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ORIGINAL ARTICLE

Disease Burden of Meningitis Caused by *Streptococcus pneumoniae* Among Under-Fives in China: A Systematic Review and Meta-analysis

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ABSTRACT

Introduction: *Streptococcus pneumoniae* is the leading cause of meningitis, with a case fatality of up to about 50%. Children younger than 5 years are at greater risk for pneumococcal meningitis compared with other populations. It is of significant importance to provide a comprehensive understanding of the burden of pneumococcal meningitis among under-fives in the low pneumococcal conjugate vaccine (PCV) coverage period in China.

Methods: A systematic review was conducted. We searched both English (PubMed, Ovid-EMBASE, Biosis, Web of Science, and Cochrane) and Chinese (CNKI, Wanfang, and ViP) databases for studies on bacterial meningitis in China published between January 1980 and July 2022. Ineligible studies were excluded based on study design and data integrity. Heterogeneity was assessed with I^2 and estimates of bacterial meningitis morbidity and mortality were pooled using random-effects models. Subgroup analysis was conducted to trace the source of the heterogeneity and summarize average estimates.

Results: A total of 13,082 studies were identified in the literature, and 56 studies were finally included for data analysis. The estimated incidence of pneumococcal meningitis was 2.10 cases per 100,000 children younger than 5 years each year (95% CI: 0.59–7.46), with a pooled case fatality rate of 24.59% (95%CI: 19.35–30.28%) in China. It was estimated that 1617.16 (95% CI: 454.35–5744.78) pneumococcal meningitis cases and 548.86 (95% CI: 474.80–627.62) deaths occurred among under-fives in China in 2020. *Streptococcus pneumoniae* played an important role in the etiology of confirmed bacterial meningitis cases, with a pooled proportion of 22.05% (95% CI: 17.83–26.27%). The most prevalent serotypes

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were 6B, 14, 19F, 19A, and 23F, which were preventable with a vaccine.

Conclusions: Pneumococcal meningitis remains one of the most important health problems among children younger than 5 years in China. Immunization programs should be promoted to avoid preventable cases and deaths.

Keywords: Meningitis; *Streptococcus pneumoniae*; Child; Immunization; China

Key Summary Points
This is the first meta-analysis of the pneumococcal meningitis burden among under-fives in the post-PCV13 era in China.
Pneumococcal meningitis remains a noteworthy health issue among under-fives in China.
Streptococcus pneumoniae plays a dominant role in bacterial meningitis infections.
Most prevalent serotypes were preventable with a vaccine, supporting future decision-making.

INTRODUCTION

Bacterial meningitis is a devastating infectious disease with a high case fatality and significant long-term sequelae in survivors [1, 2]. As one of the most prevalent pathogens causing bacterial meningitis, *Streptococcus pneumoniae* (*S. pneumoniae*) was responsible for over 300,000 meningitis cases and 40,000 deaths globally in 2017 [3–5]. Especially for under-fives, pneumococcal meningitis (PM) is a significant health problem as it is associated with 17 cases and 10 deaths per 100,000 children annually [6]. Understanding the burden of PM is also crucial to improving the under-five mortality rate, which reflects overall social and economic development. However, very few studies have focused on the incidence and mortality of PM in China, let alone that in children under 5 years old.

Thanks to the development and worldwide usage of pneumococcal conjugate vaccines (PCVs), the morbidity and mortality of PM in children have decreased [7, 8]. The 7- and 13-valent PCVs were introduced to China in 2008 and 2016, respectively, and cover approximately 60% and 80% of the common *S. pneumoniae* serotypes [9]. However, PCV coverage is relatively low in China, partly because PCVs are not included in the national immunization program (NIP) [10]. Detailed analysis of the PM disease burden in children in the early post-PCV period could provide important information for the further management and promotion of PCVs.

Despite the high case fatality rate (CFR) and disease burden of PM among under-fives, a lack of effective surveillance systems for meningitis and evidence of the disease burden related to *S. pneumoniae* among children in China hinders the work of expanding the availability of PCVs to children, including its potential inclusion in the NIP. Therefore, we performed a systematic review to summarize the morbidity and mortality of meningitis associated with *S. pneumoniae* among under-fives in China based on literature published between 1980 and 2022. The estimates potentially help to reinforce and complement existing prevention and control strategies.

METHODS

Search Strategy

This systematic review was conducted in accordance with the Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Table S1) [11]. The literature search was restricted to articles published between January 1980 and August 2022. Studies on bacterial meningitis were identified using standard search algorithms in both English (PubMed, Ovid-EMBASE, Biosis, Web of Science and Cochrane) and Chinese (CNKI, Wanfang and ViP) databases, which were constructed based on the MeSH term *Meningitis* and the keywords *China*, *child*, *mortality*, *death*, *incidence*, *prevalence*, *morbidity*, and *distribution*. Detailed search algorithms for each database are listed in Appendix S1 in the Supplementary Material. The reference lists of the retrieved articles were reviewed to identify possibly relevant studies.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Inclusion and Exclusion Criteria

Included articles had to meet the following criteria: (1) the article contained epidemiologic or etiologic information on meningitis; (2) surveillance continued for 12 months or longer; (3) children aged between 1 month and 5 years were included. Articles were excluded if they were (1) narrative reviews, guidelines, or articles without accessible data; (2) articles focusing only on specific groups of patients or reporting meningitis as one of the complications; (3) case reports with less than 50 cases; (4) studies that only reported data on a specific pathogen other than *S. pneumoniae*.

