

Influenza Vaccine Production: Current Challenges and Evolving Technologies

Annual Production Challenges

Influenza vaccine production is particularly challenging because a new vaccine must be formulated each year to provide the best possible protection against circulating influenza viruses that undergo frequent changes. Moreover, the vaccine includes three viruses, usually one influenza type B and two influenza type A strains, and each must be grown individually before the three are combined late in the production process.

The U.S. Food and Drug Administration (FDA) determines which strains to include in the U.S. vaccine each year based on surveillance data from across the globe. Strain selection is important because closer match between circulating and vaccine strains generally leads to better vaccine protection. Although influenza B strains are relatively stable, influenza A strains change more often, making optimal match a challenge. However, even in years when the strains are not particularly well matched, the vaccine still affords some level of protection against confirmed influenza infection.

Once the FDA selects the strains, the U.S. Centers for Disease Control and Prevention (CDC) prepares reference viruses that are distributed to vaccine manufacturers. All U.S. influenza vaccines are made from the same reference viruses and all are produced using egg-based technology. Egg-based technology has been used to produce influenza vaccines since the 1950s. In the six decades since, billions of influenza vaccine doses have been produced and used safely to protect people across the globe from influenza infection.

Influenza vaccine preparation takes about six to eight months, with FDA testing and approvals accounting for about four to five of those months. There is a new FDA initiative looking at ways to accelerate the vaccine review and approval process. A key element of the FDA review process is

potency testing, which must be completed for each of the three vaccine strains before they are combined to make the trivalent (i.e., three virus) vaccine.

Evolving Technologies

While evolving technologies may be of future use, their impact on production time is not yet fully known. The most promising technologies in development, cell culture and reverse genetics, would have no major impact on testing and approval time. They may, however, have an impact on time spent on non-testing and approval phases, which account for about 15 percent of overall production time.

Cell culture technology

Cell culture technology is a production method that is being explored as a possible replacement for egg-based production. Possible timing advantages of cell culture technology are speculative because the technology has not been used on a large scale in the U.S. It is likely that production could begin sooner once the reference virus is provided to manufacturers. However, this advantage would amount to just a few weeks and subsequent production timelines using cell culture and egg-based techniques are the same.

A clear advantage of cell culture is elimination of influenza vaccine contraindications for people with egg allergies. Fortunately, very few people have the types of egg allergies that contraindicate influenza vaccination (i.e., severe anaphylactic or hypersensitive reaction to eggs). There are also specific immunization protocols available to allow those with egg allergies to receive influenza vaccine.

Many other potential advantages of cell culture have been discussed widely, including safer vaccines and better protection in times of strain mismatch. However, there are limited data to determine if either of these potential advan-

tages will be realized. The possibility of lower costs has also been discussed, but, in fact, vaccine costs would likely increase due to increases in production investments (e.g., costs for new cell-culture growing facilities).

Reverse genetic technology

Reverse genetic technology could be used with either egg-based or cell culture production. This technology allows scientists to manipulate the reference virus before production begins. The virus is manipulated in an attempt to produce a vaccine that both matches the new strain of influenza and increases production yield. High-yield virus growth is essential to meet the growing demand for influenza vaccine.

The classical method, used for over 30 years to increase yield of influenza viruses, is one of natural selection, in which the reference virus and another are allowed to infect the same cell. In doing so, the two viruses share their eight genetic sequences in every possible ratio,

from seven to one to the other extreme of one to seven. Each new strain is allowed to grow over time and one generally emerges as the highest yielding strain.

Using reverse genetics, scientists determine the ratio of genetic sequences and create a new strain with chains from two or more virus strains. This may result in a virus with better yield or one that is no better than the original reference virus. It is impossible to predict the highest yielding ratio of genetic sequences.

Reverse genetic technology does provide some clear advantages. It can be useful when working with potential pandemic-causing influenza viruses. Such viruses often have an unusual genetic sequence making them more pathogenic or more difficult to grow. Reverse genetics can target these sequences for splicing. This is an extra "insurance policy" since the virus can be weakened during the production process.

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