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Review

Burden and serotype distribution of invasive Pneumococcal disease among high-risk patients from Latin America and the Caribbean: A systematic review and meta-analysis

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ABSTRACT

Background: Invasive pneumococcal diseases (IPD), caused by *Streptococcus pneumoniae*, entail significant morbidity and mortality, especially in high-risk populations. In Latin America and the Caribbean (LAC) data are scarce.
Objective: To estimate the disease burden, serotype distribution, and healthcare resource use among high-risk children and adults with IPD in LAC.
Methods: We conducted a systematic review following PRISMA guidelines and a preregistered protocol (PROSPERO CRD42025629682). We searched CENTRAL, PubMed, Embase, LILACS, EconLIT, Global Health, CINAHL, SciELO, surveillance networks, and grey literature sources (Jan 2000-Dec 2024).
Results: Search yielded 6227 records, 181 studies were included, representing 63,671 IPD cases from 20 LAC countries. Pneumonia accounted for 52% of IPD cases, followed by meningitis 22% and bacteremia 20%. Median incidence was 13.13 cases per 100,000 persons per year, global case fatality rate was 17%, in meningitis 23% and in adults ≥60 years was 35%. In 36% of patients ICU admission was required. Post-PCV introduction, vaccine serotypes declined while nonvaccine serotypes increased, particularly among children <5 years, with variability across LAC countries.
Conclusion: This review highlights the burden and patterns of IPD serotypes among high-risk populations in LAC. Optimized vaccination strategies and continuous surveillance are required.

Background

Streptococcus pneumoniae (Spn) frequently colonizes the nasopharynx and can cause disease from otitis media and sinusitis to life-threatening invasive pneumococcal diseases (IPD) [1,2]. IPD involve severe manifestations such as bacteremia, meningitis and pneumonia, with *Spn* isolated from sterile sites, representing a global public health concern with substantial morbidity and mortality [3,4].

Certain populations, including children <5 years, adults ≥60 years, and individuals with underlying conditions, are at higher risk. Immunocompromised hosts, people with specific chronic medical conditions (*e.g.,* cardiovascular, pulmonary, hepatic, or renal disease, diabetes mellitus) or anatomical vulnerabilities (cerebrospinal fluid leaks, cochlear implants, asplenia) are particularly susceptible [3,5,6]. People with malignancies have 13-50 times higher IPD incidence than the general population, while people living with HIV (PLHIV) have a sevenfold increased risk and higher mortality [5].

Introduction of Pneumococcal conjugate vaccines (PCVs) and the 23-valent pneumococcal polysaccharide vaccine (PPV23) prevent IPD, and have saved around 1.63 million lives globally [6]. In Latin America and the Caribbean (LAC), PCVs targeting 7, 10,

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or 13 serotypes have been progressively introduced into National Pediatric Immunization Programs since 2009. While newer PCV15, PCV20, and PCV21 are not yet widely incorporated in all LAC national immunization Programs (NIP).

Previous reviews in LAC have focused on the burden of pneumococcal disease and serotype distribution in the general population [7,8]. However, comprehensive epidemiologic and clinical data on IPD in high-risk LAC populations remain limited and are essential for targeted public health strategies, effective disease control, vaccination policy optimization and economic analyses [9,10].

We aimed to synthesize available evidence to estimate the burden of IPD (prevalence, incidence, and mortality), serotype distribution, and healthcare resource use over time among children and adults with high-risk conditions in LAC over the last 24 years, thereby addressing a critical evidence gap.

Methods

This systematic review and meta-analysis followed a prespecified protocol registered in the PROSPERO (CRD42025629682). We adhered to the Cochrane Handbook for Systematic Reviews of Interventions [11] and the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines. Reporting follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [12,13].

Inclusion criteria

Study Designs: We included randomized/quasi-randomized controlled trials (control arms), controlled (CBA) and uncontrolled before-and-after studies (UBA), interrupted time series (ITS/CITS), cohort studies, case-control studies, case series, and surveillance reports. Systematic reviews were used only as sources for primary studies. We sought studies focusing on individuals from LAC countries with confirmed IPD with high risks conditions. These included immunocompromised such as PLHIV, cancer, organ or bone marrow transplant recipients, dialysis patients, asplenia or primary immunodeficiencies and chronic immunosuppressive therapy. We also included immunocompetent individuals with chronic conditions like chronic heart, lung, liver, or kidney diseases, diabetes, alcoholism, chronic obstructive pulmonary disease, or cerebrospinal fluid leaks or cochlear implants. At risk ages, defined as children <5 years and adults >60 years, were included. IPD was confirmed by isolating *S. pneumoniae* from a normally sterile site, like blood or cerebrospinal fluid. A study was eligible if it documented at least 10 confirmed IPD cases. Our primary goal was to describe the disease burden, serotype distribution, IPD patterns across different time periods, age groups, specific LAC countries, diverse risk conditions. Our principal outcomes were to estimate the prevalence or incidence of IPD, case fatality rates (CFR), healthcare resource utilization (such as hospitalization, intensive care unit admissions and length of hospital stays), and serotypes distribution since PCV introduction in LAC. Our search included studies in any LAC country, published or reported between January 1, 2000, and December 31, 2024.

Information sources and search strategy

We searched the following electronic databases from inception to December 31, 2024: Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, Embase, LILACS, EconLIT, Global Health, CINAHL, Dissertations & Theses Global, SciELO, and Web of Science. We also searched specific surveillance network databases (*e.g.,* SIREVA, WHO Genome sequencing projects) and grey literature sources, including regional Ministry of Health websites, PAHO reports, conference proceedings, and hospital reports. Reference lists of included studies and relevant reviews were hand-searched. Experts in the field were consulted. The literature search was conducted without any language restrictions

Study selection, data extraction, and assessment of risk of bias

Search results were managed using Covidence systematic review software [14]. Two reviewers independently screened titles and abstracts against eligibility criteria. Two reviewers independently retrieved and assessed the full texts of potentially relevant articles. Disagreements at both stages were resolved by discussion or consultation with a third reviewer. Reasons for excluding studies at the full-text stage were documented.

