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Review

Pneumococcal conjugate vaccine against serotype 3 pneumococcal pneumonia in adults: A systematic review and pooled analysis

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ABSTRACT

Background: Serotype 3 pneumococcal disease has not substantially declined at the population level after the routine introduction of 13-valent pneumococcal conjugate vaccine (PCV13) into pediatric immunization programs across the globe. This epidemiological finding has generated debate regarding the effectiveness of PCV13 against serotype 3 disease. Evaluating PCV13 effectiveness against serotype 3 is especially critical in adults, where serotype 3 makes up an important amount of remaining pneumococcal disease.
Methods: We performed a systematic review of the published literature to assess the direct effectiveness of PCV13 against serotype 3 community-acquired pneumonia (CAP) among adults. We then estimated overall vaccine effectiveness (VE) using a pooled analysis of the individual-level, raw data.
Results: Two published studies met inclusion criteria. One was a randomized controlled trial conducted in the Netherlands and published in 2014. The other was a recently-published case-control study conducted in Louisville, Kentucky that used a test-negative design (TND). We also identified a third TND study conducted in Argentina that was recently presented as a conference abstract but is not yet published. All three studies were conducted in adults aged ≥65 years. PCV13 VE against serotype 3 hospitalized CAP was 52.5% (95%CI: 6.2–75.9%) from the pooled analysis of individual-level data from all three studies. Results were similar if the unpublished estimate was excluded (serotype 3 VE = 53.6% [95%CI: 6.7–76.9%]). No heterogeneity was observed.
Conclusions: Currently-available evidence, although limited to three studies, suggests that PCV13 provides direct protection against serotype 3 hospitalized CAP in adults aged ≥65 years.

Contents

Abbreviations: CAP, community-acquired pneumonia; CAPiTA, Community-acquired Pneumonia Immunization Trial in Adults; CDC, Centers for Disease Control and Prevention; CI, confidence interval; ECDC, European Centers for Disease Control; IPD, invasive pneumococcal disease; MeSH, Medical Subject Headings; mITT, modified intent-to-treat; PCV, pneumococcal conjugate vaccine; PCV10, 10-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; RCT, randomized controlled trial; TND, test-negative design; VE, vaccine efficacy or effectiveness.

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1. Introduction

Use of pneumococcal conjugate vaccine (PCV) in infants and toddlers has led to remarkable declines in vaccine-type childhood pneumococcal disease [1–13]. Soon after PCV introduction in children, reductions in pneumococcal disease in unvaccinated older children and adults were also documented [1,3,5,14]. This added benefit was the result of interrupting transmission in children, the primary reservoir for pneumococcal infection, thereby reducing PCV-type circulation among all age groups (i.e., indirect effects).

Unlike most serotypes contained in 13-valent PCV (PCV13), serotype 3 pneumococcal disease has not substantially declined at the overall population level after the introduction of PCV13 into routine pediatric immunization programs across the globe [15–17]. PCV13 is less immunogenic for serotype 3 compared to other vaccine serotypes [18,19] and serotype 3 may have a higher correlate of protection [20]. As a result, there is some debate regarding the effectiveness of PCV13 against serotype 3 disease.

In contrast to the relatively flat rates of serotype 3 disease observed in countries following routine pediatric PCV13 use—which have been interpreted as limited evidence of impact against serotype 3 disease [15–17], marked increases in serotype 3 disease, particularly in adults, have been observed in countries that have introduced 10-valent PCV (PCV10) [15]. PCV10 does not include serotype 3 in its formulation and thus cannot directly protect against serotype 3 disease or carriage acquisition. This contrast in surveillance data between countries that use PCV13 and those that use PCV10 [15] suggests that PCV13 provides a certain level of protection against serotype 3 disease.

