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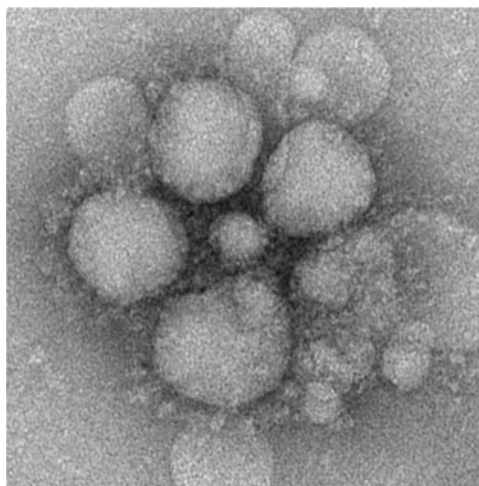
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SELECTED EPIDEMICS AND EMERGING RESPIRATORY PATHOGENS

Robin B. McFee, DO, MPH, FACPM, FAACT



MERS Coronavirus (www.cdc.gov)

INTRODUCTION

“The single greatest threat to man’s continued existence on earth is the virus.”

Joshua Lederberg, Nobel Laureate

As any health care professional can attest, there are many epidemics of public health concern in contemporary society. These include the epidemic of heroin overdoses, the epidemic of inner city violence and gunshot injuries, the epidemic of childhood obesity and childhood hunger, and the list goes on and on. And, while any of these epidemics are critically important, negatively influence health outcomes, could and likely will be addressed at least in part in future *Disease a Month* issues, the concept of epidemic that we will discuss concerns emerging pathogens.

In the developed and developing world, infections, especially respiratory illnesses still pose a significant health risk [1–10]. In spite of tremendous advances in medical research, public health and international medical cooperation, lower respiratory tract infections remain the leading cause of death worldwide, especially in regions with limited infrastructure and resources, and resulting in an estimated 3.2 million deaths in 2015 [3].

The emerging pathogen Zika virus and the recent outbreak in Brazil is yet another example of the power of viruses to threaten human health [4–8]. By 2015 international public health concerns had escalated, especially recognizing the summer Olympics of 2016 would introduce significant international visitations to the region. Zika underscored the threat, and challenges associated with emerging pathogens. Zika also demonstrates the changing nature of infection threats we face in the United States, and worldwide. Once considered the cause of mostly minimal symptoms and confined regionally [5–7], such is no longer the case, as Zika can now be found from Africa and Asia, to the Western Hemisphere, and is capable of causing significant neurological problems [5–8].

As Lederberg would likely have advised, the more we learn about virus behaviors, vector borne transmission, and host – virus – vector relationships, we recognize oceans or geography no longer isolate or protect us. Therefore it becomes evident

our patients as tourists, the military, and business travelers not only can become infected with pathogens and illnesses that we may not be accustomed to seeing in our regions, moreover they may provide the first blood meal to a mosquito that can then introduce such pathogens into the United States. It is postulated an outbreak in Cape Verde occurred this way [5,9]. As such, the need for greater attention to travel associated illness in our patients – from pre travel guidance, to return from travel follow up, an important new component to our practice patterns.

Zika and Chikungunya [10] infections are but two of several important mosquito borne illnesses which will likely pose a threat to the United States from sporadic cases to outright epidemics, and will be discussed in a subsequent edition of *Disease a Month*.

The United States health care community will increasingly be called upon to treat what most of the world still lives with - an enormous burden related to infections [2–22]. Will our training be up to the task? Recognizing billions of people worldwide are exposed to important and emerging infectious diseases, our training still has largely relegated this topic mostly to “tropical medicine” or public health or labeled the threat as a “zebra” item [3,14–27]. While most of us remember from our early medical training the old adage “If you hear hoof beats, think horses, not zebras,” the US, and our attention, including medical training, can no longer afford to follow this adage or relegate these so-called “zebras” to the dismissed column, given many of which are important global health concerns. The world has come to our country as much as we have travelled to the world [2,3,14,15,17,22,23,26–30]. And by extension – the world’s diseases have come to our communities, clinics, emergency departments and health care facilities.

