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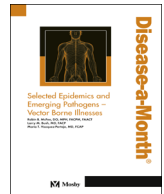
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EMERGING INFECTIOUS DISEASES – OVERVIEW



Robin B. McFee, DO, MPH, FACPM, FAACT (Guest Editor)

DeBusk College of Osteopathic Medicine, Lincoln Memorial University

Infectious diseases and the pathogens that cause them have posed significant public health threats for millennia, and plagued mankind since the dawn of humanity (Tables 1 and 2).^{1–7} Human encroachment into previously unexplored or underdeveloped regions, has led to changes in demographic migrations – human, vector and pathogen.^{4–6} This alters the ecology, as well as the adaptive ability of vectors, and pathogens and may release heretofore unidentified pathogens; all these contribute to a wider range of threat, thus posing potentially greater numbers of illness than previously reported.^{4–8}

Demographic migrations among humans and vectors are subject to a variety of influences.^{4–15} Natural disasters, civil wars and other conflicts result in displaced persons. For example, infectious threats among migrants – whether from traditional immigration or refugees seeking asylum in Europe and North America – needs to be considered, including vector borne illnesses, given insects may become attached to or transmitted with persons travelling.^{4–8} The seasonality of immigration ought to be considered, as well as region of origin. This is important, especially in view of the extent of spread involving the most common vector borne illnesses (malaria, dengue, and others), especially in the summer.^{9–18}

Not surprisingly, among the most ubiquitous, and adaptive vectors worldwide are mosquitoes and ticks.^{9–18} These two broad groups of vectors have resulted in enormous human suffering, and hundreds of millions of deaths, sickness, hospitalizations, as well as significant economic impact globally, especially in resource limited regions. Moreover, such vectors are associated with animal as well as human illness. Controlling the spread of mosquitoes and ticks remains a significant challenge; developing control measures that respect the balance between environmental sensitivity and eradication of human threats remains an important priority in public health, entomology, and veterinary medicine, and infectious disease management.

In terms of adaptability, the mosquito borne pathogens responsible for Dengue, Zika, and Chikungunya have demonstrated rapid geographical spread in recent years, causing dramatic increases in the burden of disease, including novel pathogens into the Western Hemisphere.^{9–18} It is important to recognize these, like other vectors are often capable of transmitting multiple pathogens. For example, *Aedes aegypti* (Fig. 1) and *Aedes albopictus* (Fig. 2) mosquitoes can

E-mail address: drrbmcfee@gmail.com

Correspondence address: Department of Emergency/Family Medicine, Lincoln Memorial University DeBusk College of Osteopathic Medicine.

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Table 1

Leading causes of death 1900 & 1997 US, 1992 Peru.²

Major Causes of Death (Attributable)	1900 United States	Peru 1992	1997 United States
1	Respiratory Disease	Respiratory infections	Heart Disease
2	Tuberculosis	Cancer	Cancer
3	Gastrointestinal disease	Gastrointestinal disease	Cerebrovascular disease
4	Heart Disease	Heart disease	Pulmonary disease
5	Infectious/parasitic diseases	Tuberculosis	Accidents
6	Kidney diseases	Cerebrovascular disease	Pneumonia/Influenza
7	Early infancy diseases	Urinary system disease	Diabetes
8	Cerebrovascular disease	Nutritional deficiencies	Suicide
9	Cancer	Early infancy	Homicide
10	Liver disease		HIV AIDS

transmit dengue, along with yellow fever, and West Nile virus.^{9–12,15} Moreover both *A albopictus* and *A aegypti* mosquitoes are experiencing a geographic expansion caused at least in part by the growth in global trade and travel.

As a mosquito borne illness, Dengue Virus (DENV) is the most prevalent arboviral infection in humans, and can cause severe clinical illness, including death.^{9–11} It is estimated that among the nearly fifty percent of the world's population living in regions putting them at risk for dengue infection, there are approximately 100 million cases annually. In this edition of Disease A Month, among the mosquito borne illnesses we will discuss, dengue will be covered in depth, with updates and an overview of other important similarly transmitted infections that clinicians will want to become more aware of, such as Zika, malaria, and Chikungunya virus (CHIKV). Although significant media attention, and public health efforts were given to Zika, especially during the recent Olympics in Brazil, CHIKV continues to express a wide geographic distribution,¹⁸ has resulted in over 2.5 million cases, and is well established in the Americas. Although the number of Yellow Fever cases is declining, the virus continues to cause human illness, in spite of vaccines. Of concern, vectors (mosquitoes) capable of spreading these and other illnesses can survive and thrive in North America, including many states within the United States, as will be discussed in this edition of Disease-a-Month.

