

Research progress of invasive pneumococcal disease in children

Zhengyuan Gan^{1,2}, Na Lin^{2*}

¹ College of Graduate, YouJiang Medical University For Nationalities, Baise 533000, Guangxi Zhuang Autonomous Region, China.

² Department of Pediatrics, Affiliated hospital of YouJiang Medical University For Nationalities, Baise 533000, Guangxi Zhuang Autonomous Region, China.

Abstract Invasive pneumococcal disease (IPD) is a significant threat to children's health and can lead to highly lethal complications such as sepsis and meningitis. Although the global introduction of the pneumococcal conjugate vaccine (PCV) has significantly reduced the incidence of IPD, dynamic serotype substitution and drug resistance are reshaping its epidemiology and clinical management challenges. This article summarizes the latest research advances and systematically describes the current prevalence of IPD, vaccine efficacy, drug resistance trends, and clinical management challenges. This review aims to provide a basis for optimizing diagnostic and treatment guidelines and vaccine policies.

Keywords: Invasive pneumococcal disease (IPD); serotype substitution; vaccine efficacy; drug resistance; children's health

How to cite: Zhengyuan Gan et al. Research progress of invasive pneumococcal disease in children. J Med Discov (2025); 10(4):jmd25038; DOI:10.24262/jmd.10.4.25038; Received May 1st, 2025, Revised August 6th, 2025, Accepted September 23rd, 2025, Published October 15th, 2025.

1. Introduction

Streptococcus pneumoniae causes invasive pneumococcal disease (IPD), leading to serious complications such as bacteremia and meningitis. Global data show that IPD causes more than 300,000 deaths annually in children under 5 years of age, with 70% occurring in low-income countries [1]. Although pneumococcal conjugate vaccines (PCVs) have reduced the incidence of vaccine serotypes by 50-80% [2, 3], the ecological replacement of resistant non-vaccine serotypes (such as 24F and 15B) has increased the risk of epidemics. China's PCV13 coverage rate is <50% [4], and the incidence rate in children under 2 years of age is 7.6/100,000, significantly higher than that in developed countries [4-6]. Current research needs to break through the three bottlenecks of serotype cross-protection limitations, resistance gene transmission mechanisms, and intervention synergy strategies. This review integrates multi-regional data and focuses on: ① Regional

heterogeneity of serotype evolution after PCV vaccination;

② Benefits and challenges of upgrading from PCV13 to PCV20; ③ Resistance dynamics and new therapies; ④ China-oriented multi-dimensional prevention and control system. It aims to provide evidence-based basis for optimizing IPD management decisions.

2. Epidemiological Characteristics

2.1 Incidence and Risk Factors

The epidemiological pattern of IPD exhibits significant regional imbalances. European and American countries have achieved a sustained decline in incidence through widespread PCV vaccination: from 2015 to 2020, the incidence of IPD in children under 5 years of age in the United States decreased from 45.2 to 12.1 per 100,000 (a 73% decrease), and the incidence in adults 65 years of age and older decreased by 51% [7, 8]. This achievement is closely related to high PCV13 coverage (>90% complete

*Correspondence: Na Lin, Department of Pediatrics, Affiliated hospital of YouJiang Medical University For Nationalities, Baise 533000, Guangxi Zhuang Autonomous Region, China. Email:linna7766328@163.com.

vaccination rate for children) and a regular booster strategy. In contrast, China lacks a nationwide unified surveillance system. Regional studies have shown that the incidence of IPD in children under 5 years of age in Guangdong Province (34.6 per 100,000) is 2.9 times that in Beijing (11.8 per 100,000), and this difference is highly negatively correlated with PCV vaccination rates (41% in Guangdong vs. 72% in Beijing) [9, 10].

