British Journal of Hospital Medicine

Br. J. Hosp. Med. (Lond) **2026**; 87(4): 53104
https://doi.org/10.31083/BJHM53104

Article

Epidemiology and Disease Burden of Hospitalised Children With Invasive Fungal Infection in China, 2016–2022

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Academic Editor: John Alcolado

Submitted: 15 July 2025 Revised: 24 August 2025 Accepted: 27 August 2025 Published: 20 April 2026

Abstract

Aims/Background: Invasive fungal infection (IFI) represents a significant global health challenge, particularly in paediatric populations, due to high mortality and severe long-term sequelae. This study aimed to characterize the epidemiological patterns and quantify the disease burden of IFI among hospitalised children in China. **Methods**: Data were obtained from the face sheets of discharge medical records collected between 2016 and 2022 from 30 tertiary children's hospitals, aggregated into the FUTang Updating medical REcords (FUTURE) database. Sociodemographic variables, disease spectrum, pathogen distribution, potential risk factors, length of stay (LOS), and overall disease burden among children with IFI were systematically analysed. **Results**: A total of 1250 IFI cases were identified, revealing an upward trend in incidence since 2019. The pathogen distribution among the 485 episodes with available microbiological data included *Candida* (25.36%; 123/485), *Aspergillus* (23.71%; 115/485), *Cryptococcus* (22.06%; 107/485), *Pneumocystis* (21.44%; 104/485), *Mucor* (4.12%; 20/485), *Talaromyces* (1.24%; 6/485), *Histoplasma* (0.82%; 4/485), *Blastomyces* (0.62%; 3/485), and *Sporotrichum* (0.62%; 3/485). Disseminated infections accounted for 5.76% (72/1250) of all IFI. Among the 1178 non-disseminated IFI cases, pneumonia (73.34%, 864/1178), central nervous system (CNS) infections (15.53%, 183/1178), and bloodstream infections (8.66%, 102/1178) were the predominant disease types. The most prevalent risk factors were haematological malignancies and myelosuppression. Overall, 181 patients died during their hospitalisation, representing a mortality rate of 14.48%. **Conclusion**: The incidence of IFI among hospitalised children in tertiary centres in China has risen since 2019, with *Candida*, *Aspergillus*, and *Cryptococcus* identified as the predominant pathogens. These infections are associated with considerable mortality (14.48%). The findings highlight the urgent need for enhanced surveillance, earlier diagnosis, and targeted therapeutic strategies to reduce morbidity and mortality in this high-risk population.

Keywords: invasive fungal infection; epidemiology; hospitalisation; children; *Candidiasis*; haematological malignancy

1. Introduction

Invasive fungal infection (IFI) constitutes a major global public health challenge, particularly among children [1,2]. Each year, more than 6.5 million people worldwide are affected by life-threatening fungal diseases [3]. Despite advances in medical technology, the widespread use of broad-spectrum antibiotics, glucocorticoids, organ transplantation, and deep venous cannulation has increased susceptibility to opportunistic fungal infections [4,5].

Children, especially neonates, are highly vulnerable to IFI because of their immature immune systems, which may result in long-term complications such as neurodevelopmental impairments and organ dysfunction [6]. In 2022, the World Health Organization (WHO) released its first Fungal Priority Pathogens List [7], highlighting the rising importance of IFI. Among these pathogens, *Candida* species are particularly concerning in paediatric care settings. *Candida albicans* is the predominant cause of hospital-acquired bloodstream infections in paediatric populations [8,9]. Additionally, infections caused by *Aspergillus* and other molds have increased among high-risk groups, including patients with haematological malignancies and those undergoing stem cell transplantation [10]. Mortality rates for invasive mycoses in children remain alarmingly high, at approximately 50%, despite therapeutic advances [11].

The epidemiology of IFI in children is influenced by geographical and socioeconomic disparities, differences in healthcare resources, and varying prevalence of risk factors [12]. Although awareness is growing and targeted studies have been conducted in specific paediatric populations [2,13], comprehensive, longitudinal national data on paediatric IFI in China, a country with significant regional healthcare inequalities, remain scarce. Therefore, this study retrospectively analysed 1250 cases of hospitalised children diagnosed with IFI across 30 children's hospitals in 22 provinces of China between 2016 and 2022. The findings aim to provide valuable insights into the epidemiological profile and disease burden of paediatric IFI in China, potentially bridging key knowledge gaps and contributing to the global evidence base. This information could further inform prevention, surveillance, and treatment strategies for these severe infections.

2. Methods

2.1 Data Sources

The Futang Research Centre of Pediatric Development (FRCPD, http://www.futang.org/ftgk.jhtml), established in 2016, is the first non-profit organisation dedicated to paediatric development research. The centre comprises 47 provincial and municipal medical institutions, creating a nationwide network for children's health services. Since its inception, FRCPD has systematically collected Face Sheets of Medical Records (FSMRs) from its member hospitals. By 2022, FRCPD had developed an integrated system for the collection and sharing of FSMRs from its member hospitals, thereby improving data utilisation and institutional collaboration. Beijing Children's Hospital, Capital Medical University, acting as the convening unit, collected FSMRs of paediatric inpatients from 30 tertiary children's hospitals within the FRCPD network, forming the FUTang Updating medical REcords (FUTURE) database [14]. Data organisation, verification, and quality control were performed by FRCPD personnel.

