Recent Updates to the Advisory Committee On Immunization Practices Recommendations for Pneumococcal and Herpes Zoster Vaccination

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ABSTRACT

Pneumococcal and herpes zoster – shingles – vaccination prevent a great deal of morbidity, particularly in elderly and immunocompromised hosts. Vaccination of children with conjugate pneumococcal vaccine in recent years has greatly reduced illness in older individuals as well. This article will review the historical and current recommendations for pneumococcal and herpes zoster vaccination and the rationale for changes at the level of the CDC's Advisory Committee on Immunization Practices.

KEYWORDS: vaccination, immunization, conjugate pneumococcal vaccine, herpes zoster, shingles

PNEUMOCOCCAL VACCINATION

Background

S. pneumoniae is the most commonly identified pathogen in community-acquired pneumonia (CAP) worldwide and can cause serious illness, particularly among young children, the elderly, or those with immunocompromising conditions. Severe infection may lead to invasive pneumococcal disease (IPD), including pneumococcal bacteremia or meningitis, which can result in significant neurological sequelae and death. The financial burden of IPD to the US healthcare system is substantial and is estimated to increase by $2.5 billion annually in the coming decades with an aging population.[1]

Historical ACIP Recommendations for Pneumococcal Vaccination

There are currently two licensed vaccines approved for the prevention of pneumococcal disease in the US: the 23-valent pneumococcal polysaccharide vaccine (PPSV23, [Pneumovax 23, Merck and Co., Inc]), containing antigens from 23 common serotypes, and the 13-valent pneumococcal conjugate vaccine (PCV13 [Prevnar 13, Pfizer, Inc.]), containing antigens from 13 common serotypes. There is considerable overlap among the antigens contained within each vaccine; 12 of the 13 antigens in PCV13 are common to PPSV23 apart from serotype 6A.

Recommendations for pneumococcal vaccination have evolved over time based on shifts in the epidemiology of IPD and as new products have been introduced into market. PPSV23 was first licensed in 1983 and was subsequently introduced into the routine schedule for all adults ≥65 years and for those ≥2 years with certain underlying medical conditions.[2] In 2000, the 7-valent pneumococcal conjugate vaccine (PCV7) was introduced into the routine pediatric schedule for all children <5 years, and in 2010, the approval of PCV13 led to replacement of PCV7 with PCV13 in the pediatric schedule.[3] In 2012, indications for PCV13 were broadened to all individuals ≥19 years with immunocompromising conditions, administered in series with PPSV23 eight weeks later.[4] In 2014, results from the randomized placebo-controlled Community-Acquired Pneumonia Immunization Trial in Adults (CAPiTA) demonstrated that 20–25% of IPD and 10% of CAP cases in adults ≥65 years were caused by PCV13 serotypes and were potentially preventable.[5] This prompted the 2014 ACIP recommendation for vaccination with both PCV13 followed by PPSV23 ≥ one year later in all immunocompetent adults at age 65.[6,7]

Updated ACIP Recommendations for Pneumococcal Vaccination

Historical vaccination efforts in the pediatric patient population have been essential to decreasing overall pneumococcal disease burden, morbidity, and mortality both directly and indirectly through reduction in carriage and transmission to adults.[8] In 2019, ACIP reviewed the evidence over the preceding three years to determine if there was a continued need for PCV13 vaccination in elderly immunocompetent adults in series with PPSV23 versus PPSV23 alone. A systematic review was conducted including twenty studies published from 2014–2018 to evaluate data on the safety, efficacy, and cost-effectiveness of pneumococcal vaccination in this patient population. Results demonstrated that from 2000-2014, widespread uptake of pediatric pneumococcal vaccination in the US led to a ninefold decrease in the incidence of PCV13-type IPD in adults ≥65 through reduced carriage and transmission. A similar effect was seen for those at increased risk due to age or chronic medical conditions. From 2014–2018, the incidence of PCV13-type IPD in adults ≥65 has remained stable (5 cases per 100,000), with 47% estimated vaccination coverage in immunocompetent adults ≥65 years. Based on these results, it was estimated that 26,000 adults would need to be vaccinated with PCV13

to prevent one case of IPD per year. Additionally, there were minimal indirect benefits to other patient populations, including those aged 19–64 years. Cost-effectiveness models estimated a very high cost ($200,000–500,000) per quality adjusted life years with continuation of the current recommendation versus a recommendation to administer PPSV23 alone. Limitations to the presented evidence included the limited follow-up time (only three years of data were analyzed) and low PCV13 vaccination uptake in immunocompetent adults. Furthermore, the analysis did not take into consideration vaccination hesitation, commonly known as the "anti-vax movement," a growing movement which may impact pneumococcal pediatric vaccination rates and pneumococcal burden in the coming years.

