MAJOR ARTICLE

# Safety and Antibody Response, Including Antibody Persistence for 5 Years, after Primary Vaccination or Revaccination with Pneumococcal Polysaccharide Vaccine in Middle-Aged and Older Adults

**Daniel M. Musher,[1,2] Susan B. Manoff,[3] Charlie Liss,[3] Richard D. McFetridge,[3] Rocio D. Marchese,[3] Bonnie Bushnell,[3] Frances Alvarez,[3] Carla Painter,[3] Michael D. Blum,[3,a] and Jeffrey L. Silber[3]**

[1]Michael E. DeBakey VA Medical Center and [2]Baylor College of Medicine, Houston, Texas; [3]Merck Research Laboratories, North Wales, Pennsylvania

***Background.*** This study assessed antibody levels for 5 years after primary vaccination or revaccination with 23-valent pneumococcal polysaccharide vaccine (PN23).

***Methods.*** Subjects were enrolled into 4 study groups by age (50–64 or ⩾65 years) and prior vaccination status (no prior vaccination or 1 vaccination 3–5 years previously). Blood was obtained on day 0 (before primary vaccination or revaccination), day 30, day 60, and annually during years 2–5. Levels of immunoglobulin G (IgG) to 8 vaccine serotypes were measured by enzyme-linked immunosorbent assay.

***Results.*** Of 1008 enrolled subjects, 551 completed year 5. For each serotype and age group, baseline geometric mean concentrations (GMCs) of IgG were higher in revaccination than primary vaccination subjects. Primary vaccination or revaccination with PN23 induced significant increases in levels of antibody to all serotypes tested. Although day 30 and 60 antibody levels tended to be modestly lower after revaccination, study groups had similar GMCs at later time points. For serotypes 4, 6B, 8, 9V, 12F, 14, and 23F, GMCs during years 2–5 after primary vaccination or revaccination remained higher than in vaccine-naive persons. Levels of antibody to serotype 3 returned to baseline by year 2.

***Conclusions.*** Both primary vaccination and revaccination with PN23 induce antibody responses that persist during 5 years of observation.

Several lines of evidence suggest that 23-valent pneumococcal polysaccharide vaccine (PN23), consisting of capsular polysaccharides from 23 *Streptococcus pneumoniae* serotypes, is protective [1–5] and may reduce the incidence of invasive pneumococcal disease by 50%–80% in vaccine recipients [6, 7]. Two recent studies have shown that the vaccine significantly reduced mortality, length of stay, and intensive care admissions among adults hospitalized with community-acquired pneumonia [8, 9]. Another study of elderly persons with lung disease demonstrated that vaccination with PN23 was associated with fewer hospitalizations and fewer deaths [10]. Other reports, however, have suggested that older adults and those adults whose health is compromised by underlying comorbid conditions are less likely to benefit from PN23 [2, 11–14]. Explanations include reduced antibody production, reduced antibody activity, and absence of responses in some older subjects. Patients with the greatest need of protection against pneumococcal infection (such as those with chronic lymphocytic leukemia) exhibit almost no antibody response to vaccination [15]. Although most authorities agree that PN23 is protective [5–7, 16], the issue remains controversial [17, 18].

Received 18 May 2009; accepted 25 August 2009; electronically published 21 January 2010.

Potential conflicts of interest: Authors affiliated with Merck & Co may potentially own stock and/or hold stock options in the company. The laboratory of D.M.M. received research support from Merck & Co for participation in this study.

Presented in part: 40th Interscience Conference on Antimicrobial Agents and Chemotherapy, Toronto, Canada, 17–20 September 2000; 6th International Symposium on Pneumococci and Pneumococcal Diseases, Reykjavik, Iceland, 8–12 June 2008.

Financial support: Merck & Co.

[a] Present affiliation: Wyeth Research, Collegeville, Pennsylvania.

Reprints or correspondence: Dr Daniel Musher, Veterans Affairs Medical Center, 2002 Holcombe, Room 4B370, Houston, TX 77030 (Daniel.Musher@va.gov).

**The Journal of Infectious Diseases 2010; 201:516–24**
© 2010 by the Infectious Diseases Society of America. All rights reserved.
0022-1899/2010/20104-0008$15.00
DOI: 10.1086/649839

Downloaded from https://academic.oup.com/jid/article/201/4/516/861677 by guest on 20 August 2022

The Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention [6] recommends that all persons ⩾65 years old receive PN23 and that a single revaccination be administered if ⩾5 years have elapsed since the initial dose and if they were <65 years old at the time of primary vaccination [6]. This recommendation is made despite there being limited available data on antibody persistence after vaccination [12, 19, 20] and on antibody responses to revaccination [20] in older adults. Repeated vaccination has been shown to be relatively free of adverse events [21]. Since Heidelberger et al [22] demonstrated lower antibody responses to a second immunization with capsular polysaccharides, however, there has been concern that sensitization may induce immune tolerance [23].

The present study evaluated (1) levels of immunoglobulin G (IgG) antibody to capsular polysaccharides up to 5 years after primary vaccination or revaccination of adults ⩾50 years old with PN23 and (2) adverse experiences after such vaccination.

## METHODS

***Subjects.*** This study enrolled ambulatory adults ⩾50 years old who were considered to be generally healthy and in whom underlying medical conditions were stable. Exclusion criteria included prior invasive pneumococcal disease, splenectomy, hospitalization within the preceding 3 months for an acute illness, an immunosuppressive condition, current use of immunosuppressive medication, or a previous serious adverse experience after receipt of pneumococcal vaccine. Patients were not vaccinated within 3 days of any febrile illness.

***Study groups.*** Subjects were stratified into 1 of 4 experimental groups based on age (50–64 years and ⩾65 years) and prior history of PN23 vaccination (no prior vaccination or 1 vaccination ⩾3 years before entry). Revaccination subjects who were 50–64 years old must have received their primary vaccination ⩾3 years previously, whereas revaccination subjects who were ⩾65 years old needed to have received their primary vaccination between 3 and 5 years previously. This short interval between primary vaccination and revaccination was chosen to provide a conservative assessment of revaccination safety and immunogenicity (short intervals have been associated with more reactogenicity and a lower immune response [5, 21]). Enrollment continued until the targeted number for each group or the targeted enrollment completion date was reached; enrollment goals were met for all groups except the younger revaccination group.