2.2 Study Design

This was a multicentre, cross-sectional study. Basic medical information for all paediatric patients (aged 0–18 years) hospitalised with IFI in the FUTURE database between 2016 and 2022 was retrospectively reviewed. Data were extracted using the tenth revision of the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) codes (https://icd.who.int/browse10/2019/en) for hospitalised children with an IFI diagnosis. The corresponding ICD-10 codes are listed in **Supplementary Table 1**. Extracted variables included sex, age, year of admission, place of residence, geographic region, length of stay (LOS), primary and secondary diagnoses, clinical outcomes, and hospitalisation costs. Patients were categorised into six age groups (days, d; months, m; years, y) corresponding critical stages of immune system development [15]: 0–28 days, ≥28 days–1 year, ≥1–3 years, ≥3–6 years, ≥6–12 years, and ≥12–18 years. The 30 tertiary children's hospitals were further classified into seven geographic regions: Northeast China, North China, East China, South China, Central China, Northwest China, and Southwest China. The primary risk factors assessed included haematological malignancy, myelosuppression, immune deficiency, prematurity, organ transplantation, malnutrition, surgery, diabetes, and neutropenia [16].

2.3 Inclusion and Exclusion Criteria

This retrospective study included basic medical information from the FUTURE database for all children (<18 years) admitted for the first time with IFI, identified using ICD-10 codes. Clinical manifestations and laboratory findings of the 1250 patients met the 'proven' or 'probable' diagnostic criteria for IFI, as defined based on the consensus definitions of invasive fungal diseases from the European Organisation for Research and Treatment of Cancer/Mycoses Study Group Education and Research Consortium (EORTC/MSGERC) [17]. These included, but were not limited to, invasive candidiasis (IC), aspergillosis, mucormycosis, and other IFIs. To ensure diagnostic consistency and data reproducibility across centres, all participating hospitals applied a standardised ICD-10 code list, adhered to EORTC/MSGERC criteria, and underwent audits of selected cases conducted by an expert committee. Patients were excluded if they had incomplete data for key variables (e.g., sex, age, diagnosis, or disease burden) or if they presented with only superficial fungal infections or non-IFI conditions.

2.4 Statistical Analysis

Categorical variables were expressed as frequencies and percentages. LOS and hospital expenditure are reported as medians with interquartile ranges (IQRs). The Kolmogorov-Smirnov test was applied to assess normality. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Nonnormally distributed continuous variables were analysed using the nonparametric Mann-Whitney test for two groups, and the Kruskal-Wallis test for three or more groups. Trends in hospitalisation rates were assessed using the Cochran–Armitage trend test to evaluate linear changes. All analyses were conducted with IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY, USA). Statistical significance was defined as a two-tailed p-value < 0.05.

3. Results

3.1 Epidemiological Trends and Demographic Characteristics

A total of 1250 episodes of IFI were identified between January 2016 and December 2022, based on ICD-10 codes, representing 0.14‰ of all admissions (1250/9,008,615). The demographic characteristics of patients are summarised in Table 1. Among these cases, 58.32% (729/1250) occurred in males and 41.68% (521/1250) in females, yielding a male-to-female ratio of 1.40:1. Age distribution analysis revealed that children aged 6–12 years accounted for the highest proportion at 30.08% (376/1250), followed by those aged 3–6 years (20.64%, 258/1250) and 28 days–1 year (20.00%, 250/1250). Regionally, Northwest China recorded the highest number of hospitalisations (25.68%, 321/1250), followed by East China (19.20%, 240/1250) and Central China (19.04%, 238/1250). The proportion of IFI-related hospitalisations increased significantly from 0.09‰ in 2016 to 0.24‰ in 2022 (Cochran–Armitage test, $\chi^2 = 206.40$, $p < 0.001$). The trend exhibited two distinct phases: a slight decline from 0.09‰ to 0.07‰ between 2016 and 2018, followed by a sharp increase from 0.12‰ to 0.24‰ between 2019 and 2022 (Fig. 1). This indicates a notable shift in the epidemiology of IFI hospitalisation rates after 2019. Among hospitalised children, 37.12% (464/1250) resided in urban areas, whereas 62.88% (786/1250) came from rural areas. The median LOS was 17 days (IQR 9–29), and the median expenditure was 4503.36 (IQR 1926.15–9330.83) between 2016 and 2022.

Table 1. Demographic characteristics of hospitalised children with IFI (January 2016–December 2022).

Categories	Hospitalisation
Number of patients	1250
Sex, n (%)	
Male	729 (58.32)
Female	521 (41.68)
Age group, n (%)	
0–28 days	82 (6.56)
≥28 days–1 year	250 (20.00)
≥1–3 years	176 (14.08)
≥3–6 years	258 (20.64)
≥6–12 years	376 (30.08)
≥12–18 years	108 (8.64)
Region, n (%)	
Northeast China	25 (2.00)
North China	213 (17.04)
East China	240 (19.20)
South China	91 (7.28)
Central China	238 (19.04)
Northwest China	321 (25.68)
Southwest China	122 (9.76)
Year of admission, n (%)	
2016	104 (8.32)
2017	109 (8.72)
2018	104 (8.32)
2019	177 (14.16)
2020	196 (15.68)
2021	278 (22.24)
2022	282 (22.56)
Place of residence, n (%)	
Urban	464 (37.12)
Rural	786 (62.88)
LOS [days, median (IQR)]	17 (9–29)
Hospitalisation expenditure [USD, median (IQR)]	4503.36 (1926.15–9330.83)

Abbreviations: IQR, interquartile range; LOS, length of stay; USD, United States dollar.

