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MAJOR ARTICLE

Immunogenicity and Safety of the Higher-Valent Pneumococcal Conjugate Vaccine vs the 13-Valent Pneumococcal Conjugate Vaccine in Older Adults: A Systematic Review and Meta-analysis of Randomized Controlled Trials

Thundon Ngamprasertchai,[1] Narisa Ruenroengbun,[2,a] and Rattagan Kajeekul[3]

[1]Department of Tropical Hygiene, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand, [2]Department of Pharmaceutics (Clinical Pharmacy), Faculty of Pharmacy, Slipakorn University, Nakhon Pathom, Thailand, and [3]Department of Medicine, Maharat Nakhon Ratchasima Hospital, Nakhon Ratchasima, Thailand

Background. The immunogenicity of the 15-valent pneumococcal conjugate vaccine (PCV15) and PCV20 in older adults was approved on the basis of comparative data with PCV13, although their relative immunogenicity and safety in this population remain undetermined. A systematic review and meta-analysis were conducted to provide insights, addressing the lack of large-scale efficacy studies.

Methods. This analysis included phase 2 and 3 randomized controlled trials evaluating the immunogenicity of a single dose of PCV15 or PCV20 in older adults by opsonophagocytic assay geometric mean titer (GMT) response at 1 month postvaccination as compared with PCV13.

Results. In total, 8 trials were eligible. PCV15 demonstrated superior immunogenicity vs PCV13 among older adults (GMT ratio, 1.11; 95% CI, 1.02–1.20). In immunogenicity vs PCV13, PCV20 demonstrated noninferiority, exceeding 0.5 at 1 month postvaccination (GMT ratio, 0.84; 95% CI, .81–.87). The incidence of local and systemic reactions was higher in the PCV15 group as compared with the PCV13 group, with risk ratios of 1.23 (95% CI, 1.14–1.32) and 1.15 (95% CI, 1.02–1.29), respectively. PCV20 is well tolerated and exhibits a comparable rate of local and systemic reactions to PCV13.

Conclusions. These findings support the immunogenicity and safety of PCV15 and PCV20 for pneumococcal vaccination in older adults. Given its superior immune response, PCV15 may address the gaps left by PCV13. Despite higher antibody levels, the clinical effectiveness of these vaccines remains uncertain. Ongoing surveillances are essential to evaluate the impact of both vaccines on remaining vaccine-type pneumococcal disease.

Keywords. immunogenicity; PCV15; PCV20; pneumococcal conjugate vaccine; safety.

The Advisory Committee on Immunization Practices (ACIP) currently recommends either the 20-valent pneumococcal conjugate vaccine (PCV20) alone or the 15-valent pneumococcal conjugate vaccine (PCV15) with the 23-valent pneumococcal polysaccharide vaccine (PPSV23) for adults aged ≥65 years and for adults aged 19 to 64 years with specific underlying conditions or risk factors who have not received a PCV or have an unknown vaccination history [1]. The ACIP does not preferentially endorse one PCV over another. The current evidence for higher-valency pneumococcal vaccines, specifically PCV15 and PCV20, offers significant advantages for older adults in terms of broader serotype coverage and potential reduction in invasive pneumococcal disease (IPD) beyond what is achieved with the 13-valent pneumococcal conjugate vaccine (PCV13). PCV15 includes 2 additional serotypes (22F and 33F) not present in PCV13, while PCV20 covers 7 additional serotypes (8, 10A, 11A, 12F, 15B, 22F, and 33F) [2, 3]. A study on IPD serotype distribution in older adults from high-income countries found that PCV15 and PCV20 could cover an additional 10.4% and 32.9% of IPD cases, respectively, beyond the coverage of PCV13 [4]. These findings suggest that higher-valency

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[a]Essentially intellectual contributor.

Correspondence: Thundon Ngamprasertchai, MD, PhD, Department of Tropical Hygiene, Faculty of Tropical Medicine, Mahidol University, 420/6 Ratchawithi Road, Ratchathewi, Bangkok 10400, Thailand (thundon.ngm@mahidol.ac.th).

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vaccines could significantly reduce the residual IPD burden in older adults [4].

The clinical studies supporting the approval of PCV15 and PCV20 in older adults are primarily based on safety and immunogenicity data [5–10]. Large head-to-head trials with IPD outcomes are unfeasible [11], leaving uncertainty about whether one vaccine is consistently more immunogenic or if immunogenicity differences lead to clinically significant protection [12]. A few studies have directly assessed the effectiveness of PCV20 in reducing IPD and community-acquired pneumonia in adults. In contrast, research on PCV15 has largely focused on immunogenicity and cost-effectiveness analyses. PCV20 averted more IPD and community-acquired pneumonia cases than PCV15 and PPSV23, demonstrating its superior effectiveness in reducing pneumococcal disease burden in older adults [13]. A pivotal phase 3 trial showed that PCV20 immune response was noninferior to PCV13 for the 13 shared serotypes and to PPSV23 for 6 of the 7 additional serotypes, demonstrating strong immune responses and a safety profile similar to PCV13 [8, 9, 14]. PCV15 induces serotype-specific IgG geometric mean concentrations and opsonophagocytic activity (OPA) geometric mean titers that are comparable to those induced by PCV13 for the shared serotypes and higher responses for the additional serotypes 22F and 33F [5–7].