***Study design: randomization and initial phase treatment.*** Subjects in each study group were randomized to receive either PN23 (Pneumovax 23; Merck & Co) or saline placebo containing 0.25% phenol by injection into the deltoid muscle. Thirty days later, they received the alternate material by injection into the opposite arm.

***Immunogenicity assessments.*** Blood was drawn immediately before the first injection, immediately before the second injection, and 4 weeks after the second injection. Thus, subjects who received PN23 followed by placebo had postvaccination immunogenicity assessed at 2 time points (days 30 and 60 after PN23 administration), whereas subjects who received placebo followed by PN23 had postvaccination immunogenicity assessed at 1 time point (day 30 after PN23 administration). Day 0 was defined as the day of PN23 vaccination.

The original protocol called for the annual collection of blood samples from years 1 through 5 after enrollment only from the primary vaccination groups but was later amended such that yearly blood samples were obtained from the revaccination subjects. For these subjects, collection began 2 or 3 years after the study was begun, depending on when the amendment received institutional approval.

***IgG to capsular polysaccharide.*** Serum IgG serotype-specific pneumococcal antibodies to 8 representative capsular polysaccharides contained in PN23 were quantitated by a sandwich-type enzyme-linked immunosorbent assay (ELISA), using adsorption with 10 $\mu$g/mL pneumococcal cell wall polysaccharide (Statens Serum Institut) and 100 $\mu$g/mL nonvaccine heterologous capsular polysaccharides (types 25 and 72) to remove cross-reacting antibody [24, 25]. The 8 serotypes are common causes of disease in adults and represent a range of capsular polysaccharides, including some to which antibody responses are relatively weak and short lived. Each ELISA plate included 3 dilutions of an international anti-pneumococcal reference serum (89SF; Center for Biologics Evaluation and Research, US Food and Drug Administration). The standard used in the assay (a single postimmunization adult serum sample) was calibrated against the international 89SF reference. The IgG concentration for each serum sample was calculated by comparing the optical density to that of the reference standard [24]. The assay has been shown to have moderate agreement with the World Health Organization reference ELISA, which uses Pn22F for preadsorption [25].

***Adverse experience assessment.*** For the first 4 days after each injection, subjects recorded on a vaccination report card injection-site discomfort or pain, redness, and swelling or induration; their highest oral temperature; and systemic adverse experiences of headache, body aches, chills, subjective fever, and tiredness. Subjects were asked to note, for 15 days after each injection, all other adverse experiences. Subjects categorized the severity of adverse experiences in accordance with prespecified criteria. For erythema and swelling or induration, severity was defined on the basis of the maximum diameter of the reaction (mild, <2 inches; moderate, 2 to <4 inches; and severe, ⩾4 inches). Investigators assessed the likelihood that recorded events were related to the vaccination.

***Statistical analysis of immunogenicity data.*** IgG mea-

Downloaded from https://academic.oup.com/jid/article/201/4/516/861677 by guest on 20 August 2022

**Table 1. Demographic Characteristics at Baseline**

| Characteristic | Primary vaccination groups | | Revaccination groups | |
|---|---|---|---|---|
| | 50–64 years old ($n$ = 222) | ⩾65 years old ($n$ = 222) | 50–64 years old ($n$ = 157) | ⩾65 years old ($n$ = 407) |
| Age, mean (range), years | 57 (50–64) | 72 (65–88) | 59 (50–64) | 73 (65–91) |
| Female | 66 | 49 | 48 | 46 |
| White | 91 | 94 | 85 | 92 |
| Ever smoked | 56 | 55 | 68 | 60 |
| Underlying diseases | | | | |
| Chronic cardiovascular disease | 43 | 59 | 59 | 70 |
| Chronic pulmonary disease | 14 | 15 | 36 | 24 |
| Diabetes mellitus | 4 | 8 | 18 | 15 |
| ⩾1 of the above | 50 | 65 | 76 | 79 |

**NOTE.** Data are the percentage of subjects in each group who had the specified characteristic, unless otherwise indicated.

surements were transformed to the natural log scale, and geometric mean concentrations (GMCs) were calculated for each serotype at each time point. The GMCs and the 95% confidence interval for the GMCs were obtained using an analysis of variance model. GMCs at each time postvaccination were compared within each of the 4 study groups to those on day 0 (prevaccination baseline). Models were also fit to explore the effect of prevaccination concentration on response on day 30, using prevaccination titer as a covariate. GMCs at each time point were compared for the primary vaccination and revaccination groups within each age group.

***Statistical analysis of adverse experience data.*** Within each age group, risk differences in the percentages of subjects who reported injection site and systemic adverse experiences were compared for the revaccination versus primary vaccination groups [26]. A logistic regression model explored the relationship between prevaccination concentration and the odds of having a moderate or severe injection site adverse experience. Vaccine-attributable analgesic use was determined by adjusting for the analgesic use of the same subjects receiving a placebo injection and removing analgesic use for unrelated conditions. Safety analyses included all subjects who received at least 1 vaccination and had any safety follow-up.

***Ethical conduct.*** This study was conducted in conformance with applicable national and local requirements for protecting the rights and welfare of human subjects participating in biomedical research. The study protocol was approved by the institutional review board (IRB) at each of the 7 participating centers. Subjects gave informed consent by signing consent forms that had been approved by each responsible IRB.

## RESULTS

***Subjects.*** A total of 1008 subjects were enrolled in this study in 1997–1998 and received a dose of vaccine or placebo. Of these, 964 (96%) completed 2 full months of observation from the first injection through 1 month after the second injection. Of the 44 (4%) who did not complete the initial phase, 2 withdrew because of a vaccine-attributable adverse experience; 42 withdrew or were discontinued from the study for protocol violation, being lost to follow-up, or development of an acute illness judged to be unrelated to the vaccination.

