All fall down

Dr Rashid Chotani, former Director of Global Disease Surveillance and Alert Systems at Johns Hopkins University, examines H5N1 Influenza from a global perspective and offers an independent opinion

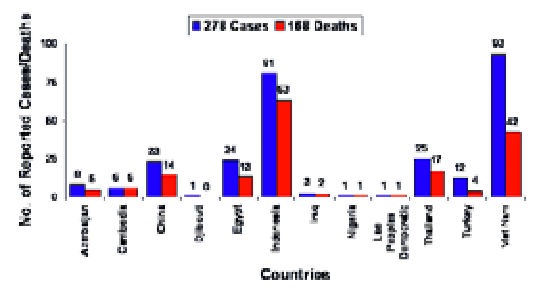
Brief History:
The first well described pandemic of influenza-like-illness (ILI) dates back to 1580. Evidence suggests that influenza virus originating from animals has caused 31 pandemics, 3 of which have occurred in the twentieth century. The last two pandemics of the 20th century, those in 1957 and 1968, were linked to avian strains and phylogenetic studies suggest that the H2N2 and H3N2 strains were reassortments of two viruses. When the virus is transmitted between species, mutation, reassortment, or recombination, may occur and pigs may act as an intermediate host between birds and humans. The ability of influenza to cause globally impetuous and omnipresent disease due to its genetic properties is well known. Avian influenza usually does not replicate efficiently to cause human disease, but the potential of new and deadly pathogens to emerge via different mechanisms was highlighted in Hong Kong in 1997 by the outbreak of H5N1. Between May and December of 1997 a novel influenza A virus H5N1 emerged in Hong Kong and caused 6 deaths among 18 confirmed cases.

Current Situation:
Since Mid-2003 as of March 8, 2007, 278 laboratory-confirmed H5N1 influenza cases have been reported by the World Health Organization (WHO) from 12 countries (Figure 1) of which 60% (168) expired (Figure 2). Since 2003 the number of human cases/deaths has increased each year (Figure 3). The case-fatality has varied from country to country. Among the five countries reporting the highest number of cases, Vietnam (93 cases) had the lowest case-fatality (45%). The second highest number of cases was reported from Indonesia with the highest case-fatality rate (78%) followed by Thailand (25 cases) with a case-fatality rate of 68%; Egypt (24 cases) with a case-fatality rate of 54% and; China (23 cases) with a case-fatality rate of 61%. (Figure 4) The current H5N1 virus is antigenically and genetically different from the 1997 H5N1 virus but certain clinical features remain similar. The current outbreak is widespread compared to 1997 and like the 1997 outbreak direct infection to humans has been confirmed. The evolutionary ability of H5N1 has been remarkable; still the virus has not developed an affective mechanism for human-to-human transmission.

Nosocomial Implication:
In 2003, a novel coronavirus which caused a respiratory syndrome emerged in Southern China. The SARS outbreak affected more than 30 countries, causing over 8000 cases and around 800 deaths worldwide (WHO). Its rapid spread and its toll on healthcare workers (HCW) and facilities stunned the world. Rapid nosocomial transmission of the virus caused hospital closings and the lack of an effective treatment regimen and no vaccine has generated the need for healthcare systems preparedness.

Influenza is a major nosocomial pathogen and transmission has been well documented from patient to HCW, HCW to patient, and HCW to HCW. Nosocomial transmission increases morbidity and mortality among patients in long-term as well as acute care facilities. The transmission predominantly occurs through person-to-person contact with large virus laden droplets during close contact with infected individuals and by small-particle aerosols or droplet nuclei.During the pandemic of 1957, influenza A reached a Chicago hospital and one-third of the patients and staff-members on affected units contracted the disease. Keech and colleagues found that HCW with influenza and influenza-like-illness (ILI) were confined to bed an average of 2.4 days, missed 2.8 days of work, and took a mean of 3.5 days after the onset of symptoms to resume normal activity.

Figure 1: Cumulative Number of Confirmed Cases/Deaths by COUNTRY, December, 26 2003 to March 12, 2007



Vaccine:
The vaccine, when a good match for the circulating viruses has been shown to prevent illness in approximately 70% to 90% of healthy persons less than 65 years of age. Researchers have shown that influenza vaccine reduced illness among young healthy HCW, and that vaccination of HCW reduced patient mortality by around 50%.

It is unclear whether there will be sufficient and/or efficacious vaccine available to vaccinate part of, or the entire, population. Although a vaccine against the H5N1 virus is under development in several countries, no vaccine is ready for commercial production and no vaccines are expected to be widely available until several months after the start of a pandemic. These include inactivated, live-attenuated and genetically engineered vaccines. Clinical trials are under way to test whether any of these candidate vaccines will provide complete or partial protection and to determine whether different formulations can economize on the amount of antigen required, thus boosting production capacity. Due to the fact that influenza virus has a high error rate, as there are ongoing changes in proteins by genetic point mutation, the vaccine needs to closely match the pandemic strain. Thus, large-scale commercial production cannot start until the new strain has emerged and a pandemic has been declared. Currently, the vaccine production process takes about 6 to 8 months, and even with advance knowledge of reference strains in the event of a pandemic only a small number of the global population could be vaccinated as the current global production capacity falls far short of the demand expected during a pandemic.

