The Two-years Immune Effect Between 0-1-2-months and 0-1-6-months of HBV Vaccination Schedule in Adults

Juan Wang
West China Hospital of Sichuan University
Chang-Hai Liu
West China Hospital of Sichuan University
Yuanji Ma
West China Hospital of Sichuan University
Xia Zhu
West China Hospital of Sichuan University
Liru Luo
West China Hospital of Sichuan University
Yulin Ji
West China Hospital of Sichuan University
Hong Tang (htang6198@hotmail.com)
West China Hospital of Sichuan University

Research Article

Keywords: Hepatitis B vaccination, anti-HBs level, long-term immune effect

Posted Date: July 26th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-665636/v1

Abstract

Background: The short-term 0-1-2-months hepatitis B virus (HBV) vaccination schedule was previously proposed in the adult population; however, its long-term immune effect remains unclear. The present study was aimed to investigate 1) the 2-months and 2-year immune effect of HBV vaccination; and 2) compliance rate between 0-1-2-months and 0-1-6-months vaccination schedules in adults.

Method: A total of 1281 subjects tested for HBsAg(-) and Hepatitis B surface antibody (anti-HBs)(-) were recruited. Participants from two distant counties were inoculated hepatitis B yeast vaccine for 10ug per dose each time, with 0-1-2-months (n=606) and 0-1-6-months (n=675) vaccination schedule, sequentially followed-up at two months and two years after the 3rd injection.

Results: There was no statistical difference in anti-HBs seroconversion rate between 0-1-2-months and 0-1-6-months vaccination schedule at two months (91.96% vs 89.42%, p=0.229) and two years (81.06% vs. 77.14%, p=0.217). Quantitative anti-HBs level of 0-1-2-months vaccination schedule was not different with 0-1-6-months vaccination schedule at 2 months (anti-HBs_1) (342.12 ± 378.42 m IU/ml vs. 392.38 ± 391.96 m IU/ml, p=0.062), but was higher at two years (anti-HBs_2) (198.37 ± 286.44 m IU /ml vs. 155.65 ± 271.73 m IU /ml, p=0.048). By subgroup analysis, 0-1-2-months vaccination schedule showed better maintenance (p=0.041) and delayed reinforcement (p=0.019) in comparison to 0-1-6 vaccination schedule. The 0-1-2-months vaccination schedule also increased the 3rd-time injection completion rate (89.49% vs. 84.49%, p=0.010).

Conclusion: the 0-1-2-months vaccination could obtain a similar short-term immune effect, but achieve a better long-term immune memory and a higher completion rate in the adult population.

Trial registration: None

Background

Hepatitis B virus(HBV) infection was estimated that the global prevalence of HBsAg in 2016 was 3.9%.[1] A modelling study[2] estimated HBsAg prevalence in China to be 6·1%,[3] other study reported the prevalence in 2018 was more than 80 million estimated chronic infections.[4] The World Health Organization (WHO) estimates that more than 658,000 individuals die annually from hepatitis B virus (HBV)-related complications, such as fulminant hepatitis, cirrhosis, and liver cancer.[5] The universal infantile HBV vaccination in the national immunization program achieved great success in preventing and controlling HBV infection in the past 20 years. HBsAg positive rate in mainland of China decreased from 14·0% in 1957–89 to 5·4% in 1990–2013.[6] In adults, the immunized population had a much lower prevalence of HBsAg than the un-immunized population.[7] Therefore, hepatitis B vaccine immunization in adults should also be recommended.[2]

HBV immunization at 0, 1 and 6 months (0-1-6-months) have been recommended by the WHO and US Centers for Disease Control and Prevention, as well as Chinese National Guidelines on chronic hepatitis B prevention and treatment (2015). However, the WHO-recommended 0-1-6-months vaccination schedule often leads to a lower completion rate of vaccination in adults.[8–10] In fact, in China there was a special population called floating population (so-called migrant workers in other countries), accounting for 230 million people per year. Generally, they leave their hometowns to find jobs in other cities and change their jobs frequently. The floating population of China had an increased risk of sexual transmission of HBV due to having lower education, lower economic income, younger age, and multiple sexual partners.[11] Therefore, previous studies proposed a vaccination schedule at months 0, 1, and 2 (0-1-2-months), resulting in a comparable short-term safety and immunogenicity.[12,13] Moreover, shortening the vaccine schedule time can effectively increase the completion rate of vaccination and even stimulate earlier and faster anti-HBs production.[12,13] Such accelerated immunization schedules (0-1-2-months, 0-1-3-months and 0-7-21-days, etc.) were verified to have the same short-term immune effect and to increase the completion rate in the general population[14], vein-injected drug users[15,16] and adults who were refused to receive the second or third dose owing to occupational reasons[17,18]. However, antibody maintenance by immune memory was even more crucial than antibody production in protecting patients from HBV infection. Therefore, the comparative results for the best vaccination schedule could not be obtained from previous short-term follow-up studies.