Specific populations are significantly more susceptible to IPD and at increased risk for adverse outcomes. Based on a multicenter cohort study in China, the incidence of IPD in premature infants (gestational age <37 weeks) was 4.2 times that of full-term infants (9.7/100,000 vs 2.3/100,000), and the mortality rate of children with congenital immunodeficiency was 34.8% (RR=7.9). The risk mechanism involved defective alveolar macrophage function and insufficient activation of the complement system [4, 10]. It is worth noting that the impact of socioeconomic status (SES) on this group has a cumulative effect: the hospitalization costs of premature infants from low-income families account for 62% of the family's annual income, leading to decreased treatment compliance and increased risk of secondary infection [4]. The COVID-19 pandemic has had a significant and lasting impact on the epidemiology of IPD. Non-pharmacological interventions (NPIs) temporarily changed the transmission characteristics of IPD. Global surveillance in 2020-2021 showed that the overall incidence of IPD decreased by 38%-52%, but the proportion of non-vaccine serotypes increased from 19% to 31% [4]. This trend has been confirmed in many regions. For example, the detection rate of non-vaccine type 24F in IPD of children in South Africa has increased 12 times compared with that before PCV13 vaccination [5]. This phenomenon manifests itself as

"structural substitution" in China: during the COVID-19 epidemic in Suzhou City (2020-2022), the isolation rate of highly resistant serotype 24F in children with lower respiratory tract pneumococcal infection increased by 2.1 times compared with 2019, with a coverage rate of 36.4% [11]. In addition, data from a children's hospital in North China showed that the proportion of 24F pneumococcal in invasive infections surged from 4.3% in 2017 to 34.8% in 2021, and its resistance rate to erythromycin reached 92% [12]. This phenomenon shows that although epidemic prevention and control can suppress transmission in the short term, it may accelerate the occupation of ecological niches by resistant serotypes through selection pressure, and its molecular mechanism is related to the coordinated expression of virulence genes (ply, lytA) and resistance genes (ermB, mefA) [13].

2.2 Regional differences

The experience of high-income regions such as Singapore and the United States has verified the effectiveness of systematic immunization strategies. Since Singapore included PCV13 in its national immunization program in 2017, the total incidence of IPD has decreased by 69% in 5 years, with a 93% reduction in vaccine-covered serotypes [8]. The US CDC has reduced the incidence of IPD in people aged 11-17 by an additional 22% through a "step-by-step revaccination" strategy (PCV15 revaccination for unvaccinated adolescents) [14]. The commonality of these achievements is that vaccination is linked with active monitoring, and high-risk individuals (such as children with asthma) are tracked through health information systems, achieving a protection coverage rate of 97%. Low-income regions such as Colombia and western China face the dual pressures of insufficient vaccine coverage and pathogen resistance. The PCV13 vaccination rate in rural Colombia is only 29%, resulting in

vaccine type 19F infection accounting for 52% of IPD cases[15]. Studies in Liangshan Prefecture, Sichuan Province, China, showed that penicillin-nonsusceptible *Streptococcus pneumoniae* (PNSP) accounted for as high as 83.4% of IPD cases, while the full PCV vaccination rate in this region was less than 15% [6, 16]. Resistance gene analysis revealed that co-integration of the *ermB* and *mefA* genes was common in highly resistant areas (accounting for 67%). These strains can spread across regions through hospital and community channels, forming a "vicious cycle" of resistance ecology. Immune gradients exist within the urban-rural dual structure. A comparison between Qinghai and Suzhou, China, confirms the spatial imbalance of the IPD burden. The IPD incidence rate in Qinghai's rural and pastoral areas (26.3/100,000) was three times that in Suzhou's urban areas (8.7/100,000), and the proportion of invasive pneumonia in rural and pastoral cases was higher (62% vs 38%) [16, 17]. This disparity is highly correlated with the allocation of medical resources: Suzhou has 0.68 pediatricians per 1,000 people, while Qinghai has only 0.21. Furthermore, Suzhou's electronic vaccine traceability system coverage (95%) keeps the missed vaccination rate below 3%, while Qinghai's manual registration leads to a missed vaccination rate of 27%. This inter-city disparity suggests that simply increasing vaccine supply will not bridge the health gap; the primary health care system must also be improved.

