IMMUNIZATIONS NEWSLETTER

PROVIDING GSA MEMBERS WITH UPDATES ON ADULT IMMUNIZATIONS

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FEATURES

News

• Better strategies are needed for enhancing the immunogenicity of seasonal influenza vaccines and their efficacy when administered annually, authors concluded in a May 15 article in the Journal of Infectious Diseases (2019;219:1586–95). B-cell and antibody responses were assessed in healthy volunteers from 2010 or 2011 to 2014 for seasonal trivalent vaccines. After the second annual vaccination, B-cell responses were diminished despite changes from year to year in the vaccine formulations.

• Affinity Living Group is mandating influenza vaccinations for its 4,000 employees during the 2019–2020 season, McKnight’s Senior Living reports. The North Carolina–based long-term care provider has been involved in the GSA National Adult Vaccination Program and drew from ideas presented at the May 2018 stakeholder meeting sponsored by GSA; ideas on increasing employee vaccinations are available in the meeting summary. Additional tools are compiled in the website of the National Adult and Influenza Immunization Summit.

• On May 6, Oregon became the first state to authorize dentists to prescribe and administer vaccines. Gov. Kate Brown signed House Bill 2220, which was passed with bipartisan support in the Legislature in response to the current measles outbreaks and with recognition of the need to improve rates of human papillomavirus vaccination. The latter vaccine is recommended for administration to pediatric patients as early as age 9 years, but many older children and adolescents do not see their pediatricians or other primary care providers regularly.

Resources

• Looking for answers to questions about measles? Check out the Measles, Mumps, and Rubella article in the Immunization Action Coalition’s Ask the Experts section of its website. There you’ll discover the number of deaths from measles during the last outbreak (>100 among 55,000 cases in 1989–1991), what to do if you think a patient has measles (isolate, report, and test for the virus), and whether to vaccinate women who are trying to become pregnant (no).
While communication with patients about the benefits of enhanced vaccines is necessary, so too is communication with those selecting which vaccines to purchase for a practice or health system. Consider seeking out decision makers involved in vaccine purchasing and request that enhanced vaccine products be available for older patients, citing data on the benefits of these products and the possibility for prevention of thromboembolic events.

A great example of such data comes from a recent systematic review and meta-analysis that show why these products should be used in this population whenever feasible. In the May 15 issue of the *Journal of Infectious Diseases* (2019;219:1525–35), Ng et al. found postvaccination titers that were 82% higher for influenza A(H3N2) with high-dose vaccines used in participants who were aged 60 years or older; this was significantly higher than the 52% greater response with MF59-adjuvanted products and a 32% increased response with intradermal vaccines.

These findings reinforce the need to strongly advocate use of enhanced vaccines in older adults, even though the practice is not preferentially recommended by the Advisory Committee on Immunization Practices.

**VACCINES: PROGRESS ON MANY FRONTS**

One of the 10 top public health accomplishments of the 20th century, vaccines are on track to make even greater strides in coming decades. As reported at the May National Adult and Influenza Immunization Summit in Atlanta and in other recent presentations, research and development into new modes of vaccine production, and relevant insights regarding the importance of social and economic factors in clinical trials are ascendant as the 2020s approach.
When someone mentions making vaccines in plants, the mind goes to monolithic — and expensive — industrial facilities with lots of sterile areas and people gowned in white. It’s thus quite a surprise when you realize that an important area of current research has to do with making vaccines in green plants, specifically tobacco plants.

Large-scale production of vaccines that use plants to make virus-like particles (VLPs) could soon take its place among the primary modes of manufacture for commercially available vaccines. The method promises several advantages over existing methods, including rapid time to market, quick scalability, less chance of viral mutations resulting in loss of efficacy, and increased cell-mediated responses.

Medicago is cultivating this VLP innovation through its U.S.-based research and production facilities in Research Triangle Park, North Carolina — an appropriate location for growing tobacco plants. In a pandemic or other time-sensitive situation, this method can produce research-grade VLPs in 19 days and clinical-grade material in 5 to 6 weeks after identification of a pathogenic strain. Construction of expensive fermenting facilities is not needed; “greenhouse” facilities with the right conditions can support growth of a few plants or thousands of plants at a comparatively low cost. In addition to making vaccines, the facilities can be used in production of other proteins or subunits, providing the basis for manufacture of antibodies.