A pair of reviewers independently extracted data from included studies using a standardized, prepiloted data extraction form. Extracted information included: study identifiers (author, year, country), study design, study period, setting, participant characteristics (age group, specific high-risk conditions, sample size, denominator if available), IPD confirmation method, clinical syndromes, serotype data (methods, specific serotypes, number/proportion per serotype), outcomes reported (prevalence, incidence, CFR, resource use metrics), PCV introduction status/details, and funding sources. Discrepancies were resolved by consensus or third-party arbitration. Authors were contacted for missing data where feasible.

The risk of bias for each included study was assessed by two reviewers independently. For RCTs, the Cochrane Risk of Bias 2 (RoB 2) tool was used [15]. For observational studies, the National Heart, Lung, and Blood Institute (NHLBI) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies was adapted [16]. Specific criteria outlined in the protocol were used for CBA, UBA, and ITS design [17]. Each domain was judged as "low risk," "high risk," or "some concerns" ("unclear risk"). Disagreements were resolved by consensus. Overall risk of bias was considered in the interpretation and sensitivity analyses.

Data synthesis

A narrative synthesis described the characteristics and findings of the included studies. Quantitative synthesis via meta-analysis was performed when methodologically possible. Proportion meta-analyses were conducted using random-effects models (DerSimonian-Laird method) to estimate pooled proportions for serotype distribution, CFR, and resource use. Theoretical coverage of PCV10, PCV13, PCV15, PCV20, and PCV21 were estimated. Studies with fewer than 20 serotyped strains were excluded from the analysis. The Freeman-Tukey double arcsine transformation stabilized variances, particularly for proportions close to 0 or 1 [18]. Pooled proportions and 95% confidence intervals (CIs) were calculated. Heterogeneity among studies was assessed using the I^2 statistic, with values $<40\%$, 40-60%, and $>60\%$ indicating low, moderate, and substantial heterogeneity, respectively [19]. Potential sources of heterogeneity were explored through prespecified subgroup analyses.

Incidence rates were calculated as cases per 100,000 person-years when data was available. All analyses were performed using R software version 4.3.3 [20] with the 'meta' package [21].

Subgroup analyses were planned based on: study design, country, specific high-risk condition, vulnerable age, IPD clinical syndrome (meningitis, bacteremia, pneumonia), and PCV implementation status (2000-2014 as pre vs 2015-2024 as post-PCV era, where specified). Sensitivity analyses for low risk of bias studies was performed.

Institutional Review Board (IRB) approval was not necessary as the systematic review analyses secondary data.

Results

The electronic database search yielded 6227 records. After removing duplicates, 6125 records were screened by title and abstract. A total of 392 full-text articles were assessed for eligibility, and of these, 181 studies met the inclusion criteria (Figure 1 PRISMA flow diagram, and S1A Table). The search strategy is available in S1 File, and the list of excluded studies with reasons is provided in S2 Table.

Of the 181 included studies, 44 focused on individuals with chronic high-risk conditions for IPD, 116 examined children under 5 years of age, 11 investigated adults over 60 years, and 10 studies encompassed both age groups S1A and S1B Table.

Studies on individuals with chronic high-risk conditions: 44 studies were published between 2002 and 2022, encompassing 4989 participants with confirmed IPD across 10 LAC countries. Most of the studies were conducted in Argentina (13), Brazil (10), and Chile (8). Clinical manifestations were documented as follows: 33 studies reported pneumonia, 16 meningitis, and 15 bacteremia. The study designs included case series (17), cohorts (15), cross-sectional (11), and one case-control study. All included populations were derived from nonprobability sampling methods. The primary high-risk categories comprised immunocompetent persons with chronic conditions (28), patients with cancer (7), PLHIV (6), and individuals with pharmacologically-induced immunosuppression (3).

Studies on age-vulnerable populations (<5 years and >60 years): The 116 studies of children under 5 years spanned from 2001 to 2024, incorporating 43,342 IPD cases from 20 countries. Brazil led with 33 studies, followed by Argentina (17) and Colombia (17). Methodological designs included cohort studies (50), cross-sectional investigations (34), case series (30), and ecological studies (2). Seventy-one studies reported pneumonia, 76 meningitis, and 50 bacteremia, while 17 provided IPD case data.

For the population over 60 years, 11 studies published between 2002 and 2023 included 4523 participants from seven countries. Argentina contributed the most studies (4), followed by Chile (3). Study designs comprised cohorts (8), case series (2), and one cross-sectional study. Four studies included pneumonia, meningitis, and bacteremia cases, while two studies provided comprehensive IPD data.

Ten studies incorporated 10,817 both target age groups (<5 and >60 years), published between 2007 and 2023. Brazil was the primary contributor with 5 studies. Study designs included cohorts (4), cross-sectional (3), interrupted time series (2), and one epidemiological study. The most frequently studied condition was IPD without specification (5), meningitis (5) and pneumonia (1).

Overall burden of invasive pneumococcal disease (IPD)

The pooled prevalence of IPD, was dominated by pneumonia, which accounted for 53% of all cases (95% CI, 48-59%, I^2=95.8%), followed by meningitis at 21% (95% CI, 17-25%, I^2=96.4%) and bacteremia at 20% (95% CI, 16-25%, I^2=95.1%). See Figure 2. Twenty–eight population–based studies reported incidence rates. The median of incidence was 13.13 cases per 100,000 persons per year (IQR 2.24-45), with marked heterogeneity between studies.

Epidemiology by diagnosis and risk group

Pneumonia

Among immunocompromised individuals, PLHIV exhibited the highest prevalence of pneumococcal pneumonia at 81% (95% CI, 71-89%; three studies, I^2=0.7%), followed by cancer patients with 43% (95% CI, 27-60%; four studies, I^2=91.7%). Immunocompetent persons with chronic high–risk conditions had a prevalence of 35% (95% CI, 22-51%; ten studies, I^2=95.8%). Age–stratified analyses revealed prevalences of 56% (95% CI, 50-61%; fifty-five studies, I^2=96%) in children <5 years and 51% (95% CI, 21-80%; five studies, I^2=96.8%) in adults ≥60 years.