In children, PCV15 and PCV20 have similar immunogenicity, but they are less immunogenic than PCV13 for serotypes shared with PCV13 [15]. The immunogenicity and safety of both higher-valency vaccines vs PCV13 among older adults have yet to be concluded. Therefore, the objective of this study is to perform a meta-analysis of head-to-head randomized controlled trials (RCTs) evaluating the immunogenicity and safety of PCV15 or PCV20 as compared with PCV13 in older adults to draw meaningful conclusions in the absence of large clinical studies focused on vaccine effectiveness.

METHODS

The systematic review was developed following the guidelines in the PRISMA extension of network meta-analysis. Immunogenicity and safety were performed for all quantitative syntheses. The review protocol was registered with PROSPERO (CRD 42024520795).

Search Strategies

We identified potential studies from MEDLINE via PubMed, SCOPUS, and EMBASE as well as the reference lists of selected studies published up to June 2024. Two investigators (T. N., R. K.) developed search strategies that were accepted by the team. The search terms and strategies for each database were generated by the targeted population, types of higher-valent PCVs, and outcome. The full search strategies are available in Supplementary Tables 1 and 2. The following keywords were used: immunogenicity, PCV13, 13-valent pneumococcal conjugate vaccines, PCV15, 15-valent pneumococcal conjugate vaccines PCV15, 15-valent pneumococcal conjugate vaccines, *Streptococcus pneumoniae*, pneumococcal conjugate vaccines, safety, adverse events, side effects, and adults.

Selection of Studies

The identified studies were independently selected according to title and abstract by 2 independent reviewers (T. N. and R. K.). Disagreement was resolved by discussion with a third reviewer (N. R.). Titles and abstracts were screened, and the full text was reviewed when a decision could not be made by abstract review. Study selection and agreement measurement were performed with the COVIDence program.

Inclusion Criteria

We included phase 2 or 3 RCTs in any language when they met the following criteria:

- Participants were adults aged ≥50 years without any immunocompromising conditions according to the 2023 ACIP recommendations [1].
- A single dose of PCV20 or PCV15 was compared with PCV13.
- The study outcome was immunogenicity and safety.
- The full text could be retrieved, and data were available for extraction.
- The study is currently published in a peer-reviewed journal or clinical trial registry.

Studies were excluded if they (1) used a placebo as a comparator, as the focus was on immune response ratios between higher-valency vaccines and PCV13; (2) used a comparator other than PCV13, given the emphasis on recent PCVs in older adults; (3) were single-arm studies without a comparator; (4) included populations receiving concomitant vaccinations; (5) had variations in adjuvants or formulations of the same pneumococcal vaccine; and (6) were lot-to-lot consistency studies. Ongoing studies or study protocols without available results were also excluded.

Data Extraction

At least 2 of the 3 reviewers (T. N., R. K., and N. R.) independently extracted data using a standardized extraction form. Discrepancies were resolved by discussion or by a third reviewer (T. N.).

Outcome of Interest

The immunogenicity of all studies was assessed by measuring functional antibacterial OPA titers with 13 serotype-specific validated OPA assays shared with PCV13. Although no specific OPA antibody level has been definitively correlated with

protection against pneumococcal disease in adults, OPA responses are widely recognized as indicators of vaccine-induced protection [16]. For the primary analysis, pooled outcomes were based on the standard definition used across studies. Noninferiority of PCV15 or PCV20 when compared with PCV13 was established if the lower limit of the 95% CI for the geometric mean titer ratio (GMTR) exceeded 0.5 (2-fold criterion) at 1 month postvaccination. Serotype-specific OPA GMTRs in the PCV15 or PCV20 group were compared with the PCV13 group and were considered superior to PPV23 if the 95% CI did not cross 1. Secondary outcomes included local reactions (pain, redness, swelling at the injection site), systemic adverse events (muscle/joint pain, chills, fatigue, headache, vomiting, decreased appetite, rash) within 14 days postvaccination, and all-cause mortality up to 1-year postvaccination.

Quality Assessment

At least 2 of the 3 reviewers (T. N., R. K., and N. R.) independently evaluated the risk of bias of each study using the Cochrane Risk of Bias 2.0 tool for RCTs. The Risk of Bias 2.0 tool evaluates 5 domains of bias. The overall risk of bias was described as low, intermediate, or high. Disagreement between 2 authors was resolved by consensus and discussion.