For each revaccination group, the median time since primary vaccination was 3.9 years. Within each age group, revaccination subjects were more likely than primary vaccination subjects to report each of 4 risk factors for pneumococcal disease (ever smoking, chronic cardiovascular disease, chronic pulmonary disease, or diabetes mellitus), presumably reflecting the presence of underlying conditions that led to their initial vaccination (Table 1).

***Prevaccination antibody levels.*** Baseline antibody levels were similar in younger and older adults who had not previously received PN23 ($P > .05$ for all comparisons), as well as in younger and older adults who had been previously vaccinated ($P > .05$ for all comparisons). For each age group, baseline antibody levels were generally 2–3 times higher in those who had previously been vaccinated than in those who had not, and differences were significant ($P < .05$) for all serotypes except type 3 (Table 2).

***Antibody levels 30 days after PN23 administration.*** After primary vaccination or revaccination with PN23, levels of IgG to all 8 serotypes increased significantly from baseline to day 30 in all 4 subject groups (Table 2). Antibody on day 30 was marginally higher for the primary vaccination groups than for the revaccination groups; differences were significant ($P < .05$) for type 8 in the older subjects and for type 14 in subjects of both age groups. Ratios of IgG GMCs on day 30 comparing revaccination to primary vaccination subjects for the 8 serotypes ranged from 0.7 to 1.0, indicating a response ranging



Downloaded from https://academic.oup.com/jid/article/201/4/516/861677 by guest on 20 August 2022

**Table 2. Antibody to Capsular Polysaccharides before and 30 Days, 60 Days, and 5 Years after Vaccination**

| | Primary vaccination groups | | | | Revaccination groups | | | |
|---|---|---|---|---|---|---|---|---|
| | 50–64 years old | | ⩾65 years old | | 50–64 years old | | ⩾65 years old | |
| Type, time point | No. | GMC (95% CI) | No. | GMC (95% CI) | No. | GMC (95% CI) | No. | GMC (95% CI) |
| 3 | | | | | | | | |
| Day 0 | 216 | 1.0 (0.9–1.2) | 221 | 0.9 (0.7–1.1) | 149 | 1.2 (1.1–1.4) | 395 | 1.1 (1.1–1.2) |
| Day 30 | 218 | 1.9 (1.7–2.1) | 215 | 1.6 (1.4–1.9) | 141 | 1.8 (1.6–2.0) | 385 | 1.5 (1.4–1.6) |
| Day 60 | 107 | 1.7 (1.5–2.0) | 103 | 1.6 (1.4–1.9) | 69 | 1.8 (1.6–2.2) | 202 | 1.6 (1.4–1.8) |
| Year 5 | 149 | 0.7 (0.6–0.8) | 159 | 0.5 (0.4–0.5) | 62 | 0.7 (0.6–0.9) | 181 | 0.6 (0.5–0.7) |
| 4 | | | | | | | | |
| Day 0 | 216 | 0.8 (0.7–1.0) | 221 | 0.9 (0.8–1.1) | 149 | 2.3 (1.9–2.8)[a] | 395 | 2.4 (2.2–2.7)[a] |
| Day 30 | 218 | 7.5 (6.4–8.8) | 215 | 6.8 (5.6–8.3) | 141 | 6.7 (5.6–8.1) | 385 | 5.9 (5.2–6.8) |
| Day 60 | 107 | 9.9 (7.3–12.6) | 103 | 8.4 (6.4–11.1) | 69 | 9.8 (7.5–12.9) | 202 | 7.7 (6.3–9.3) |
| Year 5 | 149 | 1.9 (1.6–2.3) | 159 | 1.6 (1.3–2.0) | 62 | 1.7 (1.3–2.3) | 181 | 1.6 (1.4–1.9) |
| 6B | | | | | | | | |
| Day 0 | 216 | 1.6 (1.4–2.0) | 221 | 1.5 (1.3–1.9) | 149 | 3.6 (2.4–4.6)[a] | 395 | 4.3 (3.8–4.9)[a] |
| Day 30 | 218 | 9.6 (7.8–11.8) | 215 | 7.4 (5.9–9.2) | 141 | 7.6 (6.0–9.6) | 385 | 6.8 (5.9–7.9) |
| Day 60 | 107 | 12.4 (9.3–16.7) | 103 | 11.7 (8.7–15.8) | 69 | 10.2 (7.5–13.9) | 202 | 7.2 (5.8–8.9) |
| Year 5 | 149 | 2.9 (2.4–3.6) | 159 | 2.0 (1.6–2.4) | 62 | 2.4 (1.7–3.5) | 181 | 2.7 (2.3–3.2) |
| 8 | | | | | | | | |
| Day 0 | 216 | 2.5 (1.8–3.4) | 221 | 2.2 (1.9–2.5) | 149 | 4.0 (3.5–4.6)[a] | 395 | 4.5 (4.1–5.0)[a] |
| Day 30 | 218 | 11.2 (9.8–12.8) | 215 | 8.5 (7.4–9.8)[b] | 141 | 9.1 (8.0–10.3) | 385 | 6.6 (6.0–7.3) |
| Day 60 | 107 | 9.3 (7.6–11.2) | 103 | 10.3 (8.4–12.7)[b] | 69 | 9.8 (8.2–11.6) | 202 | 7.1 (6.2–8.1) |
| Year 5 | 149 | 3.4 (3.0–4.0) | 159 | 2.9 (2.5–3.5) | 62 | 3.5 (2.8–4.4) | 181 | 3.4 (2.9–4.0) |
| 9V | | | | | | | | |
| Day 0 | 216 | 1.3 (1.1–1.6) | 221 | 1.1 (0.9–1.3) | 149 | 4.2 (3.3–5.4)[a] | 395 | 4.6 (4.0–5.3)[a] |
| Day 30 | 218 | 12.5 (10.4–15.1) | 215 | 9.6 (7.8–11.8) | 141 | 9.0 (7.3–11.2) | 385 | 8.6 (7.5–9.9) |
| Day 60 | 107 | 12.3 (9.4–16.3) | 103 | 13.0 (9.4–17.8) | 69 | 10.7 (7.7–14.9) | 202 | 10.1 (8.2–12.3) |
| Year 5 | 149 | 4.6 (3.8–5.6) | 159 | 2.7 (2.2–3.3) | 62 | 3.9 (3.0–5.2) | 181 | 4.0 (3.3–4.7) |
| 12F | | | | | | | | |
| Day 0 | 216 | 0.3 (0.2–0.4) | 221 | 0.3 (0.3–0.4) | 149 | 1.1 (0.9–1.4)[a] | 395 | 1.1 (1.0–1.3)[a] |
| Day 30 | 218 | 2.8 (2.3–3.3) | 215 | 2.5 (2.0–3.1) | 141 | 2.6 (2.1–3.3) | 385 | 1.9 (1.7–2.2) |
| Day 60 | 107 | 2.4 (1.9–3.1) | 103 | 3.0 (2.2–4.1) | 69 | 2.8 (2.1–3.6) | 202 | 2.0 (1.7–2.4) |
| Year 5 | 149 | 0.6 (0.5–0.8) | 159 | 0.6 (0.5–0.8) | 62 | 0.9 (0.6–1.3) | 181 | 0.8 (0.6–0.9) |
| 14 | | | | | | | | |
| Day 0 | 216 | 8.2 (7.1–9.4) | 221 | 7.4 (6.4–8.6) | 149 | 14.1 (11.7–17.0)[a] | 395 | 15.3 (13.6–17.2)[a] |
| Day 30 | 218 | 36.1 (30.5–42.8)[b] | 215 | 28.7 (24.1–34.1)[b] | 141 | 24.6 (20.3–29.8) | 385 | 20.8 (18.4–23.5) |
| Day 60 | 107 | 36.6 (28.3–47.3) | 103 | 37.3 (28.4–49.0) | 69 | 34.1 (25.8–45.1) | 202 | 28.1 (20.4–28.6) |
| Year 5 | 149 | 13.3 (11.3–15.6) | 159 | 10.0 (8.5–11.9) | 62 | 11.3 (8.7–14.8) | 181 | 10.2 (8.8–11.8) |
| 23F | | | | | | | | |
| Day 0 | 216 | 1.6 (1.4–2.0) | 221 | 1.4 (1.2–1.7) | 149 | 3.6 (2.9–4.5)[a] | 395 | 3.6 (3.2–4.1)[a] |
| Day 30 | 218 | 12.3 (10.3–14.7) | 215 | 8.6 (6.8–10.8) | 141 | 8.5 (6.7–10.7) | 385 | 6.5 (5.6–7.6) |
| Day 60 | 107 | 15.0 (11.6–19.4) | 103 | 11.3 (8.4–15.3) | 69 | 10.2 (7.3–14.4) | 202 | 7.7 (6.3–9.6) |
| Year 5 | 149 | 3.3 (2.8–4.0) | 159 | 2.2 (1.8–2.7) | 62 | 3.0 (2.2–4.2) | 181 | 3.2 (2.7–3.7) |

