	0.1.3	seronegative adults	807.98	98.01%
						174	YDV	10 μg	0.1.6		930.68	99.43%
						189	YDV	10 μg	0.1.12		720.28	93.65%
23	Guo M. J. et al.	RCT	2015	16–49	NA	254	YDV	10 μg	0.1.3	seronegative adults	128.75	99.61%
						212	YDV	10 μg	0.1.6		381.27	100.00%
						200	Engerix-B	20 μg	0.1.3		249.70	99.50%
						182	Engerix-B	20 μg	0.1.6		498.09	100.00%
24	Cao Y. et al.	RCT	2016	18–21	361/289	650	YDV	20 μg	0.1.3	seronegative students	486.96	89.70%
					361/289	650	YDV	20 μg	0.1.6		407.91	95.70%
25	Wang H. et al.	RCT	2016	25–55	125/168	293	YDV	20 μg	0.1.6	seronegative adults	1033.38	93.17%
					126/163	289	YDV	20 μg	0.1.6		600.75	97.23%
					126/167	293	CHO	20 μg	0.1.6		1627.05	98.98%
26	Yang L. N. et al.	RCT	2016	16–50	99/144	243	YDV	10 μg	0.1.6	seronegative adults	304.11	100.00%
					50/101	151	YDV	10 μg	0.1.6		906.07	100.00%
					107/143	250	CHO	10 μg	0.1.6		330.33	99.60%
					65/86	151	Engerix-B	10 μg	0.1.6		453.25	100.00%
					51/59	110	CHO	20 μg	0.1.6		142.98	99.10%
					48/83	131	Engerix-B	20 μg	0.1.6		1335.45	96.90%
27	Wen Q. et al.	RCT	2017	18–55	NA	160	YDV	20 μg	0.1.3	seronegative adults	NA	98.13%
						160	YDV	20 μg	0.1.6		NA	97.50%

RCT: randomized controlled trial; NA: not available; YDV: yeast-derived recombinant vaccines; CHO: recombinant hepatitis vaccine made by Chinese hamster ovary cells; Engerix-B: a hepatitis B vaccine made by Glaxo Smith Klin.

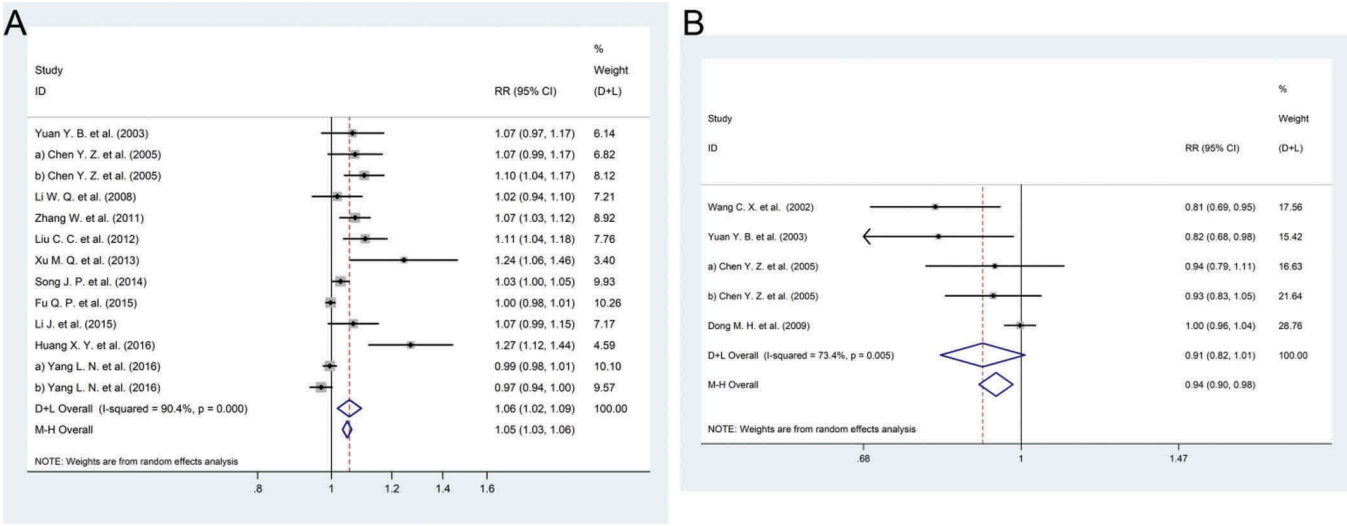

Figure 2. Forest plot. (a) The relative risks of the response to the HBV vaccine comparing the 20 μg and 10 μg doses. (b) The relative risks of the response to the HBV vaccine comparing the 5 μg and 10 μg doses.

