

May-2017

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Recommended Citation

Marintcheva, Boriana (2017). What's New with the Flu?. *Bridgewater Review*, 36(1), 10-12.

Available at: http://vc.bridgew.edu/br_rev/vol36/iss1/5

What's New with the Flu?

Boriana Marintcheva

It is hardly necessary to introduce the Flu: everyone fears getting it or knows someone who has had the misfortune of experiencing it. Every year, many of us debate with our relatives, our physicians and ourselves whether to get the anti-Flu vaccine. The impact of the Flu on our lives can be illustrated with numbers involving many zeros: yearly, thousands of people lose their lives to the Flu or complications from the Flu; millions of doctor's office visits take place; billions of dollars are spent dealing with the Flu; and countless hours of work and school are lost recovering from it. Almost a century after the pandemic Spanish flu ravaged the world, we are

still fascinated by its magnitude, which included Southeastern Massachusetts between 1918 and 1920 (see *Bridgewater Review*, May 2016), and started a scientific quest to identify and combat the infectious agent causing this devastating disease. In 2009, we experienced yet another big Flu scare with the so-called swine flu, whose impact was fortunately much less disastrous than expected.

The Flu is caused by Influenza viruses, which originate in birds and have evolved to infect many wild and domesticated bird species, as well as pigs, horses, humans and even seals and whales. Until recently, scientists knew of only three major types of Influenza, named (unremarkably) Influenza A, B and C. In September 2016, a new Influenza virus isolated from pigs and cattle was officially classified as Influenza D. The various Influenza viruses impact human health somewhat differently. The biggest troublemaker is Influenza A, which infects multiple species and has the potential to become pandemic. Influenza B infection results in disease symptoms similar

to Influenza A, but it does not cause pandemics since it infects only humans and seals, and thus is more containable. Influenza C causes mild non-seasonal disease and is not considered a serious health issue. Anti-Flu vaccines are manufactured to confer immunity against selected strains of Influenza A and B, but not Influenza C. Although Flu viruses are among the best-understood infectious agents, medicine does not offer great tools to control them. The viruses simply change too often, thus requiring our immune systems to start working from scratch as soon as a new virus arises and forcing us to take a yearly vaccine in an attempt to protect ourselves.

Just like any other virus, the structure of Influenza virus can be summarized as "a piece of bad news wrapped in a protein" (Peter Medawar, *National Geographic*, 1994). In fact, Influenza A viruses have eight pieces of bad news, each made of ribonucleic acid (RNA). RNA is similar to deoxyribonucleic acid (DNA) and contains the viral genetic code. Each piece of RNA is wrapped in a proteinaceous coat, and all eight pieces are held together by a

membrane-like structure, called an envelope (Figure 1, in purple). The outside surface of the virus is spiky (Figures 1 and 2), which allows it to attach to the surface of cells in our respiratory tract. The spike responsible for the attachment is a protein molecule called Hemagglutinin (H, in orange, Figure 1), which works like velcro. It is "sticky" because it can interact with molecules on the cell surface (sialic acid or SA) that serve as viral receptors. Once the H and SA "velcro" together, the cellular membrane bulges inward and the Influenza virus finds itself wrapped in a "bubble" inside the host cell. RNA genetic code directs the host cell to produce multiple copies of all viral components, which are then packaged as new viruses. The new viruses are released when they are "pinched out" from the cell. The enzyme Neuraminidase (Figure 1, in blue), is essential for the process, helping the new viruses escape the velcro of the cellular surface. The infected cell continues to produce viruses until it runs out of membrane material and then dies, while the new viruses go on to infect neighboring cells or are released into the environment by coughing and sneezing.

The Influenza A and B viruses propagate very quickly and trigger a robust immune response, which we experience as high fever and inflammation of the respiratory tract. Normally, the first exposure to a virus or taking a vaccine will build immunity and protect our bodies from future infections. Unfortunately, that is not exactly true for the Flu. The trouble is that the molecular machinery copying Influenza genetic code is "sloppy" and makes a lot of errors. As a result, Influenza viruses constantly change and reinvent themselves into a multiplicity of different versions, such as H1N1, H1N5 and many others. The letters H and N refer to the viral spikes, hemagglutinin and neuraminidase, which comprise the viral portrait from