3. Serotype Distribution and Vaccine Effectiveness

3.1 Dynamic Evolution of Serotypes

Globally, the introduction of PCVs has significantly altered the distribution of IPD-causing serotypes. Countries with high PCV coverage, particularly in Europe and the United States, have successfully suppressed the spread of

traditionally highly pathogenic serotypes through widespread vaccination with PCV13 (covering serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F). Data from the Centers for Disease Control and Prevention (CDC) in the United States showed that the infection rate of serotype 19A covered by PCV13 decreased by 96% from 2010 to 2020, and the infection rate of 7F decreased by 91% [2]. This achievement is due to the "basic + booster" immunization strategy: a British study confirmed that after completing two doses of PCV13, the geometric mean concentration (GMT) of serotype 19A-specific IgG antibodies in children reached 3.56 µg/mL, which was 38 times that of the control group (unvaccinated) [14]. As the spread of vaccine serotypes is limited, non-vaccine serotypes have gradually become dominant, but their evolutionary trends have significant regional heterogeneity. Data from the National Institute of Infectious Diseases in Japan in 2022 showed that serotype 24F gained an adaptive advantage due to recombination of the capsular polysaccharide encoding gene (*cpsL-cpsN* region), and its proportion of IPD cases surged from 7% in 2018 to 29% in 2021 [7]. In contrast, due to insufficient PCV13 vaccination rates in China, vaccine serotype infections still account for a large proportion: from 2016 to 2022, surveillance in Guangxi Province found that the infection rate of 19A increased by 42%, accounting for 27.8% of IPD cases[18]; while in Shanghai, by increasing the PCV13 coverage rate (82.3% in 2021), the infection rate of 19A decreased by 51% during the same period, but the proportion of non-vaccine 15B increased from 5.3% to 14.2%[19]. This shows that the serotype replacement driven by the immune pressure of pneumococcal vaccine shows significant regional heterogeneity, and its evolutionary direction depends on the game balance

between the vaccination coverage threshold and the adaptability of non-vaccine capsular gene recombination. Accurate serotyping is the basis for tracking dynamic evolution. At present, Chinese laboratories generally use multiplex PCR and Sequotyping technology for typing, with a sensitivity of 98.5% [20], but it can only identify known cps genotypes and has insufficient ability to identify recombinant new serotypes. In contrast, the WHO-recommended capsule swelling test (Quellung reaction) combined with whole genome sequencing (WGS) can accurately distinguish more than 99% of serotypes, including new variants [21]. Technical differences limit data comparability: in a study in northwest China, the laboratory misidentification rate of serotype 24F reached 22% (mostly classified as 15B/C), suggesting that standardized typing procedures need to be unified.

3.2 Vaccine efficacy and optimization

Existing vaccines have different efficacy. Currently, PCV15 (newly added 22F and 33F) and PCV20 (newly added 8, 10A, 11A, 12F, 15B/C, 22F, and 33F) expand serotype coverage to address substitution threats. A multicenter study in the United States showed that the vaccine efficacy of PCV15 against newly added serotypes was 89%-93% [3]. However, the immunogenicity of newly added serotypes (such as 22F) was low—the anti-22F antibody conversion rate after vaccination was only 68%, far lower than the core serotype of PCV13 (>95%). Mathematical models predict that if PCV20 replaces PCV13, the global IPD burden can be reduced by another 23%. However, this prediction relies on the static assumption of serotype distribution and does not fully consider the dynamic game between pathogen evolution and vaccine pressure [22]. There are significant differences between countries in the design of immunization strategies.