3.2 Proportion of IFI Hospitalisations by Region, Age Group, and Place of Residence

The proportions of IFI hospitalisations were analysed relative to total hospitalisations across different patient age groups. As shown in Fig. 2A, children aged ≥12–18 years had the highest hospitalisation rate at 42.65/100,000 (108/253,238), followed by ≥6–12 years, ≥3–6 years, ≥28 days–1 year, 0–28 days, and ≥1–3 years, with rates of 23.47/100,000 (376/1,601,889), 15.43/100,000 (258/1,672,278), 14.85/100,000 (250/1,683,423), 9.77/100,000 (82/839,248), and 5.95/100,000 (176/2,958,539), respectively. Regionally, patients from Northwest China had the highest hospitalisation proportion (27.61/100,000; 321/1,162,455), while those from Northeast China had the lowest proportion (4.15/100,000; 25/602,259). The hospitalisation proportions in Southwest, North, Central, South, and East China were 19.45/100,000 (122/627,256), 18.24/100,000 (213/1,167,759), 15.79/100,000 (238/1,507,757), 14.43/100,000 (91/630,457), and 7.25/100,000 (240/3,310,672), respectively (Fig. 2B). The IFI hospitalisation rates for rural and urban children were 19.31/100,000 (786/4,070,615) and 9.40/100,000 (464/4,938,000), respectively (Fig. 2C).

3.3 Distribution of IFI

Among the 1250 patients enrolled in this study, 5.76% (72/1250) had disseminated IFI, whereas 94.24% (1178/1250) presented with non-disseminated IFI (Fig. 3A). Within the non-disseminated group, pneumonia, central nervous system (CNS) infections, and bloodstream infections were predominant disease types, representing 73.34% (864/1178), 15.53% (183/1178), and 8.66% (102/1178), respectively. Less frequent infections included nasosinusitis (1.44%, 17/1178), endocarditis (0.51%, 6/1178), arthritis (0.34%, 4/1178), keratitis (0.08%, 1/1178), and peritonitis (0.08%, 1/1178) (Fig. 3B).

3.4 Pathogen Spectrum of IFI

Only patients with pathogen information documented in the FSMRs were included in this analysis, resulting in 485 episodes (38.8%) with available microbiological data. The fungal pathogens were: *Candida* (25.36%, 123/485), *Aspergillus* (23.71%, 115/485), *Cryptococcus* (22.06%, 107/485), *Pneumocystis* (21.44%, 104/485), *Mucor* (4.12%, 20/485), *Talaromyces* (1.24%, 6/485), *Histoplasma* (0.82%, 4/485), *Blastomyces* (0.62%, 3/485), and *Sporotrichum* (0.62%, 3/485) (Fig. 4). Table 2 shows the age-specific distribution of confirmed pathogens among IFI cases across different age groups. *Candida* was predominant in children <1 year (56.55%, 82/145), particularly in neonates aged 0–28 days (95.46%, 21/22). In children aged 1–3 years, *Aspergillus* was most common (31.25%, 20/64), whereas in those >3 years, *Cryptococcus* had the highest prevalence (31.88%, 88/276). Over the study period, the proportion of *Candida* decreased from 38.33% (23/60) in 2016 to 12.00% (12/100) in 2022. *Aspergillus* became the predominant pathogen from 2018 onwards, ranging between 24.24% (16/66) and 29.79% (28/94). *Pneumocystis*

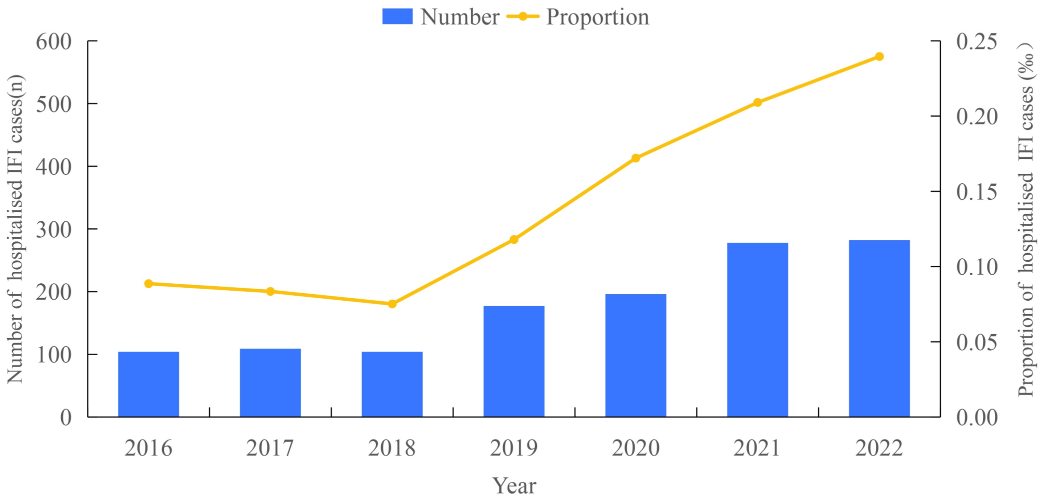

Fig. 1. Annual number proportion of hospitalised children with IFI (2016–2022). Abbreviation: IFI, invasive fungal infection.

