Newly detected pediatric melioidosis cases in a single referral children's hospital in Ho Chi Minh City indicate the probable under-recognition of melioidosis in South Vietnam

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Research Article

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Abstract

Purpose.The epidemiology of melioidosis in Vietnam, a disease caused by the soil bacterium *Burkholderia pseudomallei*, remains unclear. This study aimed to detect pediatric melioidosis in South Vietnam and describe clinical features and the geographical distribution.

Methods. We introduced a simple laboratory algorithm for detecting *B. pseudomallei* from clinical samples at Children's Hospital 2 in Ho Chi Minh City in July 2015. *B. pseudomallei* culture isolates were confirmed by molecular methods. A retrospective observational study of children aged < 16 years with culture-confirmed melioidosis between July 2015 and August 2019 was undertaken.

Results.Thirty-five pediatric cases of melioidosis were detected, with cases originating from 13 out of 32 provinces and cities in South Vietnam. The number of pediatric melioidosis cases detected from a certain region correlated with the overall number of inpatients originating from the respective geographical area. Suppurative parotitis (n = 15; 42.8 %) was the most common clinical presentation, followed by lung infection (n = 10; 28.6 %) and septicemia (n = 7; 20 %). Fourteen (40 %) children had disseminated disease, including all cases of lung infection. Four (11.4 %) deaths occurred in the disseminated disease group.

Conclusions. We report here the first series of pediatric cases of melioidosis from Vietnam detected in a single big referral children's hospital in Ho Chi Minh City. The patients' origin indicates a wide distribution of melioidosis in South Vietnam. It seems probably that cases not only in children but also in adults remain grossly undiagnosed. Further awareness raising and laboratory capacity strengthening are needed in this part of the country.

Introduction

Melioidosis is a potentially fatal infectious disease caused by the saprophytic soil bacterium *Burkholderia pseudomallei*, which is predicted to occur in the environment of many tropical and subtropical regions [1]. Humans can acquire the bacterium via inoculation, inhalation, or ingestion during daily activities when exposed to contaminated sources. Although most cases are likely to be acquired from environmental sources, human-to-human transmission is possible, including mother-to-child transmission [2]. Therefore, the disease may occur at all ages, from newborns to elderly people.

There is comprehensive literature on the wide spectrum of clinical manifestation of melioidosis in adults, ranging from localized disease with abscesses affecting almost any organ to disseminated disease with septic shock and a high rate of underlying comorbidities [3–7]. By contrast, the knowledge available on the epidemiology and clinical presentation of melioidosis in children is more limited, although specific pediatric manifestations, such as suppurative parotitis, which are common in Thailand and Cambodia have been described [8, 9]. Interestingly, this specific feature has not been described in Australia, but primary cutaneous melioidosis is most common there and neurological manifestations occur in children [10, 11]. Children in East Malaysia with localized disease present primarily with cervical node swelling

and with pneumonia if disseminated disease is present [12]. Pediatric cases of melioidosis may account for 5–15% of the total cases in endemic regions [3, 7, 11]. The mortality rate in pediatric patients varies between regions, ranging from 7 to 59% [11, 13], and can be up to 73% in neonatal melioidosis [2].

Bacterial culture is the gold standard diagnostic test for melioidosis. However, the application of this method is challenging, especially in laboratories where microbiologists have no experience in recognizing *B. pseudomallei* colonies on routine agar plates. Additionally, *B. pseudomallei* isolated from clinical specimens can be misidentified as other bacterial species when using biochemical identification methods, such as API 20 NE, or automated identification systems, such as Vitek 2 and Phoenix [14]. Moreover, a low sensitivity of blood culture has been noted [15]. Collectively, there is no doubt that these factors contribute to the underdiagnosis of cases, which qualifies melioidosis to be recognized as a neglected tropical disease [16].

