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# Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

## ABSTRACT & COMMENTARY

# Neuroimaging Before Lumbar Puncture?

***By Dean L. Winslow, MD, FACP, FIDSA***

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**Dr. Winslow reports no financial relationships relevant to this field of study.**

SYNOPSIS: The investigators retrospectively evaluated ESCMIID, IDSA, and Swedish guidelines for neuroimaging in 815 adults with acute bacterial meningitis. Swedish guidelines omit altered mental status and immunosuppression as indications for imaging prior to lumbar puncture. Adherence to Swedish guidelines resulted in decreased mortality and more favorable outcomes.

SOURCE: Glimaker M, Sjolin J, Akesson S, Naucler P. Lumbar puncture performed promptly or after neuroimaging in acute bacterial meningitis in adults: A prospective national cohort study evaluating different guidelines. *Clin Infect Dis* 2018;66:321-328.

Researchers in Sweden prospectively followed a cohort of 815 adult acute bacterial meningitis (ABM) patients between 2008 and 2015. Primary and secondary endpoints were in-hospital mortality and favorable outcome at two to six months, respectively. Swedish guidelines recommend imaging prior to lumbar puncture (LP) in suspected ABM only in the presence of clear evidence of herniation, arm or leg drift, more than four days of neurological symptoms, or other symptoms atypical for ABM. European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines additionally recommend neuroimaging prior to LP in patients with a Glasgow Coma Scale (GCS) score < 10, arm or leg drift, or new-onset seizures. The Infectious Diseases Society of America (IDSA) guidelines recommend neuroimaging in suspected ABM patients with GCS < 15, arm or leg drift, abnormal ocular motility, visual field defect, dilated pupil, new-onset seizures, immunocompromise, suspected mass lesion, stroke, focal infection, or increased intracranial pressure with papilledema.

Of the 815 patients studied, 323 (46%) underwent LP without prior CT, and 378 (54%) had LP

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performed after CT. The patients overall were well matched by baseline characteristics. Mortality overall was 8%, and favorable outcome was observed in 50% of the cohort.

LP without previous CT was associated with a 4% mortality (14 of 323), while mortality was 10% (37 of 378) in patients who underwent CT prior to LP ($P < 0.001$). Lower mortality and increased favorable outcomes were seen in patients who underwent LP prior to imaging in all groups stratified by different indications for imaging. In patients who underwent CT before LP, 47% received antibiotics prior to CT imaging. However, antibiotics and corticosteroids were administered within two hours of admission in 41% of patients who underwent prompt LP and in only 30% of patients who received CT imaging prior to LP (odds ratio [OR], 2.12 for prompt administration of antibiotics and steroids after adjustment for baseline characteristics).

## ■ COMMENTARY

The Swedish, ESCMID, and IDSA guidelines differ widely in their recommendations regarding when to perform CT prior to LP. In this study, 7%, 32%, and fully 65% of patients, respectively, had one or more indications for CT imaging prior to LP. Following the Swedish guidelines resulted in a 50% lower mortality and increased favorable outcomes compared to ESCMID and IDSA guidelines. Much of this difference in outcome might be explained by shorter delay in administration of antibiotics and steroids in patients who underwent LP without prior CT.

By way of background, I began my medical training in the early 1970s just prior to the widespread availability of CT imaging, so we generally had no central nervous system (CNS) imaging available to rule out the presence of large mass lesions in patients with either suspected ABM or stroke.

The theoretical concern was that in the presence of a mass lesion, lumbar puncture could result in transtentorial herniation in certain circumstances when the cerebrospinal fluid (CSF) hydrodynamics were affected by LP. However, even 45+ years ago, more experienced clinicians often reassured us that herniation (even in the presence of mass lesions) was distinctly unusual with simple diagnostic LP when performed with a small #20-gauge needle and removal of only 4 cc of CSF for diagnostic studies. Apparently, most historical episodes of herniation precipitated by LP actually occurred when the procedure was performed with a larger gauge needle and when large amounts of CSF were removed during pneumoencephalography or myelography.

[Following the Swedish guidelines resulted in a 50% lower mortality and increased favorable outcomes compared to ESCMID and IDSA guidelines.]

Most of my mentors back then gave us the advice that we should almost always perform a diagnostic LP if the pretest probability of ABM was high (fever, nuchal rigidity) and the patient did not have a clear large motor deficit. However, altered level of consciousness, seizures, cranial nerve palsies, or even increased intracranial pressure were not contraindications to LP. Having performed literally hundreds of diagnostic LPs over the years, I had only one patient who possibly deteriorated as a result of LP. (This was a patient I cared for prior to the advent of CT, and who, at autopsy, had a massive intracerebral bleed and had evidence of transtentorial herniation.)