The notion that PCV13 provides direct protection against serotype 3 disease in vaccinated persons is further supported by a recent systematic review and meta-analysis that documented direct, individual-level PCV13 effectiveness against serotype 3 invasive pneumococcal disease (IPD) in children [21]. The review, which included data from the US Centers for Disease Control and Prevention (CDC) and European CDC (ECDC), evaluated all published estimates of PCV13 effectiveness against serotype 3 IPD in children from observational studies across the globe, and reported a pooled serotype 3 vaccine effectiveness estimate of 64% (95% confidence interval [CI]: 37–90%) [21].

A similar comprehensive review of PCV13 effectiveness against serotype 3 pneumococcal disease in adults is not currently available. Evaluating PCV13 effectiveness against serotype 3 is especially critical in adults, where serotype 3 makes up an important amount of remaining pneumococcal disease, the majority of which is community-acquired pneumonia (CAP). We therefore performed a systematic review of the published literature to assess the direct effectiveness of PCV13 against serotype 3 CAP among adults. We then estimated overall PCV13 effectiveness against serotype 3 CAP using a pooled analysis of the individual-level, raw data from the studies identified in the systematic review.

2. Methods

2.1. Search strategy

We identified all published data available in PubMed (inclusive of MEDLINE) describing the vaccine efficacy or effectiveness (VE) of PCV13 against CAP in adults. PCV13 was licensed for adults in 2012 based, initially, on immunogenicity data, with no efficacy or effectiveness data available at the time of licensure. Thus, only studies occurring after January 1, 2012 were evaluated. Additionally, only studies published in English and conducted in human subjects were considered. Specific search terms and choice of databases were developed with the advice of a professional librarian. To be identified in the search, each article had to include a minimum of one "efficacy or effectiveness term," one "PCV13-related term," and one "adult term" in any searchable field of the publication, including Medical Subject Headings (MeSH). The search-term algorithm is listed in Table 1. We included all articles that evaluated efficacy or effectiveness of PCV13 against CAP in adults. Articles had to provide serotype 3-specific VE estimates or provide serotype-specific data that allowed for the calculation of VE against serotype 3 CAP.

2.2. Data abstraction

Two independent reviewers with expertise in pneumonia and epidemiology screened the titles and abstracts of all references identified by the search strategy to create a master list of potentially relevant references for full-text review. Abstracts for all references flagged for inclusion were reviewed to determine if the full report was eligible to be included in the analysis. All citations were independently abstracted by the two reviewers for quality control. We defined *study families* as two or more articles generated from a single protocol, population, or surveillance or data-collection system. For each study family, we identified a single primary study or main publication. All abstractions were then adjudicated to create an analyzable dataset.

2.3. Pooled analysis of individual-level data

After performing the systematic literature review, it was apparent that we had access to the individual-level, raw data for all published studies that met our selection criteria. In addition, we were

Table 1
PubMed (inclusive of MEDLINE) search algorithm for identifying articles related to PCV13 efficacy or effectiveness in adults.

Search Term Group	Algorithm
Efficacy- or Effectiveness-related Term	effectiveness[All Fields] OR efficacy[All Fields] OR effective[All Fields] OR efficacious[All Fields]
	AND
PCV13-related Term	PCV13[All Fields] OR 13-valent[All Fields] OR ("pneumococcal"[All Fields] AND "vaccines"[All Fields]) OR ("pneumococcal"[All Fields] AND "vaccine"[All Fields]) OR ("pneumococcal"[All Fields] AND conjugate[All Fields])
	AND
Adult-related Term	"adult"[All Fields] OR "adults"[All Fields] AND
Time Period After January 1, 2012*	"2012/01/01"[PDAT]: "3000/12/31"[PDAT]
	AND
English Language Requirement	English[lang]

PCV13 = 13-valent pneumococcal conjugate vaccine.
* PCV13 was licensed for adults in 2012 based on immunogenicity data (i.e., no efficacy/effectiveness data available at time of licensure), thus only studies occurring after January 1, 2012 were evaluated.

also aware of an unpublished study that evaluated PCV13 VE against vaccine-type CAP for which we also had access to individual-level data. Although unpublished, this study was recently presented as a conference abstract.

