



DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
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TO: Secretary Burwell

FROM: Nicole Lurie, ASPR

HHS Influenza Risk Management Group:
Robin Robinson, BARDA
Bruce Gellin, OASH
Carole Heilman, NIH
Jackie Katz, CDC
Karen Midthun, FDA

THROUGH: Andrea Palm
Anne Reid
Averi Pakulis

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SUBJECT: Memorandum on Influenza Process Improvements

ISSUE

The mismatched seasonal influenza vaccine in the U.S. during the 2014-2015 season highlights the need to make these vaccines better and sooner. The HHS Influenza Risk Management Group, comprised of HHS staff with expertise in influenza, has been making steady progress toward a goal of universal, highly-effective vaccines through the Influenza Manufacturing Vaccine Initiative (IVMI) -- a partnership between HHS, industry, and academics. Over the past several months the group has been working to understand the mismatch problem in detail, review how both ongoing and new activities might address the mismatch issues, and recommend actions to mitigate this problem in the future.

This memo summarizes the key challenges in the seasonal influenza vaccine development and manufacturing processes, and highlights opportunities for improvement. ASPR is responsible for monitoring and ensuring the implementation of these improvements and providing periodic updates to you.

BACKGROUND

Influenza viruses are constantly changing genetically. This process is known as antigenic drift (drift), and it allows influenza viruses to escape immunity that has built up in the population (stimulated by vaccination or past infection). For this reason, formulation of influenza vaccines may change from season to season to respond to observed changes in circulating influenza virus. Because of the time currently required to produce and distribute influenza vaccines, decisions

regarding which strains to incorporate into the annual seasonal influenza vaccines must be made approximately eight months before the onset of each influenza season. During this time, influenza viruses continue to change, and occasionally, that drift is so significant that it results in influenza vaccines that are a poor match for the predominant virus circulating in the population. In years where the vaccine is well-matched to circulating viruses, vaccine effectiveness is generally between 50 and 70 percent. It is worth noting that in addition to the match between the vaccine and circulating strains, other factors (e.g., health status) can affect how well a vaccine works.

HHS has undertaken a number of activities designed to improve the influenza vaccine development and manufacturing process and increase the likelihood that annual seasonal influenza vaccines are well-matched to the circulating strains, including the following:

- improving global surveillance and virus characterization to detect new emergent strains more quickly;
- incorporating technological improvements to speed production and regulatory timeliness;
- making better, more effective vaccines that would provide broader cross protection across potentially drifted virus strains; and
- improving the systems for distribution, administration, and monitoring of vaccines.

These activities are further detailed below.

Surveillance and Virus Characterization

Globally-coordinated surveillance is the foundation of the influenza vaccine virus selection and development process. Ensuring that the system has the best technologies at its disposal to analyze influenza viruses and contribute to the production of influenza vaccine is equally important. The World Health Organization (WHO) Global Influenza Virus Surveillance and Response System (GISRS) is a global network that provides year-round surveillance of human and animal influenza viruses, makes recommendations on the composition of seasonal influenza vaccines, and provides candidate vaccine viruses for manufacturers to use in the production of seasonal influenza vaccines. CDC and others continue to work to strengthen global surveillance and laboratory detection capacity for influenza viruses, and CDC is in the process of shifting to a new practice that first characterizes viruses by high-throughput nucleotide gene sequencing, affording a quicker and more comprehensive picture of these viruses that can be used early in the process of selecting virus strains for vaccines. In addition, NIAID and BARDA are supporting new evolutionary biology and bioinformatics visualization techniques to investigate drift and the human immune response in order to potentially enhance prediction of which strains are likely to circulate. In the long run, this could increase the likelihood that strains selected for the influenza vaccine are well matched to influenza strains circulating during the influenza season.

Here are the recommendations for surveillance, which agency is accountable for each opportunity, and the timeframe by which activities are anticipated to be completed.

