How effective is

13-Valent Pneumococcal Conjugate Vaccine (PCV13) Combined With 23-Valent Pneumococcal Polysaccharide Vaccine(PPSV23)?

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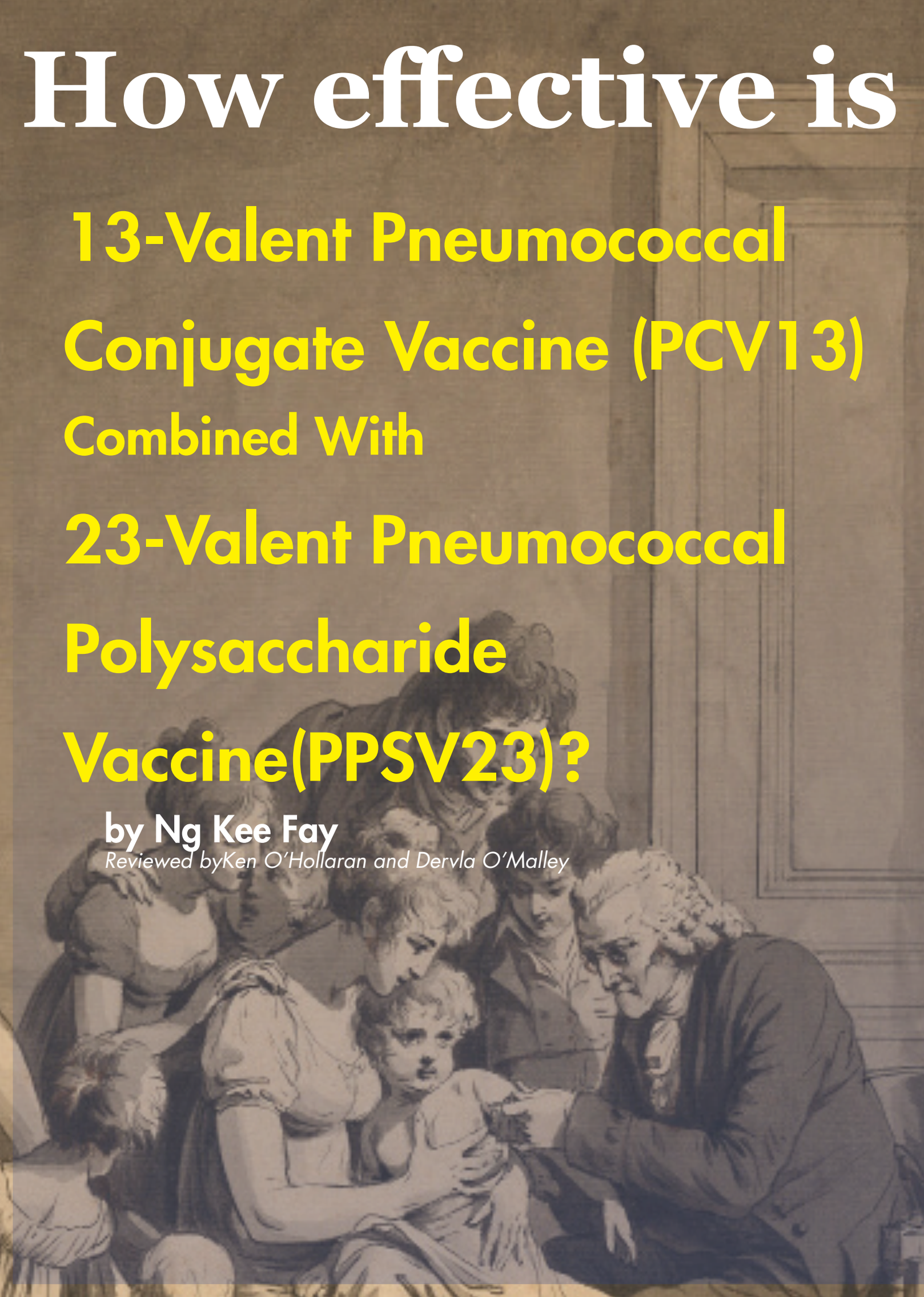

Abstract

The bacterium Streptococcus pneumoniae remains a major cause of morbidity and mortality worldwide. Currently, the 2 leading vaccines targeted against it are: 23-valent pneumococcal polysaccharide vaccine (PPSV23) and 13-valent pneumococcal conjugate vaccine (PCV13). It was only very recently, starting 22 November 2019, that the Advisory Committee on Immunisation Practices (ACIP) no longer recommends routine administration of PCV13 for all adults aged 65 and above. As such, this systematic review aims toinvestigate how the use of PCV13 combined with PPSV23 compares to using PPSV23 alone in older adults.