Data Synthesis and Statistical Analysis

We conducted our systematic review following the 2020 PRISMA guidelines. Extracted data included study year, author, location (countries), age group, study population, preexisting medical conditions, previous pneumococcal vaccine status, OPA GMTR, mortality, funding sources, and local and systemic safety events. To pool GMTRs, we estimated logarithmic GMTR values and standard errors using the reported GMTR and 95% CI from each study. Pooled OPA GMTRs by serotype were displayed in a forest plot. For safety and adverse effects, pooled risk ratios (RRs) with 95% CIs were calculated by reported adverse event proportions via a restricted maximum likelihood method with a random effects model. Pooled RRs for local reactions and systemic events were summarized. Heterogeneity was assessed with the Q test and I^2 statistic, with a random effects model applied if I^2 exceeded 25%; otherwise, a fixed effects model was used. Publication bias was evaluated with funnel plots and the Egger test. All analyses were performed in Stata version 17.0 (StataCorp LP), with statistical significance set at a 2-sided P value <.05, except for the heterogeneity test ($P < .10$).

RESULTS

Study Characteristics and Included Studies

The electronic search identified 2465 potentially relevant studies, of which 44 articles were deemed potentially eligible for analysis. After an assessment, 2421 reports were excluded as they did not meet the eligibility criteria (Figure 1). Studies were evaluated by their interventions and outcomes: immunogenicity and safety of PCV15 vs PCV13 (n = 4), immunogenicity of PCV20 vs PCV13 (n = 3), and safety of PCV20 vs PCV13 (n = 4). One study comparing PCV20 with PCV13 was excluded from immunogenicity analysis due to insufficient data. In total, 8 trials were included in the analysis, most of which were multinational studies recruiting adults aged ≥50 years with a wide range of stable chronic health conditions (30%–90%; Table 1). Most participants were pneumococcal vaccine naive. In the study by Cannon et al [10], only participants with prior PPSV23 vaccination were included in the analysis. For the study by Essink et al [8], immunogenicity data were extracted from the cohort aged ≥60 years, while safety data were derived from cohorts aged 50 to 59 and ≥60 years. Two studies reported deaths during the study period. In the study by Platt et al [19], 2 deaths were reported: 1 due to an unknown cause at 55 days postvaccination and 1 to arrhythmia at 87 days postvaccination, neither of which was related to the study vaccination. In the study by Essink et al, 1 death occurred in the PCV20 vaccination group due to traumatic injury, which was also unrelated to the study vaccination.

Quality Assessment Across the RCTs

The overall quality of the studies was assessed as having a low risk of bias. A comprehensive summary of the quality assessment across all studies is provided in Supplementary Figure 1.

Serotype-Specific Immunogenicity of PCV15 vs PCV13

Four studies were included in the analysis, comparing the immunogenicity of PCV15 and PCV13. Overall, PCV15 demonstrated superior immunogenicity vs PCV13, with significantly higher GMTRs for shared serotypes 1 month postvaccination in the PCV15 group, particularly among older adults (GMTR, 1.11; 95% CI, 1.02–1.20; Figure 2). The heterogeneity among the studies was substantial ($I^2 = 87.6\%$). Serotype 6A had relatively low heterogeneity, as indicated by an I^2 statistic of 23.3%. Notably, serotype 3 and serotype 23F demonstrated the largest treatment effects, with GMTRs of 1.54 (95% CI, 1.14–2.08) and 1.37 (95% CI, 1.16–1.60), respectively. Additionally, serotypes 6B and 18C in the PCV15 group showed significantly higher GMTRs when compared with the PCV13 group. No publication bias was found (Supplementary Figure 2).

Serotype-Specific Immunogenicity of PCV20 vs PCV13

Three studies were included to determine the immunogenicity of PCV20 as compared with PCV13. Although the GMTR for serotypes common to both vaccines showed a lower immune response in the PCV20 group among older adults at 1 month postvaccination, it still demonstrated noninferiority in immunogenicity when compared with PCV13 at the 0.5 threshold