This study is reassuring that our old mentors' advice was sound. At least in patients in whom ABM has high pretest probability, the current IDSA guidelines (which recommend imaging prior to LP in all immunocompromised patients and patients with seizures, altered level of consciousness, or cranial nerve palsies) are overly conservative and not helpful. We should adopt the Swedish guidelines. ■

ABSTRACT & COMMENTARY

# SIRS Criteria vs. qSOFA for Predicting Short-term Mortality From Sepsis

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**Dr. Watkins reports that he has received research support from Allergan.**

SYNOPSIS: A meta-analysis that included 38 studies found the SIRS criteria had a higher sensitivity than qSOFA in predicting short-term mortality from sepsis. SIRS criteria remain useful as a screening tool for sepsis and as a prompt to initiate diagnostic work-up and treatment.

SOURCE: Fernando SM, Tran A, Taljaard M, et al. Prognostic accuracy of the Quick Sequential Organ Failure Assessment for mortality in patients with suspected infection: A systematic review and meta-analysis. *Ann Intern Med* 2018;168:266-275.

In 2016, the Third International Consensus Definitions for Sepsis and Septic Shock Task Force (Sepsis-3) issued new definitions for sepsis and septic shock.[1] Two of the most significant changes were to eliminate the systemic inflammatory response syndrome (SIRS) criteria and to include the quick Sequential Organ Failure Assessment (qSOFA) score as a bedside assessment to rapidly identify patients at increased risk for poor outcomes due to sepsis. These changes have been controversial, particularly regarding the paucity of evidence for qSOFA. Therefore, Fernando and colleagues conducted a meta-analysis to compare the accuracy of the SIRS criteria and qSOFA for predicting mortality (in-hospital, 28-day, or 30-day) in adult patients with sepsis.

Researchers identified 38 studies that met the inclusion criteria for the meta-analysis. Of these, 36.8% were conducted in the United States, 23.7% were conducted in Europe, and 23.7% were conducted in Asia. Most were retrospective cohort studies (24/38, 63.2%) and none were randomized controlled trials.

The pooled sensitivity of qSOFA was 60.8% (95% confidence interval [CI], 51.4-69.4%) and the specificity was 72% (95% CI, 63.4-79.2%). The estimated diagnostic odds ratio was 3.98 (95% CI, 3.22-4.92), and the positive and negative predictive values were 2.17 (95% CI, 1.82-2.58) and 0.55 (95% CI, 0.47-0.63), respectively. The sensitivity for the SIRS criteria was 88.1% (95% CI, 82.3-92.1%), and the specificity was 25.8% (95% CI, 17.1-36.9%). The diagnostic odds ratio was 2.57 (95% CI, 2.12-3.11), and the positive and negative predictive values were 1.19 (95% CI, 1.09-1.29) and 0.46 (95% CI, 0.40-0.54), respectively.

The sensitivities for qSOFA and the SIRS criteria varied considerably based on patient location. In patients outside the intensive care unit (ICU), qSOFA sensitivity was 51.2 (95% CI, 43.6-58.7) and dropped to 46.7 (95% CI, 38.3-55.2) for patients in the emergency department (ED). By contrast, the sensitivity of the SIRS criteria for patients outside the ICU was 82.2 (95% CI, 74.5-87.9) and in the ED was 83.6 (95% CI, 75.9-89.1).

## ■ COMMENTARY

During the past several years, early recognition and prompt treatment have become well recognized as the keys to improving outcomes in sepsis. However, the goal of early recognition is challenging because there is not a gold standard diagnostic test for sepsis or a set of specific signs and symptoms.

Since the publication of Sepsis-3 in 2016, there has been widespread interest in using qSOFA as a screening tool. The qSOFA is a two-minute assessment that can be conducted at the patient's bedside. The assessment uses fulfillment of two or more criteria (respiratory rate ≥ 22 breaths/minute, altered mental status, and systolic blood pressure ≤ 100 mmHg) to identify patients at high risk of short-term mortality from sepsis. All screening tests must have a high sensitivity for the condition they are assessing to avoid missing potential cases. Fernando and colleagues have shown that, despite their exclusion from Sepsis-3, the SIRS criteria likely are superior to qSOFA for screening patients suspected to have sepsis.

Indeed, the appropriateness of using qSOFA instead of the SIRS criteria has been questioned recently.[2] It is notable that the authors of Sepsis-3 warned that qSOFA was not created to replace the SIRS criteria

in screening for sepsis, but rather was designed as an early warning tool to identify patients at high risk for death and who need an escalation of care.[1] One of the criteria in qSOFA is hypotension, which, in the setting of infection, usually indicates that clinical decompensation already has occurred. Thus, it is preferable that such patients be identified earlier in their clinical course before hypotension develops.