A quadrivalent seasonal influenza vaccine made using the VLP approach is now in a pivotal phase 3 trial of 10,000 healthy adults in 7 countries, according to Medicago. The company is ready for a 2020 launch of the product if results confirm the promising data from preclinical and early clinical trials. In those trials, VLP influenza vaccines induced broader immune responses than licensed vaccines and cross-protection through VLP’s similarity to wild-type virus and use of highly efficient ways of presenting antigens to the immune system. Adults of all ages responded to the new product, including those of advanced age.

Respiratory syncytial virus (RSV) is another prime vaccine research target. Novavax has been leading these investigations, but its vaccine candidate has faltered twice — most recently in protecting newborns through passive immunity transferred in utero following immunization of mothers during late pregnancy.

For the statistical stickler, both trials produced only one result that matters: The RSV F vaccine (ResVax) produced no statistical differences in the primary endpoints. However, anomalies and interesting secondary or exploratory findings create doubt that “no difference” is the final verdict for this product.

In the Resolve trial of older adults, the vaccine was tested during a season that turned out to have a very low RSV attack rate. As in studies with low sample sizes, this made achieving a statistical difference more difficult — a large difference in the intervention and control groups was needed for statistical significance.

At the time those results were announced in fall 2016, the phase 3 PREPARE trial was in the works. Healthy women (n = 4,636) with low-risk, singleton pregnancies received a single dose of RSV F vaccine at 28 to 36 weeks’ estimated gestation. Primary endpoints relied on site-only data regarding the frequency for medically significant RSV lower
respiratory tract infections (LRTIs); secondary endpoints added cases requiring LRTI-related hospitalization or severe hypoxemia. A third area of analysis used site and hospitalization data to reassess efficacy endpoints.

While the study failed to meet its primary endpoint, differences were established in vaccine prevention of hospitalization (25% reduction) and severe hypoxemia (40% reduction) and in subgroup analyses comparing high-income and other countries. Novavax emphasized these points in a May 2019 presentation of the phase 3 results:

- The vaccine was safe in mothers and infants.
- Significance was reached in protection against the most serious outcomes of an RSV infection in young infants, suggesting that “vaccine effects were more profound than could be detected by surveillance.”
- The effects of the RSV F vaccine were durable for all-cause effects, with significant advantages at 90 and 180 days on LRTIs with severe hypoxemia and related hospitalizations.
- The vaccine-preventable disease incidence is similar to that of highly effective pediatric vaccines that are already licensed.
- The company plans discussions with the U.S. Food and Drug Administration (FDA) and other regulatory authorities about a pathway to licensure.

Financial media reported in June 2019 that FDA was recommending an additional clinical trial for RSV F vaccine to confirm the impact of the product on medically significant LRTIs caused by the virus. European authorities have not yet responded, nor is it clear how the Bill and Melinda Gates Foundation, which funded much of the costs of clinical research to date, would respond if further clinical trials are needed.

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Another interesting finding from the PREPARE trial was that the RSV F vaccine had greater effectiveness in low- and middle-income countries (LMIC) than in high-income countries (HIC). Consistent with greater impact on more serious outcomes, the differences in vaccine effectiveness were particularly large for LRTIs with hospitalization:

- **Medically significant RSV LTRI:** All sites, 39.4%; HIC, 37.7%; LMIC, 40.2%.
- **RSV LTRI with severe hypoxemia:** All sites, 48.3%; HIC, 46.6%; LMIC, 49.3%.
- **RSV LTRI with hospitalization:** All sites, 44.4%; HIC, 7.8%; LMIC, 54.2%.

Should vaccine and other clinical trials consider the sociodemographics of participants in analyzing results? The findings shed new light on the importance of disparities as social determinants of health, or in this case, vaccine responses and effectiveness.
Especially as related to adult vaccines, clinicians have had cost-related concerns about immunizations — a concern that is borne out in a June 2019 *Medical Care* article. But despite the challenges for some providers, the study shows that vaccines are revenue positive in most situations.

At a variety of adult and pediatric practice types in North Carolina, the mean cost per vaccine administration was $14 but with substantial variation: pediatrics, $10; community health clinics, $15; family medicine, $17; obstetrics-gynecology, $23; and internal medicine, $23. Most practices generated small net incomes from vaccine-related services, but a few experienced negative income, primarily tied to Medicaid payments or the unique challenges in obstetrics-gynecology practices. This “underscores the need for providers and policymakers to design interventions and system improvements to make vaccination services financially sustainable for all provider types,” the authors conclude.