The first case of melioidosis in South Vietnam was described in 1925 [17]. More but still a limited number of indigenous cases and reports from soldiers who acquired *B. pseudomallei* infections during the Vietnam wars were documented during the following decades [18]. In 1999, surveillance at the Center for Tropical Diseases (now the Hospital for Tropical Diseases) in Ho Chi Minh City detected only nine cases from blood cultures between 1992 and 1998, and a very restricted distribution of *B. pseudomallei* in the environment [19]. Recently, a series of 16 adult cases with cavity pulmonary melioidosis have been reported from a big tertiary hospital in Ho Chi Minh City, but information on the patients' home and, thereby, the most likely place where infection occurred was not provided [20]. There is a particular gap of knowledge regarding pediatric melioidosis from Vietnam, where information on clinical and epidemiological features are very limited [3, 18].

We describe here the detection of *B. pseudomallei* from pediatric clinical samples after the introduction of a simple laboratory algorithm [3] at a large pediatric referral hospital located in Ho Chi Minh City. Subsequently, a retrospective observational study of culture-confirmed pediatric melioidosis cases was performed to describe clinical presentations, outcome, and the geographical distribution of cases in South Vietnam.

Methods

Study site and diagnosis of melioidosis

A training workshop was organized in July 2015 at the Department of Medical Microbiology at the Children's Hospital 2 (CH2) in Ho Chi Minh City to introduce the simple laboratory algorithm including a three antibiotic disc test for a presumptive diagnosis of *B. pseudomallei* from clinical specimens [3]. At the time of the visit, bacterial identification was performed using the BD Phoenix 100 automated identification system (Becton, Dickinson and Company, USA), and neither awareness of melioidosis existed nor was specific attention paid to the characteristics of *B. pseudomallei* grown on routinely used agar plates. Blood samples were cultured using the BD Bactec FX automated blood culture system

(Becton, Dickinson and Company, USA). Positive blood bottles were subcultured on blood, chocolate, and MacConkey agar plates. Other clinical specimens of pus, sputum, and body and cerebrospinal fluids were directly cultured on blood and MacConkey agar plates.

The CH2 is one of three referral children's hospitals in Ho Chi Minh City. It is a 1,400-bed government hospital that receives approximately 1,800,000 outpatients and 110,000 inpatients per year. The Department of Medical Microbiology performs microbiological cultures of approximately 28,500 blood samples, 15,000 sputum samples, 5,700 cerebrospinal fluid samples, 3,700 urine samples, and 1,900 pus samples annually. South Vietnam consists of four parts: the southeast region, south-central coast, central highlands, and Mekong river delta (Fig. 2).

The hospital provides mainly medical, surgical, and intensive care to the pediatric population in the southeast region of Vietnam. The region includes Ho Chi Minh City and five other provinces, covering an area of 23,598 km^2 (Fig. 2). According to the national census in 2019, the southeast region had a total population of 17,828,907 citizens, including 3,706,153 children aged < 15 years.

We revisited the Department of Medical Microbiology in August 2019 and reviewed culture logbooks for Gram-negative, oxidase-positive bacilli, which were resistant to colistin and gentamicin but sensitive to amoxicillin-clavulanic acid. Bacterial identification of the strains collected was reconfirmed using the *B. pseudomallei*-specific real-time PCR assay targeting TTS1 gene [3]. Antimicrobial susceptibility of the *B. pseudomallei* isolates against ceftazidime, meropenem, amoxicillin-clavulanic acid (ratio 2:1), and doxycycline (all antibiotic powders purchased from Sigma Aldrich, USA) was tested using the broth microdilution method, following the guidelines of the Clinical and Laboratory Standards Institute (CLSI) M7-A10 and M100-S24 [21, 22]. Susceptibility testing was performed for trimethoprim-sulfamethoxazole (ratio 1:19) using the E-test strip (bioMérieux SA, France), according to the manufacturer's instructions. *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853 were used as quality control. Antimicrobial susceptibility results were interpreted based on the minimal inhibitory concentration (MIC) standard values described in the CLSI M45-A2 [23]. Interpretation of meropenem against *B. pseudomallei* was based on the CLSI breakpoints of imipenem.