There are some important limitations to the study. As with all meta-analyses, the results are affected by the quality of the studies on which it is based. Of the 14 studies described as prospective, in fact only three were performed specifically to assess qSOFA. Moreover, the timing of when the scores were determined in relation to when cultures were taken and antibiotics started was not described. Finally, many of the qSOFA studies were performed on specific patient populations (e.g., patients with neutropenic fever or community-acquired pneumonia), yet the tool has been recommended for all adults with suspected sepsis. Whether this is an appropriate indication needs to be investigated further.

The study by Fernando and colleagues is useful because it cautions physicians not to put too much faith in qSOFA, and that the SIRS criteria remain clinically relevant. Perhaps the most prudent recommendation would be to use both qSOFA and the SIRS criteria, along with clinical judgment, to identify patients with early sepsis. Further studies on this combined approach would be beneficial. ■

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ABSTRACT & COMMENTARY

# Refugee Screening


***By Philip R. Fischer, MD, DTM&H***

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**Dr. Fischer reports no financial relationships relevant to this field of study.**



SYNOPSIS: Screening and potential treatment of refugees prior to travel to the United States effectively reduces the burden of infection.


SOURCE: Mitchell T, Lee D, Weinberg M, et al. Impact of enhanced health interventions for United States-bound refugees: Evaluating best practices in migration health. *Am J Trop Med Hyg* 2018; in press, doi: 10.4269/ajtmh.17-0725. [Epub ahead of print].

In the past four decades, approximately 3 million refugees have settled in the United States, with 85,000 arriving in 2016. Refugees typically undergo three steps in screening for infectious illnesses. First, two to six months prior to expected arrival in the United States, refugees undergo a history and physical exam review with some focused testing for tuberculosis and sexually transmitted infections. Then, three to five days before travel, refugees undergo a "fitness-to-travel" evaluation along with presumptive treatment for some parasitic infections. Finally, there are voluntary domestic evaluations within 90 days of arrival, but the implementation of Centers for Disease Control and Prevention (CDC) recommendations at those post-arrival exams varies from state to state. With the U.S. Department of State and the International Organization for Migration, the CDC has developed supplemental overseas health programs to improve the health of refugees and to reduce risks to public health in the United States.

Mitchell and colleagues reported on the usefulness of enhanced, additional screening and treatment interventions as evaluated in Asian refugees.

Voluntary screening (and treatment, as indicated) was offered to refugees living in three camps along the Thailand-Burma border. Screening included tests for anemia, hepatitis B infection, and intestinal parasites. Hepatitis B surface antigen-positive individuals were counseled and evaluated; those who were negative were offered a series of hepatitis B vaccines.

Typically, United States-bound refugees in Thailand receive albendazole (to presumptively treat soil-transmitted helminths) and ivermectin (to presumptively treat *Strongyloides* infection) at their fitness-to-travel visit a few days before leaving for the United States. During this study, stool and blood testing followed by albendazole and ivermectin treatment were included during the initial

pre-departure visit. Then, follow-up testing was conducted at the fitness-to-travel visit.

From July 2012 to November 2013, 2,004 refugees participated in this study; 42% were younger than 18 years of age. Comparative data were available for 89% at the pre-departure time (median 167 days from the initial evaluation/treatment) and for 39% following arrival in the United States (median 35 days after the pre-departure evaluation). Overall, 10% of travelers were hepatitis B surface antigen-positive, and 98% of the positive individuals were 12 years of age or older. Males were more at risk of hepatitis B infection; having tattoos was not a risk factor.

Overall, 73% of refugees had at least one pathogenic stool parasite, and 40% had multiple pathogens. *Ascaris*, *Trichuris*, hookworm, and *Giardia* were the most common; only 4% had *Strongyloides* infection. Three different hookworm infections were identified: *Necator americanus*, *Ancylostoma duodenale*, and *Ancylostoma ceylanicum*. Overall, 28% of refugees were anemic, with 61% of children aged 6 months to 2 years being anemic. Iron deficiency accounted for most (72%) of the anemia, with thalassemia accounting for most of the rest; hookworm likely contributed to just some of the iron deficiency.

With treatment, the rates of infection dropped; only 12% had stool positive for parasite at the U.S. evaluation, and some of those were new infections since the initial visit prior to departure. Overall, eosinophil counts dropped with the use of initial visit anti-parasitic treatment.

The authors concluded that enhanced screening and treatment were feasible. And, there was health benefit to refugees with early treatment as well as less risk of transmission of parasites following arrival in the United States.

