Transient Hepatitis B Surface Antigenemia Following Immunization with Heplisav-B

Cristina Corsini Campioli, MD; Zerelda Esquer Garrigos, MD; Mariam Assi, MD; John Raymond Go, MD; Raymund R. Razonable, MD; Elena Beam, MD; Joseph Yao, MD; and Nathan W. Cummins, MD

Abstract

Objective: To delineate the rate and duration of transient hepatitis B surface antigenemia following Heplisav-B vaccination.

Patients and Methods: We retrospectively reviewed the medical records of all adult patients who received Heplisav-B vaccination at our institution from January 1, 2019, through March 31, 2020, and who had hepatitis B surface antigen (HBsAg) testing within 30 days following immunization. Patients with laboratory evidence of prior hepatitis B virus infection or immunization were excluded.

Results: A total of 39 of 1933 patients were tested for HBsAg within 30 days after completing the Heplisav-B vaccination series; of these 39, only 6 (15.4%) had a positive HBsAg result. Compared with the patients with negative HBsAg results, those with a positive HBsAg result had a significantly lower body mass index (24.8 kg/m² [interquartile range (IQR), 23 to 26.4 kg/m²] vs 28.6 kg/m² [IQR, 26.4 to 30.6 kg/m²]; P = .01) and higher prevalence of chronic kidney disease (2 of 6 [33.3%] vs 2 of 33 [6%]; P = .04). The timing of HBsAg testing after completing the vaccination series in the HBsAg-positive group was significantly earlier compared with that of the HBsAg-negative group (2 days [IQR, 0.43 to 2.25 days] vs 12 days [IQR, 10 to 15 days]; P = .0008). Active hepatitis B infection was excluded in all 6 patients. In the HBsAg-positive group, the median time from the date of Heplisav-B administration to a negative HBsAg test result was 17 days (IQR, 8 to 36 days).

Conclusion: As with all conventional hepatitis B vaccines, transient hepatitis B surface antigenemia can be observed with Heplisav-B vaccine, particularly in those with chronic kidney disease and low body mass index.

Hepatitis B virus (HBV) infection is the seventh leading cause of death globally. Although acute HBV infection is often self-limiting, chronic HBV infection may be difficult to treat and may lead to serious long-term complications including end-stage liver disease, liver transplant, and hepatocellular carcinoma.

Although several antiviral therapies are available for patients fulfilling treatment criteria, none of them achieve a virologic cure. Therefore, disease prevention in the form of active immunization remains the mainstay strategy in the fight against HBV infection. The Centers for Disease Control and Prevention recommends hepatitis B vaccination for adult patients without evidence of prior immunization who are deemed at high risk for acquiring the infection. Currently, 3 recombinant vaccines are available in the United States. Recombivax HB (Merck & Co, Inc) and Engerix-B (GlaxoSmithKline) are known as the “conventional vaccines” and were first introduced in the 1980s. The production of these 2 vaccines uses genetically engineered yeast cells of the species Saccharomyces cerevisiae to clone the hepatitis B viral gene that codes for hepatitis B surface antigen (HBsAg), which is then extracted and purified.

Heplisav-B (Dynavax Technologies Corporation) is a newer vaccine introduced in 2017, produced in recombinant strains of the yeast form of Hansenula polymorpha. In contrast to the conventional hepatitis B vaccines that contain aluminum as an adjuvant to the recombinant HBsAg product, Heplisav-B utilizes...
a synthetic immunostimulatory adjuvant found to be more immunogenic, with higher vaccine response rates in patients who are known to be poor responders to the conventional vaccines.4

All 3 HBV vaccine formulations contain a recombinant HBsAg, and false-positive or transiently positive HBsAg test results may be observed following vaccine administration. Because the diagnosis of HBV infection is primarily based on the detection of this antigen, this feature may lead to unnecessary confirmatory laboratory testing, patient anxiety, treatment, and added cost. Earlier studies in various populations, ranging from infants and adults to healthy blood donors and patients undergoing hemodialysis, have revealed a transient hepatitis B surface antigenemia after patients have received immunization with the older 2 vaccines, which resolved at 3 weeks’ follow-up.7-23 We hypothesize that a similar phenomenon may be observed with Heplisav-B administration.

We therefore aimed to delineate the rate and duration of transient hepatitis B surface antigenemia following Heplisav-B vaccination.