Sensitivity analysis confirmed pneumonia as the predominant IPD manifestation (53%, 95% CI, 47-59%), with consistent estimates in PLHIV (81%,95% CI, 71-89%), cancer patients (43%, 95% CI, 27-60%), immunocompetent individuals with chronic conditions (32%, 95% CI, 20-47%)), children <5 years (56%, 95% CI, 50-62%), and adults ≥60 years (59%, 95% CI, 18-90%).

Meningitis

Children <5 years showed a prevalence of 23% (95% CI, 19-28%; fifty-six studies, I^2=96.6%), whereas adults ≥60 years reached 25% (95% CI, 7-62%; five studies, I^2=97.8%). Immunocompetent persons with chronic conditions showed a prevalence of 20% (95% CI, 15-27%; seven studies, I^2=78.9%). Among PLHIV, meningitis prevalence was 9% (95% CI, 6-15%; four studies, I^2=3.4%), and in patients with cancer, 4% (95% CI, 2-7%; three studies, I^2=16%).

Sensitivity analysis produced similar estimates: children <5 years 23% (95% CI, 18-28%), immunocompetent persons with chronic conditions 22% (95% CI, 17-28%), adults ≥65 years 16% (95% CI, 6-37%), PLHIV 9% (95% CI, 6-15%), and cancer patients 4% (95% CI, 2-7%).

Bacteremia

PLHIV had a prevalence of 57% (96%CI, 5-97%, two studies, I^2=97.9%). Cancer patients had a prevalence of 28% (95% CI, 9-62%; four studies, I^2=97.1%), whereas immunocompetent individuals with chronic conditions experienced 18% (95% CI, 9-31%; six studies, I^2=93.8%). Children <5 years exhibited 18% (95% CI, 14-23%; forty-six studies, I^2=94%), and adults ≥60 years exhibited 29% (95% CI, 14-50%; two studies, I^2=83.1%).

Sensitivity analysis yielded an overall prevalence of 21% (95% CI, 16-27%); PLHIV reached 57% (95% CI, 5-97%), adults ≥60 years 39% (95% CI, 28-52%), immunocompetent persons with chronic conditions 19% (95% CI, 9-36%), children <5 years 19% (95% CI, 14-25%), and cancer patients 28% (95% CI, 9-62%).

The distribution of IPD cases across the high-risk groups is shown in Figure 2.

Mortality by IPD

The overall CFR for IPD was 17% (95% CI, 13-22%, I^2=92%). Clinical–manifestation–specific analyses showed meningitis with the highest CFR at 23% (95% CI, 16-32%; nineteen studies, I^2=91%), bacteremia at 14% (95% CI, 6-29%; six studies, I^2=90.6%), and pneumonia at 13% (95% CI, 8-20%; seventeen studies, I^2=88.4%). See Figure 3.

Mortality by risk group

Adults ≥60 years had a pooled CFR of 35% (95% CI, 28-44%; four studies, I^2=17.8%). PLHIV showed 19% (95% CI, 14-26%; five studies, I^2=20.3%). Immunocompetent persons with chronic conditions experienced 18% (95% CI, 13-24%; twenty studies, I^2=89.1%). Cancer patients reported 14% (95% CI, 5-31%; five studies, I^2=90.8%). Children <5 years demonstrated 12% (95% CI, 9-15%; forty–three studies, I^2=93.8%).

Sensitivity analysis demonstrated that adults ≥60 years sustained the highest mortality across risk groups (31%, 95% CI, 17-48%), followed by immunocompetent persons with chronic conditions (20%, 95% CI, 14-27%), PLHIV 18% (95% CI, 12-25%), children