Data Extraction and Definition

Based on the recommended case definition from the World Health Organization (WHO), patients were labeled as suspected bacterial meningitis (SBM) cases if they presented a sudden onset of fever and meningeal signs including neck stiffness and altered consciousness [12]. Patients with cerebrospinal fluid (CSF) abnormalities meeting at least one of the following standards were classified as probable bacterial meningitis (PBM) cases: CSF with a turbid appearance; leukocytosis (> 100 cells/mm^3); leukocytosis (10–100 cells/mm^3 with an increased protein concentration of higher than 100 mg/dL or a decreased glucose concentration of lower than 40 mg/dL) [12]. Confirmed PM cases were those with CSF specimens positive for *S. pneumoniae*. Data from each article were extracted using a structured data collection form that included authors, publication year, province, study site, study design, etc. Adjusted incidence or mortality rates were recorded rather than raw rates if provided. Studies reporting the pathogen distribution were all based on CSF or blood specimens. For PBM cases, if either the blood culture or the CSF culture tested positive, the case was considered to be positive for the specific pathogen. It is important to note that the diagnosis of confirmed bacterial meningitis (CBM) relied not only on the results of pathogen detection but also considered the clinical symptoms manifested by the patient. Reference management and data extraction were conducted by EndNote X9.1 (Tomson, Inc., Philadelphia, USA).

Quality Assessment

The validity of the studies reporting on epidemiologic and etiologic characteristics of bacterial meningitis cases was independently assessed by two reviewers in terms of study design, length of surveillance period, reliability of diagnosis methods, and the possibility of leaving out potential cases. Based on these criteria, included studies were labeled as one of the three categories representing article quality: “A” papers, in which both reviewers judged that both criteria were met; “B” papers, in which only one reviewer judged that each criterion was met; “C” papers, in which both reviewers judged that either criterion was not met or that insufficient data were available to make a judgment. Prior to inclusion in the final dataset, a third quality assessment was performed on studies classified as “C” and all included studies. Studies remaining “C” in quality after the third assessment were discarded.

Data Analysis

Pooled incidence rates along with 95% confidence intervals (CIs) were calculated for different types of meningitis. The test for heterogeneity was performed by calculating I^2, which showed the proportion of variation across studies. An I^2 of less than 50% implied that a fixed-effects model could be used;

otherwise, a random effects model was employed. When estimating pooled CFRs, the double-arcsine method with a correction factor of 0.5 was used to handle zero events. Subgroup analyses were conducted to identify the source of heterogeneity and summarize point estimates. Poisson regression was performed to assess between-group differences in the distributions of outcomes. A P value of < 0.05 was considered significant. All analyses were conducted using R (v4.2.1, R Foundation for Statistical Computing, Vienna, Austria).

PM cases and deaths of under-fives in China were estimated by a multiplication model based on pooled results of meta-analysis and the 2020 China census data (Figure S1). Assuming that most but not all of the meningitis cases were hospitalized, the proportion of patients with acute meningitis or encephalitis (AME) who received in-hospital treatment was applied as the ratio of admitted cases of bacterial meningitis [13]. Along with the adjusted hospitalization rate assuming no vaccine use, we calculated the pooled incidence rate of PM using random-effects models. Combined with the 2020 China census data on 77,883,888 under-fives, we derived the total number of PM cases prior to the vaccines [14]. Because reported CFR values only reflect mortality in children who sought care at a health facility, we adjusted them to account for the higher CFR assumed for those not accessing care. The adjusted CFR of pathogen-specific meningitis was multiplied by the vaccine-adjusted PM cases to calculate the number of PM deaths. There is no measure of health-care seeking for children with meningitis in standardized surveys from China. Therefore, we used the proportion of children seeking care for minor illnesses (such as stomachache or diarrhea) from the China Health and Nutrition Survey (CHNS) as a proxy [15]. We applied different indicators based on the CHNS database as proxies for access to care and conducted sensitivity analysis to compare the estimated disease burdens. In order to adjust for the effect of vaccine use in China, the effective PCV7 coverage obtained by Lai et al. was applied to calculate PM incidences prior to vaccines [16]. It is worth noting that the hospitalization rate in Hong Kong reported by Pak et al. was ruled out because Hong Kong introduced PCV7 into the childhood immunization program in September 2009 [17, 18].

RESULTS

A total of 13,082 citations were initially identified through the literature search, and 5828 citations were removed due to duplication (5524 references from Chinese databases, 283 references from English databases, and 21 cross-language duplicates) (Fig. 1). After reviewing the titles and abstracts of the remaining articles based on inclusion and exclusion criteria, 955 potentially relevant studies were identified. Further examination of the obtained full text yielded 56 studies with evaluable extracted outcomes for consideration in the analysis (Table S2). After quality assessment, 98.21% (55/56) studies were labeled as being of "A" quality. Of the 56 studies considered, most were conducted in eastern China (16/56, 28.57%), followed by southern China (14/56, 25.00%) and southwest China (7/56, 12.50%). There were six studies (6/56, 10.71%) each from the Guangxi and Guangdong provinces (Fig. S2).

Epidemiological Overview of Meningitis

Six studies regarding the meningitis incidence rate were included, along with four studies on mortality rate (Tables S3 and S4). Pooled estimates of different meningitis types were calculated. The pooled annual incidence rates of PBM, CBM, and PM in China were 12.25 (95% CI: 5.48–19.02), 11.17 (95% CI: 1.34–20.99), and 2.10 (95% CI: 0.59–7.46) cases per 100,000 children, respectively (Table 1 and Fig. S6). It was estimated that 20.69 deaths per 100,000 children each year (95% CI: 12.10–29.29/100,000/year) were associated with all-cause meningitis (Fig. S6D).