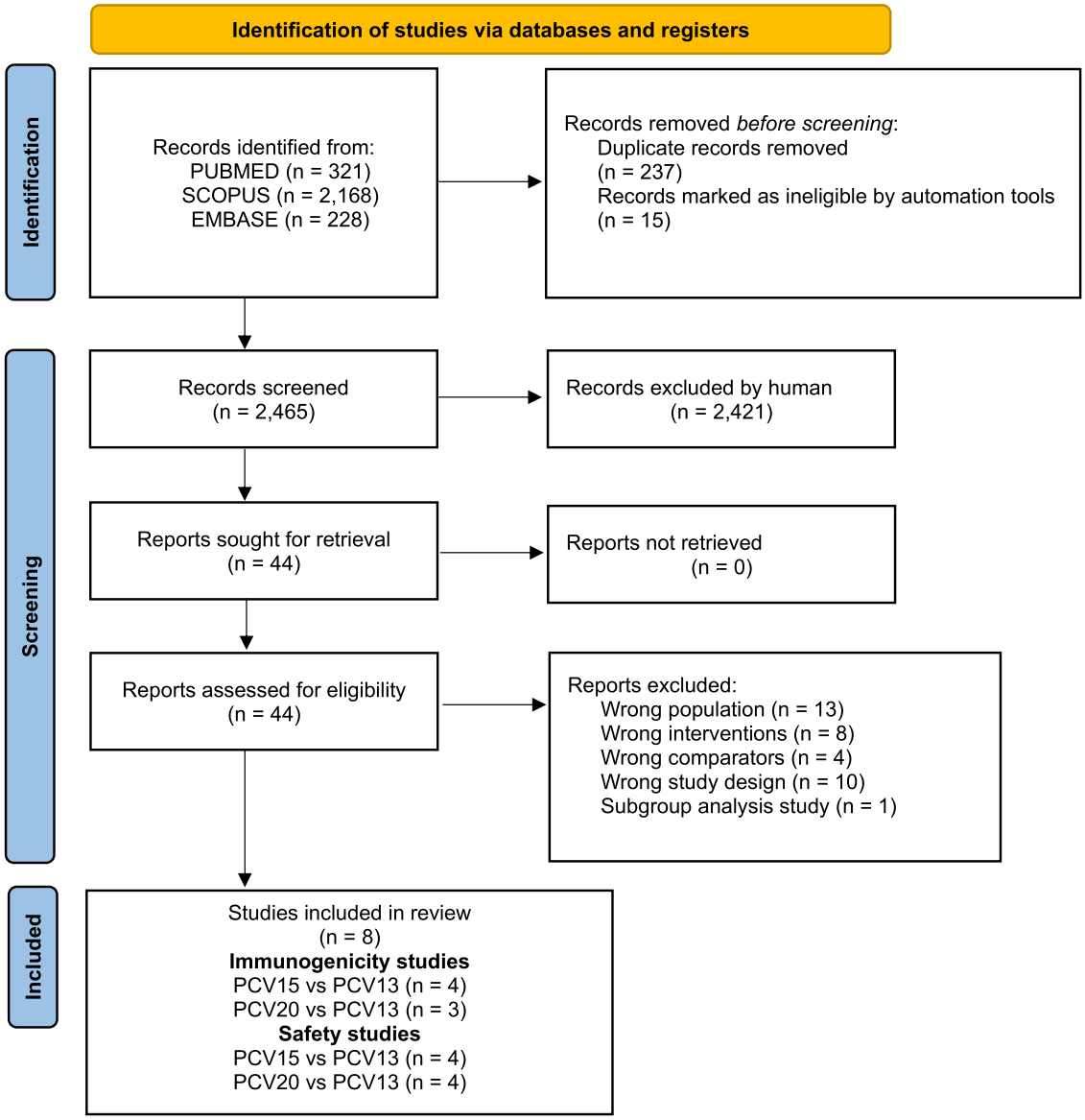

Figure 1. PRISMA 2020 [17] flow of screening studies. PCV, pneumococcal conjugate vaccine.

(GMTR, 0.84; 95% CI, .81–.87; Figure 3). The heterogeneity among the studies was low ($I^2 = 0\%$, $P = .891$). Almost all serotypes common to both vaccines exhibited a lower GMTR response in the PCV20 group vs the PCV13 group. No publication bias was found (Supplementary Figure 3).

Safety of PCV15 vs PCV13

The incidence of local and systemic reactions was higher in the PCV15 group when compared with the PCV13 group, with RRs of 1.23 (95% CI, 1.14–1.32) and 1.15 (95% CI, 1.02–1.29), respectively (Table 2). The PCV15 group showed an increased risk of mild to moderate redness or swelling, and injection site pain was significantly more common (RR, 1.26; 95% CI, 1.16–1.36), although there was no significant difference in severe pain. Systemic reactions, particularly mild to moderate and any degree of myalgia, were more prominent in the PCV15 group (RR >1). The types of adverse events demonstrated low heterogeneity among the studies ($I^2 < 25\%$). However, certain events, such as redness or erythema and fatigue, exhibited relatively high heterogeneity with I^2 values >50%. No publication bias was found (Supplementary Figures 4–10).