Relevant research papers were chosen through an electronic search in PubMed. A set of selection criteria was then applied to ensure that the papers aligned with the objectives of this paper.

The majority of the studies included in this paper demonstrated that in adults aged 50 years and above, PCV13 had the ability to generate a strong immune response in adults, even more so than PPSV23 for all of the twelve serotypes common to both vaccines. The safety of PCV13 was also demonstrated in thestudies as no PCV13-related serious adverse events (SAEs) had surfaced. Only one study included in this systematic review opposed the trend.

While the evidence for both PCV13's and PPSV23's ability to generate an immune response have been persuasive, more research that focuses on the clinical endpoint in older adults, as well as the incidence of pneumococcal infections in the population, could be done to fully address the main question of this paper.

Introduction

Pneumococcal vaccinations: An overview

With the bacterium Streptococcus pneumoniae being the most identified pathogen in communityacquired pneumonia, meningitis, as well as human immunodeficiency virus (HIV-1) seropositive individuals [1], pneumococcal vaccination is undoubtedly an important preventive health care measure worldwide. Currently, there exist two vaccines widely available for clinical use: 23-valent pneumococcal polysaccharide vaccine (PPSV23) and 13-valent pneumococcal conjugate vaccine (PCV13). Streptococcus pneumoniae is contained within a polysaccharide capsule and has over 90 distinct capsular serotypes. PPSV23 contains antigens from 23 common serotypes while PCV13 contains antigens from 13 serotypes [2]. There is substantial overlap in theantigens contained within both
vaccines, with 12 of the 13 serotypes found in PCV13 being common to those within PPSV23 (Table1).

A major difference between both vaccines lies in their mechanisms of action. As PPSV23 contains

Table 1: Capsular serotypes found in both PCV13 and PPSV23

Vaccine	Serotypes included
PCV13	1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19F, 19A, 23F
PPSV23	1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, 33F

purified polysaccharide capsules, it elicits a T-cell independent immune antibody response whichn enhances the activity of phagocytic cells, thereby inducing the killing of Streptococcus pneumoniae. On the other hand, PCV13, being a conjugate vaccine, which combines polysaccharide capsules with carrier proteins, produces a T-cell dependent immune response and hence, a greater potential for immunological memory [3].

In general, routine administration of PCV13 is recommended for all children younger than 2 years of age while routine administration of PPSV23 is recommended for all adults aged 65 and above. 7 The latter is also recommended for people over 2 years of age with certain medical conditions defined as 'at-risk', as per the guidelines of both the Centers for Disease Control and Prevention (CDC) [4]
and the Health Service Executive (HSE) [5].

Use of PCV13 with PPSV23 for older adults

However, the routine uses of PCV13, in combination with PPSV23, for older adults is much less straightforward and has been subject to numerous discussions. In fact, it was only very recently, starting 22 November 2019, that the Advisory Committee on Immunization Practices (ACIP) no longe recommends routine administration of PCV13 for all adults aged 65 and above [6]. Instead, cliniciansare to engage in a discussion regarding PCV13 use with adult patients aged 65 and above who do not have an immune-compromising condition, cerebrospinal fluid (CSF) leak or cochlear implant. Considerations mayinclude the individual patient's risk of exposure to PCV13 serotypes as well as his or her underlying medical conditions [4].

Efficacy of PCV13 for older adults

To complicate matters further, the effectiveness of PCV13 in preventing pneumococcal disease for older adults and above has been challenged. An article has stated that the use ofPCV13 is on a 'much less well-established scientific basis' [7] and another asserted that PCV13 efficacy is not statistically significant [8]. Evidently, there exist many grey areas in the use of PCV13 to be explored.

Objectives

This paper aims to collate and synthesise literature which investigated:

1. The effects of administering both PCV13 and PPSV23 in comparison to administering PPSV23 alone on older adults
2. The safety and efficacy of PCV13 for older adults

Methods

Overview

Appropriate search terms were chosen (Refer to section 3.2) before a list of inclusion/exclusion criteria was defined (Refer to section 3.3). Subsequently, a systematic search strategy was carried out in PubMed. An overview of the methods used

in selecting studies for this paper is illustrated (Figure 1).

