IMMUNIZATIONS NEWSLETTER
PROVIDING GSA MEMBERS WITH UPDATES ON ADULT IMMUNIZATIONS
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Developed by The Gerontological Society of America

FEATURES

News

- **Influenza activity** continued declining but remained elevated in April, the Centers for Disease Control and Prevention (CDC) said last month. The proportion of activity due to influenza A(H3N2) viruses was higher than earlier in the season, when influenza A(H1N1) viruses predominated. Late-season activity also included low levels of influenza B viruses. The agency advised clinicians to consider influenza as a possible diagnosis for patients with respiratory illness while local influenza activity remains elevated. Because influenza A(H3N2) viruses may be associated with severe disease in older adults, CDC reminded clinicians that early empiric treatment with antiviral medications is recommended for hospitalized and high-risk patients, especially those 65 years or older. Antiviral treatment should be started as soon as possible after illness onset and should not wait for laboratory confirmation. Since this season began in October of last year, 34.9–40.1 million Americans have had influenza illnesses, 482,000–585,000 people have been hospitalized for influenza, and 32,900–54,800 patients have died from the illness, CDC estimated in early April 2019.

Resources

- “**Leveraging Improved Vaccine Technology and the Health Care Team to Protect Older Adults**” is a webinar on GSA’s YouTube channel that continues the conversation from the Momentum Discussion at the GSA 2018 Annual Scientific Meeting. This webinar explores the exciting developments in vaccine technology, reviews the underappreciated benefits of vaccination, and shares evidence-based strategies that health care teams can use to help raise immunization rates, thereby preventing disease and its complications in older adults.

- Coming up on May 22 is a webinar on “**Hidden Consequences: The Opioid Epidemic and Rising Hepatitis B Rates**.” The 2 pm EDT presentation is part of a three-part series from the National Association of County and City Health Officials and Hep B United on the current state of hepatitis B virus (HBV) in the United States and local health department efforts and model programs to increase HBV testing, vaccination, and linkage to care. To coincide with Hepatitis Awareness Month (May), this webinar will describe populations at risk for hepatitis B infection and discuss rising rates of hepatitis B within the context of the ongoing opioid crisis. Online registration is available.
One component of the GSA webinar on leveraging vaccine technology (see Resources) includes data on the connection between influenza disease and serious complications such as heart attack and stroke. These data have been some of the most compelling in making the case for immunization when speaking with older adults.

The risk of heart attack or stroke seems more immediate than the risk of influenza to many people, and the long-term consequences are often more top of mind for older adults. This connection offers the opportunity to individualize the conversation by mentioning other risk factors or an enjoyable activity that a heart attack could keep an older adult from doing. Such statistics have also been used to convince long-term care facilities of the need to vaccinate both residents and staff.

View the GSA webinar for more information and other ideas on how to convince people of the importance of immunizations!

When deciding which vaccine products to use for the various patient populations in a practice, clinicians must balance available evidence, cost and third-party coverage, and the preferences of professionals in the practice, patients, and caregivers. This process begins by considering the available data, including the efficacy trials used in product approval by the U.S. Food and Drug Administration and effectiveness studies completed in the “real world” following marketing.

Those two descriptors—efficacy and effectiveness—have specific meanings, but they are also thrown around in conversations, marketing materials, and even scholarly journals in ways that lead to confusion in practice. Reaching the final decision about which products to use can be difficult given this uncertainty and the many other ways in which evidence can be rated, categorized, and assessed. Let’s take a look at some of these terms and the tools that are useful in making informed decisions about vaccines in adults.
Clinical study of a vaccine product invariably begins with explanatory trials, generally based on a randomized controlled design and conducted under ideal conditions. When trials reach the phase 2 and 3 stages of development, they produce efficacy data—an indication that a biologic effect can be observed under careful study conditions. Like much research conducted in the basic sciences, efficacy trials need randomization to avoid bias in the way participants are assigned to groups and blinding to avoid the ways in which results are evaluated. If they were making treatment assignments, clinicians might put some patients in the intervention group based on favored status or an unconscious fear of exposing some people to an unproven therapy.

Recruitment of patients into blinded, randomized clinical trials can be challenging. Some people harbor misconceptions about trials, they may not like the blinded and uncertain nature of the intervention, and others do not like giving up control to the random nature of assignment. Not all adult patients agree to participate in clinical trials.

Because of these factors, the results of clinical trials must be interpreted carefully for patients in groups other than the one studied. Extrapolating efficacy findings to other groups, genders, ethnicities or races, and age groups requires care and attention.

The uncertainty about efficacy data has led clinicians and payers to ask for data obtained under real-world conditions to supplement the efficacy trials. The term effectiveness refers to the effects of interventions when administered to patients in practice situations as measured in pragmatic trials. For immunizations, the term vaccine effectiveness is a particularly important metric of how well products are protecting people from target infections or conditions in routine clinical practice.

To help investigators appropriately design pragmatic trials, an international working group developed and later updated the PRECIS (PRagmatic Explanatory Continuum Indicator Summary) tool. The current PRECIS-2 tool includes these 9 domains:

- Eligibility: Who is selected to participate in the trial?
- Recruitment: How are participants recruited into the trial?
- Setting: Where is the trial being done?
- Organization: What expertise and resources are needed to deliver the intervention?
- Flexibility/delivery: How should the intervention be delivered?
- Flexibility/adherence: What measures are in place to make sure participants adhere to the intervention?
- Follow-up: How closely are participants followed-up?
- Primary outcome: How relevant is it to participants?
- Primary analysis: To what extent are all data included?

