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Pediatric Vaccines & Infectious Diseases

WITH COMMENTARY BY KRISTINA A. BRYANT, MD

The Stillmans are advocates for meningococcal disease vaccination. They are not healthcare providers. This story is of their own personal experience; other people's experience with meningococcal disease may be different.

IT STARTED AS A HEADACHE— AND ENDED IN TRAGEDY

Emily was a sophomore in college when she called her mom with a headache. They talked for a bit, said "I love you", and then hung up—it was the last time they spoke. By next morning, Emily was in a coma, and within 30 hours, she was gone.

Although meningococcal serogroup B disease (MenB) is uncommon, this is a potential outcome.[1] And if you're not vaccinating appropriate patients in your practice, you might be leaving them vulnerable.

Vaccination may not protect all recipients.

See the potential of MenB with your own eyes

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Reference: 1. Pelton SI. Meningococcal disease awareness: clinical and epidemiological factors affecting prevention and management in adolescents. *J Adolesc Health*. 2010;46:S9-S15.

Why we can't worry about just COVID-19

BY KRISTINA A. BRYANT, MD

For more than a year, a single virus has commanded an extraordinary amount of our attention. We learned about the common and uncommon clinical manifestations of SAR-CoV-2 infection in children (turns out, they are similar to many other viral infections). We've identified post-infectious sequelae in our patients, including multisystem inflammatory syndrome and "long COVID." We have enhanced infection prevention practices in our offices and embraced telehealth. We have begun to recognize and address some health disparities that have long been present but were highlighted by the pandemic.

Maybe, for a short time, we lived under the illusion that there was only one infection that we needed to worry about. With universal masking, social distancing, and in many communities, a prolonged shift to virtual education, many common infections seemed to disappear. Last winter, we prepared for concurrent outbreaks of SAR-CoV-2, influenza, and respiratory syncytial virus (RSV). Curiously, we saw plenty of kids with SARS-CoV-2 but essentially no flu or RSV. I confess: I sometimes found myself humming "where have all the viruses gone?" to the tune of the Pete Seeger classic "Where have all the flowers gone?"

In all seriousness, pediatricians and other pediatric care providers know that we do not have the luxury of worrying about just one pathogen. That's why you won't see any articles about COVID-19 in this supplement, although we have

Dr. Kristina A. Bryant

provided electronic links to some of the best posts from the last year. Instead, you'll see a few articles that you may have missed – ones that may provide a useful perspective on how we move forward providing the best care to children.

From the start of the pandemic to June 17, 2021, more than 4 million children have tested positive for COVID-19 and, according to data compiled by the American Association of Pediatrics, 0.1%-1.9% of these cases were hospitalized. By comparison, more than 2 million children under 5 years of age need medical care for RSV infection annually and 3% of these are hospitalized. Historically, RSV has been the most common medical reason for hospital admission in U.S. children aged less than 2 years. As we go to press, many communities are seeing unusual summertime outbreaks of RSV. Clearly, SARS-CoV-2 is not the only virus with a negative impact on child health.

Less than a year into the pandemic, we celebrated the emergency use authorization of three safe and effective vaccines for SARS-CoV-2. We're immunizing children as young as 12 years of age and studies in younger children are ongoing. I'm hopeful that some of the public-private partnerships that made COVID-19 vaccines possible can be leveraged to accelerate the development of other vaccines. In the interim, a few of the articles in this supplement remind us that vaccine development is often fraught with delays and disappointments. We are 60 years and counting into efforts to bring an RSV vaccine to market. Work on pertussis vaccines began more than a century ago. We have good pertussis vaccines but we need better ones, as you will read in the feature about PERISCOPE.

Early in the pandemic, rates of routine immunizations fell by as much as 90% in some communities. We braced for outbreaks of vaccine-preventable diseases such as measles, and breathed a sigh of relief when they did not materialize. We are not out of the woods yet, though. According to a recent report in the Morbidity and Mortality Weekly Report that examined vaccine administration in 10 U.S. jurisdictions (2021;70:840-5. doi: 10.15585/mmwr.mm7023a2), vaccine doses administered from June to September 2020 initially increased, generally exceeding prepandemic baseline levels. However, this increase was not sustained nor sufficient to "catch up" children and adolescents who were behind.

Of particular concern to me are human papillomavirus vaccination

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We're getting closer to a lifesaving RSV vaccine

BY SARAH STINNISSEN
MDedge News

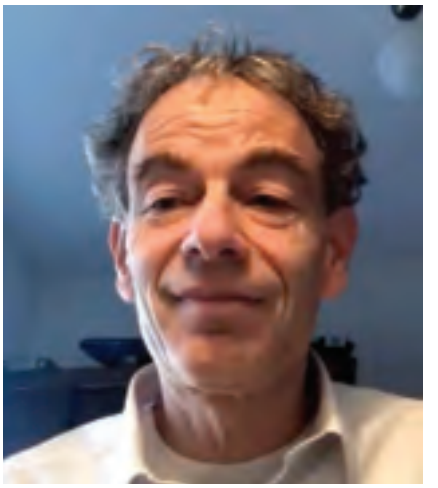
Respiratory syncytial virus vaccine development has progressed rapidly in recent years, and there is hope that an efficacious vaccine soon may be approved.

Louis Bont, MD, PhD, provided an overview of the most recent developments in the complex respiratory syncytial virus (RSV) vaccine landscape at the annual meeting of the European Society for Paediatric Infectious Diseases, held virtually.

RSV imposes significant burden worldwide, with 33 million patients, 3 million hospitalizations, and at least 120,000 deaths, reported Dr. Bont of the Wilhelmina Children's Hospital, University Medical Centre, Utrecht, the Netherlands. Of those deaths, more than 50% are in infants younger than 5 months, and "about 99% of the children dying from RSV live in low- and middle-income countries."

"There are high-risk populations, such as children with prematurity, congenital heart disease, lung disease, and Down syndrome, but about 73% of all children who are hospitalized for RSV infection were previously healthy children," Dr. Bont explained. "So, we need to find a solution for all children to prevent RSV infection."

As observed by Nienke Scheltema in a Lancet Global Health article (Lancet Glob Health. 2017 Oct. doi: 10.1016/S2214-109X(17)30344-3), population distributions of RSV infection mortality show that, regardless of whether children have comorbidities or they are previously healthy, most children die at a very young age, Dr. Bont explained. These data suggest "that a maternal vaccine or an antibody prophylaxis approach from birth onwards or during the first RSV season is the solution for the problem."



