Duration of Protection and Revaccination

Duration of Protection

Pneumococcal polysaccharide vaccine induces an initial rise in ELISA antibody levels, which then decline over time and in older adults antibody levels measured 4 to 7 years post-vaccination tend to approximate pre-vaccination baseline levels (1-5). The clinical significance of this decline is not well defined, as immune correlates of protection for pneumococcal vaccine in adults have not been established and there are relatively limited clinical data regarding the duration of protection against invasive infection induced by pneumococcal polysaccharide vaccination.

Two observational studies of pneumococcal vaccine effectiveness have evaluated the duration of protection. In the first, a large case-control study of pneumococcal vaccine effectiveness in older adults, vaccine effectiveness against invasive pneumococcal disease was documented in the study population overall, but in stratified analyses appeared to decline both with age and, among those 65 years of age and older, with duration since vaccination (Table) (6). In contrast, a large indirect cohort study reported by Butler et al of persons five years of age and older, in which the majority of subjects were over 50 years of age, vaccine effectiveness was stable over time (7). In that study, vaccine effectiveness five through eight years after vaccination was estimated to be 71% (95% CI, 24% to 89%) and nine or more years after vaccination was 80% (95% CI, 16% to 95%). Although the results of these two studies are not consistent, given the declines in antibody level over time documented by immunologic assessments, and the results of clinical assessments of other plain polysaccharide vaccines, indicating declines in efficacy over time, it is generally assumed that pneumococcal vaccine effectiveness in older adults diminishes in the years following vaccination and is likely absent after some interval, which may be on the order of 5 or more years.

Revaccination

Since plain polysaccharide vaccines are not generally believed to confer long-lasting protection, and since the incidence of pneumococcal infection in adults increases dramatically with age, revaccination may provide a benefit in reducing the risk of invasive pneumococcal infection in older adults. Considerations of possible revaccination strategies requires an evaluation of the evidence related to the safety of revaccination, the immunologic response to a second dose of pneumococcal polysaccharide vaccine, and the potential clinical benefits of revaccination.

Safety of revaccination. Although reports from the 1970s and 1980s suggested that revaccination of healthy children and adults within a few years of a first vaccination may be associated with a higher than expected frequency and severity of local injection site reactions (8-12), several more recent studies of older adults indicate that a second vaccination given five or more years after a first vaccination is well tolerated (1, 3, 13-17). The largest assessment of the safety of a pneumococcal polysaccharide

revaccination was a prospective study of 1414 adults 50 to 74 years of age (15). In that study, pneumococcal polysaccharide vaccine was given to 901 adults who were pneumococcal vaccine naïve and to 513 adults with a history of one prior pneumococcal vaccination five or more years before study enrollment. Local reactions were more frequent in the group given a second vaccination, but the reactions were not severe and were self-limited. The available data from two published retrospective studies also indicate that a third pneumococcal polysaccharide vaccination is not associated with an increased risk of medically attended adverse events in adults (18, 19).

Immunologic response to a second dose of pneumococcal polysaccharide vaccine. Several studies have documented that seniors given a second pneumococcal polysaccharide vaccine four or more years after an initial vaccination demonstrate a significant increase in anticapsular antibody levels from pre- to post- vaccination (1, 3, 13, 14). There is, however, concern that administration of a first dose of plain polysaccharide vaccine may blunt the immune response to subsequent doses, such that the antibody levels following a second vaccination, and possibly the magnitude of clinical protection, may be lower than following a first vaccination. Blunting of the immunologic response to a second vaccination is well documented in studies of meningococcal serogroup C plain polysaccharide vaccine (20-22).

The relative magnitude of the immune response to a second compared with a first pneumococcal polysaccharide vaccination has been evaluated in two ways. Two studies have compared the post-vaccination antibody response in persons being revaccinated with a concurrent group of persons being vaccinated for the first time. The first such study, of Alaska Natives with chronic illness, compared 26 adults who were revaccinated five to nine years after first vaccination with 26 adults receiving a first vaccination (3). In that study, antibody levels measured by RIA to 12 serotypes at one month post-vaccination were comparable in the two study groups. In another study of persons 50 years and older that compared 64 persons being revaccinated with 54 persons receiving a first vaccination, post-vaccination ELISA antibody levels to the three serotypes evaluated were lower in the revaccinated group, but this difference was statistically significant for only one of the three serotypes (15).

The immune response to revaccination has also been evaluated in longitudinal studies following the same individuals through their first and second vaccinations. One assessment of eight healthy older adults who received a first pneumococcal polysaccharide vaccination at a mean age of 65 years and a second vaccination six years later found that the post-revaccination ELISA levels were comparable to the levels observed following the first vaccination for six of the eight serotypes evaluated, and were substantially lower following revaccination than following first vaccination for the other two serotypes (5). A larger study evaluated 61 seniors who were first vaccinated after a hospitalization for pneumonia in conjunction with a clinical trial (23), and who then received a second pneumococcal polysaccharide vaccination an average of five years later (1). For all six serotypes evaluated, the serotype-specific geometric mean antibody concentration was lower after revaccination than after first vaccination (Figure). In both of these longitudinal studies, patients were of course older at the time of

revaccination than at first vaccination, and so the possibility that at least some of the differences in the immune response to revaccination were due to an age-effect cannot be excluded.

