



Perspective

Chasing Seasonal Influenza — The Need for a Universal Influenza Vaccine

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As clinicians in the United States prepare for the start of another influenza season, experts have been watching the Southern Hemisphere winter for hints of what might be in store for us

in the North. Reports from Australia have caused mounting concern, with record-high numbers of laboratory-confirmed influenza notifications and outbreaks and higher-than-average numbers of hospitalizations and deaths.¹ The number of notifications reached 215,280 by mid-October, far exceeding the 59,022 cases reported during the 2009 H1N1 influenza pandemic, according to the Australian Government Department of Health. Influenza A (H3N2) viruses predominated, and the preliminary estimate of vaccine effectiveness against influenza A (H3N2) was only 10%. The implications for the North-

ern Hemisphere are not clear, but it is of note that the vaccine for this upcoming season has the same composition as that used in the Southern Hemisphere. As we prepare for a potentially severe influenza season, we must consider whether our current vaccines can be improved and whether longer-term, transformative vaccine approaches are needed to minimize influenza-related morbidity and mortality.

Seasonal influenza epidemics cause 3 million to 5 million severe cases and 300,000 to 500,000 deaths globally each year, according to the World Health Organization (WHO). The United States

alone sees 140,000 to 710,000 influenza-related hospitalizations and 12,000 to 56,000 deaths each year, with the highest burden of disease affecting the very young, the very old, and people with co-existing medical conditions.²

The cornerstone of influenza prevention and epidemic control is strain-specific vaccination. Since influenza viruses are subject to continual antigenic changes (“antigenic drift”), vaccine updates are recommended by the WHO each February for the Northern Hemisphere and each September for the Southern Hemisphere. This guidance relies on global viral surveillance data from the previous 5 to 8 months and occurs 6 to 9 months before vaccine deployment. In addition, there are always several closely related strains circulating; therefore, experts must combine antigenic and

genetic characterization and modeling to predict which strains are likely to predominate in the coming season.

Vaccine mismatches have occurred in years in which circulating influenza strains change after the decision is made about vaccine composition, resulting in reduced vaccine effectiveness. For example, during the 2014–2015 influenza season in the United States, more than 80% of the circulating influenza A (H3N2) viruses that were characterized differed from the vaccine virus, and vaccine effectiveness was only 13% against influenza A (H3N2).² This mismatch most likely contributed to the severity of the 2014–2015 influenza season and the substantial related morbidity and mortality among people over 65 years of age.

Even in years when influenza vaccines are well matched to circulating viruses, estimates of vaccine effectiveness range from 40 to 60%, which is lower than that for most licensed noninfluenza vaccines.² For instance, although the 2016–2017 Northern Hemisphere influenza vaccine was updated to include a new influenza A (H3N2) component and the majority of viral isolates characterized by the Centers for Disease Control and Prevention (CDC) were antigenically similar to the vaccine reference virus,² the preliminary estimate of vaccine effectiveness was 42% overall and only 34% against influenza A (H3N2) viruses.

Suboptimal vaccine effectiveness is probably multifactorial. For example, prior influenza exposure and vaccination history could influence subsequent responses to seasonal influenza vaccines. Furthermore, host factors

such as age and coexisting conditions affect vaccine effectiveness. Some of these effects can be mitigated by using adjuvants or high-dose vaccines to generate more robust immune responses in the elderly; however, it is difficult to address all relevant contributors using our current vaccination strategies.

Another factor that may alter the effectiveness of influenza vaccines is the substrate used to produce them. In the United States, most influenza-vaccine viruses are propagated in eggs, although a small proportion are produced either in cell culture or by expressing specific viral proteins using recombinant DNA technologies. During the egg-based production process, the vaccine virus acquires amino acid changes that facilitate replication in eggs, notably changes in the hemagglutinin (HA) protein that mediates receptor binding.³ Since the influenza HA is the primary target of neutralizing antibodies, small modifications in this protein can cause antigenic changes in the virus and decrease vaccine effectiveness. Egg adaptation has been postulated to contribute to low vaccine effectiveness, particularly with influenza A (H3N2) viruses; however, the true impact is largely unknown.³

A recent study by Zost et al. highlighted a particular egg-adapted mutation (T160K) that may have contributed to low vaccine effectiveness during the 2016–2017 influenza season in the United States.⁴ The investigators determined that circulating influenza A (H3N2) viruses possessed an HA glycosylation site that was lost in the vaccine strain during egg adaptation, and both ferret and human antibodies elicited by

that vaccine strain poorly neutralized circulating virus. The researchers also compared antibody responses elicited by vaccine antigens prepared using eggs, cell culture, and the recombinant DNA baculovirus system. They found that most people who mounted a strong antibody response to influenza viruses that contained the HA glycosylation site found on circulating viruses had received the recombinant baculovirus-based vaccine, which was not affected by the egg-adapted mutation.

Notably, the cell-based vaccine used during the 2016–2017 influenza season in the United States used a seed virus that had undergone egg passage, which probably explains the presence of a T160K HA mutation in this system. Starting with the 2017–2018 influenza season in the United States, cell-based vaccines will use cell-based seed strains.² Although there are limitations to the study by Zost et al.,⁴ including the effect of higher antigenic content in baculovirus vaccines, it nonetheless highlights the need for further evaluation of the egg-based manufacturing system and its impact on vaccine effectiveness.

Egg adaptation may have public health consequences, as indicated in analyses of the 2016–2017 Australian influenza season. Interim reports suggest that the 10% vaccine effectiveness against influenza A (H3N2) viruses was not primarily attributable to antigenic mismatch between the vaccine strain and circulating viruses.¹ Instead, antigenic characterization using ferret reference antisera indicates that egg-propagated vaccine viruses acquired changes in the HA that subsequently altered antigenicity against circulating

strains. This observation lends credibility to the hypothesis that egg-adapted changes contribute to poor influenza-vaccine effectiveness. Furthermore, since most of the circulating influenza A (H3N2) viruses possessed the T160 HA discussed above, it is possible that the particular egg adaptation described by Zost and colleagues played a role.

Given that most of the U.S. influenza-vaccine supply is currently produced in eggs and the composition of the 2017–2018 Northern Hemisphere vaccine is identical to that used in Australia, it is possible that we will experience low vaccine effectiveness against influenza A (H3N2) viruses and a relatively severe influenza season if they predominate. This possibility underscores the need to strive toward a “universal” influenza vaccine that will protect against seasonal influenza drift variants as well as potential pandemic strains, with better durability than current annual

vaccines.⁵ Among other advantages, in all likelihood, such a vaccine would not be subject to the limitations of egg-based vaccine technology.

However imperfect, though, current influenza vaccines remain a valuable public health tool, and it is always better to get vaccinated than not to get vaccinated. In this regard, the CDC estimates that influenza vaccination averted 40,000 deaths in the United States between the 2005–2006 and 2013–2014 seasons.² Yet we can do better. Although targeted research to improve current vaccine antigens, platforms, and manufacturing strategies may in the short term lead to enhanced effectiveness of seasonal influenza vaccines, to achieve the ultimate objective of a universal influenza vaccine, a broad range of expertise and substantial resources will be required to fill gaps in our knowledge and develop a transformative approach to influenza-vaccine design.⁵

Disclosure forms provided by the authors are available at NEJM.org.

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