To pool individual-level data from multiple studies, we converted the original analysis population from the randomized controlled trial (RCT) we identified to match the test-negative design (TND) case-control populations of the other observational studies that were identified. Specifically, we structured the data from the RCT to reflect a test-negative study design by including only episodes of CAP from the RCT in the pooled analysis. A theoretical basis for this exists, given that previous research has shown that VE estimates from a RCT analyzed as a TND yield similar results to the original RCT analysis [22].

For the pooled analysis, we estimated a common odds ratio and corresponding 95%CI using the Mantel-Haenszel method (weighted by the sample size of each study). Consistent with a TND, this odds ratio was calculated by comparing the odds of PCV13 vaccination between serotype 3 CAP cases and non-PCV13-type CAP (i.e., test-negative) controls. As sensitivity analyses, we also estimated a common odds ratio using (i) the inverse variance weighted method and (ii) a logistic regression model where study was included in the model as a nuisance parameter. In the sensitivity analysis that used a logistic regression model, the following variables (which were available for all three studies) were assessed for any residual confounding effects: season, age, sex, risk level, and previous influenza vaccination. VE was calculated as 1 minus the odds ratio in all analyses.

3. Results

3.1. Studies identified

Our initial literature search criteria yielded 375 studies as of October 1, 2018 that were potentially relevant. After screening of titles and abstracts and removal of duplicates, nine articles were reviewed [23–31]. Of these, two [23,30] met inclusion criteria: one was a RCT published in 2014 [23] and the other a case-control study that used a TND published in 2018 [30]. In both studies, routine culture and a serotype-specific urinary antigen detection (UAD) assay (Pfizer, Inc) [32] were used to detect PCV13 serotypes in patients hospitalized with CAP.

Four studies were excluded because they were post-hoc analyses of the RCT that was already identified [25–27,31], one was a study of PCV7 [24], which does not include serotype 3 in its formulation, and one did not provide serotype-specific information [28]. An Italian TND study provided some serotype-specific information, with three cases of serotype 3 CAP identified in adults aged ≥65 years—all of which occurred among PCV13-unvaccinated persons (i.e., VE = 100%) [29]. The study did not use a serotype-specific UAD and relied predominately on polymerase chain reaction or culture of respiratory samples to identify PCV13 serotypes. Complete information for serotype-specific estimates, however, was not available in the publication (e.g., information about the controls used in the serotype 3 VE analysis or the two-by-two table describing serotype 3 VE results were not available) which prevented inclusion in our analysis [29].

Both published studies that met our inclusion criteria were conducted in adults aged ≥65 years and the primary study publications reported VE against PCV13-type (all serotypes) hospitalized CAP. Serotype 3-specific VE estimates and corresponding 95%CI for each study, however, could be estimated from the reported data. As mentioned previously, although not identified in our search of published literature, we were also aware of a third, smaller case-control study for which serotype 3-specific VE could be calculated. Data from this study were recently presented as a conference abstract [33].

3.2. Community-Acquired Pneumonia Immunization Trial in Adults (CAPiTA)

The Community Acquired Pneumonia Immunization Trial in Adults (CAPiTA) study was a large randomized placebo-controlled trial conducted in the Netherlands that evaluated PCV13 efficacy against vaccine-type CAP among immunocompetent adults aged ≥65 years [23]. For this RCT, we estimated VE against first episodes of vaccine-type hospitalized CAP caused by serotype 3 in the per-protocol (similar to the primary CAPiTA endpoint) [23] and modified intention-to-treat (mITT) populations. We also estimated PCV13 efficacy against any episode of serotype 3 CAP in the mITT population. The mITT included persons who became immunocompromised or had other protocol violations and were excluded from the per-protocol population [23]. As was pre-specified in the original study [23], CIs for serotype 3 VE were calculated using the exact binomial method.