The majority of the records on CFR from bacterial meningitis were published after the year 2008, when PCV7 and PPSV23 were introduced to China (Fig. S3). The pooled CFR from bacterial meningitis across studies was 3.85% (95%CI: 0.98–8.12%) in children aged between 1 month and 5 years in China (Fig. S7A). Similar

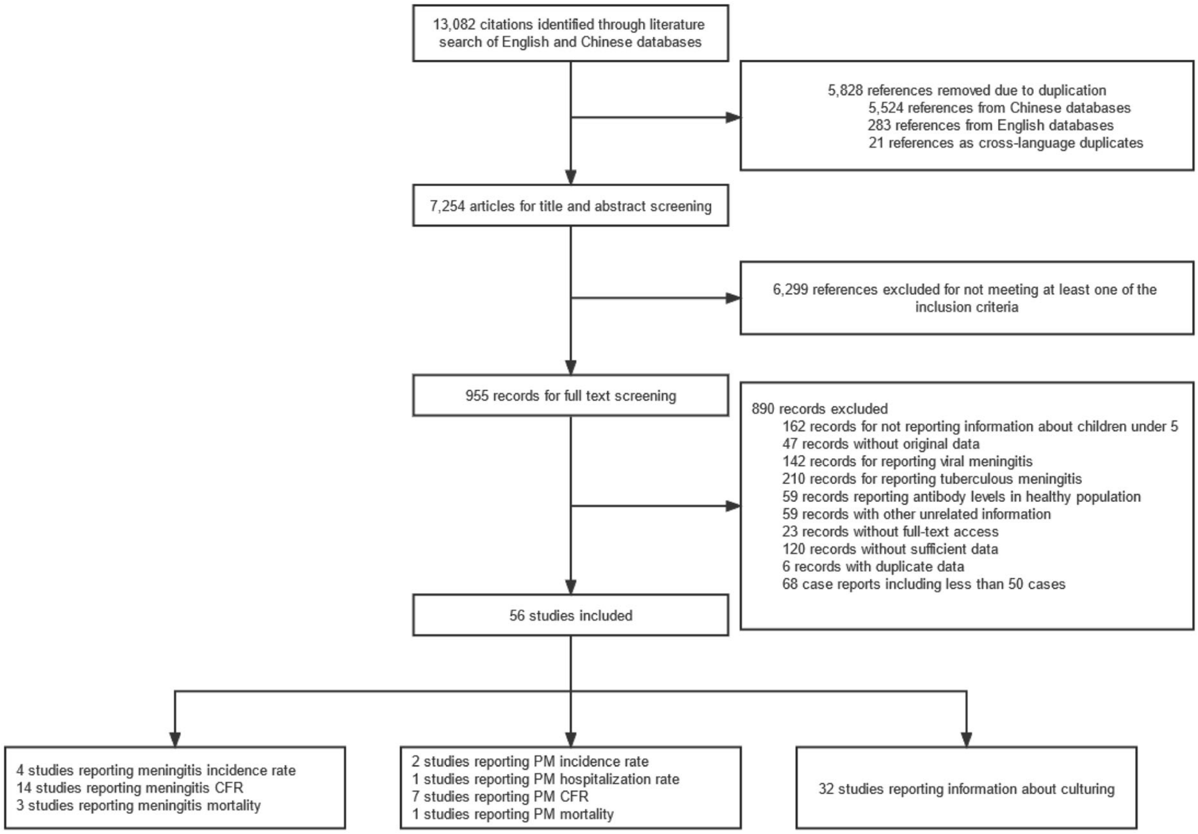

Fig. 1 Flow chart of the literature review

age distribution patterns were observed in bacterial and PM, with the highest CFR occurring in children aged between 3 and 5 years, followed by those aged between 1 and 12 months and between 1 and 3 years (Fig. 2). Subgroup analysis by study year showed a significant decrease in estimated CFR from 1980–2005 (13.47%, 95% CI: 7.11–21.36%) to 2006–2015 (0.79%, 95% CI: 0.00–2.98%) ($P < 0.001$). Disparity was observed across geographic regions, and bacterial meningitis in northeast China yielded the highest CFR (5.65%, 95% CI: 0.00–22.89%), while the lowest estimate (0.23%, 95% CI: 0.00–9.09%) was from two studies conducted in southwest China. Unlike bacterial meningitis, studies on PM were all performed during the period 2006–2015 and the overall CFR was 24.59% (95% CI: 19.25–30.28%). The highest estimated CFR from PM was found in northern China (33.95%, 95% CI: 24.19–44.40%), and the lowest was found in eastern China (0.00%, 95% CI: 0.00–60.24%).

Etiologic Distribution of Bacterial Meningitis

Culture or plus PCR was employed for the detection of pathogens in the included studies. Based on studies reporting the etiologic distribution of SBM, the weighted mean positive rate across pathogens was 0.17% (95% CI: 0.11–0.28%). Positive detection of *S. pneumoniae* was observed in all included studies on SBM, and 32 out of 8114 biological specimens were identified as *S. pneumoniae* positive (0.63%, 95% CI: 0.11–3.68%), ranking second in positive rate (Fig. 3 and Fig. S8A). In addition, *S. pneumoniae* accounted for 15.91% (95% CI: 7.15–31.74%) of all positive cases (Fig. S8B).

