

What Is New in Infectious Diseases?

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The practice of infectious diseases is an ever-changing discipline. Diseases such as syphilis and tuberculosis have been with mankind for millennia, whereas conditions such as AIDS and Zika virus are relatively new maladies. A working knowledge of clinical presentations associated with Zika virus infection, syphilis, and common parasitic infections will help the primary care provider determine whom to treat and whom to refer to a specialist. Increasing the use of vaccination for influenza and pre-exposure prophylaxis for HIV infection should reduce the burden of these common diseases.

The field of infectious diseases may not be lucrative, but it is never dull. Infectious diseases have shaped the history of mankind. Smallpox killed approximately 30,000 people in Athens, Greece, in 430 BC and millions of Mexicans and Native Americans in the 16th and 17th centuries [1]. The migration of armies—and rats with their fleas—along the Silk Road in the 14th century brought the Black Death (caused by *Yersinia pestis*) to Europe, where it killed 30%–50% of the population. Malaria, tuberculosis, influenza, dengue, epidemic typhus, measles, syphilis, cholera, and yellow fever have had an enormous impact on the course of history. More recently, the AIDS epidemic, which began 35 years ago, affects people in all parts of the globe. In many parts of the world, infectious diseases are a major cause of morbidity and mortality.

So, what is new in infectious diseases? This issue of the NCMJ will focus on several topics that are of importance for physicians and other primary care providers in North Carolina. The articles are not meant to be encyclopedic, but the reader should find the topics to be timely and interesting.

Zika virus has dominated the media for the past several months and has replaced Ebola as the virus du jour. Although the consequences of infection are more dire with Ebola, the risk of Zika infection far outweighs that of Ebola in this country. Zika is an RNA virus of the genus *Flavivirus*. Other members of this genus include West Nile virus, yellow fever virus, dengue virus, and tick-borne encephalitis virus. The Zika virus has been described for over 60 years [2], but until this year, few people in the medical community had ever heard of Zika. The virus was first isolated from rhesus macaques in the Zika forest of Uganda in 1947 [3]. Human illness was first described in Nigeria in 1953 [4]. Over the next 50 years, human infections were rarely reported. Then, in 2007, a

large outbreak occurred in the state of Yap in Micronesia [5]. A subsequent outbreak of Zika virus infection occurred in French Polynesia in 2013 and 2014 [6]. In March 2015, Zika virus infections were reported in Brazil [7]. The rapid migration eastward from the Pacific is a testimony of just how fast infectious diseases can travel given jet transportation and the proper vectors (in this case, the mosquitoes *Aedes aegypti* and *Aedes albopictus*). These vectors, familiar to both entomologists and infectious diseases practitioners, also transmit other arthropod-borne viruses (arboviruses) including dengue, yellow fever, and chikungunya.

Most Zika virus infections are subclinical, but infection in pregnant women has been associated with microcephaly in utero [8]. This condition appears to be much more likely if infection occurs in the first trimester of pregnancy [9]. The actual risk of microcephaly appears to be about 1% if infection occurs in the first trimester [10]. In a recent study in Rio de Janeiro, fetal abnormalities were present in 30% of infected pregnant women [11]. These abnormalities included microcephaly, ventricular calcifications, and fetal death. Infection with Zika virus is also associated with Guillain-Barré syndrome, although the risk appears to be small [12]. Development of a vaccine for Zika is being pursued by several companies, but it is not clear whether a vaccine will be effective or when it will be available.

Zika virus RNA can be found in blood, semen, urine, saliva, amniotic fluid, cerebrospinal fluid, vaginal secretions, and breast milk [13]. Therefore, it should come as no surprise that Zika virus infection, like the Ebola virus, can be transmitted sexually [14]. Both male-to-female and female-to-male transmissions have been documented [15].

The story of Zika is rapidly unfolding, and the consequences of infection, particularly in pregnant patients, are potentially severe. Control of this infection will require concerted efforts on the part of epidemiologists, public health workers, clinicians, and vaccine researchers. Mosquito control programs involving insecticides and larvicides should provide protection against several potential arboviral infections, including West Nile virus. All of these efforts are expensive, but it is imperative that our legislators in

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Washington, DC, appropriate adequate funding for these efforts to move forward. Failure to do so could spell disaster and is likely to be more costly to society in the long run.

