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Outpatient Visits and Antibiotic Use Due to Higher-Valency Pneumococcal Vaccine Serotypes

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Background. In 2022–2023, 15- and 20-valent pneumococcal conjugate vaccines (PCV15/PCV20) were recommended for infants. We aimed to estimate the incidence of outpatient visits and antibiotic prescriptions in US children (≤17 years) from 2016–2019 for acute otitis media, pneumonia, and sinusitis associated with PCV15- and PCV20-additional (non-PCV13) serotypes to quantify PCV15/20 potential impacts.

Methods. We estimated the incidence of PCV15/20-additional serotype-attributable visits and antibiotic prescriptions as the product of all-cause incidence rates, derived from national health care surveys and MarketScan databases, and PCV15/20-additional serotype-attributable fractions. We estimated serotype-specific attributable fractions using modified vaccine-probe approaches incorporating incidence changes post-PCV13 and ratios of PCV13 versus PCV15/20 serotype frequencies, estimated through meta-analyses.

Results. Per 1000 children annually, PCV15-additional serotypes accounted for an estimated 2.7 (95% confidence interval, 1.8–3.9) visits and 2.4 (95% CI, 1.6–3.4) antibiotic prescriptions. PCV20-additional serotypes resulted in 15.0 (95% CI, 11.2–20.4) visits and 13.2 (95% CI, 9.9–18.0) antibiotic prescriptions annually per 1000 children. PCV15/20-additional serotypes account for 0.4% (95% CI, 0.2%–0.6%) and 2.1% (95% CI, 1.5%–3.0%) of pediatric outpatient antibiotic use.

Conclusions. Compared with PCV15-additional serotypes, PCV20-additional serotypes account for > 5 times the burden of visits and antibiotic prescriptions. Higher-valency PCVs, especially PCV20, may contribute to preventing pediatric pneumococcal respiratory infections and antibiotic use.

Keywords. *Streptococcus pneumoniae*; pediatric; antibiotic; pneumococcal conjugate vaccine; outpatient; acute otitis media; pneumonia; sinusitis.

Acute respiratory infections (ARIs) are a leading cause of outpatient health care utilization [1], school absenteeism [2], and antibiotic use [3, 4] among children, resulting in considerable health and economic burdens. In 2014–2015, ARIs accounted for 544 outpatient visits and 252 antibiotic prescriptions per 1000 children annually, with acute otitis media (AOM) accounting for over a third of ARI-associated antibiotic prescriptions [5]. *Streptococcus pneumoniae* (pneumococcus) causes bacterial ARIs among children, especially AOM, and thus contributes to antibiotic use in children. Pneumococcal conjugate vaccines (PCVs) provide protection against carriage of, and disease from, vaccine-targeted serotypes. Implementation of PCV7, followed by PCV13 [6], contributed to substantial reductions in AOM and pneumonia incidence among children in the United States [7–16].

In 2022–2023, the Advisory Committee on Immunization Practices amended pediatric pneumococcal vaccine recommendations to include PCV15 and PCV20 in a series of 3 primary doses and 1 booster dose in infants [17, 18]. These vaccines extend PCV13 serotype composition (serotypes 1, 3, 4, 5, 6A, 6B, 7A, 9 V, 14, 18C, 19A, 19F, 23F) to include 22F and 33F (PCV15/20) and 8, 10A, 11A, 12F, and 15B (PCV20). Twenty-three-valent pneumococcal polysaccharide vaccine (PPSV23) is recommended for children aged > 2 years with certain comorbidities and previous PCV13/15 immunization [18].

Serotypes in PCV15 and PCV20 accounted for 31% and 44%, respectively, of invasive pneumococcal disease (IPD) cases among US children aged < 5 years in 2020–2021 [19] and PCV formulations are informed by IPD-causing serotypes [20]. Pediatric IPD incidence has reached historic lows, with 7.2 cases per 100 000 children aged < 5 years in 2019 [21]. Less is known about outpatient ARI burdens attributable to PCV15/20 serotypes. However, consideration of outpatient outcomes in vaccine recommendation development and vaccine implementation evaluation is warranted given high

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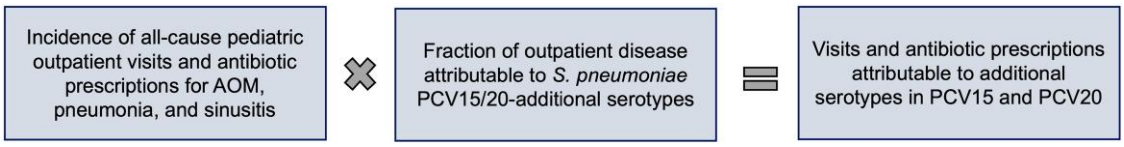

Figure 1. Estimation framework. Framework to derive estimates of visits and antibiotic prescriptions attributable to PCV15- and PCV20-additional serotypes. All-cause incidence estimation methods are detailed in Supplementary Text 1. Primary attributable fraction analysis methods are detailed in Supplementary Text 2 (AOM) and Supplementary Text 3 (pneumonia, sinusitis), and supplemental methods in Supplementary Text 5. Abbreviations: AOM, acute otitis media; PCV, pneumococcal conjugate vaccine.

burdens of outpatient outcomes [4, 5, 9, 16, 22], their role in vaccine cost-effectiveness [23, 24], and needed reductions in antibiotic use [25]. Our primary objective was to estimate the incidence of outpatient visits and antibiotic prescriptions in children aged < 5 years in the United States for AOM and pneumonia associated with the additional (non-PCV13) serotypes in PCV15 and PCV20. Our secondary objective was to estimate the burden of visits and antibiotic prescriptions for AOM, pneumonia, and sinusitis associated with these additional serotypes in children aged 5–17 years, who benefit from indirect protection from PCVs.