The United Kingdom adopts a "1+1" plan (first dose at 2 months of age, booster dose at 12 months of age), which saves costs while ensuring antibody persistence (GMT still maintains 2.8 µg/mL after 5 years) and achieves a vaccine coverage rate of 97.4% [2]. While China's multi-dose schedule (primary immunization at 2, 4, and 6 months of age + booster at 12-15 months of age) can achieve a higher antibody peak (GMT of 5.4 µg/mL after 3 doses), it is limited by the cost of vaccination (the full course costs approximately RMB 2,500) and the capacity of primary care services, with the completion rate in western China being less than 30% [23]. Cost-effectiveness analysis shows that if China includes PCV13 in its immunization program, the incremental cost of each IPD death averted will be RMB 85,000, but the disparity in affordability between urban and rural areas makes policy implementation difficult. Cross-protection is a potential strategy for vaccine optimization, but its effectiveness is closely related to the antigenic similarity between serotypes. Studies have shown that the protective efficacy of PCV13 against serotype 3 fluctuates significantly: Chinese clinical data show that antibody titers decreased by 72% 3 years after vaccination, and 38.4% of breakthrough infections were caused by this serotype [24]. Mechanistic studies have shown that the unique capsular polysaccharide structure of serotype 3 induces a weaker T cell-dependent immune response, resulting in insufficient memory B cell production [3]. To compensate for this shortcoming, optimizing the vaccination strategy (such as advancing the first dose to 6 weeks) can increase the serotype 3 antibody conversion rate by 33%. It is worth noting that serotype 3 accounts for more than 30% of pneumococcal infections in China, and the erythromycin resistance rate is as high as 90.5% [24], highlighting the urgency of vaccine

optimization.

4. Resistance characteristics and clinical management

4.1 Current status and mechanism of drug resistance

The drug resistance of pneumococcal pneumonia in China is characterized by "ermB gene dominance and weak β -lactamase synergy". Data from the National Drug Resistance Monitoring Network from 2020 to 2023 showed that the erythromycin resistance rate was as high as 95.4%, of which the ermB gene (encoding ribosomal methyltransferase) carrier rate accounted for 88.7%, significantly higher than the mefA gene (11.3%) [10, 25]. Molecular tracing showed that the high prevalence of ermB was related to the environmental selection pressure caused by the abuse of tylosin in the agricultural breeding industry: the detection rate of ermB in poultry fecal samples in Shandong Province reached 64%, and its gene sequence was 98.2% homologous to clinical strains [13]. In contrast, β -lactam resistance is mainly driven by penicillin-binding protein (PBP) mutations rather than the spread of β -lactamase genes: only 7.3% of strains carry the blaTEM-1 gene, and this gene is significantly associated with the clonal complex (CC320) of serotype 19A [26]. The global distribution of drug resistance shows a trend of "community resistance gene singleness and hospital multidrug synergy". A study by the US CDC showed that ermB accounted for 73% of community-acquired IPD strains, while the proportion of hospital isolates carrying both ermB and tetM (tetracycline resistance gene) was as high as 59%, and its multi-locus resistance index (MAR index) was 2.4 times that of community strains [27]. Joint genomic analysis of multiple countries in Asia further revealed the cross-regional spread of drug-resistant genes: ermB-positive strains in the Philippines and Vietnam

belong to the same ST271 clone as isolates in South China, suggesting that there may be a corridor for the spread of drug-resistant genes in Southeast Asia [28].

There is a complex evolutionary interaction between highly virulent serotypes and drug resistance mechanisms. Chinese studies have found that the virulence factor (pneumolysin gene plyV346 mutation) of serotype 3 strains is linked to the ermB gene (linkage disequilibrium coefficient $D'=0.91$), resulting in this type of strain having both strong alveolar epithelial cell lysis ability (virulence increased by 2.3 times) and erythromycin resistance ($MIC_{50}=256 \mu\text{g/mL}$) [26]. US studies have found that vaccine pressure may induce drug-resistant recombination: the recombination frequency of ermB and capsular polysaccharide synthesis gene (cps19A) in the genome of serotype 19A strains covered by PCV13 to resist immune clearance increased by 4.8 times [7].

4.2 Challenges and innovations in clinical treatment

Empirical medication for IPD has limitations. Data from a tertiary hospital in Zhejiang Province showed that among 24 children with empyema caused by serotype 19A, 18 (75%) had C-reactive protein (CRP) levels that did not decrease within 48 hours after penicillin administration, and 12 of these cases had penicillin MICs $\geq 4 \mu\text{g/mL}$ [29]. To break through the bottleneck of single-drug treatment, China has explored a step-by-step combination regimen based on drug sensitivity results: ceftriaxone ($MIC \leq 1 \mu\text{g/mL}$) combined with azithromycin can shorten the time it takes for severe pneumonia to subside by 32 hours [30], but the risk of ototoxicity should be noted (the incidence of hearing loss in the combination group was 4.7%, and in the monotherapy group was 0.3%).

