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Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

Measles — It's Back!

By Stan Deresinski, MD

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

SYNOPSIS: The number of measles cases in the United States has exceeded 1,000 so far in 2019, the largest number in a quarter of a century.

SOURCE: Zimmerman LA, Muscat M, Singh S, et al. Progress toward measles elimination — European Region, 2009-2018. *MMWR Morb Mortal Wkly Rep* 2019;68:396-401.

On June 6, 2019, the CDC announced that the number of measles cases for the year had exceeded 1,000, making this the largest outbreak in the United States in a quarter of a century.

An analysis of the 704 cases reported in the first four months of 2019 found that 98% had occurred in U.S. residents and that 663 (94%) were associated with 13 individual outbreaks. Six of the 13 outbreaks occurred in underimmunized, "close-knit" communities. The mean age of the cases was 5 years, but one-fifth were 20 to 49 years of age. Only 11% of cases were known to have been vaccinated. Of the total cases, 66 (9%) were hospitalized, 24 (3%) developed pneumonia, and there were no fatalities.

■ COMMENTARY

The illness caused by measles virus infection is not trivial. Pneumonia occurs in several percent of those affected and approximately one in 1,000 develop encephalitis, which is often fatal, and results in devastating consequent long-term disability among survivors. The fatality rate is reported to be 1-2/1,000 and is higher in low-income countries. An additional, albeit quite rare, delayed complication that has onset seven to 10 years after infection is subacute sclerosing panencephalitis (SSPE). Those at most risk of complications are individuals < 5 years

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Infectious Disease [ALERT]

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of age and those > 20 years of age, as well as pregnant women and those who are immunocompromised.

Measles is among the most readily transmissible of diseases, with a reproductive number (R_0) as high as 12-18. This R_0 is twice as high as that of smallpox. Because transmission is airborne, only minimal exposure is necessary. The problem of high transmission is compounded by the fact that patients are capable of transmitting the virus for four days before the onset of the measles rash and for another four days after. Perhaps among the strongest evidence of measles virus transmissibility is the fact that measles was an inevitable occurrence in children growing up in the United States before vaccine introduction. The CDC indicates that there had been a mean of 549,000 reported cases with 495 deaths reported each year in the United States in the decade prior to the introduction of the live measles vaccine in 1963. However, the CDC also indicates that measles had been vastly underreported and that the actual number of yearly cases had been closer to 3 to 4 million.

On a global scale, 19 cases per 1 million persons are reported each year, with an estimated 89,780 deaths. This is a vast underestimate of the true problem because of underreporting and because it is estimated that, in fact, 2 to 3 million people die of measles annually. The global problem of measles is not limited to low-income countries. There has been a resurgence of measles in several European countries largely because of resistance to vaccination. In 2018, the WHO European Region reported the highest number of confirmed cases in 20 years, with 80,000 cases identified in 53 countries. Five hundred or more cases were reported from each of 14 countries, including four countries where the infection had been declared eliminated — Israel, Greece, Albania, and the United Kingdom. Three of these countries are visited frequently by Americans and, thus, serve as a potential source of infection that can be transported to the United States. Among the countries from which importations have occurred recently are England, Germany, India, the Philippines, Ukraine, and France. Measles vaccine is among the most effective vaccines available and, in theory, has the ability to eradicate the infection worldwide. The number of global deaths prevented by its use since 2000 is estimated to be 21 million. However, there was a 31% increase in the reported number of global cases between 2016 and 2017, a measure of the failure of public health systems and of the emerging "vaccine hesitancy."

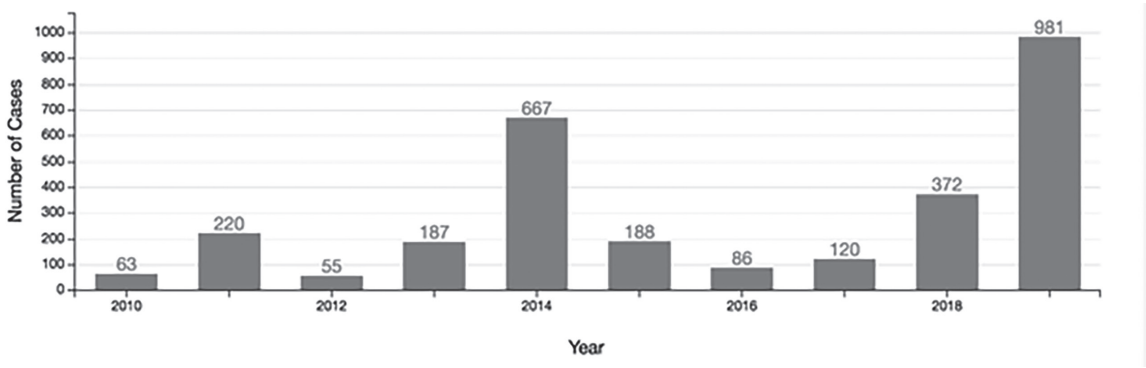
Community vaccination rates of 95% are associated with strong herd immunity and protection. Although the use of just a single dose of the attenuated live vaccine had been significantly effective, the occurrence of outbreaks in school-age children in 1989 led to a recommendation to administer a second dose to all children. A second dose increases vaccine efficacy from approximately 93% to 97% and its introduction led to a further decrease in the annual number of cases. In 2000, measles was officially declared eradicated in the United States, a designation that requires the absence of endemic transmission for three years. Since 2000, the number of cases has been as low as 37 in 2004 and as high as 667 in 2014 — an incidence that was surpassed in 2019 by April 26. (*See Figure.*)