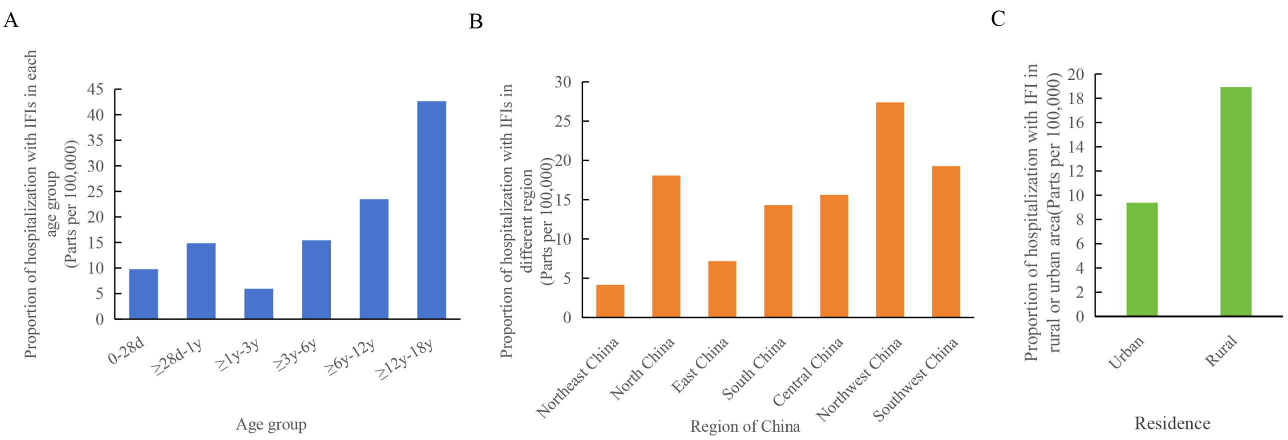

Fig. 2. Distribution of hospitalised children with IFI by category: (A) age group, (B) region, and (C) place of residence. Abbreviations: d, days; y, year(s).

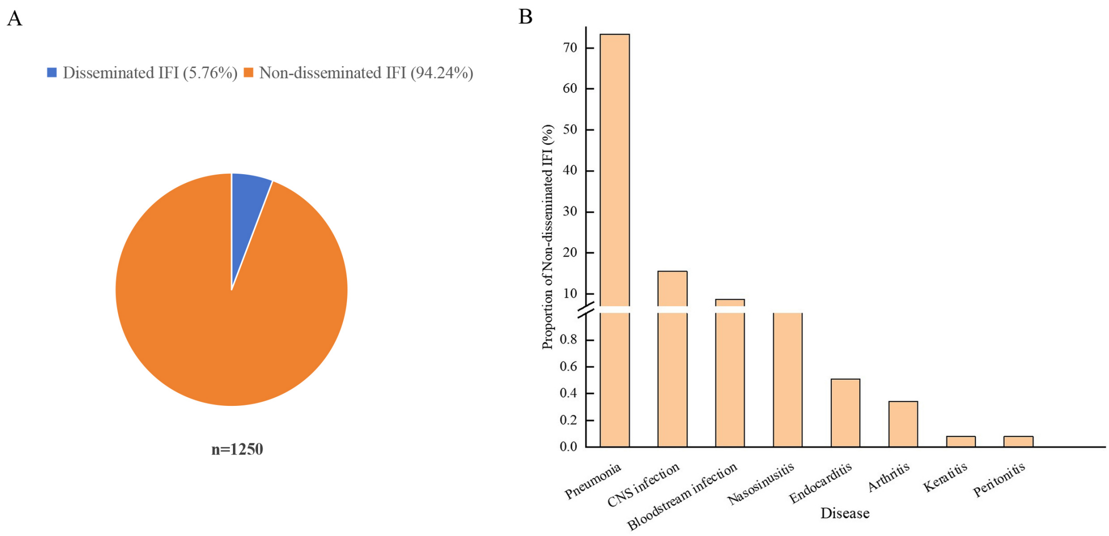

Fig. 3. Clinical spectrum of IFI in hospitalised children. (A) Proportion of disseminated versus non-disseminated infections. (B) Proportion of non-disseminated infections by type, including pneumonia, CNS infections, bloodstream infections, nasosinusitis, endocarditis, arthritis, keratitis, and peritonitis. Abbreviation: CNS, central nervous system.

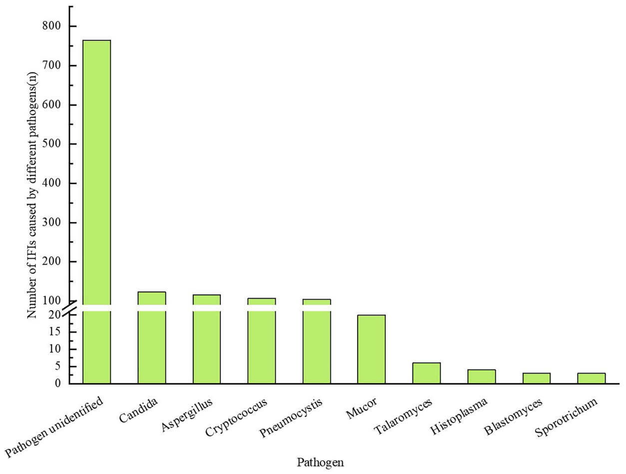

Fig. 4. Number of IFI cases stratified.

significantly increased to 34.00% (34/100) in 2022, while *Mucor* exhibited a marked increase, reaching 9% (9/100).

For disseminated IFI, *Candida* and *Cryptococcus* accounted for 45.59% (31/68) and 36.76% (25/68), respectively. In bloodstream infections, *Candida* was identified in 95.65% (22/23), while in CNS infections, *Cryptococcus* and *Candida* accounted for 66.67% (74/111) and 31.53% (35/111), respectively. In pneumonia cases, *Aspergillus* and *Pneumocystis* were predominant, representing 38.65% (109/282) and 36.88% (104/282), respectively.