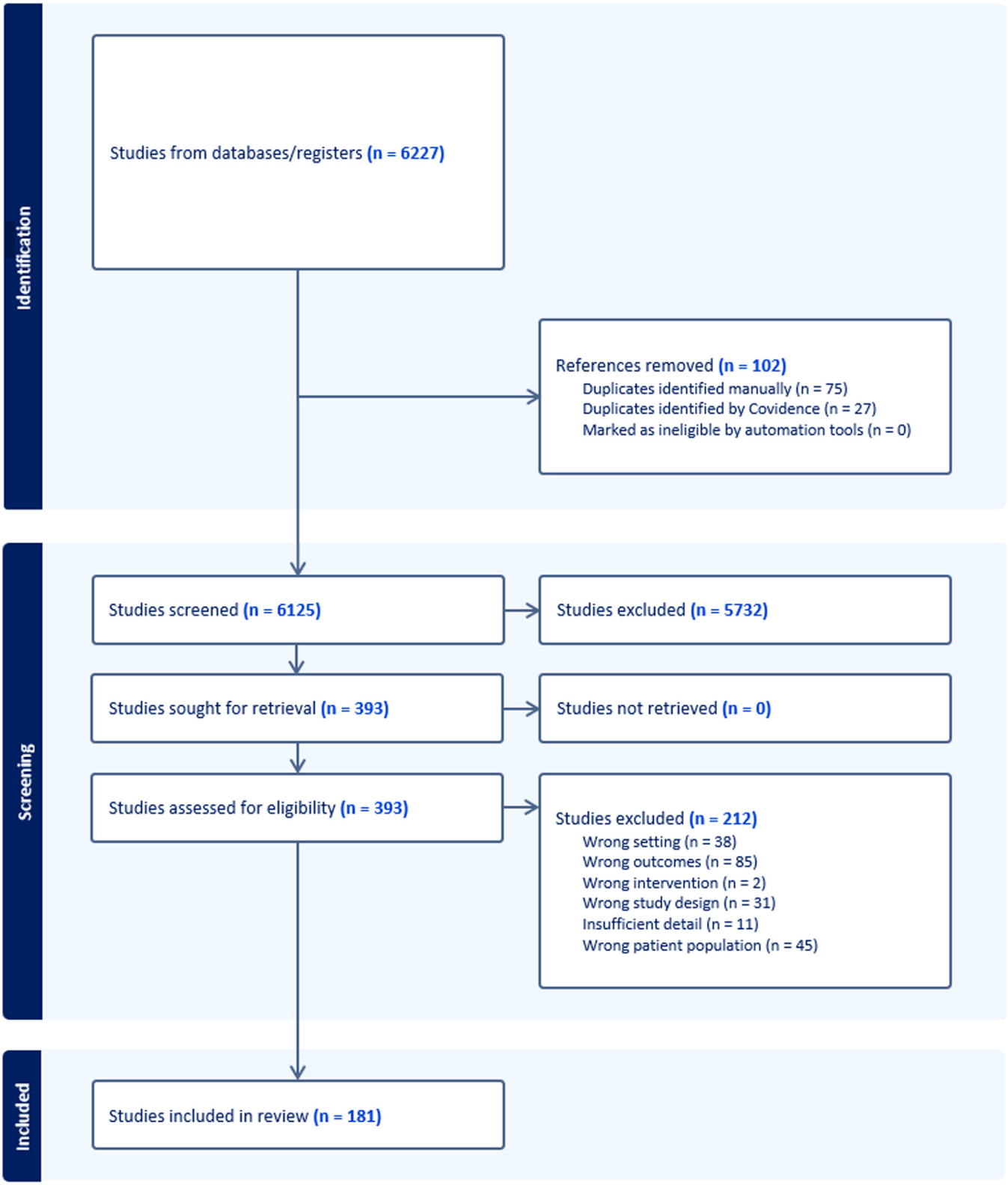


Figure 1. PRISMA flowchart.

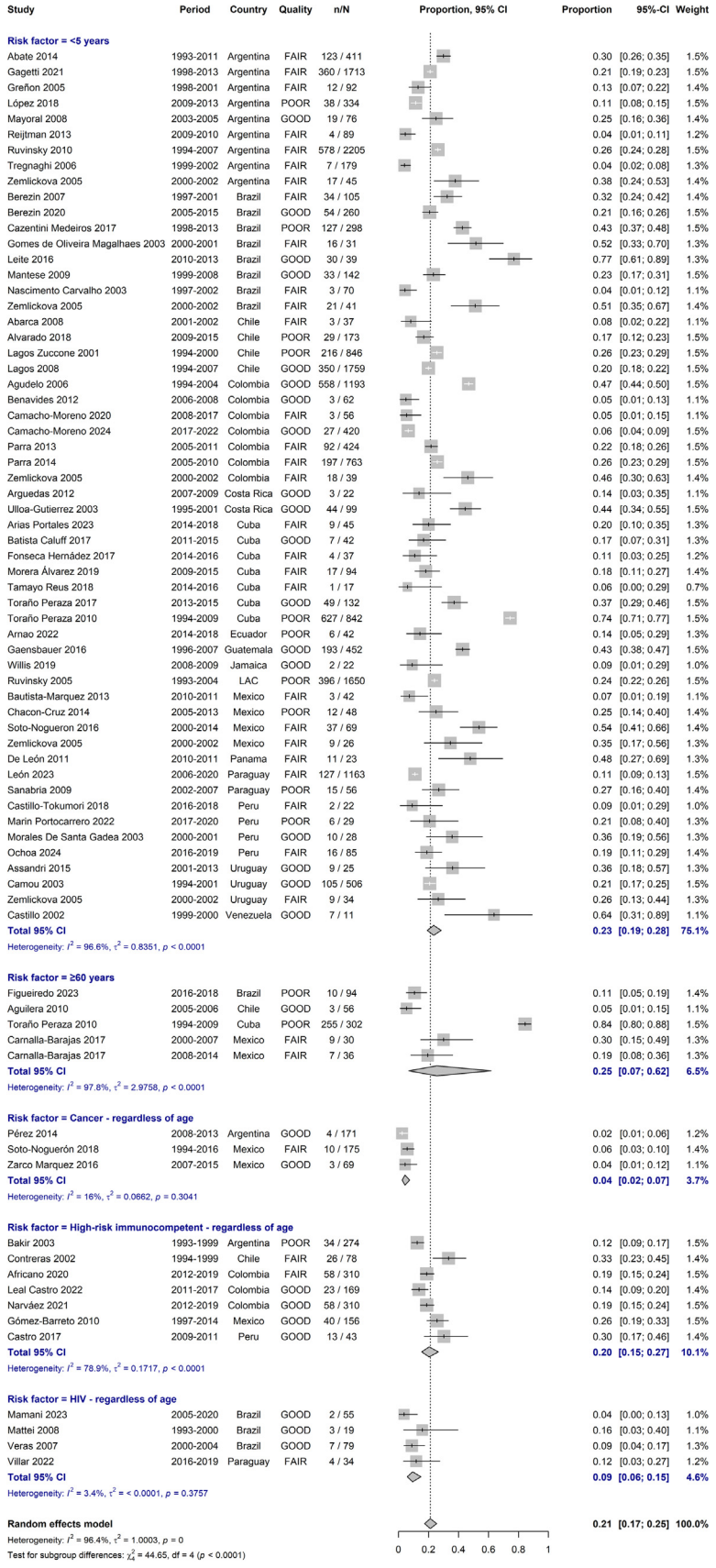


Figure 2. IPD prevalence across risk factor groups. (a) Invasive Pneumonia cases, (b) Meningitis Cases, (c) Bacteremia cases.