It is critical for everyone to be up to date regarding measles immunity. Among those to whom special attention should be paid are international travelers. Acceptable presumptive evidence of adequate vaccination consists of written documentation, laboratory evidence of immunity, laboratory confirmation of measles, or birth before 1957.[2]

The 2019 U.S. outbreak is largely the result of two factors: the introduction of infection by unvaccinated travelers returning from abroad where they acquired the infection, and subsequent exposure of other unvaccinated individuals, many of whom reside in communities that, for religious or other reasons (especially access to misinformation), resist vaccination.

Vaccine hesitancy, which is a threat to people everywhere, requires collaboration among healthcare providers, parents, government, public health, technology companies, and civil society at large to deal with the misinformation about vaccination

Figure: Number of Measles Cases Reported by Year



2010-2019** (as of May 31, 2019)
Source: Centers for Disease Control and Prevention

in general.[3] Failure will mean more measles and, potentially, loss of inclusion in the list of countries that have eliminated this dangerous infection. ■

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CONFERENCE UPDATE

Travel Medicine 2019 — A Conference Report

By John C. Christenson, MD, and Philip R. Fischer, MD, DTM&H

Dr. Christenson is an infectious disease specialist and Clinical Professor of Pediatrics at Indiana University School of Medicine in Indianapolis. Dr. Fischer is Professor of Pediatrics, Department of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, MN.

Dr. Christenson and Dr. Fischer report no financial relationships relevant to this field of study.

The International Society of Travel Medicine met in Washington, DC, from June 5-9. Overall, there were 1,250 participants in the conference. The 107 podium speakers came from 21 countries on five continents. Many of the sessions were relevant to readers of *Infectious Disease Alert*, and some key information is highlighted here.

MALARIA

Artesunate has proven effectiveness in treating severe malaria. However, there have been cases of delayed-onset hemolysis following artesunate use. Thomas Zoller from Germany reviewed data suggesting that following treatment, previously infected red blood cells can have "pitting" with altered red cell membranes that put them at risk of future hemolysis (with shorter red cell life spans). Patients with higher levels of parasitemia and patients with higher hemoglobin levels at the time of infection were at greater risk of post-treatment hemolysis. African patients seem to have less risk of delayed post-artesunate hemolysis than do patients not of African ethnic origin, but the reasons for this difference are not clear. Limited studies suggest that autoimmunity is not responsible for the delayed post-treatment hemolysis. Patients with severe malaria should be evaluated at least at 8-10 days and 14-18 days after the beginning of treatment with artesunate to rule out hemolysis.

Tafenoquine is newly available in the United States for the prevention and treatment of malaria. Katherine Tan from the Centers for Disease Control and Prevention reviewed current uses of tafenoquine.

Typically, *Plasmodium falciparum* causes severe malaria and death. However, reviews of U.S. cases of severe and fatal malaria show that 5% of severe malaria is due to *P. vivax* and that those with severe malaria have similar risks of death regardless of the species that has infected them. *P. vivax* and *P. ovale* can lie dormant in the liver in hypnozoite forms that are not killed by standard antimalarials and can emerge to cause malaria many months after the initial infection (and treatment). (Atovaquone-proguanil kills liver schizonts but not hypnozoites.) Primaquine is effective against hypnozoites, but it requires a longer daily treatment course (since it has a half-life of six hours). Tafenoquine has a longer half-life (15 hours) and is effective with less frequent dosing. Studies suggest that prophylactic tafenoquine is about 86% effective with daily doses for three days followed by weekly doses in semi-immune adults. In malaria-naïve individuals, prophylactic tafenoquine was about 95% effective. A final dose may be given one week after completion of travel. Tafenoquine can be given to adults who are not pregnant or breastfeeding and who have no history of psychiatric illness (because of possible increased risks of side effects) as long as they are known to have normal glucose-6-phosphate dehydrogenase activity.

ARTHRITOGENIC VIRUSES

Susan Hills from Atlanta, Lin Chen from Boston, and Fabrice Simon from France reviewed current epidemiology, clinical courses, and long-term management of mosquito-transmitted, alphavirus-induced arthritides. Besides chikungunya, other less common viruses that can cause arthritis include Ross River, Mayaro, O'nyong'nyong, Sindbis, and Barmah Forest viruses.