The long-term immune effect of the accelerated vaccination schedule remains unclear due to the lacking evidence.[12,19] Ren et al recently reported that the same positive seroprotection rate and the quantitative anti-HBs level between 0–1–3-months vaccination and 0–1–6-months schedule in 8 years after the vaccination.[18] However, the author also declared in limitation part that high loss to follow-up (from initial 771 participants to 242 in final follow-up, 529 participants were lost to follow-up) caused by the floating population and relatively small sample size may influence the reliability. We proposed a prospectively interventional study in two comparable towns study to investigate the short-term and long-term immune effects, as well as the completion rate between the accelerated vaccination schedule (0-1-2-months) and the standard vaccination schedule (0-1-6-months).

Mathods

1. Study design

This was a prospective study to explore the response of different vaccination schedules of hepatitis B on both HBsAg(-) and anti-HBs(-) adults. Randomization were not available due to the different 3rd injection time (participants from small towns would aware of different schedules). Thus, two similar demographic and comparable town (similar economic, diet habit, social factors, etc.) Jinfeng town and Longmen town of Mianyang city, were recruited. Participants with with 18 to 59 years old were enrroled. Participants with HIV coinfection and active HBV infection were excluded. The study was conducted from 1 June 2013 to 1 December 2017. The study protocol conformed to the ethical guidelines of the 1975 Declaration of

Helsinki. The Institutional Review Board Committee of West China Hospital of Sichuan university approved the study protocol. The study was performed by following the ethical guidelines expressed in the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. Informed consent was obtained from all subjects.

This study was supported by the National Scientific and Technological Major Project for Infectious Diseases Control in China (grant number 2018ZX10715-003) and The Science and Technology Project of The Health Planning Committee of Sichuan (grant number 16PG280). Funding body was in charge of the design of the study and collection, analysis, and interpretation of data.

Appropriate training was given to research stuff from the leading investigators. Standardized, questionnaire-based face-to-face interviews were performed after obtaining written consent. The questionnaire collected information including gender, age, height and weight, etc. Each subject was confirmed by screening identification card and taking a photo before each vaccine injection. After that, they were offered vaccination through the regular service of township hospitals, where trained medical staff performed vaccinations by intramuscular injection. Vaccinations with 10ug per dose of hepatitis B yeast vaccine (Hualan Biological Vaccine Company, Chengdu, China) in assigned to 0-1-2-months vaccination schedule in Jinfeng and 0-1-6-months vaccination schedule in Longmen.

2. Follow up

The 1st and 2nd follow-up visits were conducted at 2 months and 2 years after finishing the third vaccine injection. The follow-up time to each subject was informed by phone-calling 3 weeks before visiting. Each subject was confirmed by screening an identification card and taking a photo. Every screening card was individualized with the follow-up time of each participant as a memorandum. Both schedules were consistent with the community standard of care at the time.

3. Serum assay and Blood sample tests

Serum samples were also collected and tested at each follow-up visit in local health stations and community clinics. The anti-HBs levels at 2 months (anti-HBs_1) and 2 years (anti-HBs_2) after 3rd -time injection vaccination were analyzed for vaccine response. The serum samples were tested for the quantification of HBsAg and anti-HBs by electrochemiluminescence immunoassay (Abbott i2000SR, U.S.A) in West China Hospital. The HBsAg level < 0.05 m IU/ml was defined as negative ones. Anti-HBs level below 10 m IU/ml, 10–100 m IU/ml, 100–1000 m IU/ml and above 1000 m IU/ml were defined as no response, low response, normal response and high response, respectively.[20] Because anti-HBs ration less than 0.05 m IU/mL were unable to detect and exceeding 1,000 m IU/mL were excluded from further dilution test, a value of 0 m IU/mL and 1000 m IU/mL were assigned to these subjects respectively for quantitative analysis of anti-HBs, for reference as previous anti-HBs geometric mean concentration (GMC) test.[13,21]

To explore the reason for different maintenance of Anti-HBs level between two vaccination schedule, the subjects were divided into four different clinical scenarios: 1) “well production and good maintenance” by

anti-HBs_1(at two months) (+) and anti-HBs2(at two years) (+); 2) “well production and poor maintenance” by anti-HBs_1 (+) and anti-HBs_2 (-); 3) “persistent non-production” by anti-HBs1 (-) and anti-HBs_2 (-); and 4) “delayed production”, anti-HBs_1 (-) and anti-HBs_2 (+). Furthermore, the "well production and good maintenance" group was further divided into four subgroups: 1) “High production and good maintenance” by high anti-HBs_1 (> 100 m IU/ml) and high anti-HBs_2 (> 100 m IU/ml), 2) “well production and fast decrease” by high anti-HBs_1 (> 100 m IU/ml) and low anti-HBs_2 (10–100 m IU/ml), 3) “relative low production” by low anti-HBs_1 (10–100 m IU/ml) and low anti-HBs_2 (10–100 m IU/ml), and 4) “delayed reinforcement” by low anti-HBs_1 (10–100 m IU/ml) and high anti-HBs_2 (> 100 m IU/ml).

