Influenza Virus

Jennifer Tarner

Helena College University of Montana

Rick Henry

BIOB 272

The influenza virus causes yearly seasonal epidemics and occasionally pandemics that are responsible for millions of hospitalizations and thousands of death each year. This virus has multiple strains and evolving subtypes, which make it difficult for researchers to target those specific strains that will cause the next annual flu season. Because of the rapid viral fluctuations, new flu vaccinations are made every year to prevent the spread and to hinder the infection from occurring. The influenza strains, however, are constantly evolving and transforming in order to invade their host, which is why it is so challenging to finding a cure and a totally effective vaccine. But the host immune defense mechanisms also have the ability to evolve or be aided with medicines that could potentially save lives. By targeting certain strains of the virus, this helps human host bodies to be able to evolve and adapt to the virus from the previously administered vaccine. This approach could be the next step of protection against the influenza virus.

Influenza, usually referred to as the flu or grippe, is a highly infectious respiratory disease. This disease is caused by certain strains of the influenza virus. These strains are composed of influenza A strains which represent the H1N1 and H3N2 subtypes, and two influenza B strains which represent the Victoria and Yamagata lineages (Allen, 2018). In the northern and southern temperate parts of the world, the outbreaks of influenza occur mainly in the winter, while areas near the equator may have outbreaks at any time of the year. Influenza is transmitted from infected mammals through the air by coughing or sneezing and also from infected birds and other mammals through their fecal matter (Shao et al, 2017). When these viral strains are inhaled, it attacks the cells of the upper respiratory tract, causing flu symptoms such as fatigue, fever, chills, a cough, sore throat, headache, nasal discharge, and body aches. The World Health Organization (WHO) estimates that these infections result in 250,000 to 500,000

deaths every year (Allen, 2018). Influenza outbreaks, however, have caused widespread illness to humans throughout the past thousand years.

Influenza has an extensive history of being responsible for the annual flu epidemics and for the occasional global pandemics. The largest pandemic dates back to 1918, which is historically known as the H1N1 Spanish flu pandemic. The H1N1 Spanish flu began during World War I, and it spread quickly throughout the world as soldiers and ships moved from country to country. The H1N1 Spanish flu killed an estimated 50 million people worldwide, causing more deaths than the World War (Barrett, 2015). The H1N1 Spanish flu's death rate was very interesting since it was much higher in younger patients. Of the total number of Spanish flu related deaths from 1918-1919, 99% of them were people 65 or younger, which is different from most flu strains of today since influenza usually has dreadful outcomes for infants and the elderly (Barrett, 2015). Another three pandemics occurred later on in the twentieth century: 1) the H2N2 Asian flu in 1957, 2) the H3N2 Hong Kong flu in 1968 and 3) the H1N1 Swine flu in 2009 (Barrett, 2015). The influenza virus has been killing humans for centuries and in order to try and stop it, researchers need to find out the viruses' genetic characteristics and composition.

Influenza virus belongs to the family of Orthomyxoviridae, which is divided into the different strains of influenza and is technically a Retro virus because it only contains Ribonucleic acid (RNA). These strains can be separated into 18 hemagglutinin (HA) subtypes and 11 neuraminidase (NA) subtypes (Shao et al, 2017). HA is a trimetric glycoprotein that is comprised of a dimer HA1-HA2: HA1 is crucial for binding to the host cell receptor where HA2 for cell fusion (Voskarides et al, 2018). NA is a tetramer of four identical polypeptide chains that allow the virus to leave the infected cell as it cleaves sialic acid (SA) from the cell surface receptors. The human influenza virus only has limited subtypes of HA and NA, which are H1, H2, H3, and

N1, N2 (Shao et al, 2017). Influenza A virus (IAV), has a genome which is composed of eight

RNA strands that encode a total of 13 proteins (Shao et al, 2017). These proteins include

polymerases, structural proteins, and coat proteins. The coat protein is called hemagglutinin

(HA) that initiates the infection by binding to sialic acid (SA) containing glycan receptors on the

surface of the host cell. HA is the primary protein recognized, attacked, and remembered by the

host's immune system. In order for the strain of influenza to stay alive, it must find hosts who

have never been exposed to its version of HA or alter its HA, so the previously exposed hosts no

longer recognize it. The influenza virus is constantly mutating and changing over time to better

fit its host in order to reproduce and then go on to affect its next victim. This virus has an infinite

amount of genetic recombination that involves antigenic shift and antigenic drift. Antigenic shift

is a rapid change of the virus genome; this change involves the eight RNA fragments of the virus

resorting itself between different strains and producing new subtypes. Antigenic drifts cause

more gradual changes to the viral HA proteins; which is the cause of new strains of the influenza

virus each year. The major cause of the high evolutionary rate of influenza is the lack of its

proofreading mechanisms of the viral RNA polymerase. The mutagenesis is extremely close to

the nucleotide site that produces a high genetic variability in the viral genetic pool. Because of

the viruses' genetic variability and evolution, those who become infected are actually infected

from a diversity of viruses and not from one strain (Voskarides et al, 2018). Antigenic drifts are

extremely important for vaccine production for this particular reason. Because of the viruses'

ability to evolve so quickly, vaccines target the three dominant strains in current vaccinations,

which lower the chance of getting the flu.