**NOTE.** Data are the geometric mean concentration (GMC) of immunoglobulin G to each pneumococcal capsular polysaccharide, in micrograms per milliliter. All changes within each group from day 0 to day 30 and to day 60 were statistically significant ($P < .05$). CI, confidence interval.

[a] Statistically significant difference ($P < .05$) between the primary vaccination and revaccination groups at baseline for groups of like age.

[b] Statistically significant difference ($P < .05$) between the primary vaccination and revaccination groups at day 30 or 60 for groups of like age.

from slightly less robust to similar for revaccination subjects. There was a statistically significant reciprocal relationship between prevaccination concentration and postvaccination response for all groups in which higher IgG levels on day 30 correlated with lower prevaccination levels (data not shown).

***Antibody levels 60 days after PN23 administration.*** Among subjects who received PN23 on day 0, IgG GMCs increased from day 30 to day 60 for the older primary vaccination group, the older revaccination group, and the younger revaccination group. In the younger primary vaccination group, day 60 GMCs



Downloaded from https://academic.oup.com/jid/article/201/4/516/861677 by guest on 20 August 2022

were higher than day 30 GMCs for 4 of the 8 serotypes. Within each of the 4 groups, none of the differences between day 30 and day 60 GMCs was statistically significant.

***Persistence of antibody.*** In all, 721 subjects participated in the persistence phase from years 1–5. Participation was higher among the primary vaccination groups (97% of older subjects and 95% of younger subjects) than among the revaccination groups (59% of older subjects and 57% of younger subjects); because of the original study design, revaccination subjects had been discharged from the study after 60 days and had to be recontacted and reenrolled after the protocol amendment was approved ~2 years later. Among those who entered the persistence phase, similar proportions of each of the 4 study groups (range, 73%–79%) had a blood sample obtained at year 5. At year 5, demographic characteristics of subjects who remained were generally representative of those who had originally been randomized (data not shown).

For serotype 3, IgG GMCs returned to baseline by year 1–2 in all 4 study groups (Figure 1). For the other 7 serotypes, antibody GMCs in all 4 study groups declined, generally to ≤50% of their peak, by the first available yearly measurement (year 1 for primary vaccination recipients and year 2 for revaccination recipients). However, GMCs still exceeded baseline levels for previously vaccinated subjects and through year 5 generally remained ≥2-fold greater than those for vaccine-naive subjects. Between 2 and 5 years after vaccination, IgG levels for all 8 serotypes remained stable. Interestingly, IgG levels 5 years after vaccination were similar to baseline IgG levels in the revaccination groups, which for the majority of revaccination subjects were measured 3–5 years after primary vaccination (Table 2).

***Vaccine-related adverse experiences: injection site.*** Subjects in both revaccination groups and in the younger primary vaccination group had similar rates of vaccine-related injection site adverse experiences (~75%). In contrast, the older primary vaccination group had a significantly lower incidence of vaccine-related injection site adverse experiences (53%) ($P < .001$). The most common local adverse experience was pain, reported by 49%–78% of subjects in the 4 study groups. In two-thirds of the subjects reporting pain (range, 57%–80%), the injection site adverse experience was mild, and in most it resolved within 3 days (data not shown). Severe pain was reported by 6% of revaccination subjects versus 2% of primary vaccination subjects ($P < .001$) (Figure 2*A*). After injection with placebo, pain was reported by 10%–14% of subjects in the 4 groups, and only 1 subject (0.1%) reported severe pain (data not shown).