First recognized in Tanzania in the 1950s, chikungunya virus has spread during the past 15 years to infect people in many tropical and even subtropical areas of the world. U.S. travelers were most affected in 2014 and 2015, but cases continue to present in the United States, mostly in travelers to Asia now. Ross River virus is limited mostly to northeast Australia, with about 5,000 cases per year, but the virus also is endemic in Papua New Guinea and Irian Jaya, Indonesia. It is sometimes seen in travelers to Fiji and it might be seen on other Pacific islands. Mayaro virus was first isolated in Trinidad in 1954 and is seen sometimes in forested areas of Central and South America and the Caribbean. O'nyong'nyong virus was first isolated in Uganda in 1959 and now occurs across Central Africa; a couple of travelers have been infected. Sindbis virus was first identified in Egypt in 1952 and has been seen in Europe, Asia, Africa, and Oceania, but most virus activity is in northern Europe and South Africa. There are just about 1,000 cases of Barmah Forest virus infection in Australia each year, and many cases are asymptomatic.

In addition to alphaviruses, arthritis also can be caused by parvovirus B19, Epstein-Barr virus, hepatitis viruses, and retroviruses. Nonetheless, arthritis is most common and most severe with chikungunya virus infection. As *Aedes* mosquitoes expand their range, Mayaro virus might emerge as a more common cause of illness in coming years.

Unlike the situation with some other viruses, less than 20% of chikungunya-infected individuals remain asymptomatic. Fever is nearly uniform. Various uncommon but severe complications have been reported, especially in newborns and the elderly. Up to half of infected patients go on to develop chronic arthritis. Arthritis is more common in patients older than 45 years of age, in those with pre-existing osteoarthritis, and in those who had severe joint pain at the time of their initial presentation.

Most chronic post-chikungunya joint pain is mechanical and might relate to inflamed tendons rather than to actual joint inflammation; nonetheless, about 2% with chronic pain do have inflammatory synovitis. Chronic post-chikungunya pain is associated with fatigue, deconditioning, weight gain, and depression, with significant reduction in the quality of life. Multifaceted treatment can help with the various associated comorbidities.

Data to guide the management of joint pain are extremely limited. So far, there is no evidence to support the use of antiviral agents or monoclonal antibodies for treatment. Pain management is important. Short-term steroids often are advised, but supportive data are limited. For the couple percent of patients with inflammatory arthritis, methotrexate is advised, but treatment failures are more common if methotrexate is started after the first year of symptoms. Biologic agents are not advised because of some infection risk coupled with minimal to no known benefit. What is needed for treatment? Physical therapy is critically important, and one study suggests that Pilates is helpful. Most patients improve significantly with pain control, physical therapy, and functional restoration.

RABIES

Rabies prevention is challenging, partly when choosing who needs pre-exposure vaccination and partly because of the cost of vaccines. In April 2018, the World Health Organization released new guidelines.[1] Since the 13-dose rabies vaccine of Pasteur in 1885, there has been significant progress. Pre-exposure

prevention is suggested for travelers at higher risk of an animal bite (animal workers, children, joggers, long-distance cyclists), especially when post-exposure vaccination might not be readily available. The pre-exposure vaccine may be provided with two doses separated by a week, either with a total of two intramuscular vaccine doses or with two intradermal doses at different sites on each of the two vaccine administration days; a third dose would be given to immunocompromised patients. As discussed by an expert panel, the current standard in the United States now is for four doses of post-exposure intramuscular vaccine in patients who did not receive pre-exposure vaccination (days 0, 3, 7, and 14-21, but not given in the gluteal region, with immune globulin as soon as possible after the exposure but certainly within a week of the beginning of vaccination — intramuscularly and especially around the wounds). Smaller volumes of dosing may be used, and the total doses can be dropped to three (with cost savings) if the vaccine is given intradermally, based on reasonable effectiveness data. Two doses of post-exposure vaccine (without immune globulin) are effective to boost protection in travelers who received pre-exposure vaccine.

ANTIMICROBIAL RESISTANCE

Resistance to common antimicrobials is common in many parts of the world. David Tribble from Uniformed Services University of the Health Sciences in Bethesda, MD, reviewed bacterial resistance to antimicrobials in south and southeast Asia and the relevance of antimicrobial resistance to travelers. Multi-resistant *Enterobacteriaceae*, *Staphylococcus aureus* (even to vancomycin), and *Salmonella* Typhi are common, with risk of travelers developing resistant urinary tract infection and difficult-to-treat systemic infections. Traveler's diarrhea is increasingly resistant to ciprofloxacin in Asia, with about 20% of cases resistant now; some resistance to azithromycin is reported. Even asymptomatic travelers can transmit resistant germs to relatives and colleagues after returning from their travel.

Laura Nellums from London reviewed the impact of antimicrobial resistance in migrants after reminding her large audience that Alexander Fleming predicted antibiotic overuse and resistance in his Nobel Prize lecture 75 years ago. In Europe, 73% of multi-drug-resistant tuberculosis occurs in individuals born outside of Europe. About 10% of migrants to Europe have methicillin-resistant *Staphylococcus aureus*, and about 27% harbor multi-resistant *Enterobacteriaceae*; carriage persists long after arrival in Europe.

