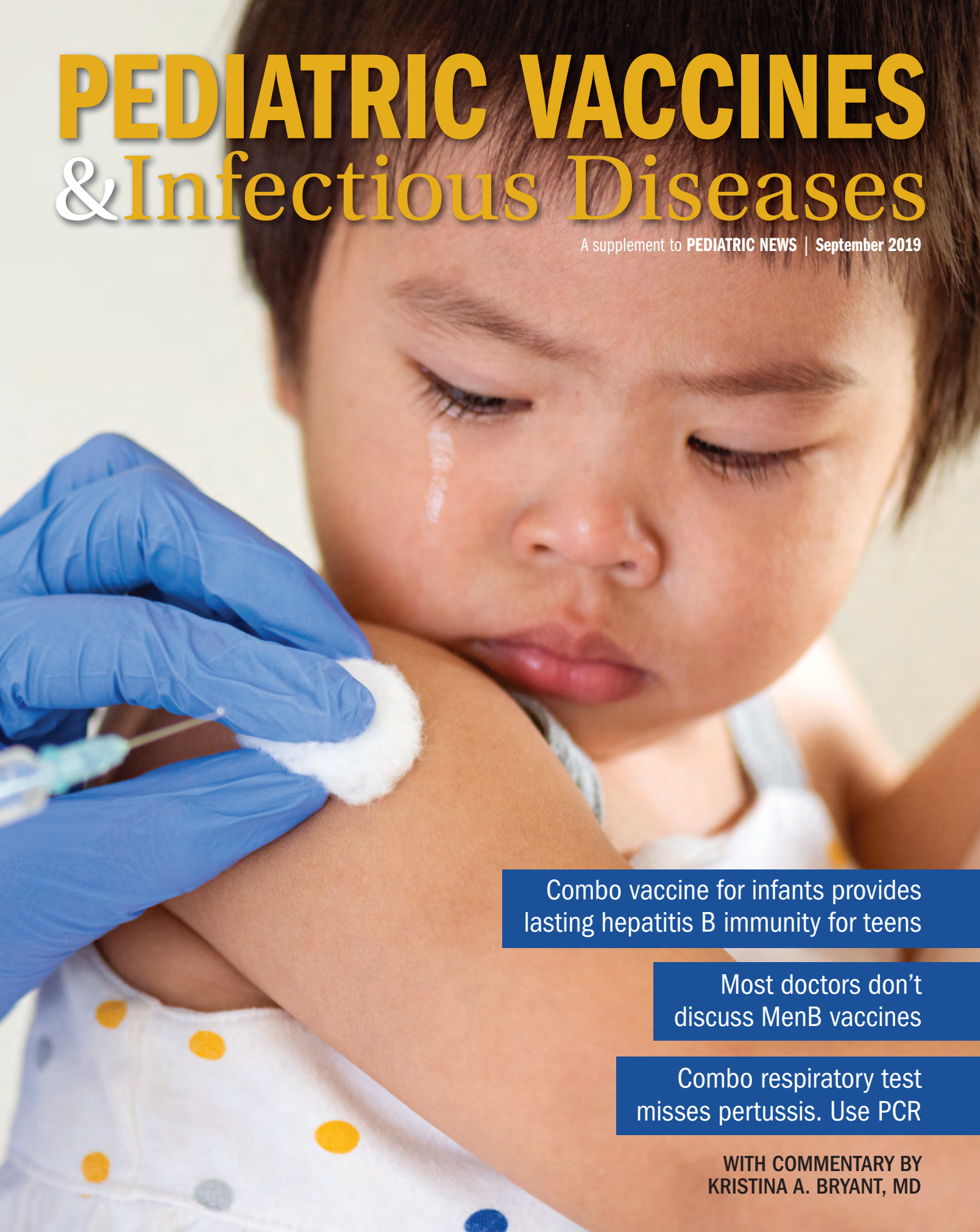
PEDIATRIC VACCINES & Infectious Diseases

A supplement to **PEDIATRIC NEWS** | **September 2019**



Combo vaccine for infants provides lasting hepatitis B immunity for teens

Most doctors don't discuss MenB vaccines

Combo respiratory test misses pertussis. Use PCR

WITH COMMENTARY BY
KRISTINA A. BRYANT, MD

Adam is a hypothetical patient example and not an actual patient.

The person depicted here is a model used for illustrative purposes only.

Adam dreams of going pro.

Making it to the big leagues is rare.

But rare happens.

MenB happens too.

Your patients are a lot like Adam, with hopes and dreams for the future. But meningococcal serogroup B disease (MenB) could put an end to those in a hurry. Although meningitis B is rare, its consequences can be devastating, even potentially fatal.[1-3] But, by choosing to vaccinate appropriate patients against meningitis B, you're helping to protect them as they pursue their dreams—whatever those dreams may be.

Vaccination may not protect all recipients.

See the stats and learn about the risk factors for meningococcal disease @ ButRareHappens.com.

Use your phone to scan the QR code. [Android users: you'll need an app that can read codes like Google Lens or Barcode Scanner. Once installed, open the app, line up the code in your camera, and tap OK.]

References: 1. Pelton SI. Meningococcal disease awareness: clinical and epidemiological factors affecting prevention and management in adolescents. *J Adolesc Health.* 2010;46: S9-S15. **2.** Thompson MJ, Ninis N, Perera R, et al. Clinical recognition of meningococcal disease in children and adolescents. *Lancet.* 2006;367(9508):397-403. **3.** Vyse A, Anonychuk A, Jäkel A, et al. The burden and impact of severe and long-term sequelae of meningococcal disease. *Expert Rev Anti Infect Ther.* 2013;11(6):597-604.

It's time to work on our stewardship

BY KRISTINA A. BRYANT, MD

The theme of the articles in this supplement could be broadly defined as "stewardship." The term "antibiotic stewardship" is now well established in the medical lexicon. As noted on the Society for Healthcare Epidemiology of America website, this refers to "a set of coordinated strategies to improve the use of antimicrobial medications with the goal of enhancing patient outcomes, reducing resistance to antibiotics, and decreasing unnecessary costs."

Choreograp/Getty Images

This concept of appropriate use could easily be extended to other therapeutic agents, such as intravenous immunoglobulin. Who is most likely to benefit from this product, which is expensive and currently in short supply?

More recently, attention has been focused on diagnostic stewardship or "modifying the process or ordering, performing, and reporting diagnostic tests to improve the treatment of infections and other conditions." As with antimicrobial stewardship, the ultimate goal is to improve patient outcomes and be cost effective ("Diagnostic Stewardship – Leveraging The Laboratory to Improve Antimicrobial Use," JAMA. 2017;318[7]:607-8).

Ordering a pertussis polymerase chain reaction test instead of the more expensive and apparently less sensitive comprehensive respiratory panel is one example of diagnostic stewardship. So is understanding the benefits and limitations of news tests for Lyme disease and how to best incorporate these tests into clinical practice.

We can think about this even more broadly though. Merriam-Webster defines stewardship as "the careful and responsible management of something entrusted to one's care, e.g. stewardship of natural resources."