Safety of PCV20 vs PCV13

Four studies reported the safety of PCV20. The overall incidence of local reactions following PCV20 vaccination was slightly significantly higher as compared with PCV13, with an RR of 1.08 (95% CI, 1.03–1.13). However, the systemic

Table 1. Characteristics of the Included Studies

Intervention: Study	Countries	Vaccine Naive		Age Group, y	Preexisting Medical Conditions per Group, %		Death, No. (%)		Funding Source
		PCV13	PPSV23		PCV15 or PCV20	PCV13	PCV15 or PCV20	PCV13	
PCV15									
Ermlich [6]	Multination[a]	Yes	Yes	≥50	72/230 (31.3)	90/230 (39.1)	0	0	Merck & Co
Peterson [7]	USA	Yes	No	≥65	NA/127	NA/126	0	0	Merck & Co
Song [18]	Multination[b]	Yes	Yes	≥50	302/326 (92.6)	305/325 (93.8)	0	0	Merck Sharp & Dohme Corp, a subsidiary of Merck & Co, Inc
Platt [19]	Multination[c]	Yes	Yes	≥50	528/602 (87.7)	522/600 (87.0)	1 (0.2)	1 (0.2)	Merck Sharp & Dohme Corp, a subsidiary of Merck & Co, Inc
PCV20									
Cannon [10]	USA, Sweden	Yes	No[d]	≥65	NA/253	NA/122	0	0	Pfizer Inc
Hurley [14]	USA	Yes	Yes	60–64	NA/221	NA/222	0	0	Pfizer Inc
Essink [8]	USA, Sweden	Yes	Yes	≥60[e]; 50–59, ≥60[f]	NA/1514	NA/1495	1	0	Pfizer Inc
Haranaka [9]	Multination[g]	Yes	Yes	≥60	310/711 (43.6)	314/710 (44.2)	0	0	Pfizer Inc

Abbreviations: NA, not applicable; PCV, pneumococcal conjugate vaccine; PPSV23, the 23-valent pneumococcal polysaccharide vaccine.

[a]Canada, Denmark, Israel, Norway, Poland, Spain, Sweden, and United States.

[b]United States, Korea, Spain, and Taiwan.

[c]United States, Spain, Canada, Taiwan, and Japan.

[d]Only prior PPSV23 cohort.

[e]Immunogenicity data.

[f]Safety data.

[g]Japan, South Korea, and Taiwan.

reactions between the vaccines were similar, with an RR of 1.01 (95% CI, .96–1.06; Table 2). The heterogeneity among the studies for local and systemic reactions was low, with an I^2 <25%. The type of reaction that showed relatively high heterogeneity was swelling, with an I^2 of 37.12%. Publication bias was identified in studies reporting redness/erythema, as evidenced by an asymmetrical funnel plot and an Egger test P value of .003. No publication bias was detected in the remaining studies (Supplementary Figures 11–17).

DISCUSSION

This systematic review and meta-analysis assess the immunogenicity and safety of higher-valency pneumococcal vaccines (PCV15 and PCV20) as compared with PCV13 in older adults who are immunocompetent. The findings indicate that PCV15 demonstrates superior immunogenicity for 13 of its 15 included serotypes when compared with PCV13. Furthermore, PCV20 meets the noninferiority criterion with a GMTR of 0.5 at 1 month postvaccination. Regarding safety, PCV15 and PCV20 display similar safety profiles to PCV13, although PCV15 is associated with a slightly higher incidence of local and systemic reactions. These results support the immunogenicity and safety of PCV15 and PCV20 as substitutes to PCV13 for pneumococcal vaccination in older adults.

The introduction of PCV13 has significantly affected the incidence of IPD reduction caused by specific serotypes across various age groups by either direct or indirect effect of vaccine [20, 21]. However, it has failed to eliminate some serotype-specific IPD, such as serotype 3, 19A, or 19F [22], particularly in older adults. In addition, there was no overall decline in IPD due to an increase in nonvaccine serotypes. Although PCV15 and PCV13 use the CRM197 protein as a carrier to enhance immune response and contain no adjuvant, immunogenicity studies have documented a stronger immune response to serotype 3 with PCV15 than with PCV13. This improved response is attributed to differences in formulation and potentially the quantity or structural configuration of the serotype 3 antigen in PCV15 [23]. Additionally, our study observed differing immunogenicity results between older adults and children, with PCV15 showing lower immunogenicity in children as compared with PCV13 [15]. Yet, it remains uncertain whether a targeted formulation approach, as applied to serotype 3 in PCV15, could similarly enhance immunogenicity and vaccine efficacy for challenging serotypes such as 19A and 19F [23].