Worldwide, according to Regina LaRocque from Harvard, 35 billion daily doses of antibiotics are used each year, and antibiotics are essential to the practice of modern medicine. Antibiotics are used widely, and 35% of rivers in Africa carry water with dangerously high levels of antibiotics. However, antibiotic resistance accounts for as many deaths as influenza, HIV, and tuberculosis combined. Multi-resistant gram-negative organisms are especially prevalent in Asia. Even in the United States, it is the first (not repeated) use of an antibiotic that increases the risk of developing resistance. Thus, prevention of antimicrobial resistance can focus on avoiding unnecessary initial prescription of antibiotics. Key risk factors for harboring resistant organisms are traveling (especially to Asia), having traveler's diarrhea, and using antibiotics during travel. At least some travelers regain their pre-trip microbiome pattern and lose resistant germs over the three months following travel. Within a large network of travel clinics during recent years, the prescription of antibiotics for stand-by use for traveler's diarrhea has dropped from about 93% to 69%.

PERTINENT POSTERS

Get a Travel History!

With concern for Zika and other travel-related illnesses, Lin Chen and colleagues at a hospital in Cambridge, MA, retrospectively reviewed pre-visit screening for a history of travel outside the United States within the 30 days of the medical visit. Overall, 5,642 patients had traveled, mostly to Latin America; 989 were of reproductive age and had been to a Zika-endemic area. Of the 161 patients who had traveled and were hospitalized, 41 had symptoms compatible with Zika (such as fever, arthralgia, or rash); two of them were confirmed Zika-positive. Attention to pre-visit screening and Zika testing might have identified many other patients either with acute Zika infection or at risk of future consequences of Zika infection.

Treat Blastocystis?

A research group from an experienced Swiss travel clinic randomized patients with gastrointestinal symptoms and blastocystis-positive stool tests to receive metronidazole or placebo. There was no difference in outcomes between the two groups. As with previous studies, these new data suggest that blastocystis is unlikely pathogenic in human intestines.

Climate Change

Obviously, the impact of travel extends far beyond infections. Admitting that air travel accounts for a significant carbon dioxide load in the environment, the conference theme centered on "Travel Medicine in a Changing Climate." The opening ceremony and initial plenary session were dedicated to the discussion of health effects of climate change. Clearly,

changing climates are associated with changing risks of infection. Participants thought about wise stewardship of environmental resources in tangible ways. There were no printed programs for the meeting, reducing paper consumption. Each participant received a commemorative mug at the beginning of the conference, and no cups were provided during meals and breaks. One day of the conference featured only plant-based snacks and meals. Conference participants were tangibly reminded that travel offers positive value and that behavioral choices can mitigate some of the negative environmental consequences of travel. ■

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ABSTRACT & COMMENTARY

Infective Endocarditis Prevalence in Dutch Patients With Positive Blood Cultures

By Richard R. Watkins, MD, MS, FACP, FIDSA

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

SYNOPSIS: Data from a nationwide registry in Denmark from 2010 to 2017 showed that patients with *Enterococcus faecalis* bacteremia had the highest prevalence of infective endocarditis (16.7%), followed by *Staphylococcus aureus* (10.1%) and *Streptococcus* spp. (7.3%).

SOURCE: Østergaard L, Bruun NE, Voldstedlund M, et al. Prevalence of infective endocarditis in patients with positive blood cultures: A Danish nationwide study. *Eur Heart J* 2019; May 30. doi: 10.1093/eurheartj/ehz327. [Epub ahead of print].

Despite advances in the diagnosis and management of infective endocarditis (IE), it still causes considerable morbidity, mortality, and healthcare expense. Although there has been an increased awareness in recent years about the association between *Staphylococcus aureus* bacteremia and IE, the risk from other pathogens is less appreciated. Using a large patient cohort, Dutch investigators sought to characterize which bloodstream infections (BSIs) are associated with the highest risk of IE.

Researchers used three nationwide patient databases to identify cases of BSIs and IE between 2010 and 2017. The investigators chose to include BSIs from *Enterococcus faecalis*, *Streptococcus* spp., *S. aureus*, and coagulase-negative staphylococcus (CoNS) because these four pathogens cause approximately 70% of IE cases. For the study, a BSI was defined as at least one positive blood culture with one of the aforementioned pathogens. Patients were included who were hospitalized at least 14 days, including those transferred between institutions, and the primary outcome was the diagnosis of IE. The underlying bacterial etiology was identified in a period of six months prior to admission in which IE was diagnosed. Furthermore, a sensitivity analysis was conducted for BSIs within 14 days prior to IE admission and up to IE discharge.

There were 3,408 cases of IE during the study period. The prevalence of IE was highest in patients with *E. faecalis* BSIs (16.7%), followed by *S. aureus* BSIs (10.1%), *Streptococcus* spp. BSIs (7.4%), and CoNS BSIs (1.6%). Investigators found a significant increase for the prevalence of *E. faecalis* IE ($P = 0.0005$; 14.4% in 2010 to 18.8% in 2017) and *Streptococcus* spp. IE ($P = 0.03$; 6.0% in 2010 to 8.0% in 2017) from the start until the end of the study. They observed a significantly higher prevalence of IE in males compared to females for *E. faecalis* ($P < 0.0001$), *Streptococcus* spp. ($P < 0.0001$), and CoNS ($P < 0.0001$), but not *S. aureus* ($P = 0.06$). Older age also was associated with a higher prevalence of IE caused by *E. faecalis*, *Streptococcus* spp., and CoNS. A sensitivity analysis that compared BSIs within 14 days to IE found the same described pattern. Another sensitivity analysis for CoNS required that two blood cultures be positive within one week of each other, with at least one day between cultures. This changed the prevalence of CoNS IE to 8.1%, compared to 1.6% when only one blood culture was positive.