Globalization, population shifts and the changing ecology, including encroachment of previously unexplored regions has altered the longstanding epidemiology of infectious diseases – causing spread where once continents and oceans contained the pathogen [3,14,17,24,31–36]. New pathogens are occurring – some through unknown means, and others through natural adaptation. It has long been recognized that influenza viruses exchange genetic material, either emerging as a new strain, as we continue to see with H5N1 [19,37], H1N1 [32], and now the latest H7N9 [6,38–40]. But this likely holds true for other viruses, as recently demonstrated with a novel coronavirus, most recently referred to as Middle East Respiratory Syndrome (MERS CoV) [11].

Social determinants of health – poverty, overcrowding, lack of infrastructure in many developing nations (and in some of our own cities), poor sanitation, inadequate clean water, under-immunization and lack of health care access, environmental changes resulting in expanding zones for mosquitoes, and the pathogens they transmit, cultural concerns about modern medicine, and restrictions on vector control – public opinion, cost, safety, impact on the ecology, and population migration – have all contributed to a resurgence in certain infectious diseases, and a spread to areas previously unaffected, including the United States.

To be sure, the multiple societal, political, and economic influences to health, and the control of potentially contagious illnesses that may seem beyond the influence of physicians and health care providers, such as demographic shifts, poverty, health care facility closures resulting in overcrowding of remaining facilities, financial constraints on services, limited public health resources, and the like. That said, health care professionals are held as important contributors to a community, and can therefore positively influence constituents, as well as make important contributions to the health of the population.

These include implementing training for workers throughout the patient encounter – from registration clerk to treating professional, from learning to better recognize travel associated illnesses, infectious and other pathologies that may be uncommon to the US but are endemic in regions of origin for migrants and travelers (visitors or returning residents) to our communities, as well as empowering employees to raise concern about, and bring in assistance in a more timely manner. The US is no longer isolated and protected as in decades past. Such complacency imposes a steep learning curve. In the 21st century where globalization is the new norm, hoof beats are no longer solely the sound of US bred horses. This is especially true given human exploration into and encroachment of regions across the globe that have been largely undisturbed through the centuries. In so doing we have or likely will release pathogens unknown to us, setting in motion the potential for outbreaks.

Not surprisingly, infectious disease transmission primarily occurs through person to person contact (respiratory, fecal oral, blood exchange, intercourse), through fomites, instruments (drug paraphernalia, inadequately cleaned medical/surgical equipment) and vectors (mosquitoes, ticks, worms).

Although great strides have been made over the last twenty years, including the ability to describe the etiology of variety of disease states by the same pathogens, and symptom syndromes that previously remained mysteries w/out clear cut etiologies, including Parvovirus B19, cytomegalovirus (CMV), Epstein-Barr virus (EBV) and others, never the less, pathogens and the vectors that facilitate their transmission, remain a persistent danger. Dr. Lederberg was prescient when he opined about the challenges for humans that viruses pose. Against this backdrop of new, reemerging, potentially travel related, and newly adapted, more virulent pathogens, one can appreciate there are numerous emerging infectious threats that are suitable for an entire edition of *Disease – a – Month* to address.

Clearly there are many pathogens to discuss [41–46], and train for in the US, but we would be remiss to ignore the most significant newly emerging infectious diseases - ones that have the potential to impact large populations, and cause serious illness, such as the highly pathogen coronaviruses – SARS and MERS, and vector transmitted malaria [47,48], dengue, Zika, and Chikungunya viruses which will be covered in a future *Disease a Month*.

Important to recognize are changing patterns of infectious illness within the United States that have evolved over the last decade; pathogens that may have had limited regional expression, or seasonal appearance in the past, have expanded in scope, but often remain unrecognized or underappreciated, such as Lyme Disease [36] or Babesiosis. The CDC suggests that the actual number of persons infected with Lyme disease is significantly greater than what is reported. Babesiosis, a malaria-like tick borne illness is an under recognized, but emerging infectious disease. Also there are pathogens new to the US, such as Chikungunya virus [6,49] – one of the most recent mosquito borne illnesses to be identified in the United States.