PATIENTS AND METHODS
We retrospectively reviewed the medical records of all adult patients who received Heplisav-B vaccination at our institution from January 1, 2019, when widespread administration of the vaccine was initiated, through March 31, 2020, and who had HBsAg testing within 30 days following any of the immunization series, given as 2 doses at least 1 month apart.

Laboratory HBsAg testing at our institution is done using the Bio-Rad GS HBsAg Enzyme Immunoassay 3.0 to screen for reactivity, followed by confirmation by neutralization with hepatitis B surface antibody using the Bio-Rad GS HBsAg Confirmatory Assay 3.0. The hepatitis B DNA quantification testing is done using the cobas HBV-Quantitative nucleic acid test for use on the cobas 6800/8800 Systems (Roche Molecular Systems, Inc).

We excluded patients with laboratory evidence of prior hepatitis B virus infection or immunization, defined as having serologic testing positive for HBsAg and hepatitis B total core antibody (anti-HBc) or positive results on hepatitis B DNA quantification.

Timing of the 2-dose Heplisav-B vaccine administration, HBsAg testing, and duration of antigenemia were documented, along with anti-HBc, repeated HBsAg testing, and hepatitis B DNA quantification if obtained. The patients were tested randomly at the discretion of the treating physician, and no specific protocol was followed. Demographic, clinical, and laboratory data from each patient were extracted from the medical record. The study was approved by the Mayo Clinic Institutional Review Board.

For statistical analyses, categorical variables were reported as count and percentage using the χ² test for comparison. Continuous variables were reported as median and interquartile range (IQR) from the 25th to the 75th percentiles using the Wilcoxon rank sum test to compare data. Statistical tests were 2-tailed with P<.05 considered significant. All analyses were performed using JMP software (SAS Institute).

RESULTS
A total of 1933 adult patients received the Heplisav-B vaccination series during the study period. Of these, a total of 39 patients (2%) were tested for HBsAg within 30 days after completing the immunization series. Among these 39 patients, 6 (15.4%) had a positive HBsAg result, and the remaining 33 patients (84.6%) had negative results (Figure). Confirmatory HBsAg testing was obtained in all 6 patients and yielded positive results. Indications for vaccination and routine HBsAg surveillance testing in the HBsAg-positive patients included hemodialysis for kidney failure (n=3), pretransplant evaluation (n=2), and routine health maintenance (n=1), whereas for the HBsAg-negative patients, indications encompassed hemodialysis for kidney failure (n=12) and routine health maintenance (n=21).

Patients’ medical and laboratory data are summarized in Table 1. There were no statistically significant differences in demographic characteristics between the HBsAg-positive and HBsAg-negative groups. Median patient age for HBsAg-positive and HBsAg-negative patients was 72 years (IQR, 49.7 to 83 years) and 58 years (IQR, 48.5 to 69 years), respectively (P=.26), and most were female (4 of 6 [54.5%] vs 18 of 33 [66.7%]; P=.58).
Compared with the HBsAg-negative group, HBsAg-positive patients had a significantly lower body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) (24.8 kg/m² [IQR, 23 to 26.4 kg/m²] vs 28.6 kg/m² [IQR, 26.4 to 30.6 kg/m²]; P = .01) and higher prevalence of chronic kidney disease (CKD; 2 of 6 [33.3%] vs 2 of 33 [6%]; P = .04). There was no significant difference in the prevalence of other medical comorbidities among patients with positive and negative HBsAg results, including end-stage renal disease (3 of 6 [50%] vs 12 of 33 [36.3%]; P = .52), diabetes mellitus (2 of 6 [33.3%] vs 9 of 33 [27.2%]; P = .76), and immunosuppression (2 of 6 [33.3%] vs 3 of 33 [9.1%]; P = .10). Although patients in the HBsAg-positive group appeared to have a lower estimated creatinine clearance rate (26 mL/min [IQR, 12.5 to 60.8 mL/min] vs 62.3 mL/min [IQR, 12 to 120.1 mL/min]) compared with those in the HBsAg-negative group, this difference was not statistically significant (P = .53).