Issues	Recommended Solutions	Responsible Party
<i>Near Term (present-15 months)</i>		
Gaps in global influenza surveillance.	Expand WHO Global Influenza Virus Surveillance and Response System (GISRS) through capacity building.	CDC and WHO (GISRS)
Improve techniques for identification and characterization of antigenic drift viruses.	Expand use of new technologies and optimize alternate assays for testing.	CDC
<i>Mid Term (2-3 yrs.)</i>		
Need for improved understanding of virus antigenicity and vaccine effectiveness to better inform vaccine strain selection.	Change paradigm for vaccine strain selection to include new CDC practice that affords a quicker and more comprehensive picture of these viruses.	CDC
	Develop US public health lab networks to supply whole genome data.	CDC
	Continue to support research on understanding the relationship between antigenic match and vaccine effectiveness.	NIH, BARDA, and CDC
<i>Long Term (4-7 yrs.)</i>		
Reduce time to identify and characterize drifted viruses.	Continue support of novel vaccine strain prediction methods.	NIH, BARDA, and CDC

Technological Improvements

Seasonal influenza vaccine manufacturing and formulation currently takes at least six months from vaccine strain selection in late February to vaccine availability in late August with manufacturers starting production at risk in late December (see Figure 1). There have been substantial improvements in the development of high-growth vaccine candidates that increase vaccine manufacturing yields sooner, and the science is continuing to progress rapidly. Vaccine manufacturers are in the process of adopting several process improvements described below for pandemic vaccine. We anticipate, and would ask, that these improvements also be applied to seasonal influenza vaccine manufacturing. **Application of these improvements to seasonal influenza could save four to six weeks in the manufacturing and formulation process; however, until these improvements are used in the seasonal process, we cannot be certain about the exact time savings.** If successful, this could potentially enable final decisions about the vaccine composition to be made with surveillance information closer to the beginning of the influenza season. **We expect these technical improvements may be tested, validated, and adopted by a subset of influenza vaccine manufacturers within two to three years for seasonal influenza vaccines.**

Seasonal influenza vaccines contain either three or four human strains of influenza; these are manufactured separately and combined near the end of the process. How rapidly this can be done depends on candidate vaccine yield (i.e. how much virus is produced in eggs or cells), how quickly the potency assay reagents to test them can be developed, and how rapidly the bulk and formulated vaccine can be tested for potency and sterility and lot released by the FDA. A persistent challenge in candidate vaccine virus production is the need to grow viruses in eggs – the vast majority of influenza vaccines are produced this way. Collaborations between CDC, FDA, WHO, and manufacturers are underway to use synthetic biology (engineering biological systems to increase speed, scale, and precision) and reverse genetics (working backward to make a mutant gene) to accelerate this process. **Generation of high-growth vaccine seeds using these new approaches may save three to five weeks in the initial steps of vaccine production within the next two to three years.**

Through the IVMI initiative, improvements are also being made in the assays that test vaccine before lot release to ensure its potency and sterility. **It is anticipated that this could further decrease vaccine manufacturing time by two to three weeks within the next two to three years.**

Another important issue is how quickly, in the event of a drift in one of the seasonal virus strains, manufacturers could produce a new strain for inclusion in the standard seasonal vaccine or a new monovalent vaccine. Doing this would require manufacturers to have early information about drifted strains, a recommendation from CDC/FDA to make a change, and the ability for potency tests to be available in time for a reformulated vaccine to be released. HHS now uses the Influenza Risk Assessment Tool (IRAT), to decide whether to make limited amounts of vaccine in response to emerging, potentially-pandemic strains. **Using the IRAT as a model, a risk assessment method should be developed by the HHS Influenza Risk Management group within the next 15 months to guide recommendations about whether to change seasonal vaccine strain composition between the WHO recommendation and June.**

It is not clear who would pay for a late-season shift, as seasonal vaccine is made and produced in the private market (unlike in a pandemic where BARDA resources would be available for development). A strong process recommendation resulting from this year's strain mismatch is that following the annual WHO strain selection meeting, FDA and CDC should meet monthly to review early evidence of drift, notify WHO, and be poised to convene an ad hoc meeting of the FDA's Vaccine and Related Biological Products Advisory Committee (VRBPAC) to consider whether to make a recommendation to change strains. In addition, continually improving prediction methods should enable the CDC to provide information to manufacturers regarding which strain(s) give them most concern about potential drift. **Manufacturers could then choose to make that strain last, which would allow them to finalize the composition of the vaccine as late as June (10-12 weeks later than the current process). Communication is key throughout the process, particularly towards late spring/early summer, as discussions with manufacturers suggest that some could also switch a strain in a quadrivalent seasonal influenza vaccine as late as June if they became aware of significant drift.**

Here are the recommendations for technological improvements, which agency is accountable for each opportunity, and the timeframe by which activities are anticipated to be completed.