■ COMMENTARY

An interesting finding from this study was the higher prevalence of IE in patients with BSIs due to *E. faecalis* compared to *S. aureus*. The current IE guidelines

from the Infectious Diseases Society of America note that *S. aureus* is the most common cause of IE in much of the developed world and that the rate of *S. aureus* IE has increased significantly relative to other causes of IE.[1] Enterococci reportedly are the third leading cause of IE, accounting for approximately 10% of cases, with *E. faecalis* constituting 97% of enterococcal IE; *E. faecium*, 2%; and other species, 1%. The high rate of enterococcal IE following BSI in the present study highlights the need for screening with echocardiography. This seems especially important for elderly patients and male patients. Why males have a higher rate of IE than females is unclear, but this also has been observed in previous studies. Perhaps males have more risk factors, such as prosthetic heart valves or intravenous drug abuse. Further epidemiologic studies will be beneficial, especially to ascertain if the prevalence of enterococcal IE is increasing compared to other common etiologies.

The study has some limitations worth mentioning. First, because of the retrospective and observational design, the findings could have been influenced by unmeasured confounding variables. Second, the data are from a small European country, so the findings might not be generalizable to other geographic areas and different patient populations. Third, the diagnosis of IE was derived from ICD-10 codes and not the modified Duke criteria, which may have led to reporting bias. Fourth, improvements in diagnostic modalities (e.g., better access to transesophageal echocardiography and nuclear imaging) may have increased the diagnostic accuracy during the last period of the study. Fifth, patients were included in the study who were hospitalized for 14 days or longer, which is quite long by current clinical practice standards. Finally, other (albeit rarer) causes of IE such as *Candida* spp. and gram-negative organisms were not included in the analysis.

The epidemiology of IE is dynamic, and studies like the one reported by Østergaard and colleagues are valuable for clinicians and public health practitioners alike. Whether BSIs due to enterococcus are leading to more cases of IE in other geographic areas, such as North America, warrants further investigation. ■

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ABSTRACT & COMMENTARY

Mechanism of Persistence of *Moraxella catarrhalis* in Patients With Chronic Obstructive Pulmonary Disease

By Joseph F. John, Jr., MD

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

SYNOPSIS: This study examines the mechanism that allows *Moraxella catarrhalis* to persist in some patients with chronic obstructive pulmonary disease.

SOURCE: Murphy TF, Brauer AL, Pettigrew MM, et al. Persistence of *Moraxella catarrhalis* in chronic obstructive pulmonary disease and regulation of Hag/MID adhesin. *J Infect Dis* 2019;219:1448-1455.

Dr. Tim Murphy in Buffalo has been working on the microbiology of symptomatic pulmonary disease for many years. Here is the latest and greatest installment from a cohort of adults with chronic obstructive pulmonary disease (COPD) studied prospectively over the past 20 years. Over the years, Dr. Murphy's multitalented group has discovered that one of the major bacterial pathogens in COPD, *Moraxella catarrhalis*, has a variability of duration of colonization. What allows this organism to colonize and then persist in some COPD patients and not in others? The reason for the variability heretofore has been unknown. This current explanation in this paper is that one of the major adhesins, Hag/MID, in its expression and then disappearance, explains the persistence of *M. catarrhalis*.

In the ongoing study from 1994 to 2014, patients with COPD were seen every month. An exacerbation caused by *M. catarrhalis* was considered to be the onset of new clinical symptoms and the acquisition of a new strain of *M. catarrhalis*. Investigators studied the genetic characteristics of the Hag/MID gene in persistent and cleared strains. Researchers also studied adherence to human epithelial cells and expression of the Hag/MID protein for the persistent and cleared strains. Earlier studies had shown that Hag/MID mediates adherence of the bacterium to respiratory epithelial cells, one of the virulence phenotypes. When Hag/MID is expressed, the bacterium shows aggregation when grown in BHI broth, a second virulence phenotype.

The major finding of the study was that most strains that expressed Hag/MID on acquisition in COPD patients ultimately lost that expression during persistence. The paper goes on to study the mechanism of the loss of Hag/MID expression. In five persistent strains, the Hag/MID gene had one of two different genetic changes. One was an out of frame mutation, thus, the protein was not expressed. Another mode of dysregulation was caused by slipped-strand misparing through changes in a polynucleotide repeat near the start codon in the open reading frame. The impact of the loss of Hag/MID was studied further with regard to virulence phenotypes. Loss of the protein resulted in decreased adherence to respiratory epithelial cells and loss of aggregation.