METHODS

Estimation Framework

Our approach to estimate the incidence of pediatric outpatient visits and antibiotic prescriptions attributable to additional serotypes in PCV15 and PCV20 (hereafter, PCV15/20-additional serotypes) included 3 components (Figure 1). First, we estimated all-cause incidence rates of outpatient visits and antibiotic prescriptions for AOM, pneumonia, and sinusitis. Second, we estimated the proportion of cases of these conditions attributable to PCV15/20-additional serotypes. Finally, we obtained incidence rates of visits and antibiotic prescriptions attributable to PCV15/20-additional serotypes by multiplying the all-cause incidence rates and corresponding attributable proportion estimates.

We considered children aged < 5 years (stratified as < 2 years and 2–4 years) as young children are targeted for universal PCV immunization and account for high proportions of outpatient visits and antibiotic prescriptions for ARIs [4, 5]. We did not consider sinusitis in children aged < 5 years as sinus development typically occurs > 5 years of age [26, 27] and sinusitis is infrequently diagnosed in younger children. To quantify total potential pediatric burdens, we additionally generated estimates for all conditions, AOM, pneumonia, and sinusitis in children aged 5–17 years and all children ≤ 17 years.

We projected incidence per 1000 person-years to national numbers of visits and antibiotic prescriptions by multiplying estimated incidence rates by corresponding 2019 bridged-race postcensal population estimates [28], rounded to the nearest thousand. Additionally, we estimated the proportion of all pediatric antibiotic prescribing attributable to PCV15/20-additional serotypes by dividing estimated PCV15/20-additional serotype-attributable incidence rates by the incidence of all pediatric outpatient antibiotic prescriptions.

All-Cause Visit and Antibiotic Prescription Incidence Rates

We estimated incidence rates of visits and antibiotic prescriptions for AOM, pneumonia, and sinusitis among children aged ≤ 17 years across US outpatient settings using the 2016 and 2019 National Ambulatory Medical Care Survey (NAMCS), 2016 and 2019 National Hospital Ambulatory Medicare Care Survey (NHAMCS), and 2016–2019 Merative MarketScan Commercial and Medicaid Databases (MarketScan) (Supplementary Text 1). Collectively, these datasets represent health care delivery across all outpatient settings (Supplementary Table 1). We used NAMCS/NHAMCS to obtain nationally representative incidence estimates from physician offices and emergency departments. We generated incidence estimates from other outpatient settings (eg, urgent care, retail health facilities) using data from MarketScan, which contains reconciled claims from all outpatient settings among a large convenience sample of individuals with commercial insurance and Medicaid. Total MarketScan rates were estimated as weighted averages from the Commercial and Medicaid databases accounting for commercial and public insurance distributions (Supplementary Text 1 and Supplementary Table 2). We identified visits and prescriptions for AOM, pneumonia, and sinusitis from *International Classification of Diseases, Tenth Revision, Clinical Modification* (ICD-10-CM) diagnosis codes using a previously validated algorithm that assigns a single diagnosis to each visit based on the diagnosis most likely to result in antibiotic prescription (Supplementary Text 1 and Supplementary Table 3) [3–5]. To estimate incidence rates across all outpatient settings, we standardized estimates from each data source per 1000 population and summed the rates from office and emergency departments (NAMCS/NHAMCS) and all other outpatient settings (MarketScan). This activity was reviewed by the Centers for Disease Control and Prevention (CDC) and was conducted consistent with applicable federal law and CDC policy (see, eg, 45 CFR part 46, 21 CFR part 56; 42 USC §241(d); 5 USC §552a; 44 USC §3501 et seq.).

Serotype-Specific Attributable Fractions

To estimate pneumococcal serotype-specific attributable fractions, we used a modified vaccine-probe approach

Table 1. Estimated Incidence of All-Cause Pediatric Visits and Antibiotic Prescriptions by Outpatient Setting and Data Source, 2016–2019

Age Stratum and Condition	Outpatient Visits per 1000 Person-Years Among US Children (95% CI)			Antibiotic Prescriptions per 1000 Person-Years Among US Children (95% CI)		
	Physician Offices/Eds, NAMCS/NHAMCS	Other Outpatient Settings,[a] MarketScan	Total[b]	Physician Offices/Eds, NAMCS/NHAMCS	Other Outpatient Settings,[a] MarketScan	Total[b]
< 2 y						
AOM	508 (333–736)	90 (77–104)	598 (423–827)	372 (236–554)	56 (46–67)	428 (291–610)
Pneumonia	38 (20–65)	7 (4–11)	45 (27–72)	32 (22–44)	2 (1–5)	34 (24–47)
Total[b,c]	547 (371–776)	98 (84–112)	645 (468–874)	404 (267–586)	59 (48–69)	462 (325–646)
2–4 y						
AOM	293 (194–421)	58 (48–69)	352 (252–480)	282 (197–387)	39 (31–48)	321 (236–427)
Pneumonia	22 (12–38)	6 (3–10)	29 (17–45)	25 (18–33)	3 (1–5)	28 (21–36)
Total[b,c]	316 (216–444)	65 (54–76)	381 (281–510)	307 (222–412)	42 (34–52)	349 (264–455)
All children < 5 y						
AOM	381 (284–496)	70 (59–82)	451 (353–567)	319 (243–409)	45 (36–55)	365 (288–455)
Pneumonia	29 (18–43)	7 (3–11)	36 (25–50)	28 (21–36)	3 (1–5)	30 (23–39)
Total[b,c]	410 (313–526)	77 (65–89)	487 (389–604)	347 (270–437)	48 (39–58)	395 (318–486)
5–17 y						
AOM	48 (28–76)	14 (9–19)	62 (41–90)	52 (41–66)	11 (7–16)	63 (51–78)
Pneumonia	7 (4–12)	3 (1–6)	10 (6–16)	7 (6–9)	1 (0–3)	8 (6–11)
Sinusitis	41 (26–60)	9 (5–14)	50 (35–70)	39 (26–57)	7 (3–11)	46 (32–64)
Total[b]	97 (71–130)	26 (19–33)	123 (96–157)	100 (81–121)	19 (13–25)	119 (99–141)
All children ≤17 y						
AOM	138 (103–180)	28 (21–36)	166 (130–209)	125 (99–154)	20 (14–26)	144 (118–174)
Pneumonia	13 (9–18)	4 (1–7)	17 (12–23)	13 (10–16)	4 (1–7)	17 (13–21)
Sinusitis[d]	41 (25–63)	8 (5–13)	49 (33–72)	40 (24–63)	4 (2–7)	44 (27–67)
Total[b,d]	193 (153–240)	40 (32–49)	234 (193–281)	178 (147–214)	27 (20–35)	206 (173–243)