Effectiveness of revaccination. Two studies have evaluated the effectiveness of revaccination against invasive pneumococcal disease. In an indirect cohort study of Alaska Native adults (mean age 45 years), the point estimates of vaccine effectiveness were similar for a first vaccination (VE, 75%; 95% CI, 19% to 92%) and for revaccination (VE, 74%; 95% CI, <0 to 94%), although the estimates for revaccination were not statistically significant (24). In a case control study of risk of invasive pneumococcal disease in Navajo adults, revaccination was not associated with a reduction in risk of invasive pneumococcal disease (VE, 40%; 95% CI, -27% to 72%). However, that study also did not document an overall effectiveness of pneumococcal polysaccharide vaccination, and the estimate of effectiveness following revaccination was not significantly different from that following any vaccination (25). Thus, there is limited evidence on the clinical effectiveness of revaccination, particularly in the general population of older adults.

In summary, revaccination with pneumococcal polysaccharide vaccine is associated with an antibody response but the magnitude of that response may be lower than with a first vaccination. The clinical significance of the lower antibody response is not known, but concern regarding possible immune tolerance has been one factor that has limited recommendations for revaccination in some countries. This is an important issue, because a strategy of, for example, a single routine vaccination at age 65 likely leaves seniors vulnerable to infection in their late 70s and 80s, when disease risk is the highest. The significance of this effect is illustrated by the results of a modeling study conducted by investigators at the CDC, in which they assumed that one-time vaccination of immunocompetent 65 years olds is associated with a vaccine efficacy against invasive pneumococcal disease of 75% in the five years following vaccination, 37% in the next five years, 18% in the five years after that, and then zero (26). In that model, an ongoing strategy that achieved vaccination of nearly all (90%) of 65 year olds in the United States would prevent only 21% of cases of invasive pneumococcal disease in persons 65 years of age and older. Thus, achievement of sustained protection is an important goal for a pneumococcal vaccination program.

References

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Table. Pneumococcal polysaccharide vaccine effectiveness against invasive pneumococcal disease in adults, by age and time since vaccination. (Adapted from Shapiro et al. [6]).

	Time since vaccination		
Age (years)	< 3 years	3-5 years	>5 years
	Vaccine effectiveness, % (95% CI)		
<55	93 (82 to 97)	89 (74 to 96)	85 (62 to 94)
55-64	88 (70 to 95)	82 (57 to 93)	75 (38 to 90)
65-74	80 (51 to 92)	71 (30 to 88)	58 (-2 to 83)
75-84	67 (20 to 87)	53 (-15 to 81)	32 (-67 to 72)
≥85	46 (-31 to 78)	22 (-90 to 68)	-13 (-174 to 54)

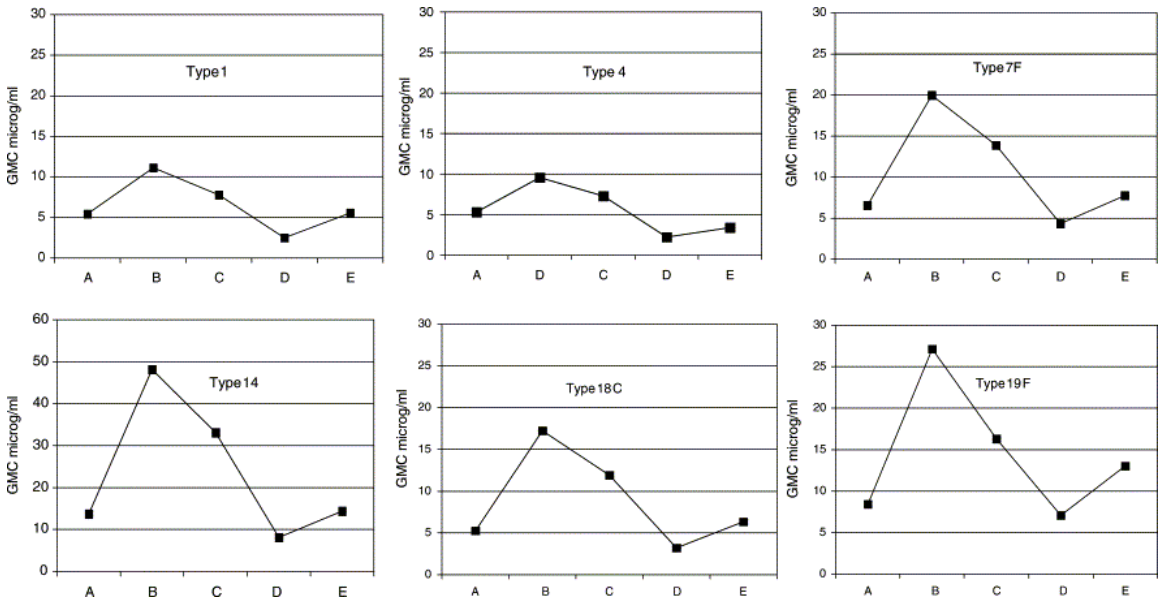

Figure. Geometric mean concentrations of serotype-specific antibody measured by ELISA in adults 50 years of age and older followed through their first and second pneumococcal polysaccharide vaccinations. Note that the Y scale for serotype 14 differs from the other serotypes. A, before first vaccination; B, 4 weeks after first vaccination; C, one year after first vaccination; D, immediately prior to revaccination 4-7 years after first vaccination; E, 4 weeks after revaccination. From Torling et al 2003 (1).