IMMUNIZATIONS NEWSLETTER
PROVIDING GSA MEMBERS WITH UPDATES ON ADULT IMMUNIZATIONS
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FEATURES

News

• Among older adults hospitalized for vaccine-type community-acquired pneumonia (CAP), effectiveness of the 13-valent pneumococcal conjugate vaccine (PCV13) exceeded 70%, researchers report in a *Clinical Infectious Diseases* article (2018;67(10):1498–506). The test-negative study was conducted in Louisville, Kentucky, and included 2,034 patients with CAP who were enrolled during April 2015 through April 2016. Comparing 68 cases (those with PCV13 serotypes) with 1,966 control participants, cases were less likely to have received the vaccine (4.4% versus 14.5%) or to be immunocompromised or overweight/obese. The adjusted vaccine efficacy range was 71.1% to 73.3%.

• Adult prevaccination and postvaccination serum samples collected from 6 seasons after 2009 illustrate factors that can influence antibody response to influenza vaccine beyond the frequently discussed mismatch between vaccine and circulating strains. In the *Journal of Infectious Diseases* (2018;218(10):1571–81), Liu et al. show how host (immune priming) and viral (egg adaptation) factors add to the variance in influenza vaccine effectiveness. The year of birth determines the timing of an individual’s first influenza virus infection, and that can produce a robust or weak response to a particular strain of influenza virus. Egg adaptation in vaccine production can diminish antibody responses to the vaccine, thus favoring recombinant or cell-based technologies for vaccine production over egg-based vaccines.

• An *Innovation in Aging* article considers the potential cost effectiveness of a universal influenza vaccine in older adults (2018;2(3):igy035). Based on a 5-year horizon in U.S. older adults, a hypothetical universal vaccine—which would be effective against many strains and over several seasons—could be cost effective or cost saving when pricing, vaccine effectiveness, and vaccine uptake are within plausible ranges.

Resources

• A new health care provider resource, *Strategies for Effectively Integrating Immunizations Into Routine Obstetric-Gynecologic Care*, offers suggestions for ob-gyns, other health care providers, and practice staff on ways to optimize immunization programs in ob-gyn practices and integrate immunizations into routine patient care. The strategies outlined in this provider resource were shown to increase patient immunization rates among ob-gyns in an American College of Obstetricians and Gynecologists adult immunization project funded by the Centers for Disease Control and Prevention (CDC). Further details about the adult immunization project and the strategies presented in the tip sheet can be found in the final report on the project’s demonstration phase.
It’s not too early to begin planning promotional activities for the 2019–20 influenza season, because they require coordination with product orders that must be placed soon. In making these plans, vaccination promotion design and messaging need to be developed with cultural factors in mind, and with consideration for patient and provider perceptions, according to a recently published study of older adults in Hong Kong.

Qualitative semistructured interviews of 40 adults provided input for the study by Siu, which was published in GSA’s The Gerontologist (10.1093/geront/gny139). Campaigns should address people’s misperceptions of vaccines as harmful and risk of getting a disease as low, counter negative rumors, demonstrate that vaccinating locations are safe, and recognize cultural differences such as a preference for traditional Chinese medicines.

As described in the January issue of this newsletter, the research needed to create a vaccine against viral and other infectious diseases is complicated. Yet, the effort has just begun when it comes to providing that vaccine to billions of people in a cost-feasible manner. Better understanding of the development pipeline and manufacturing process may help those with concerns about conspiracies and other myths.

The vaccine industry is a small one, with just four players in the United States holding 87% of the market and 60 or so smaller companies splitting the rest (Figure 1). How these companies are able to take investigational vaccines through the clinical research and governmental approval processes and bring a product to market is a complex story, one with two tracks—demonstrating efficacy and safety of the vaccine while building manufacturing capacity and processes in an economical way. To minimize the time to market and maximize income and profits, these tracks are traversed simultaneously, with completion of manufacturing facilities coinciding with advances on the clinical research path.

**FIGURE 1.** U.S. Vaccine Market Share by Company, 2014

Numbers indicate the percentage of market share. GlaxoSmithKline purchased the vaccine unit of Novartis in 2014; their market shares have been combined in this figure.