## ■ COMMENTARY

It is estimated that there are currently 65 million people (approximately 1% of the planet's population) who have been forcibly displaced from their homes by violence and persecution, and about one-third of those have fled to a different country (and are, thus, refugees).[1,2] Half of refugees are children.[2] Currently, most refugees are from Syria, Afghanistan, South Sudan, Somalia, Sudan, Democratic Republic of Congo, Central African Republic, and Myanmar.[2] Turkey, Pakistan, and Lebanon are hosting more refugees than are other countries.[2] There are three options for refugees: return home when the threat of violence and persecution seems to have resolved; integrate into the host country; or resettle elsewhere. Refugees may spend many, many years in "temporary" refugee camps, such as that in Dadaab, Kenya, with a population that at one point had reached 500,000.[3] By the time refugees are resettled in the United States, they typically have been living as refugees for more than a decade.

Mitchell's study is useful in demonstrating both the feasibility and value of enhanced screening and treatment programs for refugees. Providing such care prior to departure from the temporary host country is more likely to reach more refugees with systematic care and allows for better health at the time of arrival in the United States. Of course, the specifics of screening and treatment will vary with the specific site and population in question. United States-bound refugees have been subject to pre-departure treatment of parasitic infections since 1999, and antimalarials are included for refugees from sub-Saharan Africa. These programs have proven cost-effectiveness.[4]

Those of us trained when there were just two human hookworm species can learn from the experience of refugees. Previously thought to be an animal parasite that was an uncommon cause of human infection, *Ancylostoma ceylanicum* recently has emerged as an important human pathogen and now is known to be even more prevalent than *A. duodenale* in parts of Asia.[5,6] This parasite also has been identified in domestic pets and tourist resort soil in northern Australia.[7] Relevant to many Asian refugees, *A. ceylanicum* recently was identified in rural communities in Myanmar,[8] not surprising since it similarly had been found in refugees studied by Mitchell and colleagues. *A. ceylanicum* eggs are similar to other *Ancylostoma* eggs, as seen under the microscope, so molecular characterization is helpful.[5,8] In addition, it is thought that *A. ceylanicum* leads to more blood loss and more iron deficiency than does *Necator*.[5]

Whatever the geographic origin of refugees, whatever the local hookworm species, and whatever the pre-arrival treatment, the data in this study remind us that there is still risk that newly arrived refugees in the United States will be harboring intestinal parasites (12% with helminths and 23% with protozoa in Mitchell's study). Some of these infections apparently were new since the pre-departure testing. One way or another, physicians seeing newly arrived refugees should consider the possibility of intestinal parasite infection. ■

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ABSTRACT & COMMENTARY

# Influenza Vaccine: High Dose or Standard Dose?

***By Stan Deresinski, MD, FACP, FIDSA***

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**Dr. Deresinski reports no financial relationships relevant to this field of study.**

SYNOPSIS: High-dose inactivated influenza vaccine was superior to standard-dose vaccine in providing protection against influenza or pneumonia-associated hospitalizations.

SOURCE: Young-Xu Y, Van Aalst R, Mahmud SM, et al. Relative vaccine effectiveness of high-dose versus standard-dose influenza vaccines among Veterans Health Administration patients. *J Infect Dis* 2018 Feb 14. doi: 10.1093/infdis/jiy088. [Epub ahead of print].

Young-Xu and colleagues evaluated the relative protective efficacy of standard-dose and high-dose inactivated non-adjuvanted influenza vaccine in a retrospective cohort study that included all Veterans Health Administration patients > 65 years of age who had more than one outpatient encounter in the 2014-2015 respiratory season. The initial population evaluated consisted of 104,965 standard-dose and 125,776 high-dose vaccine recipients. After matching, these numbers were reduced to 49,091 and 24,682, respectively.

The outcomes favored the high-dose vaccine. Thus, the matched, adjusted relative vaccine efficacy was 25% (95% confidence interval [CI], 2-43%) against hospitalizations associated with influenza or pneumonia and 5% (95% CI) against influenza or pneumonia-related outpatient visits. Statistically significant benefit was not achieved with regard to influenza or pneumonia-related hospitalizations, all-cause hospitalizations or outpatient visits, or laboratory documented influenza virus infection. Thus, the high-dose vaccine appears to have modest benefit relative to the standard-dose inactivated influenza vaccine.

## ■ COMMENTARY

In their recommendations of choice of influenza vaccine for the 2017-2018 season, the Advisory Committee on Immunization Practices (ACIP) listed a bewildering array of available vaccine products.[1] These included 13 vaccines in nine categories. (*See Table.*) Clinicians must decide among attenuated, inactivated (with or without adjuvant), and recombinant vaccines, as well as between quadrivalent and trivalent products.