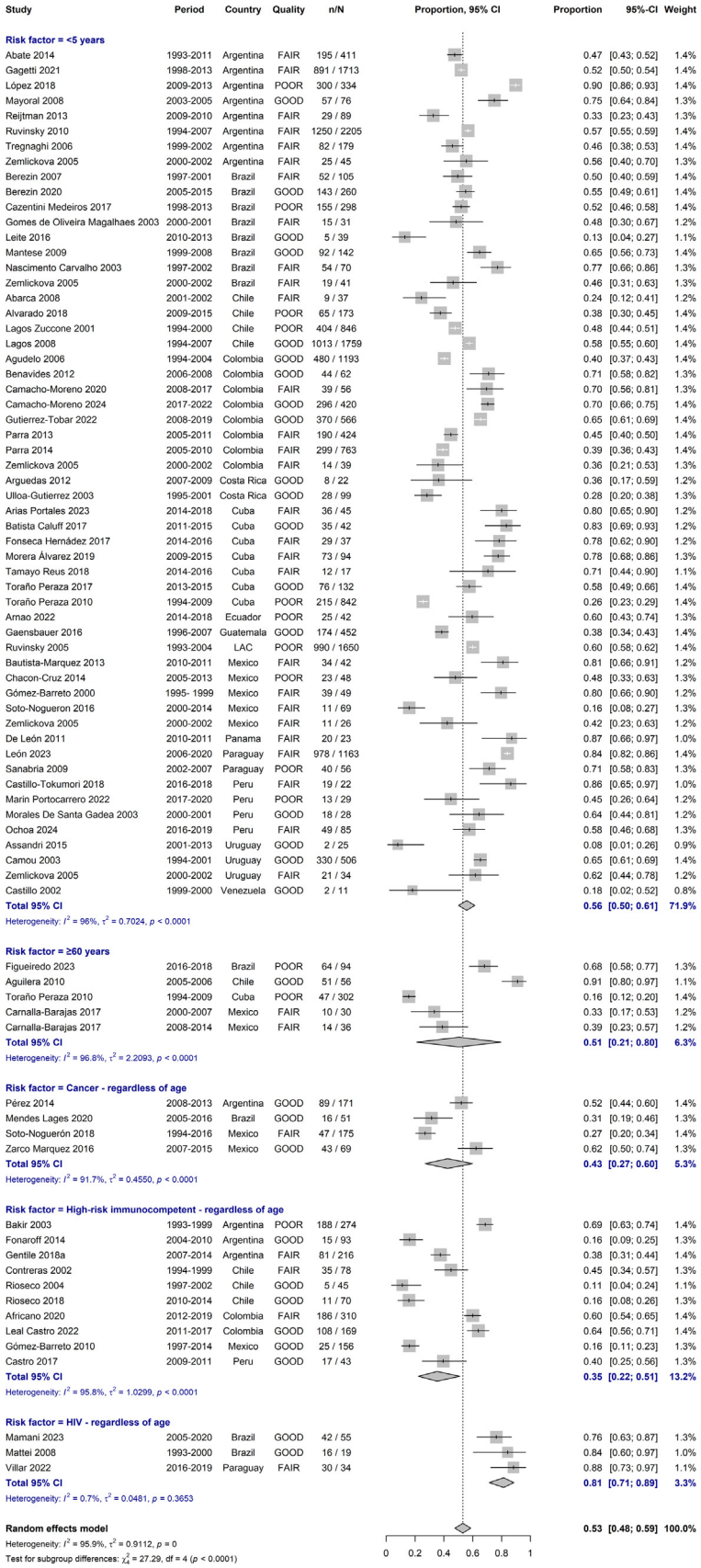
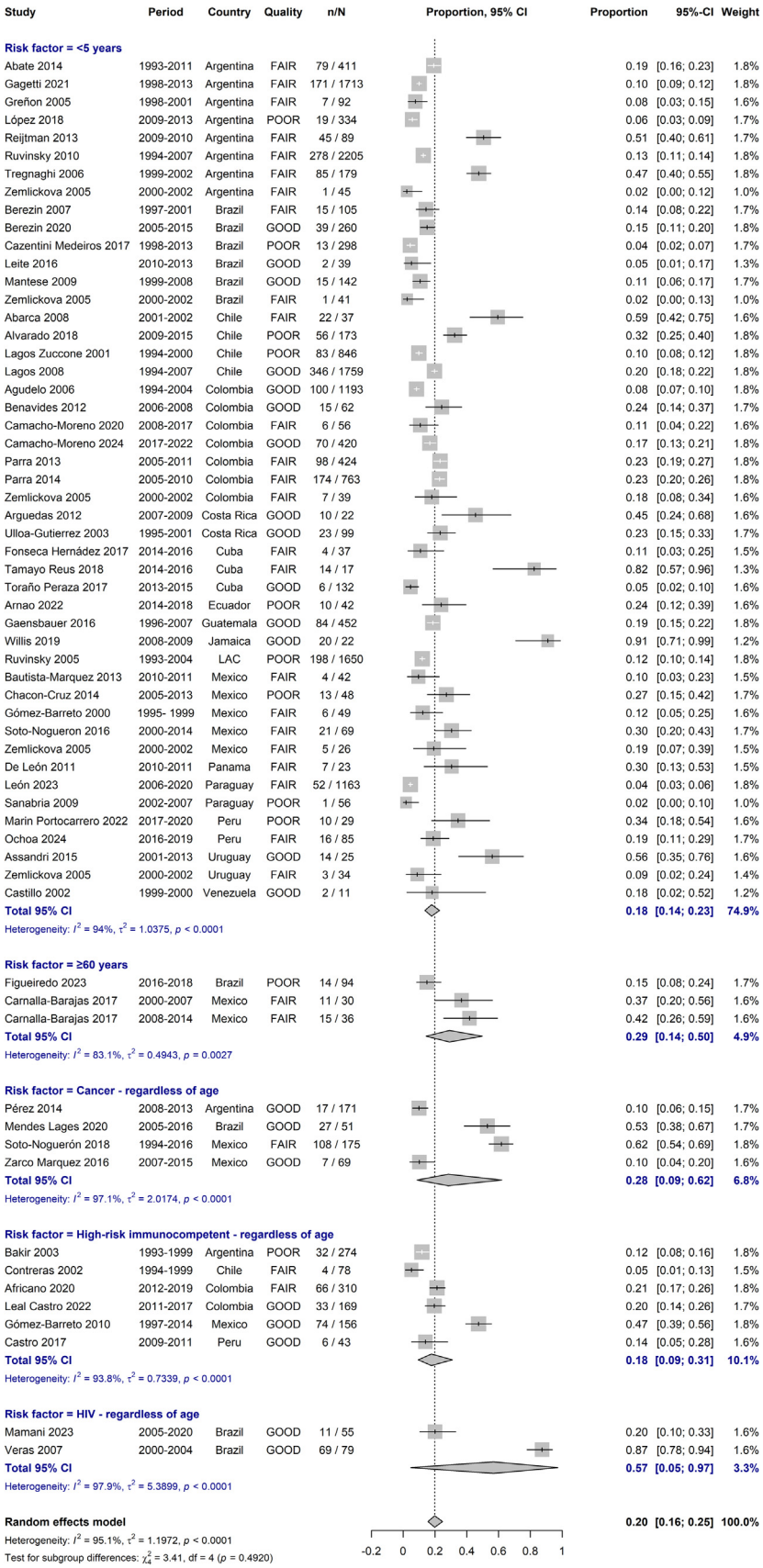