We don't talk about "vaccine stewardship," but we should. Aren't vaccines important resources that we are entrusted to provide in a manner that optimizes outcomes, namely making sure patients are protected from vaccine-preventable diseases, and reduces harms?

A vaccine stewardship program would certainly include measures to minimize vaccine administration errors as described by Moro et al. It also would emphasize evidence-based strategies to reduce barriers to vaccine uptake and maximize immunization rates. Yes, these might include programmatic efforts such as patient reminders/recalls, standing orders, and EHR templates.

For meningococcal serogroup B vaccine though, the first step is just to have a conversation with patients and parents. Some of us aren't doing that consistently. Some of us aren't doing that at all.

In the setting of a Category B recommendation, we could debate how we measure outcomes. Are immunization rates the best measure of success? Or would a better measure be the percentage of patients who are given the opportunity to make an informed decision?

Either way, we have a lot of work to do.

Dr. Bryant is a pediatrician specializing in infectious diseases at the University of Louisville (Ky.) and Norton Children's Hospital, also in Louisville. She said she has been a clinical investigator on trials of pneumococcal conjugate vaccines and MenB vaccine funded by Pfizer. Email her at pdnews@mdedge.com.

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MDedge

DTPa-HBV-IPV/Hib in infancy maintains lasting immune memory against HBV in teens

BY BRUCE JANCIN
REPORTING FROM ESPID 2018

MALMO, SWEDEN – Four doses of hexavalent diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliovirus/*Haemophilus influenza* type b vaccine given in infancy provides reassuringly long-lasting immune memory against hepatitis B among 14- to 15-year-olds, Tino F. Schwarz, MD, reported at the annual meeting of the European Society for Paediatric Infectious Diseases.

He presented the fourth and final study in a series evaluating the antibody persistence and immune memory against hepatitis B (HBV) in recipients of the complete four-dose series of hexavalent DTPa-HBV-IPV/Hib vaccine in infancy. Because exposure to HBV can increase during adolescence, it was essential to determine whether antibody persistence is maintained, explained Dr. Schwarz of Juliusspital Hospital in Wurzburg, Germany.

"As expected, we saw a decrease in anti-HBs [hepatitis B surface antigen] antibody levels over the years, with persistent seroprotection in 85% of children at age 4-5 years, 72% at 7-8 years, 61% at 12-13 years, and now 54% of adolescents at 14-15 years. But we could demonstrate a very strong anamnestic response in the trial. This is good information. It clearly shows that, in patients who are exposed to hepatitis B, we can certainly guarantee that they are protected. It's a good result for public health. The vaccine is a very robust vaccine which induces a very strong response over the years. It can be boosted, but from an immunologic point of view it is not required," he said.

The multicenter study included 268 adolescents aged 14-15 years who had received the four-dose hexavalent vaccine series in infancy. Their antibody persistence against anti-HBs was measured, then measured once again 1 month after receiving a challenge dose of monovalent HBV vaccine.

Prechallenge, 105 of the teens were seronegative, 144 were seroprotected as defined by an anti-HBs concentration of at least 10 mIU/mL, and 19 had low seropositivity marked by an antibody level of 6 to less than 10 mIU/mL. Yet 1 month after the booster, which was intended to mimic the impact of real-world exposure to HBV, 83% of the initially seronegative subjects had an anti-HBs concentration of 10 mIU/mL or more, and 67% of them had a level of at least 100 mIU/mL.


Bruce Jancin/MDedge News
Dr. Tino F. Schwarz

"We saw a clear fantastic anamnestic response," Dr. Schwarz declared.

Overall, 93% of study participants seroconverted, and 87% of them had anti-HBs titers of 100 mIU/mL, "which is the level we'd like to achieve in vaccinees," he observed.

The booster monovalent HBV vaccine was well tolerated, with one-third of subjects complaining of mild local injection site pain and 30% noting fatigue. But in response to a question posed by session chair Ronald de Groot, MD, emeritus professor of pediatrics at Radboud University in Nijmegen, the Netherlands, Dr. Schwarz said these study results indicate there's no need for routine boosting in healthy adolescents such as those in the trial. Immunocompromised individuals might be a different story, but they weren't investigated.

But what about in physicians and surgeons, where protection against HBV infection is essential? Dr. de Groot asked.

"In Germany, we require a titer of 100 mIU/mL or more in medical staff, but we're quite alone in Europe. Other countries do not require booster vaccination for medical staff. The data we've shown here is quite reassuring: If you get exposed, you in effect get a booster. It's complicated to test surgeons in their offices; better to just rely on the anamnestic response that we've demonstrated," Dr. Schwarz replied.

He reported serving as a consultant to GlaxoSmithKline, which funded the study, as well as to Pfizer and Sanofi Pasteur.

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Commentary by Dr. Bryant / Prior studies have shown that immunity persists for at least 30 years in healthy individuals who received hepatitis B vaccine beginning at 6 months of age. Studies like this one demonstrate the persistence of immunity in children immunized earlier. In Germany, diphtheria, tetanus toxoid, acellular pertussis hepatitis B inactivated poliomyelitis, and Haemophilus influenzae type b (Hib) conjugate vaccine (DTPa-HBV-IPV/Hib) is given at 2, 3, and 4 months of age, with a booster at 11-14 months. This study demonstrates that waning antibody titers against hepatitis B in healthy teenagers do not equate to waning protection. When challenged with hepatitis B antigen (mimicking natural infection), most demonstrate a robust anamnestic response that should protect against actual infection. These data support the World Health Organization position that booster doses of hepatitis B are not routinely indicated, but additional studies are needed to explore ongoing protection over a lifetime and protection in special populations such as immunocompromised hosts.

Many physicians don't discuss MenB vaccine in teen wellness visits

BY ANDREW D. BOWSER
FROM PEDIATRICS

Only one-third to one-half of physicians treating teens are discussing serogroup B meningococcal (MenB) vaccines during routine adolescent visits, survey results showed.

About half of pediatricians and one-third of family physicians said they always or often initiate discussion of MenB vaccines for adolescents aged 16-18 years, according to a report on the survey published in Pediatrics.

However, it is challenging to say whether or not that level of discussion is on track with ideal clinical practice, according to Allison Kempe, MD, MPH, of the University of Colorado at Denver and Children's Hospital Colorado, Aurora, and coauthors. While MenB vaccines are recommended in this setting, the new Category B designation used for the recommendation indicates that the vaccines "may be administered" in the context of individual clinical decision making.

While some interpret the new Category B recommendation to mean that a discussion should always occur, others may interpret the recommendation as applicable to their own assessment of risks and benefits, without the need to involve patients and parents.

"Providers not initiating a discussion may not think the time required to discuss the MenB vaccine is justified by the risks posed by the disease or the benefits offered by these vaccines," wrote Dr. Kempe and associates. "Alternatively, they may have a low level of awareness regarding the disease or the MenB vaccine and feel insufficiently knowledgeable to have an informed discussion about the pros and cons of vaccination. They also may have been entirely unaware of the ACIP [Advisory Committee on Immunization Practices] recommendation for MenB vaccination."

