HealthLeaders Virtual Roundtable

VACCINATION: KEY CONSIDERATIONS AND HEPATITIS B VACCINES

Vaccinations have become a hot-button issue during the coronavirus pandemic. There have been recent developments in vaccination for hepatitis B, with the Centers for Disease Control and Prevention (CDC) guidelines recommending hepatitis B vaccination for all adults between the ages of 19 to 59 years old. And, there is a two-dose hepatitis B vaccine as an alternative to the three-dose option that may improve adherence.

In addition to discussing changes in hepatitis B vaccination, participants at this HealthLeaders roundtable also addressed broad vaccination issues such as vaccine hesitancy and the climate surrounding vaccination in general.

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HIGHLIGHTS

HealthLeaders: *Why is it important to be vaccinated against hepatitis B?*

Staci Hermann: We know untreated disease states will lead to chronic complications. So, in the case of hep B, if untreated we know that it could lead to cirrhosis of the liver if not liver failure leading to a liver transplant. So, when you think about the management of a patient who may need to go on a liver transplant list, get a liver transplant, and then all of the management post-transplant, it's pretty significant. Vaccines are a way to prevent that from even happening.

Kelvin McKoy: Hep B is definitely a highly infectious virus that can cause serious disease and even death. And unlike hepatitis C, I do want to point out that there's no cure for hepatitis B but it is vaccine preventable. In addition to that, the incidence of hepatitis B is actually on the rise in certain segments of the U.S. population; and just like with COVID-19, the majority of people with hepatitis B are actually asymptomatic and unaware of their infection and can transfer the hepatitis B virus to other people.

Conley McCoy: The Hepatitis B Foundation estimates there are about 2.4 million Americans affected. And 70% of the adults in the United States remain unprotected against hepatitis B because of their age, because the vaccine recommendation didn't come out until the early '90s, so they weren't vaccinated.

McKoy: About 5,000 people die from hepatitis B annually. And I like to contrast that with the number of people who die from another vaccine-preventable disease, which is the human papillomavirus. So, about 4,000 people die annually from HPV, and I'd be willing to bet that most of the people on the panel today are probably acutely aware of the amount of energy, time, and resources that we put into educating people around the human papillomavirus. Yet we haven't done the same thing with respect to the hepatitis B virus, even though hep B does kill more people annually.

Laura Mark: That's interesting that you brought up HPV because I believe we've done so much education with teenagers when you go to your pediatrician. When you are going through a checklist, you and your child are told that you are due for vaccines. Taking a similar approach in adults would be beneficial. As patients become more connected and interactive with their electronic health, a vaccine checklist for adults will be helpful in facilitating those conversations during their yearly checkup with their primary care physician.

HealthLeaders: *The CDC's Advisory Committee on Immunization Practices (ACIP) recently updated the recommendations for who should receive a hepatitis B vaccine. Instead of recommending hepatitis B vaccination only for people with risk factors such as diabetes, the ACIP now recommends vaccination for all adults aged 19 to 59 and adults 60 and older with risk factors. What are the disadvantages of risk-based vaccination recommendations?*

McKoy: One thing that's specific to hep B is that it's extremely difficult for healthcare providers to remember the sheer number of risk factors for hepatitis specifically. There are at least 15 different risk factors for hepatitis B in the adult population.

HealthLeaders: *What are the advantages of age-based vaccination recommendations?*

Hermann: It's a simple process. Age-based recommendations are the easiest thing to remember and implement. The simpler we can make it for our providers, the easier it is, and a pharmacist can give a vaccine in one of the local community pharmacies. Those pharmacies often don't have access to the medical record or a complete picture of the patient, so we can increase the accessibility to vaccines for the general population the simpler we make those recommendations.

HealthLeaders: *Dynavax has developed a hepatitis B vaccine that requires a series of two doses over one month. All other hepatitis B vaccines require a series of three doses over six months. What advantages might a shorter hepatitis B dosing regimen provide to employees, healthcare providers, and patients in general?*

McCoy: Kaiser did a study and it said 44% of patients completed a two-dose regimen versus 26% completing a three-dose regimen within the time frame.