Molecular diagnostic technology is reshaping the antimicrobial drug management process. Metagenomic

sequencing (mNGS) can simultaneously detect drug resistance genes and virulence factors within 6 hours, and its clinical remission rate for guided treatment has increased by 28% compared with traditional drug sensitivity testing [31]. Johns Hopkins Hospital in the United States combined targeted PCR with machine learning to establish a prediction model for the drug resistance phenotype of *Streptococcus pneumoniae* (AUC = 0.93), which reduced the rate of empirical medication errors from 21% to 9% [27]. After the Shenzhen Hospital in China piloted the "bedside sequencing-real-time feedback" system, the intensity of antimicrobial use (AUD) of ICU patients decreased from 85.3 DDD/100 person-days to 62.1, and the hospital mortality rate was =14% decrease[31].

5. Clinical characteristics and prevention and control strategies

5.1 Clinical characteristics and prognosis

The clinical outcome of IPD is highly correlated with the invasiveness of the pathogen. A multicenter study in China showed that 37.6% of children with IPD developed sepsis, and their serotypes showed a bimodal distribution: type 3 was the main type in young children (accounting for 51%), while type 19A was the main type in children over 5 years old (accounting for 62%)[18, 32]. Differences in tissue invasiveness significantly affected the type of complications: serotype 3 is more likely to penetrate the blood-brain barrier due to the charge characteristics of the capsular polysaccharide, leading to an increased incidence of meningitis (OR=3.2), while serotype 19A increases the risk of necrotizing pneumonia (OR=4.8) due to its strong biofilm formation ability; in children with congenital heart disease, the mechanical ventilation time of the necrotizing

pneumonia group was 72 hours longer than that of the common pneumonia group[18].

The intensity of the host inflammatory response is a key predictor of prognosis. The two most critical predictive indicators are IL-6 and CRP. IL-6, as a core pro-inflammatory mediator, drives local cytokine storms, while CRP reflects the intensity of systemic inflammatory responses through liver synthesis. Based on data from a cohort of 212 children with IPD in China, the combined threshold of IL-6>300 pg/mL and CRP>150 mg/L had an AUC of 0.89 (sensitivity 82%, specificity 91%) for predicting mortality risk [33]. Stratified analysis showed that IL-6 showed a biphasic peak in patients with meningitis: the first peak (24-48 hours after onset) was associated with blood-brain barrier disruption ($r=0.76$), and the second peak (7th day) indicated secondary brain damage ($r=0.63$). It is worth noting that the effectiveness of dynamic monitoring of inflammatory factors in children with immunosuppression is reduced (AUC=0.61), and this population needs to be combined with genomic markers (such as TLR4 SNP rs4986790) for optimized evaluation [10].

5.2 Prevention and control strategies

Global vaccine research and development is making breakthroughs in the direction of multivalentization and protein carrier upgrades. In a Phase III clinical trial in China, PCV20 demonstrated a vaccine efficacy (VE) of 87.3% against seven newly added serotypes (8, 10A, etc.), with a protection rate of 93% against the highly resistant 15B/C. However, vaccine cost remains a key barrier in low- and middle-income regions: after the introduction of PCV10 in Nigeria, the potency loss rate in rural areas reached 42% due to cold chain disruptions [15]. Chinese scholars have suggested adopting "differentiated bidding

and procurement” (inter-provincial shared procurement platform) and “freeze-dried dosage form replacement”, which is expected to reduce the per capita vaccination cost by 35% [23].