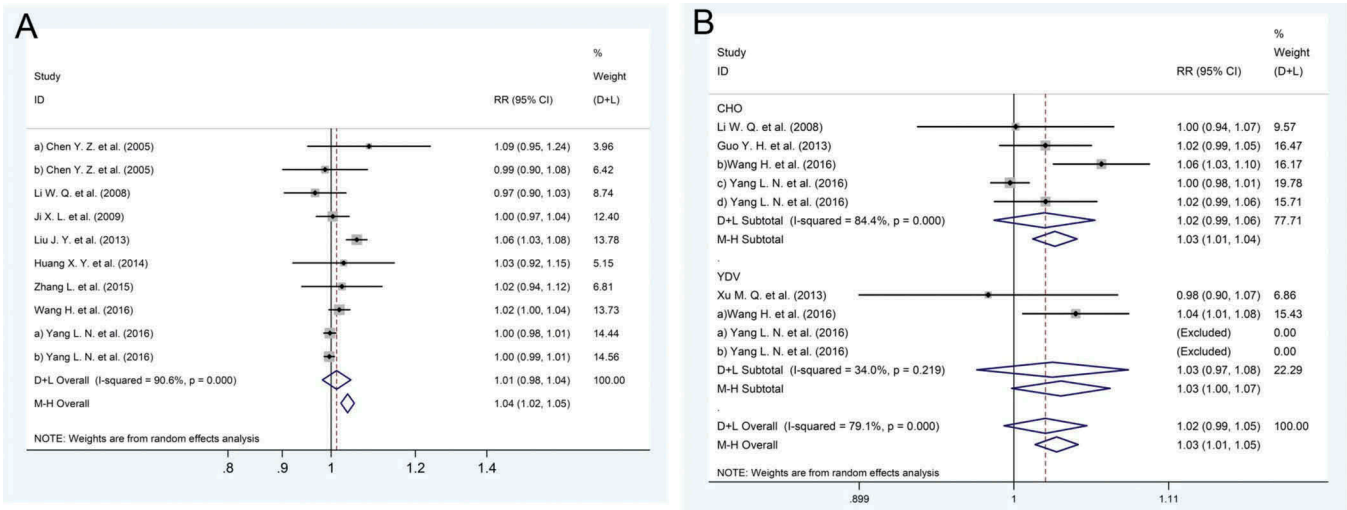

Figure 3. Forest plot. (a) The relative risks of the response to the HBV vaccine comparing CHO and YDV. (b) The relative risks of the response to the HBV vaccine comparing the domestic and imported vaccines.

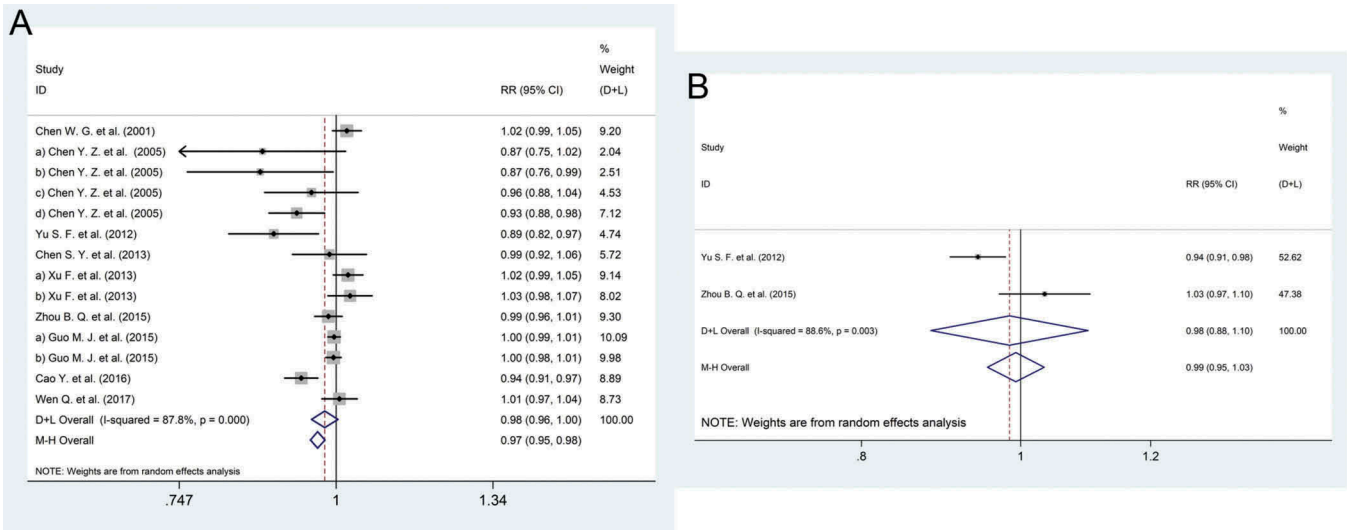

Figure 4. Forest plot. (a) The relative risks of the response to the HBV vaccine comparing the 0, 1, and 2 or 3 month schedule and the 0, 1, and 6 month schedule. (b) The relative risks of the response to the HBV vaccine comparing the 0, 1, and 12 month schedule and the 0, 1, and 6 month schedule.

imported: $z = 0.30$, $p = 0.764$; 0–1-2 or 3vs. 0–1-6 months: $z = 1.42$, $p = 0.155$, **Figs S7-S10**).

