New Safety Information for an Old Vaccine

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(See the article by Walker et al. on pages 1730–5)

The pneumococcus continues to be a major killer despite advances in medical treatment. The pneumococcus' polysaccharide capsule is its main weapon. The pneumococcus has 90 distinct versions (i.e., serotypes) of polysaccharide capsule that help the organism to avoid capture by the immune system. For approximately a century, researchers have been developing pneumococcal vaccines that are based on the polysaccharide capsule. A version targeting 6 capsular serotypes (the 6-valent vaccine) was used briefly during World War II. A 14-valent version was licensed in 1977 and was followed by a 23-valent formulation in 1983. The 23-valent version is currently in use, although, since 2003, only a single manufacturer has produced the vaccine (Pneumovax 23; Merck). The 23-valent vaccine is used in many countries for older adults and for persons aged ≥2 years with chronic illnesses that put them at a higher risk for pneumococcal disease, compared with healthy persons. Studies suggest that the 23-valent vaccine is effective against invasive pneumococcal disease (including bacteremia, pneumonia with bacteremia, and meningitis) but may not be effective against pneumonia without bacteremia [1].

Adults become increasingly at risk for invasive pneumococcal disease as they age, so, ideally, a pneumococcal vaccine should be used in a way that will provide protection over decades. Current US recommendations for pneumococcal polysaccharide vaccine use in the general population suggest that the vaccine should be given to all adults starting at age 65 [2]. Revaccination is not routinely recommended; immunocompromised persons or older persons vaccinated before age 65 should receive a second dose if at least 5 years have passed since receipt of the first dose. The recommendations of the Advisory Committee on Immunization Practices were last published in 1997, and the committee is now considering revisions. Some opinion leaders have advocated that the vaccine be given to all adults starting at age 50, when many people start to develop medical conditions that place them at a higher risk for pneumococcal disease and when patients start to receive other preventive health measures [3].

Although we have decades of experience with the pneumococcal polysaccharide vaccine, a few questions remain about its safety and performance, and these gaps in knowledge become evident when thinking about vaccinating all adults at a younger age than is currently recommended. One problem with starting vaccination for all adults at age 50 is deciding when and how often to revaccinate to provide protection as people age and as the risk of disease increases. First, it is unclear exactly how long the protective effects of the vaccine last. We know that antibody levels wane during a period of a few years and that the vaccine was not protective in adults ≥75 years of age ≥5 years after administration, according to one large case-control study [4]. Second, the effectiveness of the polysaccharide vaccine when given a second time is unknown, although immunogenicity studies suggest that the antibody response may be somewhat stronger after the first dose than after the second [5]. Nothing is known about immune response after a third dose. Finally, is it safe to give the polysaccharide vaccine repeatedly? A large study and several smaller studies suggest that giving a second dose of vaccine is safe, although self-limited local reactions are more common among those receiving a second dose of vaccine than among those receiving a first dose [6].

The article by Walker et al. [7] provides, for the first time, a look at the safety of a third dose of the polysaccharide vaccine. The study took place among Alaska Natives. Alaska Natives have rates of invasive pneumococcal disease that are much higher than those in the general US population. Because of the high risk, the Alaska Department of Health recommends that health care providers offer pneumococcal polysaccharide vaccine to
all Alaska residents starting at age 55, with revaccination every 6 years. Using an administrative database and a medical record review, the authors retrospectively evaluated medical visits for Alaska Natives after receipt of pneumococcal vaccine, comparing all identified persons who had received ≥3 doses of vaccine to a selected control group that had received either 1 or 2 doses. The authors identified few medically attended adverse events in either group and found no significant difference between the 2 groups with respect to the number of medical visits for vaccine-related adverse events during the 7 days after vaccination.

The study has some important limitations. First, vaccine histories could not be confirmed for many of the subjects, especially for doses that had been received several years earlier. This could have resulted in some misclassification of subjects in the 2 groups. Next, the study was relatively small, with only about 181 persons who received 1 or 2 doses and 179 persons who had received ≥3 doses. Therefore, the study might have missed uncommon adverse events. Alaska Natives are known to differ from other populations not only in their risk for disease due to encapsulated bacteria, but also in their response to some vaccines—for example, a particular *Haemophilus influenzae* type b vaccine [8]. Therefore, it may be possible that vaccine-related reactions occur at different rates in Alaska Natives and in the general population of adults in the United States. Finally, most of the subjects had at least 1, if not multiple, chronic illnesses, and many were elderly. Given that severity of adverse reactions has been shown to be more common among those with higher preexisting antibody levels [6], could it be that this population had a low level of preexisting antibody because of their age and comorbidities? With these caveats, the study provides some evidence that a third dose of pneumococcal polysaccharide vaccine may be as safe as a first or second dose.

Recommendations for vaccines and other medical interventions are often, of necessity, made with some amount of “expert opinion,” because results from clinical trials or good observational studies are not available to answer every question. Policy makers must weigh the benefits of using an intervention that is based on the currently available mix of study results and expert opinion versus waiting for more studies to be completed. Safety is one of the questions that has to be answered before a vaccine is licensed, and safety is routinely monitored long after a vaccine is licensed and in use. Similarly, information about the safety of repeated doses is critical for developing a policy for routine revaccination with pneumococcal polysaccharide vaccine, even though the vaccine has been licensed for decades. More evidence on the safety of repeated revaccination, perhaps in other populations, would be helpful.

New pneumococcal vaccines for adults are in development. The 7-valent pneumococcal conjugate vaccine (Prevnar; Wyeth Lederle Vaccines) has been very successful in the prevention of pneumococcal disease in young children and has reduced the burden of disease in adults through decreased transmission [9]. The conjugate vaccine consists of a mutant diphtheria toxin (CRM197) carrier protein attached individually to 7 polysaccharides or oligosaccharides from the 7 serotypes that cause most cases of invasive pneumococcal disease in children. Studies are now ongoing to determine whether the conjugate vaccine would be useful for adults. Vaccines derived from proteins common to all pneumococci are also now undergoing evaluation. Both of these potential vaccine types might be used in combination with pneumococcal polysaccharide vaccine. Because a new pneumococcal vaccine for adults may not be available for several years, new information, such as that provided by Walker et al. [7], that helps to determine how best to use the old vaccine is still very much welcome.

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**References**