Dr. Kempe and colleagues invited a nationally representative sample of primary care physicians to complete the survey, which was administered via Internet or mail between October and December 2016. They heard back from 374 of 475 (79%) pediatricians and 286 of 441 (65%) family physicians.

A total of 50% of pediatricians and 31% of family physicians said they always or often discussed MenB vaccines during routine visits with adolescents aged 16-18 years, with slightly higher percentages saying they initiated discussions during precollege physical exams, according to the report. Of the pediatricians, 58% recommended the MenB vaccine to those in this age group, compared with 50% of family physicians. Not all physicians who recommended the vaccine reported consistently initiating a discussion about it.

Nearly three-fourths of pediatricians and 41% of family physicians reported currently administering the MenB vaccine in their practices, the authors said, adding that greater awareness of disease outbreaks was linked to higher likelihood of discussing the vaccine, while working in an HMO setting was linked to lower likelihood of initiating that discussion.

Commentary by Dr. Bryant / Kempe et al. have shed light on who is discussing and offering the meningococcal serogroup B (MenB) vaccine and who is not. Now we need data about who is being vaccinated and who is potentially being denied the opportunity to be protected against diseases. It is noteworthy that not all physicians who recommend the vaccine reported consistently initiating a discussion about it.

Racial, ethnic, and socioeconomic disparities in childhood vaccinations exist, with lower rates for some vaccines among non-Hispanic black children, compared with non-Hispanic white children; among children living below the federal poverty level versus those living at or above the poverty level; and among children with no insurance or Medicaid, compared with those with private insurance. Limited data suggest disparities exist for the MenB vaccine. Emily Watkins, MD, and Kristen Feemster, MD, MPH, conducted a retrospective cohort study of more than 45,000 older adolescents and young adults aged 16-23 years receiving care in one pediatric care network from Oct. 23, 2015, to April 30, 2017 (Open Forum Infect Dis. 2018 Nov. doi: 10.1093/ofid/ofy210.2113).

Overall, vaccine uptake was low: Only 21% received at least one MenB vaccine, and a higher proportion of vaccinated patients were Asian and privately insured. Notably, MenB initiation varied widely among the 31 practice care sites that took part in the study, ranging from 1% to 45%!

The reasons for disparities in vaccination are likely to be complex, but we all are susceptible to conscious and unconscious bias. If we initiate the discussion about the MenB vaccine only some of the time, how are we deciding who gets to participate in shared decision making and who does not?

In a 2017 article, Gary S. Marshall, MD, and Litjen Tan, MS, PhD, warned that, when physicians do not initiate such a discussion, we create a disparity between the "information haves" (families who know about the disease and seek vaccination) and the "information have-nots" (those who do not know about the disease or the vaccine) (Pediatrics. 2017 May 1;139[5]:e20163484).

They argue that a Category B recommendation comes down to a choice. Vaccinated or unvaccinated? A sore arm or "continued vulnerability to a rare but potentially devastating disease?" Let's not take that choice away by failing to engage in the discussion with every family.

Rawpixel/Thinkstock

Recommending MenB vaccination was closely tied to discussing the vaccine. Physicians who said they initiated discussion almost always reported making a recommendation to vaccinate, and conversely, those who rarely initiated discussions were unlikely to recommend it, according to Dr. Kempe and her colleagues.

Factors that made physicians more likely to recommend vaccine included awareness of outbreaks, effectiveness and safety data, and duration of vaccine protection.

The Category B recommendation, on the other hand, was one of the key factors that made physicians less likely to recommend MenB vaccine, according to this survey. ACIP made the Category B recommendation in October 2015, stating that those aged 16-23 years may be vaccinated, with a preferred age of 16 to 18 years for administration. The accompanying rationale for the Category B designation referenced the low disease prevalence and insufficient data on effectiveness and safety for the two vaccines, which were both licensed under an accelerated approval mechanism following the outbreaks that have occurred on college campuses.

The Centers for Disease Control and Prevention did not provide additional guidance on how that Category B recommendation should be implemented, Dr. Kempe and her coauthors noted in their report.

"With our data, we highlight the challenges providers face with implementing recommendations for vaccination based on individual clinical decision making when they have limited experience with a disease and limited knowledge of a new vaccine," they wrote.

The research was funded by the CDC. Dr. Kempe and her coauthors reported no relevant financial relationships or potential conflicts of interest.

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SOURCE: Kempe A et al. Pediatrics. 2018 Aug 20. doi: 10.1542/peds.2018-0344.

Strength of recommendation may influence physician enthusiasm

These survey results suggest primary care physicians' zeal for discussing meningococcal serogroup B (MenB) vaccines during adolescent well visits is affected by the recommendation that they "may be administered" in this setting, according to Michael T. Brady, MD.

"When pediatricians are fortunate to have 16- to 18-year-old patients come to a routine visit, there are many important issues to discuss, such as sexual activity, tobacco, alcohol and illicit drug use, contraception, and mental health," Dr. Brady wrote in an editorial discussing the survey results.

The new Category B designation, used by the Advisory Committee on Immunization Practices to recommend MenB vaccines for adolescents and young adults not at increased risk for meningococcal B disease, puts the recommendation in the realm of individual clinical decision making, Dr. Brady noted. "Without specific and clear guidance as to how to quantify benefits, risks, and costs for their individual patients, it is easy to understand why providers would have disparate responses reflecting the challenge associated with a new vaccine and a new vaccine recommendation classification."

Pediatricians can achieve "exceptional rates of immunization" when recommendations are "evidence based, clear, and unequivocal," but by contrast, they will remain challenged by Category B or permissive recommendations when clear guidance on how to implement the recommendation is not provided, he concluded.

Dr. Brady is a pediatric infectious diseases specialist at Nationwide Children's Hospital and the Ohio State University, Columbus. These comments are from his editorial in Pediatrics (2018 Aug 20. doi: 10.1542/peds.2018-1633). Dr. Brady reported receiving royalties from Up-To-Date for a chapter on human herpesvirus 6, but received no external funding for this editorial. He reported no potential conflicts of interest.

Four syndromes suggest life-threatening PVL-positive *Staphylococcus aureus* infection

BY BRUCE JANCIN

EXPERT ANALYSIS FROM ESPID 2018

MALMO, SWEDEN – Methicillin-resistant *Staphylococcus aureus* gets the blame in the Americas as the main cause of a great wave of community-acquired severe invasive staphylococcal infections in children and adolescents during the past nearly 2 decades, but many European pediatric infectious disease specialists believe that Panton-Valentine leukocidin (PVL), a frequent co-traveler with MRSA, is the true bad actor.

"The American literature focused first on MRSA, but we've seen very similar, very severe cases with MSSA [methicillin-susceptible *S. aureus*] PVL-positive and MRSA PVL-positive infections," Pablo Rojo, MD, PhD, said at the annual meeting of the European Society for Paediatric Infectious Diseases.

"It is only because at the beginning there were so many MRSA cases in the States that they thought that was the driver of the disease. It is still unclear. There is still a discussion. But I wanted to bring you my opinion and that of many other authors that it's mostly PVL associated," added Dr. Rojo of Complutense University in Madrid.