The high-dose vaccine (Fluzone, High-Dose), which was first approved in 2009, contains 60 mcg of hemagglutinin, while the standard-dose vaccine contains only 15 mcg. Decisions to incorporate the high-dose vaccine into vaccine programs have had to address issues such as relative acquisition cost, concerns regarding the frequency of local adverse reactions, and inconsistent results of previous studies

**Table: Influenza Vaccine Categories**

- Inactivated, quadrivalent, standard dose
- Inactivated, quadrivalent, standard dose, cell culture-based
- Inactivated, quadrivalent, standard dose, intradermal
- Inactivated, trivalent, standard dose
- Adjuvanted, inactivated, trivalent, standard dose
- Inactivated, trivalent, high dose
- Recombinant, quadrivalent
- Recombinant, trivalent
- Live attenuated, quadrivalent

comparing it to standard-dose vaccine. This study, although retrospective, primarily involving male subjects, and not addressing tolerability, included a remarkably large number of subjects, and its results support the preferential use of high-dose vaccine in patients ≥ 65 years of age. ■


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# Adjuvanted Recombinant Hepatitis B Vaccine (Heplisav-B)


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**Dr. Wang reports no financial relationships relevant to this field of study.**


Heplisav-B is a new hepatitis B vaccine approved by the FDA in November 2017. The indication for Heplisav-B is the prevention of infection caused by all known subtypes of hepatitis B virus (HBV) in adults 18 years of age or older. Heplisav-B contains an antigen similar to other HBV vaccines currently on the market. However, it uses a synthetic oligonucleotide 1018 instead of alum as an adjuvant. This new adjuvant stimulates rapid activation of the innate immune system via toll-like receptor 9 (TLR9) and supports the induction of B and T lymphocytes in the adaptive immune system.[1-5]

Heplisav-B is administered in two doses over one month. This compares favorably to older HBV vaccines, which are given in three doses over a six-month period. Nelson et al conducted a population-based study using the Vaccine Safety Datalink from 1997-2004. The researchers showed low compliance rates with the three-dose hepatitis B vaccine series. Less than 60% of the HBV vaccine initiators completed the three-dose series. Compliance rates were low at 45% among adolescents and 41% in 18-29 year olds at one year. Table 1 lists costs and formulations currently available in the United States.[1-5]

## GUIDELINES

Heplisav-B was discussed in a meeting of the Advisory Committee on Immunization Practices (ACIP) on Feb. 12, 2018. Per Dynavax's press release on Feb. 21, 2018, "Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP) voted unanimously in favor of including Heplisav-B on its list of ACIP recommended products for use to vaccinate adults against hepatitis B." CDC will review and approve the ACIP recommendations before publishing in the *Morbidity and Mortality Weekly Report* (MMWR).[6]

## CLINICAL TRIALS

The immunogenicity of Heplisav-B was studied in three pivotal trials. These trials were multi-center, observer-blinded, randomized, and active controlled. Patients were excluded if they had any history of HBV infection or vaccine, were pregnant or breastfeeding, had HIV infection, immunosuppression, or any history of autoimmune disease. The primary endpoint for Heplisav-B trials was to demonstrate non-inferiority of seroprotection rates (SPR) compared with Engerix-B. SPR is defined as the percentage of patients with anti-HBV surface antibody level ≥ 10 mIU/mL. Heplisav-B was given at 0 and 4 weeks plus a placebo dose at 24 weeks. The active control group received Engerix-B at 0, 4, and 24 weeks. Patients were followed for 52 weeks after the first injection.

The first study by Halperin et al was conducted in healthy adults ages 18-55 years.[7] SPR in the

**Table 1: Hepatitis B Vaccine Cost Comparison[1]**

| Vaccine | How Supplied | Average Wholesale Price for 1 mL Vials | Usual Dose in Adults | Cost per Treatment (Average Wholesale Price) |
|---|---|---|---|---|
| Heplisav-B (Dynavax) | 0.5 mL solution in single-dose vials | $115 | 0.5 mL IM given as two doses administered at 0 and 1 month | $230 |
| Recombivax-HB (Merck) | 0.5, 1 mL suspension in single-dose vials and prefilled syringes | $74.60 (10 mcg/mL)<br><br>$199.10 (40 mcg/mL) | Immunocompetent adults: 1 mL (10 mcg/mL) IM for 3 doses administered at 0,1, and 6 months<br><br>Immunocompromised adults: 1 mL (40 mcg/mL) dose administered at 0,1, and 6 months | $224.40<br><br>$597.30 |
| Engerix-B (GSK) | 0.5, 1 mL suspension in single-dose vials and prefilled syringes | $62.85 (20 mcg/mL) | Immunocompetent adults: 1 mL IM for three doses administered at 0,1, and 6 months<br><br>Immunocompromised adults: 2 mL per dose at 0,1,2, and 6 months | $188.55<br><br>$502.80 |
| Twinrix (GSK) Hepatitis A and B | 1 mL suspension (hepatitis A virus antigen 720 ELISA units and hepatitis B surface antigen 20 mcg/mL) in prefilled syringe | $120.90 | 1 mL IM given on 0-, 1-, and 6-month schedule for a total of three doses | $362.70 |

