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Altered responses to pneumococcal vaccination in an elderly diabetic Japanese vaccine trial: The risk of concurrent vaccination strategies

In this issue, Hata and colleagues reexamine the efficacy of the 23-valent pneumococcal polysaccharide vaccine (PPSV23) from their double-blind randomized vaccine trial in 60–70-year old Japanese adults with diabetes mellitus. In their study, all subjects received PPSV23 and half received a simultaneous immunization with the live-attenuated Oka varicella vaccine while the other half received a placebo immunization.[1] The Oka varicella vaccine is normally given to children in Japan and was being evaluated as a varicella-zoster vaccine (VZV) to prevent shingles in an elderly diabetic population. In their original publication, Hata et al. found that four weeks post-vaccination the VZV-specific responses were not significantly altered compared to placebo group, indicating poor responsiveness of this population to VZV vaccination.[1] In this new analysis, they examine the cost of this dual vaccination schedule to the antibody response to PPSV23 vaccine components specific to two *Streptococcus pneumoniae* serotypes.[2] Their results show altered immunogenicity in subjects receiving PPSV23 concurrent with VZV compared to those who received PPSV23 and a placebo.

With a forecasted global increase in older and diabetic populations, the future societal and medical costs of this vulnerable population are staggering (e.g., between 2015 and 2030 diabetic Americans are projected to increase by 54% to 54.9 million and total annual medical and societal costs related to diabetes are projected to increase 53% to $622 billion[3]). In Japan, there has been a similar concern in the increased prevalence in type-2 diabetes, driven by changes in population demographics and number of older individuals.[4] Strategies to mitigate this problem are needed. One such option is vaccination campaigns specifically for older adults to reduce infections and subsequent complications as a way to maximize health span or the time an individual remains fully functional.[5,6]

Lower respiratory infections, including pneumonia and influenza continue to be a common cause of morbidity and mortality world-wide and within individual countries like Japan (ranked fourth) and the United States (ranked eighth).[7,8] Risk for pneumonia-related deaths is greater in older individuals and/or diabetes.[6] In both North American and Japan, *S pneumoniae* remains the leading cause of community-acquired pneumonia affecting adults.[7,9] There are two forms of the pneumococcal vaccine to prevent *S. pneumoniae* infections, the polysaccharide based PPSV23 in use since the 1970s and the newer polysaccharide protein conjugate PCV13. These vaccines prevent disease by targeting bacterial capsular polysaccharides for opsonophagocytic destruction; only the protein conjugate vaccine works in children whereas both vaccines can prevent pneumococcal disease in adults.[10] In the US, the Center for Disease Control (CDC) has had a long-standing recommendation that older adults receive a pneumococcal vaccine in addition to a seasonal influenza vaccine and regular Td or Tdap (tetanus, diphtheria, and pertussis) boosters.[11] In 2014, the CDC recommendation changed to sequential administration of both PCV13 and PPSV23 for US adults ≥65 years.[12] However, in other developed countries the recommended vaccine schedule for elderly individuals is highly variable, including which form of the vaccine should be given (if any) or both sequentially. In Japan the national recommendation is for a single PPSV23 immunization for adults ≥65 years.[5] In addition, while in the US adults 60 years or older are recommended to receive the Zoster vaccine to help protect against shingles, Japan has no such recommendation (although it is approved as a voluntary vaccine for adults 50 years and older).[5,13] As a result, there is concern that with recent inclusion of VZV to the national immunization program in Japan, non-immunized children could become at-risk adults in the future without community virus exposure or adult immunization programs.[13]

Reaching target populations is the key to any public health strategy, but preventative vaccination in older adults is an underutilized approach. There are several barriers to this issue,[5,14] but effective, concurrent immunizations could expand vaccination coverage. With this approach, multiple injected vaccines are simultaneously administered, reducing the number of visits to healthcare professionals. Concurrent vaccination with PPV23 and influenza has been well studied and found to be safe and effective for both vaccines, including in a recent phase III, placebo-controlled, observer-blind trial study conducted in ≥50 year old European adults where individuals with comorbidities like diabetes were also evaluated.[15] Furthermore, a vaccine efficacy metanalysis found simultaneous influenza and PPV23 vaccination to be associated with reduced pneumonia and all-cause mortality in adults ≥65 years.[16] VZV has been evaluated with influenza vaccination[17] and pneumococcal vaccination.[18] Although with the later, conflicting recommendations regarding simultaneous administration of VSV and PPV23 for protection against herpes zoster infections have been made based on study outcomes.

An important finding in the Hata et al. article is that simultaneous immunization with a vaccine that poorly boosted VZV-specific cellular immunity in this diabetic population (e.g., Oka varicella vaccine ®) altered immune responses to co-delivered PPSV23 three months post-vaccination.[2] This effect was minor. The antibody responses to the two

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serotypes examined, 6B and 23F, were still robustly enhanced with vaccination; however, the significant reduction in overall responder rates (calculated by number of individuals with a 2-fold or greater increase in 6B and/or 23F serum IgG concentration) is potentially concerning. Older adults with diabetes are already at higher risk for poor outcomes to pneumonia infections.[6] In Japan or similar countries this single PPSV23 immunization around 65 years of age is aiming to provide protection to this individual for the rest of their life. Slight changes in protection three months post-vaccination may reflect a shorter duration of this protective immunity, leaving older diabetics more susceptible to *S. pneumoniae* infection as they age and their immune system declines. Additional studies like this one are needed to identify best schedules and formulations for simultaneously administered vaccines to prevent pneumonia, Herpes Zoster, and other infections in diabetic older adults in Japan and elsewhere.[6,19]

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