He was senior author of a multinational European and Israeli prospective study of risk factors associated with the severity of invasive community-acquired *S. aureus* infections in children, with invasive infection being defined as hospitalization for an infection with *S. aureus* isolated from a normally sterile body site such as blood, bone, or cerebrospinal fluid, or *S. aureus* pneumonia. They identified 152 affected children, 17% of whom had severe community-acquired invasive *S. aureus*, defined by death or admission to a pediatric intensive care unit from respiratory failure or hemodynamic instability.

The prevalence of PVL-positive *S. aureus* infection in the overall invasive infection group was 19%, while 8% of the isolates were MRSA. In a multivariate analysis, PVL positivity was independently associated with a fivefold increased risk of severe *S. aureus* infection, while MRSA was not associated with a significantly increased risk. The other independent risk factors for severe outcome were pneumonia, with an adjusted 13-fold increased risk, and leukopenia at admission, with an associated 18-fold risk (Clin Microbiol Infect. 2016 Jul;22[7]:643.e1-6).

Of note, the virulence of PVL stems from the pore-forming toxin's ability to lyse white blood cells. Because a leukocyte count is always available once a patient reaches the ED, severe leukopenia as defined by a count of less than 3,000 cells/mm^3 at admission becomes a useful early marker of the likely severity of any case of *S. aureus* invasive disease, according to Dr. Rojo.

He highlighted four key syndromes involving severe invasive *S. aureus* infection in previously healthy children and adoles-

Commentary by Dr. Bryant / Anyone who has cared for a patient with severe, invasive *Staphylococcus aureus* infection understands the desire to do more. "J.J." is a healthy 9-year-old who is the pitcher on his baseball team. Last spring, he told his parents that he was too tired to eat dinner. They suspected he might be coming down with a virus. He complained of mild ankle pain, which they attributed to a busy week filled with near-daily baseball practice. Overnight, J.J. developed a fever of 104° F and he had worsening pain that made it impossible to walk to the bathroom on his own. By morning, he was difficult to arouse and his parents rushed him to hospital where he was ultimately diagnosed with extensive myositis of his right leg and osteomyelitis of his tibia. He required mechanical ventilation, continuous infusion of epinephrine to support his blood pressure. Multiple blood cultures grew methicillin-resistant *S. aureus*, in the setting of aggressive antibiotic therapy. He ultimately recovered completely with serial surgeries to drain infection from his leg. He never received intravenous immunoglobulin (IVIG).

As Dr. Rojo points out, there is a theoretical basis for using IVIG to treat severe invasive *S. aureus* infection. James B Wood and colleagues at Vanderbilt University in Nashville, Tenn. showed that 24 distinct lots of IVIG contained functional antibodies against LukAB, a pore-forming toxin that is produced abundantly by all disease-causing isolates of *S. aureus* and contributes to the pathogen's ability to evade the human innate immune response (Antimicrob Agents Chemother. 2017 Oct 24;61[11]. pii: e00968-17).

They also found that not all lots of IVIG are created equal and there was significant variability in actual neutralization of toxin. In describing the use of IVIG for severe bacterial infection Wood et al. noted that "... a clear understanding of the mechanism of action and of the contents of the product is lacking. Further investigation of these mechanisms will be important to understand the clinical situations in which IVIG may be most useful."

From a practical standpoint, there still is a lot we don't know about IVIG in this setting. What is the optimal dose? While IVIG is generally regarded as very safe, it carries some of the same risks as other blood products, including transfusion-related reactions and the potential for anaphylaxis. It is expensive. If it decreases mortality, it may be cost effective. What about if the benefits are more modest? I have to agree that well-designed clinical trials are needed before we start to use IVIG in the empiric treatment of all severe *S. aureus* disease.

cents that entail a high likelihood of being PVL positive and should cause physicians to run – not walk – to start appropriate empiric therapy. He also described the treatment regimen that he and other European thought leaders recommend for severe PVL-positive *S. aureus* invasive infections.

The microbiologic diagnosis of PVL can be made by ELISA (enzyme-linked immunoassay) to detect the toxin in an *S. aureus* isolate, by a rapid monoclonal antibody test, or by polymerase chain reaction to detect PVL genes in an *S. aureus* isolate. But don't wait for test results to initiate treatment because these are high-mortality syndromes, he advised.

"Many people tell me, 'My lab doesn't have a way to diagnose PVL.' And it's true, it's not available in real life at many hospitals. My message to you is that you don't need to wait for a microbiological diagnosis or the results to come back from a sample you have sent to the reference lab in the main referral center. We can base our diagnosis and decision to treat on clinical grounds if we focus on these four very uncommon syndromes involving invasive *S. aureus* infection. I think if you have any child with these symptoms you have to manage them on the assumption that PVL is present," said Dr. Rojo, principal investigator of the European Project on Invasive *S. aureus* Pediatric Infections.

The four key syndromes

The four syndromes are severe *S. aureus* pneumonia, severe *S. aureus* osteomyelitis, *S. aureus* osteomyelitis complicated by deep vein thrombosis, and invasive *S. aureus* infection plus shock.

- **Severe *S. aureus* pneumonia**. Investigators at Claude Bernard University in Lyon, France, have done extensive pioneering work on severe PVL-positive *S. aureus* invasive infections in children. In an early paper, they highlighted the characteristics that distinguish severe PVL-positive pneumonia: it typically occurs in previously healthy children and adolescents without underlying comorbid conditions, and it is often preceded by a influenzalike syndrome followed by an acute severe pneumonia with hemoptysis. Mortality was very high in this early series, with nearly half of the patients being dead within the first several days after admission (Lancet. 2002 Mar 2;359[9308]:753-9).
- **Severe osteomyelitis**. Investigators at Baylor College of Medicine, Houston, were among the first to observe that osteomyelitis caused by PVL-positive strains of *S. aureus* are associated with more severe local disease, with multiple affected areas, bigger abscesses, a greater systemic inflammatory response, and more surgeries required compared with osteomyelitis caused by PVL-negative *S. aureus* (Pediatrics. 2006 Feb;117[2]:433-40).
- **Osteomyelitis with deep vein thrombosis**. When a child hospitalized for acute hematogenous osteomyelitis from *S. aureus* develops difficulty breathing, that's a red flag for a severe PVL-positive infection involving deep vein thrombosis. Indeed, investigators at the Leeds (England) General Infirmary have reported that deep vein thrombosis in the setting of *S. aureus* osteomyelitis is associated with a greater than eightfold increased likelihood of a PVL-positive infection (Br J Hosp Med [Lond]. 2015 Jan;76[1]:18-24). Also, patients with PVL-positive osteomyelitis and deep vein thrombosis are prone to formation of septic emboli.
- **Osteomyelitis with septic shock**. The Lyon group compared outcomes in 14 pediatric patients with PVL-positive *S. aureus* osteomyelitis and a control group of 17 patients with PVL-negative disease. All 14 PVL-positive patients had severe sepsis and 6 of them had septic shock. In contrast, none of the controls did. Median duration of hospitalization was 46 days in the PVL-positive group, compared with 13 days in controls (Pediatr Infect Dis J. 2007 Nov;26[11]:1042-8).