McKoy: One of the big advantages of a shorter hep B dosing regimen in general is that it does help to improve vaccination series completion for everyone. In addition to that Kaiser study, there are other studies that

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—Staci Hermann, PharmD, MS, Chief Pharmacy Officer, Dartmouth-Hitchcock Health

traditional hepatitis B vaccination series completion rates are what I call suboptimal.

Hermann: When you think about it from an accessibility perspective, the fewer doses needed the better. So, if it's an at-risk population that may not have transportation to their provider office, we're just making it easier for those patients to get in and complete their vaccination series.

HealthLeaders: *A recent survey conducted by HealthLeaders found that only 78% of respondents were more likely to recommend the two-dose vaccine for hepatitis B over the three-dose series. What could be the reasons people may be hesitant about the two-dose vaccine?*

McCoy: From my perspective, if they're hesitant over two doses versus three doses, it comes down to cost. The two-dose vaccine is more expensive than the three-dose vaccine, so cost is probably one of the prohibitive factors in their minds. But you have to weigh that with compliance. In addition, with the three-dose vaccine, you can give it to a child. With the two-dose vaccine, you must start with someone older. The last reason may be that people have familiarity and confidence with the three-dose products.

Hermann: When you look at factors that contribute to hesitancy, cost is one of the big ones. Unless we can get the cost down or subsidize the cost somehow, it does become a significant barrier. Personally, if it was 30% more, I would also opt for the three-dose series because if you are in a high-deductible plan the cost difference is significant.

McKoy: One of the reasons for the survey response that I came up with was that due to traditions, some of the survey respondents might feel like one month is not enough time to generate a protective immune response from hepatitis B, but I think about the clinical data.

The clinical data does clearly show that that's not the case for [Dynavax's two-dose vaccine] Heplisav-B®. There have been at least three head-to-head studies between the two-dose vaccine versus one of the conventional three-dose vaccines that have been analyzed by the Food and Drug Administration. The studies did show that two doses in one month is in fact all the time that's needed to achieve protective levels with Heplisav-B.

HealthLeaders: *The CDC and World Health Organization have set a goal to eliminate hepatitis B by 2030. Can an age-based recommendation for adult vaccination and a shorter series of doses help attain this goal?*

Celia Proctor: Accessibility and cost need to be considered. The COVID vaccine was made available at no cost to patients and there was significant effort to make them broadly available, specifically to those patients that may not routinely utilize or have good access to healthcare facilities.

McCoy: The CDC estimates that only about 30% of all adults are vaccinated against Hep B, and until a month ago there were 15 risk categories recommended, so moving to an age-related recommendation can increase the vaccination rates.

Mark: To eradicate hepatitis B within the next decade, we need to think about accessibility in some countries. Many countries do not have adequate accessibility.

HealthLeaders: *What is the current climate surrounding vaccination in general, including the COVID-19 vaccine and flu vaccines?*

Hermann: Here in New Hampshire, our governor has turned a lot of the management for COVID to our cities and towns, and because of that, what we're seeing is the uptick in vaccination rates is regionalized to the local level. So, some areas of the state are highly vaccinated and others not so much.

McCoy: It's a little different here in New Mexico. The state ran the COVID vaccination programs at least initially, so we have some interesting trends. About 76% of New Mexicans have received one dose. About 63% are fully vaccinated. If we look at the social demographic characteristics, areas with higher vaccination rates are areas with more jobs and higher educational attainment. For example, we have Los Alamos labs and 40% of the population in the labs have a master's degree or PhD, and they're 93% vaccinated. Albuquerque and Santa Fe are two of the larger cities, and they're over 80% vaccinated.

McKoy: The pandemic has served to heighten the public's interest in exercising greater control over their healthcare decisions, and this includes vaccine recommendations. There's also been an increased scrutiny from the public to the risk-benefit profile of vaccines in general.

Mark: Overall, the climate surrounding vaccination is positive and we're seeing an increasing rate of vaccinations for COVID-19. We have about 60% fully vaccinated and 83% having at least one dose. There's still a lot of work to be done.

HealthLeaders: *How can clinicians successfully address vaccine hesitancy among patients?*

Proctor: One of the most important strategies is first and foremost listening to the patient. People are hesitant for different reasons, and fundamentally as a healthcare provider, making sure that we are listening to our patients will give us a better understanding of their reason for being hesitant. Is it a fear of needles, overall vaccine hesitancy, or is it a misunderstanding or misinformation that the patient may have received?

