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Reply to Letter to the Editor

Authors' reply to: Letter from Arguedas et al.

We thank you for the opportunity to respond to the letter by Arguedas et al. for their interests in our paper [1]. Although most of their concerns have already been stated in the original article, we provide additional details from our findings.

First, the cases and controls were recruited concurrently by the pre-defined criteria from the hospitals which had participated in the nationwide surveillance study for invasive pneumococcal disease (IPD) and non-bacteremic pneumococcal pneumonia (NBPP) in the elderly ≥65 years during implementation of national immunization program (NIP). One of the major inclusion criteria for both groups was the microbiological results of *Streptococcus pneumoniae* in their clinical specimens: positive for cases and negative for controls. Among the all eligible controls by the laboratory results, we used randomly selected controls (one for NBPP or two for IPD) after matching by age, sex and admission date for one case in this study.

Although age stratification (65–74 years and ≥75 years) was considered at the time of study design, sample size calculation for the case-control study was performed only for all patients ≥65 years. However, a borderline interaction effect between age and 23-valent pneumococcal polysaccharide vaccine (PPV23) vaccination in IPD ($p = 0.05$) and NBPP ($p = 0.08$) was found. Age-subgroup analyses were subsequently performed for accurate measurement of vaccine effectiveness (VE) of PPV23. Furthermore, we performed a multivariate generalized estimating equation analysis to control for confounding effects from potential sampling and selection bias.

Second, our results demonstrated the protective VE of PPV23 against IPD, particularly among young elderly patients aged 65–74 years. Additionally, we think that recent PPV23 vaccination within 5 years could offer excellent VE against IPD caused by PPV23 unique serotypes. However, lack of significant VE of PPV23 against IPD caused by 13-valent pneumococcal conjugate vaccine (PCV13) serotypes was thought to be due to the decreased VE of PPV23 against serotype 3 (ST3) because the most common serotype of IPD in our study was ST3. Decreased VE of PPVS23 against ST3 has been reported in previous studies [2,3]. Recently, an increased proportion of ST3 IPD was reported among hospitalized adults after implementation of pediatric PCV13 NIP in Canada [4], raising a question about the effectiveness of herd immunity from pediatric PCV13 NIP against ST3 IPD in the elderly. Inconsistent VE of PCV13 against ST3 has been reported from the update of the Advisory Committee on Immunization Practices (ACIP) [5].

While there have been concerns of limited VE of PPV23 against NBPP, a recent Japanese study reported low to moderate VE of PPV23 against NBPP [2]. Our study indicates an additional evidence of the VE of PPV23 against NBPP among the young elderly. We also speculate that lack of serotype-specific VE of PPV23 against NBPP may be due to the smaller number of available NBPP serotypes.

Regarding their concern on our conclusions, our primary objective was to evaluate the VE of PPV23 NIP for the elderly against pneumococcal disease who had no prior PCV13 vaccination. The VE of PPV23 was also interpreted in conjunction with herd immunity and serotype replacement from pediatric PCV NIP existed in this setting. However, considering the impact of adult PCV13 from other studies for our conclusions was beyond the scope of our research. Moreover, the ACIP update reported the overall effect from vaccinating adults with PCV13 is minimal in the context of pediatric PCV use [5].

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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