Bruce Jancin/MDedge News

Dr. Pablo Rojo

Treatment

No randomized trials exist to guide treatment, but Dr. Rojo recommends the protocol utilized by the Lyon group: a bactericidal antibiotic – vancomycin or a beta-lactam – to take on the *S. aureus*, coupled with a ribosomally active antibiotic – clindamycin or linezolid – to suppress the PVL toxin's virulence expression. The French group cites both in vitro and in vivo evidence that clindamycin and linezolid in their standard dosing have such an antitoxin effect (Clin Microbiol Rev. 2017 Oct;30[4]:887-917).

In addition, Dr. Rojo recommends utilizing any of the commercially available intravenous immunoglobulin (IVIG) products on the basis of work by investigators at Vanderbilt University in Nashville, Tenn., who have demonstrated that these products contain functional neutralizing antibodies against *S. aureus* leukocidins. This observation provides a likely explanation for anecdotal reports of improved outcomes in IVIG-treated patients with toxin-associated staphylococcal disease (Antimicrob Agents Chemother. 2017 Oct 24;61[11]. pii: e00968-17).

Challenged as to when specifically he would use IVIG in light of the global shortage of immunoglobulins, Dr. Rojo replied: "Not in every invasive *S. aureus* infection, but in serious infections that are PVL positive. I think if you have a child with one of these four syndromes who is in a pediatric ICU, you should use it. I mean, the mortality is around 30% in healthy children, so you would not stop from giving it. The risk of giving IVIG is very low, no side effects, so I highly recommend it for these severe cases."

He reported having no financial conflicts.

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Swollen knee in a kid? Above 9, treat for Lyme

BY M. ALEXANDER OTTO
REPORTING FROM IDWEEK 2018

SAN FRANCISCO – There's no need to wait for Western blot results to differentiate Lyme arthritis from septic arthritis in children, as long as your lab, like many, uses the Liaison *Borrelia burgdorferi* assay, according to investigators at the University of Minnesota, Minneapolis.

Acute, isolated monoarthritis presents with a single swollen joint and pain whether it's caused by Lyme disease or infection, so it's hard to tell them apart. Current guidelines recommend a two-tier approach to diagnose Lyme arthritis, an initial blood screen followed by Western blot confirmation. Screening results come back in a few hours, but Western blot confirmation can take days.

In the meantime, children are treated presumptively for the more concerning diagnosis – septic arthritis – which means hospitalization, surgical drainage, and IV antibiotics. Those who turn out to have Lyme are exposed to the risks and costs of unnecessary treatment and delays to proper diagnosis and doxycycline.

When "kids come in with a swollen knee, maybe 10% or 15% end up in the hospital being treated for septic arthritis that they never had. I wanted to see if we can diagnose Lyme arthritis more quickly," said lead investigator Bazak Sharon, MD, a pediatric infectious disease specialist at the university's Masonic Children's Hospital.

M. Alexander Otto/MDedge News

Dr. Bazak Sharon

Masonic and its affiliated health system use the Liaison *Borrelia burgdorferi* assay (DiaSorin) to screen for Lyme, and a careful parsing of the results seems to solve the problem.

Liaison is a chemiluminescence immunoassay that uses light to measure IgM and IgG antibodies to a *B. burgdorferi* surface protein in serum samples. Results are reported as relative light units (RLUs); below 0.9 RLUs is negative; 0.9-1.1 is equivocal, and more than 1.1 is positive.

It's where patients fall in the range of positivity that matters when it comes to differentiating Lyme from septic arthritis, Dr. Sharon said at ID Week, an annual scientific meeting on infectious diseases (Clin Vaccine Immunol. 2008 Dec;15[12]:1796-804).

He and his team reviewed 60 cases of acute, isolated monoarthritis culled from more than 700 children who presented with joint complaints from 2011 to 2016; 47 had Lyme arthritis confirmed by Western blot; 13 had septic arthritis.

It turned out that "every single patient with a" Liaison value of 9 RLUs or higher was confirmed on Western blot for Lyme. "Under 9, there was not a single case of Lyme arthritis," Dr. Sharon said. Three other patients with acute arthritis also tested positive on the screen, but their RLU values were below 4; two turned out to be trauma related and one was ultimately diagnosed with juvenile idiopathic arthritis. Western blots were negative in all three.

The RLU number reported on the screening test "appears to correlate very well with Lyme arthritis. In an otherwise healthy child presenting with acute joint swelling, utilizing this screening test can confirm clinical suspicion of Lyme arthritis within hours, and prevent the potential harmful interventions accompanying a misdiagnosis of septic arthritis. Just do the screening. If it comes up above 9, you've got Lyme arthritis," and don't need to wait for Western blot results to treat, Dr. Sharon said.

In other words, above 9, treat for Lyme.

The investigators plan to delve further into their results with sensitivity/specificity and other analyses before publishing. Ultimately, "my goal is to have a better diagnosis algorithm for kids who present with acute, isolated monoarthritis," Dr. Sharon said.

There was no industry funding for the work, and the investigators didn't have any disclosures.

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Commentary by Dr. Bryant / Lyme disease is the most common vector-borne disease in the United States, and in Lyme endemic areas, this is relatively common cause of monoarticular arthritis. Because clinical criteria cannot reliably distinguish Lyme arthritis from other causes of joint effusion – including septic arthritis – serologic testing is required.

The Liaison test studied by Sharon et al. detects IgG and IgM antibodies against VlsE, a surface lipoprotein of *Borrelia burgdorferi*. This test has performed well in modified two-tiered algorithms that utilize two different enzyme-linked immunosorbent assay (ELISA or EIA) tests rather than the standard two-step testing that includes confirmatory immunoblots. At the present time, it is not recommended as the sole test for the diagnosis of Lyme arthritis, but studies like this one are important to help inform future treatment guidelines.

SOURCE: Sharon B et al. 2018. ID Week, Abstract 286.

Additional training may be warranted for clinicians administering DTaP

BY JILL D. PIVOVAROV
FROM PEDIATRICS

Additional training may be needed for providers who administer DTaP vaccine to prevent errors in vaccination, but there are no new or unexpected safety concerns surrounding the DTaP vaccine itself, reported Pedro Moro, MD, MPH, of the Centers for Disease Control and Prevention's National Center for Immunization and Respiratory Diseases and his associates in Pediatrics.

After Dr. Moro and his associates performed an automated analysis of all reports included in the Vaccine Adverse Event Reporting System (VAERS), which is coadministered by the CDC and the Food and Drug Administration, as well as a clinical review of reported deaths and a random sampling of serious reports in the database, they concluded that safety findings concerning DTaP were consistent with those from prelicensure trials and postlicensure studies.

A total of 50,157 reports involving DTaP vaccines Jan. 1, 1991, through Dec. 31, 2016, were included in the authors' data mining of VAERS. They set out to identify DTaP adverse events occurring more frequently than expected in children up to 7 years of age.

DTaP vaccines, which included Infanrix, Daptacel, Pediarix, Kinrix, and Pentacel, were coadministered with one or more other vaccines in 43,984 (88%) of cases reported; of the reports included in the data mining, 5,627 (11%) were classified as serious, including 844 (2%) deaths. Of all reports received in the prelicensure clinical trials, injection site reactions and systemic reactions, such as fever and vomiting, were the most common reactions to DTaP vaccine.