Of note, the timing of HBsAg testing after completing the vaccination series in the HBsAg-positive patients was significantly earlier compared with that of HBsAg-negative patients (2 days [IQR, 0.43 to 2.25 days] vs 12 days [IQR, 10 to 15 days]; P = .0008), although tested at different points in time per the discretion of the physician. A hepatitis B DNA quantitative test and anti-HBc test were obtained to exclude active infection, and results were negative in all 6 patients. In the HBsAg-positive group, the median time from the date of Heplisav-B administration to a negative HBsAg test result was 17 days (IQR, 8 to 36 days).

**DISCUSSION**

By virtue of having an HBsAg introduced by the vaccine into the bloodstream, antigenemia following vaccination is a scientifically plausible consequence, and it is critical that clinicians are aware of this phenomenon because HBsAg is the first serologic marker of HBV infection and can be misinterpreted as such in the context of recent vaccination. Although

### TABLE 1. Study Patients With Transient Hepatitis B Antigenemia

| Patient No. | Date of Heplisav-B administration and hepatitis B DNA quantification | Time (d) from Heplisav-B administration to reactive HBsAg test result | Antigen confirmation | Hepatitis B DNA quantification | Estimated CrCl (mL/min) | Time (d) from Heplisav-B administration to negative HBsAg test result |
|-------------|-------------------------------------------------------------------|------------------------------------------------------------------|---------------------|-------------------------------|------------------------|-------------------------------------------------------------|
| 1           | 11/5/2019                                                         | 2                                                                 | Positive            | Undetected                    | 12.7                   | 16                                                         |
| 2           | 11/4/2019                                                         | 2                                                                 | Positive            | Undetected                    | 40.8                   | 18                                                         |
| 3           | 11/5/2019                                                         | 0                                                                 | Positive            | Undetected                    | 121                    | 8                                                          |
| 4           | 2/7/2020                                                          | 3                                                                 | Positive            | Undetected                    | 13                     | 15                                                         |
| 5           | 10/1/2019                                                         | 2                                                                 | Positive            | Undetected                    | 12                     | 36                                                         |
| 6           | 2/4/2020                                                          | 0                                                                 | Positive            | Undetected                    | 39.1                   | 37                                                         |

CrCl, creatinine clearance; HBsAg, hepatitis B surface antigen.
| Reference, year | Type of study | No. of HBsAg-positive patients | Mean age (y) | Sex, M:F | Study population | Vaccine administered | Mean time (d) to positivity after vaccine dose | Mean time (d) to negative HBsAg seroconversion after vaccine dose |
|-----------------|---------------|-------------------------------|--------------|----------|------------------|---------------------|-----------------------------------------------|-------------------------------------------------------------|
| Kloster et al, 1995 | Retrospective | 9                            | 19-59        | NA       | HBD              | Engerix b            | 1.4                                           | 21-259                                                      |
| Janzen et al, 1996 | Retrospective | 6                            | 63.6         | 1:5      | HD patients      | Engerix b            | 3.5                                           | 18                                                         |
| Brodersen et al, 1997 | Retrospective | 1                            | 55           | 0:1      | HD patient       | Engerix b            | 2                                             | 14                                                         |
| Olde & Garcia, 1998 | Retrospective | 4                            | NA           | NA       | HD patients      | Engerix b            | 2.12                                          | 49                                                         |
| Ly et al, 2002 | Prospective | 3                            | 56.4         | 4:4      | HD patients      | Engerix b            | 2.12                                          | 49                                                         |
|                |               | 3 Recombivax HB c             |              |          |                  |                     |                                               |                                                             |
| Otag, 2003 | Prospective | 1                            | NA           | NA       | HBD              | Engerix b            | 1                                             | 3                                                         |
|                |               | 1 Recombivax HB d             |              |          |                  |                     |                                               |                                                             |
|                |               | 1 GenHevac B e                |              |          |                  |                     |                                               |                                                             |
| Davis et al, 2003 | Retrospective | 1                            | 21           | 0:1      | HBD              | Twinrix f           | 2                                             | 78                                                        |
| De Schryver et al, 2004 | Retrospective | 4                            | 33-37        | 2:2      | Healthy volunteers | Twinrix f           | 1                                             | 18.6                                                      |
| Dow et al, 2002 | Prospective | 7                            | NA           | 2.5      | HBD              | Recombivax HB d      | 3                                             | 5.2                                                       |
| Onuigbo et al, 2010 | Retrospective | 1                            | 81           | 0:1      | HD patient       | Engerix b            | 2                                             | 7                                                         |
| Ziaee et al, 2010 | Prospective | 7                            | 21.14        | 3:4      | Healthy medical students | Engerix b            | 1.8                                           | 3.14                                                      |
|                |               | 1                              | 21           | 1:0     |                  | Recombivax HB d      | 5                                             | NA                                                        |
| Mohan et al, 2011 | Retrospective | 1                            | 83           | 0:1      | HD patient       | Engerix b            | 5                                             | 21                                                       |
| Rysgaard et al, 2012 | Retrospective | 11                           | 61.2         | 6:5      | 10 HD patients; 1 pretravel laboratory test | Engerix b            | 4                                             | 21                                                       |
| Lee et al, 2014 | Retrospective | 1                            | 51           | 0:1      | Preemployment screening | Twinrix f           | 8                                             | 13                                                       |
| Anjum, 2014 | Retrospective | 3                            | 31.3         | 3.0     | Annual health screening | Engerix b            | 0                                             | 7                                                        |
| Haddad & Bassett, 2017 | Retrospective | 1                            | 21           | 0.1      | Annual health screening | NA                 | 1                                             | 6                                                         |
| Saparamadu et al, 2019 | Retrospective | 1                            | NA           | 0:1      | HD patient       | Engerix b            | 2                                             | 21                                                       |