Thirteen studies on PBM cases yielded a pooled positive rate of 2.41% (95% CI:

Table 1 Pooled incidence and mortality rate of meningitis

Meningitis type	Incidence rate				Mortality rate			
	Studies	Meningitis cases	Denominator (child-years)	Pooled incidence rate per 100,000 (95%CI)	Studies	Deaths	Denominator (child-years)	Pooled mortality rate per 100,000 (95%CI)
All-cause meningitis	–	–	–	–	2	677	2,799,817	20.69 (12.10–29.29)
Probable bacterial meningitis	1	1164	9,897,699	12.25 (5.48–19.02)	–	–	–	–
Confirmed bacterial meningitis	3	98	1,124,734	11.17 (1.34–20.99)	1	7	306,947	2.28
Pneumococcal meningitis	3	40[a]	1,336,739	2.10(0.59–7.46)[b]	1	1	307,692	0.325

[a] Original case numbers derived from studies
[b] The hospitalization-adjusted incidence rate was taken into consideration

1.95–2.98%). With a positive rate of 5.01% (95% CI: 3.09–8.04%), *S. pneumoniae* ranked second among the 31 identified pathogens (Fig. S9A). This dominant distribution pattern remained after stratifying the available records into four age groups (< 3 months, < 1 year, < 3 years, and < 5 years), except for the < 3 months group, as none of the studies of this group reported *S. pneumoniae* detection (Fig. 4). The estimation of pathogen-specific proportions in CBM cases, including laboratory-positive cases of PBM, was conducted. Similarly, subgroup analysis of the proportions of CBM cases in which pathogens were positively detected showed that *S. pneumoniae* ranked the first in the < 3 years group and second in the < 1 year and < 5 years groups (29.86%, 95% CI: 23.87%–36.64%; 21.68%, 95% CI: 16.14%–28.48%; 21.07%, 95% CI: 12.77%–32.74%) (Fig. S4).

The pooled proportion of PM among confirmed bacterial meningitis cases was 22.05% (95% CI: 17.83–26.27%) (Fig. S9B). Subgroup analysis by age revealed variation in the proportion of PM among CBM cases and in the positive rate of *S. pneumoniae* among PBM cases. The proportion of PM was the highest in the < 3 years group ($P < 0.001$), while the positive rate was the highest in the < 1 year group (Fig. 5). Most of the studies were conducted between 2008 and 2017, namely the period between the introduction of PCV7 and PCV13 (Fig. S5). The positive rate and the proportion of *S. pneumoniae* displayed different distribution patterns across different periods, and the proportion reached its highest pooled estimates in the period 2006–2015 ($P < 0.05$) (Fig. 5). The estimated proportion of PM in CBM cases was highest in eastern China, while the positive rate was highest in multi-center sites.

Antibiotic Resistance Profile of *S. pneumoniae*

There were seven studies containing data on the antimicrobial resistance of *S. pneumoniae* (Table S5). A total of 104 *S. pneumoniae* isolates were tested and 27 antibiotics were involved. Among them, *S. pneumoniae* displayed more

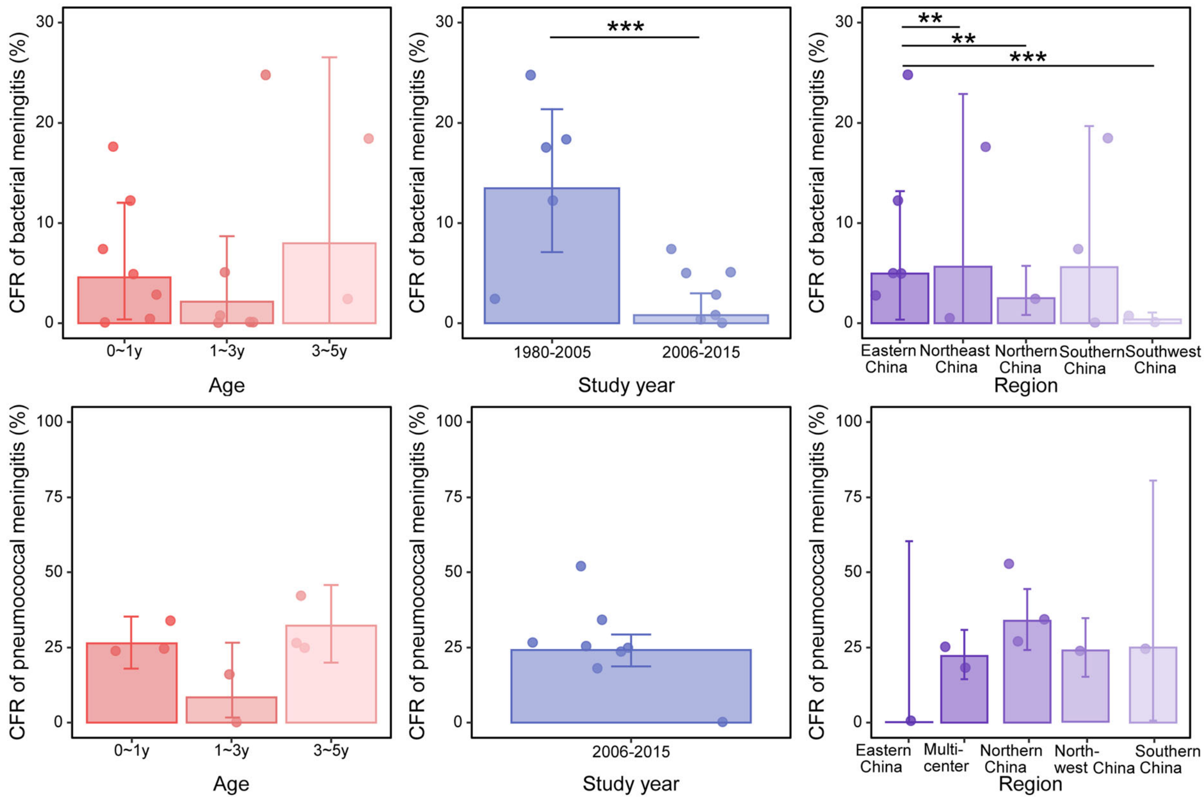

Fig. 2 Subgroup analysis of the CFR from bacterial meningitis and pneumococcal meningitis by age, study year, and region. *CFR* case fatality rate. The *dots in the background* represent the CFRs in each study. *Error bars* represent 95% CIs. ** $P < 0.01$. *** $P < 0.001$

than 90% resistance towards ampicillin, clindamycin, and tetracycline separately (Fig. 6). None of the *S. pneumoniae* isolates were resistant to vancomycin. Also, *S. pneumoniae* was susceptible to nine antibiotics, including moxifloxacin and linezolid.