In a 5% random sample of the 4,783 serious nondeath reports included in the study, 25% were neurologic, 23% gastrointestinal, and 20% were caused by general disorders and vaccine site conditions. Fully 80% of those flagged as neurologic were seizure related. In another 79%, for which intussusception was the most common gastrointestinal condition, all but two cases had rotavirus vaccine coadministered with DTaP. Altogether, there were 182 cases of anaphylaxis reported.

Serious events were characterized as death, life-threatening illness, hospitalization, lengthening of existing hospital stay, or permanent disability. In cases of death, reports that followed DTaP vaccine were manually reviewed by a physician, who evaluated autopsy report, death certificate, or medical records. The authors also included in their evaluation of records any reports of postvaccine anaphylaxis.

Of the 844 deaths, death certificates, autopsy reports, or medical records were obtained for 86%. Among these, sudden infant death syndrome (SIDS) was found to be the most frequent cause of death in 48%; of these, 62% were male infants, and 91% were infants under 6 months of age.

"It would not be uncommon to observe a coincidental close temporal relationship between vaccination and SIDS because this condition peaks at a time when children receive a relatively large number of recommended vaccinations," said Dr. Moro and his associates. "There is a large body of evidence in which it is shown that vaccination is not causally associated with SIDS."

The authors identified disproportional reporting for injection site reactions, as well as other events and conditions, to which they attribute, at least in part, administration of the wrong vaccine or formulation and administration at the wrong site. Such mistakes can be lessened or even prevented with provider education and training on appropriate recommendations and package insert specifications put forth by the CDC's Advisory Committee on Immunization Practices, they advised.

The authors had no relevant financial disclosures. The study was funded by the CDC and the FDA.

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SOURCE: Moro P et al. Pediatrics. 2018. doi: 10.1542/peds.2017-4171.

Commentary by Dr. Bryant / We can be reassured by the data from Moro et al. that available pertussis vaccines are safe when used as directed. The most striking finding in this study related to the disproportional reporting of injection site reactions and other adverse events thought to be associated with administration of the wrong vaccine or formulation and administration of vaccine at the wrong site.

A 2018 report analyzing data reported to the Institute for Safe Medication Practices National Vaccine Errors Reporting Program suggests that reducing vaccine administration errors should be a priority. In 2017, 575 events were reported, 100 more than in previous years. Errors involved the wrong vaccine (23%), wrong dose (19%), expired vaccines or contamination/deterioration of the product (19%), and administration at the wrong age (17%). DTaP and inactivated poliovirus vaccine were cited in 9% of the reports and DTaP was the second most common vaccine involved in errors. Unfamiliarity with indicated patient ages for the product was a contributing factor in nearly one-third of cases.

The American Academy of Pediatrics has published guidance to reduce vaccine administration errors on its website, focusing on the seven rights: Right patient; right vaccine or diluent; right time; right dosage; right route, needle length, and technique; right site; and right documentation.

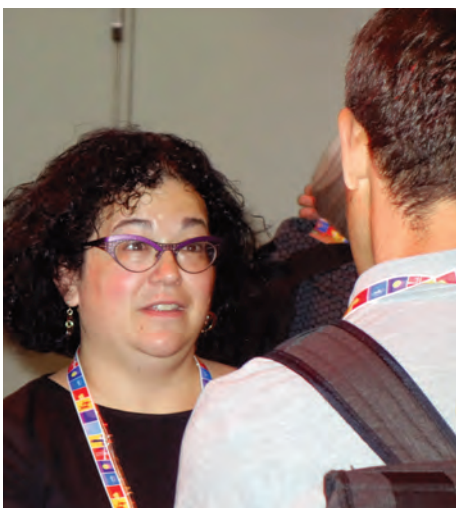
Impact of varicella vaccination on herpes zoster is not what was expected

BY BRUCE JANCIN
REPORTING FROM ESPID 2018

MALMO, SWEDEN – The unique 20-year U.S. experience with pediatric universal varicella vaccination hasn't resulted in the anticipated increase in herpes zoster predicted by the exogenous boosting hypothesis, Lara J. Wolfson, PhD, reported at the annual meeting of the European Society for Paediatric Infectious Diseases.

In fact, the opposite has occurred. And this finding – based upon hard data – should be of considerable interest to European health officials who have been considering introducing universal varicella vaccination into their national health care systems but have refrained because of theoretical concerns raised by the venerable exogenous boosting hypothesis, noted Dr. Wolfson, director of outcomes research at the Merck Center for Observational and Real-World Evidence, Kenilworth, N.J.

The exogenous boosting hypothesis, which dates back to the mid-1960s, holds that reexposure to wild circulating varicella virus prevents development of herpes zoster later in life. Conversely, by vaccinating children against varicella, opportunities are diminished for reexposure to wild type virus among adults who weren't vaccinated against varicella, so the hypothesis would predict an increase in the incidence of herpes zoster that should peak 15-35 years after introduction of universal varicella vaccination.



Bruce Jancin/MDedge News

Dr. Lara J. Wolfson fields questions.

"The same virus that causes varicella in children later reactivates after going dormant in the dorsal root ganglia, and it reactivates as herpes zoster, which is 10 times more severe than chicken pox and leads to 10 times the health care costs. So if in fact implementing a universal varicella vaccine program would lead to an increased incidence of herpes zoster, this would be a bad thing," the researcher explained.

However, the predictive models based upon the exogenous boosting hypothesis are built upon scanty data. And the models have great difficulty in adjusting for the changes in population dynamics that have occurred in the United States and Western Europe during the past quarter century: namely, declining birth rates coupled with survival to an older age.

Dr. Wolfson presented a retrospective study of deidentified administrative claims data from the MarketScan database covering roughly one-fifth of the U.S. population during 1991-2016. Her analysis broke down the annual incidence of varicella and herpes zoster

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Commentary by Dr. Bryant / Before varicella vaccine was added to the U.S. childhood immunization schedule in 1995, approximately 4 million people – the equivalent of an entire birth cohort – developed chickenpox every year, and 100 of them died. An estimated 5%-10% of healthy children developed a complication from infection, most commonly secondary bacterial infection from group A *Streptococcus* or *Staphylococcus aureus*.

The current strategy for the prevention of varicella zoster virus infection with an initial dose of vaccine given at 12-15 months and the second at 4-6 years, has been a resounding success: cases declined 97% between 1995 and 2010. Today, many young pediatricians have never seen a case of chickenpox.

We also know that children vaccinated against varicella have a lower risk of herpes zoster or "shingles." A recently published study of more than 6 million children found that rates of herpes zoster were 78% lower in vaccinated children (Pediatrics. 2019 Jun 10. doi: 10.1542/peds.2018-2917). This is a wonderful bonus for vaccinees. Unfortunately, not all of us were lucky enough to be vaccinated against varicella. More than 99% of people born in the United States who are now 40 years or older have a history of infection with natural varicella and therefore are at risk for zoster. One out of three of us will develop this painful and occasionally debilitating reactivation of the varicella zoster virus.