According to a study by Prasad et al, replacing PCV13 with PCV15 in the routine infant immunization program in the United States is projected to prevent 92 290 additional pneumococcal disease events and 22 associated deaths among children [24], as well as expected indirect effects for adults. PCV15 demonstrated a stronger immune response than PCV20 in older adults, likely due to its specific formulation and conjugation methods that enhance immunogenicity, particularly for serotype 3 [25]. Despite higher antibody levels as

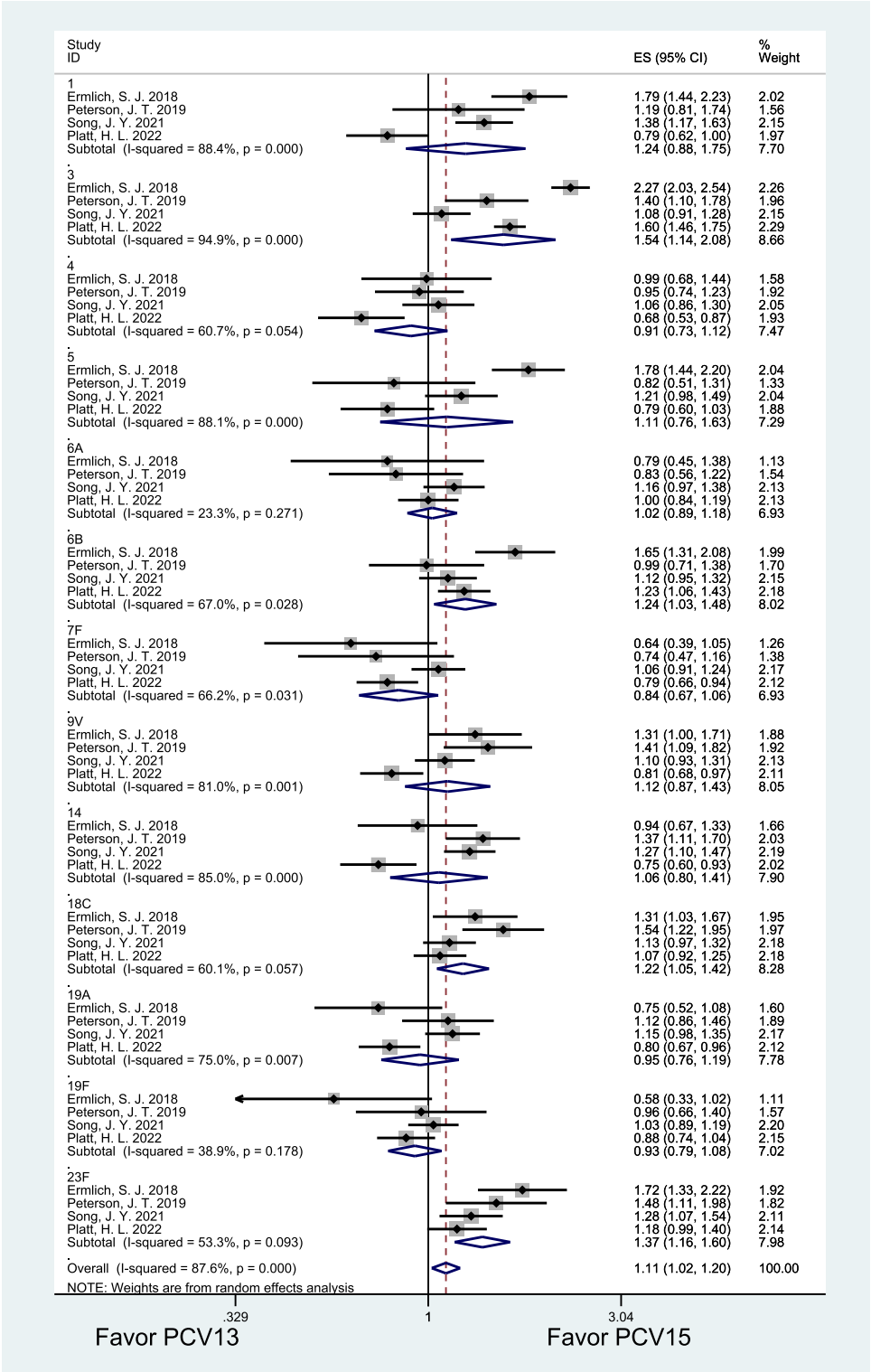

Figure 2. The pooled serotype-specific immunogenicity (geometric mean titer ratio) of PCV15 vs PCV13 via a random effects model. PCV, pneumococcal conjugate vaccine.

compared with PCV13, the clinical effectiveness of these antibodies remains uncertain. Historically, serotype 3 has shown lower vaccine effectiveness in clinical settings. For example, a systematic review by McLaughlin et al reported moderate protection from PCV13 against serotype 3 community-acquired pneumonia in adults aged ≥65 years, with a vaccine