Serotype Distribution of *S. pneumoniae*

Only two studies provided information about the serotype distribution of *S. pneumoniae*. Sixty-four isolates of *S. pneumoniae* were successfully serotyped, and serotypes 6B, 14, 19F, 19A, 23F, and 15B/C were found in both studies. The pooled serotype coverages of pneumococcal polysaccharide vaccines were 78.95% (95% CI: 69.03–88.87%) for PCV7, 91.10% (95% CI: 80.05–100.00%) for PCV13, and 100.00% (95% CI: 97.12–100.00%) for PPSV23 (Table S5).

Estimates of the Burden of PM

Based on the 2020 China census data and the pooled PM incidence rate, we calculated that 1635.56 (95% CI: 459.51–5810.14) *S. pneumoniae*-associated meningitis cases occurred in under-fives without considering the impact of PCV in China in 2020. After adjusting the PCV impact for the PCV coverage reported by Lai et al. and a vaccine effectiveness of 73.5%, we estimated that there were 1617.16 (95% CI: 454.35–5744.78) PM cases [16, 19]. Multiplied by the adjusted CFR, we estimated that there were 548.86 (95% CI: 474.80–627.62) deaths related to PM among children younger than 5 years in China in 2020.

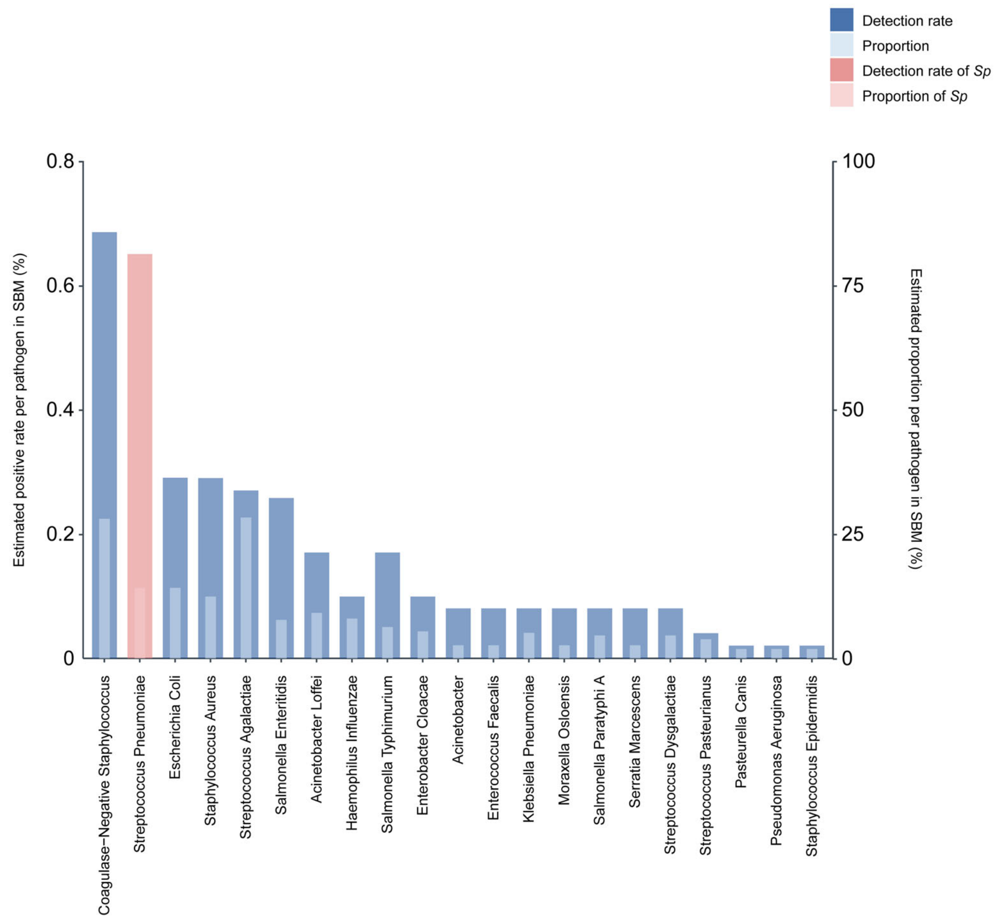

Fig. 3 Pooled positive rate and proportion per pathogen in suspected bacterial meningitis. *SBM* suspected bacterial meningitis

DISCUSSION

Since the introduction of pneumococcal polysaccharide vaccines in the twentieth century, a number of studies have been conducted to assess its disease burden after the licensing of PCVs in various regions around the world. However, among the limited studies reporting on the pneumococcal burden in China, most were based on WHO or Maternal and Child Epidemiology Estimation Collaboration country-specific estimates or focused on residents in local areas. To the best of our knowledge, this is the first systematic review and meta-analysis to estimate the burden of bacterial and PM among under-fives in China in the post-PCV13 period. The present study serves as an important complement to the limited data on PM and indicates that PM remains a significant health problem for children in China. We found that the annual incidence rates for PBM, CBM, and PM in China were 12.12, 11.17, and 2.10 cases per 100,000 children younger than 5 years, respectively. Generally, SBM patients were recognized from the typical clinical syndromes they manifested, and bacterial meningitis cases should be confirmed by lumbar punctures and pathogen detection [20]. The ratio of PM incidence rate to that of confirmed bacterial meningitis reflected the contribution of *S. pneumoniae*. In our study, over 20% of the CBM cases were caused by *S. pneumoniae*, indicating that *S. pneumoniae* may be a major contributor to the disease burden in under-fives. This distribution pattern could potentially provide significant guidance for expediting diagnosis and