Ticks are ubiquitous and spread a wide array of bacterial, viral, and parasitic illnesses, including Anaplasmosis, Babesiosis, Rocky Mountain Spotted Fever, Ehrlichiosis, Rickettsia, Lyme Disease, and Tularemia, as well as others.^{16,17,19,20} Patients infected with these often go undiagnosed initially, or are misdiagnosed. Contributing to this is the fact that the tick (*Ixodes scapularis*) that is capable of spreading Lyme Disease, can also spread Babesiosis, Anaplasmosis, and *Borrelia mayonii* (also causative of Lyme pattern of disease).^{19–22} Of note many of us were trained in an era when the arachnid vector for Lyme Disease was considered near exclusively to be “the deer tick” – *Ixodes dammini*.

Table 2

Top 5 Causes of Death for Persons 65 years of age and older.²

Whites	Blacks	American Indians	Asian or Pacific Islanders	Hispanics
1. Heart Disease	Heart Disease	Heart Disease	Heart Disease	Heart Disease
2. Cancer	Cancer	Cancer	Cancer	Cancer
3. Stroke	Stroke		Stroke	Stroke
4. COPD	Diabetes	Stroke	Pneumonia/Influenza	COPD
5. Pneumonia/ Influenza	Pneumonia/ Influenza	COPD	COPD	Pneumonia/ Influenza



Fig. 1. – *A. aegypti* from CDC.Gov.⁴⁴

Ticks (*Ixodes*) also have wide geographic distribution, and there are many capable of transmitting a wide range of pathogens that cause human and animal illnesses across North America. Some of these will also be discussed in this edition. Of concern, pathogens may be expanding their range of transmission capability; for example Lyme was initially thought to be relegated to the deer tick primarily. That has changed, and once considered limited to one or two tick vectors, is now spread more widely.^{19–22}

Not surprisingly, one of the most important tick borne illnesses we will discuss is Lyme disease,^{19–22} which continues to pose significant diagnostic and therapeutic challenges to patients, and health care providers. It remains an underappreciated epidemic in the United States. Of concern is the growing geographic distribution of ticks across North America, including ones capable of transmitting Lyme disease, resulting in rising numbers of persons afflicted. And, in spite of continued research in Lyme disease, this tick borne illness continues to present clinical challenges. Lyme Disease will be the primary focus of tick borne illness for this edition of Disease a Month, but others will be discussed so that the clinician can consider other similarly transmitted infections. Just as malaria is not the only mosquito borne illness capable of sickening humans, including travelers – vacationers, businesspersons, and the military, Lyme is not the only tick borne illness our patients can experience from a tick bite.

In *Emerging Pathogens - Part 1*, which was published in the September 2017 edition of Disease a Month, we talked about potentially contagious respiratory pathogens specifically, and emerging threats in general,^{23–29} especially Influenza viruses, and Middle East Respiratory Syndrome (MERS) Coronavirus.^{23,24,28,29} In this edition we will discuss a slightly different form of disease propagation – vector borne illnesses. One of the interesting aspects of VBI is the fact



Fig. 2. – *A. albopictus* from CDC.Gov.⁴⁴

that if someone is infected with a pathogen that is heretofore not present in a region, but has a mosquito or similar vector that is capable of contracting and spreading that pathogen, the potential exists for small amounts of individuals to introduce a disease into a region previously naïve to that infection.

Emerging pathogens – respiratory or vector borne – are a reminder that we must always be vigilant against public health threats. Yes there has been a significant shift in the top ten causes of death in the United States from the beginning to the end of the 20th century, and into the present, (Tables 1 and 2).^{1–3} Where once infectious diseases were leading health care concerns, these have been largely replaced by cardiovascular disease and cancer. Because of our location, significant public health resources and medical infrastructure, along with wide spread immunizations against a broad array of pathogens, the United States (US) has been fortunately isolated from many infectious diseases, that typically cause much suffering for other regions of the globe, with the notable exception of tuberculosis (TB), HIV/AIDS, Lyme, West Nile, pneumonia, and influenza related illness, as well as hospital acquired infections. That notwithstanding, for a large proportion of the planet, infectious diseases remain the leading causes of death, disability, in some cases preventable blindness^{25,26} and other serious sequelae. But with widespread travel – nearly a billion people travelled through airports and other transportation hubs – along with dramatic growth in imported agriculture and other products, land and sea borders no longer provide the significant protections they once did, and North America now faces the potential for a resurgence in infections. Zika, Chikungunya, Dengue, and Malaria, are just a few of the vector borne pathogens that likely will continue to threaten the US, and other regions.

There are many vector borne illnesses that can or do present a threat to the US and North America, as well as other regions globally, but recent events in Brazil, the Caribbean, Europe and the US, including changes in epidemiology, clinical presentation, and therapeutics involving Zika, Dengue, and Chikungunya, make it reasonable to discuss these mosquito borne illnesses, along with an overview of other clinically important vector borne illnesses.