Medical records of all cultured-confirmed cases of melioidosis in patients aged under 16 years were collected. Details on the demography, underlying medical conditions, signs and symptoms, physical findings, laboratory results, case management, and outcome were retrieved for retrospective analysis. During this period of time, hematology was analyzed using CELL-DYN Ruby and CELL-DYN Sapphire (Abbott Diagnostics). Serum biochemical parameters were obtained from the Architect ci16200 Integrated System (Abbott Diagnostics).

Case definitions

A pediatric melioidosis case was defined as a patient aged < 16 years in whom *B. pseudomallei* isolates were cultured from at least one clinical specimen. Cases were classified as either localized or disseminated infections, as previously described [12]. Disseminated disease was defined as the presence

of ≥ 2 discrete body sites of infection and/or a *B. pseudomallei* blood culture (Mohan *et al.*, 2017). Suppurative parotitis and abscesses of lymph nodes or soft tissues were diagnosed based on ultrasound or surgical findings. Chronic disease was defined as the presence of symptoms ≥ 60 days prior to admission [13]. Age-specific vital signs of heart rate, respiratory rate, and systolic blood pressure were interpreted based on the cutoff values used for the definition of pediatric sepsis [24]. Primary and secondary foci of infection were determined based on the initial organ-specific symptoms and the physical, laboratory, or radiological findings. Central nervous system infection was diagnosed based on pleocytosis of the cerebrospinal fluid and physical examination [25].

Appropriate initial and intensive antibiotic therapy was defined as using ceftazidime or carbapenems within the first 24 h of admission. Appropriate eradication therapy was the prescription of trimethoprim-sulfamethoxazole, amoxicillin-clavulanic acid, or doxycycline after hospital discharge. Recurrent infection was defined as culture-confirmed infection after hospital discharge [13].

Data management and analysis

The distribution map of pediatric melioidosis cases was created based on the children's home addresses using the QGIS software version 3.22.1. Population data were obtained from the 2019 Vietnam Population and Housing Census. Nutritional status was accessed in children aged from 0 to 10 years by calculating weight-for-age z-scores using WHO AnthroPlus version 1.0.4. Moderately underweight was defined in children > 10 years if their weight was below the 3rd percentile, as described previously [11]. Statistical analyses were performed using GraphPad Prism version 5.04 (GraphPad Software, Inc.). Numerical data and categorical data were compared using the Mann-Whitney U test and Fisher's exact test, respectively. Correlation analysis was performed using Spearman's rho test.

Results

Demographic characteristics

A total number of 35 children with culture-confirmed melioidosis were involved in our retrospective analysis. Demographic and clinical details are presented in Supplementary Table 1. The median age was 6.0 years (IQR from 3.0 to 8.0 years; range from 7 days to 15 years), and the male/female ratio was 1.3:1. Twenty-three cases (66.7%) occurred during the wet season from May to October (Fig. 1), and the number of cases correlated moderately with the number of rainy days per month ($r = 0.61$, $P = 0.04$). Three (8.6%) neonatal symptomatic patients were diagnosed on day 7, day 8, and day 13 after birth. The gross nutritional assessment showed five (14.3%) children to be underweight to a moderate (n = 3) to severe degree (n = 2).

Microbiological characteristics

From July 2015 to August 2019, 44 Gram-negative oxidase-positive bacilli resistant to colistin and gentamicin but sensitive to amoxicillin-clavulanic acid were reported in the microbiological laboratory logbooks. These isolates were cultured from 88 clinical specimens collected from 36 children. Bacterial

identification was reconfirmed by *B. pseudomallei*-specific real-time PCR. One child was excluded because the isolate was negative with the real-time PCR assay and was later identified as *B. thailandensis* by *recA* gene sequencing analysis. Of the 87 clinical specimens derived from 35 *B. pseudomallei*-positive children, 43 *B. pseudomallei* isolates were obtained from blood (n = 9), pus (n = 27), sputum (n = 6), and pleural fluid (n = 1) (Table 1).