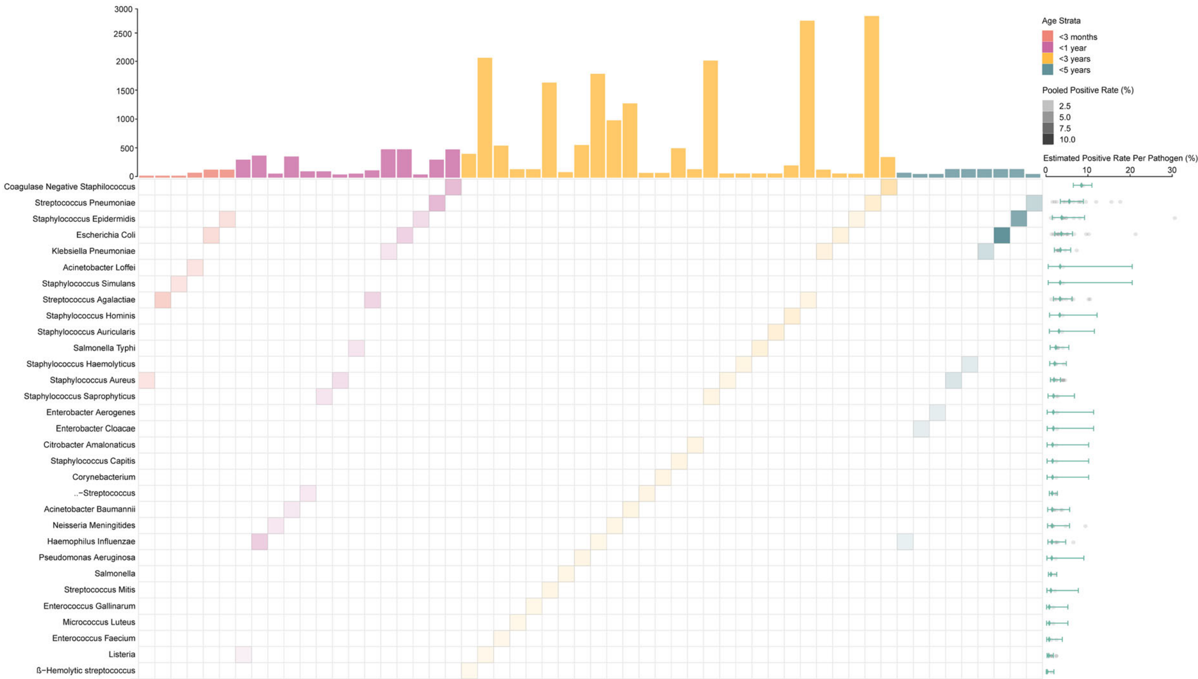

Fig. 4 Distribution of detected pathogens in cases of confirmed bacterial meningitis. Pooled positive rates of different pathogens in various age strata. Deeper colors indicate higher pooled positive rates

implementing precise therapeutic interventions.

Compared with the estimated incidence rate of PM of 2.10 cases per 100,000 children in the present study, Chen et al. reported that 1.33 cases occurred among 100,000 children younger than 5 years in the year 2010 [21]. Though incidence rates for PM were calculated based on the all-cause incidence rate of meningitis and the etiological proportion of *S. pneumoniae* in the aforementioned study, and we obtained pneumococcal incidence rates directly from the included studies, the consistency between our results strengthens the overall validity of the present study. Apart from that, we also report a pooled mortality rate for all-cause meningitis of 20.69 deaths per 100,000 children younger than 5 years, which was in accordance with the trend shown by the GBD study [22]. Despite using different methods and data sources to estimate the mortality rate, the GBD study produced similar results, suggesting the robustness of our findings. Nevertheless, a lack of abundant records hampered the analysis of the mortality rate in CBM and PM cases. It was estimated that there were 1617.16 (95% CI: 454.35–5744.78) PM cases and 548.86 (95% CI: 474.80–627.62) deaths among children younger than 5 years in China in 2020, which may seem relatively small compared with the number of cases (8686, 95% CI: 5213–11,980) and deaths (1114, 95% CI: 669–1537) in 2015 obtained by Wahl et al. [23]. These differences may be attributed to the designed models and the sources of data used. Wahl et al. used mortality data from GBD-sourced modeled estimates combined with the pathogen-specific CFR to generate pneumococcal cases, while we utilized the pooled incidence rate to estimate the number of pneumococcal deaths. Similarly, both of the studies considered PCV use and hypothesized a higher CFR for patients without access to care.