Dr. Louis Bont said high-risk populations but also very young and previously healthy children die from RSV.

The path to developing an RSV vaccine has now narrowed its focus onto a structural element of RSV, the prefusion F protein. This shift started with the discovery by Jason McLellan (Science, 2013 [two papers]) that there are two variants of the RSV F-fusion protein: the very stable postfusion conformation and the prefusion active conformation, a metastable protein that exists for a "fraction of a second," Dr. Bont said (J Virol. 2011 Aug. doi: 10.1128/JVI.00555-11; Science. 2013 Nov 1. doi: 10.1126/science.1243283).

"The interesting thing is that epitopes that are visible at the prefusion, metastable state … induce highly neutralizing antibodies, whereas epitopes at the postfusion conformation do not," Dr. Bont explained. "So, by stabilizing the prefusion state, we start inducing neutralizing antibodies that will protect against severe RSV infection, and this is the basic concept of all the vaccine developments currently ongoing."

These RSV vaccine developments fall into five approach types: live-attenuated or chimeric vaccines, vector-based vaccines, monoclonal antibodies, particle-based vaccines, and subunit or protein-based vaccines (Lancet Infect Dis. 2018 Oct. doi: 10.1016/S1473-3099(18)30292-5).

One breakthrough, which was presented at the 2019 ESPID meeting, is the monoclonal antibody nirsevimab. In addition to being nine times more potent than the broadly used antibody palivizumab, it is also more stable; whereas many antibodies have a half-life of 3 weeks, nirsevimab has a half-life of 100 days. "The idea is that a single injection at the start of the RSV season protects children in the first RSV season of their life, a dangerous episode for them." Dr. Bont explained.

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(HPV) rates. Early in the pandemic, many adolescent health visits were deferred and not surprisingly, HPV doses delivered to 13 to 17 year-olds declined a median of 71.3%, compared with doses given during the same time period in 2018 and 2019. During June to September 2020, HPV doses declined by a median of 28.1% in kids of the same age, compared with baseline. As noted by Dr. Szu-Ta Chen and colleagues, we were not meeting our HPV vaccination goals before the pandemic. Now we are even further behind.

An incredible effort is currently underway to immunize adolescents with COVID-19 vaccine. We need to capitalize on this effort to make sure adolescents receive all routinely recommended vaccines, including HPV vaccine. Both the CDC and the AAP have issued guidance that COVID-19 vaccine may be administered concurrently with other routine vaccines. Visit the CDC website and AAP publications to view these documents.

Dr. Bryant is a pediatrician specializing in infectious diseases at the University of Louisville (Ky.) and Norton Childrens' Hospital, also in Louisville. Dr. Bryant had no relevant financial disclosures. Email her at pdnews@mdedge.com.

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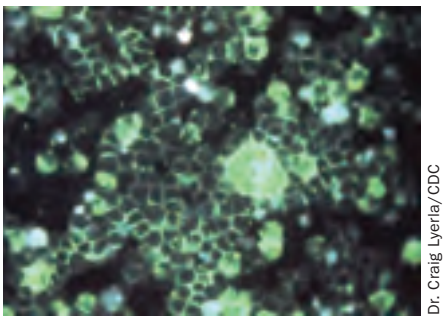
The originators, AstraZeneca and Sanofi Pasteur, have "the vision that every child on this planet should receive a single injection with this antibody in the first season," he explained.

Studies of nanoparticle-based maternal vaccines have also revealed interesting results: Although a phase 3 trial investigating such vaccines didn't achieve its primary endpoint, "interestingly, 15% of all RSV infections were mild, and only 2% were very severe and leading to hypoxemia," Dr. Bont noted. "But if we look at vaccine efficacy, we see the opposite – the vaccine was not very efficacious to prevent mild disease, but very efficacious to prevent severe hypoxemia; actually, this is exactly what you would like to see in a vaccine."

Investigations into live-attenuated and vector-based vaccines have been promising as well, Dr. Bont shared. Studies of live-attenuated vaccines suggest they have a future and that we can move onto their next phase of clinical development, and a study investigating adenoviral vector-based vaccines has demonstrated safety, efficacy, and immunogenicity, though it has also shown that we should anticipate some side effects when using them



Dr. Craig Lyerla/CDC

"But if we look at vaccine efficacy, we see the opposite – the vaccine was not very efficacious to prevent mild disease, but very efficacious to prevent severe hypoxemia; actually, this is exactly what you would like to see in a vaccine."

(J Infect Dis. 2020 Aug 26. doi: 10.1093/infdis/jiaa409).

Simple subunit vaccines for RSV are also being explored – a study of DS-Cav1, a stabilized prefusion F subunit protein candidate vaccine, has shown that it has a superior functional profile, compared with previous pre-F subunit vaccines. However, it seemed to be more efficacious against strains of RSV A than strains of RSV B, the dominant strain.

Dr. Bont also discussed exciting work by Sesterhenn et al., in which they used a computer-based program to develop their own vaccine. Using their in-depth knowledge of the RSV prefusion F protein and a computer program, Sesterhenn et al. developed a trivalent vaccine, produced it, and showed – both in vitro and in monkeys – that such vaccines can work up to the level of preclinical in vivo experiments (bioRxiv, 2020 Feb 14. doi: 10.1101/685867).

"We can now make vaccines behind our computer," Dr. Bont declared. "And the system doesn't only work for RSV vaccines, but also for other pathogens – as long as you have an in-depth molecular knowledge of the target epitope," he added.

Dr. Bont reported the following disclosures: ReSViNET (a nonprofit foundation); investigator-initiated studies with the Bill & Melinda Gates Foundation, AbbVie, MedImmune, and MeMed; participation with Pfizer, Regeneron, and Janssen; and consultancy with GlaxoSmithKline, Ablynx, Novavax, and Janssen.

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Commentary by Dr. Bryant // As noted by Dr. Bont, the highest burden of respiratory syncytial virus (RSV) disease and associated mortality occurs in infants in low- and middle-income countries, but impact on U.S. infants is not insignificant. According the Centers for Disease Control and Prevention, RSV infection annually results in 2.1 million outpatient visits, 500,000 ED visits, and 58,000 hospitalizations in children aged less than 5 years. It is the most common cause for hospital admission in U.S. children aged less than 2 years and hospitalization rates are highest in infants aged less than 6 months.

A paper published last year in the Journal of Infectious Diseases (2020;221:1256-70) highlighted the long-term health effects in the first year of life: Infected preterm and term infants have higher rates of health care resource utilization than uninfected infants for at least 5 years. This includes cumulative rates of physician and ED visits, as well as cumulative hospitalization rates.