McKoy: Another idea is talking to the patient about how you've either taken the vaccine yourself or would recommend the vaccine to a family member or a loved one.

McCoy: We've forgotten to remind people that vaccines are one of the most important public health interventions in reducing disease spread and complication of death that there's been, and people have forgotten about polio, tetanus, measles, mumps, chickenpox, and how successful we've been at eradicating and reducing those diseases.

Hermann: The technology of vaccines is also the way of the future when we look at prevention of non-infectious disease. One of the vaccines available now prevents cancer. I'm hearing more and more about vaccines to prevent AIDS and vaccines to prevent other types of cancers.

From a technology standpoint, we need to do more education with the public because the use of vaccine technology isn't always about infectious disease prevention. It could be about preventing other health conditions that someone may care more about than they may about measles, mumps, the flu, and pneumonia. So, we could also work that angle as well to build the confidence in vaccines as a technology.

Mark: Some of the hesitancy that we've heard about the COVID-19 vaccines is how fast they came to market. So, it's important to talk about the technology and the science behind it. If we can educate the public with their community leaders, that is helpful in explaining why and how the vaccines came to market quickly.

HealthLeaders: *I'm wondering about vaccine hesitancy among populations such as African Americans who have reasons to mistrust the medical system. How do you cut through that?*

McCoy: What we missed was we were so concerned with preparing for the rollout, such as making sure we had the capacity to get the vaccines to the clinics, that we didn't involve a lot of the local community leaders at first. So, in November and December 2020 and January 2021, when we were just overwhelmed with getting the vaccine out, we missed bringing in the church pastors. I had a pastor say when I finally went and I started to give talks at their churches, "Why didn't you come to me two months ago, because people have been asking me what to do."

Proctor: One of our biggest successes was in partnerships with community leaders, including different parishes and community outreach groups.

Hermann: Even internally in our health system as we mandated the COVID-19 vaccination, there was a portion of the employees who did not want to get it. So, many leaders within our organization started having one-on-one conversations with employees, and it's through those one-on-one conversations that they were able to alleviate the fears and the concerns and help those employees understand the benefits of the vaccine.

HealthLeaders: *What are the primary elements of a one-on-one conversation about vaccination? Let's take the COVID-19 example.*

Hermann: It really drives down to the why, right? Why is that person hesitant to get the vaccine? Celia started to talk through a number of those reasons, such as a phobia of needles. You need to drive down to what it is that is making that person hesitant to get the vaccine and then help them understand risk/benefits, solutions to their concerns, etc.

HealthLeaders: *Some local and state officials have been blocking COVID-19 vaccination or not being particularly cooperative. How can health systems work with local and state officials to promote vaccines?*

Mark: It's working and partnering with them. What we've done is partner with our local department of health and our local leaders within the communities and our legislature. We've really engaged with our corporate community affairs group to help work with those leaders and bridge those gaps.

HealthLeaders: *How have health systems worked well with local and state officials?*

Mark: We had regular meetings with the department of health and worked with state and local officials to understand what our capacity was to administer COVID vaccines with a combination of

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mass and hospital-based vaccine clinics plus community and mobile outreach. Having those conversations helped us in the beginning so that we could rely on a consistent shipment of vaccines for our first and second doses.

Another piece the state provided is a list of senior high-rises, long-term care facilities, and some of the mobile harder-to-reach locations that we could assist and provide vaccines. As an organization or pharmacy, you could sign up for the location then arrange a date and time to visit and provide vaccines to their residents.

Hermann: During the initial phases of the COVID vaccine rollout, the New Hampshire Hospital Association was a great bridge between the state Department of Health and Human Services and all of the hospitals in the state. We would have weekly meetings talking about vaccine distribution, and it was through those meetings that the providers were able to give DHHS information back about the different patient populations the providers were concerned about, such as the homebound and the homeless.

HealthLeaders: *How do you connect with those hard-to-reach patients, such as underserved and homeless populations?*

Hermann: It's mainly the popup clinics and the vans that are driving around into various areas. The state has data for which parts of the state have more homebound versus non-homebound people.