In this trial, patients were randomized 1:1 to PCV13 or placebo. Based on 139 first-episodes of hospitalized CAP due to PCV13 serotypes (49 persons in the PCV13 group and 90 persons in the placebo group), overall PCV13 VE was 45.6% (95.2%CI: 21.8–62.5%) in the per-protocol population [23]. Of these, 23 (16.5%) were caused by serotype 3 (7 persons in the PCV13 group and 16 persons in the placebo group) [23] corresponding to a serotype 3 VE of 56.3% (95% CI: −12.4% to 84.8%) [34–36]. PCV13 against first-episodes of hospitalized CAP due to serotype 3 in the mITT population was 60.0% (95%CI: 5.2–84.8%; 8 persons in the PCV13 group and 20 persons in the placebo group) [34–36]. Serotype 3 VE against all episodes of hospitalized CAP in the mITT population was similar (9 persons in the PCV13 group and 20 persons in the placebo group; serotype 3 VE = 55.0%; 95%CI: −3.4% to 82.0%; Pfizer data on file).

As previously described, two of the three VE studies for which we had individual-level data were observational TND case-control studies where the study population was restricted only to patients with CAP [30,33]. Thus, it was not possible to combine these two TND studies [30,33] with the original cohort structure of the RCT [23]. Consequently, to pool the individual-level, raw data from all three studies, we structured the data from the RCT [23] to reflect a test-negative study design by including only patients who developed CAP [22]. We used the mITT population and the endpoint of all episodes of serotype 3 CAP in the pooled TND analysis. This endpoint was most similar to the other two TND studies, both of which included any episode of CAP and immunocompromised patients [30,33]. Although the RCT did not enroll immunocompromised patients (unlike the TND studies), the mITT population of the RCT included patients who became immunocompromised during the trial [23].

When the RCT data [23] were analyzed as a TND, there were 1661 episodes of hospitalized CAP included. Of these, 29 were episodes of serotype 3 CAP (i.e., cases) and 1632 were test-negative controls (i.e., non-PCV13-type CAP). Nine of the 29 cases (31.0%) and 806/1632 controls (49.4%) were vaccinated with PCV13 (unadjusted serotype 3 VE = 53.9%; 95%CI: −1.9% to 79.1%; Table 2). This serotype 3 VE estimate derived from a TND analysis was similar to the aforementioned original RCT serotype 3 VE estimates [23], confirming previous research that has shown vaccine RCT data analyzed as a TND yield similar results [22].

3.3. Louisville TND case-control study

The Louisville case-control study used a TND [30] and was nested within a large population-based study of adults hospitalized with CAP in nine adult hospitals in Louisville, Kentucky [37]. Like

Table 2
Effectiveness of PCV13 against serotype 3 hospitalized CAP in test-negative designs by study.

Study Population/Method	Serotype 3 Cases (PCV13/No PCV13)	Test-negative Controls (PCV13/No PCV13)	VE	95%CI
CAPiTA [23] as TND				
Modified intent-to-treat "TND-like" all episodes of CAP analysis	9/20	806/826	53.9	−1.9 to 79.1
Louisville TND [30]				
All episodes of CAP	2/25	285/1681	52.8	−100 to 88.9
Argentina TND [33] (unpublished)				
All episodes of CAP	0/11	17/283	100 (29.6)*	−1145 to 96.0
Pooled TND Analysis				
All episodes of CAP	11/56	1108/2790	52.5†	6.2 to 75.9†

CAP = community-acquired pneumonia; CAPiTA = Community-Acquired Pneumonia Immunization Trial in Adults [23]; CI = confidence interval; TND = test-negative design; PCV13 = 13-valent pneumococcal conjugate vaccine; VE = vaccine effectiveness.
* VE = 29.6% (and corresponding CIs) calculated after applying a 0.5 continuity adjustment to each cell.
† Calculated using Mantel-Haenszel stratified common odds ratio with continuity adjustment for the Argentina TND study [33]. If the inverse variance method was used in the pooled TND analysis, results were similar (VE = 52.6% [95%CI: 6.8–75.9%]).

the aforementioned RCT [23], the study was conducted among adults aged ≥65 years. Unlike the RCT [23], patients with immunocompromising conditions were included in the Louisville TND study, and made up 46% of the study population [30]. PCV13 vaccination status was based on health-insurance records, and patients for whom insurance records could not be obtained were excluded. The Louisville TND study showed that PCV13 was 72.8% (95%CI: 12.8–91.5%) effective against hospitalized PCV13-type CAP [30].