Prior to the pandemic, it looked like RSV was on track to be the next vaccine-preventable disease. Although that distinction went to SARS-CoV-2, robust work continues on RSV prevention. As of April 2021, 18 different candidate vaccines were in phase 1, 2, or 3 clinical trials worldwide, and another 14 were in preclinical trials (www.path.org/resources/rsv-vaccine-and-mab-snapshot/).

Work is also continuing on passive immunoprophylaxis, which remains an important strategy for protecting the youngest infants. Nirsevimab is a recombinant monoclonal antibody that works by binding to an epitope on the prefusion conformation of the RSV fusion protein. It has more potent neutralizing activity than palivizumab and a longer half-life, meaning that a single dose could offer protection that lasts for months.

In a placebo-controlled, randomized trial of 1,453 preterm infants, the incidence of medically attended RSV lower respiratory tract infection was 70% lower in recipients who received a single dose of nirsevimab; hospitalizations were nearly 80% lower (N Engl J Med. 2020;383:415-25). Infants were followed for 150 days after dosing, the equivalent of an entire RSV season.

New tool may provide point-of-care differentiation between bacterial, viral infections

BY STEVEN WALKER, MD
MDedge News

The World Health Organization estimates that 14.9 million of 57 million annual deaths worldwide (25%) are related directly to diseases caused by bacterial and/or viral infections.


Ms. Pennisi

The first crucial step in order to build a successful surveillance system is to accurately identify and diagnose disease, Ivana Pennisi reminded the audience at the annual meeting of the European Society for Paediatric Infectious Diseases, held virtually. A problem, particularly in primary care, is differentiating between patients with bacterial infections who might benefit from antibiotics and those with viral infections where supportive treatment is generally required. One solution might be a rapid point-of-care tool.

Ms. Pennisi described early experiences of using microchip technology to detect RNA biomarkers in the blood rather than look for the pathogen itself. Early results suggest high diagnostic accuracy at low cost.

It is known that when a bacteria or virus enters the body, it stimulates the immune system in a unique way leading to the expression of different genes in the host blood. As part of the Personalized Management of Febrile Illnesses study, researchers have demonstrated a number of high correlated transcripts. Of current interest are two genes which are upregulated in childhood febrile illnesses.

Ms. Pennisi, a PhD student working as part of a multidisciplinary team at the department of infectious disease and Centre for Bioinspired Technology at Imperial College, London, developed loop-mediated isothermal amplification (LAMP) assays to detect for the first time host RNA signatures on a nucleic acid–based point-of-care handheld system to discriminate bacterial from viral infection. The amplification reaction is then combined with microchip technology in the well of a portable point-of-care device named Lacewing. It translates the nucleic acid amplification signal into a quantitative electrochemical signal without the need for a thermal cycler.

The combination of genomic expertise in the section of paediatrics lead by Michael Levin, PhD, and microchip-based technologies in the department of electrical and electronic engineering under the guidance of Pantelis Georgiou, PhD, enabled the team to overcome many clinical challenges.

Ms. Pennisi presented her team's early experiences with clinical samples from 455 febrile children. First, transcription isothermal amplification techniques were employed to confirm bacterial and viral infections. Results were then validated using standard fluorescent-based quantitative polymerase chain reaction (PCR) instruments. In order to define a decision boundary between bacterial and viral patients, cutoff levels were determined using multivariate logistic regression analysis. Results then were evaluated using microarrays, reverse transcriptase PCR (RT-PCR), and the eLAMP to confirm comparability with preferred techniques.

In conclusion, Ms. Pennisi reported that the two-gene signature combined with the use of eLAMP technology in a point-of-care tool offered the potential of low cost and accurate discrimination between bacterial and viral infection in febrile children. She outlined her vision for the future: "The patient sample and reagent are loaded into a disposable cartridge. This is then placed into a device to monitor in real time the reaction and share all the data via a Bluetooth to a dedicated app on a smart phone. All data and location of the outbreak are then stored in [the] cloud, making it easier for epidemiological studies and tracking of new outbreaks. We hope that by enhancing the capability of our platform, we contribute to better patient care."

Ms. Pennisi had no relevant financial disclosures.

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Commentary by Dr. Bryant // It is a familiar scenario for many parents. You have been up half the night with a sick child. The child's pediatrician, after a careful exam, reassures you confidently that "it's just a virus" and no treatment is needed other than supportive care. You trust the doctor, but you can't help but worry and wish for some sort of test to support the diagnosis.

Maybe you have been that pediatrician. The child has copious yellow nasal drainage and a barky cough. The ears look normal and the lungs are clear. You wish you felt quite as confident as you sounded when reassuring the parent. All signs point to viral infection but the tests for influenza, respiratory syncytial virus, and SARS-CoV-2 are negative. Those of a certain age may think of enviously of Star Trek's Dr. "Bones" McCoy and his medical tricorder, an imaginary device that allowed him to instantly and accurately diagnose medical conditions.

Antibiotics are commonly prescribed for ambulatory children with acute upper respiratory tract infections and up to one-third of these – more than 10 million prescriptions annually in the United States – are inappropriate. Point-of-care tools as those being developed by Ms. Pennisi and colleagues could be a boon for antimicrobial stewardship.

