VACCINEINSIGHTS

ADVANCES IN VACCINE MANUFACTURING
PART 1: UPSTREAM ADVANCES &
INTENSIFYING PRODUCTION

SPOTLIGHT

Leveraging modernization of the US influenza vaccine manufacturing base to make better vaccines: a work in progress

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"The time is right to leverage our newly demonstrated manufacturing platforms to design and develop the next generation of influenza vaccines."

VIEWPOINT

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When highly pathogenic avian influenza emerged in Hong Kong in 1997, killing 6 of 18 people with confirmed infections [1], US public health and national security experts realized the vulnerability of the US and global populations to pandemic influenza. At the time, there was a single US manufacturer of influenza vaccines, Sanofi Pasteur, which relied on seasonal supplies of embryonated eggs to grow the influenza viruses used to make their split virus vaccine.

In response to the 1997 outbreak, the US Homeland Security Council released two documents that laid out plans to improve public health preparedness for pandemic influenza: a national strategy in 2005 [2] and a national strategy implementation plan in 2006 [3]. A key aspect of the preparedness pillar of the national strategy was: "Establish domestic production capacity and stockpiles of countermeasures to ensure… sufficient vaccine to vaccinate the entire US population within 6 months of the emergence of a virus with pandemic potential" [2]. Starting in fiscal year 2004, Congress began supplying funds to address this aspect of the national strategy, with funding through the US Department of Health and Human Services (HHS) and the Department of Defense (DoD). This effort, a several billion-dollar investment, resulted in part in the creation of the Biomedical Advanced Research and Development Authority (BARDA) in 2006 [4] to be the point organization for leading the development of the domestic influenza vaccine manufacturing infrastructure.

Initial efforts to build up domestic vaccine manufacturing started in 2004. HHS funded contracts to bolster supplies of embryonated eggs so they were available year-round [5] and to develop a cell-based influenza vaccine with a provision to build a domestic facility for vaccine production [5]. BARDA followed these contracts with additional cell-based influenza vaccine [6], adjuvant [7], recombinant influenza vaccine [8], and influenza vaccine production facility [7,8] contracts. In parallel, the DoD funded the development of alternate platforms for influenza vaccine production [9].

These efforts have resulted in the licensure of new cell-based, recombinant, and adjuvanted or dose-sparing influenza vaccines [10]. Other improvements include an enlarged domestic capacity to produce adjuvants and influenza vaccines using egg-based, cell-based, and recombinant vaccine platforms [7,8]. The US now has the domestic capacity to produce enough influenza vaccine to provide pandemic influenza protection within six months. But even with improved manufacturing infrastructure and more types of vaccines, is the job of preparing for pandemic influenza finished? Do we have better vaccines? I would argue there is still work to be done to achieve pandemic preparedness with better vaccines.

The majority of influenza vaccines use egg adaptation for egg-based vaccine manufacturing which has been shown to alter how closely a vaccine matches circulating influenza viruses [11–13]. Recombinant and cell-based vaccines, which do not require egg-adaptation mutations for efficient manufacturing, are more effective than egg-based vaccines [14,15] because they avoid egg adaptation and more closely represent viruses circulating in the population. This has led to the committees that select strains for influenza vaccine production recommending two different strain formularies depending on whether a vaccine is to be egg-based or non-egg-based (cell-based, recombinant).

While the use of non-egg-based vaccines is growing, the field effectiveness data in the years since their licensure suggest that we are still being served by mediocre vaccines. The CDC influenza vaccine effectiveness data [16,17] from 2004 to today shows the overall average effectiveness at 41%. Between 2004 and 2012, before any new vaccines were licensed, the average effectiveness over this period was 41%. Between 2016 and 2023, after the last of the new vaccines were licensed, average effectiveness only increased to 42%.

Why is vaccine effectiveness not improving? The tremendous improvements to our influenza vaccine manufacturing capacity and expanded vaccine manufacturing platforms have not expanded into the design and manufacture of better vaccines. We are still largely

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making injectable influenza vaccines focused on making antibodies to the virus hemagglutinin (HA), which appear to only provide 60% protection in the best of years. McLean *et al.* [17] report the mid-season effectiveness at 71% for the 2022–2023 influenza season but since it is known that vaccine effectiveness declines over time through the influenza season [18] it is expected that the final effectiveness percentage will be lower by the end of the season.

I argue that in order to design and manufacture better influenza vaccines, focus is needed on three areas that leverage our expanded platforms and manufacturing capacity to improve influenza vaccines:

1. Incorporating more conserved antigens (neuraminidase (NA), M2 protein) into influenza vaccines would broaden immunity and increase baseline protection, especially in years of a vaccine mismatch;
2. Designing vaccines to stimulate mucosal immunity to protect the initial route of infection and;
3. Designing vaccines to stimulate T cell immunity to limit and control infections. Ideally, we will design improved influenza vaccines that incorporate all three of these improvements over current vaccines.

Manufacturing lessons from vaccines against SARS-CoV-2 may have paved the way for influenza vaccines with improved effectiveness. The capacity for the manufacture of mRNA-based vaccines has been clearly demonstrated by the hundreds of millions of doses of SARS-CoV-2 mRNA vaccines produced. These mRNA-based vaccines were shown to stimulate T cell responses [19,20]. Influenza vaccines based on this technology, designed to incorporate both HA and NA targets into a single vaccine, could offer broader protection with improved T cell responses to control infections when they occur.

Although not as widely used as mRNA vaccines, vectored adenovirus vaccines could demonstrate even greater promise as a future platform for more effective influenza vaccines. Vectored adenovirus vaccines can be delivered by mucosal immunization [21]. Adenovirus-vectored influenza vaccines incorporating both HA and NA targets could stimulate mucosal immunity to protect the initial route of infection along with immunity to a more broadly protective set of antigens, and stimulation of T cell responses to influenza virus.

The time is right to leverage our newly demonstrated manufacturing platforms to design and develop the next generation of influenza vaccines. The improved designs will not only be rapid to manufacture but more effective in combating seasonal and pandemic influenza infections. These steps are needed to ensure we have established and built the rapid development capabilities and manufacturing infrastructure to respond to future pandemics.

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AUTHORSHIP & CONFLICT OF INTEREST

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