Heplisav-B group at week 12 (95.1%) was non-inferior and superior to that of the Engerix-B at week 28 (81.2%). Peak SPR occurred in the Heplisav-B group at week 24 compared to week 28 in the Engerix-B group. SPR rate also was achieved earlier in the Heplisav-B group at week 8 (88.5%) than Engerix-B at week 28 (81.1%).[7]

Heyward et al conducted a second study in adults 40-70 years of age.[8] SPR at week 12 for Heplisav-B was significantly higher (90.1%) than SPR of Engerix-B at week 32 (70.5%). Peak SPR of Heplisav-B was 95.1% at 24 weeks compared to 72.8% at 28 weeks for Engerix-B. More Heplisav-B patients achieved SPR at week 8 (76.6%) than the Engerix-B group at week 28 (72.8%).[8]

The third study conducted by Jackson et al looked at adults 18-70 years of age.[9] The researchers evaluated SPR in patients with type 2 diabetes mellitus and stratified patients by age group.

In patients with type 2 diabetes, SPR at 28 weeks was 90% in Heplisav-B compared to 65.1% in Engerix-B group. SPR rates decreased with increasing age. However, SPR rates were all significantly higher in the Heplisav-B (95.4% at 24 weeks) than the Engerix-B (81.3% at 28 weeks) group.[9]

## ADVERSE EFFECTS

The most common reported adverse effects were at the injection site.[1,2] They include pain (22.8-38.5%), erythema (0.7-4.1%), and swelling (0.6-2.3%). The most common general adverse reactions reported are fatigue (10.8-17.4%), headache (8.1-16.9%), malaise (7-9.2%), myalgia (6.4-8.5%), and fever (≤ 2%). Injection site adverse reactions were reported more frequently compared to the Engerix-B group. Serious adverse events and deaths were similar between the two groups.[1,2]

## SIGNIFICANT DRUG INTERACTIONS

It is important to note that immunosuppressive therapies may reduce the effectiveness of Heplisav-B.[1,2]

## CONCLUSION

Heplisav-B is a recently approved hepatitis B virus vaccine with a synthetic oligonucleotide immunostimulatory adjuvant. It is FDA-indicated for prevention of hepatitis B in adults ≥ 18 years of age. In clinical trials, Heplisav-B induced significantly more immunogenicity and higher SPR at earlier time points than Engerix-B. Heplisav-B also produced a safety profile similar to Engerix-B. Because Heplisav-B has a one month dosing regimen, it may improve challenges of HBV vaccine completion by improving adherence. ■

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Infectious Disease [ALERT]

# Updates

By Carol A. Kemper, MD, FACP

## Online Sex and Sexually Transmitted Diseases

SOURCE: Cabecinha M, Mercer CH, Gravningen K, et al. Finding sexual partners online: Prevalence and associations with sexual behavior, STI diagnoses and other sexual health outcomes in the British population. *Sex Transm Infect* 2017;93:572-582.

It has been debated whether finding sexual partners via the internet is inherently riskier, or if seeking out relationships online is biased toward those more likely to have sexually transmitted disease (STD). While the use of online dating has been well described in men who have sex with men (MSM), less is known about the modern heterosexual online dating habits and consequences.

From 2010-2012, the British performed a National Survey of Sexual Attitudes and Lifestyles (Natsal-3) involving a cross section of 15,162 individuals aged 16 to 74 years. Using data from participants with at least one lifetime sexual partner, the researchers found that 17.4% of men and 10.1% of women had used the internet to find sexual partners within the previous year. Surprisingly, use of the internet to find sexual partners was more common in individuals aged 35-44 years (on average, 30.6% for men and 17.7% for women) and lowest in younger people aged 16-24 years (on average, 10.1% for men and 4.2% for women).

Following adjustments for age, non-heterosexual persons were significantly more likely to use the internet to locate sexual partners, compared with straight or married persons (odds ratio [OR], 12.75). Women "not in a steady relationship" were also more likely to use the internet for finding partners (OR, 3.14). Men who paid for sex within the previous year also were significantly more likely to find sexual partners online.