4. Statistical analysis

Mean values and prevalence of baseline characteristics were calculated. Data were reported as the mean ± standard deviation for normal and median (interquartile range) for non-normal continuous variables (when sample size > 40, mean ± standard deviation was used to express data), while the frequency was used for discrete variables. In the univariate comparisons, we used the Student t-test and ANOVA with Bonferroni adjustments for continuous samples and the chi-square test or Fisher's exact test for the qualitative ones. Non-parametric alternatives (Mann–Whitney U and Kruskal-Wallis tests) were used for non-normal distributions. Logistic regression models were used to estimate adjusted odds ratios (aORs) with our principal outcome of full-time completion rate and 3rd -time injection rate. Covariates were selected for analysis according to their biologically plausible potential to act as confounders or predictors for each outcome. The potential predictors at baseline were as follows: age, gender, BMI, previous hypertension, previous type 2 diabetes mellites (T2DM), abnormal alanine aminotransferase (ALT) level. The collinearity between factors included in the multivariable analyses was checked by using variance inflation factor (VIF) and tolerance (1/VIF) values. Variables with very high VIF values indicating possible redundancy entered into different multivariable models. All statistical analyses and figures were performed in SPSS (version 20) and PRISMA (version 8). A p value < 0.05 was considered as statistical significance.

Results

1. Characteristics of the included population and follow-up

A total of 1281 subjects with both HBsAg (-) and anti-HBs (-) were enrolled. Of them, 606 subjects from Jinfeng were assigned to vaccinate on 0-1-2-months, while the other 675 subjects from Longmen were vaccinated on 0-1-6-months. (Supplementary Figure 1) After that, 511 subjects in the group of 0-1-2-months vaccination schedule and 550 subjects in the group of 0-1-6-months vaccination schedule finished all three injections. The baseline characteristics of the included participants were shown in table 1. Briefly, the age (37.74 ± 12.64 vs. 38.80 ± 12.13, p=0.129), sex (male: 45.37% vs. 54.63%, p=0.256) and BMI (23.02 ± 3.54 vs. 22.85 ± 3.85, p=0.422) of vaccination schedule were equal distribution between 0-1-2-months and 0-1-6-months vaccination schedule, respectively. (Table 1)

There were 621 participants completed both 2-month and 2-year follow-up visits. The information obtained from phone-calling indicated that subjects who unfinished the three injections or did not show-up at follow-up time were mainly owing to occupied working schedules or migrant workers working in distant places. The distribution equally were re-assessed since almost half of participants were lossed followed-up. (Supplementary table 1)

2. Comparison of the short- and long-term immune effects of two vaccination schedules

(1)No difference was found in anti-HBs seroconversion between two vaccination schedules

Anti-HBs seroconversion rates were no significant difference between 0-1-2-months and 0-1-6-months vaccination schedule at short-term seroconversion (at two months) (89.42% vs. 91.96%, p=0.229) (Figure 1A), as well as at long-term seroconversion rate (81.06% vs. 77.14%, p=0.217) (Figure 1B). Therefore, a similar immune effect was obtained by 0-1-2-months vaccination schedule, and even an earlier protection was gained at second months rather than at sixth months compared to 0-1-6-months vaccination schedule.

(2) 0-1-2-months vaccination schedule showed a higher anti-HBs level at 2-year follow-up

The quantitative analysis of anti-HBs of 0-1-2-months vaccination schedule was not different at 2-months follow-up (342.12 ± 378.42 m IU/ml vs. 392.38 ± 391.96 m IU/m, p=0.062), but higher at 2-year followed-up (198.37 ± 286.44 m IU/ml vs. 155.65 ± 271.73 m IU/ml, p=0.048), in comparison to the 0-1-6-months vaccination schedule. (Table 2) Furthermore, among the subjects with successful seroconversion (anti-HBs_1>10 m IU/ml), no difference was found in the proportion of low response (10 m IU/ml< anti-HBs_1<100 m IU/ml), normal response (100 m IU/ml< anti-HBs_1<1000 m IU/ml) and high response (anti-HBs_1>1000 m IU/ml) between 0-1-2-months and 0-1-6-months vaccination schedule at 2-months follow-up (p for ANOVA=0.517) (Figure 1C) However, 0-1-2-months vaccination schedule induced better maintenance of anti-HBs at 2-year followed up, with a higher proportion of normal response (44.73% vs. 32.87%) and high response (7.69% vs. 6.48%), and a lower proportion of low response (7.69 vs. 6.48%) (p for ANOVA=0.010). (Figure 1D)

(3) 0-1-2-months vaccination schedule showed better maintenance and a delayed reinforcement

To explore the reason for different maintenance of Anti-HBs level between two vaccination schedules, the subjects were divided into four different clinical scenarios (detailed in methods part). We found that the 0-1-2-months vaccination schedule showed a lower proportion of the "well production and poor maintenance" group than that in 0-1-6-months vaccination (12.56% vs. 18.61%, p=0.041), suggesting the 0-1-2-months vaccination schedule induced better maintenance than 0-1-6 vaccination schedule. (Figure 2) The "well production and good maintenance" group was further divided into four subgroups by qualitative level of anti-HBs. The result showed that the proportion of the 4^{th} subgroup (low anti-HBs_1 and high anti-HBs_2) in the 0-1-2-months vaccination schedule was higher than that in the 0-1-6-months vaccination schedule (9.33% vs. 3.51%, p=0.019), suggesting 0-1-2-months vaccination schedule

possibly induced a “delayed reinforcement” of antibody production, as having low anti-HBs at initial but high anti-HBs at two years. (Figure 2)

