There are numerous examples of infectious diseases that have wreaked havoc on the human population. Analysis of previous outbreaks has provided insight into the various ways that infectious diseases can be transmitted both between members of different species and among members of the same species. Furthermore, a thorough understanding of past outbreaks enables public health agencies to develop an informed approach to predict when new emerging or re-emerging infectious diseases will surface. Anticipating an infectious disease outbreak is essential to preparing an effective response strategy. The transfer of disease between species is of particular concern as a reservoir of emerging infectious diseases (EIDs) since approximately 75 percent of EIDs are estimated to have zoonotic origin. Bird-flu, or influenza strain H5N1, is an emerging disease of avian origin that is expected to cause the next influenza pandemic and has already begun to surface in humans from a wide geographic area. Frontline clinicians need to be aware of the signs and symptoms of H5N1 infection. Successful control of an H5N1 outbreak relies upon accurate identification by clinicians, reporting of an outbreak to public health authorities, and implementation of infection control procedures in a timely manner. The continued development of new technological advances that surpass traditional national boundaries, in order to track and report infectious diseases, is integral for rapid and efficient communication among public health agencies.

Introduction

Throughout history, numerous infectious diseases have had a large impact upon human health, through well-known epidemics such as the bubonic plague, (which most recently broke out in China in 1855 and is still ongoing) influenza (in 1918 and again in the 1950s), the current HIV pandemic, and also through the re-emergence of infectious agents such as Methicillin Resistant Staphylococcus aureus (MRSA). Emerging Infectious Diseases (EIDs) are infectious diseases that have either an increasing range or incidence. EIDs are discovered for various reasons: a previously unknown disease variant is discovered (e.g. *Helicobacter pylori* as a cause for ulcers); a new agent is created (e.g. Avian Flu is currently an emerging infectious disease); and the re-emergence of a disease after an initial period of decline (e.g. plague caused by *Yersinia pestis* is known to have caused at least 3 known pandemics which occurred hundreds of years apart). Factors that precipitate or enhance the spread of EIDs can be categorized as either those that aid in the introduction into the host population of the infectious agent, or those that allow the infectious agent to become established and spread throughout the population (Table 1).
Table 1: Factors that promote the introduction and spread of emerging infectious diseases.

<table>
<thead>
<tr>
<th>Activity</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factors that promote introduction of EIDs</td>
<td>Economic Development and Land Use</td>
</tr>
<tr>
<td></td>
<td>Exposure to living conditions that allows for zoonotic transfer (e.g. H5N1)</td>
</tr>
<tr>
<td></td>
<td>Microbial Adaptation</td>
</tr>
<tr>
<td></td>
<td>Methicillin Resistant S. aureus (MRSA)</td>
</tr>
<tr>
<td>Factors that promote spread of EIDs</td>
<td>International travel &amp; commerce</td>
</tr>
<tr>
<td></td>
<td>Severe Acute Respiratory Syndrome (SARS)</td>
</tr>
<tr>
<td></td>
<td>Change/breakdown of public health measures</td>
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<tr>
<td></td>
<td>Measles and Rubella outbreaks</td>
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<td></td>
<td>Technology &amp; Industry</td>
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<tr>
<td></td>
<td>Food poisoning outbreaks</td>
</tr>
<tr>
<td></td>
<td>Human demographics/behaviour</td>
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<tr>
<td></td>
<td>Human Immunodeficiency Virus (HIV)</td>
</tr>
</tbody>
</table>

There are two categories of factors that promote EIDs: those that promote EID introduction, and those that promote EID spread. Note that the activities are taken directly from Institute of Medicine’s factors for EID.\textsuperscript{2,3}

One analysis of 335 EID events from 1940 to 2004 demonstrated that there has been a significant increase in EIDs over time, even when accounting for reporting bias.\textsuperscript{5} Based upon this analysis, the majority of EIDs diseases came from zoonotic events (60.3%), and were caused by either \textit{Rickettsia} (gram negative bacteria) and other bacteria (54.3%).\textsuperscript{5} Globally, the distribution is non-random. Indeed, EIDs are most likely to occur in the lower latitudes, where the fewest global resources are focused, and reporting is least common.\textsuperscript{5} Furthermore, despite the development of numerous antibiotics and vaccines, diseases caused by viruses, protozoa, helminths and fungi are still difficult to treat and eradicate.\textsuperscript{2}