McCoy: I didn't know about New Mexico; I moved here three years ago, so I had no idea how poor it is. It's in the top 10 for Medicaid recipients in the nation, so it's a poor state. We had to find who the community leaders were and get them to help campaign because when people are homeless or in a woman's shelter, they often don't trust you. So, you establish trust early and often.

"When you would schedule your first dose, you would know automatically when your second dose was scheduled. Especially for the mass vaccine clinics, you would receive your first dose and be reminded of your date for your second dose to return at the same time and location."

—Laura Mark, PharmD, MS, Vice President of Pharmacy, Allegheny Health Network

Mark: When the redistribution approval process became a little less onerous, we were able to help other providers with access. With our network having the sub-temperature freezers, we were able to act as a hub-and-spoke system, to break down the larger supplied trays and provide to more rural hospitals, pharmacies, and physician practices.

HealthLeaders: *Given that the Moderna and Pfizer COVID-19 vaccines are multidose vaccines, what measures does your health system have in place to help ensure vaccination series completion?*

Proctor: When a patient would receive their first dose, they were scheduled for their second dose. This ensured that at minimum they had a date and knew when they needed to receive their next dose. We used tools such as MyChart to support scheduling and patient notifications. In addition, a call center and community volunteers were tremendously helpful in expanding the follow-up for patients.

Mark: We did something similar. When you would schedule your first dose, you would know automatically when your second dose was scheduled. Especially for the mass vaccine clinics, you would receive your first dose and be reminded of your date for your second dose to return at the same time and location. And if necessary, with having so many other clinics during the week, we had the ability to reschedule a second dose into different clinics.

HealthLeaders: *Some patients get vaccine information from social media and other questionable sources. How can clinicians address vaccine misinformation with their patients?*

McCoy: You have got to meet people where they are, because they're going to come in and they're going to come in ready with their questions, concerns, and issues. I hear them out. I try not to react [negatively] to the questions. You just have to hear them, then give your responses respectfully and as kindly as you can.

HealthLeaders: *What opportunity is COVID-19 providing to stress the importance of adult vaccination in general?*

Proctor: COVID-19 has been an opportunity to campaign around vaccinations and the benefits that they have to prevent disease. In addition, it has provided insight into how we distribute and make vaccines available equitably to all populations.

McCoy: With COVID-19, we are thinking about marginalized communities a lot more. For example, about 11% of our state is Native American, and they were hit hard by COVID. So, we had to think quickly about getting the vaccine out to marginalized, poor communities. I hope some of the lessons learned will serve us well when we roll out other things.

*NOTE: * The CDC also recommends that all adults 60 years of age and older with risk factors for hepatitis B should be vaccinated and adults 60 years of age and older without risk factors for hepatitis B may be vaccinated.*

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

HEPLISAV-B [Hepatitis B Vaccine (Recombinant), Adjuvanted] Solution for Intramuscular Injection

1 INDICATIONS AND USAGE

HEPLISAV-B is indicated for prevention of infection caused by all known subtypes of hepatitis B virus. HEPLISAV-B is approved for use in adults 18 years of age and older.

2 DOSAGE AND ADMINISTRATION

For intramuscular administration.

2.1 Dose and Regimen

Administer two doses (0.5 mL each) of HEPLISAV-B one month apart.

2.2 Administration

HEPLISAV-B is a clear to slightly opalescent, colorless to slightly yellow solution.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If either of these conditions exists, the vaccine should not be administered.

Administer HEPLISAV-B by intramuscular injection in the deltoid region using a sterile needle and syringe.

3 DOSAGE FORMS AND STRENGTHS

HEPLISAV-B is a sterile solution for injection available in 0.5 mL single-dose prefilled syringes. [see *How Supplied/Storage and Handling* (16.1)].

4 CONTRAINDICATIONS

Do not administer HEPLISAV-B to individuals with a history of severe allergic reaction (e.g. anaphylaxis) after a previous dose of any hepatitis B vaccine or to any component of HEPLISAV-B, including yeast [see *Description* (11)].

5 WARNINGS AND PRECAUTIONS

5.1 Managing Allergic Reactions

Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of HEPLISAV-B.

5.2 Immunocompromised Individuals

Immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to HEPLISAV-B.