We calculated serotype 3 VE estimates using the same methodology as used for the overall vaccine-type analysis [30]. The only difference in the current serotype 3 analysis was that cases were restricted to any episode of serotype 3 hospitalized CAP (rather than any episode of PCV13-type CAP as in the primary analysis). Thus, cases of CAP caused by the other 12 PCV13 serotypes were excluded from the analysis. The control population remained the same as the original analysis (i.e., non-PCV13-type CAP), as did the method for calculating 95%CIs (i.e., Wald method) [30].

In the Louisville TND [30], of the 68 cases of PCV13-type CAP that were originally identified, 27 (39.7%) were due to serotype 3. Serotype 3 cases were less likely to have received PCV13 than controls (2/27, 7.4% *vs* 285/1966, 14.5%; unadjusted serotype 3 VE = 52.8% [95%CI: −100.0% to 88.9%]; Table 2). The range of serotype 3 VE estimates in models adjusted for patient demographic and clinical characteristics, time period, and history of PPV23 or influenza vaccine was 49.0% to 54.8%, suggesting no evidence of confounding.

3.4. Argentina TND case-control study

This case-control study evaluated PCV13 VE against vaccine-type CAP in Argentinian adults aged ≥65 years [33]. The study used an identical design, selection criteria, definition of cases and controls, and statistical analysis as the Louisville TND [30] described previously. The study enrolled CAP patients from hospitals in the city of Roca, Argentina. PCV13 vaccination status was obtained from the national immunization registry for each enrolled participant included in the analysis population. The study, which was the smallest of the three, included 328 patients in the TND analysis, 28 of whom had a PCV13 serotype identified, and showed 47.1% (95%CI: −346% to 93.7%) adjusted VE against any episode of PCV13-type CAP.

Of the 28 PCV13-type CAP cases, 11 (39.3%) were serotype 3. None of the serotype 3 cases were vaccinated compared to 17/300 (14.5%) controls (serotype 3 VE of 100%). We applied a continuity adjustment of 0.5 added to each cell to allow for calculation of CIs, and the corresponding VE against serotype 3 hospitalized CAP was 29.6% (95%CI: −1145% to 96.0%; Table 2).

3.5. Pooled analysis of individual-level data

In the pooled analysis of individual-level data, there were 3965 total patients (n = 1661 from the RCT [23], n = 1993 from the Louisville TND [30], and n = 311 from the Argentina TND [33]) hospitalized with CAP. Of these, serotype 3 was identified in 67 patients (1.7%), including 29 from the RCT [23], 27 from the Louisville TND [30], and 11 from the Argentina TND [33] (Table 2). Serotype 3 cases were less likely to have received PCV13 than controls (11/67, 16.4% *vs* 1108/3898, 28.4%; unadjusted serotype 3 VE = 52.5% [95%CI: 6.2–75.9%]; Table 2). Results were similar when we used inverse variance weights for each study, rather than sample-size weighting (serotype 3 VE = 52.6% [95%CI: 6.8–75.9%]), or if the unpublished Argentina TND study [33] was excluded (serotype 3 VE = 53.6% [95%CI: 6.7–76.9%]). No heterogeneity was observed. Further, no evidence of residual confounding was observed in the logistic regression analysis, with serotype 3 VE point estimates ranging from 53.5% to 55.3% in models adjusted for season, age, sex, risk level, and previous influenza vaccination.