\textbf{Zoonotic origins of EIDs}

In general, one of the greatest causes for concern of newly EIDs is the reservoir found in animals.\textsuperscript{3,6} Such diseases can transfer to humans either directly, or through a vector (such as arthropods), and have the potential to cause epidemics. The potential for epidemics is especially a cause for concern if the disease develops the ability to easily transmit between individuals within a population.\textsuperscript{3} Diseases such as HIV and H5N1 (bird-flu) are examples of diseases of zoonotic origins. HIV, which is one of the most prominent examples of an infectious disease of zoonotic origins, is thought to have transferred from simians in Africa through the consumption of bush meat.\textsuperscript{4}

Bird-flu, or influenza strain H5N1, is a newly emerging disease of particular public health concern.\textsuperscript{5} Influenza is a rapidly mutating disease with two key surface proteins (hemagglutinin and neuraminidase) that have a large effect upon the successful spread and virulence of the disease. Hemagglutinin is an influenza surface protein that helps the virus to bind to cell surface receptors. Key mutations in hemagglutinin allow the influenza virus to bind host cells when host immunity has developed against other hemagglutinin antigens.\textsuperscript{4} There are at least 16 known hemagglutinin subtypes. Neuraminidase is another influenza surface enzyme that confers virulence to influenza.\textsuperscript{4} It is a glycosidic hydrolase enzyme with nine subtypes, many of which are present only in birds.\textsuperscript{4} H5N1 represents an influenza strain that has not previously infected humans, and contains a combination of the H5 hemagglutinin and N1 neuraminidase subtypes.\textsuperscript{3} Currently, H5N1 is highly virulent in chickens, and has begun to infect migratory birds.\textsuperscript{3} It also has the ability to jump to humans and other mammals (including pigs), where it causes a high death toll.\textsuperscript{3}
H5N1: the next pandemic?

Although H5N1 is largely expected to cause the next influenza pandemic, the following conditions must first be met for this to occur: 1) a new influenza virus subtype must emerge, 2) it must be capable of infecting humans and causing serious illness, and 3) it must spread easily from human to human. H5N1 is of particular concern because it has already fulfilled the first two criteria and more recent reports from the World Health Organization (WHO) suggest that partial human-to-human transmission of H5N1 may have occurred in isolated cases in Thailand, Indonesia, and Vietnam. However, at present, human-to-human transmission has occurred sporadically and with very low efficiency and therefore does not meet the third criteria. Nonetheless, influenza-like viruses are highly mutagenic and may become freely transmissible among humans at some point in the future, which means that the threat of an avian influenza pandemic remains very real.

Based upon past influenza epidemic outcomes, the United States Congressional Budget Office (CBO) has projected that a potential influenza pandemic could involve 200 million people infected, 90 million clinically ill, and 2 million dead. This would yield a case-fatality ratio of 2.5%. Furthermore, the economic cost could reach $675 billion. As of September 2008, the WHO reported that H5N1 has already infected 387 humans and killed 245 patients worldwide, with a case-fatality rate of 63%. Therefore, the CBO’s projection likely underestimates the actual impact of an H5N1 pandemic given that the case-fatality ratio of H5N1 reported by the WHO is 25 times greater than the estimate put forth by the CBO (63% vs. 2.5%).

Signs of Symptoms of H5N1 Infection

Frontline clinicians need to be aware of the signs and symptoms of H5N1 infection because identifying the illness, reporting it to public health authorities, and implementing infection control procedures in a timely manner offers the best chance of controlling the spread of infection. Symptoms include typical influenza-like symptoms: fever greater than 38°C (100%), cough and sore throat (67%), myalgias (30%), pneumonia (58%), and diarrhea and vomiting (50%). Symptom onset occurs within 2-14 days of exposure. Complications include acute respiratory distress syndrome (ARDS), pulmonary hemorrhage, myocarditis, pericarditis, encephalitis, multi-organ failure with renal dysfunction, and sepsis. Common radiographic findings include diffuse, multi-focal or patchy infiltrates and segmental or lobar consolidation with air bronchograms. The majority of the deaths have been attributed to respiratory failure.