3.5 Risk Factors for IFI

Among hospitalised patients diagnosed with IFI, 84.00% (1050/1250) exhibited identifiable risk factors for fungal infections. The predominant risk factor was haematological malignancy, affecting 36.80% (460/1250) of children, followed by myelosuppression in 18.08% (226/1250). Immune deficiency, prematurity, and organ transplantation were observed in 8.72% (109/1250), 7.20% (90/1250), and 4.4% (55/1250) of the patients, respectively. Among those with immunodeficiency disorders, organ transplant recipients, and patients with haematological malignancies, *Pneumocystis* was the predominant pathogen, followed by *Candida* and *Aspergillus*. In premature infants and surgical cases, *Candida* predominated, while *Mucor* was the leading pathogen in patients with diabetes (**Supplementary Table 2**).

3.6 LOS and Hospitalisation Expenditures

This study assessed LOS and hospitalisation costs in paediatric patients with IFI (Table 3). Significant differences were observed based on age, region, disease, and pathogen ($p < 0.05$). Infants aged 0–28 days had the longest LOS and incurred the highest costs, whereas children aged 6–12 years had the shortest LOS. Regionally, patients in Northwest China experienced the longest LOS, while those in North China had the highest expenses. No significant differences were observed between urban and rural patients. Among disease categories, arthritis cases showed the longest LOS (median: 35 days) and highest costs (median: $8162.46), while keratitis cases had the shortest LOS (median: 6 days) and lowest costs (median: $581.36). Additionally, patients with histoplasmosis, candidiasis, and cryptococcosis demonstrated prolonged hospitalisations, with a median LOS of 22–23 days. Notably, talaromycosis was associated with the highest median costs ($9686.49).

3.7 Mortality Rates

Among the discharged patients, 181 (14.48%) died, all of whom were included in the analysis. Mortality varied significantly across age groups (Table 4). Children aged ≥28 days to 1 year had the highest mortality (19.60%), followed by those ≥3–6 years (18.99%) and aged ≥1–3 years (17.05%) (χ^2 = 25.15, $p < 0.001$). Disease type and pathogen also appeared to influence outcomes. Bloodstream infections had the lowest mortality (7.84%, 8/102), while disseminated IFI (16.67%, 12/72), pneumonia (15.51%, 134/864), and CNS infections (14.21%, 26/183) presented higher risks. Regarding pathogens, *Pneumocystis* exhibited the highest mortality (24.04%, 25/104), whereas rates for *Candida* (15.45%, 19/123), *Aspergillus* (13.04%, 15/115) and *Cryptococcus* (11.21%, 12/107) were lower. However, these differences were not statistically significant (p = 0.299 for disease types; p = 0.301 for pathogens).

4. Discussion

IFI remains a major cause of morbidity and mortality in immunocompromised children. Its global burden is rising, driven by the increased use of immunosuppressive therapies and the presence of more complex underlying conditions [2,18]. Children represent a considerable proportion of IFI cases, with incidence and associated healthcare costs continuing to escalate worldwide [3]. This large nationwide epidemiological study of paediatric IFI was conducted across 30 tertiary hospitals in seven regions of China.

Between January 2016 and December 2022, 1250 paediatric IFI cases were diagnosed in China, corresponding to a prevalence of 0.14‰ among hospitalised patients, which is lower than global data [19]. To date, no epidemiological studies on paediatric IFI have been reported in China. Internationally, incidence rates in adults are higher: Spain (0.243‰, 2017–2021), the Netherlands (0.186‰ in 2017), France (0.216–0.236‰, 2012–2018), and the United States (approximately 0.272‰, 2006–2015) [20–23]. The lower incidence in children is largely attributed to reduced exposure to risk factors such as chronic obstructive pulmonary disease, diabetes, and malignant tumours, which are more common in adults. These comorbidities significantly compromise immune function, creating a favourable environment for fungal infections [24]. Despite the overall low prevalence, hospitalisation rates for IFI rose from 0.09‰

Table 2. Distribution of IFI cases with identified pathogens by year, age group, and disease type.

Category	Total, n	*Candida*, n (%)	*Aspergillus*, n (%)	*Cryptococcus*, n (%)	*Pneumocystis*, n (%)	*Mucor*, n (%)	Others, n (%)
Year							
2016	60	23 (38.33)	7 (11.67)	19 (31.67)	5 (8.33)	1 (1.67)	5 (8.33)
2017	55	22 (40.00)	7 (12.73)	17 (30.91)	5 (9.09)	2 (3.64)	2 (3.64)
2018	32	6 (18.75)	9 (28.12)	5 (15.62)	7 (21.88)	3 (9.38)	2 (6.25)
2019	78	19 (24.36)	23 (29.49)	20 (25.64)	12 (15.38)	1 (1.28)	3 (3.85)
2020	66	13 (19.70)	16 (24.24)	16 (24.24)	16 (24.24)	2 (3.03)	3 (4.54)
2021	94	28 (29.79)	28 (29.79)	10 (10.64)	25 (26.60)	2 (2.13)	1 (1.06)
2022	100	12 (12.00)	25 (25.00)	20 (20.00)	34 (34.00)	9 (9.00)	0 (0.00)
Age							
0–28 days	22	21 (95.45)	1 (4.54)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
≥28 days–1 year	123	61 (49.59)	20 (16.26)	3 (2.44)	32 (26.02)	0 (0.00)	7 (5.69)
≥1–3 years	64	17 (26.56)	20 (31.25)	16 (25.00)	4 (6.25)	3 (4.69)	4 (6.25)
≥3–6 years	82	11 (13.41)	21 (25.61)	28 (34.15)	17 (20.73)	1 (1.22)	4 (4.88)
≥6–12 years	137	10 (7.30)	39 (28.47)	40 (29.20)	36 (26.28)	11 (8.03)	1 (0.73)
≥12–18 years	57	3 (5.26)	14 (24.56)	20 (35.09)	15 (26.32)	5 (8.77)	0 (0.00)
Disease type							
Disseminated IFI	68	31 (45.59)	4 (5.88)	25 (36.76)	0 (0.00)	4 (5.88)	4 (5.88)
Non-disseminated IFI							
Pneumonia	282	34 (12.06)	109 (38.65)	7 (2.48)	104 (36.88)	16 (5.67)	12 (4.26)
CNS infection	111	35 (31.53)	2 (1.80)	74 (66.67)	0 (0.00)	0 (0.00)	0 (0.00)
Bloodstream infection	23	22 (95.65)	0 (0.00)	1 (4.35)	0 (0.00)	0 (0.00)	0 (0.00)
Nasosinusitis	0	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Endocarditis	0	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Arthritis	1	1 (100)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Keratitis	0	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Peritonitis	0	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)

