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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

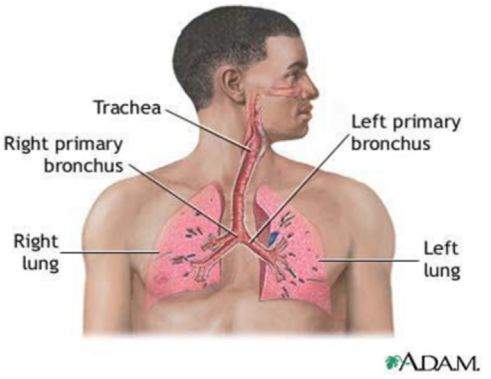
CoV [11,12], it seems worthwhile to discuss these infectious agents. It is hoped that lessons learned from these latest outbreaks can be applied towards preparedness against a wide range of pulmonary threats, and enhance our infection control capacity.

Regardless which emerging pathogen we discuss – Avian Influenza H5N1, H7N9, MERS CoV, swine flu or other viruses, it is important to recognize that preparedness efforts as a response to a potential pandemic caused by swine or avian influenza, SARS or MERS, can also enhance awareness, promote vaccine use, advances in diagnostic and treatment capabilities toward other significant infectious disease worldwide.

Controlling infectious diseases can be challenging given the large number of disease causing pathogens, their capacity for adaptation to environmental changes and antimicrobial therapies, and opportunities for spread. Respiratory contagions remain an issue of enormous concern in the containment of infections, especially with overcrowding and other population, social, and travel determinants.

The spread of pulmonary infections occurs readily from both the upper and lower respiratory tracts (Figure 1)

Fig. 1 – Respiratory infections (Upper and Lower) can readily be spread airborne [6,26–30].



How respiratory illnesses spread [6,26–28]

- Droplets
- Proximity (Less than 6 feet social distancing especially)
- Environment (overcrowding for example)
- Fomites
- Mucosa
- Prior immunity (or lack thereof)
- Poor hygiene
- Inherent transmissibility of pathogen (Ro)

In the next section we will discuss influenza viruses, including the newest pathogenic one H7N9, and coronaviruses. Although traditionally they caused mild respiratory illness, from 2003 there are more highly pathogenic CoV illness causing ones, as seen with SARS coronavirus, and MERS coronavirus.

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EMERGING RESPIRATORY DISEASE – INFLUENZA VIRUS OVERVIEW

The term “influenza” describes an acute viral disease of the respiratory tract often referred to colloquially as “the flu.” It is caused by viruses belonging to the orthomyxovirus family, which includes the genera of influenza virus A, B, and C. These are defined by the antigenicity of their nucleocapsid and matrix proteins (Figure 2) [1–8]. Influenza A viruses are negative sense, single-stranded RNA viruses, with an 8 segment genome that encodes for 10 proteins [3,5,9], and are usually associated with more severe human illness, epidemics, and pandemics. These viruses are further classified or subtype based upon two surface proteins – haemagglutinin (H), which attaches the viral particle to the host cell allowing entry, and neuraminidase (N) which facilitates the spread of progeny virus. The Neuraminidase protein is the target for the class of antiviral therapy referred to as neuraminidase inhibitors [1,2,4,6,7,9–14]. There are 16 H proteins, and 9 N subtype proteins – the combination of which make up all the known Influenza A subtypes [11,12].

Important to recognize from the perspective of pathogenicity, and potential contagion, even pandemic threats are the concepts of “antigenic drift” and “antigenic shift.” “Antigenic drift” refers to the various mutations and changes in surface antigenicity of surface proteins as a response to host immunity. H9N2 viruses that were isolated in chickens from China were noted to undergo antigenic drift, in order to evolve into distinct antigenic groups [15–21] This may have resulting in some of the immunization failure noted during China’s long term vaccination program for chicken farms [15,20]. “Antigenic shift” is an event that can lead to the creation of a novel virus against which humans have little or no immunity. Recognizing influenza has a segmented genome, shuffling of gene segments can occur if two different subtypes of influenza A virus co-infect the same cell. Conditions that favor the emergence of such “Shifts” have been surmised to involve humans living in proximity to farm animals (human – animal interface), especially poultry and pigs [15,19]. Of note, swine are susceptible to infection from both avian and mammalian host preference influenza viruses [15,19].

In Southern china dogs were noted to have serology positive avian origin H9N2 influenza. Ferrets and other mammals have been noted to have avian infection as well. Such an expanded host range reveals a potential threat whereby a pathogenic influenza virus with low human to human transmission can intermingle and share genetic material with an influenza virus possessing high capability for human spread. To date, H9N2 is endemic in Eurasia, and has caused significant morbidity and mortality in poultry, as well as lost egg production [15].

Of note, co-infection with other pathogens is possible in the animal, as well as human host range. For example, H9N2 has been shown to make poultry more susceptible to secondary infection, especially E Coli, with a resulting fatality rate estimated at 10% [15].

The expansion of host range is not uncommon in influenza viruses. For example, if an H3N2 and an H5N1 virus co-infect a human or pig, it is possible a new virus such as H5N2 could emerge; a hybrid could combine the high virulence of H5N1 with the efficiency of human to human transmission found in the “parent” human virus. [13,21].

According to the World Health Organization (WHO) influenza at the human-animal interface report for 20 December 2016 – 16 January 2017 [22] there are new human influenza infections reported. These include Influenza A (H7N2), A (H7N9), and A (H9N2).

H9N2 is a low pathogenicity virus, with wide distribution, and seropositivity is not uncommon in occupationally exposed poultry workers [15–21,23]. Because it circulates at the human avian interface, the potential for new reassortants, not the least of which would be a new epidemic or pandemic subtype underscores the importance of better infection control, and human protective measures, including occupational hygiene. In rural areas, domiciles shared with flocks, undercooking of birds, eating raw eggs and poultry blood are also risk factors.

During this period, China also reported to WHO 100 laboratory confirmed human cases of H7N9, the majority from Mainland China [22]. To date 918 laboratory-confirmed human cases of H7N9 were reported, with at least 359 deaths.