Discussion

The aim of this meta-analysis was to help develop a better immunization strategy for adults in China. This meta-analysis showed that adults in China will achieve a higher response with a 20-μg dose, and a 0–1-6 or a 0–1-12 schedule after completion of vaccination against hepatitis B.

Currently, the WHO recommends a standard pediatric dose of 5–10 μg HBsAg and a standard adult dose of 10–20 μg,[44] and in America, ACIP recommends that adults above 20 years of age be vaccinated with a 20-μg dose of hepatitis B vaccine.[45] In China, due to early yeast derived recombinant HB vaccine(YDV) was transferred from Merck of America in 1989 and other recombinant HB vaccines were later self-developed, doses of 5–10 μg and 10–20 μg HBsAg were commonly used by children and adults, respectively. But now, 10 and 20 μg doses of hepatitis B vaccines are widely used in different populations. Our study showed that the immunization effect of the 20-μg dose was significantly better than that of the 10-μg dose (RR: 1.05, 95% CI: 1.02 to 1.08). This result is consistent with the results of previous studies in other countries. An RCT in India showed that a 20-μg dose of vaccine had a better immune effect than the 10-μg dose,[46] and another study in Italy showed that the 20-μg dose of hepatitis B vaccine had no significant higher positive rate but had a significant higher GMT compared with a 10-μg dose.[47] In addition, we compared the immunological effects of the 5- and 10-μg doses, and the RR was 0.94 (95% CI: 0.88 to 1.01), indicating that there was no significant difference in the positive response rate. However, it was noteworthy that the RR was 0.96 (95% CI: 0.92 to 0.99) in the fixed model, and the sensitivity analysis showed that the result was significantly different when the study conducted by Dong M et al.[28] was excluded, meaning that it is likely that the 10-μg dose hepatitis B vaccine had a better effect than the 5-μg dose; however, more studies are needed to confirm this result. Therefore, we can conclude that the 20-μg dose of hepatitis B vaccine may be more suitable for adults in China.

The first recombinant subviral particle vaccine, recombinant hepatitis B vaccine was licensed by FDA in 1986. Subsequently, inactive hepatitis B vaccine from the plasma of chronically infected patients was gradually replaced in the world, and China stopped producing this kind of vaccine in 1998.[48,49] At present, there are two main types of recombinant hepatitis B vaccines derived from yeast and Chinese Hamster Ovary cells (CHO) expressing S or preS1/preS2/S gene. Yeast derived recombinant HB vaccine(YDV) is widely used around the world, and CHO derived recombinant HB vaccine is licensed in Israel and in some countries in East Asia.[44]. In China, the hepatitis B vaccines made by Saccharomyces cerevisiae, Hansenula polymorpha, and Chinese hamster ovary cells (CHO) are widely used. Many studies have compared the immune effects of the CHO and YDV in China, but the results were inconsistent.[14,19–21,27,29,34,39] Our study showed there was no significant difference in the positive rate between CHO and YDV (RR: 1.01, 95% CI: 0.98 to 1.04), meaning that the CHO and YDV vaccines are both suitable for adult vaccination in China. In addition, in China, some people believe that the imported hepatitis B vaccine had a better immune effect, but the meta-analysis showed that the domestic hepatitis B vaccine had the same positive rate as the imported hepatitis B vaccine (RR: 1.02, 95% CI: 0.99 to 1.05). There are also no significant differences in side effects between domestic and imported vaccines.[50,51] Therefore, adults in China can choose the CHO or YDV and domestic or imported as they please.

Three doses of HBV vaccine are recommended by the WHO for children, adolescents, and adults, with the second dose administered at least 1 month after and the third dose and 6 months after the first dose.[44] However, in China, there are more than 230 million migrant workers who regularly move between cities and are at high risk for HBV infection.[52] For these migrant workers, the 0-, 1-, and 6-month schedule may not be appropriate because they sometimes stay in one place for a few months and then move on to their next location. Therefore, many researchers have suggested administering the third dose 2 or 3 months after the first dose and have compared the immune effect between this schedule and the normal schedule.[14,23–25,31,36,40,43] This meta-analysis showed that compared with the normal schedule, the 0-, 1-, and 2- or the 3-month schedule may had a lower positive response rate. However, the sensitivity analysis showed that result changed when some studies were excluded, meaning that more studies should be conducted to explore this problem. Another 0-, 1-, and 12-month immune schedule has been suggested because nearly all migrant workers return home during the Spring Festival. This meta-analysis showed that there was no significant difference between the 0-, 1-, and 12-month schedule and the normal schedule. However, only two studies were included in this meta-analysis. Therefore, we suggest that the 0-, 1-, and 6-month schedule should still be the first choice, but for those who cannot complete this schedule, the 0-, 1-, and 12-month schedule is also worth considering.