Newly identified, reemerging or more virulent strains of more commonly identified pathogens have occurred, such as the pandemic avian influenza also referred to as highly pathogenic avian influenza HPAI H5N1, or the latest to be reported from China – Influenza H7N9. Severe acute respiratory syndrome (SARS) coronavirus from 2003 demonstrated that a previously considered low acuity pathogen could emerge in a more deadly form; this is underscored by the most recent and more deadly coronavirus - Middle East Respiratory Syndrome coronavirus (MERS CoV), which will be discussed later in this issue.

Moreover infectious diseases previously considered controlled, such as pertussis, even varicella (Image 1) measles (Image 2) and mumps, have reemerged, in no small measure to the anti-vaccine movement that remains a strong voice in contemporary society, and a challenge for health care providers, as well as dangerous to public health preventive measures.

Consider the dynamic interplay between basic reproductive rates (R_0) for pathogens and the percent of the population that must be immunized to control illness [50]. R_0 is representative of the contagion potential, the human to human communicability, or the average number of persons who become infected by a single source. Put another way, it represents secondary transmission from one case. For example the transmission rate of Measles (R_0) is estimated at 12 – 18, i.e. the number of persons expected to become sick after contact with that one infected patient. Pertussis, another respiratory pathogen has caused local outbreaks, sharing a similar R_0 with Measles of 12 – 17. To optimize herd immunity, a community must have at between 83 – 94% vaccinated against measles, and 92 – 94% vaccinated against Pertussis, to limit spread. Although some have suggested the R_0 of measles to be less in the post vaccination era for developing countries, the fact remains that it is still a highly contagious pathogen, and requires continued high vaccine rates for effective control. Developing countries continue to have lower than necessary vaccine rates; travelers from such regions can therefore pose a health risk if infected. [50]

Other contributors to communicable disease spread include inability to adequately control vectors – especially mosquitoes and ticks which have expanded their regions of influence, and with that, the ability to spread a variety of pathogens. Of note US mosquitoes are more than capable of spreading Dengue (Image 3), and other dangerous microbes. Notably if cases are identified in a region, they pose a threat as a source for mosquitoes to further spread the infection.

Clearly contributing to infection spread is overcrowding – from poverty where many persons live in close quarters, to public transportation which increasingly is overburdened, to emergency departments that more often than not fail to provide space for social distancing, e.g. cohorting/isolating potentially contagious patients. A recent visit to a medical center revealed how sub-optimal are efforts at infection control, where hand sanitizers, masks and instructions on basic hygiene practices were difficult to find, and when available, poorly placed. Clearly there is a need to develop the culture of infection control.



Image 1 – Varicella/Chicken Pox



Image 2 – Measles (www.cdc.gov)



Image 3 - Chikungunya

Cohorting contagious patients from injured or non-infectious persons should not be a Herculean task in 21st century healthcare. Can we not do better than inadequately following up with persons ill with pathogens that if undertreated, could lead to antimicrobial resistance as well as outbreaks in an era of computerization? Lack of resources to clean hospital rooms, and other health care facility associated issues such as catheters, test equipment, curtain/bed contamination, and antimicrobial resistance all contribute to infection spread. According to the Centers for Disease Control and Prevention (CDC) 1 in 25 hospitalized patients has a healthcare-associated infection [24].

Other Infection Controls

Additional low hanging fruit, which is not to say barriers don't exist to improvement, include good environmental and infection control practices remain inconsistent across departments, and facilities; hospital acquired infection rates, and delayed diagnosis rates of travel associated illness are testament to the learning curve and challenges we face. More research is needed into how best to cohort patients, the use of quarantine and isolation, along with more efficient ways of implementing these if necessary. Working with facilities and other management – nursing, infectious disease, administrators - we can create less infection friendly environments from the emergency department to the hospital room, and testing sites within the facility.