FIGURE 1. Format of a PRECIS-2 umbrella for displaying the strengths and weaknesses of a pragmatic trial.
Source: PRECIS-2 website.
Results are presented as 1–5 scores and graphically displayed on a “wheel” or “umbrella” similar to the one in Figure 1. Trialists can use the scoring system and visual image as the trial is designed to realize where weaknesses in their design will limit interpretation of the results and attain the highest possible ratings for each parameter based on the aims, goals, and realities of the trial.

In vaccine effectiveness research, pragmatic trials are needed to assess how products are performing in broad populations such as states and countries. These are frequently case–control studies, a type of observational trial in which people are categorized by clinical symptoms, presence of disease, and vaccination status. Those with symptoms or disease are cases, and controls must be either recruited or identified in a valid manner. The difference in vaccination status between cases and controls provides a measure of vaccine effectiveness.

Figuring out the best way of conducting vaccine effectiveness studies is truly a study of human behavior, as bias is increased or minimized depending on how patients are recruited into the study, how they are assigned to case versus control groups, and how results are determined. People who are not vaccinated are also less likely to present for medical care when they are ill—creating selection bias right off the bat. If comparisons are made with patients who have other conditions requiring routine medical care, they cannot be assumed to be “similar” to those with influenza. Those presenting with influenza-like illness (ILI) who have pathogens other than the influenza virus often recover on their own and can be lost to follow-up—increasing the bias in results.

The test-negative case–control study was adopted for vaccine effectiveness research in recent years to overcome many of these concerns. As depicted in Figure 2, eligibility for study inclusion is simply presentation with ILI. This assures similarity among those participating in the study. All patients are tested for influenza. Those testing positive become the “cases,” while those with negative test results become the “controls.” Through patient interviews, review of medical records, or searching in immunization information systems, trialists determine who received the seasonal influenza vaccine for that year, when those patients were vaccinated, and which vaccine they received. No one is lost to follow-up since all data are collected at the incident visit. Percentages are calculated to determine vaccine effectiveness and statistical tests used to assess significance and determine confidence intervals.

Vaccine effectiveness figures are very important when cost-effectiveness studies are conducted for influenza and other types of vaccines. These studies seek to assign a value to vaccines, usually on the basis of money, although some types of analyses use measures of value (e.g., time tradeoffs, years of life gained or lost, years of healthy life gained or lost). The time horizon is very important; influenza vaccine can be looked at within a single influenza season of a few months, while a shingles vaccine usually requires a lifetime assessment. The perspective is likewise critical; costs to the patient, the health system, the payer, and society give very different results.
When all these aspects are combined—study design, strengths, and weaknesses; vaccine effectiveness; and incorporation of a product’s value to those with very different perspectives—numbers can morph into “lies, damned lies, and statistics.” Add in today’s sophisticated marketing strategies, and weak or misleading data can confuse clinicians, patients, and those practicing in health systems and under managed care programs.

In the pharmaceutical industry, “real-world” pragmatic data often come through trials funded by marketing dollars. That’s where the story can take an unexpected and sometimes sinister turn. Some studies are funded by marketing as nothing more than that—a kind of “sampling” so that physicians who are opinion leaders in the real world use a new drug product and learn of its benefits. Further, these studies have all kinds of biases and weaknesses. The physicians conducting the “study” are not blinded to which patients are getting the drug, and the physicians’ investment of time and effort into the study can produce unintentional bias in their favorable assignment of patients, overestimating drug benefits, or discounting of adverse effects.

Other real-world studies are designed to provide pragmatic data to formulary committees at health systems and managed care organizations. Since the company conducting the study has a vested interest in positive results, investigators can be pressured to release more positive results and suppress negative analyses. If a study is deemed too negative, the marketing staff with ultimate control over the data may refuse to release the data at all, and investigators can be limited in what they can say about the data based on confidentiality clauses in contracts.

Finally, in the hands of advertising and social media staff members, pragmatic results are crunched to the taglines people get stuck in their heads: “This is the only vaccine with real-world data” or “the only significant differences from randomized controlled trials.” Depending on the details, both of these can be true—and completely irrelevant to the patient who needs a vaccine.

Health professionals, patients, caregivers, and vaccine advocates can take a number of actions to stay current on vaccinology while sorting through the cacophony of confusing claims:

- Focus on studies published in the most respected journals such as The New England Journal of Medicine and other major medical weeklies, The Journal of Infectious Diseases, Clinical Infectious Diseases, Pediatrics, Vaccine, the GSA journals, and the Journal of the American Geriatrics Society.
- Look at the authors and what affiliations and conflicts of interest they have.
- Check for sponsorship of trials and consider the methodology in light of potential bias or influence.
- Go through the PRECIS-2 domains. Watch for conditions or types of patients excluded from care, and think about whether all the patients are accounted for in the results.
- Most of all, look at the study methodology. Use the evidence-based medicine acronym PICO to check what population or problem was studied and who was excluded (do those patients look like yours?), types of interventions (randomized, blinded?), comparators (placebo or active controls, how comparator groups were identified in observational studies), and what outcomes were measured (short or long term, what perspective and horizon in cost-effectiveness studies).

Numbers, numbers everywhere—but their meaning is clear only when you think. It’s not an easy process, but it’s necessary to be an informed advocate or consumer of vaccines.
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