Reports of erythema and induration occurred in 35% and 40%, respectively, of revaccination subjects versus 15% and 20% in primary vaccination subjects ($P < .001$ for both). Severe erythema and induration were also more common among revaccination subjects (between 10% and 12%), compared with primary vaccination subjects (between 1% and 3%) (Figure 2*A*). After placebo injection, <5% of subjects in all groups reported erythema and induration, none severe. A significantly higher percentage of revaccination subjects reported any severe injection site adverse experience (16% and 17% for subjects 50–64 and ≥65 years old, respectively) than primary vaccination subjects (4% and 3% for subjects 50–64 and ≥65 years old, respectively) ($P < .001$) (Figure 2*B*).

In all 4 study groups, the magnitude of the prevaccination antibody level correlated with the likelihood of having a moderate or severe injection site adverse experience. The odds ratios ranged from 1.2 to 2.9; these were significantly >1 for 30 of the 32 serotype/study group pairs (8 serotypes each in 4 study groups; data not shown).

***Systemic adverse experiences.*** The most common vaccine-related systemic adverse experiences were tiredness, muscle aches, and chills. These occurred with similar frequency (~35%) in the 2 revaccination groups and the younger primary vaccination group (Figure 2*C*) but were less frequent in older subjects receiving primary vaccination (22%) ($P < .001$). In all groups, the incidence of severe vaccine-related systemic adverse experiences was <5%, including myalgia (2%), fatigue (1%), and headache (1%). Placebo-associated generalized adverse experiences occurred in 8%–13% of subjects in the 4 groups; <1% of these were severe.

Fever (oral temperature, ≥37.8°C [100°F]) occurred in <3% of subjects in any group. Four percent of subjects in the older revaccination group had increased use of analgesics attributable to vaccination, compared with 13% in the younger revaccination group, 0% in the older primary vaccination group, and 4% in the younger primary vaccination group. In all 4 groups, analgesic use returned to prevaccination levels by day 5.

No deaths or vaccine-related serious adverse experiences occurred during the 14 day follow-up period after each vaccination. Only 2 subjects (both revaccination recipients; 1 in each age group) discontinued participation in the study because of local and systemic adverse experiences.

## DISCUSSION

Our study examined IgG levels for 5 years after primary vaccination or revaccination with PN23 in adults ≥50 years old. In previously unvaccinated adults, baseline levels of IgG to 8 serotypes were generally low, consistent with earlier observations in healthy older adults [27]. Persons who had been vaccinated 3–5 years previously had higher baseline IgG levels than did vaccine-naive participants for 7 of the 8 serotypes tested, consistent with the persistence of anticapsular antibody after PN23 administration.

By 30 days after administration, primary vaccination or revaccination with PN23 resulted in significant increases in IgG to all serotypes tested. Antibody levels appeared to peak at 30–



Downloaded from https://academic.oup.com/jid/article/201/4/516/861677 by guest on 20 August 2022