Table 1 Demographic data, clinical characteristics, laboratory findings and outcomes of 35 children with culture-confirmed melioidosis admitted to the Children's Hospital 2, Ho Chi Minh City, Vietnam from July 2015 to August 2019.

Characteristics	All patients	Disseminated infection	Localized infection	P value[d]
No. of children	35	14	21	
Demographic data				
Age (years), median (IQR)	6.0 (3.0 – 8.0)	5.5 (0.7 – 9.0)	6.0 (4.0 – 8.0)	0.701
Male/female ratio	1.3 : 1	1.8 : 1	1.1 : 1	0.728
Underlying medical conditions	7	7	0	< 0.001
Poor nutrient status	5	3	2	0.369
Signs and symptoms on admission				
Time from onset to admission (days), median (IQR)	10.0 (7.0 – 18.5)	8.5 (2.0 – 17.7)	12.0 (8.0 – 20.0)	0.133
Fever	27	13	14	0.108
Body temperature (^{o}C), median (IQR)	39.0 (38.0 – 39.5)	39.5 (39.0 – 40.0)	38.3 (37.0 – 39.0)	< 0.001
Tachycardia for age	7	5	2	0.089
Tachypnea for age	31	13	18	0.635
Hypotension for age	24	8	16	0.283
Swelling of jaw and neck regions	24	5	19	0.003
Fatigue or paleness	7	5	2	0.089
Cough or dyspnea	5	5	0	0.006
Vomiting, abdominal pain, or diarrhea	4	4	0	0.019
Lethargy	4	4	0	0.019
Laboratory findings				
WBC (x 10^9 cells/L), median (IQR)[a]	17.3 (13.8 – 29.2)	21.5 (17.3 – 31.8)	15.1 (11.8 – 21.5)	0.021
Neutrophils (x 10^9 cells/L), median (IQR)[a]	12.3 (8.4 – 19.3)	15.9 (11.8 – 25.6)	10.2 (6.5 – 16.6)	0.025
Lymphocytes (x 10^9 cells/L), median (IQR)[a]	3.6 (2.8 – 5.3)	4.2 (1.9 – 7.3)	3.6 (2.8 – 5.2)	0.581
Platelets (x 10^9 cells/L), median	388 (306 –	375 (253 – 443)	412 (323 –	0.272

(IQR)[a]	470)		495)	
RBC (x 10^9 cells/L), median (IQR)	4.6 (4.2 – 4.8)	4.3 (3.4 – 4.6)	4.6 (4.4 – 4.9)	0.012
Hemoglobin (g/dL), median (IQR)	12.0 (10.5 – 13.0)	10.3 (9.7 – 12.6)	12.3 (11.5 – 13.1)	0.014
C-reactive protein (mg/L), median (IQR)	57.0 (22.0 – 92.7)	63.0 (33.8 – 116.8)	46.0 (14.1 – 83.1)	0.275
AST (U/L), median (IQR)	32.0 (21.5 – 55.5)	27.0 (19.0 – 110.0)	32.5 (22.5 – 51.5)	0.991
ALT (U/L), median (IQR)	26.0 (15.5 – 50.0)	21.0 (12.5 – 50.0)	28.5 (16.5 – 54.0)	0.508
Creatinine (μmol/L), median (IQR)	50.3 (46.0 – 53.4)	53.0 (49.6 – 57.9)	46.4 (44.4 – 51.6)	0.023
Urea (mmol/L), median (IQR)	4.8 (2.7 – 8.0)	6.7 (3.1 – 10.2)	4.1 (2.6 – 5.7)	0.219
Source of *B. pseudomallei* isolation				
Blood (No. tested)	9 (36)		0	
Pus (No. tested)	27 (29)			
Sputum (No. tested)	6 (10)			
Pleural fluid (No. tested)	1 (1)			
Diagnosis[c]				
Bacteremia	7	7	0	< 0.001
Suppurative parotitis	15	2	13	0.007
Abscess of lymph nodes under the jaw	4	0	4	0.133
Abscess of soft tissues at the jaw and neck regions	2	0	2	0.506
Pneumonia	10	10	0	< 0.001
Gastroenteritis	4	4	0	0.019
Osteomyelitis	2	0	2	0.506
Meningitis	4	4	0	0.019
Treatment and outcome				
Length of hospital stay (days),	18 (13 –	17 (13 – 25)	22 (12 – 29)	0.552