4. Discussion

Our evaluation suggests that PCV13 provides direct protection against serotype 3 hospitalized CAP in adults aged ≥65 years. Efficacy point estimates from the Community-Acquired Pneumonia Immunization Trial in Adults (CAPiTA) study [23] suggest a direct, individual-level effect of PCV13 against serotype 3 CAP in older adults. Specifically, in this trial, PCV13 efficacy against serotype 3 hospitalized CAP was 55% (95%CI: −12% to 85%) and 60.0% (95% CI: 5.2–84.8%) against first episodes of vaccine-type CAP where serotype 3 was identified in the per-protocol and mITT populations respectively [34–36]. VE was 56% (95%CI −3% to 82%) against all events of serotype 3 hospitalized CAP in the mITT population (the study population and endpoint used in our pooled analysis). The recent Louisville TND study [30] showed a point estimate for VE against serotype 3 CAP of 53% (95%CI: −100% to 89%), which is similar to the RCT [23] but with wider CIs. We also had access to data from a TND study conducted in Argentina that was recently presented as a conference abstract [33] but is not yet published. This study showed no cases of serotype 3 CAP in PCV13-vaccinated adults (VE = 100%). This observational study, however, had the least statistical power of the three studies that we identified. None of the studies were individually powered for serotype-specific endpoints, and the relative paucity of data describing PCV13 effectiveness against serotype 3 CAP in adults emphasizes the value of pooling all currently-available evidence.

Because of the limitations inherent in pooling estimates from only a few studies that varied in study type and design, we compared methodological approaches and found similar results. Exclusion of the unpublished estimate [33] and choice of methodology for study weighting (inverse variance *vs* sample size) did not affect study interpretation. Moreover, multivariable modeling in the pooled analysis confirmed that VE estimates were robust to adjustment for important potentially-confounding factors.

Another limitation is that the studies included in the pooled analysis had different selection criteria and were conducted in different populations (i.e., the Netherlands, United States, and Argentina). The small number of studies included in our analysis is also a key limitation and could make these differences more acute. Serotype 3 VE point estimates from the two published studies [23,30], however, were similar. In the future, additional studies evaluating the effectiveness of PCV13 (and future PCVs) against serotype 3 CAP, as well as other pneumococcal disease syndromes, in adults are needed. Specifically, a well-powered single-site study or a multisite study using a common protocol to independently verify our results would be useful. Our findings in older adults, however, are supported by most reports of PCV13 effectiveness against serotype 3 IPD in children [20,38–43], including studies conducted by the US CDC [42] and ECDC [38] and a recently-published systematic review and meta-analysis [21].

Only two studies describing PCV13 VE against serotype 3 IPD in adults are available [23,44]. In the Community-Acquired Pneumonia Immunization Trial in Adults (CAPiTA) RCT [23] there were five first episodes of serotype 3 IPD in the per-protocol population (1 person in the PCV13 group and 4 persons in the placebo group; serotype 3 VE = 75%; 95%CI: −153% to 99%) and six first episodes in the mITT population (1 person in the PCV13 group and 5 persons in the placebo group; serotype 3 VE = 80%; 95%CI: −79% to 100%) [23,34]. A recent matched case-control study conducted by CDC based on 37 serotype 3 discordant pairs showed a VE estimate of 26% (95%CI: −58% to 65%) against serotype 3 IPD in US Medicare beneficiaries aged ≥65 years [44–46]. This point estimate is lower than those for PCV13 VE against serotype 3 CAP seen in our current study of the same age group. However, these data are difficult to interpret for several reasons. First, the CDC study also found lower overall VE against all PCV13 serotypes (VE = 47%; 95%CI: 4–71%) [44–46] as compared to estimates from the RCT setting (VE = 75%; 95%CI: 41–91%) [23] and another similar CDC case-control study (VE = 59%; 95%CI: 11–81%) [44–46]. Second, for IPD, it is difficult to disentangle the effects of 23-valent plain polysaccharide vaccine from PCV13 in real-world effectiveness studies. Third, CDC IPD VE studies used age-matched Medicare beneficiaries as controls rather than test-negative controls as have been used in CAP VE studies. Not using test-negative controls increases the likelihood of introducing confounding by healthcare-seeking behavior or other forms of selection bias [47–50]. Further, the biological mechanisms behind developing and preventing IPD may be different from those for CAP, although CAP is hypothesized to have a higher correlate of protection than does IPD [51–55]. These factors add to the complexity in drawing comparisons between IPD and CAP VE studies.

