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LETTER

Will We Ever be Able to Defeat Human Influenza?

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DEAR EDITOR,

Mankind has successfully defeated many dangerous infections that caused harm to human health and safety. In the past, smallpox was considered to be one of the deadliest diseases of humans. Today, this infection does not exist [1]. Mankind has eradicated or can control plaque, polio, tuberculosis, measles and many other infectious diseases.

Influenza is responsible for 3-5 million severe illness worldwide and up to 650 thousand respiratory deaths [2]. The unpredictable character of the influenza virus spread is a significant threat to humans. Will we be able to defeat influenza soon?

In the last eight decades after the first human influenza virus was isolated by Smith *et al.* [3], huge progress has been made in studying, preventing and treating influenza at that time. Replication cycle of influenza viruses, genome structure, evolution, pathogenesis, mechanisms of the immune response to virus infection, epidemiology of influenza, its express diagnostics, clinical course, and complications, were discovered in detail. Full genome sequencing and reassortment by reverse genetics became routine techniques.

Vaccines remain the first measure to prevent influenza. Currently, a number of different types of influenza vaccines, such as inactivated whole virion vaccine, inactivated split virus .vaccine, inactivated subunit vaccine, inactivated subunit virosomal vaccine, live attenuated vaccine, recombinant vaccine, DNA vaccine, peptide-based vaccine, *etc*. exist. They are licensed or their clinical trials were successfully completed [4]. However, influenza vaccines have some limitations that cause a reduced efficacy compared to immunization against other pathogens of lower genetic diversity.

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Unlike other respiratory viruses, influenza viruses, especially type A display vast natural genetic variability. They circulate in different animal species of birds and mammals [5], undergo a high mutation rate and frequent genetic reassortment that lead to variability in surface proteins, HA and NA [6]. High genetic flexibility of influenza A virus forces World Health Organiztion (WHO) experts to update recommendations on the composition of influenza virus vaccines twice a year [7]. As for influenza B viruses, since the mid-1980s, two influenza B lineages B/ Victoria and B/Yamagata are circulating globally in the human population [8]. Importantly, one or the other lineage is more prevalent in specific countries and regions; also, it is not always possible to predict which influenza B lineage will dominate in the circulation in a particular area during the next influenza season [9].

Currently, available trivalent influenza vaccines include an influenza A(H1N1) virus, an influenza A(H3N2) virus and one influenza B virus, B/Victoria or B/Yamagata. Viruses recommended for inclusion in the trivalent vaccines for the upcoming influenza season may or may not be prevalent. The wrong choice may lead to lower effectiveness of mismatched vaccine efficacy [10].

In the first decade of the XXI century, the use of quadrivalent influenza vaccine containing one strain from each B genetic lineage in addition to A(H1N1) and A(H3N2) strains was suggested [11, 12]. WHO first made recommendations for the composition of a quadrivalent influenza vaccine in September 2012 [13]. The quadrivalent influenza vaccine should provide the best match-up between vaccine strains and circulating influenza B viruses. However, the opposing opinions regarding the use of the quadrivalent influenza vaccine have been raised [10]. In particular, increased production time and costs, vaccine price and cost-effectiveness make some manufacturers think about the appropriateness of using quadrivalent influenza vaccine; various countries still

produce trivalent inactivated or/and live attenuated influenza vaccines.

Besides vaccines, three types of antiviral drugs against influenza are available in the market [8]: (i) neuraminidase inhibitors that block the neuraminidase and is active against influenza A and B viruses (Tamiflu®, Relenza®, and Rapivab®); (ii) cap-dependent endonuclease inhibitors that block replication of influenza A and B viruses interfering with viral RNA transcription (Xofluza®); (iii) inhibitors of the M2 ion channel protein (adamantanes) which are active against influenza A viruses (Flumadine®).

Vaccines can be used to prevent influenza and antiviral medications - for their treatment. Unfortunately, little progress in controlling influenza infection has been made despite all efforts. Why does the flu continue to be a poorly controlled infection? What the causes of our failure to eradicate influenza worldwide are? A number of reasons may contribute to insufficient control for influenza and be the cause of our failure to eradicate influenza worldwide [14 - 18], for instance:

- Influenza viruses spread easily with rapid transmission in crowded areas.
- Persistence of avian and animal influenza A viruses in nature.
- The mixed infections.
- Remarkable genetic flexibility of influenza viruses based on their high mutation rate; rapid evolution of the viral genome.
- The capacity to avoid the immune response (escape immunity).
- The global spread of drug-resistant influenza strains.
- The development of secondary immunodeficiency of the population.
- Irrational pharmacotherapy.
- Weak immunity in the population.
- Vaccination coverage of the entire population should not be less than 60%.

So, is it possible to eradicate influenza?

The paradox of the current situation is a clear contradiction between the achievements of theoretical science and practical results of the fight against influenza infection. Science has created all theoretical prerequisites for defeating influenza. Yet the influenza virus is always one step ahead of us. It seems that it is not futile to think that complete influenza eradication is possible in the nearest future.

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