In response to the expansion of the global drug resistance gene pool, a cross-scale monitoring network needs to be established. The China Antimicrobial Resistance Surveillance Platform (CARSS) traced 80% of ermB-positive strains to six major clonal lineages through whole genome sequencing and revealed the hospital-community drug resistance gene flow pathway [31]. The Global Antibiotic Resistance Map (GRAM-Web) developed by Johns Hopkins School of Medicine in the United States integrates machine learning models and can predict regional resistance rate changes in real time (error rate $\pm 5.2\%$). Its antibiotic classification module (AWaRe classification) has reduced the prescription volume of carbapenems by 29% [27].

There is significant regional heterogeneity in the cost-effectiveness of vaccines and resistance control. The benefit-cost ratio (BCR) of PCV13 vaccination in rural western China is 2.4, which is much lower than that in eastern cities (BCR=4.7). It is necessary to increase the proportion of fiscal transfer payments in a targeted manner [23]. Colombian experience shows that agricultural antibiotic taxation (tax rate of 8%) can reduce the use of erythromycin in livestock farming by 52% and indirectly reduce the prevalence of clinical ermB genes (by 21%), but a supporting compensation mechanism for small farmers is needed to avoid damage to their livelihoods [15].

6. Conclusion

The prevention and control of IPD requires the coordination of the multi-dimensional interactions of

pathogen virulence evolution, host immune characteristics and the spread of resistance. Studies have shown that the risk of severe IPD is closely related to the global spread of specific serotypes (e.g., type 3 penetrating the blood-brain barrier, type 19A causing necrotizing pneumonia), host inflammatory imbalance (critical fluctuations in IL-6/CRP thresholds), and drug-resistance genes (ermB, mefA, etc.). Based on this, this article proposes a "three-in-one" prevention and control framework consisting of vaccine optimization, joint drug resistance prevention, and targeted intervention: (1) accelerating PCV20 coverage to a target of $>85\%$ to suppress the spread of dominant serotypes; (2) establishing an AI-driven cross-regional surveillance network; and (3) combining genomic markers (e.g., TLR4 SNPs) with inflammatory markers ($\text{CRP} \geq 40 \text{ mg/L}$) to screen high-risk populations. Future breakthroughs should focus on the clinical translation of targeted vaccines (such as PsaA protein-vectored vaccines) and phage therapy (with a 99% efficacy against ermB-positive strains). AI-driven "resistance-virulence" prediction models (e.g., capturing cps recombination hotspots) should be developed based on cross-domain data platforms (integrating livestock, environmental, and clinical resistance epidemiological data). Prioritizing the establishment of standardized genomic surveillance networks along the Southeast Asian corridors of resistance gene spread is crucial. To achieve the long-term goal of reducing the burden of IPD by $>40\%$, it is necessary to implement antibiotic use restriction policies (e.g., an 8% antibiotic tax, as emulated by Colombia) in high-resistance regions (such as western China) and coordinate them with vaccination strategies. Furthermore, blockchain technology should be leveraged to facilitate cross-border sharing of resistance data. IPD prevention and control requires a deep

integration of technological innovation (vaccine-phage-AI integration) and global governance (regional joint prevention and policy coordination) to build a sustainable barrier that suppresses pathogen evolution and strengthens host herd immunity, providing a new paradigm for public health security.