        Millions of people are affected by the flu every year and getting the seasonal flu vaccine

can lower ones chance of getting the flu by half (Barrett, 2015). Each season's flu vaccine

contains three virus strains that are most likely the ones that will be encountered that flu season. The virus strains that are used to make the vaccine are inactive influenza viruses and will not cause the flu in the host cells (Barrett, 2015). There are two methods by which to receive influenza vaccines: the flu shot and the flu mist. The flu shot consists of the inactive influenza viruses and is injected into the muscle, where the flu mist, is alive but a weakened version of the influenza strain. This flu mist is sprayed into the nostrils, but unlike the shot, the mist is not intended for those over the age of 49. This is because the immune response diminishes with age; the elderly and the chronically ill will not receive the same level of protection from the mist as they would from the shot vaccine. The vaccine is not a guarantee of not getting the flu, but even if people contract it, the vaccine typically diminishes the severity and helps prevent complications. However, with the high degree of variability amongst the influenza viruses and its ever-evolving characteristics, developing these vaccines can be challenging.

The current seasonal influenza vaccines are effective when the antigenicity of the strains used to make the vaccines is closely matched with the circulating influenza strains. Every year the seasonal influenza strains need to be reformulated by researchers in order for the bodies' immune response to recognize and protect itself from the virus. However, the effectiveness of current influenza vaccines is limited since they only protect ones immunity when there is an antigenic similarity between the selected vaccine strains. If there is antigenic mismatch between the current vaccine and the circulating influenza, then people who are vaccinated will not be adequately protected (Sautto et al, 2018). In the United States, the influenza season of 2017-2018 had extremely high levels of contagious volume and increased intensity of influenza. This was documented by high levels of outpatient clinic and emergency department visits for influenza-like illness, high hospitalization rates of influenza and elevated widespread influenza activity

across the county (Garten et al, 2018). The Centers for Disease Control (CDC), collected,

complied and analyzed data on influenza activity and viruses in the U.S. The CDC tested 4,619

influenza viruses from the U.S. collected since October 1, 2017 for resistance to the influenza

neuraminidase (NA) inhibitor antiviral medications that were recommended for use against the

seasonal influenza. Among the 1,147 influenza A (H1N1) viruses tested, 11 were resistant to

both drugs that were found in the vaccine the other 3,472 viruses tested did not show any levels

of resistance (Garten et al, 2018). The reason for this difference might be due to the fact that the

majority of American produced influenza vaccines are manufactured using egg-adapted process.

There were amino acid changes in these egg-adapted viruses that might have contributed to the

differences in antigenicity from circulating viruses. This change occurred more in the A strain

viruses that were in the egg-adapted virus vaccine, where half on them showed reduced

inhibition to one of the drugs (Sautto et al, 2018). Because of these findings, the next vaccines

will hopefully be genetically altered and certain strains of the virus and drugs used will be

modified or not used in the future of influenza vaccines (Sautto et al, 2018). Even during seasons

when vaccine effectiveness is reduced, getting the vaccination can offer a significant benefit and

reduce the risk of getting the flu, hospitalization, and even death.

In the 2017-2018 influenza season, a survey was conducted on influenza coverage

among health care personnel in the United States. Annual influenza vaccination is recommended

for health care personnel to reduce the influenza-related morbidity and mortality rates. In the opt-

in Internet panel survey that was assessed, the influenza vaccination coverage among health care

personnel during this 2017-2018 season was 78.4% (Black et al, 2018). Those that took part in

the survey were the health care personnel that were more likely do get the vaccine. The employer

vaccination requirements, offerings, and promoting of workplace vaccination were associated

with higher coverage. However, the coverage was lowest among long-term care setting personnel who worked in assisted living facilities, were least likely to report employer vaccination requirements or workplace vaccine availability and promotion. Influenza vaccines are especially important for health care personnel in long-term care settings since the elderly have weaker immune systems, which increase the risk for severe illness and disease. It is essential for heath care personnel in all settings to get vaccinated in order to lower the exposure of the influenza virus.