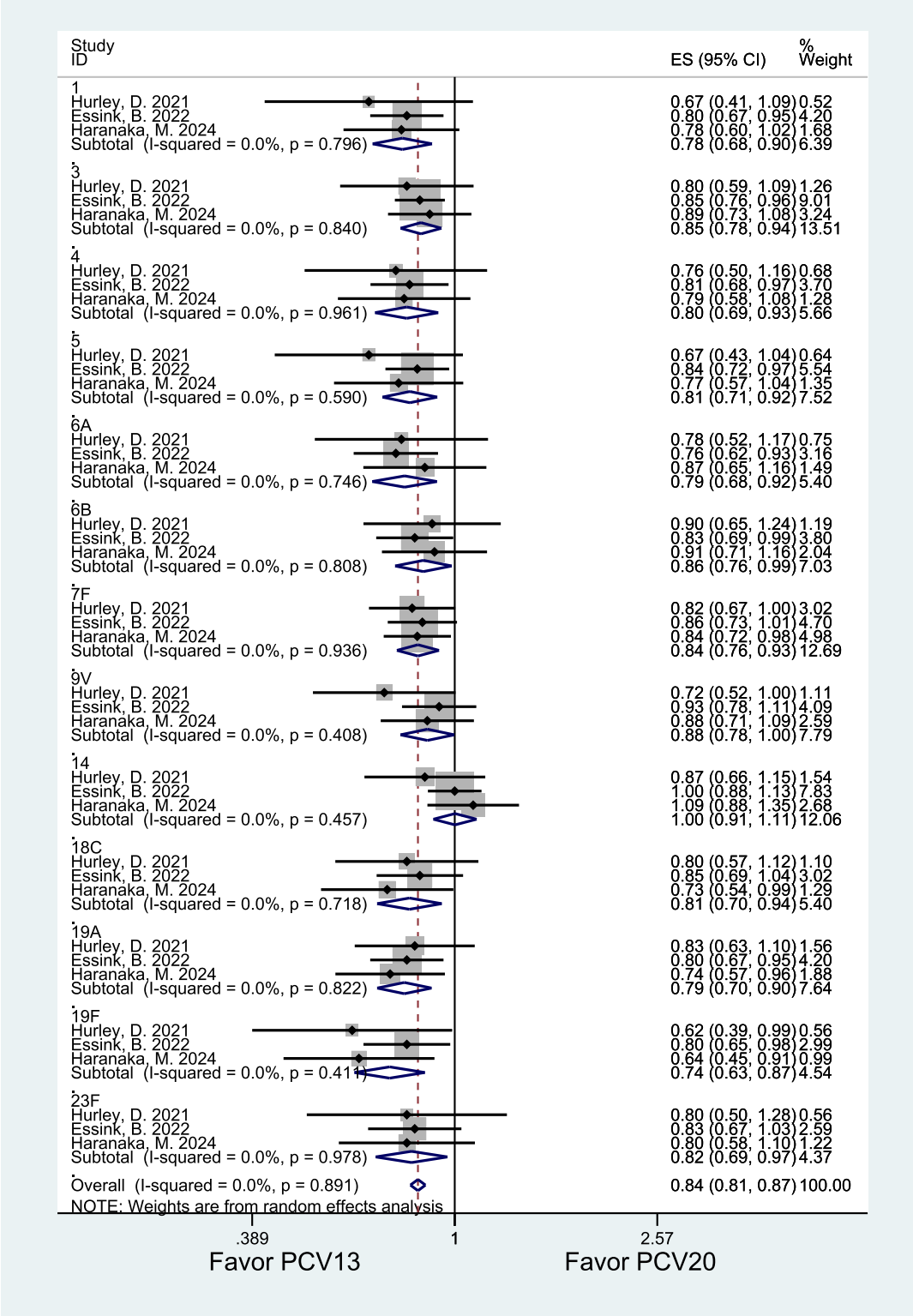

Figure 3. The pooled serotype-specific immunogenicity (geometric mean titer ratio) of PCV20 vs PCV13 via a random effects model. PCV, pneumococcal conjugate vaccine.

effectiveness of 52.5% [26]. Continued surveillance and real-world studies are needed to assess PCV15's clinical impact on serotype 3 and other serotypes.

Although PCV20 demonstrated a lower immune response than PCV13 across the shared serotypes, it achieved noninferiority in immunogenicity for these 13 serotypes. Additionally,

Table 2. Overall Pooled Local Reactions and Systemic Events Reported up to Day 14 After Vaccination