3. Factors associated with anti-HBs seroconversion

In the multivariant analysis, no significant difference of anti-HBs seroconversion rate was found between 0-1-2-months and 0-1-6-months vaccination schedule both at two months (OR 0.73, 95% CI 0.46-1.18, p=0.211) and two years (OR 1.27, 95% CI 0.85-1.90, p=0.241). Besides, the younger age (OR 0.97, 95%CI 0.95-0.99, p=0.007), lower BMI (OR 0.86, 95%CI 0.81-0.92, p<0.001) and lower Anti-HBc (OR 0.88, 95% CI 0.83-0.94, p<0.001) were significant associated with anti-HBs seroconversion at two months cheek. Only the lower BMI (OR 0.91, 95% CI 0.86-0.96, p=0.002) was significantly associated with anti-HBs seroconversion at two years (Table 3)

4. Comparison of vaccination completion rate

Since the 3rd-time injection completion rate at 2nd or 6th months were the main different timepoints between 0-1-2-months and 0-1-6-months vaccination schedule, we further analyzed the 3rd-time injection completion rate. The 3rd-time injection completion rate of the 0-1-2-months vaccination schedule was higher than the 0-1-6-months vaccination schedule (89.49% vs. 84.49%, p=0.010). (Supplementary Figure 2) Moreover, after adjusting age and BMI, the 0-1-2-months vaccination schedule (OR 1.69, 95% CI 1.19-2.39, p=0.003) significantly increased the 3rd-time injection completion rate by using the 0-1-6-months vaccination schedule as reference. (Table 4)

Discussion

In the present study, we found that the short- and long-term anti-HBs seroconversions were not different between 0-1-2-months and 0-1-6-months vaccination procedures. However, 0-1-2-months vaccination schedule showed a higher anti-HBs level at 2-year follow-up by inducing better maintenance and a delayed reinforcement in comparison to the 0-1-6-months vaccination schedule. In the multivariant analysis, no significant difference of anti-HBs seroconversion rate was found between 0-1-2-months and 0-1-6-months vaccination schedule at two months and two years. However, the 0-1-2-months vaccination significantly increased the 3rd -time injection completion rate. Therefore, In conclusion, the 0-1-2-months vaccination could obtain a similar short-term immune effect, but achieve a better long-term immune memory and a higher completion rate in the adult population.

In a recent systematic review, the different vaccination schedule obtain the similar short-term immune effect, demonstrating that anti-HBs concentrations ≥ 10 m IU/ml were approximately 65.0–85.0% using the 0-1-2-months schedule, approximately 77.0–90.8% using the 0-7-21-day schedule, 87.0% using the 0-2-6-week schedule, and around 79.0% after the 0-14-28-day schedule, respectively.[22] Ren et al[18] also reported that the accelerated schedule (0–1–3-months) and the standard schedule (0–1–6 months) enhanced the long-term immune memory (8 years after) in comparison to (0-1-12-months) schedule,

which we found a similar long-term immune effect in the present study (2 years after). Regarding the short-term immune effect, we speculate that the different short-term immune effect may be explained by that the measurement was taken at a different time (4th months for “0-1-3-months”, 7th months for “0-1-6-months” and 13th months for “0-1-12-months), since the 6-months and 12-months injection serve as a booster dose, which was known to increase the seroconversion rate.[22] Regarding the long-term immune effect, we further explored that the longer immune memory of shorter interval of 0-1-3-months was induced by a “better maintenance” and “delayed reinforcement" in the present study. Thus, the shorter interval of vaccination schedule provided a stronger re-estimation to the immune system, resulting in a higher anti-HBs level at 2 years after three injections.

The in-developing immune system in children was different from the mature immune system in adults, therefore the vaccination schedule could be modified according to a specific population. Cesare Belloni[23] reported that in children the 0-1-6-months vaccination schedule presented a higher percentage of seroconversion than the 0-1-3-months vaccination schedule, but also pointed out that the reduced response after the 0-1-3-months vaccination schedule was mainly due to the relative immaturity of the immune system in the younger infants.[24] Similarly, the bacterial conjugate vaccines were also recommended for adult to use only one dose at initial and a booster immunization, which is sufficient for adults to stimulate memory B cells and to maintain the antibody due to the mature immune system.[25] Thus, the decision of shorter or longer period of vaccination injection was dependent on the mature or immature status of the host immune system. The immature immune system in children was responded differently in 0-months, 1-months and 6-months since the system was still developing; thus the 3rd injection at 6 months in children could induce a better response by a relatively more mature immune system at 6 months than that at 3 months or earlier. However, the mature immune system in the adults was responded similarly at 0 months, 1 month, 3 months or 6 months, thus a shorter period could gain more completion rate.