■ COMMENTARY

What is going on here? An adhesion molecule aids a bacterium to inhabit initially an abnormal respiratory tract, perhaps causing a frank exacerbation of bronchitis. Then, for it to persist, it loses the very adhesin that aided its initial colonization. Why does the bacterium even care to make this small genetic change that results in a radical change in protein expression (in this case, a protein that is related to virulence)? The paradox may reside mainly in the concept that pathogens in COPD do not want to kill the host. In the case of the COPD patient, the host houses an immense surface area of respiratory epithelium that offers a sanctuary if the bacterium can reside relatively peacefully. Getting in is the first order for *M. catarrhalis*, but guaranteed survival in a demanding environment is paramount. Indeed, in the study, Hag/MID continued to be expressed in 28 of 30 strains that were cleared, whereas only 17 of 30 strains that were persistent continued to express the protein. The longer the persistence, the less likely it was that Hag/MID would be expressed. Hag/MID is a multifunctional autotransporter. Why would its persistence be facilitated by its absence?

Hag/MID does elicit an immune response, both mucosal and systemic. Perhaps these responses select the Hag/MID-negative phenotype, allowing the organism to escape some immune control. Analogously, there are prospects for immunization with Hag/MID. Vaccines may reduce initial colonization with *M. catarrhalis*, an apparent advantage for the COPD patient. Enter the airway microbiome, the last consideration in this paper. Clearly, compared to the airway microbiome in healthy people, the airway microbiome in COPD patients contains several pathogens, including *M. catarrhalis*. Even the COPD airway has to come to some equilibrium, and in that sense, the downregulation of Hag/MID serves an equilibrium of the microbiome even in the altered pulmonary airway.

This work by Murphy et al, a composite over many years using a most cooperative COPD cohort, shows the complexity of the bacterial pathogens' flux into and out of the pulmonary environment. One of these pathogens, *M. catarrhalis*, is well armed to invade this environment, but once there, is happy to downregulate its virulence. This research group may have discovered a trait of some pathogens to invade but, once established in a milieu, to use genetic mechanisms to modify its protein expression to become part of the microbial background. ■

ABSTRACT & COMMENTARY

A Maternal Antibody Protects Infants From Severe Malaria

By Micaela A. Witte and Philip R. Fischer, MD, DTM&H

Ms. Witte is a student at Mayo Clinic Alix School of Medicine. Dr. Fischer is Professor of Pediatrics, Department of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, MN.

Ms. Witte and Dr. Fischer report no financial relationships relevant to this field of study.

SYNOPSIS: Transplacental antibodies against *Plasmodium falciparum* Schizont Egress Antigen-1 may protect infants from severe malarial infection during the first year of life. This new knowledge about these antibodies potentially can inform vaccine development.

SOURCE: Kurtis JD, Raj DK, Michelow IC, et al. Maternally derived antibodies to Schizont Egress Antigen-1 and protection of infants from severe malaria. *Clin Infect Dis* 2019;68:1718-1724.

Falciparum malaria kills approximately 300,000 African children each year. Children older than 6 months of age are at the greatest risk. In contrast, neonates and young infants seem to be relatively spared from severe malaria infection. Although it has been hypothesized that this protection is a result of the transplacental transfer of maternal antibodies, the specific maternal antibody had not yet been identified.

Thus, Kurtis and colleagues studied 647 newborns in Tanzania for one year after birth to determine whether levels of anti-Schizont Egress Antigen-1 (PfSEA-1) in cord blood were predictive of protection against severe malarial infection. On the day of birth, maternal peripheral, placental, and cord blood were collected from 647 infants in a northeast Tanzania hospital. These infants were monitored every two weeks for one year with wellness checks that included blood smear analysis. Ultimately, complete follow-up data were collected from 583 infants.

Overall, 166 infants developed a severe malarial infection within the first 12 months of life, as defined by a positive blood smear and at least one symptom of severe infection (i.e., respiratory distress, severe anemia, temperature greater than 40° C, convulsions, hypoglycemia, or prostration). Cord blood levels of anti-PfSEA-1 were negatively correlated with severe infection. When grouped by level of anti-PfSEA-1, infants with levels in the top 10% had 51.4% fewer cases of severe malarial infection compared to infants with lower levels. Importantly, cord blood antibodies against other *P. falciparum* proteins were not predictive of this reduced rate of severe infection.

In addition, Kurtis and colleagues vaccinated female mice with the analogous *Plasmodium berghei* Schizont Egress Antigen-1 (PbSEA-1) before mating them and infecting their offspring with *P. berghei*. Pups whose mothers had been vaccinated with PbSEA-1 lived 32-67% longer than those whose mothers had not been vaccinated. Furthermore, 40% of the pups with vaccinated mothers completely cleared the infection.

In summary, the team in Tanzania found that cord blood anti-PfSEA-1 was predictive of a reduced risk of severe malarial infection during the first 12 months of life. Their vaccination study in mice suggests that immunity to SEA-1 may reduce the severity of malarial infection.