On the clinical track that follows testing in animals, vaccine candidates go through the usual phases of testing (phases 1, 2, and 3, which include increasingly large numbers of participants). The risk of failure is high; fewer than 1 in 15 vaccine candidates successfully advances from phase 1 to phase 2 testing. Products generally fail because researchers have not fully elucidated the biology of protection, animal models do not always accurately predict vaccine behavior in people, the human immune system is unpredictable in how it will react to antigens, and what will happen when multiple vaccine components are combined is not known.

An important strategic document guides the clinical development of vaccine candidates. The target product profile, or TPP, provides the company, research, and interested stakeholders with guidance on the key characteristics and features of the product, attributes of the product that will result in a competitive advantage in the marketplace, and a roadmap of preclinical and clinical studies needed to evaluate the product in the target population.

The time required for clinical development totals 10 to 15 years. Assays are developed, preclinical toxicology tests conducted, dose-ranging and pivotal clinical trials completed, and a Biologics License Application filed with the U.S. Food and Drug Administration (FDA).

While clinical trials help determine safety and efficacy of the vaccine, manufacturing capacity to supply vaccine for the trials is simultaneously developed. The company needs to pass an FDA inspection of the manufacturing plant before vaccine can be released. Overall, $50 million to $300 million is needed to design and construct the manufacturing facility as clinical development proceeds—that is, without any assurance that the product will ever reach the market. Cleaning of equipment and validation of the manufacturing process add another 20% to this capital cost.

Less visible than clinical development, process development steps are equally important and often just as expensive. Bulk operations must be developed so that cell-culture and/or fermentation-based manufacturing can provide sufficient product for phase 2 and 3 trials and later be scalable based on anticipated market demand. Finishing operations include product formulation with the antigen, adjuvants, and stabilizers; vial or syringe filling (or lyophilization for live vaccines); and later labeling, packaging, and controlled storage.

This investment is seen by manufacturers as reasonable, since vaccines generally fare better in later clinical trials than do small-molecule drugs. Attrition is great during phase 1 testing, but vaccine candidates generally get licensed at the completion of phase 2 and 3 trials.
Given these high costs and complexities of vaccine development, the size of the vaccine market is not sufficient to ensure an adequate supply of new and innovative products that can address the many bacterial and viral challenges people can encounter. Shen and Cooke recently described the array of innovative partnerships among public, private, and governmental stakeholders that has coalesced to fund vaccine development and implementation.

The vaccine-intensive manufacturers provide the bulk of funds for vaccine development, but new knowledge also emanates from basic and/or targeted research funded through federal grants from the National Institutes of Health and its vaccine trials network or through the Biomedical Advanced Research and Development Authority. Policy and funding decisions have a large impact on this process, ultimately improving the chances of success and reducing the cost of vaccines when they are marketed.

The U.S. Department of Defense has funded or stimulated research into vaccines needed for supporting military operations. When vaccines are needed for children younger than 5 years of age in developing countries, the U.S. Agency for International Development is often involved. The CDC both conducts postlicensure studies and develops recommendations for vaccine use through the Advisory Committee on Immunization Practices (ACIP). Government programs such as Vaccines for Children and Medicare Parts B and D are major payers for vaccines once they reach the market.

Nongovernmental organizations are also involved in paving the way for vaccine development. The Bill and Melinda Gates Foundation has funded much research into vaccines against human immunodeficiency virus, malaria, and tuberculosis. The Program for Appropriate Technology in Health, known as PATH, partners with vaccine manufacturers to develop technologies needed in the developing world.

Older adults in the United States are currently wondering why the new shingles vaccine is in such short supply. Some have posited that the manufacturer must be holding back on the supply to justify an increase in vaccine prices. On the contrary, a shortfall in supply can easily develop when demand is strong, as it has been for this highly effective product. Years before the clinical trials even began, the company had to estimate demand as part of the plant-planning process. No one knew then how effective the vaccine would be or how surprisingly strong and immediate acceptance would be of the product. The impact of the ACIP decision to make a preferential recommendation was surprising to many; the recommendation increased demand for the product and contributed to the insufficient manufacturing capacity.

As vaccine advocates, we should have a sound understanding of the vaccine development process so that our patients, family members, and friends can be educated when myths and misinformation begin spreading. All the partners in the immunization neighborhood can “inoculate” the public by spreading accurate and relevant information, describe the delicate structure among the partners in this process, and advocate for vaccine funding by public and private sources. It’s an important part to play in the effort to get all older adults fully vaccinated against the serious and debilitating diseases that people face.