Two pneumococcal vaccines are currently licensed for use in the United States: the 13-valent pneumococcal conjugate vaccine (PCV13 [Prevnar 13, Wyeth Pharmaceuticals, Inc., a subsidiary of Pfizer Inc.]) and the 23-valent pneumococcal polysaccharide vaccine (PPSV23 [Pneumovax 23, Merck and Co., Inc.]). The Advisory Committee on Immunization Practices (ACIP) currently recommends that a dose of PCV13 be followed by a dose of PPSV23 in all adults aged ≥65 years who have not previously received pneumococcal vaccine and in persons aged ≥2 years who are at high risk for pneumococcal disease because of underlying medical conditions (Table) (1–4). The recommended intervals between PCV13 and PPSV23 given in series differ by age and risk group and the order in which the two vaccines are given (1–4).

On June 25, 2015, ACIP changed the recommended interval between PCV13 followed by PPSV23 (PCV13–PPSV23 sequence) from 6–12 months to ≥1 year for immunocompetent adults aged ≥65 years. Recommended intervals for all other age and risk groups remain unchanged. This report outlines the rationale for this change and summarizes the evidence considered by ACIP to make this recommendation.

In August 2014, ACIP recommended routine use of a dose of PCV13 followed by a dose of PPSV23 6–12 months later among immunocompetent adults aged ≥65 years (1). Adults aged ≥65 years with immunocompromising conditions, functional or anatomic asplenia, cerebrospinal fluid (CSF) leaks, or cochlear implants are recommended to receive PCV13 first, followed by PPSV23 ≥8 weeks later (2). ACIP also recommended that all adults aged ≥65 years who already received PPSV23 should receive a dose of PCV13 ≥1 year after receipt of PPSV23 (PPSV23–PCV13 sequence). The difference in the recommended interval depending on the order in which the two vaccines were given added significant complexity to the recommendation and created implementation challenges for this age group. To simplify the recommendations, ACIP reviewed existing data to evaluate potential areas for harmonization of recommended dosing intervals. Specifically, ACIP assessed whether available evidence would support changing the recommended interval for the PCV13–PPSV23 sequence for immunocompetent adults aged ≥65 years from 6–12 months to ≥1 year and thus be harmonized with the recommended interval for the PPSV23–PCV13 sequence in the same age group.

No clinical studies evaluating efficacy of the two vaccines given in series are available. Therefore, current recommendations are based on best available evidence from immunogenicity studies. The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework was used by ACIP to formulate the existing recommendations for immunocompromised children (http://www.cdc.gov/vaccines/acip/recs/grade/pneumo-immuno-child.html), immunocompromised adults (http://www.cdc.gov/vaccines/acip/recs/grade/pneumo-immuno-adults.html), and adults ≥65 years (http://www.cdc.gov/vaccines/acip/recs/grade/pneumo-immuno-adult.html) (1–3). No new evidence was available to inform harmonization of intervals; therefore, the GRADE process was not repeated. In addition, the immunogenicity studies were not designed to evaluate the optimal interval between the two vaccines. When both PCV13 and PPSV23 are to be administered, PCV13 is recommended before PPSV23, based on studies demonstrating a better response to serotypes common to both vaccines when PCV was given first (5–7).

Studies evaluating the immune response to a conjugate vaccine (PCV7 or PCV13) followed by the polysaccharide vaccine (PCV–PPSV23 sequence) at intervals of 2, 6, or 12 months or 3–4 years demonstrated that following the PPSV23 dose,
antibody levels against serotypes common to both vaccines were higher than the pre-PCV baseline (5,6,8–13). Eight studies compared immune responses among immunocompetent adults aged ≥50 years after a PCV–PPSV23 sequence with responses following PCV or PPSV23 administered alone (5,6,8–13). Four studies showed that antibody responses (measured by opsonophagocytic activity [OPA] or immunoglobulin G [IgG] levels or both) following PCV7–PPSV23 doses given 6 months apart were better than or equivalent to responses following PCV7 or PPSV23 alone for most pneumococcal serotypes measured (6,8,11,12). Another study showed that a 1-year interval between receipt of conjugate vaccine and polysaccharide vaccine (PCV7–PPSV23 sequence) also led to improved immune responses compared with those following a single PPSV23 dose (13). Comparison of antibody responses after a PCV13–PPSV23 sequence to responses following PCV13 or PPSV23 alone, across two studies with intervals of 1 year and 3–4 years between the two vaccines, indicated that the responses to a larger number of serotypes are improved with a 3–4 year interval compared with a 1-year interval (5,9).

One study among pneumococcal vaccine–naïve Alaska Native adults aged 55–70 years included direct comparison between intervals of 2 months and 6 months between receipt of PCV7 and PPSV23. No differences in the immune responses were observed; however, the group with a 2-month interval between doses reported more injection site swelling than the group with a 6-month interval (10).