In a commentary in this issue, Brian Byrd reminds us that the Zika virus is not the only arbovirus of concern to North Carolinians [16]. La Crosse encephalitis, caused by La Crosse virus, is a common cause of arboviral infections in North Carolina. Although the disease is more common in the western part of the state, I personally diagnosed a case of La Crosse encephalitis in an elderly man from Eastern North Carolina several years ago. As discussed by Byrd, most cases of La Crosse virus infection are subclinical, but those who develop encephalitis frequently have lifelong neurologic complications.

Also in this issue, Tom Linden gives a thoughtful and entertaining perspective on the role of journalists in reporting emerging infections, using the recent outbreak of Zika virus in South America as an example [17]. In discussing these outbreaks, journalists have a different task than do clinicians and scientists, who are mainly communicating with their peers. Journalists must digest the vast and ever-changing body of scientific information and present it in a manner that can be understood by the lay public. Needless to say, this process is not always neat or easy.

Another topic discussed in this issue is the challenge of antimicrobial stewardship. Resistance of bacteria, fungi, and viruses to antimicrobial agents is becoming increasingly common. Misuse of antimicrobial agents in the inpatient and outpatient settings is a major factor that is contributing to this problem. It is estimated that up to half of antibiotics administered in the hospital setting are unnecessary [18]. Thus, antimicrobial stewardship has become a way of life in many large hospitals over the past decade. Interventions by pharmacists, with oversight from infectious diseases physicians, are crucial to patient safety. Antimicrobial stewardship in the hospital setting reduces unnecessary antibiotic use, saves money and resources, improves antimicrobial resistance patterns, and decreases rates of *Clostridium difficile* infection [19].

But what is the role of antimicrobial stewardship in other settings, such as outpatient clinics, office practices, and nursing homes? In a commentary in this issue, Philip Sloane and his colleagues discuss the challenges involved in antimicrobial use in the nursing home setting [20]. This population is typically elderly with multiple comorbidities. Antimicrobial use in nursing homes is frequently not clinically indicated (for example, in the treatment of asymptomatic bacteruria). Long-term care facilities are a setting where antimicrobial stewardship could have a positive impact on antibiotic resistance and *C. difficile* infection rates. Sloan and colleagues offer several suggestions that could potentially reduce unnecessary antimicrobial use and improve patient care. Given the directives from The Joint Commission [21], it is likely that we are going to see implementation of more protocols in the nursing home setting, similar to what hap-

pened in the acute hospital setting.

In the outpatient setting, the inappropriate use of antibiotics is no better. More than 70% of patients with a diagnosis of acute bronchitis receive antibiotics in this country, despite guidelines recommending that antibiotics not be used for this condition [22]. In our commentary in this issue, Muhammad Ashraf and I describe the use of antibiotics in various settings [23], and we discuss the importance of reducing antimicrobial use in each setting. Point-of-care testing and use of biomarkers such as procalcitonin may help clinicians feel more comfortable in withholding antibiotics when patients have a low risk of bacterial infection [24]. Given the problems associated with antibiotic use—diarrhea, hypersensitivity reactions, tendon rupture, and antimicrobial resistance—it behooves clinicians to think carefully before prescribing a drug that is not likely to help the patient. Clearly, this is a work in progress.

Benjamin Franklin's comment, "An ounce of prevention is worth a pound of cure," is certainly pertinent to the area of health care-associated infections. In an enlightening commentary, Zack Moore and his colleagues discuss the effects of several programs on the prevention of health care-associated infections in North Carolina [25]. Public reporting of infection rates has made administrators of hospitals, long-term care facilities, and rehabilitation centers acutely aware of this problem. Moore describes how nurse-driven protocols to limit urinary catheter use have been effective in reducing the incidence of catheter-associated urinary tract infections in one hospital in North Carolina.

The prevention theme is discussed further in Dennis Clements' article on vaccinations [26]. Vaccinations have transformed the field of medicine. Previously common, frequently lethal infections—such as tetanus, diphtheria, measles, and varicella—are now rarely seen because of effective vaccines for these diseases. Over the past several decades, researchers have come to appreciate the causal effect of chronic hepatitis B and human papilloma virus infection on the development of certain malignancies. Both hepatitis B and human papilloma virus vaccines have been shown to be highly effective in preventing hepatocellular cancer and cervical and anal cancers, respectively. Clements also discusses the use of cancer vaccines as adjuvant treatments for various cancers. Needless to say, more research in this area is needed.