Abbreviations: AOM, acute otitis media; CI, confidence interval; ED, emergency department; NAMCS, National Ambulatory Medical Care Survey; NHAMCS, National Hospital Ambulatory Medical Care Survey.

[a]Other outpatient settings include retail health clinics, urgent care facilities, outpatient hospital departments, telehealth, and other. All outpatient settings are detailed in Supplementary Table 1. Incidence estimates stratified by commercially and noncommercially insured children in MarketScan are available in Supplementary Table 2.

[b]Incidence per stratum and setting may not sum to totals due to rounding.

[c]Estimates for sinusitis not included in age-stratum totals for < 2 years, 2–4 years, and all children < 5 years. In these strata, sampled visit counts for sinusitis do not meet NAMCS/NHAMCS minimum sample size requirements for valid projection to national estimates [36]. Sinusitis is uncommon in children < 5 years due to sinus development [26, 27].

[d]To generate total estimates for all conditions across all children, visits and antibiotic prescriptions for sinusitis in children < 5 years were included in the sinusitis and total estimates.

comparing observed changes in incidence of each condition following PCV13 implementation (Supplementary Text 2 and 3). In vaccine-probe studies, the proportion of disease attributable to a vaccine-targeted pathogen is estimated by dividing vaccine effectiveness (VE) against all-cause disease by VE against the vaccine-targeted pathogen [29]. Analyses accounted for secular trends in incidence using "negative-control" conditions not likely to have been impacted by PCVs (Supplementary Table 4). We projected PCV13 estimates from the vaccine probe analysis to PCV15/20 serotypes using the ratio of PCV13 versus PCV15/20 serotype frequencies in the studied ARI conditions, estimated through meta-analyses of published estimates of serotype distributions (Supplementary Text 4 and Supplementary Table 5). We categorized serotypes as PCV13, PCV15-additional, and PCV20-additional as described in Supplementary Table 6. As PPSV23 is only recommended in select children, we did not consider PPSV23 serotypes in this analysis. Studies in older children were limited; we assumed serotype distribution was consistent across age groups.

Etiology data sources differed across conditions. For AOM, microbiological surveillance data were available from Israeli children aged < 3 years from 2009–2011 and 2013–2015 [30], allowing us to directly compare changes in all-cause and PCV13-serotype AOM. Similar to the United States, PCV13 replaced PCV7 in Israel in 2010 [31, 32]. We used these data to estimate VE against all-cause and PCV13 serotype AOM, with nonpneumococcal AOM as a negative control (Supplementary Text 2 and Supplementary Table 4). As similar, microbiologically detailed studies of pneumonia and sinusitis etiology were not available, we estimated VE against all-cause pneumonia and sinusitis in children aged < 3 years from 2009–2010 and 2013–2015 using NAMCS/NHAMCS, with skin and soft tissue infections as a negative control (Supplementary Text 3 and Supplementary Table 4) and assumed PCV13 serotype VE was equivalent for these conditions as for AOM.

Attributable Fraction Sensitivity Analyses

We supplemented this analysis using 2 additional attributable fraction estimation methods (Supplementary Text 5). First,