aF, female; HBD, healthy blood donors; HBsAg, hepatitis B surface antigen; HD, hemodialysis; M, male; NA, not available.

- **Recombinant, yeast-derived** 20 μg/mL.
- **Recombinant, mammalian-derived** 20 μg/mL.
- **Hepatitis B vaccine** (recombinant, yeast-derived) 40 μg/mL.
- **Hepatitis B vaccine** (recombinant, yeast-derived) 10 μg/mL.
transient HBsAg positivity following Heplisav-B vaccination has not been reported previously, our findings confirm that transient HBsAg positivity following Heplisav-B immunization may be observed in patients tested within 72 hours after completion of the vaccine series, with the highest risk in those with lower BMI and CKD.

Hepatitis B infection was ruled out in these patients, as evidenced by undetectable HBV DNA testing results and negative results on repeated HBsAg testing. This phenomenon was observed predominantly early in the post-immunization period, with a median time to positive HBsAg results of 2 days. In studies of HBsAg positivity rates following conventional hepatitis B vaccines, transient HBsAg positivity has been reported, with rates as high as 43.5% (Table 2). The median time to HBsAg positivity with Heplisav-B appears to be consistent with reported observations following conventional hepatitis B vaccines. In our cohort, patients in whom transient HBsAg positivity was not observed had been tested much later, with a median time from immunization to HBsAg testing of 12 days. This substantial difference in the timing of routine HBsAg testing postimmunization may explain why transient HBsAg positivity was not captured in those patients who were tested later, raising the possibility that transient HBsAg positivity may have occurred earlier in the postimmunization period before any testing was done. In patients in whom HBsAg positivity was observed, negative seroconversion was observed after a median of 17 days, although it is possible that seroconversion occurred before retesting was done. In a large number of patients, Rysgaard et al. found that positive HBsAg results are unlikely to persist beyond 14 days postvaccination, underscoring the importance of confirmatory testing. Conversely, Lunn et al. reported prolonged antigenemia that persisted as long as 28 days postvaccination.

It is known that patients with CKD and low BMI are more likely to have a false-positive or transiently positive HBsAg test result. Similar trends were observed in our cohort, with a statistically significant lower median BMI and higher proportion of patients with CKD observed in the HBsAg-positive group compared with the HBsAg-negative group. Earlier testing, lower BMI, and lower kidney function may explain why transient antigenemia was captured in the former group of patients. Currently, there are no recommendations for renal adjustment of the Heplisav-B vaccine, and clinical trials evaluating the immunogenicity and safety of Heplisav-B in adults with end-stage renal disease undergoing hemodialysis are ongoing.