Seeking sexual partners online was associated with several higher-risk sexual behaviors, including condomless sex with two or more partners and higher partner numbers. For those who used the internet for sexual hook-ups, compared to those who did not, the odds of hooking up with five or more partners in the previous year was significantly greater (adjusted OR, 5.9 for men and 7.0 for women).

Online sex also was associated with higher rates of non-viral STDs (syphilis, gonorrhea, and chlamydia). In those aged 16-44 years who sought sexual partners online and who had available STD testing, 9.3% of men and 6.2% of women developed one or more non-viral STDs in the previous year. In contrast, for those not seeking partners online, 3.2% of men and 5.7% of women developed one or more non-viral STDs. This suggests an increased risk of STDs in those using the internet for sexual partners or hook-ups. An additional finding was the frequency of HIV testing, which appeared to be higher in men but lower in women who used the internet for locating sexual partners.

Use of the internet to find future partners isn't limited to the comfort of your own home.

Networking mobile smartphone apps, such as Grindr, Tinder, and GROWLr, with GPS capability allow for fast and ready hook-ups. Several of us, sitting in the HIV clinic at the county, tried this technology once and were stunned to locate within seconds an individual interested in sex only 75 feet away in the same building — with particular descriptions of what kind of sex he or she was interested in. I'm seldom accused of prudishness, but this took me aback. I liken this kind of sexual encounter to fast food — feels good while it's going down but is really bad for you.

[Rates of STDs continue to skyrocket in Americans, hitting the greatest number of cases ever recorded in 2016.]

The practice of finding sexual partners online has been faulted, in part, for the resurgence of STDs, especially in the United States. Rates of STDs continue to skyrocket in Americans, hitting the greatest number of cases ever recorded in 2016.

Just one small example: Rates of syphilis in California have climbed from a nadir of 2,880 cases in 1999, during the height of the AIDS epidemic, to 17,665 cases in 2016 (along with 207 cases of congenital syphilis).

However, California and New York were only sixth and seventh on the list of states with the highest rates of STDs in 2016. Surprisingly, states with the highest rates of STDs in 2016 were, in descending order, Louisiana, North Carolina, Georgia, Mississippi, and South Carolina. Researchers say the biggest culprit is poverty.

The increase in STDs throughout the United States also may be attributed to the reduction of public health infrastructure support and shuttering of many county-based STD clinics over the past decade. The increased use of methamphetamines and what is euphemistically termed "prevention fatigue" may be additional factors. As one man phrased it, younger people who did not live through the AIDS crisis in the 1980s-1990s lack "healthy fear."

## Swingers Come Out

SOURCE: Spauwen LWL, Niekamp AM, Hoebe CJPA, Dukers-Muijrers NHTM. Do swingers self-identify as swingers when attending STI services for testing? A cross-sectional study. *Sex Transm Infect* 2018; Jan. 30. doi: 10.1136/sextrans-2017-053321. [Epub ahead of print].

Sexual behaviorists lament that clinicians don't do enough to identify individuals who "swing" when providing medical care or administering sexual behavior and STD questionnaires. Swingers are an interesting group — and, although they can be defined in different ways, the term generally implies someone who freely engages in sex, but the term has become more narrowly defined as those who exchange spouses for sexual activities and/or indulge in group sex at organized meetings.

It is estimated there are more than 1 million swingers in the United States, many of whom are "hidden" or unrecognized, even when they present for medical care. As a group, they may have higher than recognized rates of STDs, and since some may be bisexual, the swinging community may be an important "transmission bridge" to the entire population.

Researchers in the Netherlands have been attempting to track this group and their STD rates since 2007, when it was first recognized that combined rates of gonorrhea and chlamydia were twice as high in swingers than in female prostitutes (10.4% vs. 5%). Further, female swingers often did not self-identify as swingers, and therefore were less likely to seek STD screening. Further research in this group in 2014 found rates of gonorrhea and chlamydia in swingers in the Netherlands had increased to 13%, and recreational drug use was reported by nearly half.

The current study sought to determine whether a group of 289 swingers self-identify as swingers, and to assess their awareness of safe sex and STD testing. The median age was 45 years, and 49% of the group was female. While meeting the definition of a swinger, only 56% of participants self-identified as such. While safe sex was considered important (77%), only 62% reported routine STD testing and 56% routinely used condoms. Of the women, condomless vaginal sex was reported by 57%. Interestingly, those who self-identified as swingers "swinged more often," had more partners, and more often swinged at home. Thirteen percent were positive for STDs.

The authors maintain that many STD clinics do not identify clients as swingers, which is a missed opportunity for identifying a high-risk group, with focused counseling and more extensive partner notification.