Metapneumovirus infections clinically indistinguishable from flu, RSV

BY NEIL OSTERWEIL
MDedge News

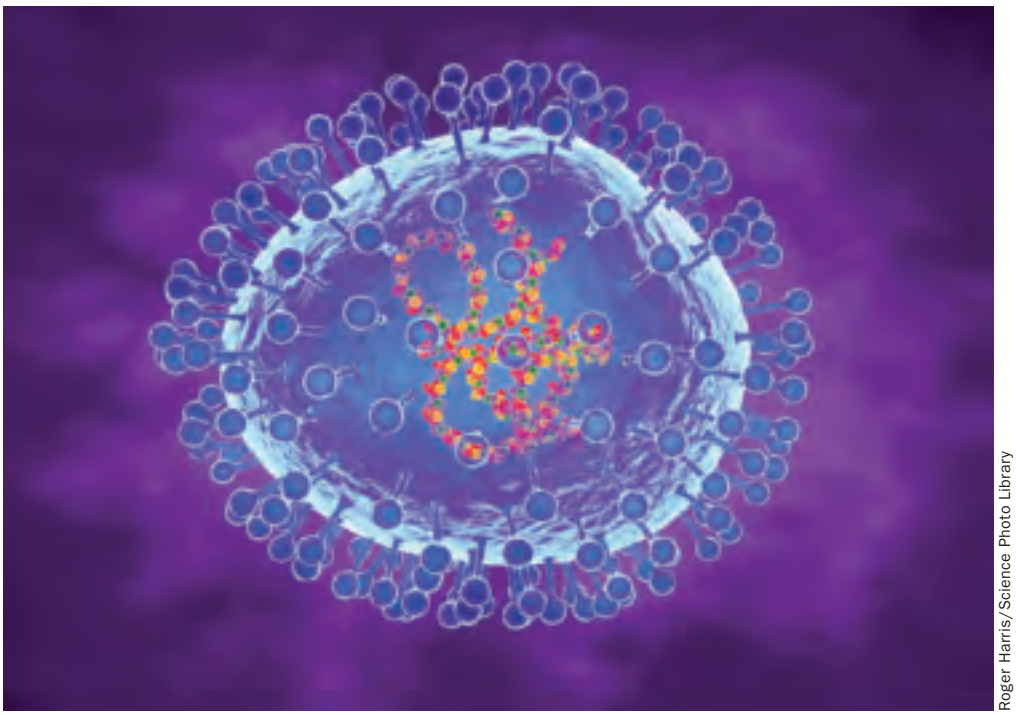
The all-consuming news about SARS-CoV-2 and COVID-19 has overshadowed other viral pathogens that are the cause of severe or fatal lower respiratory infections (LRI) including human metapneumovirus (HMPV).

"MPV is really a leading cause of LRI not just in children but in adults, with high mortality rates in the frail elderly, long-term care facilities, and cancer patients with pneumonia," said John Williams, MD, from the department of pediatric infectious diseases at the University of Pittsburgh Medical Center.

"Right now we have no effective antivirals. There are monoclonal antibodies in development that my group and others have discovered. In fact, some of these treat MPV and RSV [respiratory syncytial virus], so we may have good options," he said in an online presentation during an annual scientific meeting on infectious diseases.

The virus preys, wolf-like, on the most vulnerable patients, including children and frail elderly adults, as well as other adults with predisposing conditions, he said.

HMPV causes acute respiratory illnesses in approximately 2%-11% of hospitalized adults, 3%-25% of organ transplant recipients or cancer patients, 4%-12% of chronic obstructive pulmonary disease exacerbations and 5%-20% of asthma exacerbations, and it has been identified in multiple outbreaks at long-term care facilities.



Roger Harris/Science Photo Library

Relative newcomer

Metapneumovirus was isolated and discovered from children with respiratory tract disease in the early 2000s. Once included in the family of paramyxoviruses (including measles, mumps, Nipah virus, and parainfluenza virus 1-4), HMPV and RSV are now classified as pneumoviruses, based on gene order and other characteristics, Dr. Williams explained.

Various studies have consistently placed the prevalence of HMPV ranging from 5%-14% in young children with LRI, children hospitalized for wheezing, adults with cancer and LRI, adults with asthma admissions, children with upper respiratory infections, and children hospitalized in the United States and Jordan for LRI, as well as children hospitalized in the

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Commentary by Dr. Bryant // In 2018, globally, there were more than 14 million cases of human metapneumovirus acute lower respiratory tract infection in children aged less than 5 years. According to a recent systematic review and modeling study, there were an estimated 643,000 human metapneumovirus–associated hospital admissions, 7,700 human metapneumovirus–associated in-hospital deaths, and 16,100 overall (hospital and community) human metapneumovirus–associated acute lower respiratory tract infection deaths. About 64% of the in-hospital deaths occurred in children aged less than 6 months and nearly 80% of these occurred in low- and low-middle–income countries.

Clearly, both preventive and therapeutic strategies are needed. Part of the solution might rest with the messenger RNA vaccine construct that was used to develop two highly effective vaccines against SARS-CoV-2. Moderna has developed a combined human metapneumovirus and human parainfluenza virus type 3 vaccine that is currently enrolling patients in phase 1B clinic trials. According to information posted at clinicaltrials.gov, the study will assess the safety and immunogenicity of two dose levels of mRNA-1653 in healthy adults (18-49 years of age) and three dose levels in children (12-59 months of age) with serologic evidence of prior exposure.

Seeking new vaccines against whooping cough: The PERISCOPE project

BY STEVEN WALKER, MD
MDedge News

Although there is an effective vaccine against *Bordetella pertussis*, whooping cough remains a leading cause of death. Cases are increasing, and scientists face challenges in developing new vaccines.

In a key research session at the start of the annual meeting of the European Society for Paediatric Infectious Diseases, held virtually, Dimitri Diavatopoulos, PhD, associate professor at the Radboud University Medical Centre Nijmegen, the Netherlands, summarized the pertussis vaccination problem and what the Pertussis Correlates of Protection Europe (PERISCOPE) project seeks to achieve. Dr. Diavatopoulos has a long-standing interest in pertussis and immunity and will soon take over as the scientific coordinator of PERISCOPE.

Pertussis is a highly contagious infectious disease that causes uncontrollable coughing. The disease begins with an atypical cough and rhinorrhea before entering a paroxysmal stage characterized by cyanosis, lymphocytosis, vomiting, and whoops. Generally, fever is absent and coughing increases at night. Finally, after weeks to months, the patient enters a convalescent stage. The World Health Organization estimates that there are 16 million pertussis cases annually and approximately 195,000 deaths in children. Most cases are caused by *Bordetella pertussis* and are preventable by vaccination.

In the United States, following the introduction of a national immunization program using a whole-cell vaccine in the 1950s, cases fell

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Jacopo Werther/Wikimedia Creative Commons

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United States and Peru with acute respiratory infections.

A study tracking respiratory infections in a Rochester, N.Y., cohort from 1999 through 2003 showed that healthy elderly patients had an annual incidence of HMPV infections of 5.9%, compared with 9.1% for high-risk patients, 13.1% for young patients, and 8.5% among hospitalized adult patients (Arch Intern Med. 2008 Dec 8;168[22]:2489-96).

> "I can tell you as a pediatrician, **this is absolutely true in children,** that metapneumovirus is indistinguishable from other respiratory viruses in kids."

"These percentages are virtually identical to what has been seen in the same cohort for respiratory syncytial virus, so in this multiyear prospective cohort, metapneumovirus was as common as RSV," Dr. Williams said.

Although the incidences of both HMPV and RSV were lower among hospitalized adults, "clinically, we can't tell these respiratory viruses apart. If we know it's circulating, we can make a guess, but we really can't discriminate them," he added.