Our results indicated that the 0-1-2-months vaccination established a better completion rate than the 0-1-6-months vaccination schedule. However, a previous study reported that a 0–1–12-months vaccination schedule may be more suitable for the floating population and 0–1–6-months schedule is recommended for the fixed population, both of them had a better completion rate than the 0-1-3-months schedule.[8] The floating population of China was characterized by changing their jobs frequently and returning home annually to celebrate the spring festival after 11 months of working and rest for one month. The different results between the present and previous studies could be explained by calculating the 3^{rd-}time injection rather than a full-time injection since the 1st and 2nd injections were the same at 0 and 1 months.

There were limitations in the present study. Firstly, there were patients lost follow-up patient in the first and second follow-up visit. Nevertheless, the lost follow-up was inevitable in follow-up visit, because the secondary outcome of the present study was designed to investigate the completion rate on a floating population. Moveover, we re-assessed the baseline characteristics of followed up patients, resulting a destribustion equally between 2 groups (supplementary table 1). Secondly, information on the

participants' status (including smoking, drinking and diabetes) were not recorded (even the HIV coinfection and active HBV were excluded), which might affect antibody response after hepatitis B vaccination. Lastly, a standardized time point for the measurement of anti-HBs antibody levels, to enhance comparability of the immune response between different studies; although we found better maintenance and a delayed reinforcement of anti-HBs by 0-1-2-months vaccination schedule,the insufficient observed time points within 2 years limited us to explore the anti-body production tendency.

Conclusion

The 0-1-2-months vaccination could obtain a similar short-term immune effect, but achieve a better long-term immune memory and a higher completion rate in the adult population.

Abbreviations

HBV
hepatitis B virus;
WHO
World Health Organization;
HBsAg
Hepatitis B surface antigen;
anti-HBs
Hepatitis B surface antibody;
BMI
Body Mass Index;
anti-HBs_1
the anti-HBs level 2 months after 3rd -time injection vaccination;
anti-HBs_2
the anti-HBs level 2 years after 3rd -time injection vaccination;
aORs
adjusted odds ratios;
T2DM
type 2 diabetes mellites;
ALT
alanine aminotransferase;
CI
confidence interval.

Declarations

Ethics approval and consent to participate: Yes, this study was approved by the Medical Ethics Committee of West China Hospital of Sichuan University (No. 55, Version 2013-4-15) (in related files). The

study was performed by following the ethical guidelines expressed in the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. Informed consent was obtained from all subjects.

Consent for publication: None, present study was retrospective study design and did not contains specific personal medical information (video or image) about an identifiable living individual. However, the consent of information for each participantets was obtained before the first vaccination.

Availability of data and materials: Yes, supplementary data. All data generated or analyzed during this study are included in this published article and its supplementary information files.

Competing interests: No.

Funding: This study was supported by the National Scientific and Technological Major Project for Infectious Diseases Control in China (grant number 2018ZX10715-003) and The Science and Technology Project of The Health Planning Committee of Sichuan (grant number 16PG280). Funding body was in charge of the design of the study and collection, analysis, and interpretation of data.

Authors' contributions: Guarantor of the article: HT. Study design: HT, JW. Drafting the manuscript: CHL, HT, JW. Statistical analyses and interpretation: CHL. Data acquisition:YJM, XZ, LRL, YLJ. Critical revision of the manuscript: HT, CHL, YLJ. All authors have read and approved the manuscript.

Acknowledgements: We thank the workers at the Center for Disease Control and Prevention of Mianyang City, Jiangyou County, and Fucheng District for their assistance in carrying out the present study. We also thank the physicians and nurses at the community health service centers and township hospitals that helped us perform this work.

Checklist for the appropriate reporting statement: STROBE (in supplementary file).

References

1. Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: a modelling study. *The lancet Gastroenterology & hepatology.* 2018;3(6):383-403.

2. Weinbaum C, Williams I, Mast E, et al. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. *MMWR Recommendations and reports : Morbidity and mortality weekly report Recommendations and reports.* 2008;57:1-20.

3. Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: a modelling study. *Lancet Gastroenterol Hepatol.* 2018;3(6):383-403.

4. Cooke GS, Andrieux-Meyer I, Applegate TL, et al. Accelerating the elimination of viral hepatitis: a Lancet Gastroenterology & Hepatology Commission. *Lancet Gastroenterol Hepatol.* 2019;4(2):135-184.

5. Organization WH. Global health sector strategy on Viral hepatitis 2016–2021. http://www.who.int/hepatitis/strategy2016-2021/ghss-hep/en/. Published 2016. Accessed.

6. Schweitzer A, Horn J, Mikolajczyk RT, Krause G, Ott JJ. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. *Lancet.* 2015;386(10003):1546-1555.

7. Liang X, Bi S, Yang W, et al. Epidemiological serosurvey of hepatitis B in China–declining HBV prevalence due to hepatitis B vaccination. *Vaccine.* 2009;27(47):6550-6557.

8. Yao J, Li J, Chen Y, et al. The response of hepatitis B vaccination on seronegative adults with different vaccination schedules. *Hum Vaccin Immunother.* 2015;11(5):1102-1107.

9. Williams WW, Lu PJ, O'Halloran A, et al. Surveillance of Vaccination Coverage among Adult Populations - United States, 2015. *MMWR Surveill Summ.* 2017;66(11):1-28.

