2009 Novel H1N1 Influenza: The Impact of Viral Genomic Reassortment on Immune Evasion and Vaccine Strategy

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The outbreak of the novel H1N1 influenza A, which began in Mexico, has attracted global attention due to the initial high mortality rate and rapid spread since April 2009. Zoonotic infection from pig to human was initially considered as most of the infected cases in Mexico had a history of close contact with pigs.

By genotyping and sequencing the causative virus, it was found that the candidate virus is a novel reassortant virus derived from a triple-reassortant swine influenza A (H1) virus and a Eurasian swine influenza virus.[1,2] The triple-reassortant swine virus, composed of genetic material from pigs, humans, and birds, has been known of in pigs for a decade. Sporadic cases of swine-to-human transmission of the triple-reassortant swine virus have been reported,[3] but human-to-human transmission of the triple-reassortant swine virus is rare. Influenza virus is a negative-strand RNA virus, belonging to the *Orthomyxoviridae*.[4] The error-prone feature of the RNA polymerase causes the virus to evolve constantly. The novel H1N1 influenza A virus is the consequence of an additional viral genomic segmental reassortment gaining the ability to be transmitted among humans.[2] So far, the virulence of the novel virus remains unknown, but its transmissibility may be substantially higher than that of seasonal flu based on a World Health Organization (WHO) report.[5]

The history of influenza pandemics includes outbreaks recorded in 1918 (Spanish flu), 1957 (Asian flu), and 1968 (Hong Kong flu). It is estimated that influenza pandemics occur every 30–50 years.[6] In addition to the pandemics, several milder influenza epidemics, such as swine flu in 1976, Russian flu in 1977, and avian flu beginning in 1999, occur periodically around the world and continue to threaten human beings. The rapid global spread of the novel H1N1 influenza A virus implies its pandemic potential.[5]

The clinical manifestations of the novel H1N1 influenza are similar to those of seasonal influenza, and include fever, cough and sore throat; gastrointestinal symptoms with vomiting or diarrhea are also common.[1] An early finding suggests that the mortality rate caused by the novel H1N1 influenza virus is less than that of the 1918 pandemic, but comparable to that of the 1957 pandemic.[5] Antiviral drugs, including oseltamivir (Tamiflu) and zanamavir (Relenza), have so far been effective against the novel virus; however, oseltamivir resistance in the H1N1 influenza strain has already been reported. Therefore, the best way to counteract the disease is to have an effective vaccine.

Since the manufacture of vaccines and immunization against seasonal influenza takes place annually, why does influenza persist? The envelope of the influenza A virion is composed of glycoprotein spikes of hemagglutinin (HA) and neuraminidase (NA). Not only are these surface glycoproteins used simply as a basis of genotypic classification, they are also immunogenic antigens.[4] Antibody to the HA protein is the neutralizing antibody and correlates with immunity to influenza. Therefore, seasonal trivalent influenza vaccines typically contain HA antigens from 3 viral strains. The sequential steps to produce the current seasonal inactivated influenza vaccine include characterization of new isolates by WHO, recommendation of potential vaccine strains for the coming season by WHO, and then manufacture and delivery of the vaccine.[7] In general, this process will take up to 6 months to produce

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sufficient quantities of vaccine for global needs. The efficacy and effectiveness of a vaccine relies on an identical or optimal antigenic match between the vaccine virus and the subsequent epidemic virus.[7] Of note, the antigenic features of the influenza virus are continuously changing and unstable. Antigenic drift occurs constantly. The genome of the influenza virus is also capable of antigenic shift to acquire HA or NA segments from a different subtype virus and create novel antigenic proteins (segmental reassortment).[4] The novel H1N1 influenza virus is the consequence of genomic segmental reassortment, which is currently susceptible and immunologically naïve to most people, especially in adolescents and children. Existing seasonal influenza vaccine is unlikely to protect humans from the novel H1N1 influenza A virus. Mutation to escape from vaccine-induced immunity is not limited to the influenza virus. One example is the case of hepatitis B virus (HBV) vaccine. HBV with surface antigen G145R mutation has been detected in HBV-vaccinated cases.[8]

A vaccine for the novel H1N1 influenza virus is in development, but several problems need to be overcome. These include shortening the time from vaccine strain selection to vaccination, increasing the capacity of production, broadening the vaccine-induced immune response, and evaluating the vaccine's effectiveness and safety.[7,9] Many factors depend on the manufacturing plants, but scientists can put in more effort to enhance vaccine immunogenicity and efficacy. Induction of a broadened vaccine-induced immune response can provide better protection against infection from the ever changing virus. Apart from the neutralizing effect of the antibodies to HA protein, it is suggested that antibodies to NA are also included in influenza vaccine.[4,7] Combination of HA and NA proteins as candidate vaccine antigens should be considered. In the envelope of the influenza virus, there are matrix (M2) ion channels that transverse the lipid envelope. The ectodomain of the M2 protein can also induce host immunity.[10] Similarly, incorporation of M2 protein as a vaccine antigen might further expand the spectrum of vaccine-induced protection. Although vaccine-induced antibody response provides neutralizing effect and protective immunity, cellular immunity is considered to be able to elicit the required humoral response. So far, the protective role of cellular immune response on influenza vaccination is uncertain, but induction of an effective T-cell response in conjunction with antibody production might be a promising vaccine strategy to broaden antiviral immune response and enhance the level of cross-protective immunity against antigenic variants.[7] Identification of adequate T cell epitopes in the influenza virus should be undertaken.

Viruses have every means to escape from host immunity. The story of the influenza pandemic will repeat itself. It is almost certain that the novel H1N1 influenza A virus will not be the last virus to threaten human beings. However, we should be fully equipped for the coming threats. To be able to obtain an effective vaccine, in a timely manner, that can induce broad-spectrum immunity should be the issue of highest priority at present.

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