5.3 Limitations of Vaccine Effectiveness

Hepatitis B has a long incubation period. HEPLISAV-B may not prevent hepatitis B infection in individuals who have an unrecognized hepatitis B infection at the time of vaccine administration.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice.

A total of 9597 individuals 18 through 70 years of age received at least 1 dose of HEPLISAV-B in 5 clinical trials conducted in the United States, Canada, and Germany. Data from 3 of these trials are provided below.

Study 1 in Subjects 18 through 55 Years of Age

Study 1 was a randomized, observer-blind, active-controlled, multicenter study in Canada and Germany in which 1810 subjects received at least 1 dose of HEPLISAV-B and 605 subjects received at least 1 dose of Engerix-B® [Hepatitis B Vaccine (Recombinant)]. Enrolled subjects had no history of hepatitis B vaccination or infection. HEPLISAV-B was given as a 2-dose regimen at 0 and 1 month followed by saline placebo at 6 months. Engerix-B was given at 0, 1, and 6 months. In the total study population, the mean age was 40 years; 46% of the subjects were men; 93% were white, 2% black, 3% Asian and 3% Hispanic; 26% were obese, 10% had hypertension, 8% had dyslipidemia, and 2% had diabetes mellitus. These demographic and baseline characteristics were similar in both vaccine groups.

Solicited Local and Systemic Adverse Reactions

Subjects were monitored for local and systemic adverse reactions using diary cards for a 7-day period starting on the day of vaccination. The percentages of subjects who reported local and systemic reactions are shown in Table 1.

Table 1
Study 1: Percent of Subjects Who Reported Local or Systemic Reactions Within 7 Days of Vaccination

	HEPLISAV-B %		Engerix-B %		
	Post-Dose*		Post-Dose*		
Reaction	**1**	**2**	**1**	**2**	**3**
Local	N=1810	N=1798	N=605	N=603	N=598
Injection Site Pain	38.5	34.8	33.6	24.7	20.2
Injection Site Redness†	4.1	2.9	0.5	1.0	0.7
Injection Site Swelling†	2.3	1.5	0.7	0.5	0.5
Systemic					
Fatigue	17.4	13.8	16.7	11.9	10.0
Headache	16.9	12.8	19.2	12.3	9.5
Malaise	9.2	7.6	8.9	6.5	6.4
	N=1784	N=1764	N=596	N=590	N=561
Fever‡	1.1	1.5	1.8	1.7	1.8

Note: only subjects having data are included. Clinical trial number: NCT00435812
*HEPLISAV-B was given as a 2-dose regimen at 0 and 1 month followed by saline placebo at 6 months. Engerix-B was given at 0, 1, and 6 months
† Redness and swelling ≥ 2.5 cm.
‡ Oral temperature ≥ 100.4°F (38.0°C).

Unsolicited Adverse Events:

Unsolicited adverse events within 28 days following any injection, including placebo, were reported by 42.0% of HEPLISAV-B recipients and 41.3% of Engerix-B recipients.

Serious Adverse Events (SAEs)

Subjects were monitored for serious adverse events for 7 months after the first dose of vaccine. The percentage of subjects reporting serious adverse events was 1.5% in the HEPLISAV-B group and 2.1% in the Engerix-B group. No acute myocardial infarctions were reported. No deaths were reported.

Potentially Immune-mediated Adverse Events

Potentially immune-mediated adverse events that occurred within 7 months of the first dose of vaccine were reported in 0.2% (n = 4) of HEPLISAV-B recipients and 0.7% (n = 4) of Engerix-B recipients. The following events were reported in the HEPLISAV-B group in one subject each: granulomatosis with polyangiitis, lichen planus, Guillain-Barré syndrome, and Grave's disease. The following events were reported in the Engerix-B group in one subject each: Bell's palsy, Raynaud's phenomenon, and Grave's disease. One additional Engerix-B recipient with a history of mixed connective tissue disease had p-ANCA-positive vasculitis.