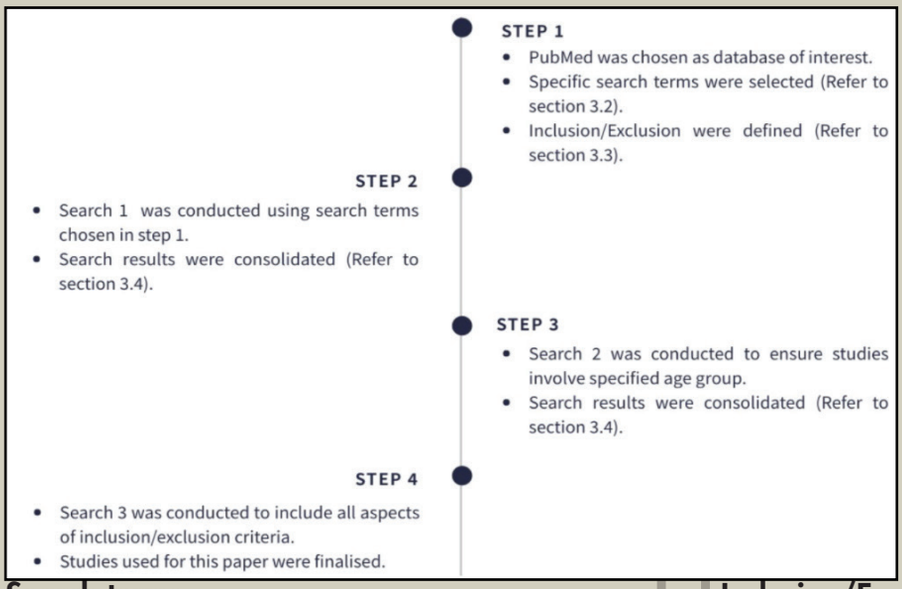

Figure 1:
Overview of methods

Search terms

The following Medical Search Headings (MeSH) search terms were utilised in PubMed:

1. (("23-valent pneumococcal capsular polysaccharide vaccine" [MeSH])
2. "13-valent pneumococcal vaccine" [MeSH])

A Boolean search using 'AND' and 'OR' was conducted.

Inclusion/Exclusion criteria

Subsequently, a set of inclusion/exclusion criteria was designed to further refine and streamline the search process (Table 2).

Details of search strategy

A 3-step approach was taken in selecting the studies from PubMed. The details of each step are described below (Table 3).

Results

Overall evaluation of studies

The final 10 studies selected were then subject to critical appraisal using the Critical Appraisal Skills Programme (CASP) framework. Evaluations of each study are found in Table 4 in the appendix.

Table 2:
Inclusion and exclusion criteria

	Inclusion	Exclusion
Date	Articles published from January 2013 to present	Articles published prior to January 2013
Language	English	Languages other than English
Population of interest	Adults aged 50 and above	Studies that did not include participants aged 50 and above Animal studies
Intervention of interest	Administration of PCV13 Administration of PPSV23	Studies which involved administration of other types of vaccines (e.g., flu vaccine)
Study type	Randomised controlled trials (RCTs) Cohort studies	Cross-sectional studies Case-control studies Opinion pieces Meta-analyses Systematic reviews
Publication	Free full text and abstract availability	Free full text and abstract unavailable
Outcome of interest	Efficacy of vaccines on older adults	Any other outcomes irrelevant to study

	Search terms/Scope of search	Objective of search	Results from PubMed
Search 1	Refer to section 3.2	To gather all relevant studies	56
Search 2	Search 1 AND population of interest	To ensure that the studies selected only involve population of interest	17
Search 3	Search 1 AND 2 with application of inclusion/ exclusion criteria	To ensure that all the studies chosen are fully relevant to the objectives of this paper	10

Table 3: Details of search strategy

Comparison between PCV13 and PPSV23

Schmoele-Thoma et al. found that in the PPSV23/ PCV13 group (PPSV23-pre immunized adults who received subsequent PCV13), the opsonophagocytic activity (OPA) geometric mean fold-rise (GMFR) was >1 for most serotypes. Additionally, OPA geometric mean titers (GMTs) were numerically higher for 12 out of 13 serotypes after a second PCV13 vaccination than after the first dose of PCV13. In addition, among the PPSV23-naive subjects, the highest GMFRs were found in the PCV13/PPSV23 group (along with the PCV13/PCV13 group) for all serotypes other than serotype 5 [9].