In the Rochester cohort the frequency of clinical symptoms – including congestion, sore throat, cough, sputum production, dyspnea, and fever – were similar among patients infected with HMPV, RSV, or influenza A, with the exception of a slightly higher incidence of wheezing (80%) with HMPV, compared with influenza.

"I can tell you as a pediatrician, this is absolutely true in children, that metapneumovirus is indistinguishable from other respiratory viruses in kids," he said.

Supportive care only

"Do we have anything for treatment? The short answer is, no," said Dr. Williams.

Supportive care is currently the only effective approach for patients with severe HMPV infection.

Ribavirin, used to treat patients with acute RSV infection, has poor in vitro activity against HMPV and poor oral bioavailability and hemolysis, and there are no randomized controlled trials to support its use in this situation.

"It really can't be recommended, and I don't recommend it," he said.

Dr. Williams' research is supported by the National Institutes of Health, Henry L. Hillman Foundation, and Asher Krop Memorial Fund of Children's Hospital of Pittsburgh. Dr. Williams reported no relevant conflict of interest disclosures.

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significantly. After a lag phase, the adoption of an acellular vaccine in the United States in 1997 and the Netherlands in 2005 – usually in combination with diphtheria and tetanus via DTaP – saw an increase in case numbers. Dr. Diavatopoulos stated that control is no longer as good, compared with other infectious diseases prevented by the MMR vaccine, such as mumps, measles, and rubella.

In the face of increasing numbers, how do we move to the next generation of vaccines to improve control? There are several barriers to licensure, including the following:

- Universal recommendation for pertussis prevention means that more than 90% of the population will have received DTaP (usually in combination with polio and *Haemophilus influenzae* B) and be protected for several years after vaccination.
- Because DTaP vaccines are only efficacious for a limited time, the problem is not immediately apparent.
- Pertussis epidemics are cyclical, occurring every 3-5 years. These peaks and troughs complicate the development of epidemiological studies.

What this means is that large-scale phase 3 efficacy studies, in which disease is used as the endpoint, are not feasible. Also, formal correlates of protection have not been identified.

The PERISCOPE project started in March 2016 and is designed to respond to some of these issues. Funding is made available by a public-private consortium involving the Bill & Melinda Gates Foundation, the European Union, and European Federation of Pharmaceutical Industries and Associations (EFPIA) partners, and in this case, GlaxoSmithKline and Sanofi Pasteur. In total, there are 22 partners in this project.

Pertussis epidemics are cyclical, occurring every 3-5 years. These peaks and troughs complicate the development of epidemiological studies.

The strategic objectives of this partnership include the following:

- Foster expertise and increase capacity in Europe to evaluate new pertussis vaccines both in clinical and preclinical models.
- Identify early biomarkers of long-lasting protective immunity to pertussis in humans. (This step will accelerate and de-risk clinical development of next generation pertussis vaccines.)
- Investigate the impact of maternal vaccination on infant response to pertussis vaccination.

The problem is that there is no one single study design that addresses all questions about the pertussis vaccine. For example, in PERISCOPE, the results of preclinical studies using the baboon or mouse models and addressing disease and colonization endpoints or immunogenicity do not perfectly model human infection and disease.

By comparison, controlled human infection studies provide information on colonization but not disease endpoints. Such studies, however, do provide information on immunogenicity endpoints. Also available are booster vaccination studies and infant vaccination studies providing data on immunogenicity, as well as safety information.

Finally, there are patient studies, such as household contact studies where immunogenicity can be correlated to disease endpoints. From these studies, it will be seen that what is needed is integration of evidence from clinical and preclinical studies to support a new vaccine registration.

PERISCOPE addresses these issues by developing novel, functional antibody and cellular assays and employing cutting-edge methods to characterize innate immune responses and cell-mediated systemic and mucosal immunity. PERISCOPE combines two major industrial partners with public researchers from academic and public health institutes and small and medium-sized enterprises with expertise in clinical trials, vaccinology, immunology, molecular microbiology, challenge models, and bioinformatics.

GSK and Sanofi Pasteur have cofunded the PERISCOPE Project. Dr. Diavatopoulos made no other financial disclosures.

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Commentary by Dr. Bryant // PERISCOPE is a unique public-private partnership that is laying the groundwork for better, more effective pertussis vaccines. A key component of this work is understanding the differences in the immune responses induced by natural infection, whole cell, and acellular pertussis vaccines.

The collaborative is also developing the tools that will be necessary to test effectiveness of newly developed pertussis vaccines, including a human challenge model for pertussis. De Graaf and colleagues administered intranasal doses of a fully virulent *Bordetella pertussis* to adult volunteers who were then monitored in an inpatient setting for the development of pertussis symptoms, colonization, and organism shedding. They demonstrated that humans can be safely and asymptomatically colonized with *B. pertussis* and most of those colonized developed IgG to pertussis toxin. According to the investigators, their data suggest that asymptomatic *B. pertussis* colonization of humans is "part of the natural life cycle of the organism" and transmission from colonized people to susceptible hosts likely contributes to sporadic cases of pertussis as well as outbreaks. Ideally, next-generation pertussis vaccines will be able to reduce or eliminate carriage *B. pertussis* so that this reservoir is eliminated.

To learn more about the work of PERISCOPE, check out the list of recent publications at https://periscope-project.eu/publications/.

Dried blood spot tests show sensitivity as cCMV screen

BY HEIDI SPLETE
MDedge News

Dried blood spot testing showed sensitivity comparable with saliva as a screening method for congenital cytomegalovirus infection in newborns, based on data from more than 12,000 newborns.

Congenital cytomegalovirus (cCMV) is a common congenital virus in the United States, but remains underrecognized, wrote Sheila C. Dollard, PhD, of the Centers for Disease Control and Prevention in Atlanta, and colleagues.

"Given the burden associated with cCMV and the proven benefits of treatment and early intervention for some affected infants, there has been growing interest in universal newborn screening," but an ideal screening strategy has yet to be determined, they said.

In a population-based cohort study published in JAMA Pediatrics, the researchers screened 12,554 newborns in Minnesota, including 56 with confirmed CMV infection (2021 Feb 1. doi: 10.1001/jamapediatrics.2020.5441). The newborns were screened for cCMV via dried blood spots (DBS) and saliva collected 1-2 days after birth. The DBS were tested for CMV DNA via polymerase chain reaction (PCR) at the University of Minnesota (UMN) and the CDC.

