Editorial

Influenza: Our Old Fickle Foe

This year marks the 100-year anniversary of the devastating influenza pandemic of 1918, which killed an estimated 20-40 million people globally. Given the ever-evolving nature of the virus, it is not surprising that we now find ourselves in the midst of yet another particularly brutal flu season that has taken our immune systems and healthcare infrastructure off guard yet again. The H3N2 strain of influenza A virus, which is typically associated with more severe illness and higher mortality, has dominated both hemispheres this year. However, influenza type B viruses are also wreaking havoc this season.

Although we have learned much about influenza virus biology in 100 years, it is hard not to feel frustrated that we don’t have a more effective, and more broadly-protective, “universal” vaccine. The current egg-based inactivated vaccine approach for protecting the population against seasonal influenza hasn’t changed much at all since the 1940s. Each year, the World Health Organization makes a recommendation on which strains to include in a given year’s vaccine formulation. However—due to the virus’s high mutation rate and variable transmission patterns—in some years, these best estimates unfortunately result in an immunological mismatch against the predominantly circulating strain(s). The goal of a universal vaccine, therefore, is to induce a broadly protective immune response to unchanging component(s) of the virus that are conserved across viral strains, and that are not susceptible to seasonal antigenic drift.

Several approaches are underway toward this end. Researchers at UCLA, for example, have shown recently in Science that by systematically knocking out multiple virulence sites on the virus they were able to produce an attenuated virus that was highly-susceptible to interferon, but that was viable enough to induce a potent immune response capable of providing protection against heterologous viruses. This approach, if successful in humans, should have the benefit of not only providing cross-protection against ever-evolving seasonal strains but also the live nature of the virus will make it suitable for convenient nasal spray administration. Researchers have also been trying for years to make a vaccine that will induce broadly neutralizing antibodies directed against the unvarying stem (stalk) of the viral surface hemagglutinin protein, yet challenges with immunogenicity have delayed getting this approach into human clinical trials. Another approach directed targeting the viral nucleoprotein and matrix 1 proteins has been shown to be safe in humans, and is just now moving into a two-year phase II trial. We eagerly await the results of this first-ever human universal influenza vaccine trial.

The limited arsenal of antivirals we have against influenza is also, unfortunately, not necessarily broadly effective or beneficial. Of the three antivirals we have available, oseltamivir is the most commonly prescribed, and works by targeting the viral neuraminidase protein. However, in order to work, the drug must be taken within a short therapeutic window of 48 hours of becoming ill—and is thought to reduce severity and shorten symptoms by about 1-2 days. According to the CDC, side effects of oseltamivir include nausea, vomiting and headache—and in rare cases, severe skin and neuropsychiatric events. Although this year’s circulating strains of influenza still appear to be mostly susceptible to oseltamivir, given the high mutation rate—resistance should be anticipated. Clearly, we need next-generation influenza antivirals that are well-tolerated and effective with a longer therapeutic window. Antivirals against the viral polymerase, drugs that prevent attachment to the host cell, and therapeutic antibodies are all interesting avenues currently under development.

Lastly, there is a serious therapeutic need for more accurate rapid diagnostic tests for influenza infection. Although false positive results using the current swab-based rapid test are likely less common, false negatives can occur in about 4 out of 10 instances. Sending a high-risk patient home due to an inaccurate test is obviously not a desirable outcome in any context. Improving on sensitivity of the rapid influenza test is therefore high on the list of therapeutic imperatives for treatment. A broad screening panel that can help clinicians identify a wide range of pathogens causing flu-like illnesses—not just influenza—would also obviously be very useful, and with today’s advance genetic screening technologies, this seems likely not far down the horizon.

The 2017-2018 flu season is an unwelcome reminder that this virus should never be underestimated, and the race is on for a better arsenal of preventative and prophylactic therapeutics. However, even the best, most efficacious vaccine will need strong public uptake to obtain herd immunity and protect the vulnerable who cannot be immunized.