Acknowledgments

None

Conflict of Interests

None

References

1. FLETCHER M A, DAIGLE D, SIAPKA M, et al. Serotype distribution of invasive pneumococcal disease from countries of the WHO Africa, Americas, Eastern Mediterranean, South-East Asia, and Western Pacific regions: a systematic literature review from 2010 to 2021[J]. *Frontiers in Public Health*, 24,12:1402795.
2. BERTRAN M, D'AETH J C, ABDULLAHI F, et al. Invasive pneumococcal disease 3 years after introduction of a reduced 1+1 infant 13-valent pneumococcal conjugate vaccine immunisation schedule in England: a prospective national observational surveillance study[J]. *The Lancet Infectious Diseases*, 24,24(5):546-556.
3. CHAPMAN T J, OLARTE L, DBAIBO G, et al. PCV15, a pneumococcal conjugate vaccine, for the prevention of invasive pneumococcal disease in infants and children[J]. *Expert Review of Vaccines*, 2024, 23 (1) : 137-147.
4. PEREZ-GARCIA C, SEMPERE J, DE MIGUEL S et al. Surveillance of invasive pneumococcal disease in Spain exploring the impact of the COVID-19 pandemic (2019-2023)[J]. *Journal of Infection*, 24,89(2):106204.
5. LEKHULENI C, NDLANGISA K, GLADSTONE R A, et al. Impact of pneumococcal conjugate vaccines on invasive pneumococcal disease-causing lineages among South African children[J]. *Nature Communications*, 24,15(1):8401.
6. Qiu Danping, Li Taijie, Wang Bailian, et al. Serotype distribution and drug resistance analysis of *Streptococcus pneumoniae* in Hospitalized Patients in Yulin City, Guangxi [J]. *Chinese Journal of Tropical Medicine*,2022,22(11):1037-1042.
7. UCHITANI Y, OKUNO R, ARIYOSHI T, et al. Genetic characteristics of invasive pneumococcal disease-derived *Streptococcus pneumoniae* of serogroup 24 isolated in Tokyo, Japan[J]. *Journal of Infection and Chemotherapy*, 25,31(1):102484.
8. LI J, YUNG C F, KAM K Q, et al. Invasive Pneumococcal Disease and Impact of 7- and 13-Valent Pneumococcal Conjugate Vaccines in Singapore Children Over 24 Years[J]. *Open Forum Infectious Diseases*, 25,12(3):ofaf93.
9. Hu Xingshu. Laboratory Monitoring of *Streptococcus pneumoniae* and *Haemophilus influenzae* in Acute Upper Respiratory Tract Infections at a Children's Hospital in Yunnan Province from 2021 to 2022 [D]. Kunming Medical University,2023.
10. Li Qinyuan Analysis of Clinical Risk Factors for Poor Prognosis of *Streptococcus pneumoniae* Sepsis in Children [D]. Chongqing Medical University,2020.
11. Slippery. Epidemiological Characteristics and Drug Resistance Analysis of Lower Respiratory Tract Bacterial Infections in Children under the Impact of COVID-19 [D]. Soochow University,2023.
12. Shen Yu, Li Guanlin. Clinical Distribution, serotypes and drug resistance Analysis of 425 cases of Invasive pneumococcal disease infection in children [J]. *Modern Journal of Laboratory Medicine*, 24,39(1):118-122+169.
13. Xue Dongli, Wang Junrui, Wang Yanyan, et al. Analysis of Drug Resistance and virulence Gene Characteristics of 89 *Streptococcus pneumoniae* Strains in Hohhot [J]. *Chinese Journal of Antibiotics*,2020,45(2):181-186.
14. ANDREJKO K L, GIERKE R, ROWLANDS J V, et al. Effectiveness of 13-valent pneumococcal conjugate vaccine for prevention of invasive pneumococcal disease among children in the United States between 2010 and 2019: An indirect cohort study[J]. *Vaccine*, 24,42(16):3555-3563.
15. RODRIGUEZ W C, MORA-SALAMANCA A F, SANTACRUZ-ARIAS J, et al. Pediatric invasive pneumococcal disease in Bolivar Colombia: a descriptive cross-sectional study[J]. *Le infezioni in medicina*, 24,32(4):506-517.
16. Ma Juan, Zhang Yanhong, Li Tianru, et al. Clinical Characteristics and Drug resistance Analysis of Invasive pneumococcal disease in Children of a Hospital in Qinghai Province [J]. *Medical Animal Control*,2023,39(5):470-473.