> "Diagnostic methods are always improving, and therefore, our results show the potential of [dried blood spots] to provide low-cost CMV screening with **smooth integration of sample collection, laboratory testing, and follow-up.**"

The overall sensitivity rate was 85.7% for a combination of laboratory results from the UMN and the CDC, which had separate sensitivities of 73.2% and 76.8%, respectively.

The specificity of the combined results was 100.0% (100% from both UMN and CDC), the combined positive predictive value was 98.0% (100.0% from UMN, 97.7% from CDC), and the combined negative predictive value was 99.9% (99.9% from both UMN and CDC).

By comparison, saliva swab test results showed sensitivity of 92.9%, specificity of 99.9%, positive predictive value of 86.7%, and negative predictive value of 100.0%.

The study findings were limited by several factors including the false-positive and false-negative results from saliva screening. Overall, the false-positive rate was 0.06%, which is comparable to rates from other screening techniques, the researchers said. "The recent Food and Drug Administration approval of a point-of-care neonatal saliva CMV test (Meridian Bioscience), underscores the importance of further clarifying the role of false-positive saliva CMV test results and underscores the requirement for urine confirmation for diagnosis of cCMV," they added.

However, the study findings support the acceptability and feasibility of cCMV screening, as parents reported generally positive attitudes about the process, the researchers said.

The study is ongoing, and designed to follow infants with confirmed cCMV for up to age 4 years to assess clinical outcomes, they added. "Diagnostic methods are always improving, and therefore, our results show the potential of DBS to provide low-cost CMV screening with smooth integration of sample collection, laboratory testing, and follow-up," they concluded.

Dr. Dollard had no financial conflicts to disclose.

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Commentary by Dr. Bryant // One of every 200 babies in the United States is born with congenital cytomegalovirus (cCMV) infection. Approximately 90% will look normal at birth but will ultimately be diagnosed with significant sequelae, including sensorineural hearing loss, neurodevelopmental impairments, and chorioretinitis. Sensorineural hearing loss, the most common of these, occurs in 15%-20% of babies with asymptomatic infection and may not be diagnosed for months to years after birth. The development of a sensitive and specific dried blood test to diagnose cCMV in the newborn takes us one step closer to feasible, universal screening.

The International Congenital Cytomegalovirus Recommendations Group outlined the benefits of universal screening in a consensus report published in the Lancet in 2017 (doi: 10.1016/S1473-3099[17]30143-3). Congenitally infected but asymptomatic infants can undergo serial hearing and neurodevelopmental screens, facilitating early diagnosis and intervention if abnormalities are identified. In an ideal world, we would have an effective treatment for at-risk infants to prevent the development of complications from congenital CMV infection, but we are not there yet. At the present time, antiviral treatment is not recommended for asymptomatic infants or even those with isolated hearing loss. An ongoing phase 2 clinical trial is evaluating a 4-month treatment course of valganciclovir to prevent development of sensorineural hearing loss in infants with asymptomatic congenital CMV infection and normal hearing at birth (ClinicalTrials.gov Identifier: NCT03301415). Funded by the National Institute of Allergy and Infectious Diseases, the study is expected to be completed in late 2024.

Direct-acting agents cure hepatitis C in children

BY VISHAKHA SABHARWAL, MD; CAROLE MOLONEY, PNP; AND STEPHEN I. PELTON, MD

Between 23,000 and 46,000 U.S. children live with chronic hepatitis C virus with a prevalence of 0.17% anti–hepatitis C virus (HCV) antibody positivity in those aged 6-11 years and 0.39% in children aged 12-19 years. In the United States, genotype 1 is most frequent, followed by genotypes 2 and 3. About 99% of cases result from vertical transmission; transfusion-related cases have not been observed in recent decades. Only viremic mothers are at risk of transmission as those who have spontaneously cleared HCV viremia or have been treated successfully do not risk transmission. Maternal HCV viral load appears to be a risk factor for HCV transmission; however, transmission is reported at all levels of viremia.

In conjunction with the opioid epidemics, the prevalence of HCV infection has increased over the last decade. The Centers for Disease Control and Prevention reported that, between 2009 and 2014, the prevalence of HCV infection increased from 1.8 to 3.4 per 1,000 live births. They identified substantial state-to-state variation with the highest rate in West Virginia (22.6 per 1,000 live births), and the lowest in Hawaii (0.7 per 1,000 live births). The implications are clear that increasing numbers of newborns are exposed to HCV and, if transmission rates are between 1% and 5%, 80-400 U.S. infants each year acquire HCV infection.

Dr. Sabharwal

Ms. Moloney

Dr. Pelton

HCV in children

HCV in children is almost always associated with persistent transaminitis. Chronic infection is defined as the persistence of HCV RNA for at least 6 months, and clearance of HCV infection is determined by the persistent disappearance of HCV RNA. Regardless of infection status, an infant may have detectable maternal anti-HCV antibody in serum until 18 months of age, resulting from passive transfer. In addition, prolonged infection can lead to cirrhosis, hepatocellular carcinoma, or decompensated liver disease. Potential extrahepatic manifestations including reduced physical and psychosocial health also are linked to chronic HCV. Autoimmune disease also has been reported in children with HCV. The stigma of HCV elicits fear in school and child care settings that is a result of public misunderstanding regarding routes of hepatitis C transmission. No restriction of regular childhood activities is required in the daily life of HCV-infected children.

Taken together, increasing rates of HCV infection in pregnant women, increasing numbers of exposed and infected infants, potential for both short- and long-term morbidity, and curative nontoxic treatment, the paradigm for early identification and treatment at age 3 years is changing.

Screening for HCV

There is considerable discussion about which strategy for screening of at-risk infants is more appropriate. Some groups advocate for HCV-RNA testing within the first year of life. Proponents argue the use of a highly sensitive RNA assay early in life has potential to increase detection of infected infants while a negative result allows the conclusion the infant is not infected. Advocates hypothesize that early identification has potential to improve continued follow-up.

Opponents argue that early testing does not change the need for repeat testing after 18 months to

Commentary by Dr. Bryant // The burden of hepatitis C disease in children is substantial. As Sabharwal and coauthors emphasize, all infected children are candidates for treatment. Direct-acting antiviral therapies are effective and available for children as young as 3 years of age, but they are also expensive and some experts – and some payers – debate the cost-effectiveness of early treatment. A new modeling study published in the Journal of Pediatrics compared treating children at 6 years of age with delaying treatment to 18 years of age (2021 Mar;230:38-45.e2. doi: 10.1016/j.jpeds.2020.08.088). Over a 20-year period, treating a theoretical cohort of 10,000 hepatitis C–infected children at age 6 would prevent 330 cases of cirrhosis, 18 cases of hepatocellular carcinoma, and 43 liver-related deaths and was cost effective.