Figure 2. Continued



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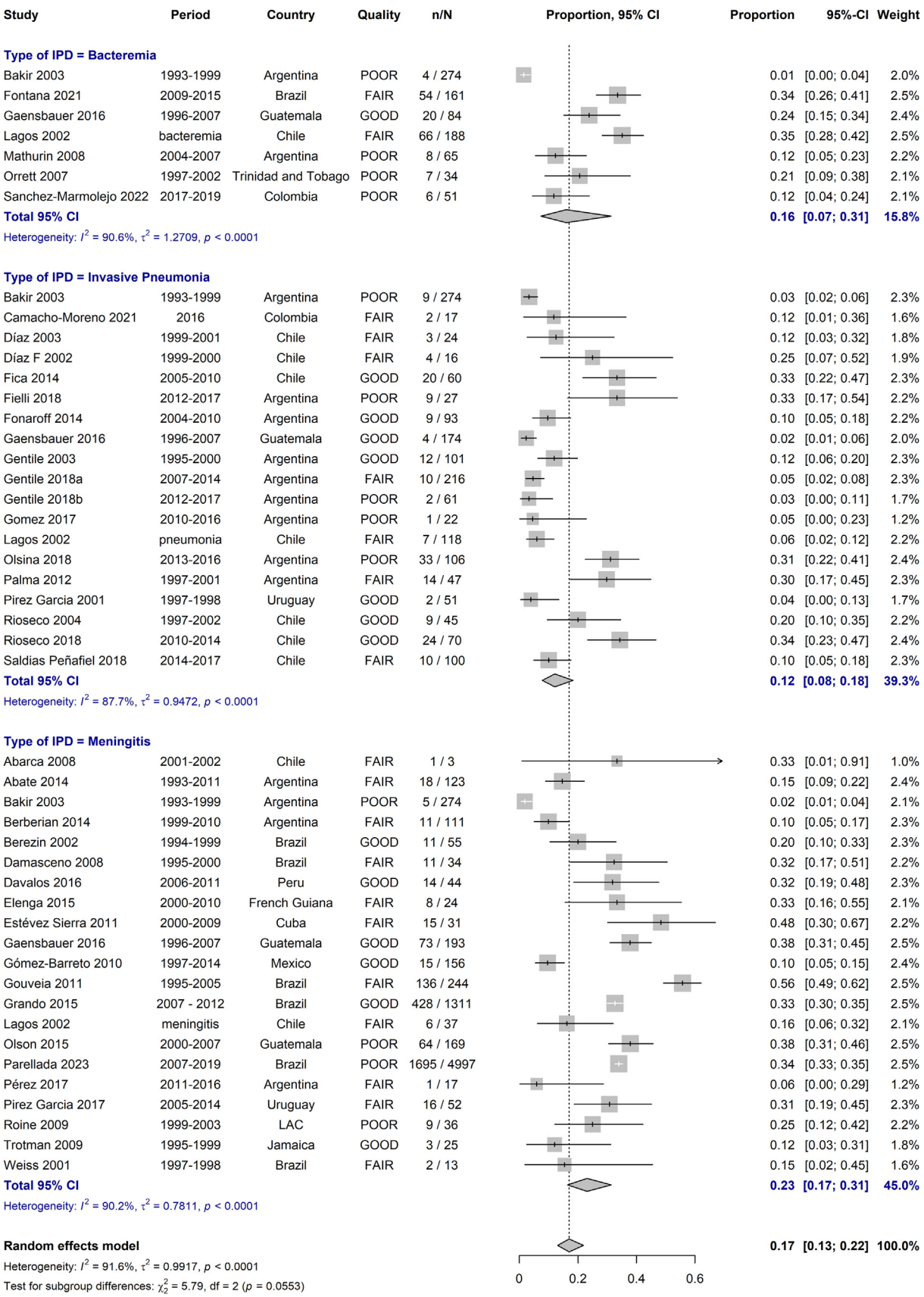

Figure 3. Global mortality according to IPD diagnosis.

Table 1
Prevalence of serotypes contained in PCVs during the pre (2000-2014) and post (2015-2024) implementation of PCV-10 and PCV-13 in the region.

Group	PCV-10		PCV-13		PCV-15		PCV-20		PCV-21	
	2000-2014	2015-2024	2000-2014	2015-2024	2000-2014	2015-2024	2000-2014	2015-2024	2000-2014	2015-2024
Overall high-risk population[a] pooled proportion (95% CI)	68% (64-72%)	12% (6-24%)	80% (76-83%)	58% (53-62%)	80% (77-83%)	59% (55-63%)	83% (80-86%)	69% (63-74%)	19% (16-21%)	70% (58-79%)
<5 y Pooled proportion (95% CI)	73% (69-76%)	11% (5-23%)	84% (81-86%)	58% (53-63%)	84% (81-86%)	60% (55-64%)	87% (84-89%)	69% (62-75%)	18% (16-21%)	70% (57-81%)
≥60 y Pooled proportion (95% CI)	41% (21-64%)	NA	54% (29-77%)	NA	56% 28-81%)	NA	70% (30-93%)	NA	36% (22-53%)	NA

[a] High-risk population regardless of age.