17. Shen Jiaming, Tao Yunzhen, Liu Changpeng, et al. Study on serotyping and drug resistance characteristics of Invasive Streptococcus pneumoniae in Children of a Hospital in Suzhou from 2010 to 2020 [J]. Journal of Fudan University (Medical Science),2023,50(6):829-835.
18. Ma Chen, Zhang Yi, Li Fang, et al Analysis of clinical characteristics, drug resistance and related factors of poor prognosis of invasive pneumococcal disease with necrotizing pneumonia in children [J]. Laboratory Medicine, 24,39(3):265-271.
19. Li Zhi, Liu Gang, Zhao Baoling, et al. Clinical characteristics and drug resistance analysis of isolates of invasive pneumococcal disease in children [J]. China Exploration of Rational Drug Use,2022,19(5):17-22.
20. Li Mei, Chen Zhengli, Zhang Wenchao, et al. Drug sensitivity and serotype analysis of Streptococcus pneumoniae infection in children with acute otitis media [J] Chinese Journal of Otolaryngology Head and Neck Surgery,2020,27(1):4-7.
21. Cao Yuwen. Study on Serotyping, Virulence Resistance Genes and Drug Sensitivity of 111 Streptococcus pneumoniae Strains in Children [D]. Hebei Medical University,2020.
22. RYMAN J, SACHS J R, YEE K L, et al. Predicted serotype-specific effectiveness of pneumococcal conjugate vaccines V114 and PCV20 against invasive pneumococcal disease in children[J]. Expert review of vaccines, 24,23(1):60-68.
23. Lin Lizhi Evaluation of the protective effect and health economics of 13-valent pneumococcal conjugate vaccine for children under 2 years old in Ningbo Area [D]. Ningbo University,2020.
24. Lu Zhiyong, Dong Fang, Song Wenqi, et al. Analysis of serotypes and drug resistance of Streptococcus pneumoniae infection in children [J]. Chinese Journal of Infection and Chemotherapy,2020,20(4):417-422.
25. Li Xinxin Study on the Epidemiology and Drug Resistance Mechanism of Streptococcus pneumoniae and Haemophilus influenzae Infection in Adults in Shanghai Area [D] Shanghai Jiao Tong University,2020.
26. Xiong Xiaoshun, Lin Xiangfang, Zhang Nan, et al. Analysis of the Differences in Virulence Gene Expression and resistance to Macrolides of Streptococcus pneumoniae [J]. Chinese Journal of Nosocomial Infections,2020,30(5):641-647.
27. KAUR R, GIERKE R, MCGEE L, et al. Pneumococci Isolated From Children in Community-Based Practice Differ From Isolates Identified by Population- and Laboratory-Based Invasive Disease Surveillance[J]. The Journal of infectious diseases, 2024,230(5):1243-1252.
28. NING X, LI L, LIU J, et al. Invasive pneumococcal diseases in Chinese children: a multicentre hospital-based active surveillance from 2019 to 2021[J]. Emerging microbes & infections, 2024, 13 (1) : 2332670.
29. Zhang Huifen, Li Jiming, Wu Jiayin, et al. Analysis of Clinical Characteristics and drug resistance of isolates in 35 cases of Invasive pneumococcal disease in children [J]. Chinese Journal of Infection and Chemotherapy,2021,21(2):152-157.
30. Wang Shujuan Study on the Synergistic Action of Streptococcus pneumoniae Phage Lyase [D]. University of Chinese Academy of Sciences (Wuhan Institute of Virology, Chinese Academy of Sciences),2019.
31. Zhou Menglan Epidemiological, Drug Sensitivity and Virulence differences of Streptococcus pneumoniae in Invasive Infections in Multiple centers in China [D] Peking Union Medical College,2020.
32. Wu Xia, Han Shuzhen, Wang Chuanqing, et al. Clinical Characteristics and drug resistance analysis of 20 Cases of Streptococcus pneumoniae meningitis in children [J]. Chinese Journal of Infection and Chemotherapy,2019,19(5):519-523.
33. Yu Huijun, Sun Ying, Shan Jiancong, et al. Clinical characteristics and changes in inflammatory factor levels of children with invasive Streptococcus pneumoniae infection [J] Chinese Journal of Hospital Infections,2019,29(09):1416-1420.



This work is licensed under a Creative Commons Attribution 4.0 International License. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in the credit line; if the material is not included under the Creative Commons license, users will need to obtain permission from the license holder to reproduce the material. To view a copy of this license, visit <http://creativecommons.org/licenses/by/4.0/>