10. Kisangau E, Awour A, Juma B, et al. Prevalence of hepatitis B virus infection and uptake of hepatitis B vaccine among healthcare workers, Makueni County, Kenya 2017. *Journal of public health (Oxford, England).* 2019;41(4):765-771.

11. Yan YP, Su HX, Ji ZH, Shao ZJ, Pu ZS. Epidemiology of Hepatitis B Virus Infection in China: Current Status and Challenges. *J Clin Transl Hepatol.* 2014;2(1):15-22.

12. Van Herck K, Leuridan E, Van Damme P. Schedules for hepatitis B vaccination of risk groups: balancing immunogenicity and compliance. *Sex Transm Infect.* 2007;83(6):426-432.

13. Wouters K, Leuridan E, Van Herck K, et al. Compliance and immunogenicity of two hepatitis B vaccination schedules in sex workers in Belgium. *Vaccine.* 2007;25(10):1893-1900.

14. Hwang LY, Grimes CZ, Tran TQ, et al. Accelerated hepatitis B vaccination schedule among drug users: a randomized controlled trial. *J Infect Dis.* 2010;202(10):1500-1509.

15. Shah DP, Grimes CZ, Nguyen AT, Lai D, Hwang LY. Long-term effectiveness of accelerated hepatitis B vaccination schedule in drug users. *Am J Public Health.* 2015;105(6):e36-43.

16. Jin H, Tan Z, Zhang X, Wang B, Zhao Y, Liu P. Comparison of Accelerated and Standard Hepatitis B Vaccination Schedules in High-Risk Healthy Adults: A Meta-Analysis of Randomized Controlled Trials. *Plos One.* 2015;10(7):e0133464.

17. Bowman S, Grau LE, Singer M, Scott G, Heimer R. Factors associated with hepatitis B vaccine series completion in a randomized trial for injection drug users reached through syringe exchange programs in three US cities. *BMC Public Health.* 2014;14:820.

18. Ren W, Ren J, Wu Z, et al. Long-term persistence of anti-HBs after hepatitis B vaccination among adults: 8-year results. *Hum Vaccin Immunother.* 2020;16(3):687-692.

19. Estévez ZC, Betancourt AA, Muzio González V, et al. Immunogenicity and safety assessment of the Cuban recombinant hepatitis B vaccine in healthy adults. *Biologicals.* 2007;35(2):115-122.

20. Mast EE, Weinbaum CM, Fiore AE, et al. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) Part II: immunization of adults. *MMWR Recomm Rep.* 2006;55(Rr-16):1-33; quiz CE31-34.

21. Zhang X, Wang J, Chen X, et al. Short-term immunogenicity of standard and accelerated hepatitis B virus vaccination schedules in healthy adults: a comparative field study in China. *Biosci Rep.* 2018;38(5).

22. Van Den Ende C, Marano C, Van Ahee A, Bunge EM, De Moerlooze L. The immunogenicity and safety of GSK's recombinant hepatitis B vaccine in adults: a systematic review of 30 years of experience. *Expert Rev Vaccines.* 2017;16(8):811-832.

23. Belloni C, Pistorio A, Tinelli C, et al. Early immunisation with hepatitis B vaccine: a five-year study. *Vaccine.* 2000;18(14):1307-1311.

24. Belloni C, Orsolini P, Martinetti M, et al. Control of hepatitis B: evaluation of two different vaccinal schedules in newborns from HBsAg negative mothers. *New Microbiol.* 1993;16(3):237-244.

25. Rappuoli R. Glycoconjugate vaccines: Principles and mechanisms. *Sci Transl Med.* 2018;10(456).

Tables

Table 1. Baseline characteristics of included participants

Variables	0-1-6-months vaccination (n=675)	0-1-2-months vaccination (n=606)	p value
Age, years	38.80 ± 12.13	37.74 ± 12.64	0.129
Sex Male	288 (54.63%)	239 (45.37%)	0.256
Female	387 (51.33%)	367 (48.77%)	
BMI, kg/m^2	22.85 ± 3.85	23.02 ± 3.54	0.422
Waistline, cm	76.20 ± 11.04	77.45 ± 9.31	0.030

BMI, body mass index

Table 2. Short-term and long-term comparison of quantitative anti-HBs between 0-1-2-months and 0-1-6-months vaccination schedules

Variables	0-1-6-months vaccination (n=231)	0-1-2-months vaccination (n=390)	p value
	Mean ± SD	Mean ± SD	
Anti-HBs_1 (m IU/ml)	392.38 ± 391.96	342.12 ± 378.42	0.062
Anti-HBs_2 (m IU/ml)	155.65 ± 271.73	198.37 ± 286.44	0.048

Anti-HBs_1, hepatitis B antibody at 2 months after three vaccination injections;

Anti-HBs_2, hepatitis B antibody at 2 years after three vaccination injections.