<5 years 17% (95% CI, 13-21%), and cancer patients 17% (95% CI, 3-55%).

Serotype distribution

A temporal cut–off at 2014-marking the widespread introduction of PCV–10 and PCV–13 in Latin America and the Caribbean-was performed to analyze serotype prevalence. PCV–10 serotypes decreased from 68% (95% CI, 64-72%) before 2014 to 12% (95% CI, 6-24%) after 2014. PCV–13 serotypes falling from 80% (95% CI, 76-83%) to 58% (95% CI, 53-62%). PCV–15 coverage declined from 80% (95% CI, 77-83%) before 2014, to 59% (95% CI, 55-63%) post–2014. PCV–20 serotypes showed a similar drop from 83% (95% CI, 80-86%) to 69% (95% CI, 63-74%) across these periods. Conversely, PCV–21 serotypes rose from 19% (95% CI, 16-21%) before 2014 to 70% (95% CI, 58-79%) afterwards Table 1; Figure S7.

Age–specific trends

When we analyzed serotypes distribution before and after 2014 in children <5 years, PCV–10 serotypes decreased from 73% (95% CI, 69-76%) to 11% (95% CI, 5-23%), PCV–13 from 84% (95% CI, 81-86%) to 58% (95% CI, 53-63%), PCV–15 from 84% (95% CI, 81-86%) to 60% (95% CI, 51-64%), and PCV–20 theoretical coverage from 87% (95% CI, 84-89%) to 69% (95% CI, 62-75%). PCV–21 coverage increased from 18% (95% CI, 16-21%) to 70% (95% CI, 57-81%). Data were insufficient to perform comparable analyses in adults ≥60 years Table 1.

Healthcare resource utilization

A total of 39 studies provided data regarding resource utilization, but only a meta–analysis of proportions for ICU admission was feasible because most studies did not provide the size of the population at risk for the other use of resources. Among hospitalized high-risk patients, the overall pooled proportion requiring ICU admission was 36% (95% CI, 28-43%; 29 studies, I^2= 92.2%). In the subgroup analysis, persons over 60 years of age showed the highest requirement for ICU, being 50% (95% CI, 40-59%; two studies, I^2= 0%), followed by the immunocompetent persons with chronic conditions which showed 37% (95% CI, 27-48%; thirteen studies, I^2= 92.7%) and finally children under 5 years of age being 36% (95% CI, 23-52%; twelve studies, I^2= 92.9%).

In the subgroup analysis by country, the highest requirement for ICU was observed in Cuba, of 57% (95% CI, 37-75; two studies, I^2=77%), followed by Colombia with 48% (95% CI, 37-58%; seven studies, I^2=95.8%), Chile with 37% (95% CI, 20-57%; four studies, I^2=85.3%), Brazil with 33% (95% CI, 23-45%; four studies, I^2=80.8%) and Argentina with 29% (95% CI, eight studies, I^2=83.9%).

Risk of bias assessment

Among the 131 cohort and cross-sectional studies evaluated, 67 studies (51.1%) were rated as fair quality, 43 studies (32.8%) as poor quality, and 21 (16.1%) as good quality. The most common methodological limitations included inadequate sample size justification, lack of exposure assessment at multiple time points, insufficient control for confounding variables, and high loss to follow-up rates exceeding 20%. The 46-case series demonstrated better overall quality, with 32 studies (69.6%) rated as good quality and 14 studies (30.4%) as fair quality. Common strengths included clear study objectives, well-described exposures and outcomes, and adequate follow-up periods. The single case-control study was rated as fair quality with clear research objectives and appropriate case-control selection but lacked sample size justification and blinded exposure assessment. Both interrupted time series studies showed significant methodological limitations and were rated as poor quality. Across all study designs, the most frequently compromised critical domains were adequate control for confounding variables, sufficient sample size justification, and appropriate statistical analysis methods (S3-6 tables).

Discussion

This systematic review and meta-analysis from 2000 to 2024, showed that IPD remains a substantial burden in high-risk children and adults across LAC. Our study found high proportions of vaccine-preventable serotypes, significant case fatality rates particularly for bacteremia and meningitis, with considerable healthcare use. However, this burden varies across countries, time periods and high-risk groups.

The main representativeness of Argentina, Brazil, and Chile likely reflects their active participation in national and regional pneumococcal surveillance networks [10]. In our study, the most frequent clinical presentations were pneumonia (53%), meningitis (21%) and bacteremia (20%) similar to other regions [22]. High-risk populations including immunocompromised patients and individuals with chronic underlying conditions [23], showed elevated case fatality rates (19% and 18%, respectively) consistent with reports of poorer prognosis, longer hospital stays, and elevated risk of long-term disability and mortality [24,25]. IPD incidence in immunocompromised patients reached 56 cases/100,000 persons/y versus 4.8/100,000 persons/y in nonimmunocompromised individuals [26].