As an aside, the original definition of "swing" was to oscillate or move in a violent circulatory motion, but by 1545 the word more commonly meant "to move freely back and forth." By 1899, it was used to suggest a shift in public opinion. The origins of our idea of a swinger likely originates from the 1930s-1940s big band period with its swinging rhythms, and the idea that swingers are people who "live in an unrestrained way." What would Benny Goodman say to this?

## HIV-positive Patients Require Hepatitis B Vaccine

SOURCE: Weiser J, Perez A, Bradley H, et al. Low prevalence of hepatitis B vaccination among persons receiving medical care for HIV infection in the United States, 2009-2012. *Ann Intern Med* 2018;168:245-254.

Hepatitis B vaccination is one of the simplest and most effective interventions we can offer patients with HIV infection. Such individuals are at much higher risk for exposure to hepatitis B virus (HBV), and at higher risk for chronic infection, cirrhosis, hepatic failure, and hepatocellular carcinoma. Studies suggest that 8-9% of patients with HIV are chronically infected with HBV, compared with 0.3% of American adults. HBV vaccination is one of those key baseline interventions listed on every guideline for HIV care.

So, how is it this survey of 18,089 HIV-positive persons in the United States found that 44.2% showed no evidence of immunity to HBV, or a history of vaccination, nor evidence of HBV infection, and were candidates for HBV vaccination? During a one-year surveillance period of observation, only 9.6% of those identified as candidates for HBV vaccination received the vaccine, and another 7.5% had no documentation of vaccination but new evidence of immunity or infection. This left more than one-third (36.7%) of HIV-positive individuals at risk for HBV infection.

Baseline characteristics of this group indicate they are in care and receiving active medical therapy: 91% had received anti-retroviral therapy in the previous year, and 75% had undetectable viral loads (< 200 copies per mL). More than half of the patients attended large HIV specialty clinics providing care for more than 400 patients. Approximately 15.8% had recognized hepatitis C virus infection, and 3.3% had chronic HBV infection.

When examining risk factors for non-vaccination, patients cared for in smaller private offices were less likely to receive vaccine than those in larger, non-private clinics (5.6% vs. 11.8% received vaccine, respectively). And those not receiving funding from Ryan White programs were less likely to receive vaccination than those facilities that did (3.7% vs. 12.5% received vaccine, respectively). Factors associated with a higher prevalence of vaccination included lower income levels, lower educational attainment, black race, younger age, recent homelessness, and a mean CD4 count < 500 cells per mL, probably all factors associated with attendance in a larger non-private clinic supported by Ryan White funding. No relationship was observed between receipt of anti-retroviral therapy and vaccination.

[Patients cared for in smaller private offices were less likely to receive vaccine than those in larger, non-private clinics.]

Ironically, HIV-positive individuals with insurance and cared for in the private sector are more likely to not receive HBV vaccination. But many HIV-positive individuals remain at risk for HBV infection, regardless of where they receive their care. The authors speculated that the inconsistent and changing recommendations on timing and administration of HBV vaccine may play a role in healthcare provider confusion or fatigue. ■

ABIM CME MOC ACCREDITED

## CME INSTRUCTIONS

To earn credit for this activity, please follow these instructions:
1. Read and study the activity, using the provided references for further research.
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4. After successfully completing the test, a credit letter will be emailed to you instantly.
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## CME QUESTIONS

**1. Which of the following is true regarding refugees arriving in the United States?**

a. They are not screened routinely for infectious illnesses prior to arrival in the United States.

b. They likely have been treated fully for intestinal parasites as part of pre-arrival testing.

c. They might have received anti-helminth treatment prior to arrival in the United States.

d. They rarely have hepatitis B infection.

**2. Heplisav-B differs from older hepatitis B virus vaccines in which one of the following ways?**

a. It contains an adjuvant.

b. Its viral antigen is significantly different.

c. It contains a synthetic oligonucleotide.

d. It routinely requires administration of four doses.

**3. Which of the following is *not correct* regarding patients with suspected meningitis in the study by Glimaker and colleagues?**

a. Performance of a lumbar puncture (LP) without first performing computerized tomography (CT) of the brain was associated with a 4% mortality rate.

b. Performance of brain CT prior to LP was associated with a 10% mortality.

c. Performance of LP without first performing brain CT is associated with a greater likelihood of early initiation of antibiotic therapy.

d. All of the above are correct.

## CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- discuss the diagnosis of infectious diseases;
- explain current data regarding the use of new antibiotics for commonly diagnosed diseases and new uses for traditional drugs;
- discuss the latest information regarding risks, benefits, and cost-effectiveness of new and traditional diagnostic tests; and
- discuss new information regarding how infectious diseases are transmitted and how such information can lead to the development of new therapies.