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Lessons Learned: Role of Influenza Vaccine Production, Distribution, Supply, and Demand—What It Means for the Provider

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ABSTRACT

The Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention (CDC) has been increasing the size of the population for whom influenza vaccine is recommended to reduce the substantial and persistent annual health burden of influenza. Realization of current and future public health influenza immunization goals requires assuring vaccine supply will be adequate to meet demand. This has posed distinct challenges for the many stakeholders in the influenza vaccine program—government agencies, federal, state, and local policymakers, vaccine manufacturers and distributors, and the medical community—each of whom must make critical decisions in a constantly shifting environment. Factors such as the yearly changes in influenza virus strains, the complicated vaccine production and distribution process, revisions in vaccination recommendations, and changing demographics can all affect the delicate balance between supply and demand. While vaccine shortages and delays have been well-publicized concerns in the recent past, there has been a marked increase in supply in the past several years, with substantial growth in supply expected in the future. The primary issue today is to strengthen the demand for the influenza vaccine, which would in turn help ensure the continued availability of the vaccine to reduce disease burden. A number of strategies are discussed, including increased efforts to publicize and fully implement current CDC recommendations and to offer influenza vaccine beyond the typical vaccination season of October and November, because in the great majority of years, vaccination into January and beyond will still provide health benefits.

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Influenza causes the greatest vaccine-preventable burden of disease in the United States, accounting for an estimated annual average of 36,000 deaths and 226,000 hospitalizations.[1,2] To decrease this burden, the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) gradually has increased the size of the population recommended for annual vaccination, which now covers about 73% of the US population, or 218 million people.[3] This includes persons at high risk for complications from influenza and the individuals who might transmit the virus to them, such as their household contacts and healthcare workers. Starting no later than the 2009-2010 influenza season, vaccination recommendations will be extended to include all children 5 to 18 years of age,[4] which will add approximately 30 million children (~10% of the US population) to the group who should be vaccinated annually. In addition, the ACIP encourages anyone who wants to avoid influenza to obtain the vaccine. Thus, almost the entire US population is either recommended to be vaccinated annually or is covered by a permissive recommendation.

Influenza vaccine is different from all other vaccines because it is administered annually to persons for whom it is recommended. More doses of influenza vaccine are used annually than of any other vaccine.[5] Nevertheless, the burdens of providing influenza vaccine have left many provid-

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ers frustrated. The purpose of this article is to explain the reasons why there may be problems in vaccine supply in a given season and to outline potential steps providers can take to help their patients avoid the burdens of influenza while at the same time enhancing production and distribution capacity to meet present and future demands.

In the United States, the major stakeholders in the influenza immunization program include government agencies, state, federal, and local policymakers, vaccine manufacturers, distributors, and clinicians, including community immunizers as well as those who provide influenza vaccine at the workplace.[6] These participants must make decisions regarding the vaccine composition, the assessment of vaccine potency and purity, the amount of vaccine to produce, how many doses to order, how to distribute, how to finance, when to administer the vaccine and to whom, and how to reach patients. Numerous factors come into play, many of them subject to change. For example, influenza viruses undergo frequent mutations. Thus, the vaccine must be reformulated each year to include new strains experts think are likely to circulate the following season. In any given year, availability of vaccine may be affected by low production yields, higher-than-expected demand, and changes in vaccine recommendations. Longer-term factors (e.g., demographic), such as the increase in the elderly population, a group at high risk for influenza-related complications, may also influence future supply and demand.

There have been several influenza supply disruptions since the 2001-2002 season.[7,8] Disruptions have occurred, for example, when manufacturers have exited the marketplace or when manufacturers' products became available after the traditional influenza vaccination season, which the CDC had previously defined as October through November (now considered to be October into January and beyond).[3,9,10] A highly publicized shortage occurred in 2004-2005, when contamination forced the vaccine manufacturer Chiron to suspend production of its anticipated 46 million influenza doses at its facility in Liverpool, England. At the time, Chiron was 1 of only 3 companies providing the influenza vaccine to the US market, and these lost doses represented about half of the anticipated US vaccine supply for 2004-2005. Although federal agencies moved quickly to prioritize who should receive the vaccine, concern eventually focused on the country's inability to administer all doses of even this limited supply.[11,12] With the subsequent entry of additional manufacturers into the marketplace, which now includes sanofi pasteur, Novartis, GlaxoSmithKline, MedImmune, and CSL Biotherapies, the vaccine production capacity appears to be less vulnerable. It is estimated that a record 130 million doses were produced for the 2007-2008 influenza season,[13] and in the future, a steady and plentiful supply of vaccine is expected. Thus, the overriding issue today involves complying with ACIP recommendations to prevent the influenza burden each season. This requires increasing consumer demand and providing incentives to providers to ensure sufficient supply. For example, annual coverage for persons ≥65 years, 1 of the priority groups for vaccination, is typically <70%, when national targets call for ≥90%.[14] This article discusses the current system of vaccine production, distribution, and financing in the context of supply and demand. It also highlights new developments and approaches that may help achieve immunization goals to the benefit of all influenza vaccine stakeholders.

PRODUCTION OF THE INFLUENZA VACCINE

Although a larger manufacturing base will help to avert vaccine supply shortages, some degree of uncertainty is inevitable, given the inherent complexities of the influenza vaccine production process. Unlike manufactured drugs, biologics are natural products and therefore are less predictable.[15] The lack of predictability begins with influenza viruses themselves. One or more of 3 strains of influenza viruses are responsible for seasonal influenza epidemics–2 strains of type A influenza (A/H1N1 and A/H3N2) and influenza type B. These viruses undergo antigenic changes (antigenic drift), resulting in new strains that may not be recognized by the body's immune system.[16] To keep up with these changes and remain effective, the influenza vaccine is reevaluated each year and reformulated when new variants appear to be emerging. Even if there is no reformulation, vaccine must be produced anew each year because it is not until March that the strains to be included in the following season's vaccine are decided upon. Thus, the previous year's vaccine expires and must be discarded before the next influenza vaccination season.

Vaccine production takes about 8 or 9 months, but is actually an ongoing process if one considers the importance of year-round global influenza surveillance.[17] Based on global surveillance data collected by World Health Organization (WHO) Collaborating Centers, including the CDC, the US Food and Drug Administration (FDA) selects 3 influenza strains (type B, A/H1N1, and A/H3N2) thought to be the likely cause of influenza epidemics in the upcoming season. The efficacy of the vaccine depends in part upon a close match between the vaccine strains and circulating strains. However, even when the vaccine is not optimally matched to the predominant viruses, it usually still affords some protection, inasmuch as antibodies made in response to the vaccine can protect against related strains (cross-protection).[18] In January, the CDC provides influenza "reference" viruses to the FDA, which distributes them, in turn, to the manufacturers.[17] It should be noted that at this early point in the production process, well in advance of the upcoming influenza season, manufacturers must consider issues of both supply and demand. For example, they must estimate demand, taking into account "prebookings" from government, large public/private purchasers, and small private purchasers, as well as the previous year's demand.[15,17] They must consider the "yield," or growth potential, of each strain, because this dictates the amount of vaccine that can be produced, while also estimating the number of doses that will be produced by other manufacturers.