Vaccination

Another area of concern that all health care providers can make an important contribution is vaccination rates. They are not universal across the populations within our midst. This is supported by government studies, and well described in a recent report from the Trust for America's Health (TFAH) [58], a nonpartisan, nonprofit research enterprise. They recently published a study designed to assess the performance of 50 states and Washington, DC based upon 10 indicators that relate to the treatment/prevention of infectious diseases (including HIV, influenza, and pertusis). TFAH relied upon publicly available and government data to examine the emergence and reemergence of specific infectious diseases. The results are not inspiring. Based on a scale of 1 to 10 – with 10 being the highest positive ranking – the majority of states earned a score of 5 or lower. New Hampshire earned the highest score – 8. Georgia, Nebraska and New Jersey were ranked at the bottom with a score of 3. Of additional concern, more than 2 million American children under 3 years of age do not receive all of the vaccinations recommended by the Department of Health and Human Services, and at risk for whooping cough and measles. Not surprisingly both illnesses have reemerged in the last few years. Not to put too fine a point on this, but according to the TFAH study, only two states – Connecticut and Delaware – met the recommended requirement of fully vaccinating 90 percent of children ages 19 months to 35 months.

As an aside, years ago my colleagues and I started a church based flu shot clinic; often providing 100 free influenza vaccinations at the event; with a congregation of 125 that's not insignificant, especially given the remaining persons received their vaccines elsewhere. Each recipient also received a vaccine card for their medical records.

Non-traditional, community based approaches to healthcare have continued to increase throughout the US, and can be utilized to increase surveillance and provide vaccines, as well as front line care. These will be needed as public health resources continue to dwindle. Critical of course is interconnecting these enterprises so that in the process of increasing access, we don't create multiple isolated islands. Throughout history, faith based enterprises have been good places to reach often at risk populations. Schools and other community enterprises are important points of contact.

HCPs are noted for resourcefulness, and this is nowhere needed more than in encouraging, and increasing immunizations for adults and children, especially as pertain to respiratory and other communicable pathogens that include but not limited to influenza and pneumonia to pertusis and hepatitis.

An entire edition of *Disease a Month* could be devoted to immunizations – what are needed, what are in development, what we have, and how effective at delivery for adults, children, and immigrants. Let it suffice, there is room for improvement in providing the vaccines we do have while encouraging development of those we need to address emerging pathogens.

TRAVEL AND IMMIGRATION RELATED ILLNESS

Travel

An introduction on epidemics and emerging pathogens would be incomplete without a discussion of travel associated illnesses (TAI) which is an important conduit between diseases found overseas and the people who can become exposed by travelling to areas of illnesses endemic to their location but perhaps not found in the US, and therefore may be unfamiliar to our health care providers. Not only does this pertain to immigrants, vacationers, and business travelers, but also our returning military. Servicemen and women are tasked with working in a variety of inhospitable and dangerous regions with endemic illnesses not typically found in the United States, such as malaria,

Physicians can be an important source of counseling about pre-vacation or pre-business travel health concerns – from specific information about local travel clinics which are becoming increasingly prevalent in urban centers, to infection and vector risks, to safety, and health resources to guiding patients towards CDC, and CIA sites [51,52]. The importance of our efforts – which can be accomplished by placards and chart prompts – cannot be underestimated. A recent study of tourists visiting a national park in the United States Virgin Islands where mosquito borne illnesses, including Chikungunya virus are present, revealed most visitors surveyed did not research destination related health concerns and were unaware that Chikungunya virus was present or problematic [53]. This is similar to other studies where travelers did not access pre-trip health information sources, many of which are readily available on the Internet [53–57].

A more in depth discussion of TAI is in the Prevention Section of this edition.