Table 3. Univariate analysis to identify variables associated with short-term and long-term anti-HBs seroconversion rate

Variables	Anti-HBs seroconversion at two months		Anti-HBs seroconversion at two years	
	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Age years	0.97 (0.95-0.99)	0.007	0.98 (0.97-1.00)	0.165
Male sex	1.17 (0.73-1.90)	0.503	0.73 (0.48-1.11)	0.147
BMI	0.86 (0.81-0.92)	<0.001	0.91 (0.86-0.96)	0.002
Anti-HBc	0.88 (0.83-0.94)	<0.001	1.04 (0.98-1.09)	0.148
ALT	0.99 (0.99-1.00)	0.282	1.00 (0.99-1.00)	0.910
0-1-2-month vs. 0-1-6-month (reference) vaccination schedule	0.73 (0.46-1.18)	0.211	1.27 (0.85-1.90)	0.241

Table 4. Univariate and multivariant analysis to identify variables associated with 3rd-time injection completion rate

	Successful 3rd-time injection completion rate			
	Univariant aOR (95% CI)	p value	Multivariant aOR (95% CI)	p value
Age	1.04 (1.03-1.06)	<0.001	1.04 (1.03-1.06)	<0.001
Sex (Female)	1.38 (0.99-1.93)	0.053		
BMI	1.06 (1.01-1.11)	0.012	0.99 (0.94-1.04)	0.092
Hypertension	7.25 (0.35-35.98)	0.146		
T2DM	7.10 (0.97-51.91)	0.530		
Abnormal ALT	1.55 (0.974-2.47)	0.065		
vaccination type (0-1-2-months vs. 0-1-6-months)	1.56 (1.112-2.20)	0.010	1.68 (1.19-2.39)	0.003

BMI, body mass index; T2DM, type 2 diabetes mellitus; aORs, adjusted odds ratios; ALT, alanine aminotransferase.

Figures

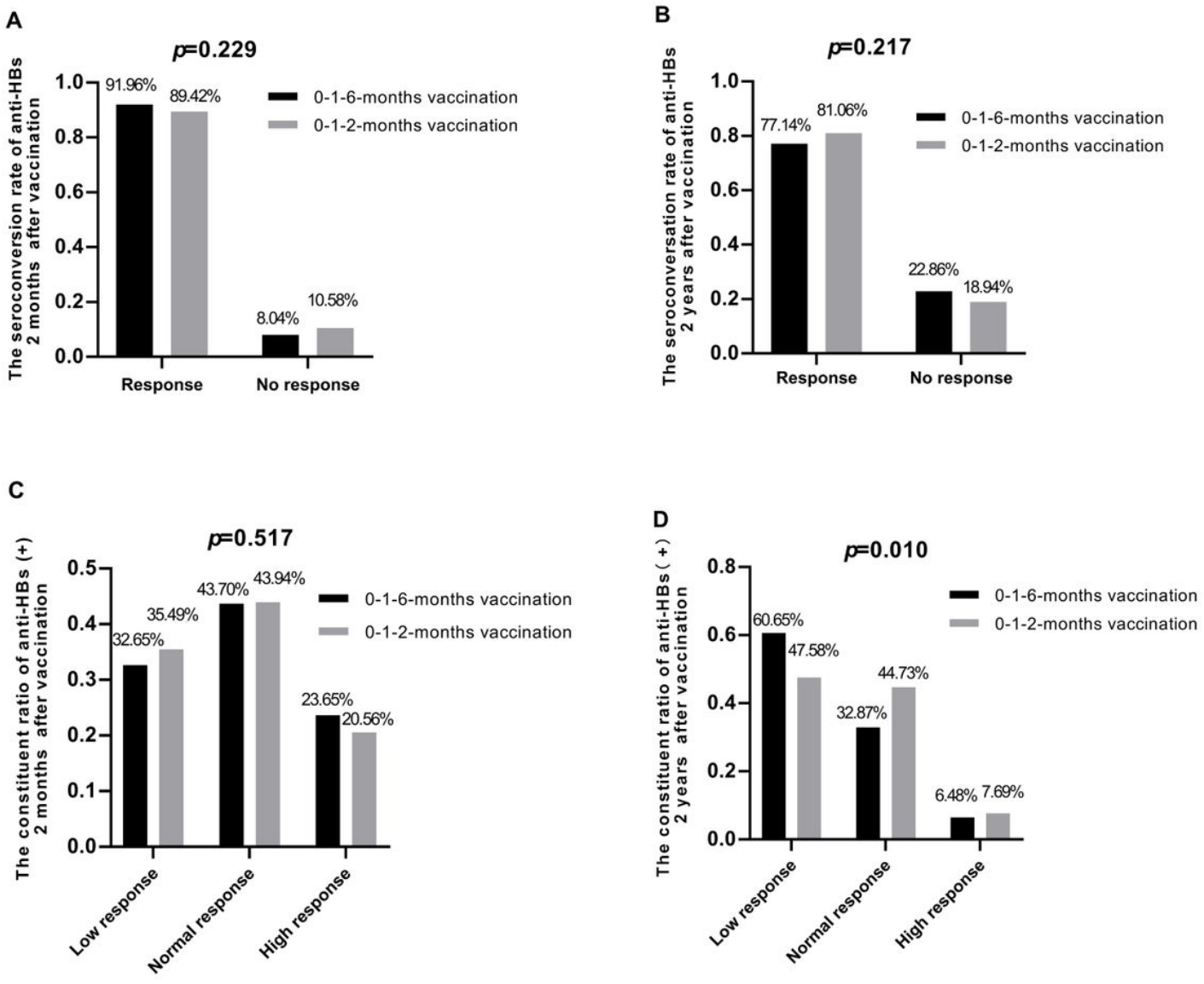

Figure 1

Short- and long-term anti-HBs seroconversion. The rate of anti-HBs seroconversion at 2 months (A) and 2 years (B) after vaccination; the proportion of anti-HBs level according to no response (10-100 m IU/ml), low response (100-1000 m IU/ml) and high response (≧1000 m IU/ml) at 2 months (C) and 2 years (D) after vaccination.