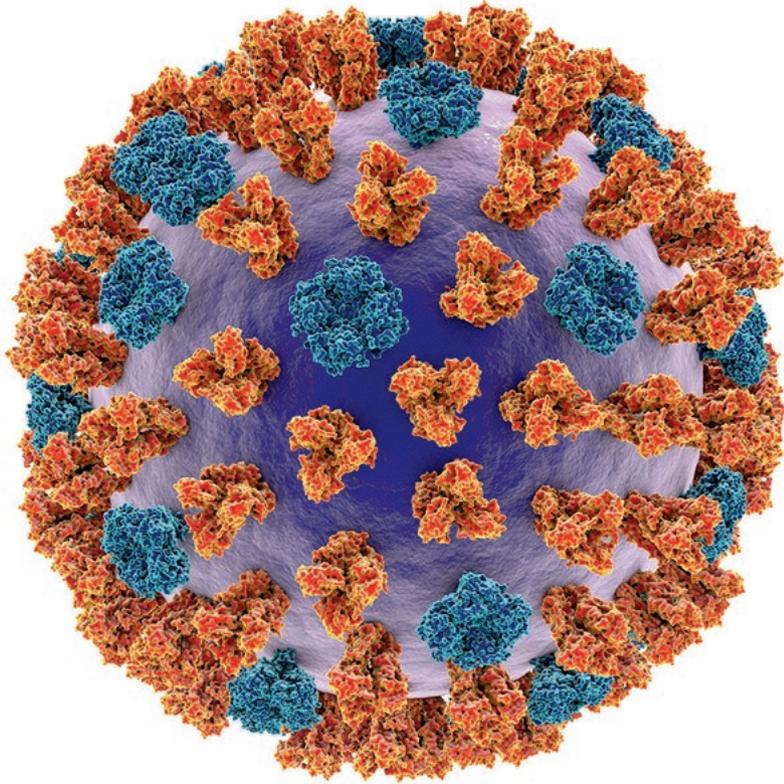


Figure 1. *Creative Illustration of Influenza Virus. The surface glycoprotein spikes: emagglutinin and neuraminidase are displayed in orange and blue, respectively. The eight pieces of genetic code (not shown) are wrapped in the membrane of the viral envelope depicted in purple (Image by Kateryna Kon).*

the viewpoint of the immune system. Every time our body encounters Influenza virus, there is a good chance that it will be a new version, and thus previous illness or vaccine will not be relevant (or as relevant as it could be if the virus was not changing). An additional level of complexity comes from the fact that the Influenza virus has multiple pieces of “bad news” in its genetic makeup. If two different versions of Influenza virus happen to infect the same cell, RNA pieces can be mixed, thus increasing the diversity of newly made viruses even further. Generally, Influenza A viruses change faster than Influenza B, presumably due to their different abilities to infect various hosts. Influenza B infects mainly humans, and so it has a lower probability for producing new versions. Our biological understanding of Influenza virus directly informs the methods that medical and public health officials use to deal with the

Flu globally. We take advantage of the seasonal nature of the Flu, which correlates with virus stability in the environment. The World Health Organization collects information regarding Influenza virus versions in different parts of the planet and recommends updates of the anti-Flu vaccine. For example, the high Flu season in the northern hemisphere spans the winter months; thus information about the current Flu strains collected in our winter (the southern hemisphere’s summer) is used to produce an updated vaccine for the southern hemisphere winter, and vice versa. As with many other disastrous phenomena, prevention of the Flu is our best bet. But unlike many other diseases, we do not have a vast array of tools to help patients with recovery. Only a single class of drugs, inhibitors of the N protein, is available on the market and they work well only if taken at the onset of Flu symptoms. The

drugs block the release of the army of newly produced viruses from infected cells, thus stopping the infection at its roots. If taken past the onset of the symptoms, the drug still does its job, but does not deliver spectacular results simply because the body is already flooded with too many viruses to tackle.