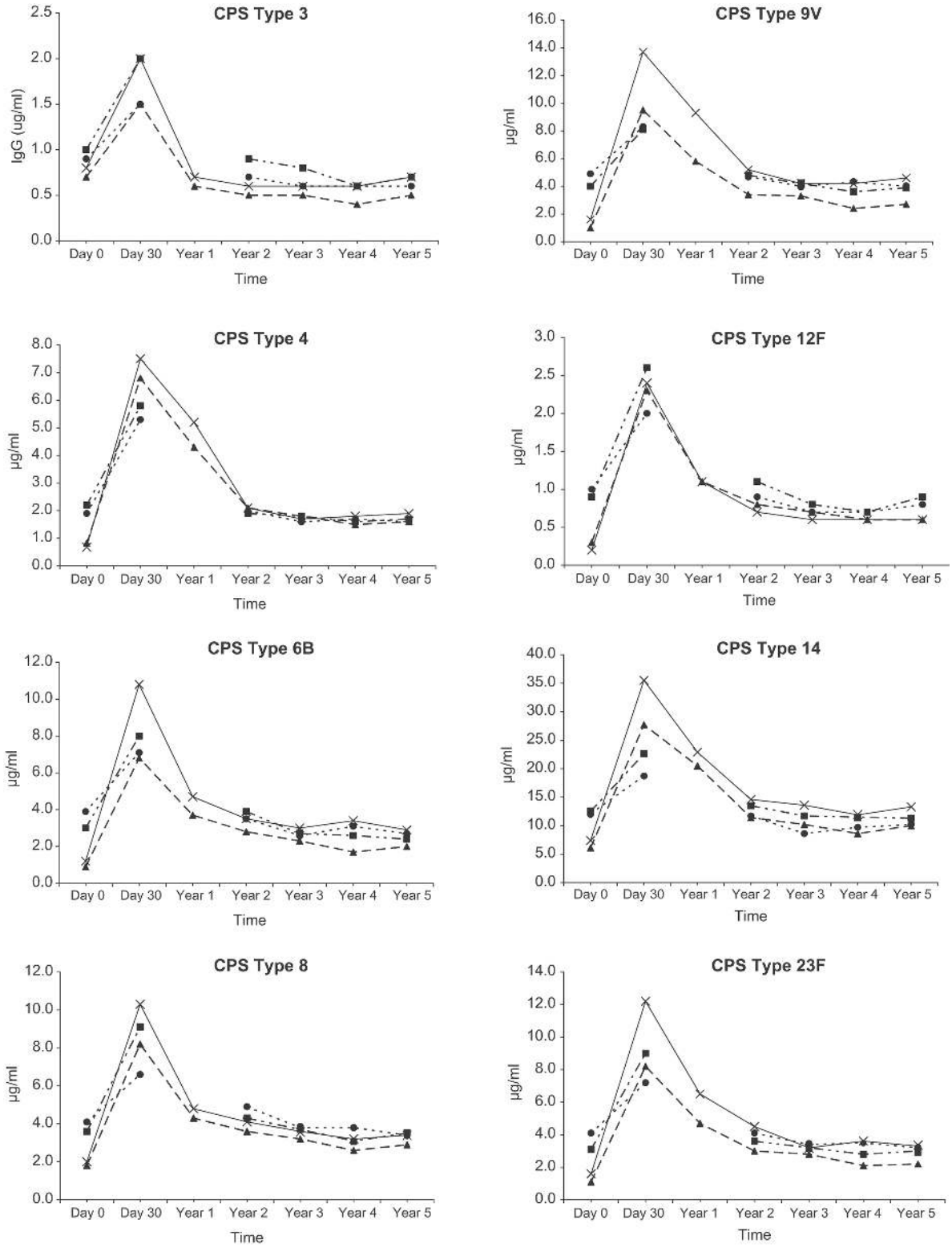


**Figure 1.** Antibody levels for 8 serotypes during a 5-year follow-up study. Geometric mean concentrations of immunoglobulin G (IgG) to 8 pneumococcal capsular types are shown for baseline, day 30, and then yearly thereafter for 5 years after administration of 23-valent pneumococcal polysaccharide vaccine. Note that the vertical axis (which shows IgG levels in $\mu$g/mL) is different for each capsular polysaccharide (CPS). The younger primary vaccination group (50–64 years old) is represented by solid lines and Xs; the older primary vaccination group (≥65 years old) is represented by dashed lines and triangles; the younger revaccination group (50–64 years old) is represented by dashed-dotted lines and squares; and the older revaccination group (≥65 years old) is represented by dotted lines and circles.

Downloaded from https://academic.oup.com/jid/article/201/4/516/861677 by guest on 20 August 2022

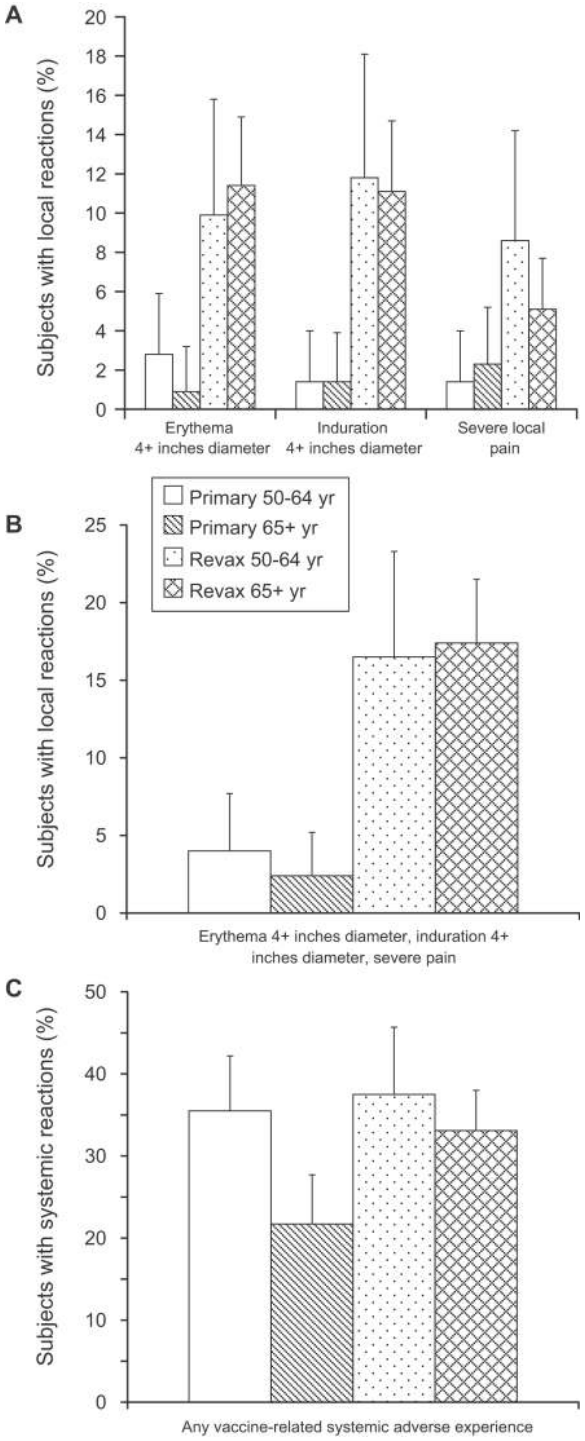


**Figure 2.** *A,* Percentage of subjects in each group reporting severe erythema (≥4 inches in diameter), severe induration (≥4 inches in diameter), or severe pain at the injection site after receipt of 23-valent pneumococcal polysaccharide vaccine (PN23). *B,* Percentage of subjects in each group reporting any severe injection site adverse experience after receipt of PN23. *C,* Percentage of subjects in each group reporting a vaccine-related systemic adverse experience after receipt of PN23.

60 days (although additional increases for some serotypes might have been observed at later time points) and then subsided over the ensuing 1–2 years, to a plateau that remained about 2-fold higher than the mean baseline levels for vaccine-naive subjects. Interestingly, at this plateau, antibody levels were nearly identical to baseline levels for the subjects in the 2 revaccination groups, most of whom had been vaccinated 3–5 years before enrollment. The sole exception was antibody to serotype 3; for this serotype, baseline antibody levels were identical in persons who had and those who had not been previously vaccinated and, after an initial increase at 30–60 days, levels returned to baseline within 1 year after vaccination. It is not known why the IgG response to serotype 3 was so poor or short-lived.

Consistent with the findings of previous studies [20–22, 28], antibody levels 30 days after revaccination were generally modestly lower than those observed after primary vaccination. Induction of relatively long-lived memory suppressor T regulatory cells may be responsible for the observed suppression and may be intrinsic to the immune response to polysaccharide antigens [29]. Musher et al [30] recently reported that subjects who had received PN23 within a year of prior vaccination had almost no response to revaccination, whereas IgG levels increased in proportion to the time elapsed since prior vaccination. In the present study, anticapsular antibodies increased significantly after primary vaccination and revaccination, even in persons ≥65 years old. Differences in antibody levels between primary vaccination and revaccination subjects were less apparent by day 60 and were no longer present by years 1–2. Moreover, IgG levels after primary vaccination or revaccination persisted above those in vaccine-naive subjects throughout the 5 years of observation. These data do not support a theoretical concern of immunologic tolerance after revaccination with PN23 at a 3–5-year interval. Instead, they suggest that the early marginal differences in antibody levels after revaccination are transient and are not likely to be clinically meaningful.