In the Jackson et al. study, OPA GMT ratios comparing the PCV13/PPSV23 and PPSV23 groups were >1 for all 13 serotypes [10].

In the study conducted by Jackson et al., for the 60-64 years age group, PCV13 OPA GMTs were noninferior to PPSV23 for all 12 common serotypes and statistically significantly greater in 8 11 serotypes. Additionally, OPA GMTs in 50–59-year-olds were noninferior to 60–64-year-olds for all 13 serotypes, and were statistically significantly greater in 9 serotypes [12].

Shiramoto et al.'s study found that GMFRs post-vaccination were higher for PCV13 recipients than in PPSV23 recipients for all serotypes except serotype 3 [16].

Efficacy of PCV13

In the Schmoele-Thoma study, among PPSV23-naive subjects, the highest GMFRs were found in the PCV13/PCV13 group alongside the PCV13/PPSV23 group for all serotypes except serotype 5 [9].

The Jackson et al. study indicated that OPA GMTs following administration of a 2nd dose of PCV13 (PCV13/PCV13) were statistically significantly greater than 1 dose of PCV13. However, 3 serotypes yielded inferior responsesin the 50-59-years age group (GMT ratios <1). Additionally,the Jackson et al. study noted that OPA GMTs following a second dose of PCV13 (PCV13/PCV13)were numerically greater than following a second dose of PPSV23 (PPSV23/PPSV23) [10].

The Vila-Corcoles et al. study stated that unadjusted incidence rates (per 100,000 person-years) for pneumococcal pneumonia were higher in PCV13-vaccinated than unvaccinated populations(289.3 and 82.1, respectively). The trend persists in all-cause pneumonia and all-cause death. Even following multivariable adjustments, PCV13 was not found to be effective [11].

Solanki et al. found that the GMFRs before and approximately 1 month after PCV13 administration in the participants ranged from 6.6 to 102.7. No statistically significant differences in immune responses were observed between the 50-59-years and 60-64-years age groups [13].

OPA GMFRs in the Tinoco et al. study showed a significant increase in OPA GMTs from immediately before to 1 month after PCV13 vaccination. OPA GMFRs were higher in the 50-64-year age

group (ranges from 5.3 to 63.6) than the ≥65-year age group (ranges from 3.4 to 35.8) [14].
12 In the CAPiTA trial conducted by van Deursen et al., OPA GMTs in PCV13 recipients increased at 1-month post vaccination and decreased at 12- and 24-months post-vaccination but remained above baseline for all serotypes (GMFRs remained >1). The IgG geometric mean antibody concentrations (GMCs) showed a similar trend. In addition, OPA GMFRs and IgG GMCs in PCV13 recipients aged ≥80 years were generally lower than in younger recipients [15]. In Bonten et al.'s per-protocol analysis, vaccine efficacy for community-acquired pneumonia (CAP), non-bacteremic and non-invasive CAP as well as invasive pneumococcal disease (IPD) were 45.6%, 45.0% and 75.0%, respectively. Similar efficacy for all3 end points was observed in the modified intention-to-treat analysis (37.7%, 41.1% and 75.8%), but not for CAP from any cause (vaccine efficacy: 5.1%) [18].

Safety of PCV13

After multivariable adjustments, Vila-Corcoles et al. stated that PCV13 was found to not cause significant alterations in the risks of pneumococcal pneumonia (multivariable Hazard Ratio [mHR]: 1.17) or all-cause death (mHR: 1.07), though its association with increased risk of all-cause pneumonia remained significant (mHR: 1.69) [11]. In the studies conducted by Jackson et al. [12], Solanki et al. [13], Tinoco et al. [14], Bonten et al. [18] and Shiramoto et al. [16], no vaccine related SAEs or deaths were reported.

Efficacy of PPSV23

Jackson et al. discovered that OPA GMTs following revaccination of PPSV23 were statistically significantly lower for 9 serotypes when compared to those following initial administration of PPSV23, with a GMT ratio of less than <1 for all 9 serotypes. OPA GMTs were non-inferior for 4 serotypes [10]. The study conducted by Shiramoto et al. showed that OPA GMTs 1-month post-vaccination increased significantly in PPSV23 recipients, with GMFRs ranging from 8.2 to 65.4 for all 12 serotypes found in common with PCV13 [16].
13 Following multivariable adjustments by Ochoa-Gondar et al., they reported that recent vaccination with PPSV23 (<5 years ago) was associated with decreased risk of bacteremic pneumococcal CAP(HR:0.38), non-bacteremic pneumococcal CAP (HR: 0.52) and all-cause CAP (HR: 0.75) [17].