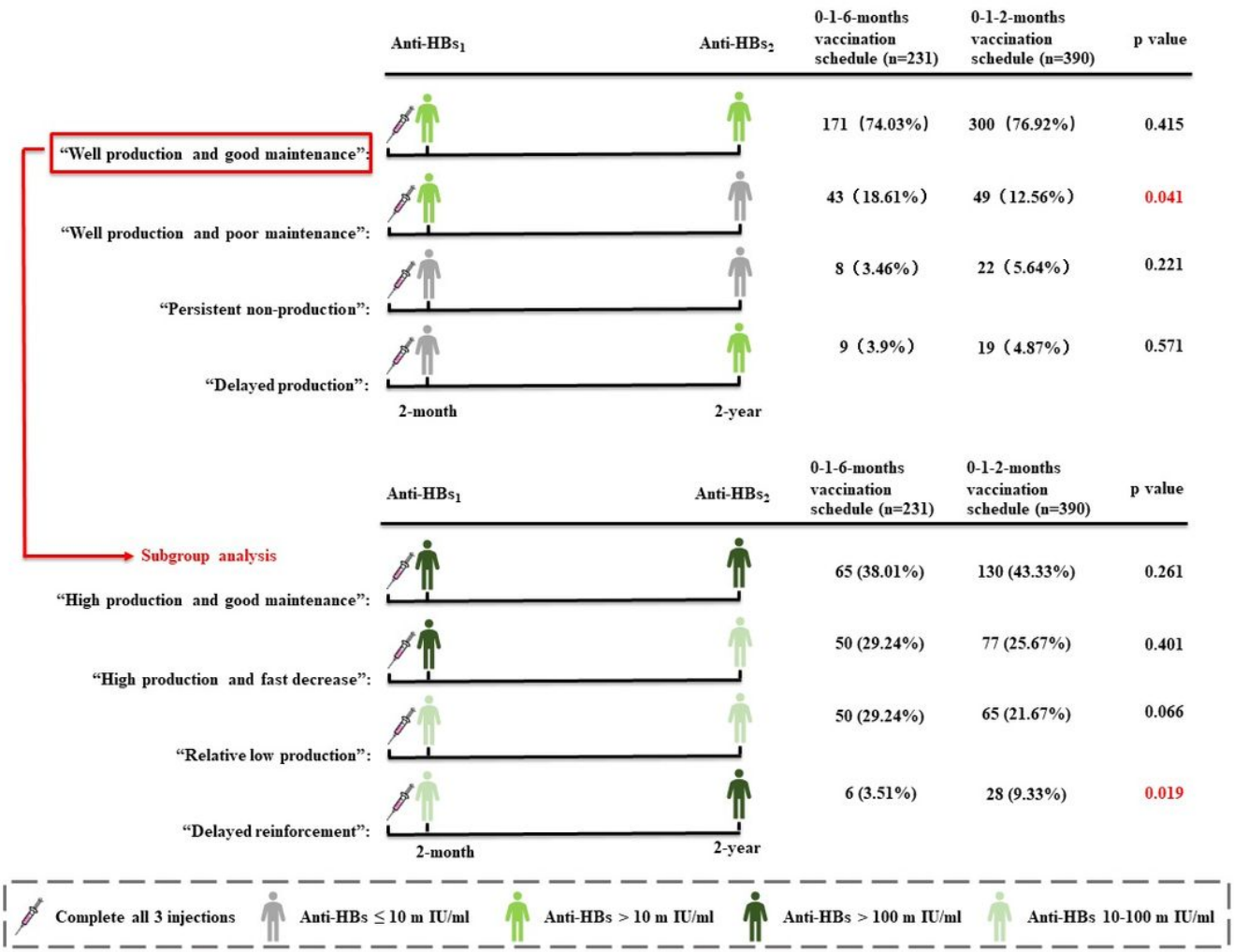

Figure 2

Comparison the different immune memory between the different vaccination schedules by classifying 2-months and 2-years anti-HBs levels. The 621 participants who completed both 2-year and 2-year follow-up were included in the first part of analysis; 471 participants who were defined as "well production and good maintenance" in the first part of analysis with anti-HBs1(+) and anti-HBs2(+) were included in the second part of analysis, and were further divided into four different subgroups. Anti-HBs1, hepatitis B antibody at 2 months after three vaccination injections; Anti-HBs2, hepatitis B antibody at 2 years after three vaccination injections;

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Rawdata2021.1.18.xlsx
- STROBEchecklistcohortstudies.doc

- Supplementarytable1.docx