But in order to treat infected children, we first need to identify children at risk. That is going to be easier now that the Centers for Disease Control and Prevention, the U.S. Preventive Services Task Force, and the American Association for the Study of Liver Diseases all recommend universal screening of pregnant women for HCV. The CDC notes that, while the optimal time for testing during pregnancy has not been identified, testing during the first prenatal visit harmonizes with testing for other infectious disease. Women with ongoing risk factors should be considered for repeat testing later in pregnancy. As clinicians who care for children, we need to make sure we have reliable processes in place for knowing maternal HCV status, and ensuring follow-up testing of exposed infants.

confirm diagnosis. They also argue that HCV-RNA testing is more expensive than antibody-based testing, and treatment will not begin prior to age 3 as there is still opportunity for viremia to spontaneously clear.

Direct-acting agents licensed

Ledipasvir/sofosbuvir (Harvoni) was initially demonstrated as curative for genotype 1, 4, 5, or 6 infection in a phase 2, multicenter, open-label study of 100 adolescents with genotype 1 treated for 12 weeks. Sustained virologic response (SVR) was documented in 98% of participants. The regimen was safe and well tolerated in this population, and the adult dosage formulation resulted in pharmacokinetic characteristics similar to those observed in adults. Two clinical trials supported the efficacy of ledipasvir/sofosbuvir in the pediatric population aged 3-11 years. This regimen also is recommended for interferon-experienced (± ribavirin, with or without an HCV protease inhibitor) children and adolescents aged 3 years or older with genotype 1 or 4. A 12-week course is recommended for patients without cirrhosis; 24 weeks is recommended for those with compensated cirrhosis. The combination of ledipasvir/sofosbuvir is the only treatment option for children aged 3-6 years with genotype 1, 4, 5, or 6 infection.

The efficacy of sofosbuvir/velpatasvir (Epclusa) once daily for 12 weeks was first evaluated in an open-label trial in children aged 6 years and older with genotype 1, 2, 3, 4, or 6 infection, without cirrhosis or with compensated cirrhosis. Subsequently, the "cocktail" was evaluated in children aged 6-12 years, with 76% genotype 1, 3% genotype 2, 15% genotype 3, and 6% genotype 4. Sofosbuvir/velpatasvir was approved in March 2020 by the Food and Drug Administration for pediatric patients aged 6 years and older. Given its pangenotypic activity, safety, and efficacy, sofosbuvir/velpatasvir is currently recommended as a first choice for HCV treatment in children and adolescents aged at least 6 years.

The daily fixed-dose combination of glecaprevir/pibrentasvir (Mavyret) was approved in April 2019 for adolescents aged 12-17 years and weighing at least 45 kg. Treatment is for 8 weeks, and includes treatment-naive patients without cirrhosis or those with compensated cirrhosis. SVR12 rates for Mavyret have ranged from 91% to 100% across clinical trials. FDA approval and HCV guideline treatment recommendations for direct-acting antiviral (DAA)–experienced adolescents are based on clinical trial data from adults. Given its pangenotypic activity, safety, and efficacy record in adult patients, glecaprevir/pibrentasvir is recommended as a first choice for adolescent HCV treatment. Glecaprevir/pibrentasvir, once approved for children less than 3 years of age, will be safe and efficacious as a pangenotypic treatment option in children with chronic HCV infection.

Current recommendations

Tools for identifying HCV-infected infants as early as a few months of age are available, yet studies demonstrate that a minority of at-risk children are tested for HCV using either an HCV polymerase chain reaction strategy early in life or an anti-HCV antibody strategy after 18 months of age.

Therapy with DAAs is now licensed to those aged 3 years and offers the potential for cure, eliminating concern for possible progression after prolonged infection. Such therapy offers the potential to eliminate the stigma faced by many children as well as the hepatic and extrahepatic manifestations observed in children. Medication formulation and the child's ability to take the medication need to be considered when prescribing DAAs. It is important to assess if the child can successfully swallow pills. Currently, Harvoni is the only medication that comes in both pellet and pill formulations. The dose is based on weight. The pellets need to be given in a small amount of nonacidic food; they cannot be chewed.

All children with chronic HCV infection are candidates for treatment. When significant fibrosis and/or cirrhosis is present, treatment should not be delayed once the child is age 3 years; when only transaminitis is present, treatment can be delayed. In our experience, parents are eager to complete treatment before starting kindergarten.

Liver biopsy for obtaining liver tissue for histopathologic examination is not routinely indicated in children with chronic HCV infection but should be evaluated case by case. Noninvasive tests of hepatic fibrosis have been used in children – these include serologic markers (that is, FibroSure) and radiologic tests such as ultrasound-based transient elastography (that is, Fibroscan). Validation for pediatric patients is variable for the different serologic tests. Studies have shown that Fibroscan using the M probe is feasible for a wide range of ages, but poor patient cooperation may make measurement difficult.

Further details regarding dosing and choice of formulation is available at https://www.hcvguidelines.org/unique-populations/children.

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Dr. Pelton is professor of pediatrics and epidemiology at Boston University and public health and senior attending physician at Boston Medical Center. *Boston Medical Center received funding from AbbVie for study of Harvoni in children 3 years of age and older.*

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HPV vaccination remains below Healthy People goals despite increases

BY HEIDI SPLETE
MDedge News

Rates of human papillomavirus vaccination increased for both boys and girls in the United States over the past decade, but remain below target levels and vary widely across states based on data from a nested cohort study including more than 7 million children.

"Understanding regional and temporal variations in HPV vaccination coverage may help improve HPV vaccination uptake by informing public health policy," Szu-Ta Chen, MD, of Harvard University, Boston, and colleagues wrote in Pediatrics.

To identify trends in one-dose and two-dose human papillomavirus (HPV) vaccination coverage, the researchers reviewed data from the MarketScan health care database between January 2003 and December 2017 that included 7,837,480 children and 19,843,737 person-years. The children were followed starting at age 9, when HPV vaccination could begin, and ending at one of the following: the first or second vaccination, insurance disenrollment, December 2017, or the end of the year in which they turned 17.

Overall, the proportion of 15-year-old girls and boys with at least a one-dose HPV vaccination increased from 38% and 5%, respectively, in 2011 to 57% and 51%, respectively, in 2017. The comparable proportions of girls and boys with at least a two-dose vaccination increased from 30% and 2%, respectively, in 2011 to 46% and 39%, respectively, in 2017.

