The incidence of invasive pneumococcal disease (IPD) rises with age. Among adult IPD patients, the avidity of antipneumococcal polysaccharide antibodies against the infecting serotype increased with age and severity of disease, indicating that susceptibility to IPD in the elderly may rather be due to flaws in other aspects of opsonophagocytosis.
to infection or that antibodies against the infecting serotype had already been expended at the time of hospital admission. A preexisting deficit would be less likely if the avidity of these antibodies is similar to the avidity of those in healthy adults, indicating that the process from antigen presentation to affinity-maturated antibody production was not disturbed.

In IPD patients, the median IgG antibody avidity against their infecting serotypes was 0.19. For the control pool, a similar distribution of IgG antibody avidities was observed against the 11 serotypes considered (median, 0.12; Mann-Whitney U test, $P = 0.21$; Fig. 2). Notably, IgG antibody concentration and avidity were not inversely correlated in IPD patients ($r = -0.01$, $P = 0.2$). The similar antibody avidity against the infecting serotype in IPD patients compared with healthy controls differs from what was observed in a previous study in which a lower avidity of antibodies against the infecting serotype was observed (14). An important difference with our study is that in the previous study the healthy adult control group was a selection of highest responders after 23-valent pneumococcal polysaccharide vaccination, whereas our controls were unvaccinated like the IPD patients, which may be more informative on differences in susceptibility to pneumococcal disease.

More-severe bacteremic pneumococcal pneumonia according to pneumonia severity index (PSI) risk class was associated with increased IgG antibody avidities against the infecting serotype (Spearman $r = 0.59$, $P = 0.0016$; Fig. 3A). Furthermore, the IgG antibody avidity against the infecting serotype was positively correlated with age (Spearman $r = 0.42$, $P = 0.028$) in IPD patients (Fig. 3B). High-avidity antibodies result from the process of affinity maturation, which requires previous exposure to the pneumococcal polysaccharide involved. The higher avidity in older IPD patients than in younger IPD patients may be due to more extensive nasopharyngeal pneumococcal carriage. Although among the elderly pneumococcal carriage rates below 10% have been reported (15–17), other studies demonstrate increasing carriage rates with senior age (18, 19). Moreover, pneumococcal carriage was recently shown to be present in 33% of the Dutch elderly (20) and may still induce an anti-PPS memory response at this age (21). However, the higher avidity of anti-PPS antibodies in the elderly may also have been elicited in the initial phase of pneumococcal infection prior to disease.

Antibody avidity may serve as a surrogate measure for other, more elaborate functional antibody tests such as in vitro opsonophagocytic killing or passive protection in mice (8, 14, 22). However, it is unknown how each of these assays actually correlates with protection from pneumococcal disease in adults. In addition, if there were a relationship, it could be serotype specific. To understand whether high-avidity anti-PPS antibodies are desir-

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**FIG 1** Concentrations of IgG antibodies in IPD patients are lower against the PPS of the infecting serotype than against PPS 19A (two patients infected with serotype 19A excluded). Short horizontal lines, medians. Dashed line, protective antibody concentration in infants. ***, $P < 0.01$.

**FIG 2** Similar avidities of anti-PPS IgG antibodies were measured in IPD patients against the infecting serotype compared to the healthy control pool. Black bars, median avidity of patients infected with a particular serotype.
able in the elderly, their functional consequences should be studied in more detail in relation to acquisition and severity of disease in IPD patients of different ages infected with different serotypes.

In adult IPD patients, we observed an age-related increase in avidity of antibodies against the infecting serotype, indicating that the rise in IPD incidence with aging is not caused by a lack of avidity in anti-PPS antibodies. Therefore, among the elderly, flaws in other aspects of opsonophagocytosis, such as complement activation or intracellular killing, may play a more important role in the increased susceptibility to pneumococcal disease.

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FIG 3 Avidity of anti-PPS antibodies in IPD patients increases with PSI risk class (A) and with age (B). Short horizontal lines in panel A indicate medians. Infecting serotypes against which IgG avidity is measured are displayed next to the corresponding dot in panel B. **, P < 0.01.

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