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Letter to the Editor

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*Dear Sirs,*

Kim et al. report the results of a case-control study of 23-valent pneumococcal polysaccharide vaccine (PPVS23) effectiveness against invasive pneumococcal disease (IPD) and non-bacteremic pneumococcal pneumonia (NBPP) in adults ≥65 years old in the Republic of Korea [1]. The authors concluded that their data provide support for PPSV23 use among adults in the context of a pediatric 13-valent pneumococcal conjugate vaccine (PCV13) program.

Due to the relevance of the study for both public health officials and policymakers, we would like to highlight a few concerns around methods, interpretation of results and overall conclusions. From a methodological point of view, there is little description of controls, including no description of whether they were identified concurrently at the time of case enrollment or retrospectively, whether they were selected from all hospitalized patients or a subset, or how the authors determined that controls did not have evidence of pneumococcal disease (presumably not by prospectively testing each patient). Since the key source of bias in a case control study often is control selection, absence of these data makes assessment of potential bias impossible. Additionally, it will also help if the authors could describe the number of stratified analyses they conducted, to better understand whether results are robust or more likely due to chance.

We are also concerned with the interpretation of results. The unadjusted analyses showed that PPSV23 afforded no protection against the primary outcome, namely IPD or NBPP among all persons age 65+ years, while the adjusted analysis had a 57.4% or 35.0% vaccine effectiveness (VE), respectively (Table 2). Among non-primary outcomes, there was no protection against IPD or NBPP for persons age 75+ (Table 2); in particular, there was failure to show protection in the older age group aged 75+ for 7 of 12 analyses assessing serotype specific VE against IPD (Table 3); and failure to show protection for any of the 12 analyses assessing serotype specific VE against NBPP (Table 4). The most robust finding was PPSV23 VE against IPD among persons age 65–74 years, which in any event confirms studies demonstrating short term protection of PPSV23 against IPD but not NBPP [2].

The current study found that PPSV23 afforded no protection against PCV13 serotypes, effectively making the policy decision whether to use a conjugate vaccine against PCV13 serotypes or a polysaccharide vaccine against PPSV23 unique serotypes. As reported in Tables 3 and 4, there were 36 and 169 PCV13 serotypes among IPD and NBPP cases, respectively, versus 28 and 85 PPSV23 unique serotypes. Moreover, unlike PPSV23, PCV13 consistently has demonstrated VE against NBPP in a randomized controlled trial [3] and real-world study [4], has relatively high direct VE against serotype 3 [5], provides at least four years of undiminished protection to adults [6], and is effective among adults > age 74 years [7].

Finally, and given all the above, we think that the authors conclusions in the current manuscript might be qualified further. For example, taking the authors data at face value, and considering the extensive data on impact and mechanism of PCV13 vs. PPSV23, use of both PCV13 and PPSV23 vaccines is likely to provide the most efficient public health intervention, even in the context of a pediatric PCV13 program [8–11].

## Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: All authors declare they are employed by Pfizer Inc.

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