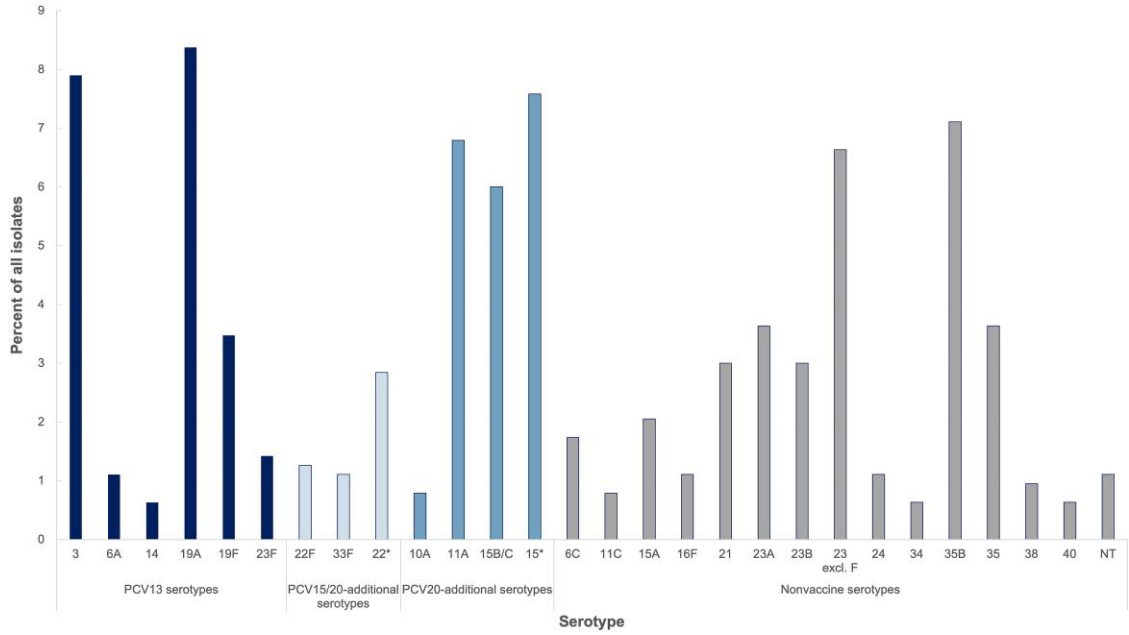

Figure 2. Pooled pneumococcal serotype distribution among children with acute respiratory infections from studies included in meta-analyses. Aggregated serotypes are denoted by *; PCV categorization is detailed in Supplementary Table 6. Only serotypes representing ≥ 1% of isolates are presented. Estimates are pooled directly from included studies (Supplementary Table 5); Supplementary Table 9 presents PCV category Markov-chain Monte Carlo estimates. Abbreviations: NT, nontypeable pneumococcal isolates; PCV, pneumococcal conjugate vaccine; excl., excluding.

we estimated the difference in pneumococcal nasopharyngeal carriage prevalence among children with ARI/AOM and healthy children and defined this prevalence difference as the proportion of cases attributable to pneumococci (differential carriage approach). This approach was grounded in findings from previous studies demonstrating increased pneumococcal carriage prevalence during ARI episodes [33, 34]. We undertook a systematic literature review and meta-analysis to determine pneumococcal carriage prevalence among healthy children and those with AOM/ARIs (Supplementary Text 5 and Supplementary Table 7) and used the previously estimated nasopharyngeal serotype distributions. We conducted this analysis for AOM and all ARIs. Second, for AOM, we also undertook a meta-analysis estimating attributable fractions using published estimates of pneumococcal prevalence and serotype distribution in middle ear fluid samples from children with AOM (Supplementary Text 5 and Supplementary Table 8).

We undertook additional sensitivity analyses to evaluate the impact of study selection on our findings. First, we restricted included studies of serotype distributions to those undertaken ≥4 years after PCV13 implementation (Supplementary Text 6). In the second, we excluded published isolate counts aggregated across multiple serotypes except 15B/C (Supplementary Text 4).

Total Burden Due to PCV15/20 Serotypes

Finally, to quantify the total serotype coverage of these vaccines, we estimated incidence attributable to all serotypes in PCV15/20 including disease from PCV15/20-additional serotypes, residual PCV13 disease, and disease prevented by PCV13 during the study period (Supplementary Text 2 and 3). This analysis was based on a counterfactual of no PCV use (distinct from the continued PCV13 use counterfactual in primary analyses), as the total benefit of these vaccines includes continuation of PCV13 serotype protection [35].

RESULTS

All-Cause Incidence

Among children aged < 5 years, there were 487 (95% confidence interval [CI], 389–604) outpatient visits and 395 (95% CI, 318–486) outpatient antibiotic prescriptions per 1000 person-years among US children during 2016–2019 (Table 1 and Supplementary Table 2), projecting to 9.5 (95% CI, 7.6–11.8) million outpatient visits and 7.7 (95% CI, 6.2–9.5) million antibiotic prescriptions annually. By condition, AOM accounted for the highest incidence rates, with 451 (95% CI, 353–567) visits and 365 (95% CI, 288–455) antibiotic prescriptions per 1000 person-years among children < 5 years. Among all children ≤ 17 years and for all conditions, there were 234 (95% CI, 193–281) outpatient visits and 206 (95% CI, 173–243) outpatient antibiotic prescriptions per 1000 person-years, equivalent to 17.1 (95% CI, 14.1–20.5) million outpatient visits and 15.0 (95% CI, 12.7–17.7) million antibiotic prescriptions annually.

Table 2. Outpatient Visits Attributable to Any Pneumococcal Serotype, PCV15-Additional Serotypes, and PCV20-Additional Serotypes, 2016–2019

Age Stratum and Condition	Estimated Incidence per 1000 Person-Years Among US Children (95% CI)		
	All Pneumococci	PCV15-Additional Serotypes[a]	PCV20-Additional Serotypes[a]
< 2 y			
AOM	116.5 (80.3–165.9)	6.1 (3.6–10.0)	31.2 (20.8–46.3)
Pneumonia	12.3 (6.5–22.7)	0.4 (.2–.8)	2.8 (1.5–5.2)
Total[b,c]	129.3 (92.2–179.8)	6.5 (4.0–10.5)	34.2 (23.4–49.5)
2–4 y			
AOM	68.4 (47.7–96.2)	3.6 (2.1–5.8)	18.3 (12.3–26.9)
Pneumonia	7.9 (4.2–14.3)	0.3 (.1–.5)	1.8 (.9–3.3)
Total[b,c]	76.6 (55.3–105.2)	3.9 (2.4–6.1)	20.2 (14.0–29.0)
All children < 5 y			
AOM	87.6 (66.4–114.8)	4.6 (2.9–7.1)	23.5 (17.0–32.4)
Pneumonia	9.7 (5.8–16.3)	0.3 (.2–.6)	2.2 (1.3–3.7)
Total[b,c]	97.7 (75.7–125.8)	4.9 (3.2–7.5)	25.8 (19.0–34.8)
5–17 y			
AOM	12.1 (7.9–18.0)	0.6 (.4–1.1)	3.2 (2.1–5.0)
Pneumonia	2.7 (1.4–5.0)	0.1 (.0–.2)	0.6 (.3–1.2)
Sinusitis	22.9 (13.7–38.3)	0.8 (.5–1.4)	5.2 (3.1–8.8)
Total[b]	38.2 (26.7–55.5)	1.6 (1.0–2.4)	9.2 (6.4–13.4)
All children ≤17 y			
AOM	32.3 (24.5–42.3)	1.7 (1.1–2.6)	8.7 (6.3–11.9)
Pneumonia	4.6 (2.8–7.6)	0.2 (.1–.3)	1.1 (.6–1.7)
Sinusitis[d]	22.6 (13.1–38.9)	0.8 (.4–1.4)	5.1 (2.9–8.9)
Total[b,d]	60.1 (45.8–80.5)	2.7 (1.8–3.9)	15.0 (11.2–20.4)

