Impact of 7-Valent and 13-Valent Pneumococcal Conjugate Vaccines in the United States: A Systematic Literature Review

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BACKGROUND

- Pneumococcal disease manifests as invasive pneumococcal disease (IPD), including meningitis and bacteremia, and noninvasive disease, including nonbacteremic pneumonia, otitis media (OM), bronchitis, and sinusitis. It is a major global cause of morbidity and mortality.[1]
- 7-valent pneumococcal conjugate vaccine (PCV; PCV7, Prevenar®) was introduced in the United States in 2000. In 2010, a 13-valent vaccine (PCV13, Prevnar 13®) replaced PCV7.[2,3]
- Evidence shows PCVs have substantially reduced the occurrence of pneumococcal disease. For instance, the Centers for Disease Control and Prevention (CDC) reported overall IPD incidence in children under 5 years in the United States declined from 100 cases per 100,000 in 1998 to 9 cases per 100,000 in 2015.[4]
- However, published data have not been systematically collated to provide an estimate of total impact of PVCs on pneumococcal disease burden in US children.

OBJECTIVE

- This systematic literature review (SLR) aimed to identify real-world evidence to assess the impact of the PCVs in reducing the occurrence of pediatric IPD since their introduction in the United States.

METHODS

- Procedures followed established best methods used in the science of systematic review research.[5,6] The SLR was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[7]
- Search conducted May 23, 2019, in Medline and EMBASE. Articles identified using search strategies that include a combination of indexing terms (medical subject headings [MeSH] terms in Medline, and Emtree terms in EMBASE) and free-text terms.
- Additionally, reference lists of SLRs or topical reviews, the proceedings of conferences not indexed on Medline or EMBASE (International Symposium on Pneumococci and Pneumococcal Diseases [ISPPD] 2018, IDWeek 2017 and 2018, and the European Society for Paediatric Infectious Diseases [ESPID] 2018 and 2019), and cited material on the CDC website were searched.
- Searches were limited to the last 20 years (1999–2019) for United States only and English-language-only articles.
  - PICOS criteria were as follows: Population = <19-year olds; Intervention = PCV7 or PCV13; Comparators = no vaccination; Outcomes = incidence, prevalence, frequency, mortality, costs, healthcare resource utilization (HCRU) that included hospitalizations, outpatient, and emergency department visits; Study design = observational or surveillance.
- Citations that passed abstract screening were retrieved in full text. Two investigators independently screened full-text papers to identify relevant studies based on PICOS criteria.
- A list of accepted studies was produced after article inclusion identification, as well as a list of full-text excluded articles organized by reason for exclusion.
- Information from included studies was extracted, including study and patient characteristics and outcomes reported by year.

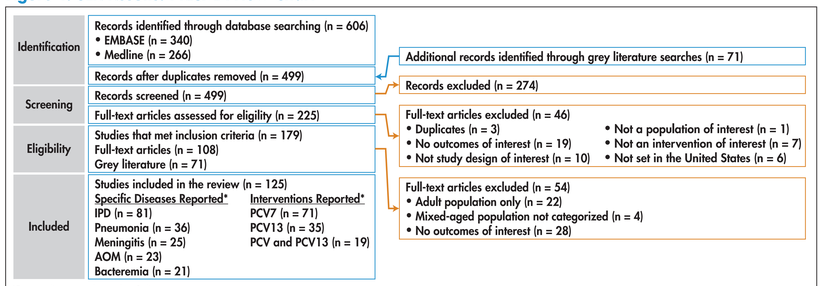
RESULTS

- There were 125 articles that met inclusion criteria. The PRISMA diagram in **Figure 1** shows the flow of the evidence identification and selection.
- Included studies covered large populations from all US geographic areas and typically reported data from multiple centers (92% of studies).
- Over half of the included evidence was reported from active laboratory- and population-based surveillance studies, mostly, the Active Bacterial Core surveillance was cited as the data source. Other data sources and study designs identified are listed in **Table 1**.
- All studies indicated clear reductions in multiple manifestations of pneumococcal disease with PCV7 and PCV13 use. For instance, 4 studies from different locations reported reductions in the incidence rate of IPD per 100,000 persons for children under 18 years since the introduction of PCV7[8,9] and PCV13[10,11] **(Figure 2)**.
- Variations across studies in outcome definitions, study years, and age strata confounded assessment of PCV impact on specific pneumococcal disease outcomes and key burden indicators, such as tympanostomy tube placement and antibiotic prescriptions.