■ COMMENTARY

In 2017, *Plasmodium falciparum* caused nearly 219 million cases of malaria and nearly 435,000 deaths. Children younger than 5 years of age were by far the most vulnerable, accounting for 61% of all malarial fatalities (primarily in sub-Saharan Africa). Despite continued efforts and increased funding, the extent of mortality plateaued during the preceding three years and did not continue the steady decline noted earlier this millennium.[1]

Although malaria is especially problematic for young children, infants are relatively spared from malaria during the first six months of life. Even most congenitally infected newborns clear their infection without adverse consequences. Nonetheless, some newborns become sick with malaria and die, and placental and congenital malaria have been associated with increased anemia and clinical malaria after the first few months of life.[2] It is not clear why some infected newborns and young infants get sick with malaria and others seem to be protected; further research with the PfSEA-1 antibodies might yield clues.

For prevention of malaria, development of a vaccine has proven difficult. *P. falciparum* exhibits wide antigenic variation and mutates quickly, as exemplified by its rapid resistance to many antimalarial drugs. Furthermore, *P. falciparum* encodes approximately 5,300 genes, providing a wide range of potential vaccine targets. Most importantly, the complexity of the malarial life cycle adds a unique set of challenges.[3]

The life cycle of *P. falciparum* in humans can be divided into three stages: the infectious pre-erythrocyte stage, the symptomatic erythrocyte stage, and the transmitting gametocyte stage.[3] While vaccines targeting the first stage have the potential to prevent disease formation all together, they have no true correlate in natural malarial immunity. In contrast, vaccines targeted to the second stage seem to mimic the process of natural immunity, but delay immune activation until after infection and possible symptom development. The third stage has produced less interest, as immunization targeting this stage would provide no direct immunity to the already symptomatic individual.[3]

The RTS vaccine was an attempt to target the first stage of *P. falciparum*'s life cycle in humans. Briefly, the RTS vaccine consists of a truncated circumsporozoite

protein (CSP) fused to hepatitis B surface antigen.[4] It was intended to boost immunity before *P. falciparum* invades erythrocytes and children begin showing symptoms. This vaccine has been the most successful malarial vaccine to date, proving effective at inducing complement-fixing antibodies and leading to a 36.3% average rate of protection against clinical malaria during the first 48 months.[4,5]

Unfortunately, this limited protection wanes quickly, and the vaccine has limited efficacy in children with prior malaria exposure. Specifically, after seven years of follow-up, the RTS vaccine was determined to have a 4.4% average rate of protection.[5] At four years post-vaccination, its efficacy was near zero, and by five years, it actually showed negative efficacy, especially in children with higher malaria exposure.[5] This reduction in efficacy is paralleled by the rapid decay in functional antibodies that became nearly undetectable at 8.5 months post-vaccination.[4]

It is hypothesized that while the RTS provides early protection against malaria sporozoite infection, it delays development of immunity to blood-stage parasites, increasing the risk of later infection.[5] Furthermore, children who already have been exposed to malaria at the time of vaccination show reduced antibody induction. Interestingly, these children also had higher levels of antibodies to blood-stage antigens compared with children who had lower malarial exposure.[4]

It is possible that a vaccine targeting blood-stage antigens may prove more efficacious against *P. falciparum*. In 2014, Kurtis and colleagues discovered that antibodies against PfSEA-1, an antigen expressed on Schizont-infected erythrocytes, impaired parasite replication during the blood-stage of infection.[6] In addition, African adolescents and adults with anti-PfSEA-1 had lower parasite burden, and children with these antibodies did not experience episodes of severe malaria.[6]

The new work by Kurtis and colleagues provides additional support to the notion that immune response to PfSEA-1 may reduce the severity of malarial infection. Specifically, transplacental anti-PfSEA-1 was associated with a reduction in risk of severe malarial infection after birth and even into the high-risk period after six months, when levels of maternal antibodies are rapidly declining. The results of Kurtis' experiment in mice suggest that immunity to this antigen alone may provide protection, bolstering hope for future vaccine development.

While a PfSEA-1 vaccination may fall prey to the same waning effects as RTS, it is possible that its mimicry of the natural immune response to blood-stage parasites may show improved longevity. And, blocking just the symptom-producing blood stage could allow children to develop their own natural immunity to the pre-erythrocytic stages of infection. Future research also should examine the effects of anti-PfSEA-1 after 12 months when maternal IgG has completely disappeared, as well as the efficacy of PfSEA-1 vaccination in humans. ■

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Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

Changing Herpes Zoster Risk in Adults

SOURCE: Harpaz R, Leung JW. The epidemiology of herpes zoster in the United States during the era of varicella and herpes zoster vaccines: Changing patterns among older adults. *Clin Infect Dis* 2018; Nov 29. doi: 10.1093/cid/ciy953. [Epub ahead of print].

There are approximately 1 million adult cases of herpes zoster (HZ) every year in the United States. The epidemiology of HZ in adults appears to be changing, with younger adults at increasing risk. This study examined the age-specific risk of HZ in adults > 35 years of age throughout the United States from 1993 to 2015. The HZ incidence was based on ICD-9/10 coding for varicella zoster and

for post-herpetic complications. The prospective population at risk was an estimated 27 million individuals, with a median follow-up of 49 months. From population tables, there was an estimated number of 934,000 HZ cases in individuals 35 years of age or older, whereas insurance enrollment tables identified 804,000 HZ cases in a similar age group. Approximately 62% of HZ cases were in women, and the median ages from 1993 to 2003 and from 2004 to 2016 were similar (59.4 years and 59.3 years, respectively).