For reasons that are not entirely clear, rates of herpes zoster have been increasing in the United States. According to the Centers for Disease Control and Prevention, the increases started before varicella vaccine was introduced in the United States; similar increases also were seen in countries that do not routinely vaccinate against chickenpox. The data presented by Wolfson et al. add to the body of evidence demonstrating the benefits of varicella vaccine for those who receive it. They also show that our national strategy of universal immunization against varicella is not bad for the rest of us. We can hope that widespread uptake of shingles vaccine by adults 50 years and older will turn the tide against herpes zoster.

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in three eras: 1991-1995, which was the pre–varicella vaccination period; 1996-2006, when single-dose universal varicella vaccination of children was recommended; and 2007-2016, when two-dose vaccination became standard.

The first key study finding was that herpes zoster rates in the United States already were climbing across all age groups back in 1991-1995; that is, before introduction of universal varicella vaccination. Why? Probably because of those changes in population dynamics, although that's speculative. The second key finding was that contrary to the exogenous boosting hypothesis prediction that the annual incidence of herpes zoster would accelerate after introduction of universal varicella vaccination, the rate of increase slowed, then plateaued during 2013-2016, most prominently in individuals aged 65 or older.

"In comparing the pre–universal varicella vaccination period to the one- or two-dose period or the total 20 years of vaccination, what we saw consistently across every age group is that herpes zoster is decelerating. There is actually less increase in the rate of herpes zoster than before varicella vaccination," Dr. Wolfson said.

Uptake of the herpes zoster vaccine, introduced in the United States in 2008, was too low during the study years to account for this trend, she added.

Most dramatically, the incidence of herpes zoster among youths under age 18 years plummeted by 61.4%, from 88 per 100,000 person-years in 1991-1995 to 34 per 100,000 in 2016.

And of course, varicella disease has sharply declined in all age groups following introduction of universal pediatric varicella vaccination, Dr. Wolfson observed.

Her study was supported by her employer, Merck.

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Combo respiratory pathogen tests miss pertussis

BY M. ALEXANDER OTTO
REPORTING FROM PAS 2019

BALTIMORE – Comprehensive respiratory pathogen panels (RPAN) cannot be relied on to detect pertussis, a study found.

Respiratory pathogen panels are popular because they test for many things at once, but providers have to know their limits, said Colleen Mayhew, MD, a pediatric emergency medicine fellow at the University of Michigan, Ann Arbor.

"Should RPAN be used to diagnosis pertussis? No," she said at the Pediatric Academic Societies annual meeting. RPAN was negative for confirmed pertussis 44% of the time in the study.

"In our cohort, [it] was no better than a coin flip for detecting pertussis," she said. Even when it missed pertussis, it still detected other pathogens, which raises the risk that symptoms might be attributed to a different infection. "This has serious public health implications."

"The bottom line is, if you are concerned about pertussis, it's important to use a dedicated pertussis PCR [polymerase chain reaction] assay, and to use comprehensive respiratory pathogen testing only if there are other, specific targets that will change your clinical management," such as mycoplasma or the flu, Dr. Mayhew said.

In the study, 102 nasopharyngeal swabs positive for pertussis on standalone PCR testing – the university uses an assay from Focus Diagnostics – were thawed and tested with RPAN.

Dr. Mayhew

RPAN was negative for pertussis on 45 swabs (44%). "These are the potential missed pertussis cases if RPAN is used alone," she said. RPAN detected other pathogens, such as coronavirus, about half the time, whether or not it tested positive for pertussis.

"Those additional pathogens might represent coinfection, but might also represent asymptomatic carriage." It's impossible to differentiate between the two, she noted. In short, "neither positive testing for other respiratory pathogens, nor negative testing for pertussis by RPAN, is reliable for excluding the diagnosis of pertussis. Dedicated pertussis PCR testing should be used for diagnosis."

There was no industry funding. Dr. Mayhew didn't report any disclosures.

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Commentary by Dr. Bryant / Understanding the strengths and limitations of laboratory tests is an essential component of diagnostic stewardship. Comprehensive respiratory pathogen panels may be attractive because they provide a lot of information in a short amount of time. Nevertheless, at the University of Michigan, Ann Arbor, where this study was conducted, the dedicated pertussis polymerase chain reaction (PCR) is less expensive and more sensitive for the detection of pertussis. The same is true in the hospital system where I practice, although results from the dedicated pertussis PCR are generally available in about 1 day, compared with a few hours for the respiratory pathogen panel.

Mayhew et al. make a simple, actionable recommendation: When pertussis is suspected, use a dedicated PCR test rather than a comprehensive respiratory pathogen panel. Remember to keep a high index of suspicion for pertussis when patients present with prolonged cough illness without a clear alternative diagnosis. Classic symptoms – paroxysmal cough, inspiratory whoop, and post-tussive emesis – may be absent, especially in adolescents and adults.

French warn of pneumococcal meningitis upsurge

BY BRUCE JANCIN
REPORTING FROM ESPID 2018

MALMO, SWEDEN – A French national study has documented a sharp increase in pneumococcal meningitis since 2015 in children under age 15 years.

The culprit has been identified as serotype 24F, which is not covered by the infant 13-valent conjugate pneumococcal vaccine (PCV13), Naim Ouldali, MD, reported at the annual meeting of the European Society for Paediatric Infectious Diseases.

The rapid emergence of serotype 24F has been accompanied by a disturbing change in its penicillin susceptibility. Indeed, penicillin resistance was present in only 18% of serotype 24F isolates in France during 2000-2014, then jumped to 74% during 2015-2016, according to Dr. Ouldali of René Descartes University in Paris.

"PCV13 has strongly reduced the pneumococcal meningitis burden in children, but its benefit now seems to be jeopardized, at least in France. So serotype 24F could become a major concern in the coming years because of its characteristics. And now the question is, is this emergence an epidemic phenomenon or not? And if it's confirmed in future studies and in other countries, probably it should drive the development of next-generation PCV formulations," he said.

Dr. Ouldali presented a population-based interrupted time-series analysis of a nationwide prospective survey conducted in France during 2001-2016. He noted that the Cochrane Collaboration has deemed this study design second only to the randomized controlled trial in terms of quality of evidence.

The study, which included 227 French pediatric wards and 168 microbiology departments, identified 1,778 children under age 15 years with pneumococcal meningitis. This is believed to be more than 60% of all cases that occurred in the country during the study years.

The purpose of the study was to determine the impact of implementation of routine PCV13 as part of the national vaccine strategy. Rates of PCV13 coverage in French children are very high: in excess of 90% during 2015 to 2016.

Implementation of PCV13 led to a dramatic 38% reduction in the monthly incidence of pneumococcal meningitis, from 0.12 cases per 100,000 children before PCV13 to a low of 0.07 cases per 100,000 in December 2014. But after that the rate rebounded sharply, by 2.3% per month during 2015-2016, to a high of 0.13 cases per 100,000 per month by the end of 2016. Drilling down into the data, Dr. Ouldali and his coinvestigators learned that the resurgence of pneumococcal meningitis was due largely to the emergence of serotype 24F.