Discussion

Overall choice of studies

Of the 10 studies, 8 are RCTs while 2 are prospective cohort studies. The former is regarded as themost reliable form ofscientific evidence in the hierarchy of evidence [19]. The latter is considered to provide stronger evidence than other observational studies as exposure is identified before outcome [20]. Sample sizes were generally large, ranging from 322 to 2,025,732, which aided in providing more credible results with greater precision. It is worth noting that Tinoco et al. [14], whose study had the smallest sample size, utilised statistical methods to ensure that the sample size was sufficient in providing adequate precision in the results.

Use of both PCV13 and PPSV23 vaccines in older adults

There is consensus among the studies that PCV13 was able to elicit robust immune responses in-adults aged 50 years and above. While most of the studies utilised OPA GMTs as evidence, Bontenet al.'s [18] use of the incidences of diseases was able to prove the same point. Although theefficacy of PPSV23 has also been demonstrated in the studies conducted by Jackson et al. [10],Shiramoto et al. [16] and Ochoa-Gondar et al. [17], all studies that compared immune responsesbetween PCV13 and PPSV23 have shown that PCV13 was able to produce greater immuneresponses for all 12 serotypes common to both vaccines (Refer to section 4.2). However, there are slight disagreements among studies which compared post vaccination immune responses between different age groups. While the Jackson et al [12] and van Deursen et al. [15] studies found that older age groups (60-64 years age group and ≥ 80 years age group, respectively)have decreased immune responses following PCV13 vaccination, the Tinoco et al. [14] and Solanki et al. [13] studies found no significant differences between the immune responses across age
14 groups. Interestingly, all four studies share a common limitation of being done in a single country, which could possibly explain the differences in their findings. Nevertheless, immune

responses remained greater than pre-vaccination levels across all studies, which once again proved PCV13's ability to generate an immune response in adults aged 50 and above. Four studies also found that PCV13 was generally safe and well-tolerated in adults aged 50 years and above, as no PCV13-related SAEs or deaths were reported.
The only study that refutes the consensus, both in terms of the efficacy and safety profile of PCV13, is the cohort study conducted by Vila-Corcoles et al. [11]. Its major limitations lie in its nonrandomised, observational nature and that it was made in a single geographical region, Catalonia. Logically, PCV13 efficacy varies across different geographical settings and depends on multiple factors such as PPSV23 coverage as well as susceptibility for pneumococcal infections among the population. However, it is noteworthy that the authorsacknowledged the inherent limitations of this study and adjusted accordingly, such as performingmultivariable analysis, and the study provided valuable data from a clinical and public health point of view.
Considering all of the evidence, this review concludes that the use of PCV13 with PPSV23 would be able to provide a greater immune response (measured by OPA GMTs and GMFRs as well as IgG GMCs) when compared to receiving PPSV23 alone for older patients aged 50 and above.However, to answer the question of whether the former is truly superior to the latter, more studies would need to be reviewed.

Limitations

A limitation of this literature review arises from the limited number of studies chosen for this review. Most studies focused on the immune response in terms of OPA GMTs following the use of PPSV23 and PCV13 rather than the efficacy of both vaccines on clinical endpoints.
Additionally, it would have been useful to study the impact of introducing PCV13 to the paediatric population on the incidence of pneumococcal strains in the population. Examining these topics [15] could possibly help navigate questions surrounding the necessity of PCV13 in older populations, hence allowing the main clinical question of this paper to be better understood with greater breadth and depth.

Future research

While reviewing the selected studies, other exploratory areas such as the impact of age on the immune responses elicited in vaccinated patients as well as the duration of protection conferred byboth vaccines emerged. Hence, RCTs focusing on these specific areas are highly desirable. In addition, more data regarding the sequential use of both vaccines would be beneficial.

Conclusion

In conclusion, evidence hasshown that each vaccine can generate immune responses on their own. While PPSV23 covers a greater number of serotypes, PCV13 seems to produce a greater immuneresponse for the 12 serotypes common to both vaccines. The combination of both PPSV23 and PCV13 should provide a greater immune response than just receiving PPSV23 alone in adults aged 50 and above. However, as for determining whether the use of PCV13 alongside PPSV23 is indeed necessary and superior to just using PPSV23, there is still room for research asthe choice is a multifaceted one in which other aspects such as the impact of both vaccines on age as well as various clinical endpoints should be considered.[16]

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