Study 2 in Subjects 40 through 70 Years of Age

Study 2 was a randomized, observer-blind, active-controlled, multicenter study in Canada and the United States in which 1968 subjects received at least 1 dose of HEPLISAV-B and 481 subjects received at least 1 dose of Engerix-B. HEPLISAV-B was given as a 2-dose regimen at 0 and 1 month followed by saline placebo at 6 months. Enrolled subjects had no history of hepatitis B vaccination or infection. Engerix-B was given at 0, 1, and 6 months. In the total population, the mean age was 54 years; 48% of subjects were men; 82% were white, 15% black, 1% Asian and 6% Hispanic; 44% were obese, 30% had hypertension, 30% had dyslipidemia, and 8% had diabetes mellitus. These demographic and baseline characteristics were similar in both vaccine groups.

Solicited Local and Systemic Adverse Reactions

Subjects were monitored for local and systemic adverse reactions using diary cards for a 7-day period starting on the day of vaccination. The percentages of subjects who experienced local and systemic reactions are shown in Table 2.

Table 2
Study 2: Percent of Subjects Who Reported Local or Systemic Reactions Within 7 Days of Vaccination

	HEPLISAV-B %		Engerix-B %		
	Post-Dose*		Post-Dose*		
Reaction	**1**	**2**	**1**	**2**	**3**
Local	N=1952	N=1905	N=477	N=464	N=448
Injection Site Pain	23.7	22.8	18.4	15.9	13.8
Injection Site Redness†	0.9	0.7	0.6	0.2	0.2
Injection Site Swelling†	0.9	0.6	0.6	0.6	0.2
Systemic					
Fatigue	12.6	10.8	12.8	12.1	9.4
Headache	11.8	8.1	11.9	9.5	8.5
Malaise	7.7	7.0	8.6	7.1	5.1
Myalgia	8.5	6.4	9.6	8.0	4.5
	N=1923	N=1887	N=472	N=459	N=438
Fever‡	0.6	0.6	0.6	0.9	0.7

Note: only subjects having data are included. Clinical Trial Number: NCT01005407
*HEPLISAV-B was given as a 2-dose regimen at 0 and 1 month followed by saline placebo at 6 months. Engerix-B was given at 0, 1, and 6 months
† Redness and swelling ≥2.5 cm.
‡ Oral temperature ≥ 100.4°F (38.0°C).

Unsolicited Adverse Events
Unsolicited adverse events within 28 days following any injection, including placebo, were reported by 35.4% of HEPLISAV-B recipients and 36.2% of Engerix-B recipients.

Serious Adverse Events
Subjects were monitored for serious adverse events for 12 months after the first dose of vaccine. The percentage of subjects reporting serious adverse events was 3.9% in the HEPLISAV-B group and 4.8% in the Engerix-B group. Acute myocardial infarction occurred in 0.1% (n=2) of HEPLISAV-B recipients and 0.2% (n=1) of Engerix-B recipients.

Autoimmune Adverse Events
Subjects were monitored for the occurrence of new-onset potentially immune-mediated adverse events for 12 months after the first dose of vaccine. Events were adjudicated as to whether they were autoimmune by an external group of experts blinded to treatment assignment. As determined by the adjudicators, new-onset autoimmune adverse events were reported in 0.2% (n=3) of HEPLISAV-B recipients: two subjects with hypothyroidism and one subject with vitiligo. None of these events was considered related to vaccination by the expert group. No new-onset autoimmune adverse events were reported in the Engerix-B group. Although not referred to the external group of experts, one HEPLISAV-B recipient was determined to have Tolosa-Hunt syndrome which is presumed to have an immune-mediated etiology. This event was not considered related to vaccination.

Deaths
One subject (0.05%) died of a pulmonary embolism in the HEPLISAV-B group and 1 subject (0.2%) died of heart failure in the Engerix-B group. Neither death was considered related to vaccination.

Study 3 in Subjects 18 through 70 Years of Age

Study 3 was a randomized, observer-blind, active-controlled, multicenter study in the United States in which 5587 subjects received at least 1 dose of HEPLISAV-B and 2781 subjects received at least 1 dose of Engerix-B. Enrolled subjects had no history of hepatitis B vaccination or infection. HEPLISAV-B was given as a 2-dose regimen at 0 and 1 month followed by saline placebo at 6 months. Engerix-B was given at 0, 1, and 6 months. In the total study population, the mean age was 50 years; 51% were men; 71% were white, 26% black, 1% Asian, and 9% Hispanic; 48% were obese, 36% had hypertension, 32% had dyslipidemia, and 14% had type 2 diabetes mellitus. These demographic and baseline characteristics were similar in both vaccine groups.