Issues	Recommended Solutions	Responsible Party
<i>Near Term (present-15 months)</i>		
Need to better facilitate candidate vaccine virus development.	Provide more potential vaccine viruses for production of egg-based candidate vaccine virus (CVVs) and information/viruses to manufacturers. Provide cell-grown seed viruses. Evaluate synthetic biology/genetic engineering to improve antigenic properties of egg-grown CVVs.	CDC, WHO (GISRS), and academic labs producing CVVs
Limited availability of vaccine potency assay reagents to test antigenically-drifted virus strains.	Begin potency assay reagent development early (i.e., at risk) if drifted strains appear to be of concern.	FDA (CBER) and vaccine manufacturers

Issues	Recommended Solutions	Responsible Party
Limited formal evaluation of seasonal influenza antigenic drift risks and remediation.	<p>Develop and apply a risk assessment method to the analysis of seasonal antigenic drift.</p> <p>Convene global partners to communicate risk mitigation steps identified to address late identification of antigenic drift and its impact on seasonal vaccine production.</p>	<p>CDC and FDA</p> <p>HHS Influenza Risk Management Group</p> <p>HHS with global partners</p>
HHS review (other than CDC) of virus surveillance data following WHO/VRBPAC recommendations is limited.	<p>CDC and FDA meet monthly from March through June of each year to review new virus surveillance data, with results communicated to the ASPR and the VRBPAC chair.</p> <p>Convene VRBPAC meeting if strong evidence of drift.</p>	<p>CDC and FDA (CBER)</p> <p>FDA (CBER)</p>
Limited communication with manufacturers on virus antigenic drift possibilities and potential solutions.	<p>Communicate early with manufacturers when antigenic drift is a concern.</p> <p>Convene manufacturers to discuss further additional steps they or the government could take to make strain changes late in the manufacturing process.</p>	<p>CDC and WHO Collaborating Centers with vaccine manufacturers</p> <p>HHS Influenza Risk Management Group with vaccine manufacturers through International Federation of Pharmaceutical Manufacturers and Associations (IFPMA)</p>
Virus passaging of candidate virus seeds for high growth may lead to mismatches with circulating virus.	Develop new virus reassortants (combinations) with high-growth potential & match to circulating virus strains.	IVMI initiative (CDC, FDA, NIH, BARDA, and academic and industry partners)
<i>Mid Term (2-3 yrs.)</i>		
Long turnaround for vaccine potency reagents and testing.	Complete work on potency assay development and potency testing methods.	IVMI initiative (CDC, FDA, NIH, BARDA, and academic and industry partners)

Making Better Vaccines

Long-term development and realization of more effective and “universal” influenza vaccines may best address the potential for mismatched seasonal vaccine. **Several promising candidates are anticipated to be ready for NIAID-supported clinical trials in the next two years.**

BARDA recently announced a new Request for Proposals to support advanced development of More Effective/Universal Influenza Vaccines that provide broader, longer-lasting immunity to a range of drifted influenza viruses. These vaccines might also provide an important priming response to prepare a population for the emergence of a novel influenza virus, such that only a single dose of pandemic influenza vaccine might be needed if such a virus begins to infect people.

Here is the recommendation for making better vaccines, which agency is accountable for this opportunity, and the timeframe by which activities are anticipated to be completed.

