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Does 23-Valent Pneumococcal Polysaccharide Vaccination Decrease All-Cause Mortality?

To the Editor—We read with interest the recently published study by Murata et al [1]. The authors conducted a retrospective matched cohort study using data registers in Japan. The aim was to examine the effectiveness of the 23-valent pneumococcal polysaccharide vaccine (PPSV23) on pneumonia-related mortality and all-cause mortality in older adults (≥65 years). The authors concluded that PPSV23 was associated with reduced all-cause mortality but not pneumonia-related mortality. While this is an important subject, we are concerned about confounding factors and interpretation of the findings. The authors estimate a reduction of all-cause mortality of almost 50%. Assuming that the vaccine is less than 100% effective in preventing pneumococcal infections, this would suggest that the majority of all deaths in older adults are caused by pneumococcal serotypes included in PPSV23. So what is driving this spurious association between receipt of PPSV23 and all-cause death? There are several elements of the analysis that could bias the estimates toward high values.

First, the authors used the Charlson Comorbidity Index (CCI) in this study, which was balanced between cases and controls. However, medical expenses were higher in unvaccinated individuals, potentially indicating greater frailty in unvaccinated individuals. Frailty is an age-related decrease in physical reserve and function [2]. Although CCI correlates with frailty, it has been shown that survival is lower in individuals with the same CCI score but higher frailty [3]. Older adults with frailty have a higher risk of not being included in clinical studies, which can cause bias in the findings [4, 5]. Murata et al used data from the Longevity Improvement & Fair Evidence (LIFE) study in Japan, and according to the findings of the LIFE study, the PPSV23 vaccination coverage for the entire eligible population was 33.6% [6]. Moreover, factors such as hospital visit history, specific health check-ups, and socioeconomic status were significantly associated with PPSV23 vaccination in the LIFE study [6]. We would like to add that a lower socioeconomic status is also associated with increased all-cause mortality, and this can be a reason for higher mortality in unvaccinated individuals [7].

Second, the authors correctly mentioned in the discussion that the lack of information regarding influenza vaccination was one of the study's limitations. We would like to highlight this again and add that the coadministration of other vaccines with PPSV23 is another factor that can potentially impact the findings. The analysis would be more robust if negative controls were included to detect residual confounding and bias—for instance, receipt of shingles vaccines as a control for pneumonia mortality [8].

Last, the duration from the cohort entry date (CED) until death was used as the dependent variable in the Cox regression model, suggesting that the risk of all-cause mortality in vaccinated individuals at any time was 48% lower compared to unvaccinated individuals. However, without further information about the median follow-up time for vaccinated and unvaccinated individuals or the median time from CED to death, it is not possible to determine how long this reduced risk has persisted. The effects of PPSV23 are believed to last for just a few years; thus, the effect would be expected to decline rapidly over time.

The potential impacts of PPSV23 in decreasing morbidity and mortality are of importance. However, we believe that addressing these issues can improve our understanding of the benefits of PPSV23 vaccination for older adults.

Notes

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