Coverage lacks consistency across states

However, the vaccination coverage varied widely across states; two-dose HPV vaccination coverage ranged from 80% of girls in the District of Columbia to 15% of boys in Mississippi. In general, states with more HPV vaccine interventions had higher levels of vaccination, the researchers noted.

Legislation to improve vaccination education showed the strongest association with coverage; an 8.8% increase in coverage for girls and an 8.7% increase for boys.

Pediatrician availability also was a factor associated with a 1.1% increase in coverage estimated for every pediatrician per 10,000 children.

Cumulative HPV vaccinations seen among children continuously enrolled in the study were similar to the primary analysis, Dr. Chen and associates said. "After the initial HPV vaccination, 87% of girls and 82% of boys received a second dose by age 17 in the most recent cohorts."

However, HPV vaccination coverage remains below the Healthy People 2020 goal of 80% of children vaccinated by age 15 years, the researchers said. Barriers to vaccination may include a lack of routine clinical encounters in adolescents aged 11-17 years. HPV vaccination coverage was higher in urban populations, compared with rural, which may be related to a lack of providers in rural areas.

"Thus, measures beyond recommending routine vaccination at annual check-ups might be necessary to attain sufficient HPV vaccine coverage, and the optimal strategy may differ by state characteristics," they wrote.

The study findings were limited by several factors including the use of data from only commercially insured children and lack of data on vaccines received outside of insurance, the researchers noted.

However, the results were strengthened by the large, population-based sample, and support the need for increased efforts in HPV vaccination. "Most states will not achieve the Healthy People 2020 goal of 80% coverage with at least two HPV vaccine doses by 2020," Dr. Chen and associates concluded.

The study received no outside funding. Dr. Chen had no financial conflicts to disclose. Several coauthors reported research grants to their institutions from pharmaceutical companies or being consultants to such companies.

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Commentary by Dr. Bryant // Lower than targeted rates of human papillomavirus vaccination are indeed old news. While increasing immunization rates over time are encouraging, nationally millions of young men and women have entered adulthood unprotected against a virus that causes 36,000 cases of cancer each year. According to the Department of Health & Human Services, fewer than half of young adults in the United States have received one or more doses of the HPV vaccine, and only 22% have completed the vaccine series.

On Jan. 6, 2021, the HHS announced the HPV VAX NOW campaign, a comprehensive effort that aims to increasing human papillomavirus (HPV) vaccination rates among young adults aged 18-26. As noted by Chen and colleagues, vaccination rates have varied wildly by state. HPV VAX NOW specifically targets young adults and health care providers in Mississippi, South Carolina, and Texas, three states with some of the lowest HPV immunization rates. Campaign resources include guidance, tips, and tool kits for health care providers, as well as information for young adults who may not have a primary care doctor and may not know how to access the vaccine.

Mortality trends in childhood after infant bacterial meningitis

BY JIM KLING
MDedge News

Among infants younger than 1 year of age, bacterial meningitis is associated with worse long-term mortality, even after recovery from the initial infection. Heightened mortality risk stretched out to 10 years, and was highest in the wake of infection from *Streptococcus agalactiae*, according to a retrospective analysis of children in the Netherlands.

"The adjusted hazard rates were high for the whole group of bacterial meningitis, especially within the first year after onset. [*Staphylococcus agalactiae*] meningitis has the highest mortality risk within 1 year of disease onset," Linde Snoek said during her presentation of the study (abstract 913) at the annual meeting of the European Society for Paediatric Infectious Diseases, held virtually this year. Ms. Snoek is a PhD student at Amsterdam University Medical Center.

Over longer time periods, the mortality associations were different. "The adjusted hazard rates were highest for pneumococcal meningitis compared to the other pathogens. And this was the case for 1 year, 5 years, and 10 years after disease onset," said Ms. Snoek.

The study appears to be the first to look at extended mortality following bacterial meningitis in this age group, according to Marie Rohr, MD, who comoderated the session where the research was presented.

"In a quick review of the literature I did not find any [equivalent] study concerning short- and long-term mortality after bacterial meningitis in under 1 year of age," said Dr. Rohr, a fellow in pediatric infectious diseases at University Hospitals of Geneva. But the message to physicians is clear. "Children with history of bacterial meningitis have a higher long-term mortality than children without a history of bacterial meningitis," said Dr. Rohr.

Dr. Marie Rohr, at the University Hospital of Geneva, Switzerland, said children with a history of bacterial meningitis have a higher long-term mortality.

> "The adjusted hazard rates were highest for **pneumococcal meningitis** compared to the other pathogens. And this was the case for 1 year, 5 years, and 10 years after disease onset."

The study did have a key limitation: For matched controls, it relied on anonymous data from the Municipal Personal Records Database in Statistics Netherlands. "Important information like cause of death is lacking," said Dr. Rohr.

Bacterial meningitis is associated with significant mortality and morbidity. Pathogens behind the infections vary with age group and geographic location, as well as immunization status.

To examine long-term mortality after bacterial meningitis, the researchers collected 1,646 records from an exposed cohort, with a date range of 1995 to 2018, from the Netherlands Reference Laboratory for Bacterial Meningitis. Included patients had a positive culture diagnosis of bacterial meningitis during the first year of life. Each exposed subject was compared with 10 controls matched by birth month, birth year, and sex, who had no exposure to bacterial meningitis.

Staphylococcus pneumoniae accounted for the most cases, at 32.0% (median age of onset, 180 days), followed by *Neisseria meningitidis* at 29.0% (median age of onset, 203 days). Other pathogens included *S. agalactiae* (19.7%, 10 days), *Escherichia coli* (8.8%, 13 days), and *Haemophilus influenzae* (5.4%, 231 days).

The mortality risk within 1 year of disease onset was higher for all pathogens (6.2% vs. 0.2% unexposed). The highest mortality risk was seen for *S. agalactiae* (8.7%), followed by *E. coli* (6.4%), *N. meningitidis* (4.9%), and *H. influenzae* (3.4%).

Hazard ratios (HR) for mortality were also higher, particularly in the first year after disease onset. For all pathogens, mortality rates were higher within 1 year (HR, 39.2), 5 years (HR, 28.7), and 10 years (HR, 24.1). The consistently highest mortality rates were associated with *S. pneumoniae* over 1-year, 5-year, and 10-year follow-up (HR, 42.8; HR, 45.6; HR, 40.6, respectively). Within 1 year, the highest mortality rate was associated with *N. meningitidis* (HR, 58.4).

Ms. Snoek and Dr. Rohr have no relevant financial disclosures.

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