Issues	Recommended Solutions	Responsible Party
<i>Long Term (4-7 yrs.)</i>		
Limited cross protection of current influenza vaccines against drifted viruses.	Continue support of more effective seasonal and universal influenza vaccines.	NIH, BARDA, CDC, and FDA

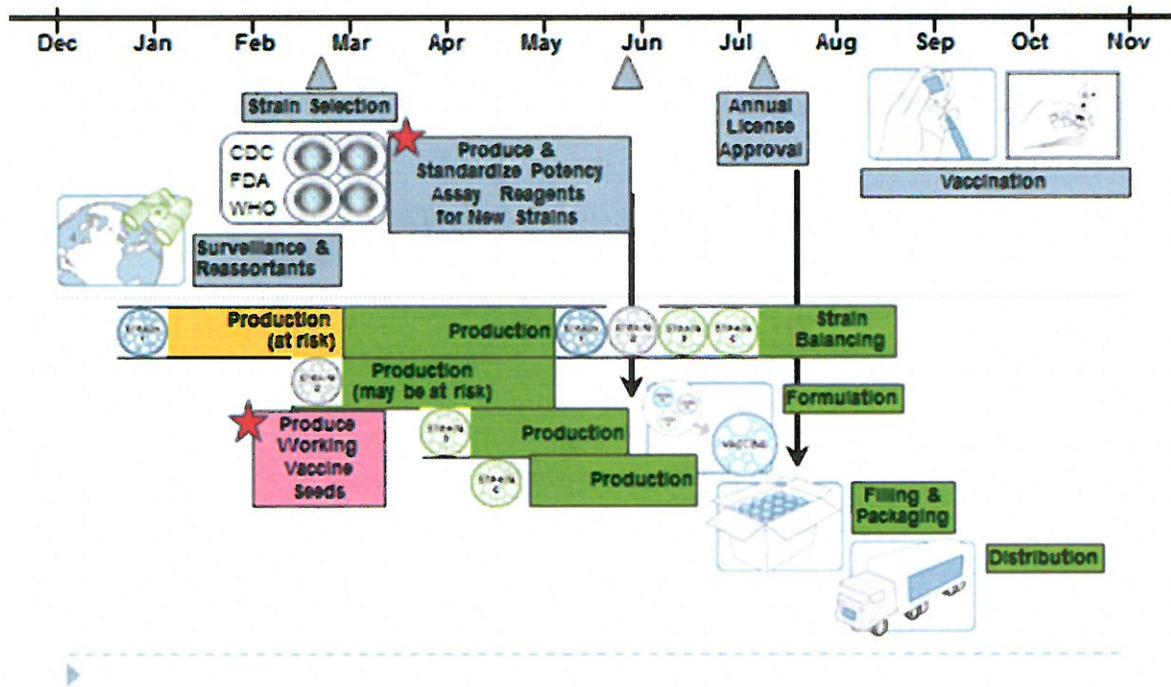
Vaccine Distribution and Administration

It is critical to remember while selecting strains and manufacturing vaccine are complex, so are distribution, administration, tracking, and safety monitoring. Improvements are needed in the vaccine distribution chain so inventory can be tracked throughout and reallocated to address shortages in tracking and vaccine registries, and in adoption of technologies such as radio frequency identification (RFID) technology for vaccine vials, containers, and packaging, so that vaccine can be monitored, tracked, and more easily be evaluated for safety and efficacy. Some of these improvements are underway as part of pandemic preparedness.

Here is the recommendation for vaccine distribution, which agency is accountable for this opportunity, and the timeframe by which activities are anticipated to be completed.

Issues	Recommended Solutions	Responsible Party
<i>Mid Term (2-3 yrs.)</i>		
Limited visibility on vaccine distribution, tracking, and monitoring.	Continue improvements to vaccine distribution, tracking, and monitoring.	CDC, FDA, and BARDA

Figure 1. Seasonal influenza vaccine strain selection, manufacturing, and vaccination steps for the U.S. market with on-going improvement projects in manufacturing.



Red stars (★) indicate the on-going projects to improve and expedite influenza vaccine manufacturing through the IVMI initiative. The gray triangles indicate current time of strain selection and bulk manufacturing completion and annual license approval. The period from strain selection to completion of production represents the period in which a strain change might occur if needed.