Abbreviations: AOM, acute otitis media; PCV, pneumococcal conjugate vaccine.

[a]Includes vaccine serotypes and corresponding aggregated serotypes/serogroups as detailed in Supplementary Table 6. PCV-15 additional serotypes (not included in PCV13): 22F, 33F. PCV20-additional serotypes: 8, 10A, 11A, 12F, 15B, 22F, 33F.

[b]Incidence by condition may not sum to total due to rounding.

[c]Estimates for sinusitis not included in age-stratum totals for < 2 years, 2–4 years, and all children < 5 years. In these strata, sampled visit counts for sinusitis do not meet NAMCS/NHAMCS minimum sample size requirements for valid projection to national estimates [36]. Sinusitis is uncommon in children < 5 years due to sinus development [26, 27].

[d]To generate total estimates for all conditions across all children, visits and antibiotic prescriptions for sinusitis in children < 5 years were included in the sinusitis and total estimates.

Pneumococcal Serotype Distribution in ARIs With Pneumococcal Detection

Five studies contained data on pneumococcal serotype distributions in nasopharyngeal carriage among children experiencing ARI; 4 enrolled children with AOM, and 1 enrolled children with lower respiratory tract infection (Supplementary Table 5). Across these studies, the most common serotypes were 19A, 3, 15B/C, 35B, and 11A (Figure 2). PCV15/20-additional serotypes accounted for 3.6% (95% CI, 2.8%–4.4%) and 22.7% (95% CI, 21.0%–24.5%), respectively, of pneumococcal isolates from nasopharyngeal samples in ARIs (Supplementary Table 9). In AOM, PCV15-additional and PCV20-additional serotypes accounted for 5.2% (95% CI, 3.7%–7.1%) and 26.9% (95% CI, 23.5%–30.4%) of pneumococcal isolates. Nonvaccine serotypes accounted for 48.6% (95% CI, 44.6%–52.5%) of isolates in children with AOM and 54.0% (95% CI, 51.9%–56.1%) of isolates in children with ARI.

Fraction of ARIs Attributable to PCV15/20-Additional Serotypes

Using the vaccine probe method, we estimated that PCV15-additional serotypes accounted for 1.0% (95% CI, 0.7%–1.5%), 1.0% (95% CI, 0.6%–1.5%), and 1.6% (95% CI, 1.1%–2.6%) of current all-cause AOM, pneumonia, and sinusitis, respectively (Supplementary Table 10). PCV20-additional serotypes accounted for 5.2% (95% CI, 4.2%–6.5%), 6.2% (95% CI, 4.2%–9.3%), and 10.4% (95% CI, 7.1%–15.5%) of all-cause AOM, pneumonia, and sinusitis. Estimates of PCV15/20 serotype coverage in AOM from alternative approaches closely resembled those from our primary vaccine-probe analyses. However, the differential carriage approach yielded lower estimates of the fraction of pneumonia and sinusitis cases attributable to pneumococci. Under this framework, PCV15-additional serotypes accounted for 0.4% (95% CI, 0.0%–0.8%) of all-cause disease, while PCV20-additional serotypes accounted for 2.7% (95% CI, 0.2%–5.2%).

Burden Due to PCV15/20-Additional Serotypes

Annually per 1000 children aged < 5 years, PCV15-additional serotypes accounted for 4.9 (95% CI, 3.2–7.5) ARI visits and 4.0 (95% CI, 2.6–6.0) antibiotic prescriptions (Table 2 and Table 3). Projecting these rates nationally yielded 97 000 (95% CI, 63 000–146 000) visits and 78 000 (95% CI, 51 000–118 000) antibiotic prescriptions attributable to PCV15-additional serotypes annually (Table 4 and Table 5). In contrast, PCV20-additional serotypes resulted in 25.8 (95% CI, 19.0–34.8) ARI visits and 21.0 (95% CI, 15.5–28.1) antibiotic prescriptions annually per 1000

Table 3. Antibiotic Prescriptions Attributable to Any Pneumococcal Serotype, PCV15-Additional Serotypes, and PCV20-Additional Serotypes, 2016–2019