Immigration

In addition to well established pathogens within the US, the rising numbers of immigrants from regions that typically don't enjoy the same robust public health services, availability of vaccines, or good medical care, pose a threat of contagion from communicable diseases long since controlled, or not typically encountered in the United States, such as multidrug resistant tuberculosis (MDR TB). According to the CDC approximately 80,000 refugees and 500,000 immigrants come to the United States from around the globe [17,24].

Immigration demographics have changed over the years, and in the aftermath of war torn regions, have invited refugees from the Middle East and Africa, in addition to Mexico, and South America. Each region is nuanced in terms of pathogens that pose a communicable risk, as well as causing illnesses such as food borne diseases that may be initially misdiagnosed or attributed to more localized pathogens. Even the limited belongings can transport pathogens and insects [17].

Related to immigration is the concept of population mobility – which may increase the potential for establishing transmission of new infections- as seen with dengue and Chikungunya fever - in areas where vector mosquitoes preexisted but did not prior to these changing demographics spread such infections. Immigrants have ongoing links with populations in their countries of origin that may provide a channel through which infectious diseases potentially can be introduced to new areas. This is consistent with epidemiology data. The CDC Emerging and Zoonotic Infectious Disease Initiative budget request outline notes that Chikungunya Virus is emerging to the point where over 900,000 suspected cases reported since the first local transmission in the Western Hemisphere was noted in 2013.

An important subgroup of immigrants involves children, as refugees, immigrants, or having been adopted – many of whom are not vaccinated for communicable diseases such as polio, chicken pox (Varicella – Image 1), and measles (Image 2). As noted in the mass migration of children to the US Southern border a few years ago, scabies and lice were also problematic, and can cause significant challenges to treating as well as housing facilities, hospitals, and providers' offices.

Lessons Learned From Recent Events

In the December 2013 Disease a Month issue [25] we discussed the threat of multiple global infectious diseases – and the possibility that many of the illnesses described typically located in distant lands could and would emerge in the United States. This included an in depth look at the viral hemorrhagic fever virus (VHF) Dengue, with an overview of VHFs that could pose a threat, including Ebola.

If any benefit can be attributed to the Ebola epidemic of 2013 – 2016 it may be the increased sensitization of our health care professionals, including emergency departments, referable to travel related disease, occupational exposures and emerging threats. The increase in face masks, instructions to patients who might be infected with a contagion, and attempts at isolating such persons, are important steps towards limiting outbreaks.

One important VHF - Ebola demonstrated in the outbreak of 2013 through 2016 how historically stable patterns of outbreaks can change, and what was once considered an isolated, regional pathogen can become widespread. Ebola taught us to expect changes in outbreak patterns. Previous to the Ebola Virus (EV) 2013 – 2016 outbreak involving thousands of persons infected, most EV outbreaks involving this viral hemorrhagic fever virus resulted in very limited numbers of patients.

Taking all these into consideration, it is not surprising infections remain a leading cause of death worldwide, and will likely reemerge as a significant problem for the US. Historically the United States has been able to significantly control many of the infectious disease that continue to afflict much of the rest of the world; unfortunately the pathogens long held to be other nations' problem, are increasingly becoming a threat to us nevertheless.

Conclusion

There are many emerging pathogens of interest that could be contained in this edition, and were we to address all of them you would be holding a large textbook instead of an article. In future editions, the issues of hospital acquired infections will be revisited, as will other emerging threats of importance as timely information becomes available. We are fortunate to be in a somewhat quiet period in terms of deadly outbreaks such as SARS, avian flu, the recent swine flu epidemic, Ebola, and MERS; but we cannot afford to be lulled into complacency. It is our hope this article will increase awareness for, and spur interest in, as well as catalyze activity towards addressing our vulnerabilities to emerging pathogens. In doing so, our patients will be healthier, and our communities can become better prepared for the next epidemics.

Table 1 Leading causes of death 1900 & 1997 US, 1992 Peru [11].

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

Table 2: Leading causes of death US 2015 CDC FASTATS [11].