In summary, these studies of PCV–PPSV23 sequence among immunocompetent adults suggest that 1) shorter intervals (e.g., 8 weeks), may be associated with increased local reactogenicity when compared with longer intervals, and 2) longer intervals (e.g., ≥1 year) may lead to an improved immune response against serotypes in both vaccines compared with a single dose of PCV13 or PPSV23. Additionally, changing the recommended interval for the PCV13–PPSV23 sequence to ≥1 year would allow the recommended interval for immunocompetent adults aged ≥65 years to be the same, regardless of the order in which the two vaccines are given (Box).

ACIP considered additional factors when determining whether a change to the intervals is warranted. These factors include the risk window for protection against disease caused by serotypes unique to PPSV23, the timing for the next visit to the vaccination provider, as well as revised Centers for Medicare and Medicaid Services (CMS) regulations allowing for coverage of the two pneumococcal vaccines when given in series and administered 1 year apart. Approximately 40% of
invasive pneumococcal disease among adults aged ≥65 years is caused by serotypes unique to PPSV23. The potential change in the interval for the PCV13–PPSV23 sequence is most likely to affect the youngest adults in this age group who are more likely to be pneumococcal vaccine naïve. The incidence of disease caused by serotypes unique to PPSV23 is lowest among these adults (14).

The 2012 National Health Interview Survey results suggest that >85% of adults in the United States aged ≥65 years had at least one encounter with a health professional within the preceding 6 months, and >93% within the preceding year (15). Therefore, the 1-year interval would offer the best opportunity for the majority of eligible adults aged ≥65 years to receive the recommended pneumococcal vaccine series during their existing healthcare encounters and not require an extra visit.

The recently revised CMS regulations for pneumococcal vaccines allow for Medicare coverage of a different, second pneumococcal vaccine 1 year after the first vaccine is given (16). The change in the ACIP recommended interval for the PCV13–PPSV23 sequence would make ACIP recommendations consistent with the current Medicare policy.

Recommended intervals between PCV13 and PPSV23 for persons aged ≥2 years with medical indications to receive both vaccines remain unchanged (Table). PPSV23 is recommended to be given ≥8 weeks after PCV13 for children and adults aged ≥19 years with certain underlying medical conditions (including adults aged ≥65 years with immunocompromising conditions, functional or anatomic asplenia, CSF leaks, or cochlear implants). Studies among HIV-positive adults evaluating the immune response to PPSV23 administered 4 or 8 weeks after PCV7 showed statistically significant increases in antibody levels compared with response to PPSV23 alone (17,18). The currently recommended 8-week interval minimizes the risk window for invasive pneumococcal disease caused by serotypes unique to PPSV23 in these highly vulnerable groups.

**ACIP Recommendations for Intervals Between PCV13 Followed by PPSV23 for Immunocompetent Adults Aged ≥65 Years**

For immunocompetent adults aged ≥65 years who have not previously received pneumococcal vaccine, ACIP makes the following recommendation for intervals between PCV13 followed by PPSV23: A dose of PPSV23 should be given ≥1 year following a dose of PCV13. The two vaccines should not be co-administered. If a dose of PPSV23 is inadvertently given earlier than the recommended interval, the dose need not be repeated.

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**Acknowledgments**

Summary

What is currently recommended?
The Advisory Committee on Immunization Practices (ACIP) currently recommends that both 13-valent pneumococcal conjugate vaccine (PCV13) and 23-valent pneumococcal polysaccharide vaccine (PPSV23) be given to all immunocompetent adults aged ≥65 years. ACIP recommends that PCV13 be given first followed by PPSV23 6–12 months later. ACIP also recommends that adults aged ≥65 years who already received a dose of PPSV23 should also receive a dose of PCV13 ≥1 year after the dose of PPSV23. Among persons aged ≥2 years with medical indications to receive both PCV13 and PPSV23 in a series, including adults aged ≥65 years with immunocompromising conditions, functional or anatomic asplenia, cochlear implants, or cerebrospinal fluid leaks, a dose of PPSV23 should be given ≥8 weeks after a dose of PCV13.

Why are the recommendations being modified now?
To simplify the recommendations for PCV13 and PPSV23 use among immunocompetent adults aged ≥65 years, ACIP recommended harmonization of recommended intervals between PCV13 and PPSV23 regardless of the order in which the two vaccines are given.

What are the new recommendations?
ACIP recommends that both PCV13 and PPSV23 be given in series to adults aged ≥65 years. A dose of PCV13 should be given first followed by a dose of PPSV23 at least 1 year later to immunocompetent adults aged ≥65 years. The two vaccines should not be co-administered. If a dose of PPSV23 is inadvertently given earlier than the recommended interval, the dose need not be repeated.

References