Updated pneumococcal vaccination recommendations are summarized in **Table 1**. Based on these findings, ACIP voted to remove PCV13 from the routine immunocompetent adult immunization schedule in November 2019. As some adults may still benefit, the decision to administer PCV13 vaccination should be based on shared clinical decision-making between patient and provider depending on the individual's risk for exposure and invasive disease. PCV13 is still routinely recommended as a one-time vaccination for adults ≥19 years with an immunocompromising condition, cerebrospinal fluid leak, or cochlear implant.[8] Additionally, a single dose of PPSV23 is still routinely recommended for all adults at age 65.

Shared Decision-Making: Who Should Still Receive PCV13 At Age 65?

Some adults may be at higher risk for exposure to PCV13 serotypes or at higher risk for complications based on certain factors, such as local pediatric vaccination rates or underlying medical conditions. The CDC provides guidance for shared clinical decision-making based on an individual's risk.

The CDC recommends considering regularly offering PCV13 to the following individuals:

- Those residing in a nursing home or other long-term care facilities
- Those residing in settings with low pediatric PCV13 uptake
- Those traveling to settings with no pediatric PCV13 program
- Those with chronic heart, lung, or liver disease; diabetes; or more than one chronic medical condition
- Those with alcoholism or those who smoke cigarettes

Table 1. Updated ACIP Recommendations for Pneumococcal Vaccination in Individuals ≥19 years

Patient Population	Age Group		Total Number of doses of PCV13 or PPSV23
	19–64 years	≥65 years	
Immunocompetent individuals	PCV13: none	PCV13 based on shared clinical decision-making; if administered give PCV13 first and PPSV23 ≥1 year after PCV13	PCV13: 0 or 1 dose
	PPSV23: none	PPSV23 x 1 dose	PPSV23: 1
Immunocompetent individuals with alcoholism; chronic liver, heart, or lung disease; diabetes mellitus; or smoking cigarettes	PCV13: none	PCV13 based on shared clinical decision-making; if administered give PCV13 first and PPSV23 ≥1 year after PCV13	PCV13: 0 or 1 dose
	PPSV23 x 1 dose	PPSV23 x 1 dose, give ≥5 years after any previous PPSV23 prior to age 65	PPSV23: 2 doses
Immunocompetent individuals with cochlear implant(s) or cerebrospinal fluid leaks	PCV13 x 1 dose	PCV13 x 1 dose if no previous PCV13 vaccination	PCV13: 1 dose
	PPSV23 x 1 dose, give ≥8 weeks after PCV13	PPSV23 x 1 dose, give ≥8 weeks after PCV13 and ≥5 years after any previous PPSV23 prior to age 65	PPSV23: 2 doses
Immunocompromised individuals*	PCV13 x 1 dose	PCV13 x 1 dose if no previous PCV13 vaccination	PCV13: 1 dose
	PPSV23 x 2 doses, give first dose ≥8 weeks after PCV13, give second dose ≥5 years after initial PPSV23	PPSV23 x 1 dose, give ≥5 years after any previous PPSV23 prior to age 65	PPSV23: 3 doses

*Includes those with anatomic or functional asplenia, sickle cell disease/hemoglobinopathies, chronic renal failure or nephrotic syndrome, congenital or acquired immunodeficiencies, iatrogenic immunosuppression, generalized malignancy, Hodgkin disease, leukemia, lymphoma, multiple myeloma, HIV infection or solid organ transplant

HERPES ZOSTER VACCINATION

Background

Herpes Zoster (HZ) is another infection that affects elderly and immunocompromised patients due to decreased immune control of the virus. It is caused by reactivation of primary Varicella Zoster Virus (VZV) infection in the neuronal ganglia leading to a painful vesicular rash along one or more dermatomes. According to the CDC, there are approximately 1 million cases of HZ per year in the United States.[9] Many studies have shown that the incidence of HZ has increased over time.[10,11] Harpaz and colleagues found that incidence has continued to rise from the 1990s to the most recent decade. The incidence per 1,000 persons has increased from 2.5 in 1993 to 6.1 in 2006 to 7.2 in 2016.[10] HZ is a vaccine preventable illness that carries significant morbidity and cost implications for the healthcare system. The most well-known complication, post-herpetic neuralgia (PHN), can persist for years after initial infection and is often refractory to traditional analgesics. Furthermore, treatments such as tricyclic antidepressants and gabapentin carry significant risks of toxicity in the elderly patient population that is most susceptible to this condition. Other potential complications include bacterial superinfection of the skin, HZ opthalmicus, acute retinal necrosis, HZ oticus, and meningitis/encephalitis. It is estimated that the total cost of HZ is 5 billion dollars annually in the United States.[12]