Major Causes of Death	2015 US	Number of deaths
1.	Heart disease	614,348
2.	Cancer	591,699
3.	Chronic lower respiratory diseases	147,101
4.	Accidents (unintentional injuries)	136,053
5.	Stroke (Cerebrovascular diseases)	133,103
6.	Alzheimer's disease	93,541
7.	Diabetes	76,488
8.	Influenza and pneumonia	55,227
9.	Nephritis, nephrotic syndrome, and nephrosis	48,146
10.	Intentional self-harm (suicide)	42,773

As Table 2 demonstrates, the United States continues to have significant and largely preventable infection related deaths in spite of improvements to healthcare, newer medications and more advanced interventions over the last two decades. Influenza and pneumonia are vaccine preventable diseases. Albeit host immunity plays a role in the success rates of immunization, nevertheless, if vaccination penetration were significantly improved, there is great likelihood of protection from herd immunity which could contribute to a decline in morbidity as well as mortality.

Although one could fill entire editions of medical journals with many of the emerging or persistent and significant pathogens facing health care professionals in the United States, this edition of *Disease a Month* will focus on emerging respiratory pathogens, influenza viruses, including H7N9, and coronaviruses including MERS CoV, along with a brief discussion on some preventive strategies.

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SELECTED EPIDEMICS & EMERGING PATHOGENS – RESPIRATORY ILLNESSES – AN OVERVIEW

As discussed earlier, infections remain a leading cause of death worldwide, as well as in the United States [1]. Of concern, some of these infections are associated with vaccine preventable pathogens, such as *S. pneumoniae*, and influenza [1,2], the morbidity and mortality of which could thus be significantly reduced or prevented were immunization rates higher, in both the developed and developing countries. In addition to well studied pathogens, novel and more virulent ones continue to be identified, that are capable of causing human and animal illness. These include various avian influenza strains [2–6], metapneumovirus [7], multidrug resistant tuberculosis [8], more aggressive coronaviruses [9–12], and others. Respiratory Syncytial Virus (RSV) is an underappreciated respiratory pathogen. While it is well known as the most common etiology of lower respiratory tract infections in children, resulting in nearly 2.1 million outpatient visits among those less than 5 years of age, and over 57,000 hospitalizations in the same cohort, it is estimated that RSV causes 177,000 hospitalizations, and 14,000 deaths among adults over 65 years of age [13–15]. RSV clinically is variable in presentation, referable to age, patient health and comorbidities. Young healthy individuals typically experience mild, cold-like symptoms, with recovery expected in one to two weeks. Infants present with bronchiolitis, adults mild upper respiratory infections (URI). Severe pneumonia may occur, especially the elderly who have comorbidities, and/or impaired cellular immunity. Aerosolized Ribavirin can be used for RSV in infants. Risk benefit must be balanced when considering the use of Ribavirin in adults.

New pathogens are being discovered – some through unknown means, and others through natural adaptation. Globalization, population shifts and the changing ecology, including encroachment of previously unexplored regions has altered the longstanding epidemiology of infectious diseases – causing spread where once continents and oceans contained the pathogen.

Influenza viruses are ubiquitous in the animal population, with a wide array of natural hosts, and possess the capacity through the phenomenon of reassortment to infect an expanded range of hosts, including humans, as well as acquire greater pathogenicity [16–22]. Pandemic influenza viruses can thus emerge [16,18–22].

It has long been recognized that influenza viruses exchange genetic material, (reassortment) either emerging as a new strain, as we continue to see with H5N1 [16,23–25], H1N1 [26–28], and now the latest H7N9 [3,4,29,30]. But this likely holds true for other viruses, as recently demonstrated with a novel coronavirus, most recently referred to as Middle East Respiratory Syndrome (MERS CoV) [11,12].

Given the proximity of people to animals, through occupation and avocation, the human-animal interface becomes a significant risk for human illness from influenza viruses, as has been seen in several outbreaks, including H5N1 since 1997 [16].

There are a multitude of respiratory pathogens worth describing. However, with the recent emergence of yet another highly pathogenic avian influenza – H7N9 [29,30] and novel coronavirus (MERS CoV) which appears more deadly than SARS