Gaps in the Evidence

- Few studies were identified to report the following:
  - Medical costs associated with PCV's use (n=7)
  - Data on risk groups with underlying diseases (eg, sickle cell anemia and other genetic disorders, HIV+, or malignancies) or children from diverse ethnicities (n=15)
  - Data on net effect (cases averted) due to PCV's introduction (n=22)
- For acute otitis media (AOM; n=23) and pneumonia (n=36), there was a lack of consistent data reporting from the 3 periods of interest.
  - No single study reported empirical outcomes data over the entire period of interest.
  - The sources available reported a range of definitions and outcomes, making comparison difficult (eg, outcomes for AOM included AOM episodes, AOM incidence rates, AOM visits, AOM hospitalizations, simple AOM, complex AOM).
  - Data for pneumonia and AOM rarely provided the causal pathogen and instead all-cause data were reported.
  - Impact on pneumonia varied depending on the etiology of disease, treatment location (inpatient/outpatient), and severity (x-ray confirmed).
  - Data were rarely available, attributing pneumonia or AOM cases to specific serotypes.
- There are limited recent data reported (post-2017), especially for AOM and pneumonia where no data were reported.

Figure 1. SLR Results: PRISMA Flow Chart

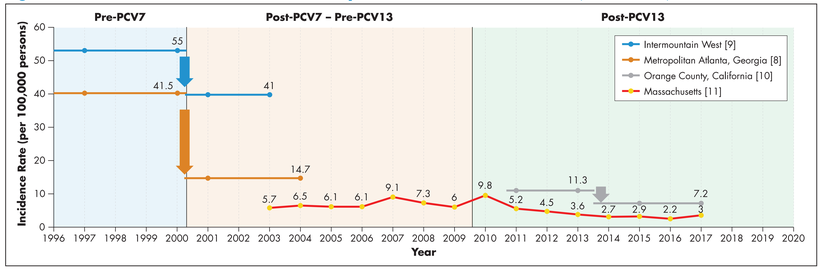


*Some studies reported more than 1 disease.
AOM = acute otitis media; IPD = invasive pneumococcal disease; PRISMA = Preferred Reporting Items for Systematic Meta-Analysis; SLR = systematic literature review.

Table 1. SLR Results: Study Characteristics

Study Characteristics	Results (Number of Studies)	
Data Source	• Active Bacteria Core surveillance (ABCs; n = 37) • National Inpatient Sample (NIS; n = 9) • US Pediatric Multicenter Pneumococcal Surveillance Study Database of 8 children's hospital (n = 8) • Kaiser Permanente Northern California (KPNC; n = 4) • MarketScan database (n = 4) • PROTEKT US study (n = 2)	• Kids' Inpatient Database (KID, n = 2) • Healthcare Cost and Utilization Project (HCUP) State Inpatient Database (SID, n = 2) • Enhanced surveillance system in Massachusetts (n = 2) • Other large database sources (1 each; n = 5) • Single center sources (1 each; n = 10) • Intermountain Health Care (IHC) data warehouse (n = 3)
Study Design	• Laboratory/population-based surveillance (n = 64) • Retrospective observational (n = 25) • Model (n = 10) • Prospective observational (n = 11) • Observational study not specified (n = 5) • Ecologic study (n = 4)	• Time-series analysis (n = 2) • Serial cross-sectional surveillance (n = 2) • Epidemiologic analysis (n = 1) • Quasi-experimental cohort study, pretest-postest study design (n = 1) • Medical audit using self-reported measures collected from physicians (n = 1)

Figure 2. SLR Results: Incidence of IPD in <18-year-olds in the United States (1996–2017)



CONCLUSIONS

- **PCVs have greatly decreased multiple manifestations of pneumococcal disease in the United States, including IPD, pneumonia, OM, mastoiditis, osteomyelitis, and sinusitis.**
- **Granular data on frequency and morbidity associated with specific pneumococcal diseases with consistent reporting over time and on associated HCRU are needed to quantify the public-health impact of these vaccines.**

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