Of note, every effort has been made to provide the most up to date information on the vector borne illnesses covered in this edition of *Disease-a-month*. Moreover, when there is a divergence of expert opinion and recommendations referable to any of these illnesses, we will provide both options. For example, the Centers for Disease Control and Prevention (CDC)^{30–32} is now recommending the use of doxycycline in the treatment of Rocky Mountain Spotted Fever, and other vector borne illnesses susceptible to tetracycline antimicrobials in patients under the age of 8 years old.

The CDC references a study on the use of doxycycline in the treatment of rickettsial infections, the highlights of which include^{30–32}:

- Doxycycline is the most effective antibiotic for the treatment of suspected rickettsial infections, including Rocky Mountain spotted fever (RMSF). Misperceptions about the use of doxycycline for children prevent kids from getting lifesaving treatment.
- Delay in treatment of rickettsial diseases may lead to severe illness or death. Children are five times more likely than adults to die from RMSF.
- Misperceptions about the use of doxycycline for children prevent kids from getting lifesaving treatment.
- Doctors often avoid prescribing doxycycline to young children because of a warning that tooth staining may occur when used in children less than 8 years old.
- In a new study, experts at the CDC and Indian Health Service (IHS) found that short courses of the antibiotic doxycycline can be used in children without causing tooth staining or weakening of tooth enamel.

The CDC notes that the concern about teeth being stained arises mostly from early tetracycline antibiotics, but that doxycycline binds less readily to calcium, and has not shown the same degree of staining as earlier tetracycline. In a study by Todd et al., the authors concluded

among children who received short-term courses of doxycycline that it failed to demonstrate dental staining, enamel hypoplasia, or tooth color differences. In a study by Volvitz,³¹ the authors noted that in children who received doxycycline for asthma, there was no evidence of dental staining. CDC raises concerns that the case fatality rate is highest among the youngest patients with Rocky Mountain Rickettsial infection; delaying treatment for rickettsial infection can lead to severe disease or death.

On the other hand, the Infectious Diseases Society of America³³ cautions against the use of doxycycline in that cohort. Both organizations present cogent arguments on behalf of their recommendations. As always, the clinician must weigh the risks and benefits of our approaches to treating patients.

In Part 1 of this recent series on Emerging Pathogens published in *Disease –a – Month*, we discussed the epidemiology of infectious diseases, focusing on some of the more problematic respiratory threats, including the newly identified coronavirus Middle East Respiratory Syndrome Coronavirus (MERS CoV),^{28,29} and the H7N9 influenza virus.²³ In this edition, we will discuss vector borne pathogens that are clinically significant, especially to North America, along with diagnostic, therapeutic and preventive strategies. To be sure there are a variety of intermediaries that allow pathogens to invade their ultimate hosts – often humans. Owing to the significant increase in arbovirus and other infections globally, with dramatic expansion into North America, it seems prudent to focus on Emerging Pathogens – Vector Borne Illnesses in this edition of *Disease-A-Month*, especially on mosquito and tick borne illnesses in general, and some of the most problematic pathogens in each category.

In addition to many of these being endemic to North America, some remain predominantly (at least for the moment) in other nations. We recommend referring to <https://wwwnc.cdc.gov/travel/notices> for updates on illnesses in countries of interest to future travelers, as our patients could potentially return with a travel related illness. In addition to the CDC Yellow Book, this site is useful for clinicians who advise such patients.

Most of the world still bears an enormous burden related to infections. Recognizing the US is a major international tourist attraction and business venue for persons from across the globe, many visitors – tourists, immigrants, business and military travelers^{7,8,34–37} - coming from regions where infectious diseases are far more common than in our nation, we must be aware of, and prepared to recognize the cascade of symptoms (biodrome)³⁸ often associated with the most severe of those diseases we may be called upon to treat. This will allow us to better care for such patients, along with reducing the risk of outbreaks. Moreover we must continue with the progress gained in the aftermath of the recent Ebola outbreak, in terms of improved awareness of international travel among our patients; this includes Americans as returning vacationers, military, and business travelers who have been to regions where a wide array of infectious diseases persist. Not to put too fine a point on this but in 2015 over 1.2 billion persons represented tourist arrivals in all countries. Depending upon destination site, between 22 and 64% of travelers report some form of illness, and a not insignificant percent will not seek pre-travel health consultation.^{39–41} Malaria remains a concern in travelers returning to their countries of origin.³⁹ Billions of people worldwide are exposed to important and emerging infectious diseases, some of which will visit North America.^{39–41} it is important that we provide greater training to our health care professionals. Studies suggest suboptimal diagnosis in travel related illness patients upon initial presentation to treating sources.^{42,43} Consequently, it is our hope that this edition of *Disease-a-Month* will be a useful component in training about and preparedness for such emerging pathogens.

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