This study had some limitations. First, the number of studies included was too small. Publication bias may exist in some meta-analyses because of the small number of eligible studies. Second, quality assessment is lacking in this study. When we used various methods[53-57] to evaluate the quality of the research, we found that almost all articles were similar in quality because the Chinese literature is simple in the description of the methods. Third, significant heterogeneity was present in this study, perhaps due to differences characteristics in different study populations. In the included studies, all participants were aged over than 15 years; some studies only included college students, while others included participants aged over than 40 years. Age is an important factor that affects the immune response, and the combination of studies with different age groups may result in significant heterogeneity. In addition, the prevalence of HBsAg varies from region to region, although the studies included were all from China. Furthermore, some personal factors, such as BMI, smoking status, alcohol status, and concomitant disease, were poorly reported in some included studies, with limited inclusion in subgroup analyses. Despite these limitations, in this work, several measures had been taken to avoid clinical and

methodological heterogeneity. For example, we only selected RCTs in our study, we excluded studies with small samples, we defined the ending variables, and all participants in the studies were Chinese adults. Therefore, we believe that our study will make a great contribution to hepatitis B vaccination in adults in China.

Conclusion

This meta-analysis showed that the 20-μg dose of HBV vaccine is recommended for adult immunization in China. The immune effect between CHO and YDV was not significantly different, and the use of imported or domestic vaccines did not affect the immune effect. The standard schedule is the most appropriate in adult immunization, but the 0-, 1-, and 12-month schedule is also worth choosing when it is not possible to complete the standard schedule.

Material and methods

Search strategy

The search was performed in December 2017 with no restrictions regarding publication dates. Studies were identified through searches of the following 5 databases: the China Knowledge Resource Integrated Database (CNKI), Wanfang Med Online, the VIP database, PubMed, and the Cochrane Library. The search terms were 'hepatitis B vaccine' OR 'hepatitis B vaccination' OR 'HBV vaccine' OR 'HBV vaccination' OR 'hepatitis B immunity' OR 'HBV immunity' and 'adult' OR 'adolescent' and 'China'. In addition, the reference lists of potentially relevant manuscripts were reviewed to obtain other eligible studies.

Inclusion criteria

The included studies met the following criteria: (1) The design of the study was a randomized controlled trial (RCT), and the sample size was ≥ 20; (2) the subjects were from the general population aged ≥ 15 years and had never been vaccinated for hepatitis B, and they were negative for anti-HBs, HBsAg, and HBeAg before vaccination; (3) the vaccine was the monovalent recombinant type, and the schedule consisted of 3 doses that were not given with accelerated timing, irrespective of type, dosage, route, or site of injection; and (4) seroprotection was defined as anti-HBs≥ 10 mIU/ml, and the serum should be tested 2–8 weeks after the last dose.

Data collection

Two authors (W.Z.K and B.H.D) independently assessed the studies to determine whether they met the inclusion criteria and fulfilled the objective of this meta-analysis, and disagreements were resolved through discussion with a third author. The authors were not blinded to the names of the studies, authors, journals, or results. We extracted the following data from the eligible studies: author, publication year, study design, age of participants, numbers of male and female participants, vaccination schedule, type and dosage of the vaccine, and the seroprotection rate after the last dose.

Statistical analysis

In this study, we calculated the relative risks (RR) and 95% confidence intervals (CIs) by comparing the seroconversion rates in the experimental and control groups of the included studies. Statistical heterogeneity among studies was examined by the Q and I^2 statistics; an I^2 value > 50% indicated significant heterogeneity. In addition, a random effects model was used to analyze the data when there was significant heterogeneity; otherwise, a fixed-effect model was selected.

Subgroup analyses were defined according to the reported data, and studies or results were grouped according to the type of vaccine (Chinese hamster ovary (CHO) or yeast-derived recombinant vaccine (YDV)), the origin of vaccine (domestic or imported), vaccination schedule (0.1.2–3, 0.1.6 or 0.1.12), and the dose of vaccine (5, 10 or 20 μg). A sensitivity analysis was performed to estimate the stability of the model by removing each study in turn, and publication bias was assessed through Begg's Test. All statistical analyses in this study were conducted with Stata 12.0 software (Stata Corp., College Station, TX, USA).

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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