As seen with conventional HBV vaccines, we presume that circulating HBsAg protein was introduced by the Heplisav-B vaccine and was detected by the chemiluminescent immunoassay. The recombinant HBsAg used in these immunogenic HBV vaccines is bound by the commercially available HBsAg detection assays, and the overall pooled sensitivity and specificity is 99.8% and 99.5%, respectively. This detectable vaccine antigen is a noninfectious subunit produced in yeast cells, and it does not pose a risk for vaccine-transmitted disease. Dow et al. inferred that antigen reactivity depends on the diagnostic assay used. The same conclusion was postulated by Ziaee et al., who found in a clinical trial among healthy adults that HBsAg positivity depended on the type of vaccine and the diagnostic testing technique. Otag offered a different opinion, concluding that vaccine-induced antigenemia could be a possibility with any kind of hepatitis B vaccine administered, as documented in our study. Halperin et al. reported the superiority of the seroprotection rates for the Heplisav-B vaccine, and this superiority is explained by the components of the vaccine that enhance the immune response.

Our study has some limitations, primarily the retrospective design and small sample size that make any conclusions about risk factors for transient antigenemia following Heplisav-B vaccination difficult. Furthermore, the patients were tested at the discretion of the treating physician without consistency, making it difficult to capture the clearance of the transient phenomena, the full serologic timeline, and the exact timing of seroconversion.

CONCLUSION
As reported for conventional hepatitis B vaccines, transient hepatitis B surface antigenemia following Heplisav-B vaccination may occur, particularly in patients with CKD and low
BMI if tested within the first 72 hours after receiving the Heplisav-B vaccine. We highlight the importance of exercising caution when interpreting HBsAg test results in the context of recent hepatitis B immunization and suggest that HBsAg not be tested within 7 days of receipt of hepatitis B vaccination.

**Abbreviations and Acronyms:**
- anti-HBc = hepatitis B total core antibody
- BMI = body mass index
- CKD = chronic kidney disease
- IQR = interquartile range
- HBsAg = hepatitis B surface antigen
- HBV = hepatitis B virus

**Potential Competing Interests:** Dr Razonable has received research grants (not related to this work) from Regeneron Pharmaceuticals and Roche Diagnostics. The other authors report no competing interests.

**Correspondence:** Address: Nathan W. Cummins, MD, Division of Infectious Diseases, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (Cummins.Nathan@mayo.edu).

**ORCID**
- Cristina Corsini Campioli: https://orcid.org/0000-0003-0976-7905;
- Zerelda Esquer Garrigos: https://orcid.org/0000-0003-4561-7883;
- Raymund R. Rasonable: https://orcid.org/0000-0001-5248-0227;
- Elena Beams: https://orcid.org/0000-0002-5807-2299;
- Nathan W. Cummins: https://orcid.org/0000-0002-0703-1550