Major technological advances are in the works which, we hope, will improve our success rate of combating the Flu. No, there is no app for that; but the time has come for us to reach higher ground for managing the Flu. Those of us who have been getting the anti-Flu vaccine as recommended will have noticed over the last few years that things have changed for the better. The vaccine becomes available much earlier in the year (usually late August as opposed to October or November), and those who are allergic to eggs can now get vaccinated, which was not possible a few years ago. These improvements are a direct result of extensive efforts to advance technology for vaccine production and move the process away from eggs. For more than 50 years, the vaccine was manufactured in eggs, simply because Influenza is a bird virus and readily propagates in that environment. Unfortunately, the Influenza virus also infects chickens

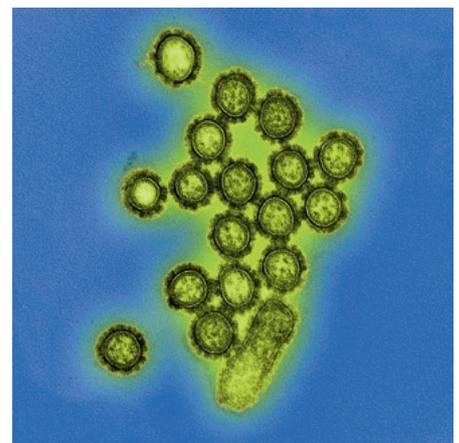


Figure 2. *Digitally-colored Transmission Electron Microscope Image of H1N1 Influenza Virus Particles. Courtesy of National Institute of Allergy and Infectious Diseases.*

and can wipe out huge numbers of them in a short time. When that happens, our capacity for producing anti-Flu vaccine is diminished, resulting in vaccine shortage, something that actually happened at the time of the swine Flu outbreak in 2009. Obviously, individuals allergic to eggs could not be vaccinated due to the risk of severe allergic reaction. The problem was solved with the development of methods to produce classical anti-Flu vaccine in tissue culture of mammalian

strains cannot really be appreciated or changed before the Flu season is over. Naturally, the question “Does it make sense to get vaccinated?” arises. The records say “yes.” There is a great difference between the outcomes of Flu seasons before and after vaccine was made available. Even a 60%-effective vaccine helps combat the virus. When scientists compare the impact of the last pandemic Influenza strain—the swine flu of 2009—with previous ones, they see a huge contrast. In the

universal protection against the forever-evolving Flu. So far, experiments in mice look promising.

Another avenue to diminish the impact of the Flu on our society is to increase the vaccination rates, thus minimizing chances for virus transmission. Painless microneedle patches for syringe-free vaccine delivery are in human clinical trials both in the US and Europe and are expected to revolutionize vaccination not only for individuals with needle-phobia, but globally. It is hoped that, one day, patches will be paired with vaccines that do not require refrigeration and will be delivered by mail to our homes for self-application, thus saving us trips to the doctor’s office, time and travel resources (especially in rural areas). New ideas are being explored involving social media and big-data approaches for the purpose of Flu tracking and forecasting, such as Google Flu Trends, Flu Outlook (Northeastern University, Boston) and FluNearYou (Boston Children’s Hospital). While all advancements toward combating the Flu are exciting and have great potential to improve our lives, it is important to emphasize that they are not justification for skipping the simple and low-cost tools we always have at our disposal. Believe it or not, frequent hand-washing, covering our mouths and noses when sneezing or coughing, not touching our faces, and staying home until our fever is gone can make a huge difference.

The effectiveness rate of the anti-flu vaccine is about 60%, which is understandable given the fact that Influenza viruses constantly change. In some years, the forecast of the most prevalent Influenza strains is off target and the vaccine effectiveness is lower.

cells and new types of vaccine based on recombinant proteins produced in a lab, neither of which involves eggs. An added bonus is the option to freeze mammalian cells and purified proteins to ensure adequate back-up resources for vaccine production, which was not possible with the old technology.

While anti-Flu vaccine supply is no longer an issue, its effectiveness is a different story. The effectiveness rate of the anti-flu vaccine is about 60%, which is understandable given the fact that Influenza viruses constantly change. In some years, the forecast of the most prevalent Influenza strains is off target and the vaccine effectiveness is lower. At present, not much can be done to improve that, since the virus

2009 pandemic, the human death toll was much smaller, at least in part due to “leftover” protection from past vaccines. The development of a universal anti-Flu vaccine protecting against all Flu viruses seems like a perfect solution and hopes are on the rise due to recent technological advancements. Biologists’ analyses of mutations in Flu spikes reveal that certain parts of them do not tolerate change. These parts are not “protected” from mutations; rather, even slight changes in them destabilize the virus—just like even small alterations in the key beams of a house will result in its collapse. Currently, scientists are working to generate a vaccine targeting these unchanging, or constant regions of Flu spikes, thus hoping to find



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