Great strides have been made for new and faster acting vaccines to protect oneself from the influenza virus. In 2018, the Food and Drug Administration (FDA) has approved a new, single-dose flu medication to treat individuals 12 and older who have had the flu for no more than 48 hours. Baloxavir marboxil (Xofluza™; baloxavir) is a single- dose oral medicine approved to treat the flu. It has been shown to significantly reduce the duration of symptoms (Heo, 2018). The drug blocks the influenza virus by inhibiting the initiation of mRNA synthesis. This new flu medication can help reduce influenza infections worldwide and would significantly improve the safety and effectiveness of treating, diagnosing and preventing the influenza virus from becoming another pandemic.

The influenza virus has caused deadly outbreaks for centuries and has triggered worldwide alarm every flu season. With the virus having several strains because it constantly evolves and adapts to different environments, is it difficult to find a reliable and consistent cure. However, by targeting certain strains, we are one step closer to finding a vaccine. Getting the yearly flu vaccine is the best and most effective way of protecting oneself from the seasonal flu. The CDC recommends a yearly flu vaccine as the first and most important step in protecting against influenza and its potentially serious complications. While there are many different flu

viruses, flu vaccines protect against the 3 or 4 viruses that research suggests will be most

common for that year (Black et al, 2018). By targeting the certain strains it can help in making

the new flu vaccinations become more effective and therefore, could help prevent the spread of

the virus from occurring. With new medications such as Xofluza being approved to treat the flu,

this can help reduce influenza infections worldwide and can prevent pandemic from reoccurring.

Hopefully these approaches can help lower the chance of getting the virus and protect the general

public against the influenza virus.

References

Allen, J.D., & Ross, T.M. (2018). H3N2 influenza viruses in humans: Viral mechanisms,
        evolution, and evaluation. *Human Vaccines & Immunotherapeutics, 14(8),* 1840-1847.
        doi: 10.1080/21645515.2018.1462639.

Barrett, J., & Frey, R.J. (2015). Influenza. *The Gale encyclopedia of Medicine, 5th Edition.*
        Retrieved from
        http://link.galegroup.com/apps/doc/OABWGX725268019/HWRC?u=mtlib_1_1041&sid
        =HWRC&xid=69379a8c.

Black, C.L., Yue, X., Ball, S.W., Fink, R.V., De Perio, M.A., Laney, S.A., Williams, W.W.,
        Graitcer, S,B., Fiebelkorn, A.P., Lu, P.J., & Devlin, R. (2018). Influenza vaccination
        coverage among health care personnel-United States 2017-18 influenza season. *Centers
        for Disease Control and Prevention, 67(38),* 1050-1054. Retrieved from
        http://www.altmetric.com/details.php?domain=www.cdc.gov&citation_id=48943718.

Garten, R., Blanton, L., Elal, A.I.A., Alabi, N., Barnes, J., Biggerstaff, M., Brammer, L., Budd,
        A.P., Burns, E., Cummings, C.N., Davis, T., Garg, S., Gubareva, L., Jang, Y., Kniss, K.,
        Kramer, N., Lindstrom, S., Mustaquim, D., O'Halloran, A., Sessions, W., Taylor, C., Xu,
        X., Dugan, V.G., Fry, A.M., Wentworth, D.E., Katz, J., & Jernigan, D. (2018). Update:
        Influenza activity in the United States during the 2017-18 season and composition of the
        2018-19 Influenza vaccine. *MMWR Morbidity and Mortality Weekly Report, 67(22),* 634-
        642. doi: 10.15585/mmwr.mm6722a4.

Heo, Y.A. (2018). Baloxavir: First global approval. *Springer International Publishing, 78(6),*
        693-697. doi: 10.1007/s40265-018-0899-1.

Sautto, G.A., Kirchenbaum, G.A., & Ross, T.M. (2018). Towards a universal influenza vaccine:
        different approaches for one goal. *Virology Journal, 15(17),* 1-22. doi: 10.1186/s12985-
        017-0918-y.

Shao, W., Li, X., Goraya, M.U., Wang, S., & Chen, J.L. (2017). Evolution of influenza A virus
        by mutation and re-assortment. *International Journal of Molecular Sciences, 18(8),* 1650.
        doi: 10.3390/ijms18081650.

Voskarides, K., Christaki, E., & Nikolopoulos, G.K. (2018). Influenza virus-host co-evolution. A
        predator-prey relationship?. *Frontiers in Immunology, 9.* 1-13. doi:
        10.3389/fimmu.2018.02017.