Unsolicited Medically-Attended Adverse Events
Subjects were monitored for unsolicited medically-attended adverse events, those for which a subject sought medical care, for 13 months after the first dose of vaccine. Overall, medically-attended adverse events were reported in 46.0% of HEPLISAV-B recipients and 46.2% of Engerix-B recipients. Herpes zoster was reported in 0.7% of HEPLISAV-B recipients and 0.3% of Engerix-B recipients. Unsolicited medically-attended adverse events within 28 days following any injection, including placebo, were reported by 20.1% of both HEPLISAV-B and Engerix-B recipients.

Serious Adverse Events
Subjects were monitored for serious adverse events for 13 months after the first dose of vaccine. The percentage of subjects who reported serious adverse events was 6.2% in the HEPLISAV-B group and 5.3% in the Engerix-B group. Acute myocardial infarction (AMI) was reported in 0.25% (n=14) of HEPLISAV B recipients and 0.04% (n=1) of Engerix-B recipients. An analysis of serious adverse events likely representing myocardial infarction (MI) was conducted using the standard Medical Dictionary for Regulatory Activities (MedDRA) query (SMQ) for MI. This analysis identified a total of 19 HEPLISAV-B subjects (0.3%) and 3 Engerix-B subjects (0.1%) with events included in the SMQ for MI (these events include the 15 reports of AMI). Additional evidence, including information on temporal relationship and baseline risk factors, does not support a causal relationship between HEPLISAV-B administration and AMI. Among the 19 events identified as MI in HEPLISAV-B recipients, three occurred within 14 days, nine occurred within 53-180 days, and seven occurred more than 180 days following any dose of HEPLISAV-B. Among the three events identified as MI in Engerix-B recipients, one each occurred 13, 115, and 203 days following any dose. All 19 HEPLISAV-B recipients and 3 Engerix-B recipients reported one or more baseline risk factors for cardiovascular disease.

Autoimmune Adverse Events
Subjects were monitored for the occurrence of new-onset potentially immune-mediated adverse events for 13 months after the first dose of vaccine. Events were adjudicated as to whether they were autoimmune by an external group of experts who were blinded to treatment assignment. As determined by the adjudicators, new-onset autoimmune adverse events were reported in 0.1% (n=4) of HEPLISAV-B recipients [one each of: alopecia areata, polymyalgia rheumatica, ulcerative colitis, and autoimmune thyroiditis (with concurrent diagnosis of papillary thyroid carcinoma)]. None of these events was considered to be related to vaccination by the external experts. No new-onset autoimmune adverse events were reported in the Engerix-B group.

Deaths
During the study death was reported in 25 subjects (0.4%) in the HEPLISAV-B group and 7 subjects (0.3%) in the Engerix-B group. No death was considered related to vaccination.

7 DRUG INTERACTIONS

7.1 Use with Immune Globulin
There are no data to assess the concomitant use of HEPLISAV-B with immune globulin. When concomitant administration of HEPLISAV-B and immune globulin is required, they should be given with different syringes at different injection sites.

7.2 Interference with Laboratory Tests
Hepatitis B surface antigen (HBsAg) derived from hepatitis B vaccines has been transiently detected in blood samples following vaccination. Serum HBsAg detection may not have diagnostic value within 28 days after receipt of HEPLISAV-B.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Pregnancy Exposure Registry
There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to HEPLISAV-B during pregnancy. Women who receive HEPLISAV-B during pregnancy are encouraged to contact 1-844-443-7734.

Risk Summary
All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In clinically recognized pregnancies in the US general population, the estimated background risk of major birth defects is 2% to 4% and of miscarriage is 15% to 20%.

There are no clinical studies of HEPLISAV-B in pregnant women. Available human data on HEPLISAV-B administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.

In a developmental toxicity study, 0.3 mL of a vaccine formulation containing 2.5 mcg HBsAg and 3000 mcg cytosine phosphoguanine (CpG) 1018 adjuvant was administered to female rats prior to mating and during gestation. These animal studies revealed no evidence of harm to the fetus due to this vaccine formulation *[see Data]*.