There were certain discrepancies between our estimated CFR for PM and GBD-sourced results (24.59% versus 4.84%). The estimates from the GBD databases were generated using more complex models with global surveillance data, only a few of which were from China. In the present study, most of the CFR records from PM cases were based on hospital-based case

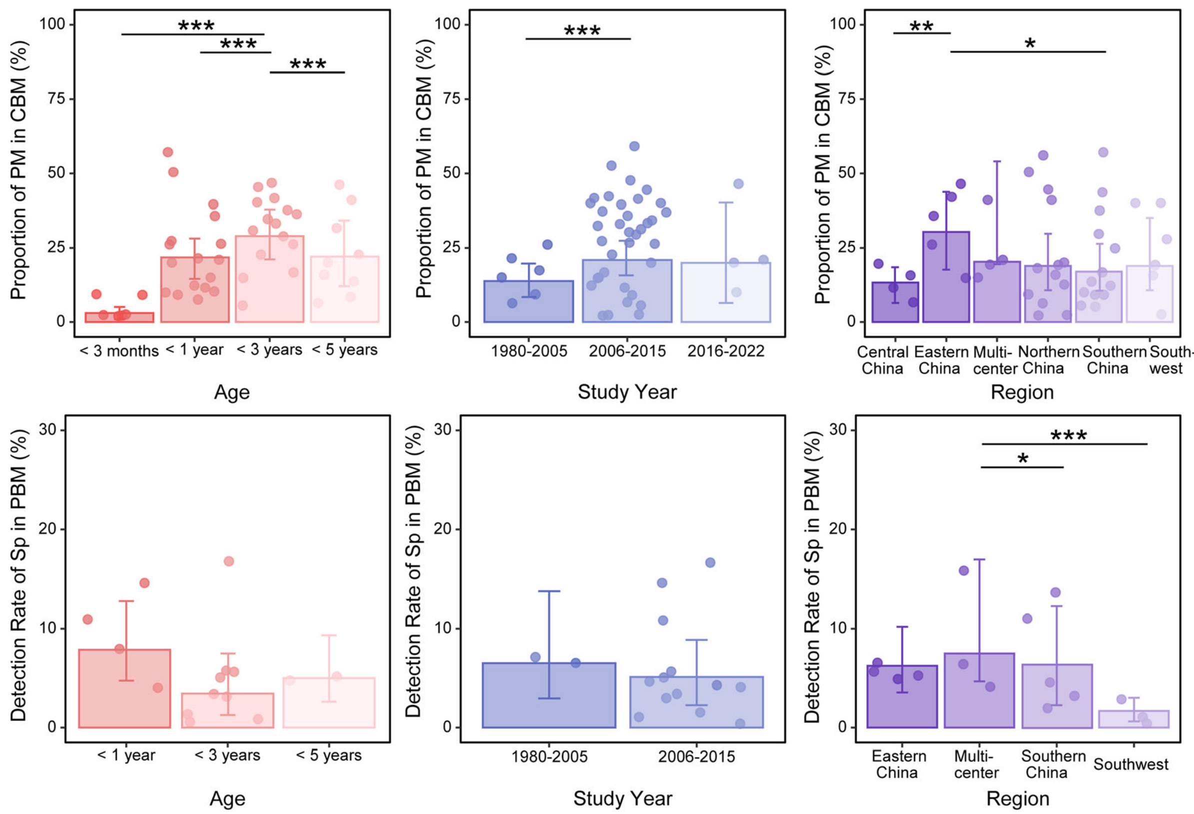

Fig. 5 Subgroup analysis of the positive rate of *Streptococcus pneumoniae* in probable bacterial meningitis cases and the proportion of pneumococcal meningitis in confirmed bacterial meningitis cases by age, study year, and region. *Sp Streptococcus pneumoniae*, *PM* pneumococcal meningitis, *CBM* confirmed bacterial meningitis, *PBM* probable bacterial meningitis. * $P < 0.05$. ** $P < 0.01$. *** $P < 0.001$

reports; only one out of the six (16.67%) studies were based on community-based surveillance data. Usually, hospital-based studies tend to report cases manifesting more typical clinical symptoms, and physicians are likely to pay attention to severe cases [24]. It is possible that the hospital-based case reports were those with higher CFRs, which may have led to our overestimated CFR for PM. In addition, Lai et al. applied a literature-based CFR of PM when modeling the disease burden caused by *S. pneumoniae*, which was also extracted from mostly hospital-based studies, and the CFR of 12.85% further reinforced the validity of our findings [10].

Similar age distribution patterns of the CFR were observed for bacterial meningitis and PM. A steep decrease in the bacterial meningitis CFR from the period 1980–2005 to 2006–2015 indicates that improved accessibility to health care and the introduction of vaccines over time may help to prevent avoidable deaths. Regarding disease severity across geographic regions, a lower CFR of PM was found in eastern China, which may be attributed to a better healthcare capacity and higher PCV coverage. PCVs were one of the most inequitably distributed vaccines among non-NIP vaccines in China, due primarily to wealth disparity [25]. The eastern China region is more developed and the higher income levels there lead to better access of the residents to healthcare and possible immunization. However, it was observed that the pooled CFR of bacterial meningitis cases in eastern China was relatively high. This may be attributed to the inclusion of mostly rural cases in selected PM studies.