Protective levels of antibody to *S. pneumoniae* have never been ascertained for adults. However, the finding that IgG levels remained above the baseline for vaccine-naive subjects throughout the 5-year study period is consistent with the persistence of a beneficial effect from both primary vaccination and revaccination. A case-control study by Shapiro et al [2] found that the efficacy of pneumococcal vaccine exceeded 50% for 3 years and waned thereafter, but with some protection persisting beyond 5 years in inverse proportion to the age of the subjects. Other studies of adults hospitalized for community-acquired pneumonia have shown that prior PN23 vaccination is associated with reduced mortality, complications, length of stay, and rate of intensive care admissions [8, 9]

The present trial was conducted among ambulatory adults ≥50 years old who had an expected prevalence of common



Downloaded from https://academic.oup.com/jid/article/201/4/516/861677 by guest on 20 August 2022

comorbid conditions. Our findings, however, are similar to those of Heidelberger et al [22], who documented the persistence of antibody for 5–8 years in healthy young adults. The findings of the present trial are different from those of 2 prospective studies of patients with hospital-treated pneumonia. One study [30] of subjects with documented pneumococcal pneumonia found that vaccination with PN23 stimulates increases in antibody levels at 4–8 weeks; thereafter, however, IgG levels fall off very rapidly, returning nearly to baseline within 6 months. In the second study [20], which was conducted in subjects vaccinated shortly after recovery from community-acquired pneumonia, IgG levels remained elevated 1 year after vaccination but returned to baseline levels 5 years after vaccination. The longer antibody persistence observed in the present study may be explained by the fact that persons with a history of proven pneumococcal disease were excluded. A history of pneumococcal disease may indicate a reduced ability to mount an immune response to pneumococcal antigens.

Our results confirm those of Jackson et al [21], which showed that revaccination is generally well tolerated. Most subjects had some local adverse experiences at the injection site, more commonly among those being revaccinated and less commonly in the older group receiving PN23 for the first time. Severe local events, as defined in the protocol, occurred in 14%–15% of revaccination subjects versus 2.5%–4.5% of primary vaccination subjects, but none was judged to be seriously injurious to health. Systemic adverse experiences were equally common after primary vaccination and revaccination except in those ⩾65 years old, who reported fewer such experiences after primary vaccination.

This study was not designed to answer the question of whether revaccination is required or, if so, at what interval following earlier vaccination. The immune response to capsular polysaccharides is T cell independent and should have a limited duration. If waning antibody levels are associated with decreased clinical protection, then it is reasonable to conclude that revaccination may be appropriate.

Some studies have questioned the functional capacity of anticapsular antibody in adults who have a variety of underlying diseases [13], in patients who have measurable antibody at the time of hospitalization for pneumococcal pneumonia [31], and even in persons of advancing age in the absence of specific diseases [13]. Data on the functional capacity of the antibody detected in the present study are contained in a companion article [32]. The functional antibody results are consistent with the IgG findings presented here.

In conclusion, primary vaccination or revaccination with PN23 in adults >50 years old was generally well tolerated and induced IgG antibody to all 8 serotypes tested. This antibody persisted at similar levels for 5 years in all study groups and for all serotypes except type 3. These immunogenicity findings are consistent with epidemiologic observations on PN23 vaccine efficacy and support the current ACIP recommendations [6], which state that PN23 should be administered to all persons ⩾65 years old even if they have been vaccinated previously.

## Acknowledgments

We thank the members of the Pneumococcal Revaccination Study Group who participated in the conduct of this study. The members include Renee White (VA Medical Center, Houston, Texas); Mark Goldberg, Toni Goldberg, Peggy Porter-Helbig, and Christine Ore'Giron (Saguaro Research, Tucson, Arizona); Richard Tucker, Bradley Cromar, and Anita Ashenbrenner (Wenatchee Valley Clinic, Wenatchee, Washington); Gregory Poland, Robert M. Jacobson, Shelly Roberts, and Delana Weiss (Mayo Medical Center, Rochester, Minnesota); Burton Lazar and Chris Bielke (Portland Clinic, Portland, Oregon); Delmar Greenleaf, John Allen, Cheryl Foltos, and Janet Wilkerson (Bend Memorial Clinic, Bend, Oregon); and Joseph Bertino, Anne Nafzeger, Anne Menhenick, and James B. Harbison (Bassett Healthcare, Cooperstown, New York).