Individuals with underlying malignancies, particularly hematological malignancies (HMS), and those undergoing chemotherapy or biological therapies, are highly vulnerable. Prolonged neutropenia and bone marrow suppression related with higher susceptibility. [5,27]. Pneumonia and bacteremia are the most frequent IPD presentations, consistent with our findings in HMS patients (43% pneumonia, 28% bacteremia) [28]. Adults with HMS have markedly higher IPD incidence than the general population (482 vs

15/100,000) [27]. Introduction of Pneumococcal Conjugate Vaccines (PCVs) into childhood immunization programs appears to confer indirect benefits in adults, with overall IPD declining 3.5% annually and 9% in vulnerable groups like HMS patients [7,26,29]. Despite the availability of effective PCVs and their T-cell-dependent immune response providing protection with acceptable safety profile in HMS patients [28], IPD remains a significant threat [28] due to suboptimal vaccine uptake; as cancer treatment often takes precedence. The INSIGHT study in multiple myeloma showed pneumococcal vaccination within the previous 5 years improved overall survival, yet coverage remained low (30.2%), with regional disparities (*e.g.,* 4.7% in Asia vs 42.8% in the USA) [30]. These findings emphasize the importance of appropriated vaccine type and timing, including PCVs 6-12 months posthematopoietic stem cell transplantation (HSCT) [28], revaccinating in children with acute lymphoblastic leukemia (ALL) 6 months after chemotherapy and vaccination ≥2 weeks before splenectomy [31].

Pneumococcal prevention continues to evolve. The introduction of the PCV10/PCV13 vaccines in LAC countries, substantially decreased the proportion of vaccine serotypes, particularly in Argentina, Brazil and Peru, while nonvaccine serotypes have emerged [32]. However, notable heterogeneity was observed across the region, with countries such as Colombia and Cuba, still reporting relatively high proportions of vaccine serotypes included in PCV10/PCV13. These trends are consistent with previous regional surveillance data focusing on the general population in LAC [33,34] and align with our findings, which showed a post-2014 shift toward nonvaccine serotypes, especially among children under 5 years of age.

PCV15 showed similar theoretical coverage to PCV13 in the post-2014 period, in agreement with previous evidence indicating improved immunogenicity against serotype 3, which remains prevalent in IPD cases in the region [35]. PCV20 and PCV21 could offer high theoretical coverage for high-risk populations, although PCV21 is currently licensed only for the adults [36,37].

Our findings on PCV13 serotype coverage and IPD outcomes in high-risk populations provide a nuanced perspective compared with previous reviews in the general LAC population [32,33] and high-risk cohorts elsewhere. The higher CFR for meningitis in our study versus the general pediatric population [38], highlights the vulnerability of these groups. Such heterogeneity likely reflects differences in susceptibility profiles, healthcare access, surveillance capacity, and PCV rollout timing across countries. Understanding IPD burden among high-risk populations is essential to guide vaccination strategies and inform policy, particularly given the relative scarcity of targeted LAC data. Despite reductions in IPD following PCV introduction, gaps in coverage, waning immunity, serotype replacement, and antimicrobial resistance persist as major challenges in the region [39].

This systematic review has several strengths, including a comprehensive search of multiple databases and grey literature, adherence to PRISMA guidelines with a preregistered protocol, dual screening and data extraction, inclusion of studies spanning more than two decades, and focus on high-risk populations in LAC.

However, certain limitations must be acknowledged. Included studies were heterogeneous in design, definitions of high-risk populations, diagnostic methods, and reporting quality. Most were observational and hospital-based, introducing potential selection bias and limiting generalizability. Furthermore, data were scarce for certain specific high-risk conditions and for several countries within the LAC region, thereby precluding more robust subgroup analyses in some instances. The determination of high-risk status itself may have been inconsistent across the primary studies, and statistical methods may not have been uniform. These sources of variability likely contributed to the high I^2 values observed across several pooled analyses. Although a substantial proportion of the included studies were rated as fair or poor quality, sensitivity analysis limited to studies with a low risk of bias yielded estimates consistent with the main analyses, indicating that the overall patterns of results were generally comparable despite the study limitations. To account for between-study heterogeneity, we applied random-effects models and conducted subgroup analyses; however, the limited number of eligible studies precluded more advanced approaches, such as meta-regression. While we endeavored to mitigate publication bias by actively searching grey literature, its complete exclusion cannot be guaranteed. Data on hospitalization duration could not be quantitatively summarized due to insufficient reporting of the population at risk in the included studies, representing a limitation in the assessment of healthcare resource use. Finally, defining clear pre and post-PCV introduction periods proved challenging due to the staggered and varied rollout of PCV programs across different countries and age groups within the region.

Despite these limitations, our findings highlight the continued public health impact of IPD in high-risk LAC populations, even with widespread PCV use. The considerable proportion of IPD caused by serotypes in current (PCV10/PCV13) and emerging higher-valent vaccines (PCV15, PCV20, PCV21) emphasizes the potential gains from optimized vaccination strategies such as targeted catch-up campaigns, strengthened adult vaccination recommendations, and the judicious consideration and adoption of higher-valent vaccines where appropriate and feasible. CFR and healthcare resource utilization data further reinforce the clinical and economic burden of IPD, supporting the need for prioritizing preventive measures.

Looking forward, strengthened surveillance across LAC is important, with particular attention to high-risk groups, comprehensive serotyping and ongoing antimicrobial resistance monitoring. Further research is urgently needed to more accurately quantify IPD incidence in specific high-risk conditions, to better understand barriers to vaccine uptake, and evaluate the clinical and cost-effectiveness of vaccination strategies (*e.g.,* PCV13 vs PPSV23 vs higher-valent PCVs) specifically tailored to these vulnerable populations.

In conclusion, invasive pneumococcal disease continues to impose a substantial burden on high-risk children and adults in Latin America and the Caribbean, with considerable mortality and healthcare resource use. While pneumococcal conjugate vaccines have reduced this burden, a considerable fraction remains preventable. Enhanced surveillance, targeted vaccination strategies, and focused research are essential to further reduce disease impact in these vulnerable populations.

Author contributions

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by MR, TA, CV and MB. The first draft of the manuscript was written by AB, SR, PG, MB, CV, TA, MR and AC. All authors read and approved the final manuscript.

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S1A Table. Characteristics of Studies included
S1B Table. High-risk subgroups and study characteristics
S1 Text. Search Strategy
S2 Table. List of Excluded Studies with Reasons
S3- 6 Table. Risk of Bias Assessment Summary
S7 Figure. Serotype coverage before and after PCV introduction.
Checklist. PRISMA 2020 Checklist

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

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