Diagnosis and Treatment of H5N1

Diagnosing H5N1 infection poses a challenge because there are no pathognomonic signs and symptoms making it difficult to distinguish from other causes of influenza-like illness, severe community-acquired pneumonia, or ARDS. The only findings that would raise suspicion of avian influenza (H5N1) is a history of presence in an endemic area and/or contact with poultry. Therefore, obtaining a detailed history including travel and animal exposure is crucial. When H5N1 infection is suspected, the preferred test to confirm the diagnosis is real-time reverse transcriptase polymerase chain reaction (qRT-PCR) on a nasopharyngeal swab.

Current opinion of the WHO states that patients presenting with the symptoms and historical features that are strongly suggestive of H5N1 infection should promptly be started on a course of Oseltamivir, pending the diagnostic results of PCR testing. Oseltamivir is an antiviral agent that inhibits neuraminidase, which has been shown to reduce H5N1 infection-associated mortality in observational studies when it is administered in a timely manner.

Mandatory Reporting of H5N1

Laboratory confirmation of a human case of H5N1 by qRT-PCR should trigger an immediate notification of local, sub-national, and national public health and agricultural authorities. However, the collection, shipment, and testing of specimens can often take several days or longer. Therefore, it is often necessary to notify the appropriate public health officials and initiate an
investigation before laboratory test results are available for persons suspected of having H5N1 infection.\textsuperscript{18,19} National health authorities must then notify the WHO and readily share information and biological specimens.\textsuperscript{19,20}

**New methods of surveillance and reporting EIDs**

Although this reporting structure provides a solid basis in order to approach outbreaks in a globally concerted manner, the hierarchical nature of the system could cause unwanted delays in communication from the local governmental level to the WHO. Furthermore, some parties may be less willing to report potential new H5N1 infections for fear of local or national economic repercussions, leading to further delay.\textsuperscript{20} For these reasons, new structures of communication are being created by public health scientists to share information more rapidly. ProMED-mail is an e-mail based group dedicated to infectious diseases with a membership exceeding 30,000, giving the group global reach and influence.\textsuperscript{21} ProMED is known to report outbreaks before local authorities. During the 2003 SARS epidemic, that spread from the Guangzhou province in China to nearly 37 countries\textsuperscript{22}, the first public report of the epidemic was posted on ProMED more than a month before the Chinese government’s official announcement.\textsuperscript{21} ProMED’s membership is volunteer-based and not affiliated with a governmental organization. Therefore, they have greater freedom to report what they observe than official organizations, which may have political constraints on what they can publicly report. This on-the-ground reporting is thought to push governments to disclose more information than they might normally.\textsuperscript{21}

HealthMap (http://www.healthmap.org/) is a newer surveillance system that continuously monitors the internet, aggregating real-time information on infectious disease outbreaks from news media sources, blogs, and discussion groups.\textsuperscript{23} HealthMap illustrates the distribution of reported infectious diseases by superimposing these incidents on a map of the world. The WHO is one of its top users.\textsuperscript{23} This is significant because it allows WHO to learn of emerging infectious disease without having to exclusively rely on local public health agencies.

**Conclusion**

In summary, there are a variety of infectious agents capable of causing disease in humans. H5N1, a virus of avian origin capable of crossing the species boundary to infect humans, has the potential to cause the next influenza pandemic and is thus of particular concern. In order to adequately respond to the next outbreak, frontline clinicians need to be eternally vigilant at the community level. Furthermore, clinicians must be aware of the need to act in a concerted manner with other nations at the global level. New technological advances should be fully exploited to facilitate such globally coordinated responses. The next pandemic will not observe national boundaries, and our approach to the control of EIDs should reflect an awareness of this. The global community cannot afford to let state boundaries prevent a necessary response to the emerging pandemic threat posed by avian influenza, or any other emerging pandemic threat.

**References**