Age Stratum and Condition	Estimated Incidence per 1000 Person-Years Among US Children (95% CI)		
	All Pneumococci	PCV15-Additional Serotypes[a]	PCV20-Additional Serotypes[a]
< 2 y			
AOM	83.2 (55.3–122.0)	4.3 (2.5–7.3)	22.3 (14.3–34.0)
Pneumonia	9.4 (5.7–15.5)	0.3 (.2–.6)	2.1 (1.3–3.6)
Total[b,c]	92.9 (64.4–132.2)	4.7 (2.8–7.7)	24.5 (16.4–36.4)
2–4 y			
AOM	62.4 (44.7–85.8)	3.3 (2.0–5.2)	16.7 (11.5–24.1)
Pneumonia	7.6 (4.7–12.1)	0.3 (.2–.5)	1.7 (1.1–2.8)
Total[b,c]	70.2 (51.9–94.0)	3.5 (2.2–5.5)	18.5 (13.1–26.0)
All children < 5 y			
AOM	70.9 (54.0–92.4)	3.7 (2.4–5.7)	19.0 (13.8–26.0)
Pneumonia	8.3 (5.2–13.2)	0.3 (.2–.5)	1.9 (1.2–3.0)
Total[b,c]	79.5 (61.9–101.7)	4.0 (2.6–6.0)	21.0 (15.5–28.1)
5–17 y			
AOM	12.3 (9.6–15.8)	0.6 (.4–1.0)	3.3 (2.4–4.5)
Pneumonia	2.3 (1.5–3.6)	0.1 (.0–.1)	0.5 (.3–.8)
Sinusitis	21.2 (12.7–35.2)	0.8 (.4–1.3)	4.8 (2.9–8.1)
Total[b]	36.0 (26.2–51.3)	1.5 (1.0–2.2)	8.7 (6.3–12.4)
All children ≤17 y			
AOM	28.0 (22.0–35.5)	1.5 (.9–2.2)	7.5 (5.6–10.1)
Pneumonia	4.6 (2.9–7.2)	0.2 (.1–.3)	1.0 (.7–1.6)
Sinusitis[d]	20.2 (11.2–35.7)	0.7 (.4–1.3)	4.6 (2.5–8.2)
Total[b,d]	53.1 (40.6–71.8)	2.4 (1.6–3.4)	13.2 (9.9–18.0)

Abbreviations: AOM, acute otitis media; PCV, pneumococcal conjugate vaccine.

[a]Includes vaccine serotypes and corresponding aggregated serotypes/serogroups as detailed in Supplementary Table 6. PCV-15 additional serotypes (not included in PCV13): 22F, 33F. PCV20-additional serotypes: 8, 10A, 11A, 12F, 15B, 22F, 33F.

[b]Incidence by condition may not sum to total due to rounding.

[c]Estimates for sinusitis not included in age-stratum totals for < 2 years, 2–4 years, and all children < 5 years. In these strata, sampled visit counts for sinusitis do not meet NAMCS/NHAMCS minimum sample size requirements for valid projection to national estimates [36]. Sinusitis is uncommon in children < 5 years due to sinus development [26, 27].

[d]To generate total estimates for all conditions across all children, visits and antibiotic prescriptions for sinusitis in children < 5 years were included in the sinusitis and total estimates.

children, corresponding to 505 000 (95% CI, 372 000–682 000) visits and 410 000 (95% CI, 304 000–551 000) antibiotic prescriptions each year. PCV15- and PCV20-additional serotypes accounted for 0.5% (95% CI, 0.3%–0.8%) and 2.9% (95% CI, 2.0%–4.0%), respectively, of antibiotic use among US children < 5 years of age (Supplementary Table 11).

For all children and including sinusitis, there were 197 000 (95% CI, 133 000–287 000) visits and 173 000 (95% CI, 118 000–252 000) antibiotic prescriptions attributable to PCV15-additional serotypes annually and 1 098 000 (95% CI, 816 000–1 489 000) visits and 968 000 (95% CI, 722 000–1 318 000) antibiotic prescriptions attributable to PCV20-additional serotypes (Table 4 and Table 5). In total, PCV15- and PCV20-additional serotypes accounted for 0.4% (95% CI, 0.2%–0.6%) and 2.1% (95% CI, 1.5%–3.0%), respectively, of antibiotic use among US children (Supplementary Table 11).

Sensitivity Analyses for Attributable Fractions

Compared with primary analyses, restricting analyses to studies undertaken ≥4 years after PCV13 implementation yielded greater proportions of disease attributable to PCV15-additional and PCV20-additional serotypes (Supplementary Tables 12 and 13), reflecting the enhanced contribution of these serotypes and declines in PCV13 serotype disease due to serotype replacement following PCV13 implementation. Compared with primary analyses, lower proportions of disease attributable to PCV20-additional serotypes were observed when analyses included only counts disaggregated by serogroup/serotype (Supplementary Tables 14 and 15) due to the exclusion of samples categorized as serogroup 15.

Total PCV15 and PCV20 Serotype Burdens

Considering disease associated with PCV15/20-additional serotypes and PCV13 serotypes (prevented by PCV13 and residual), we estimate all PCV15 serotypes would account for 50.9 (95% CI, 22.6–91.6) outpatient visits and 45.0 (95% CI, 20.2–79.6) antibiotic prescriptions per 1000 person-years, while all PCV20 serotypes would account for 62.4 (95% CI, 32.0–106.8) outpatient visits and 55.1 (95% CI, 28.5–93.0) antibiotic prescriptions per 1000 person-years (Supplementary Tables 16 and 17).