Vaccination time lines are important considerations when evaluating population data for varicella and shingles. Following the introduction of the varicella vaccine in 1996, the reported incidence of acute primary varicella continued to decline by 97% by 2014. However, mild varicella infections continued to occur in those receiving one dose of varicella vaccine, leading to modified recommendations in 2006 for two doses of vaccine in children. In addition, once the first commercially available shingles vaccine (Zostavax) was licensed in 2008, adults > 60 years of age began, slowly, to receive this vaccine (up from 2% in 2007 to 14% in 2010 to 33% by 2016). At the same time, the age for vaccination was extended to those > 50 years of age in 2011. It is important to remember that vaccine immunogenicity from this vaccine probably wanes within 10 years, so vaccine received in 2006 may no longer provide protection in 2016. (The newest HZ vaccine approved in 2017 would not affect these data.)

Despite the introduction of these two vaccines, the age-related incidence of HZ in adults > 35 years of age has been increasing steadily. In adults > 35 years of age, HZ incidence in 1993 was as low as 2.5 cases per 1,000 population. By 2006, this figure had increased to 6.1/1,000, and by 2016 had increased further to 7.2/1,000. This increase is largely due to a steady increase in HZ cases in individuals aged 35 to 50-55 years. Earlier analysis indicated that adults 50-55 years and older also were at increased risk for HZ, but since 2006-2016, the risk seems to be declining. In fact, the data have starkly diverged, with a steady increase in younger adults and a decline in HZ risk among older adults.

The authors were unable to provide an explanation for this finding. Obviously, comorbidity, diabetes, and immunosuppression, which would be more frequent in older adults, does not provide an explanation. Although it is conceivable that the broader use of varicella vaccine in children has reduced any possible VZV immunological boosting effect in adults, it is not at all clear why that effect would be differentially expressed in younger vs. older adults. Perhaps the present-day stressors on younger adults are just that much greater than for older adults. Or, perhaps older adults had repeated exposure and priming in their earlier years — resulting in somewhat more durable immunity — whereas younger adults are dependent on what limited exposure has existed the past 10 to 20 years with effectively no "communal vaccination." ■

Trends in Herpes Zoster Risk Among Children

SOURCE: Harpaz R, Leung JW. The epidemiology of herpes zoster in the United States during the era of varicella and herpes zoster vaccines: Changing patterns among children. *Clin Infect Dis* 2018. doi: 10.1093/cid/ciy954. [Epub ahead of print].

Although the epidemiology of herpes zoster (HZ) in adults continues to evolve, the risk of HZ in children < 18 years of age has declined steadily. These authors examined the risk of HZ in approximately 13 million children from 1998 to 2016, representing approximately 51 million person-years of follow-up. The number of children enrolled in successful years of the study remained fairly stable. In contrast to adults, with nearly 1 million HZ cases per year, there were 35,405 cases of HZ in children during the entire time period.

Trends in HZ in children from 1998 to 2016, based on all age cohorts, showed steady increases during the first years of observation, through about 2006-2007. However, since then, the risk of HZ has declined steadily. This likely is related to the different risks of reactivation in younger cohorts vs. more modern cohorts. It is largely believed that the risk of reactivation from vaccine strain VZV (vs-VZV) is substantially less than from wild type VZV (wt-VZV). Thus, children born prior to 2010, who may have received only one dose of VZV vaccine, were at greatest risk for developing wild type infection; some may have had mixtures of vaccine strain and WT virus. However, by 2010, more than 90% of children had received at least one dose, if not two doses, of VZV vaccine, and were infected almost exclusively with vs-VZV. Thus, the risk of reactivation HZ has declined steadily since 2008-2010.

The current risk of HZ among children in the two youngest age cohorts is approximately 0.22/1,000. This suggests that, although the risk of HZ may never reach zero, the risk of HZ may continue to decline as these cohorts age and become adults. ■

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CME QUESTIONS

1. Which of the following statements is correct?

a. In an analysis of the first 704 reported cases of measles in the United States in 2019, only 28% occurred in U.S. residents.

b. Ninety-five percent of reported measles cases in 2019 in the United States occurred in children younger than 5 years of age.

c. Measles is predominantly transmitted by direct contact.

d. Measles is transmissible from a patient for approximately four days prior to development of a rash.

2. Once *Moraxella catarrhalis* has caused an exacerbation of chronic obstructive pulmonary disease, what usually happens to its virulence?

a. It continues to cause inflammation.

b. It changes genetically to allow it to persist in the airway.

c. It becomes resistant to antibiotics.

d. It proceeds to colonize the intestinal tract.

3. Which of the following is true regarding symptomatic childhood malaria?

a. It is mostly a problem in Asia.

b. It is prevented in more than 85% of cases by the RTS,S vaccine.

c. It is most common during the first six months of life.

d. It is less common in babies with a newly described maternal antibody.

CME OBJECTIVES

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

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