	PCV15 vs PCV13			PCV20 vs PCV13		
Adverse Event	RR (95% CI)	*P* Value	I^2, %	RR (95% CI)	*P* Value	I^2, %
Local reactions						
Any local reactions	1.23 (1.14–1.32)	<.001	2.70	1.08 (1.03–1.13)	<.001	0.01
Redness/erythema				1.31 (1.10–1.57)	<.001	5.52
Any	1.12 (.78–1.61)	.55	52.32			
Mild	1.05 (.66–1.66)	.83	50.44			
Moderate	1.39 (.62–3.13)	.42	50.74			
Severe	1.00 (.06–15.96)	>.99	…			
Swelling				1.15 (.90–1.47)	.26	37.12
Any	1.26 (1.03–1.53)	.02	…			
Mild	1.20 (.95–1.53)	.13	…			
Moderate	1.06 (.67–1.69)	.81	…			
Severe	1.50 (.42–5.28)	.53	…			
Pain				1.06 (1.01–1.11)	.03	0.00
Any	1.26 (1.16–1.36)	<.001	0.00			
Mild	1.20 (1.09–1.32)	<.001	0.00			
Moderate	1.73 (1.29–2.32)	<.001	0.00			
Severe	0.73 (.24–2.20)	.58	6.87			
Systemic reactions						
Any systemic reactions	1.15 (1.02–1.29)	.02	27.90	1.01 (.96–1.06)	.76	5.85
Arthralgia				0.91 (.79–1.05)	.20	0.00
Any	1.12 (.85–1.47)	.41	2.60			
Mild	1.13 (.79–1.60)	.51	18.16			
Moderate	1.33 (.76–2.33)	.32	0.00			
Severe	1.25 (.34–4.63)	.74	0.00			
Fatigue				1.01 (.93–1.10)	.78	2.49
Any	1.14 (.97–1.34)	.11	58.98			
Mild	1.15 (.93–1.41)	.19	42.70			
Moderate	1.25 (.87–1.79)	.22	0.00			
Severe	0.86 (.29–2.54)	.78	0.35			
Myalgia				1.07 (.99–1.15)	.07	0.00
Any	1.38 (1.15–1.65)	<.001	0.00			
Mild	1.36 (1.10–1.69)	.01	0.00			
Moderate	1.76 (1.10–2.83)	.02	0.00			
Severe	0.47 (.16–1.44)	.19	0.00			
Headache				0.94 (.85–1.05)	.27	0.00
Any	0.95 (.78–1.15)	.58	0.00			
Mild	0.96 (.75–1.24)	.76	0.00			
Moderate	1.00 (.66–1.49)	.99	0.00			
Severe	0.66 (.19–2.35)	.53	0.00			

Abbreviations: PCV, pneumococcal conjugate vaccine; RR, risk ratio.

PCV20 offers broader protection by covering 7 more serotypes. Its introduction to pediatric populations is projected to prevent >55 000 IPD cases in the United States [27], >11 000 IPD cases in Canada [28], and 15 301 IPD cases in Germany over a 10-year period [29], demonstrating its significant potential in reducing the burden of pneumococcal diseases in adults and children. However, direct comparisons between PCV15 and PCV20 are lacking, emphasizing the need for ongoing surveillance of pneumococcal epidemiology to inform future vaccination strategies. Additionally, the development of new pneumococcal vaccines that include serotypes more reflective of the current epidemiology of IPD in adults is necessary. This effort should be supported by robust IPD surveillance across high-income countries and low- and middle-income countries to ensure global relevance [30].

Local and systemic reactions following 1 month of PCV15 vaccination were significantly more frequent when compared with PCV13, likely due to the heightened immunogenic response. Health care providers should inform patients of these potential side effects prior to vaccination. Importantly, in real-world settings, no serious adverse events or deaths related to PCV15 were reported. However, postlicensure safety data for PCV15 remain limited. Similarly, data analysis for PCV20

did not identify any new or unexpected adverse events following its administration [1].

This meta-analysis has several limitations. First, all studies were industry funded, which introduces potential bias. Nevertheless, these studies demonstrated strong methodological rigor and well-conducted designs. Second, a direct head-to-head comparison between PCV15 and PCV20 was not feasible. Future research should consider using indirect comparison methods, such as network meta-analysis. Third, all studies were conducted in high-income countries, limiting the generalizability of the findings to low- and middle-income countries. Finally, some heterogeneity was observed due to variations in the background characteristics of the studies. To address this, random effects modeling was applied when pooling the outcomes to control for potential biases.

In conclusion, these results support the immunogenicity and safety of PCV15 and PCV20 as substitutes to PCV13 for pneumococcal vaccination in older adults. In light of the better immune response, PCV15 will fill the gaps left behind by PCV13. Despite higher antibody levels as compared with PCV13, the clinical effectiveness remains uncertain. Continued surveillance and real-world studies are needed to assess both vaccines' clinical impact on remaining vaccine-type pneumococcal disease.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. Conceptualization: T. N., N. R. Data curation: T. N., N. R., R. K. Formal analysis: T. N., N. R. Funding acquisition: T. N. Methodology: T. N., N. R. Resources: T. N., N. R., R. K. Validation: T. N., N. R., R. K. Visualization: T. N., N. R. Writing–original draft preparation: T. N., N. R. Writing–review and editing: T. N., N. R., R. K.

Data availability. Data can be made available upon reasonable request to thundon.ngm@mahidol.ac.th.

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Potential conflicts of interest. All authors: No reported conflicts.

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