Data
Animal data
Developmental toxicity studies were conducted in female rats. Animals were administered 0.3 mL of a vaccine formulation containing 2.5 mcg HBsAg and 3000 mcg CpG 1018 adjuvant twice prior to mating, and on gestation days 6 and 18 (a single human dose of HEPLISAV-B contains 20 mcg HBsAg and 3000 mcg CpG 1018 adjuvant). No adverse effects on pre-natal and post-natal development up to the time of weaning were observed. There were no vaccine-related fetal malformations or variations observed.

8.2 Lactation
Risk Summary
It is not known whether HEPLISAV-B is excreted in human milk. Data are not available to assess the effects of HEPLISAV-B on the breastfed infant or on milk production/excretion.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for HEPLISAV-B and any potential adverse effects on the breastfed child from HEPLISAV-B or from the underlying maternal condition. For preventive vaccines, the underlying condition is susceptibility to disease prevented by the vaccine.

8.4 Pediatric Use
Safety and effectiveness of HEPLISAV-B have not been established in individuals less than 18 years of age.

8.5 Geriatric Use
Clinical trials included 909 adults 65 through 70 years of age who received HEPLISAV-B.

Among subjects who received HEPLISAV-B, a seroprotective level of antibody to HBsAg was achieved in 90% of those 65 through 70 years of age compared to 96% of those aged 18 through 64 years of age.

Safety and effectiveness of HEPLISAV-B in adults older than 70 years of age were extrapolated from findings in subjects younger than 70 years of age.

8.6 Adults on Hemodialysis
Safety and effectiveness of HEPLISAV-B have not been established in adults on hemodialysis.

17. PATIENT COUNSELING INFORMATION

- Inform vaccine recipient of the potential benefits and risks associated with vaccination, as well as the importance of completing the immunization series.
- Emphasize that HEPLISAV-B contains non-infectious purified HBsAg and cannot cause hepatitis B infection.
- Advise vaccine recipient to report any adverse events to their healthcare provider or to the Vaccine Adverse Event Reporting System (VAERS) at 1-800-822-7967 and www.vaers.hhs.gov.
- Provide the Vaccine Information Statements, which are available free of charge at the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines).

DYNAVAX

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US-20-00-00172

ACIP VOTES **YES ON HEPATITIS B VACCINATION** RECOMMENDATION FOR ALL ADULTS AGES 19-59*

IN 2022

PROTECTING YOUR ADULT PATIENTS FROM HEPATITIS B IS AS EASY AS 1, 2, 3

WITH HEPLISAV-B®
Hepatitis B Vaccine (Recombinant), Adjuvanted

HEPLISAV-B IS **THE ONLY 2-DOSE, 1-MONTH** HEPATITIS B VACCINE FOR ADULTS[1,2]

INDICATION

HEPLISAV-B is indicated for prevention of infection caused by all known subtypes of hepatitis B virus in adults 18 years of age and older.

IMPORTANT SAFETY INFORMATION

Do not administer HEPLISAV-B to individuals with a history of severe allergic reaction (e.g., anaphylaxis) after a previous dose of any hepatitis B vaccine or to any component of HEPLISAV-B, including yeast.

Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of HEPLISAV-B.

Immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to HEPLISAV-B.

Hepatitis B has a long incubation period. HEPLISAV-B may not prevent hepatitis B infection in individuals who have an unrecognized hepatitis B infection at the time of vaccine administration.

The most common patient-reported adverse reactions reported within 7 days of vaccination were injection site pain (23%-39%), fatigue (11%-17%), and headache (8%-17%).

Please see Brief Summary of full Prescribing Information on the preceding pages.

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HEPLISAV-B®
Hepatitis B Vaccine (Recombinant), Adjuvanted

2 DOSES. 1 MONTH. DONE.[1]

*Adults 60+ who have risk factors for hepatitis B infection should receive hep B vaccination. Adults 60+ without known risk factors may receive hepatitis B vaccination Abbreviation: ACIP, Advisory Committee on Immunization Practices.

REFERENCES: 1. HEPLISAV-B [package insert]. Emeryville, CA: Dynavax Technologies Corporation; 2020. **2.** Freedman M, Kroger A, Hunter P, Ault KA. Recommended Adult Immunization Schedule, United States, 2020. *Ann Intern Med.* 2020;172(5):337-347.

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