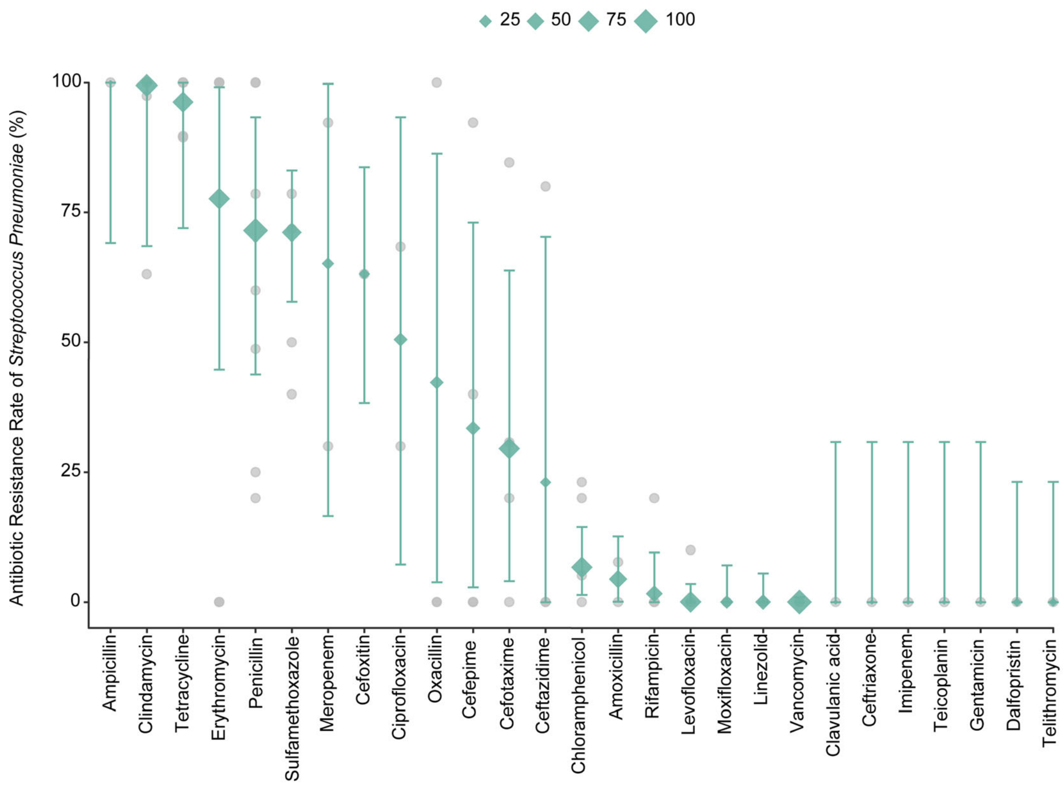

Fig. 6 Antibiotic resistance profile of *Streptococcus pneumoniae* in bacterial meningitis cases. The *dots in the background* represent the antibiotic resistance in each study

Our analysis of positively detected pathogens demonstrated that *S. pneumoniae* is one of the most significant pathogens of bacterial meningitis. Its dominant role in the etiologic distribution remained stable across different age groups, which was in accordance with previous studies [26]. Compared with the 1980–2006 period, the drastic decrease in both the pooled detection rate of and the proportion of cases with *S. pneumoniae* implies that PCVs helped prevent bacterial meningitis cases associated with *S. pneumoniae*. However, it is difficult to estimate the contribution of *S. pneumoniae* to bacterial meningitis accurately since antimicrobial treatment can distort pathogen detection and pre-diagnostic antibiotic usage was not available in most studies.

Timely antimicrobial therapies are crucial for improving survival and preventing adverse sequelae [27], but it is worth noting that inappropriate usage of antibiotics has led to worldwide resistance to penicillin and other antibiotics, threatening the traditional treatment of PM [28]. In the present study, *S. pneumoniae* displayed pooled resistance rates of 71.50% and 29.56% towards penicillin and cefotaxime, respectively, whereas all of the *S. pneumoniae* strains were reported to be sensitive to vancomycin, which is recommended by van de Beek et al. as an advanced treatment of PM [29]. Given that culture remains the gold standard for detecting *S. pneumoniae*, we only included studies that used cultured specimens for analysis, which eliminated the potential bias introduced by the use of different specimen collection methods.

Data extracted from two studies identified 6B, 14, 19A, 19F, and 23F as the serotypes of *S. pneumoniae* most commonly detected in bacterial meningitis, which is consistent with previous studies [21]. The majority of the reported serotypes were covered by PCV7 (78.95%) and PCV13 (91.10%), while PPSV23 showed full coverage. The high serotype coverage of PCVs provides useful information for the further management and promotion of PCVs in China, encouraging the potential inclusion of PCVs in the NIP.

There are certain limitations of our study. First, due to inadequate data, subgroup analysis with covariates including age, study year, and gender was not feasible. The insufficiency of available information underscores the need for further investigation. Second, estimates of incidence rates and case numbers may suffer from an inherent problem of underestimation, which is mainly attributable to the overuse of antibiotics in the early stage of the disease and the incomplete ascertainment of cases when children do not reach a health facility for diagnosis [30]. Thirdly, since China has not integrated PCVs into the NIP, caution should be exercised when attempting to generalize the estimates to other countries or regions with different PCV strategies. While our study provides valuable insights into the burden of PM in China, further studies using surveillance data are necessary to help develop targeted policies, particularly for disease mortality. Authorized local surveillance systems should be established to monitor the prevalence, antimicrobial resistance, and serotypes of pneumococcal strains that cause meningitis, which could provide valuable insights into the prevention of PM. In addition, comprehensive immunization programs targeting children at risk will help reduce the incidence of PM with great efficiency.

CONCLUSION

In the present study, we confirmed that meningitis associated with *S. pneumoniae* remains one of the most important health dilemmas among under-fives in China, and PCVs display a high coverage of prevalent serotypes. Given the increasing resistance of *S. pneumoniae* to commonly used antibiotics, priority should be given to advanced treatment and immunization programs by policy-makers.

Author Contributions. Tao Zhang and Biying Wang were responsible for the idea of the topic. Biying Wang and Wanjing Lin did the literature research, article screening, and data extraction for meningitis. Biying Wang, Chen Qian, and Youyi Zhang did the meta-analyses for incidence and mortality rates for different types of meningitis. Biying Wang and Wanjing Lin established the disease burden model for pneumococcal meningitis. BW wrote the first draft of the manuscript and Tao Zhang helped revise the manuscript. Tao Zhang, Weibing Wang and Genming Zhao had a supervisory role on the project.

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Data Availability. The data that support the findings of this study are available from the authors upon reasonable request.

Declarations

Conflicts of Interest. Biying Wang, Wanjing Lin, Chen Qian, Youyi Zhang, Genming Zhao, Weibing Wang, and Tao Zhang declare no conflicts of interest.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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