in 2016 to 0.24‰ in 2022. This upward trend, particularly pronounced after 2019, suggests shifting epidemiological patterns and highlights global concerns over the growing complexity and vulnerability of hospitalised children [25]. The marked increase after 2019 may be partially linked to the COVID-19 pandemic. During this period, some children likely delayed medical visits for non-COVID-19 conditions, including those predisposing to IFI. Moreover, several studies show that severe COVID-19 increases IFI risk, particularly *Aspergillus*- and *Candida*-related infections, due to factors such as dual immune damage from both virus and host, intensive care unit-related complications, widespread immunosuppressive therapy, microbial imbalance, and antibiotic overuse [26]. Additionally, the growing use of advanced diagnostic technologies, including metagenomic sequencing in China, may have further contributed to increased IFI detection rates [27].

Our findings showed that children aged ≥6–12 years represented the highest proportion of IFI cases (30.08%, 376/1250), and hospitalisation rates for those ≥6 years were generally higher than those <6 years, consistent with previous studies [28,29]. This may reflect greater exposure to risk factors such as haematologic malignancies, prolonged antibiotic use, and immunosuppressive therapies, highlighting the need for age-specific prevention strategies. The relatively low proportion of cases in neonates (0–28 days, 6.56%) is notable, as they are typically considered high-risk for severe infections. This finding may reflect the effectiveness of neonatal care protocols or potential underdiagnosis, highlighting the need for further investigation.

The pathogen detection rate in this study was low (38.8%), consistent with the findings of Puerta-Alcalde *et al.* [30], highlighting persistent challenges in diagnosing paediatric IFI. Contributing factors include the limited sensitivity of available diagnostic tests, difficulty in obtaining adequate paediatric samples, especially from sterile body sites, and prior antifungal therapy masking pathogen detection. Reliance on medical records for pathogen identification presents limitations, as complex clinical scenarios or insufficient emphasis on microbiological confirmation may result in underdiagnosis. The high proportion of missing pathogen data raises concerns about selection and information bias, as confirmed cases may disproportionately represent patients with severe disease or obvious clinical features. Thus, caution is warranted when interpreting pathogen frequency or age-related distribution, since these patterns may not accurately reflect the true epidemiology.

Table 3. LOS and hospitalisation costs in children with IFI stratified by age, region, residence, disease type, and pathogen.

Category	LOS [days, Median (IQR)]	H/U	*p*-value	Expenditure [USD, Median (IQR)]	H/U	*p*-value
Age group		45.4392	<0.0001		27.7998	<0.0001
0–28 days	32 (16–49)			7828.02 (3932.51–13,113.69)		
≥28 days–1 year	18 (10–35)			4003.26 (1822.39–8808.02)		
≥1–3 years	16 (10–28)			4011.02 (2372.01–6367.87)		
≥3–6 years	17 (9–28)			4099.94 (1853.97–8122.16)		
≥6–12 years	14 (8–22)			4268.01 (1971.15–7868.83)		
≥12–18 years	16 (8–24)			5607.21 (2733.97–10,731.06)		
Region		22.3903	0.0010		20.0842	0.0027
Northeast China	14 (7–36)			4427.93 (1294.05–13,304.77)		
North China	18 (10–31)			5963.46 (2760.36–11,281.56)		
East China	16 (8–29)			4541.68 (1829.32–9647.31)		
South China	11 (6–21)			3661.27 (1508.86–6561.97)		
Central China	16 (8–33)			3949.74 (1760.14–8801.70)		
Northwest China	19 (11–28)			4526.09 (2743.17–6934.69)		
Southwest China	15 (8–27)			3530.44 (1816.36–7869.42)		
Residence		0.0061	0.9378		0.7641	0.3821
Rural	17 (9–29)			4296.45 (2088.57–8908.03)		
Urban	16 (9–33)			4431.53 (2263.19–8908.03)		
Disease type		108.1920	<0.0001		60.7752	<0.0001
Disseminated IFI	25 (7–44)			5942.60 (1635.03–12,761.15)		
Pneumonia	15 (9–23)			3947.78 (2092.17–6939.30)		
CNS infection	28 (7–58)			6711.32 (1745.63–13,867.10)		
Bloodstream infection	32 (18–45)			7774.66 (4287.36–11,902.03)		
Nasosinusitis	8 (4–9.5)			2259.63 (1476.30–3704.76)		
Endocarditis	20 (6–34)			4791.32 (2500.21–22,032.34)		
Arthritis	35 (29–46)			8162.46 (4349.41–12,758.40)		
Keratitis	6 (6–6)			581.36 (581.36–581.36)		
Peritonitis	34 (34–34)			6712.83 (6712.83–6712.83)		
Pathogen		22.7164	0.0069		20.8394	0.0134
Candida	22 (8–43)			6262.34 (1755.02–12,426.40)		
Aspergillus	13 (8–21)			4087.72 (2375.70–7997.47)		
Cryptococcus	22 (6–23)			4252.98 (1614.97–12,119.31)		
Pneumocystis	15 (10–20)			4925.80 (2732.27–10,662.48)		
Mucor	19 (8–40)			7259.04 (2066.23–15,740.04)		
Talaromyces	19 (7–36)			9686.49 (1496.05–15,604.36)		
Histoplasma	23 (11–43)			1589.24 (389.29–7231.84)		
Blastomyces	8 (7–9)			1198.37 (859.28–1358.10)		
Sporotrichum	18 (8–27)			4021.45 (3644.92–13,520.24)		