DISCUSSION

We estimate that additional serotypes in PCV15 (22F, 33F) account for approximately 97 000 outpatient visits and 78 000

Table 4. National Projection of Outpatient Visits Attributable to Any Pneumococcal, PCV15-Additional, and PCV20-Additional Serotypes, 2016–2019

Age Stratum and Condition	Estimated Annual Outpatient Visits by US Children, in Thousands (95% CI)		
	All Pneumococci	PCV15-Additional Serotypes[a]	PCV20-Additional Serotypes[a]
< 2 y			
AOM	886 (610–1261)	46 (27–76)	237 (158–352)
Pneumonia	94 (49–173)	3 (2–6)	21 (11–39)
Total[b]	983 (701–1367)	50 (30–80)	260 (178–376)
2–4 y			
AOM	818 (571–1151)	43 (26–69)	220 (147–322)
Pneumonia	94 (50–171)	3 (2–6)	21 (11–39)
Total[b]	917 (661–1259)	46 (29–73)	242 (167–347)
All children < 5 y[c]			
AOM	1715 (1300–2246)	90 (57–138)	460 (333–634)
Pneumonia	190 (113–319)	7 (4–12)	43 (25–73)
Total[b]	1912 (1481–2461)	97 (63–146)	505 (372–682)
5–17 y			
AOM	646 (423–962)	34 (19–57)	173 (110–267)
Pneumonia	147 (77–268)	5 (3–10)	33 (17–61)
Sinusitis	11228 (733–2052)	44 (25–77)	279 (164–469)
Total[b]	2043 (1431–2971)	84 (55–128)	491 (341–719)
All children ≤17 y[c]			
AOM	2362 (1794–3091)	123 (78–191)	634 (458–872)
Pneumonia	339 (206–556)	12 (7–21)	77 (46–127)
Sinusitis	1655 (957–2841)	59 (32–106)	375 (215–651)
Total[b]	4392 (3347–5884)	197 (133–287)	1098 (816–1489)

Abbreviations: AOM, acute otitis media; CI, confidence interval; PCV, pneumococcal conjugate vaccine.

[a]Includes vaccine serotypes and corresponding aggregated serotypes/serogroups as detailed in Supplementary Table 6. PCV-15 additional serotypes (not included in PCV13): 22F, 33F. PCV20-additional serotypes: 8, 10A, 11A, 12F, 15B, 22F, 33F.

[b]Number of visits by condition may not sum to total due to rounding.

[c]Number of visits across age groups may not sum to all children totals due to rounding.

antibiotic prescriptions for AOM and pneumonia among US children aged < 5 years annually. Including older children and sinusitis, PCV15-additional serotypes account for an estimated 197 000 outpatient visits and 173 000 antibiotic prescriptions among US children annually. Non-PCV13 serotypes in PCV20 (8, 10A, 11A, 12F, 15B, 22F, and 33F) account for an estimated 505 000 outpatient visits and 410 000 antibiotic prescriptions annually among children < 5 years and 1 098 000 visits and 968 000 antibiotic prescriptions among all children. ARIs attributable to PCV15- and PCV20-additional serotypes account for 0.4% and 2.1%, respectively, of all antibiotic prescribing in children. Sensitivity analyses restricted to studies ≥4 years after PCV13 implementation indicate primary results may underestimate the burden of ARIs associated with PCV15/20-additional serotypes due to increases in their prevalence through serotype replacement, although post-PCV13 serotype replacement has not driven considerable increases in US IPD cases [37]. Among conditions, AOM accounted for the largest all-cause visit and antibiotic prescription burdens, consistent with previous studies [4, 5], and consequently the greatest numbers of visits and antibiotic prescriptions attributable to PCV15/20-additional serotypes.

In these analyses, PCV20-additional serotypes accounted for at least 5 times the incidence of outpatient visits and antibiotic prescriptions compared with PCV15-additional serotypes. These findings contrast with IPD surveillance data, where IPD due to 22F and 33F, contained in both PCV15/20, exceeds the burden of all non-PCV15 serotypes in PCV20 [19]. The pattern in outpatient ARIs, in part reflects the predominance of 15B/C and 11A carriage among children with ARIs. Among included studies, serotype 15B/C alone accounted for 6% of pneumococcal isolates in nasopharyngeal carriage among children experiencing ARIs. A recent review of pneumococcal serotype distribution in middle ear fluid and nasopharyngeal carriage in pediatric AOM across countries identified 15B/C as a dominant serotype in 13 out of 17 study populations [15]. Our findings indicate that PCV15 and PCV20 may offer differential coverage of serotypes contributing to pediatric ARIs, in contrast to IPD.

Because differences in design, enrollment criteria, and microbiologic methods across studies of ARI etiology could preclude generalization of findings to all outpatient ARI cases, our primary analyses used a vaccine-probe design. Attributable fraction estimates based on this approach for AOM were similar to those estimated in analyses based on data from middle ear fluid samples or differential carriage of pneumococcal serotypes (children with AOM vs healthy children). For pneumonia and sinusitis we observed greater variability in estimates generated by different

Table 5. National Projection of Antibiotic Prescriptions Attributable to Any Pneumococcal, PCV15-Additional, and PCV20-Additional Serotypes, 2016–2019

Age Stratum and Condition	Estimated Annual Outpatient Antibiotic Prescriptions Among US Children, in Thousands (95% CI)		
	All Pneumococci	PCV15-Additional Serotypes[a]	PCV20-Additional Serotypes[a]
< 2 y			
AOM	633 (421–928)	33 (19–55)	170 (109–259)
Pneumonia	71 (43–118)	3 (1–4)	16 (10–27)
Total[b]	706 (490–1006)	36 (21–58)	186 (124–277)
2–4 y			
AOM	747 (535–1027)	39 (24–62)	200 (138–288)
Pneumonia	90 (57–145)	3 (2–5)	20 (13–33)
Total[b]	840 (621–1125)	42 (27–66)	222 (157–311)
All children < 5 y[c]			
AOM	1387 (1057–1809)	72 (46–111)	372 (269–509)
Pneumonia	162 (103–259)	6 (3–10)	37 (23–59)
Total[b]	1555 (1211–1991)	78 (51–118)	410 (304–551)
5–17 y			
AOM	659 (512–845)	34 (22–52)	177 (130–239)
Pneumonia	122 (78–194)	4 (3–7)	28 (18–45)
Sinusitis	1135 (681–1885)	40 (23–70)	257 (153–431)
Total[b]	1925 (1402–2744)	80 (54–119)	465 (335–663)
All children ≤17 y[c]			
AOM	2049 (1606–2597)	107 (69–162)	550 (408–737)
Pneumonia	333 (214–523)	12 (7–20)	75 (48–120)
Sinusitis	1473 (815–2602)	52 (28–97)	334 (184–597)
Total[b]	3881 (2969–5248)	173 (118–252)	968 (722–1318)