"This serotype is of particular concern because of two characteristics: First, it is already known to have a high disease potential – one of the highest, along with serotype 12F – and second, this rapid emergence was accompanied by a change in its penicillin susceptibility," he noted.

Most of the French rebound in pneumococcal meningitis has occurred in children under 2 years of age. Of note, German investigators also have recently reported a rebound in invasive pneumococcal disease in German children under 16 years of age. Non-PCV13 serotypes accounted for 84% of all invasive pneumococcal disease during 2015-2016, with serotypes 10A and 24F leading the way. As in France, most of the resurgence has involved children less than 2 years old. However, unlike in France, most of the German increase has been in nonmeningitis forms of invasive pneumococcal disease (Vaccine. 2018 Jan 25;36[4]:572-7).

In response to a question from a concerned audience member, Dr. Ouldali said that, while the penicillin susceptibility of serotype 24F has taken a sharp turn for the worse, cephalosporin susceptibility has not. "To date, we have not seen any cephalosporin-resistant strains. To date, there is no need to use vancomycin," he said. Dr. Ouldali said the next step he and his colleagues plan to take is to see if there is a clonal expansion or a particular underlying genetic pattern which could explain the explosive emergence of 24F.

The study was funded by a research grant from Pfizer and by the French Pediatric Infectious Diseases Group.

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Commentary by Dr. Bryant / Pneumococcal disease surveillance and serotyping of invasive isolates, as Ouldali et al. have done, are critically important to inform future vaccine development strategies. The truth is, there are more than 90 different pneumococcal serotypes, and we can currently prevent 13 of them with the conjugate vaccine (PCV13).

What's the answer? Higher-valency vaccines are in the clinical pipeline. Phase 2 trials of a 15-valent pneumococcal vaccine containing serotypes currently in PCV13 plus 22F and 33F look promising, but that won't address the problem described by Dr. Ouldali and other investigators. U.S. researchers participating in the United States Pediatric Multicenter Pneumococcal Surveillance Group previously have described a recent increase in invasive pneumococcal disease secondary to serotype 35B, another nonvaccine serotype that has high rates of penicillin nonsusceptibility (J Clin Microbiol. 2017;55[3]:724-34).

Use of PCV vaccines has had a dramatic public health impact, decreasing disease in vaccinated individuals as well as in unvaccinated individuals though herd effects. Further reductions in invasive pneumococcal disease will require broader protection. Future strategies may involve purified protein vaccines that incorporate antigens shared by nearly all pneumococci, irrespective of serotype or whole-cell vaccines. Michael E. Pichichero, MD, has written an excellent review of this topic entitled "Pneumococcal whole-cell and protein-based vaccines: Changing the paradigm" (Expert Rev Vaccines. 2017;16[12]:1181-90).

Which infants with invasive bacterial infections are at risk for adverse outcomes?

BY DOUG BRUNK
REPORTING FROM PAS 2018

TORONTO – Among infants up to 60 days old with an invasive bacterial infection, adverse outcomes are associated with prematurity, ill appearance, and bacterial meningitis, a multicenter retrospective analysis found.

"Young infants are susceptible to serious bacterial infections, particularly when they're less than 60 days of age," Christopher Pruitt, MD, said at the annual Pediatric Academic Societies meeting. "Among these infants, bacteremia and bacterial meningitis, also referred to as invasive bacterial infections, are associated with higher rates of morbidity and mortality."

While many studies have reported the rates of serious bacterial infections in infants, few have examined clinical outcomes for infants with invasive bacterial infections who are initially evaluated in the ED, said Dr. Pruitt, who directs research for the division of pediatric emergency medicine at the University of Alabama at Birmingham. To this end, he and his associates at 11 children's hospital emergency departments in the United States set out to describe the outcomes of infants up to 60 days old with invasive bacterial infections and to identify factors associated with adverse outcomes.

In this 5-year study, they included infants aged 60 days and younger who presented to the ED with pathogen growth in the blood and/or cerebrospinal fluid (CSF). Subjects were excluded from analysis if their cultures were treated clinically as contaminants. "If there was bacterial growth only from CSF broth cultures, we excluded these infants if there was no associated CSF pleocytosis and if there was an associated negative blood culture," Dr. Pruitt explained. "If one of these criteria was absent, the infant was considered to have bacterial meningitis."

The primary outcome measure was occurrence of an adverse clinical outcome within 30 days following the index ED visit. Adverse outcomes were defined as use of mechanical ventilation, vasoactive medications, any neurologic sequelae, and death.

Of the 442 infants in the final analysis, 80% had bacteremia, 14% had bacterial meningitis plus bacteremia, and 6% had bacterial meningitis only. "For purposes of this study, patients with bacterial meningitis with or without bacteremia were categorized as having bacterial meningitis," Dr. Pruitt said.

He and his associates found that 14.5% of infants had one or more adverse outcomes. Adverse outcomes occurred in 39% of infants with bacterial meningitis, compared with 8% of infants with isolated bacteremia. Need for mechanical ventilation, vasoactive medications, and neurologic disability also was more common among infants with bacterial meningitis than it was among children with isolated bacteremia. There were 10 deaths overall, which amounted to about 2% in both groups.

On multivariate analysis, the rate of adverse outcomes was significantly higher for patients with bacterial meningitis than it was for those with isolated bacteremia (adjusted odds ratio, 8.8), for premature versus term infants (AOR, 5.9), and for infants who were ill appearing versus non–ill appearing (AOR, 3.9).

"When looking at the most common scenario – a full-term infant without an ill appearance, and bacteremia as opposed to bacterial meningitis – 3 of these 219 infants, or 1.4%, had an adverse outcome," said Dr. Pruitt of Children's of Alabama in Birmingham. "And there were no deaths."

He also reported that 12 infants with invasive bacterial infections were discharged from the index ED visit without antimicrobial treatment. All had bacteremia; none had an adverse outcome.

The study was supported in part by a grant from the National Institutes of Health. Dr. Pruitt reported having no financial disclosures.

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Commentary by Dr. Bryant / It's somewhat intuitive that young infants with bacterial meningitis have worse outcomes than those who have bacteremia alone. Pruitt et al. acknowledge that in their paper published earlier this year (J Pediatr. 2019 Jan;204:177-82.e1). Nevertheless, their findings have the potential to inform clinical practice. These data may help physicians better evaluate the risks and benefits of lumbar puncture in young infants, and explain these to parents who are understandably nervous about their babies undergoing an invasive procedure. They may help physicians on the front line explain the potential significance of abnormal cerebrospinal fluid findings in this population. Finally, the quantitation of adverse outcomes may help inform the decision about where young infants with meningitis should receive care after they leave the ED.

This research also highlights the importance of the clinical exam. "Ill appearance" at clinical presentation was statistically associated with adverse outcomes. Ill appearing was defined as any of the following terms appearing in the ED physical exam: "ill appearing," "toxic," "limp," "unresponsive," "gray," "cyanotic," "apnea," "weak cry," "poorly perfused," "grunting," "listless," "lethargic," or "irritable." When I was an intern, a wise upper-level resident told me, "There are kids who are sick and kids who are not sick. You need to learn to recognize the difference." Turns out she was right.