Given vaccine is likely to be limited, a priority list has to be created to assure the vaccine is administered in an orderly fashion. It is proposed that HCW, emergency medical personnel, high risk patients and their immediate household contacts, home healthcare workers, those at the greater risk according to the American Council of Immunization Practitioners (ACIP), school nurses, police, fire department personnel, sanitation workers, public water supply workers, utility workers, and others necessary for essential community services should be vaccinated first. Furthermore, among healthcare workers priority should be given to those likely diagnosing and caring for cases (emergency room, medical and pediatric nurses and physicians, family practitioners and primary care providers, respiratory and x-ray technicians, and phlebotomist and microbiologists). Other important considerations are adequate and secure storage of large amounts of vaccine, which would require training and law enforcement agency protection of vaccine administrating sites, as well as vaccine manufacturer commitment to produce large quantities of vaccine and distribute them adequately.

Antivirals:
In healthy adults, post-exposure, prophylactic, antiviral agents such as amantadine and rimantadine reduce the severity and duration of illness (70%-90%) caused by influenza A when administered within 48 hours of illness onset. These drugs however are associated with adverse effects, particularly in the central nervous system as well as emergence of drug resistance. Similarly, new neuraminidase inhibitors, with fewer side-effects, such as zanamivir and oseltamivir prevent influenza.

Antivirals, which interfere with the replication of influenza virus, would be scarce in a pandemic situation. Hospital pharmacies traditionally do not stock these agents and companies produce limited supply. In the absence of a vaccine, however, their utility becomes of paramount importance. During the 1997 H5N1 outbreak, most of the critical stage patients received amantadine which is known to be most effective when it is given within two days of disease onset, thus, the true efficacy of antivirals could not be tested due to limited experience. The associated adverse effects and the emergence of drug-resistant strains may limit their use. Current global production capacity of antivirals is limited. In the event of a pandemic, the limited supply will have to be rationed to the highest risk individuals.

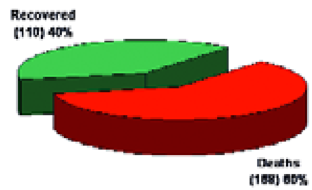
Space/beds:
Most healthcare facilities have downsized and have reduced surge capacity. Hence, during a pandemic or an epidemic, hospitals would need contingency plans to house patients due to inadequate hospital beds or staff. As nursing homes would be filled, large facilities such as malls, gymnasiums, auditoriums etc. would need to be identified by local public health authorities. Some care could be delivered at home except when high tech services such as intravenous therapy and specially ventilators are needed, as it would not only decrease the burden on hospitals but also help decrease the spread of influenza.

Healthcare Workers (HCW):
It is unlikely that an efficacious vaccine, sufficient vaccine and antiviral supply, and advance information regarding an impending pandemic allows vaccination or prophylaxis of all HCW. Thus, in the event of a pandemic or a major outbreak scenario, there is no doubt that HCW would also get infected. The recent SARS outbreak highlight that these fears are real and may even result in ostracism. Additionally, panic and fear of infection and caring the infection to their homes would likely prevent many HCW from reporting to work. As a result, staffing shortages are likely during an influenza pandemic. This shortage would grow exponentially as hospitals become filled to capacity and patients have to be housed elsewhere.

Diagnostic Reagent:
The supply of reagents for rapid testing may be limited and their indiscriminate use, apart from wasting of resources, will jeopardize the care of other patients who are in need. The conditions that merit detection by rapid direct antigen test should be limited or cost-effective tools that are highly sensitive need to be produced.

Basic Supplies:
In addition to shortages of vaccines, antivirals, beds, diagnostic reagents, and personnel previously mentioned, in the event of a pandemic, hospitals should also anticipate a shortage of surgical masks, linens, gowns, gloves, eye-protectors and waterless hand cleaners. In some settings N95 (example SARS) or face shields would be needed. The US Centers for Disease Control and Prevention (CDC) recommends eye protection when within 3 feet of the patient. Although, such supplies are inexpensive, they are nonetheless not currently stockpiled due to tight hospital budgets, limited space and just-in-time inventory concepts. Satellite health care facilities that are set up to support the public health response in the event of a pandemic would also be in need of such supplies.

Figure 2: Number and Percent - Deaths vs. Recovered December, 26 2003 to March 12, 2007



Discussion:
The first line of defense against an influenza pandemic will be healthcare providers. Experience from the SARS outbreak demonstrates how critical planning in healthcare settings is to a coordinated public health response. While a few institutions have a detailed response plan, healthcare systems regardless of their size may have limited capacity to respond. This response will require flexibility and an operational capacity to quickly move from identification of a novel or unusual strain to patient protection phase. An ability to triage patients, screen HCW and patients, isolate and prevent transmission is tantamount to the healthcare system success. As with SARS, the limited surveillance and delays in reporting lead to a large number of patients presenting to the healthcare system prior to the medical and public health community recognizing the magnitude of the problem. Such delays can lead to inadvertent transmission within the healthcare setting. Thus, a comprehensive plan has to be developed in order to effectively deal with an influenza pandemic.