Our results demonstrating direct, individual-level effectiveness of PCV13 against serotype 3 CAP among adults must be reconciled with national surveillance data from across the globe showing minimal population-level impact against serotype 3 IPD among all age groups [15–17]. One hypothesis is that although PCV13 provides some direct protection against serotype 3 disease, it has more limited impact against serotype 3 carriage [18]. Thus, serotype 3 transmission may continue to occur and, over time, serotype 3 may become a replacement serotype as other PCV13 serotypes become less prevalent in carriage. This, in turn, may lead to an increased risk of serotype 3 disease among unvaccinated persons.

Recent evidence supports this hypothesis. First, it is generally accepted that higher antibody levels are needed to prevent pneumococcal carriage acquisition compared to pneumococcal disease [55]. Secondly, a RCT in Israeli children showed that PCV13 has more limited impact against serotype 3 colonization compared to other PCV13 serotypes [18]. Thus, evidence to date suggests that PCV13 elicits an immune response that is sufficient to provide direct, individual-level protection against serotype 3 pneumococcal disease but is insufficient to reduce carriage to the extent necessary to fully interrupt serotype 3 transmission. As mentioned previously, population-based surveillance data also support this notion. Marked increases in serotype 3 disease have been observed in many countries after the routine pediatric introduction of PCV10 [15], which does not include serotype 3. By contrast, in countries where PCV13 has been introduced in children, no large increases in serotype 3 disease have been observed [15–17].

Other hypotheses should also be explored. This includes whether a recent genetic evolution of serotype 3 pneumococcal clones has occurred [56] and whether this has affected the antibiotic susceptibility of serotype 3 pneumococci or the bacteria's response to vaccine antigens, or both. Increasing rates of antimicrobial resistance for serotype 3 pneumococci [56] could partially explain why it remains a persistent serotype, as could the potential for reduced vaccine effectiveness to certain emerging serotype 3 clones.

While our study suggests PCV13 provides direct, individual-level protection against serotype 3 CAP in adults, determining the public health impact of adult vaccination against serotype 3 disease will require further evaluation. For example, in the United Kingdom [16] and Germany [57], where PCV13 is used in children but not in adults, serotype 3 disease has started to increase in older adults in recent years. However, future research is needed to determine if an adult PCV13 program could alter this trajectory (e.g., as compared to the United States where PCV13 is routinely used in adults).

In summary, surveillance data have shown that while serotype 3 disease has remained relatively flat in populations where PCV13 has been introduced into routine pediatric immunization programs [15–17], serotype 3 disease is increasing in almost every population using PCV10, which does not contain serotype 3 [15]. In addition, current evidence suggests that PCV13 provides direct, individual-level protection against serotype 3 IPD in vaccinated children, as shown in a recent systematic review and meta-analysis [21], and against serotype 3 CAP in vaccinated older adults as shown in our current study. Consequently, even if population-level decreases in serotype 3 disease have not been observed following PCV13 introduction into routine pediatric immunization programs, direct immunization of children and adults—with high vaccine coverage—is likely still a useful tool for serotype 3 disease prevention and control. This hypothesis will require further evaluation by better-powered studies of direct protection against different pediatric and adult disease outcomes, and ongoing surveillance in settings where adult PCV13 vaccination has been implemented on a population basis. In the meantime, directly vaccinating adults with PCV13 should be considered as a strategy to reduce the risk of serotype 3 CAP.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: This study was sponsored by Pfizer Inc. All authors are employees and shareholders of Pfizer Inc. The sponsor was involved

with study concept and design, conduct, analysis, and interpretation of the data; drafting of the manuscript; and the decision to submit the manuscript for publication.

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