However, our findings align with previous reports [18] identifying *Candida*, *Aspergillus*, *Cryptococcus*, *Pneumocystis*, and *Mucor* as the predominant paediatric IFI pathogens. *Candida* species are most common, especially in neonates and infants [25]. *Aspergillus* is the leading invasive mold among children aged 1–3 years and in immunocompromised populations, while non-*Aspergillus* molds such as *Mucorales* are increasingly reported in paediatric cancer and diabetes. Rising rates of *Cryptococcus* and *Pneumocystis* among older children may reflect age-related changes in immunity, environmental exposure, and comorbidities. Given the shifting pathogen spectrum, the emergence of antifungal resistance, especially among *Candida* and *Aspergillus*, represents a growing clinical concern. Recent surveillance studies highlight increasing azole resistance in *Aspergillus fumigatus* and the global spread of multidrug-resistant *Candida* strains, including *C. auris*, which complicate management and may worsen outcomes in paediatric IFI [31,32]. These trends underscore the importance of ongoing antifungal susceptibility monitoring and integration of resistance data into therapeutic decision-making.

In our cohort, 94.24% of paediatric IFI were non-disseminated, with invasive fungal pneumonia being the most common presentation, confirming the respiratory tract as a principal entry point for fungal pathogens in immuno-

Table 4. Mortality analysis in hospitalised children with IFI by sex, age group, disease type, and pathogen.

Categories	Deaths, n (%)	Survivors, n (%)	χ^2 value	*p*-value
Sex (n, %)			0.821	0.365
Male	100 (13.72)	629 (86.28)		
Female	81 (15.55)	440 (84.45)		
Age group (n, %)			25.15	<0.0001
0–28 days	7 (8.54)	75 (91.46)		
≥28 days–1 year	49 (19.60)	201 (80.40)		
≥1–3 years	30 (17.05)	146 (82.95)		
≥3–6 years	49 (18.99)	209 (81.01)		
≥6–12 years	41 (10.90)	335 (89.10)		
≥12–18 years	5 (4.63)	103 (95.37)		
Disease type (n, %)			Fisher's Exact Test	0.299
Disseminated IFI	12 (16.67)	60 (83.33)		
Pneumonia	134 (15.51)	730 (84.49)		
CNS infection	26 (14.21)	157 (85.79)		
Bloodstream infection	8 (7.84)	94 (92.16)		
Endocarditis	1 (16.67)	5 (83.33)		
Nasosinusitis	0 (0.00)	17 (100.00)		
Arthritis	0 (0.00)	4 (100.00)		
Keratitis	0 (0.00)	1 (100.00)		
Peritonitis	0 (0.00)	1 (100.00)		
Pathogen (n, %)			Fisher's Exact Test	0.301
No identified pathogen	107 (13.99)	658 (86.01)		
Candida	19 (15.45)	104 (84.55)		
Aspergillus	15 (13.04)	100 (86.96)		
Cryptococcus	12 (11.21)	95 (88.79)		
Pneumocystis	25 (24.04)	79 (75.96)		
Mucor	2 (10.00)	18 (90.00)		
Histoplasma	1 (25.00)	3 (75.00)		
Talaromyces	0 (0.00)	6 (100.00)		
Blastomyces	0 (0.00)	3 (100.00)		
Sporotrichum	0 (0.00)	3 (100.00)		

compromised children [33]. CNS and bloodstream infections were the next most frequent, consistent with previous reports identifying these sites as highly vulnerable in high-risk populations. Pathogen distribution correlated with disease syndromes: *Candida* and *Cryptococcus* predominated in disseminated IFI and CNS infections, consistent with multicentre studies highlighting their systemic invasiveness and the need to consider them in children presenting with neurological symptoms [34,35]. In invasive fungal pneumonia, *Pneumocystis* was the predominant pathogen, followed by *Aspergillus*, reflecting recent data on immunocompromised paediatric patients [36,37]. Bloodstream infections were primarily caused by *Candida* species, the leading fungal bloodstream pathogen in hospitalised children, especially in neonates and infants [38]. These findings highlight the critical need for targeted diagnostic algorithms and empiric antifungal regimens tailored to address the most likely pathogens across distinct clinical presentations.