**REFERENCES**

1. Wong GL-H, Wong VW-S. Eliminating hepatitis B virus as a global health threat. Lancet Infect Dis. 2016;16(6):1313-1314.
2. Nelson NP, Easterbrook PJ, McMahon B. Epidemiology of hepatitis B virus infection and impact of vaccination on disease [published correction appears in Clin Liver Dis. 2017;21(2):xiii]. Clin Liver Dis. 2016;20(4):607-628.
3. Fattovich G, Bortotelli F, Donato F. Natural history of chronic hepatitis B: special emphasis on disease progression and prognostic factors. J Hepatol. 2008;48(2):335-352.
4. Schillie S, Harris A, Link-Gelles R, Romero J, Ward J, Nelson N. Recommendations of the Advisory Committee on Immunization Practices for use of a hepatitis B vaccine with a novel adjuvant. MMWR Morb Mortal Wkly Rep. 2018;67(5):465-458.
5. Schillie S, Vellozzi C, Reingold A, et al. Prevention of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices. MMWR Recomm Rep. 2018;67(1):1-31.
6. HEPLISAV-B [package insert]. Emeryville, CA: Dynavax Technologies Corporation; 2017-2019. US Food and Drug Administration website. https://www.accessdata.fda.gov/ 505(e2).
7. Koster B, Kramer R, Eastlund T, Grossman B, Zarvan B. Hepatitis B surface antigenemia in a blood donor following vaccination. Transfusion. 1995;35(6):475-477.
8. Janzen L, Minuk GY, Fast M, Bernstein KN. Vaccine-induced hepatitis B surface antigen positivity in adult hemodialysis patients: incidental and surveillance data. J Am Soc Nephrol. 1996;7(8):1228-1234.
9. Brodersen HP, Beckers B, Kohler H, Dahlmanns C, Kruka L, Larbig D. The test for hepatitis B surface antigen is transiently positive after vaccination with recombinant vaccine. Nephrol Dial Transplant. 1997;12(12):2756-2757.
10. Olde C, Garcia M. Hepatitis B vaccine as a cause of false positive hepatitis B surface antigen. J CAN NV. 1997;8(4):20-21.
11. Ly D, Yee HF Jr, Brezina M, Martin P, Gilnick G, Saab S. Hepatitis B surface antigenemia in chronic hemodialysis patients: effect of hepatitis B immunization. Am J Gastroenterol. 2002;97(1):138-141.
12. Otak F. False positive HBsAg result in blood donors due to administration of three different recombinant DNA hepatitis B vaccines. Vaccine. 2003;21(25-26):373-377.
13. Davis AR, Brotchie HL, Mundisir BA, Ismay SL. Transient hepatitis B surface antigenemia in a blood donor after a combination hepatitis A and B vaccine. Transfusion. 2003;43(4):545.
14. De Schryver A, De Gendt K, Francois G, Van Damme P, Meheus A. Hepatitis B surface antigenemia following vaccination with a combined vaccine against hepatitis A and B. J Viral Hepat. 2004;11(1):88-90.
15. Dow BC, Yates P, Galea G, Munro H, Buchanan I, Ferguson K. Hepatitis B vaccinees may be mistaken for confirmed hepatitis B surface antigen-positive blood donors. Vox Sang. 2002;82(1):15-17.
16. Onuigbo MAC, Nisbet A, Weisenbeck J, Hurlburt J. Hepatitis B surface antigenemia following recombinant Engerix B hepatitis B vaccine in an 81-year-old ESRD patient on hemodialysis. Ren Fail. 2010;32(4):531-532.
17. Ziaee M, Saidatjoo A, Mohamadpour M, Namazi MH. Induced HBs antigenemia in healthy adults after immunization with two different hepatitis B recombinant vaccines. Hepat Mon. 2010;10(4):298-301.
18. Rygaard CD, Morris CS, Drees D, et al. Positive hepatitis B surface antigen tests due to recent vaccination: a persistent problem. Am J Clin Pathol. 2012;138:5462.
19. Anjum Q. False positive hepatitis B surface antigen due to recent vaccination. Int J Health Sci (Qassim). 2014;8(2):189-193.
20. Saparamadu AADN, Lee MY, Lui TT, Lam CW. Engerix-B vaccine induced transient hepatitis B surface antigenemia: a case report and review of the literature. J Intensive Crit Care. 2019;5:5.
21. Haddad JD, Bassett J. Transient hepatitis B surface antigen positivity following vaccination [abstract]. Am J Gastroenterol. 2017;112(suppl):S1281-S1282.
22. Lee Y, Kim J-S, Park J-Y, Kim SY, Hwang IH, Cho HC. Hepatitis B surface antigen positivity after Twinrix vaccination: a case report. J Travel Med. 2014;21(3):352-353.
23. Mohan D, Railey M, Al Pulkhami M. Vaccination and transient hepatitis B surface antigenemia. ND T Plus. 2011;4(3):190-191.
24. Lunn ER, Hoggart BJ, Cook WJ. Prolonged hepatitis B surface antigenemia after vaccination. Pediatr. 2000;105(6):E81.
25. Fan W, Chen X-F, Chen S, Guo Z-R, Dong C. Hepatitis B vaccine response in obesity: a meta-analysis. Vaccine. 2011;29(40):4835-4841.
26. Weber DJ, Rutala WA, Samsa GP, Bradshaw SE, Lemon SM. Impaired immunogenicity of hepatitis B vaccine in obese persons. N Engl J Med. 1986;314(21):1393.
27. Medicine NIHUSNL. Evaluating the immunogenicity and safety of HEPLISAV-B® in adults with end-stage renal disease (ESRD) undergoing hemodialysis: ClinicalTrials.gov NCT03934736. 2019.
28. Amin I, Varsaneux O, Kelly H, et al. Diagnostic accuracy of tests to detect hepatitis B surface antigen: a systematic review of the literature and meta-analysis. BMC Infect Dis. 2017;17(suppl 1):698.
29. Halperin SA, Ward B, Cooper C, et al. Comparison of safety and immunogenicity of two doses of investigational hepatitis B virus surface antigen co-administered with an immunomodulatory phosphorothioate oligodeoxynucleotide and three doses of a licensed hepatitis B vaccine in healthy adults 18-55 years of age. Vaccine. 2012;30(15):2556-2563.