Historical ACIP Recommendations for Herpes Zoster Vaccination

Zoster Vaccine Live (ZVL, [Zostavax, Merck and Co., Inc]) was licensed in 2006 as a single subcutaneous dose and was recommended by the ACIP for use in immunocompetent adults aged ≥60 years. FDA approval was based on the Shingles Prevention Study, which was a double-blinded, multi-centered, randomized controlled trial. The study followed subjects for three years and compared incidence of HZ infection and PHN in patients receiving ZVL or placebo. For patients between 60-69 years of age, there were statistically significant decreases in both conditions in those who received ZVL compared to placebo: 66% decrease in HZ and 66% decrease in PHN.[13] However, post-marketing studies have shown marked decreases in effectiveness against HZ over time, especially in older subjects (age > 60 years old).[13] The incidence of injection site reactions such as erythema and pain was 35.8% and 34.5%, respectively. Systemic adverse events were similar in the vaccine group compared to placebo (24.7% vs 23.7%).[13] Furthermore ZVL is a live vaccine and therefore contraindicated in many immunosuppressed populations, which are one of the highest risk groups for developing HZ.

Updated ACIP Recommendations for Herpes Zoster Vaccination

Recombinant Zoster Vaccine (RZV, [Shingrix, GlaxoSmith-Kline]) was approved in October of 2017 as a two-dose intramuscular injection administered at 0 and 2–6 months. This inactivated vaccine contains a new VZV glycoprotein E antigen combined with adjuvant $AS01_B$ to promote humoral immune response and has the potential to be used in immunocompromised populations. RZV quickly became the preferred HZ vaccine in the adult immunization schedule in January of 2018.[15] This change was driven primarily by the increased effectiveness in primary prevention of HZ as well as superior sustained protection post-vaccination. Two multi-national, randomized, placebo-controlled clinical trials led to approval of RZV. The ZOE-50 study showed overall efficacy rates of 97.2%.[16] Furthermore, in older subjects aged 60–69 years old, it maintained efficacy at 97.4%. No significant differences were seen in regards to age. ZOE-70 enrolled patients over the age of 70 and showed an 89.8% decrease in incidence of HZ.[17] Pooled data from these studies showed an overall 91.2% decrease in PHN in those in the active treatment arm. Data from these studies demonstrate that RZV vastly outperforms ZVL across all age groups. Long-term efficacy has yet to be established, as the published data only includes 36 months of follow-up. The ZOE-50 study plans to complete a total follow-up of 60 months, but this data has not been published at the time this article was written.

Although RZV has shown superior efficacy, there is a higher incidence of adverse drug reactions likely related to the increased immunogenicity of the adjuvant. For example, in ZOE-50, a total of 81.5% of participants in the RZV arm reported injection site reactions.[16] While most of these reports were mild to moderate in nature, 9.5% had grade 3 reactions. In terms of systemic reactions, incidence was 66.1% with myalgia (46.3%) and fatigue (45.9%) as the most common in RZV-vaccinated subjects. However, median duration of reactions was less than 4 days. Despite the higher incidence of adverse reactions when compared to ZVL, the remarkable efficacy of RZV in preventing HZ and PHN warrants its place as the preferred HZ vaccine.

In addition to increased rate of side effects, availability of the vaccine has been a barrier to vaccination. The supply of the vaccine has been sporadic, and it is frequently under allocation limits. This presents a challenge for patients who have received one dose but have not received the second dose in the series. If more than 6 months have elapsed after the initial dose, there is no need to restart the series. RZV is recommended for patients previously vaccinated with ZVL and can be given simultaneously at different anatomic sites with other vaccines.[15]

Of note, ACIP currently provides no recommendation on the use of RZV in patients with high levels of immunosuppression, including those on chronic steroids (≥20 mg of prednisone equivalent per day), those who have received a transplant, or persons living with HIV due to insufficient data in these populations.[15] A recent phase 3 clinical trial in patients with renal transplant has shown sufficient rates of immunogenicity and a similar adverse event profile.[18] As new data becomes available for immunocompromised patients, these recommendations may change.

CONCLUSION

ACIP's recommendations for pneumococcal and herpes zoster vaccination have recently been updated. For pneumococcal vaccination, ACIP now recommends shared clinical decision-making rather than routine administration of PCV13 in immunocompetent individuals ≥65 years. A single dose of PPSV23 is still routinely recommended for all adults at age 65, and a one-time dose of PCV13 should still be administered for adults ≥19 years with an immunocompromising condition, CSF leak, or cochlear implant.

For herpes zoster vaccination, the ACIP now recognizes RZV as the preferred zoster vaccine for all eligible patient populations. RZV is preferred over ZVL due to higher efficacy and sustained protection over time and can be administered to patients who have previously received ZVL.

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