## References

1. Broome CV, Facklam RR, Fraser DW. Pneumococcal disease after pneumococcal vaccination: an alternative method to estimate the efficacy of pneumococcal vaccine. N Engl J Med **1980**; 303:549–552.
2. Shapiro ED, Berg AT, Austrian R, et al. The protective efficacy of polyvalent pneumococcal polysaccharide vaccine. N Engl J Med **1991**; 325:1453–1460.
3. Jackson LA, Neuzil KM, Yu O, et al. Effectiveness of pneumococcal polysaccharide vaccine in older adults. N Engl J Med **2003**; 348:1747–1755.
4. Musher DM, Rueda-Jaimes AM, Graviss EA, Rodriguez-Barradas MC. Effect of pneumococcal vaccination: a comparison of vaccination rates in patients with bacteremic and nonbacteremic pneumococcal pneumonia. Clin Infect Dis **2006**; 43:1004–1008.
5. Fedson DS, Musher DM. Pneumococcal vaccine. In: Plotkin SA, Orenstein WB, eds. Vaccines. 4th ed. Philadelphia, PA: W. B. Saunders, **2003**:529–588.
6. Centers for Disease Control and Prevention. Prevention of pneumococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep **1997**; 46(RR-8): 1–24.
7. Moberley SA, Holden J, Tatham DP, Andrews RM. Vaccines for preventing pneumococcal infection in adults. Cochrane Database Syst Rev **2008**:CD000422.
8. Fisman DN, Abrutyn E, Spaude KA, Kim A, Kirchner C, Daley J. Prior pneumococcal vaccination is associated with reduced death, complications, and length of stay among hospitalized adults with community-acquired pneumonia. Clin Infect Dis **2006**; 42:1093–1101.
9. Johnstone J, Marrie TJ, Eurich DT, Majumdar SR. Effect of pneumococcal vaccination in hospitalized adults with community-acquired pneumonia. Arch Intern Med **2007**; 167:1938–1943.
10. Nichol KL, Baken L, Wuorenma S, Nelson A. The health and economic benefits associated with pneumococcal vaccination of elderly persons with chronic lung disease. Arch Intern Med **1999**; 159:2437–2442.
11. Musher DM, Luchi MJ, Watson DA, Hamilton R, Baughn RE. Pneumococcal polysaccharide vaccine in young adults and older bronchitics: determination of IgG responses by ELISA and the effect of adsorption of serum with non-type-specific cell wall polysaccharide. J Infect Dis **1990**; 161:728–735.
12. Rubins JB, Puri AKG, Loch J, Charboneau D, MacDonald R, Opstad N, et al. Magnitude, duration, quality, and function of pneumococcal vaccine responses in elderly adults. J Infect Dis **1998**; 178:431–440.
13. Romero-Steiner S, Musher DM, Cetron MS, et al. Reduction in func-

Downloaded from https://academic.oup.com/jid/article/2011/4/516/861677 by guest on 20 August 2022

tional antibody activity against *Streptococcus pneumoniae* in vaccinated elderly individuals highly correlates with decreased IgG antibody avidity. Clin Infect Dis **1999**; 29:281–288.
14. Simberkoff MS, Cross AP, Al-Ibrahim M, et al. Efficacy of pneumococcal vaccine in high-risk patients: results of a Veterans Administration cooperative study. N Engl J Med **1986**; 315:1318–1327.
15. Safdar A, Rodriquez GH, Rueda AA, et al. Multiple-dose granulocyte-macrophage-colony-stimulating factor plus 23-valent polysaccharide pneumococcal vaccine in patients with chronic lymphocytic leukemia. Cancer **2008**; 113:383–387.
16. Dear K, Holden J, Andrews R, Tatham D. Vaccines for preventing pneumococcal infection in adults. Cochrane Database Syst Rev **2003**; CD000422
17. Conaty S, Watson L, Dinnes J, Waugh N. The effectiveness of pneumococcal polysaccharide vaccines in adults: a systematic review of observational studies and comparison with results from randomised controlled trials. Vaccine **2004**; 22:3214–3224.
18. Lipsky BA, Hirschmann JV. Pneumococcal polysaccharide vaccines do not protect the elderly from pneumococcal infections. Neth J Med **2004**; 62:33–35.
19. Sankilampi U, Honkanen PO, Bloigu A, Leinonen M. Persistence of antibodies to pneumococcal capsular polysaccharide vaccine in the elderly. J Infect Dis **1997**; 176:1100–1104.
20. Torling J, Hedlund J, Konradsen HB, Ortqvist A. Revaccination with the 23-valent pneumococcal polysaccharide vaccine in middle-aged and elderly persons previously treated for pneumonia. Vaccine **2003**; 22: 96–103.
21. Jackson LA, Benson P, Sneller VP, et al. Safety of revaccination with pneumococcal polysaccharide vaccine. JAMA **1999**; 281:243–248.
22. Heidelberger M, DiLapi MM, Siegel M, Walter AW. Persistence of antibodies in human subjects injected with pneumococcal polysaccharides. J Immunol **1950**; 65:535–541.
23. O'Brien KL, Hochman M, Goldblatt D. Combined schedules of pneumococcal conjugate and polysaccharide vaccines: is hyporesponsiveness as issue? Lancet Infect Dis **2007**; 7(9):597–606.
24. Wernette CM, Frasch CE, Madore D, et al. Enzyme-linked immunosorbent assay for quantitation of human antibodies to pneumococcal polysaccharides. Clin Diagn Lab Immunol **2003**; 10:514–519.
25. Marchese RD, Jain NT, Antonello J, et al. Enzyme-linked immunosorbent assay for measuring antibodies to pneumococcal polysaccharides for the PNEUMOVAX 23 vaccine: assay operating characteristics and correlation to the WHO international assay. Clin Vaccine Immunol **2006**; 13:905–912.
26. Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med **1985**; 4:213–226.
27. Musher DM, Groover JE, Watson DA, et al. Genetic regulation of the capacity to make immunoglobulin G to pneumococcal capsular polysaccharides. J Investig Med **1997**; 45:57–68.
28. Heidelberger M, MacLeod CM, diLapi MM. The human antibody response to simultaneous injection of six specific polysaccharides of pneumococcus. J Exp Med **1948**; 88:369–372.
29. Heilmann C. Vaccination-induced activation of human blood T cells suppressing pneumococcal polysaccharide-specific B cells. Acta Pathol Microbiol Immunol Scand C **1987**; 95:65–69.
30. Musher DM, Rueda AJ, Graviss EA, Rodriguez-Barradas M. Response to pneumococcal polysaccharide and protein-conjugate vaccines singly or sequentially in adults who have recovered from pneumococcal pneumonia. J Infect Dis **2008**; 198:1019–1027.
31. Musher DM, Phan HM, Watson DA, Baughn RE. Antibody to capsular polysaccharide of *Streptococcus pneumoniae* at the time of hospital admission for *Pneumococcal pneumonia*. J Infect Dis **2000**; 182:158–167.
32. Manoff SB, Liss C, Caulfield MJ, et al. Revaccination with a 23-valent pneumococcal polysaccharide vaccine induces elevated and persistent functional antibody responses in adults aged ⩾65 years. J Infect Dis **2010**; 201:525–33 (in this issue).

Downloaded from https://academic.oup.com/jid/article/201/4/516/861677 by guest on 20 August 2022