Both the capacity and ability to

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recognize and respond rapidly to an influenza pandemic remain a permanent and growing global challenge. There is a time lag between exposure and development of symptoms which follow casualties/fatalities. The time difference between potential infection and the epidemic or an outbreak can be hours to days; the key is to a favorable outcome is early detection. Early detection, prompt investigation, and organization of timely and efficient interventions requires a continuous and on-going synchronization between several international, national, as well as local public health, commerce and academia, including epidemiology, laboratory, water and sanitation, disaster preparedness, health care personnel, food safety, and the scientific research community. The need for creating an early warning and rapid response systems has been recognized for sound intervention strategies and processes for decision-making. The cornerstone remains the exchange of information and mechanisms of communication between multiple stakeholders. A more rapid, efficient, effective, and mainly coordinated response within and between all stakeholders would make it possible to reduce and limit the frequency and severity of infectious disease outbreaks and its dissemination across the nation.

The number of cases reported has increased every year. In the first 3 months of 2006, 15 confirmed cases resulting in 10 deaths have been reported (Figure 3). Although these numbers are small but if the tend of the past years continue we can see much more cases. All indications related to the spread of wild bird and poultry infected with H5N1 in Europe and the human cases in Turkey are an ominous sign that the disease is spreading slowly but consistently around the globe. The current outbreak has illustrated a very high case-fatality rate. This rate has varied over time and between countries (Figure 4). Vietnam, which has reported the highest number of cases to date, has a case-fatality rate of 45% with the last case reported in 2005. In 2005, the overall case-fatality due to H5N1 was 43% (Figure 3). Since, the case-fatality has increased to 69% and 67% in 2006 and 2007 respectively. Furthermore, in Indonesia the case-fatality rate is 78% and in 2007 6 cases were reported out of which 5 died. This can be due to two reasons: 1) the healthcare infrastructure in regards to disease recognition and patient care was much better in Viet Nam or 2) the virus that affected the population in Vietnam was not as virulent as when it affected Indonesia. Here one has to appreciate that the case-fatality rate in Egypt (54%), China (61%) and Thailand (68%) which are amongst the top five countries reporting the disease is different. The question of whether the virus is becoming more virulent over time or it it's the indigenous healthcare infrastructure that plays a role in the case-fatality needs to be determined.

Several lessons learned from the SARS epidemic need to be considered. First, there is no doubt that healthcare facilities are a critical pillar in the public health sector. Hospitals have cared and screened patients, diagnosed cases and have illustrated how disease transmission within them can serve as a vector of transmission. This will always be the case. Secondly, the knowledge of the infection control community has been critical to prevention and control efforts of this disease. This will likely be true for influenza also. Unbeknownst to the medical community, this skill set [infection control] is unique to those working in the healthcare settings and the use of barrier precautions, isolation and cohorting along with the identification of exposed and infected persons have helped abort further dissemination of the disease. Finally, the need to have supplies readily available to assure ones ability to protect healthcare workers and patents is critical to the operational success of any pandemic, epidemic or a large-scale outbreak management response.

Conclusions:

If the anthrax bioterrorism event in the US is used as an example of community disruption and increased demand for medical services a pandemic would cause mass chaos. SARS is the most recent example of a respiratory illness that has disrupted patient care and resulted in a global healthcare crisis. Contrary to earlier beliefs that influenza pandemics occur every 10-14 years, it has been over thirty years since the last influenza pandemic (H3N2) emphasizing the fact that a pandemic whether it is due to H5N1 strain or a new influenza strain that emerges may occur at an unpredictable interval. Thus, a novel influenza virus causing a pandemic may occur at anytime. The US Centers for Disease Control and Prevention (CDC) estimated that the potential impact of next pandemic could result in 2-7.4 million deaths globally. In high income countries there would be, 134-233 million outpatient visits, 1.5-5.2 million hospitalizations and approximately 25% increase demand for ICU beds, ventilators, etc. Any such scenario has the capability to cause severe health, social and economic consequences. Implementation of exhaustive, proactive, and action-oriented policies is required to minimize this impact.

The full text of this article, including references, can be found on www.cbrneworld.com

Figure 3: Cumulative Number of Confirmed Cases/Deaths (Case-Fatality Rate) by YEAR, December, 26 2003 to March 8, 2007

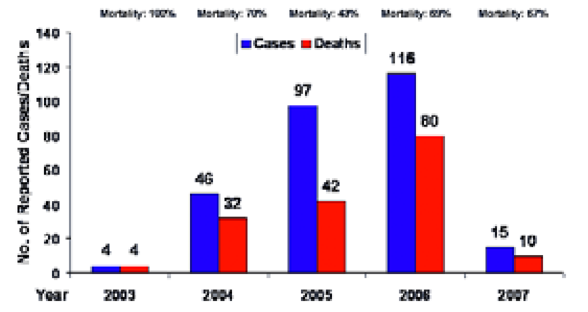

Figure 4: Percent Case-Fatality in Confirmed Cases by COUNTRY December, 26 2003 to March 12, 2007