Abbreviations: AOM, acute otitis media; CI, confidence interval; PCV, pneumococcal conjugate vaccine.

[a]Includes vaccine serotypes and corresponding aggregated serotypes/serogroups as detailed in Supplementary Table 6. PCV-15 additional serotypes (not included in PCV13): 22F, 33F. PCV20-additional serotypes: 8, 10A, 11A, 12F, 15B, 22F, 33F.

[b]Number of antibiotic prescriptions by condition may not sum to total due to rounding.

[c]Number of antibiotic prescriptions across age groups may not sum to all children totals due to rounding.

methods, with attributable fraction estimates of 0.4%–1.6% for PCV15-additional serotypes and 2.7%–10.4% for PCV20-additional serotypes. This wide range reflects uncertainty from limited availability of pediatric ARI etiology studies. However, incidence rates for these conditions were low compared with AOM; PCV15/20 impacts on pediatric outpatient health care utilization will likely be driven by AOM.

Our study has limitations. First, we used ICD-10-CM codes to identify ARIs and could not validate diagnosis accuracy. Second, we used meta-analyses of multiple studies, including studies from non-US high-income countries with similar PCV13 implementation history, to estimate serotype distribution and pneumococcal prevalence. Although these measures may vary across settings, use of multiple studies mitigated bias from single studies/regions. Studies of pediatric ARI etiology in representative samples of US children are needed to monitor pneumococcal disease and inform vaccine formulations. Third, our analyses included estimates of aggregated serotype prevalence from primary studies; sensitivity analyses showed resulting bias to be low. Cross-protection with PCVs has been observed within certain serogroups (eg, 6A/6C), although not all (eg, 19A/19F) [38]. Notably, antibody cross-reaction has been observed for 15B/C, an important contributor to ARIs in our study, but not 15A [39]. Fourth, although we use negative controls, secular factors not captured by these controls could cause residual bias, especially for sinusitis, for which new diagnostic criteria were introduced in 2013 [26]. Fifth, our analyses address burdens associated with PCV15- and PCV20-additional serotypes, and do not quantify disease preventable by vaccination [24]. While trials have demonstrated that PCV15/20 are safe and immunogenic in children, VE against ARIs is unknown. Vaccine impact will depend on direct and indirect protection and vaccine coverage. Sixth, we do not consider additional PPSV23 serotypes, which is only recommended for select children and not known to prevent carriage and induce herd protection [40]. Seventh, long-term PCV use among US children presents challenges in determining total burdens from PCV15/20 serotypes. While replacing PCV13 with PCV10 was associated with increased serotype 3 and 19A disease in Belgium [35], dynamics of serotypes under scenarios without PCV use in the United States are unknown. Seventh, given limited data in older children, we assumed that disease etiology was similar across ages. Eighth, we excluded sinusitis from our estimates of burdens in children aged < 5 years as sinus development is typically incomplete in these ages [26, 27] and sampled sinusitis visits in NAMCS/NHAMCS did not

meet size requirements for projection to national estimates [36]. However, a 2023 study using MarketScan data found similar burdens of amoxicillin/amoxicillin-clavulante prescriptions for sinusitis in children aged 0–5 years and 6–11 years [41]. We include sinusitis-related burdens in children < 5 years in the less conservative all-children ≤ 17 years totals to account for contributions from sinusitis in young children. Finally, our study uses data from before the coronavirus disease 2019 (COVID-19) pandemic. Long-term changes in outpatient health care utilization following acute phases of the pandemic are unknown.

CONCLUSION

In US children aged < 5 years, additional serotypes in PCV15 and PCV20 account for an estimated 97 000 and 505 000 outpatient visits and 78 000 and 410 000 outpatient antibiotic prescriptions, respectively, each year. When the total burden is considered in all US children aged ≤ 17 years, ARIs attributable to PCV15- and PCV20-additional serotypes account for 0.4% and 2.1%, respectively, of all pediatric antibiotic prescriptions. Compared with PCV15-additional serotypes, we estimated PCV20-additional serotypes account for > 5 times the burden of visits and antibiotic prescriptions. Our findings demonstrate a basis for PCV15 and PCV20, especially PCV20, in preventing pneumococcal ARIs and averting antibiotic use in children.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (http://jid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Author contributions. L. M. K. conceptualized and designed the study, conducted all literature reviews and data analysis, and drafted the initial manuscript. J. A. L. conceptualized and designed the study, oversaw all statistical analyses, and drafted the initial manuscript. M. K. and K. L. A. conceptualized and designed the study, assisted with literature reviews, and provided administrative support. S. K. and L. A. K. contributed substantially to study conception and design, and provided administrative support and data access. S. Y. T. and A. L. C contributed substantially to study conception and design. All authors critically reviewed and revised the manuscript.

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Data availability. MarketScan data are proprietary and thus data are not publicly available.

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