This study reports a high prevalence of IFI risk factors, particularly haematological malignancies (36.80%) and myelosuppression (18.08%), consistent with previous studies and clinical guidelines that identify severe neutropenia and haematological malignancies as key risk factors [2,39,40]. Both conditions impair host immunity, increasing susceptibility to opportunistic fungi such as *Candida* and *Aspergillus*. The study also confirms established epidemiological trends: *Pneumocystis* is common in patients with immunodeficiencies or organ transplant recipients. *Candida* remains a leading pathogen in preterm infants and surgical patients [41], while *Mucor* is closely associated with diabetes, reflecting global evidence of its rising incidence among children with hyperglycaemia and ketoacidosis [42].

Cost analysis indicates that non-neonatal paediatric IC in the United States incurs an average incremental hospital charge of approximately $92,266 per episode (95% CI: $65,058–$119,474) [43], while invasive aspergillosis (IA) can exceed a median of $49,309 per case [44]. In this study, the median LOS for IFI was 17 days, with median hospitalisation cost of $4503.36 per case. Costs were $6262.34 and $4087.72 for IC and IA, respectively. These findings underscore the significant healthcare and financial burden paediatric IFI imposes on families and the healthcare system.

In our study, the mortality rate during hospitalisation was 14.48%, falling within the lower range of reported values (10–70%) [2]. This comparatively lower rate may partly reflect the lack of post-discharge follow-up, as only in-hospital outcomes were captured in our analysis. Disease type strongly influences prognosis, with previous studies reporting higher mortality in subgroups such as patients with disseminated invasive fungal disease or CNS involvement [2]. Our findings are consistent with these reports, likely due to diagnostic delays, multi-organ dysfunction, and inadequate drug penetration, particularly in CNS infections. In our cohort, pathogen-specific mortality for pneumocystis pneumonia was 24.04%, exceeding the 11.7% reported in a national study from the United States [45], underscoring the urgent need for effective prevention and early intervention in immunodeficient children in China.

This study has several limitations. First, because the data were derived from discharge face sheets, information on the causative pathogen was incomplete in some cases, limiting a full characterisation of the pathogen spectrum. Second, long-term follow-up data for hospitalised patients were unavailable, leading to missing information on severe or fatal cases and affecting evaluations of LOS and associated costs. Third, FSMRs contained only basic patient details, and the absence of clinical information and laboratory test results constrained further analyses. To gain deeper insights into this disease, a prospective multicentre cohort study that integrates comprehensive clinical and laboratory data, pathogen distribution, antifungal resistance dynamics, and structured long-term follow-up is warranted.

5. Conclusion

In this 7-year nationwide retrospective study of 1250 hospitalised children with IFI across China, hospitalisation rates rose sharply after 2019, with haematological malignancies and bone marrow suppression identified as the primary predisposing factors. *Candida*, *Aspergillus*, and *Cryptococcus* are the most prevalent pathogens, predominantly causing pneumonia, CNS infections, and bloodstream infections. Despite advances in antifungal therapy, IFI-related mortality remains high, particularly in disseminated and CNS infections, imposing significant socioeconomic and healthcare burdens. These findings highlight the urgent need for strengthened epidemiological surveillance and targeted interventions to improve paediatric IFI outcomes in China.

Key Points

• The FRCPD established the FUTURE database, collecting FSMRs from 30 tertiary children's hospitals in China to investigate IFI in children between 2016 and 2022.

• A total of 1250 IFI cases were identified among 9,008,615 hospital admissions, with a prevalence of 0.14‰, lower than rates reported in Spain, the Netherlands, France, and the United States.

• IFI hospitalisation rates rose markedly from 0.09‰ in 2016 to 0.24‰ in 2022, with a notable increase post-2019, potentially associated with the COVID-19 pandemic and improvements in diagnostic technology.

• The most common pathogens were *Candida*, *Aspergillus*, and *Cryptococcus*, with *Candida* predominating in neonates and bloodstream infections, *Aspergillus* in pneumonia, and *Cryptococcus* in CNS infections.

• Haematological malignancies (36.80%) and myelosuppression (18.08%) were the leading risk factors for IFI, with *Pneumocystis* the primary pathogen in immunocompromised patients and *Candida* in premature infants.

• The median hospitalisation cost reached $4503.36, with an overall mortality rate of 14.48%, highlighting the urgent need for preventive strategies.

Availability of Data and Materials

Due to privacy restrictions, the raw data cannot be shared publicly; however, aggregated data are available from the corresponding author upon reasonable request.

Author Contributions

WYF, XYW and GL conceived and designed the study. WYF and XYW collected the data and designed the analysis. GL, WYF, XYW and GSF interpreted the data. WYF wrote the first draft of the paper. All authors contributed to the important editorial changes in the manuscript. All authors have read and agreed to the published version of the manuscript. All authors had access to the full dataset and agreed to take responsibility for the integrity and accuracy of the research.

Ethics Approval and Consent to Participate

This study was conducted following the ethical principles of the Declaration of Helsinki and received approval from the Ethics Committee of Beijing Children's Hospital, Capital Medical University (Approval Number: [2025]-E-028-R). Owing to the retrospective design of the study, involving only secondary analysis of aggregated and de-identified medical record data, the requirement for informed consent was waived by the ethics committee following national regulations (Measures for the Ethical Review of Biomedical Research Involving Humans in China, 2023 edition).

Acknowledgment

We are grateful to investigators from members of the Futang Research Center of Pediatric Development (FRCPD).

Funding

This work was supported by the Capital's Funds for Health Improvement and Research (2024–1-2092); 2022 Beijing Major Epidemic Prevention and Control Specially Construction Project (2-1-2-6-15); Beijing Municipal Administration of Hospitals Incubating Program (PX2024042); and Training Plan for High level Public Health Technical Talents Construction Project (Discipline Leader-02-02).

Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/BJHM53104.

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