Commentary

The 2009 Swine-Origin H1N1 Influenza Virus and Its Implications to Public Health

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The major public health event in 2009 is the outbreak of a new influenza virus infection in almost every region of the world. Because the original source of this virus was pigs, this virus was named "Swine-Origin Influenza A (H1N1) Virus (S-OIV)" in leading medical journals such as the *New England Journal of Medicine*. However, due to concerns regarding the potential for a misunderstanding that would lead the public to blame pigs for the outbreak as was the case in some Mideast countries where the national slaughter of pigs was started shortly after the outbreak, the World Health Organization (WHO) renamed the virus as "Type A H1N1 Influenza Virus", which has generated significant confusion not only among the general public but also among healthcare professionals.

The Name and Classification of Influenza Viruses

Influenza viruses, or "Flu" as the influenza virus is commonly referred to by the general public, can be classified into three types: Types A, B, and C. Type A influenza viruses are the one that cause most human flu and can be further divided into many subtypes based on the combination of two of their key proteins: hemagglutinin (HA, 16 subtypes from H1 to H16) and neuraminidase (NA, 9 subtypes from N1 to N9). Seasonal flu infections in humans, so-called since they typically occur every year in the winter season, are caused mostly by two major Type A subtypes, H1N1 and H3N2 in recent years; however, Type B viruses can also cause human seasonal influenza infections. This leads to the confusion behind naming the 2009 swine-origin influenza virus "Type A H1N1" as it makes it difficult to differentiate this new emerging H1N1 virus from other existing seasonal H1N1 influenza viruses.

Where Did the 2009 Swine-Origin Influenza Virus Come from?

The origin of the 2009 swine-origin influenza virus can be traced back to the major influenza outbreak of 1918. During that time, a major influenza epidemic caused by an H1N1 virus had led to millions and millions human deaths. This outbreak was the first and the well-documented outbreaks. This was called "pandemic" due to the spread of the virus to various regions throughout the world and the devastating public health outcome. This original H1N1 virus continues to circulate in the human population today despite a lapse in infections from 1957 to 1977. Today, human H1N1 viruses are derived from but are different from the 1918 virus, due to extensive drift of the virus within the human population for more than 70 years.

In 1918, H1N1 influenza viruses also caused a pandemic in pigs. The swine 1918 virus was very similar to the human 1918 virus, and they share a common ancestor. Since 1918, the H1N1 virus established a swine lineage independent of the human lineage, and it drifted in pigs for more than 90 years. These swine H1N1 viruses are named "classical swine H1N1" to distinguish them from other more recent swine viruses that have been affecting the pig population more recently.

From 1918 to 1997, there were no major surprises associated with the spread of swine influenza viruses in the Americas. While humans experienced two pandemics after 1918 (H2 and H3 pandemics), no changes in the subtypes of influenza viruses circulating in pigs were observed, as they remained classical H1N1 viruses. However, in 1997, there was a change observed regarding influenza infections in pigs. Many new influenza virus genotypes emerged; one genotype, in particular, became prevalent and began to co-circulate with the classical swine H1N1 viruses. This was a triple reassortant virus, with some genes derived from classical swine H1N1 virus (NP, M, and NS), genes from avian influenza viruses (PB2 and PA), and genes from a human H3N2 virus (H3N2). H3N2 viruses have been circulating in pigs since 1997 and established an independent lineage from the human H3N2 viruses. In addition, these viruses have continued to reassort with classical H1N1 viruses in the pig population, allowing for the establishment of different genotypes in swine since 1997.

The virus causing the 2009 outbreak is one of these swine reassortants. It contains the H1 from classical swine influenza, and some other genes derived from swine, avian, and human viruses coming from the H3N2 triple reassortant. In addition, it also contains some genes from the Eurasian lineage of swine influenza viruses, however, it is unclear how Eurasian swine viruses have arrived in the Americas and reassorted with the American swine lineages. The 2009 flu

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outbreak indicates that the new swine-origin H1N1 viruses are able to transmit from human to human, and this distinguishes these viruses from other viruses present in nature.

Health Impact of the 2009 Swine-Origin Influenza Virus

There are two major approaches to control a human influenza infection. The first is treatment. The new H1N1 S-OIV virus is sensitive to neuraminidase inhibitors, such as zanamivir (Relenza) and oseltamivir (Tamiflu) but resistant to more traditional drugs, such as amantadine and rimantadine. The second is vaccination. Since the HA protein of this 2009 S-OIV is also of H1 subtype but from a swine lineage, the antigenic differences between the HA of S-OIV and the HA of regular human H1N1 viruses circulating in the last winter season are greater than one would expect during the usual yearly drift, making the development of a vaccine necessary based on these new H1 HA antigens.

Because the worldwide capacity to produce annual season flu vaccines is already very limited, this unexpected need for the production of an additional single-valent influenza vaccine to target S-OIV, in addition to the regular trivalent flu vaccine against seasonal H1N1, H3N2 and a Type B flu virus, in a same season was a major challenge to the flu vaccine industry. While there have been many complaints regarding the slow or late arrival of the S-OIV vaccine in the late fall of 2009, relative to the seasonal flu vaccines, the world community should really feel fortunate for the fact that several safe and effective S-OIV vaccines were actually produced by multiple vaccine companies in different countries and that they became available just prior to the start of the winter season.

Lessons Learned from the 2009 Flu Outbreak

While we can not predict whether we have seen the worst of this new S-OIV, the spread of S-OIV has not generated any significant and major health threat, at least through the end of 2009. The initial outbreak in the Spring of 2009, and the subsequent spread to the Southern Hemisphere, including countries such as Australia or Brazil in summer, and to the Northern Hemisphere, to countries such as China or USA, lead to widespread infections to diverse human populations; however, the severity was somewhat limited even when taking into account higher risk populations with the overall estimated mortality rate not surpassing that caused by annual seasonal flu infection for any given year.

One interesting finding, which may help to understand the observed decreased clinical severity of S-OIV, comes from observation showing that there may be existing, albeit low-level, immunity against previously circulating H1N1 viruses in many individuals, with the exclusion of young children, which can also cross-react with the new 2009 S-OIV. This pre-existing immunity may have been beneficial to the immune system of some individuals, leading to two possible outcomes. The first possibility is a reduction in the number of vaccinations needed to achieve protection. For a completely naïve human host, it was established that two vaccinations are generally needed to elicit a full scale protective level of immune response against influenza infection. However, studies of S-OIV vaccines in adult humans have shown that a one-time vaccination was sufficient. The second possibility is a minimization of the severity of infection by this new S-OIV among infected people.

If there truly is pre-existing, low level immunity due to previous infection by other unrelated human H1N1 viruses and if such immunity can at least partially protect individuals from an emerging H1N1 virus from swine origin, we may need to review whether the 2009 S-OIV infection should be truly called a “pandemic”. According to the classic definition for a flu pandemic, it is the result of entry of influenza viruses from subtypes that have not been circulating in humans for quite some time – a phenomenon called “antigen shift” - into the human population. Therefore it appears that although the 2009 swine-origin H1N1 influenza virus is a distant cousin of the current circulating H1N1 viruses, they are only separated by “antigen drift” and are still not different enough to be considered part of a shift from the same family. A better understanding on this issue will teach healthcare officials, both at the national and international levels, to make more accurate assessment on the true nature of an emerging influenza epidemic and, more importantly, will greatly reduce the emotional stress experienced by the general public during a pending pandemic.