The field of infectious diseases has been dominated by the AIDS epidemic for the past 35 years. It is estimated that nearly 37 million people worldwide are living with HIV. More than 50,000 new HIV infections occur each year in this country. With few exceptions, infection with HIV is a lifelong disease process. High-risk populations include men who have sex with men and intravenous drug users, both groups that are disproportionately represented in our prison system. In his commentary in this issue, David Wohl discusses the topic of HIV in the prison system, where the infection rate is approximately 5 times higher than in the general population

[27]. Given that nearly one-quarter of the world's prisoners reside in this country's prisons, the problem is anything but trivial. Wohl makes a strong case that incarceration leads to social disruption, which increases the risk for transmission of HIV in high-risk individuals. The transition from prison to society is frequently associated with poor linkage to care for HIV-infected individuals. Thus, reform of our penal system is necessary to deal with the HIV epidemic in high-risk populations.

Prevention of HIV infection is also a high priority. Methods of prevention include abstinence (100% efficacious but much less effective), condoms (effective if used), and vaccination (to date, not effective). Pre-exposure prophylaxis, using a combination of 2 medications approved by the US Food and Drug Administration (tenofovir and emtricitabine), has been shown to be extremely effective in preventing infection in high-risk individuals. In a sidebar in this issue, Nada Fadul discusses the data supporting the use of pre-exposure prophylaxis, including the patient population most likely to benefit from it [28].

Influenza, pink eye, head lice, and shigellosis are common infections that sometimes prevent children from attending day care or school. But what are the actual risks of allowing children with conditions such as head lice to attend school or day care? David Hill gives several examples of the risks of various conditions [29]. Although there are guidelines concerning these conditions from the American Academy of Pediatrics, it is clear that some school policies trump these recommendations. Often, children are excluded from school and day care by teachers and administrators with little or no medical background. Suffice it to say that there is much room for improvement in this area.

Influenza is responsible for thousands of deaths in this country each year. Epidemic and pandemic influenza A, as occurred in 1918, killed more people (20-50 million) than died in World War I [1]. Because of the antigenic shift that occurs within the viral genome, there is always the potential for another pandemic similar to the 1918 pandemic. Efficacious vaccines are available to reduce the risk and severity of infection, but vaccination rates are historically low for a variety of reasons. In this issue, Evette Cordoba and Allison Aiello discuss social factors involved in the susceptibility to infection with influenza [30]. Although racial and ethnic factors are important, the authors make a strong case that access to medical care and vaccination are the most significant factors to prevent infection.

Skin rashes are common in the primary care setting. Infectious etiologies are frequent causes of acute rashes, but many primary care providers are not comfortable diagnosing parasitic infections in this context. Practitioners frequently associate parasitic infections with travel outside of the country, and that perception is certainly true with conditions such as leishmaniasis, tungiasis, and trypanosomiasis. However, other parasitic infections—such as scabies, pediculosis, and cutaneous larva migrans—are commonly

acquired in this country, including in North Carolina. Scabies is frequently misdiagnosed, but it should be considered in elderly individuals, homeless persons, and impoverished populations. In their commentary, Mark Ash and Chuck Phillips give a very organized approach to the diagnosis and treatment of common parasitic infections [31]. Clearly, a heightened awareness of the problem is key to making a timely diagnosis so that appropriate therapy can begin early.

According to Sir William Osler, "he who knows syphilis knows medicine." Syphilis is a disease of antiquity. It may be forgotten, but it is certainly not gone. The incidence of syphilis dropped dramatically following the widespread use of penicillin in the 1940s, but there has been an increase in the number of cases over the past 15 years. The disease is much more prevalent in the western and southern United States. In North Carolina, the number of syphilis cases is higher in metropolitan areas (Mecklenberg, Wake, Guilford, and Forsyth counties), but the rates of infection are frequently higher in the rural areas of the state. Hertford County, for example, had the highest rate of syphilis in the state in 2014.

There has also been a recent increase in ocular syphilis in the country and in the state. Ocular syphilis typically causes posterior uveitis or panuveitis, and patients with ocular syphilis present with decreased visual acuity. In their commentary in this issue, Candice McNeil and Laura Bachmann describe the increase in syphilis rates and discuss the epidemic of ocular syphilis [32]. The primary care physician should consider ocular syphilis in the differential diagnosis of a patient with visual loss. Prompt referral to an ophthalmologist is critical, as early diagnosis and treatment are key to preserving vision.

In summary, this issue of the NCMJ discusses many common and timely infectious diseases that are important for the primary care provider to know. The articles are not meant to be encyclopedic, but they provide information and resources so that physicians will have a better working knowledge of the conditions in order to provide better care for their patients. **NCMJ**

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