median (IQR)[a]	28)			
Initial appropriate treatment on admission	5	5[b]	0	0.006
Appropriate intensive antibiotic therapy	27	12	15	0.431
Recommended eradication antibiotic therapy[a]	23	6	17	0.381
Deaths	4	4	0	0.019

[a]Deaths were excluded from analysis

[b]Including three cases with fatal outcome

[c]Diagnosis was based on laboratory findings, physical examinations, imaging investigations, and bacterial cultures

[d]P values were calculated from two data sets of disseminated and localized infections

Abbreviations: White blood cells (WBC); Red blood cells (RBC); Interquartile range (IQR); aspartate aminotransferase (AST); alanine aminotransferase (ALT)

All of 33 *B. pseudomallei* isolates tested for antimicrobial susceptibility were susceptible to ceftazidime (MIC range from 1 to 4 μg/ml), meropenem (MIC range from 0.5 to 1 μg/ml), amoxicillin-clavulanic acid (MIC range from 2/0.5 to 8/4 μg/ml), doxycycline (MIC range from 0.25 to 1 μg/ml), and trimethoprim-sulfamethoxazole (MIC range from 0.094/1.786 to 0.25/4.75 μg/ml).

Clinical features and outcomes

The median duration of symptoms prior to admission was 10 days (IQR from 7 to 18.5 days; range from 1 day to 91 days). Only one 3-year-old girl presented chronic melioidosis, with a diagnosis of palm osteomyelitis (Supplemental Table 1). The most common presenting symptoms on admission were fever (n = 27; 77.1%), followed by swelling of the jaw or neck region (n = 24; 68.6%), fatigue or paleness (n = 7; 20%), and cough or dyspnea (n = 5; 14.3%). The most common vital sign on examination was tachypnea (n = 31; 88.6%), followed by hypotension (n = 24; 68.5%) and tachycardia (n = 7, 20%).

Suppurative parotitis (n = 15; 42.8%) was the most common clinical diagnosis, followed by lung infections (n = 10; 28.6%) with eight pneumonia and two bronchitis cases, and septicemia (n = 7; 20%). Most children (n = 28/35; 80%) had no identifiable risk factors for melioidosis. The remainder (n = 7; 20%) had underlying medical conditions, such as chronic lung diseases (n = 2; one congenital cystic adenomatoid malformation and one pulmonary sequestration), a retroperitoneal tumor (n = 1), thalassemia (n = 1), near drowning (n = 2), and trauma (n = 1).

Primary infection sites were the parotid gland (n = 15), the lung (n = 8), lymph nodes under the jaw (n = 5), soft tissues at jaw and neck regions (n = 4), a palm bone (n = 1), and a leg bone (n = 1). Only one neonate had bacteremia without an evident focus of infection. Secondary infection sites involved the central nervous system (n = 4), the lung (n = 2), the gastrointestinal tract (n = 4), and the middle ear (n = 1). Abdominal ultrasound was performed on only three children, and no liver or spleen abscesses were detected.

Twenty-one (60%) children presented with localized disease, and the remainder (n = 14; 40%) had disseminated infection. All children with lung infections (n = 10) were in the disseminated infection group. Of those, seven (70%) children had bacteremia. Four (11.4%) deaths, with three taking place within 48 h after hospital admission, occurred in the group with disseminated infection.

Only five (14.3%) children received appropriate initial intensive antibiotic therapy with ceftazidime (n = 1), meropenem (n = 3), or imipenem (n = 1), including three cases with a fatal outcome (Supplementary Table 1). During the hospital stay, eight (22.8%) children did not receive any antibiotics recommended for the intensive phase, including the remaining fatal outcome, and seven (20.0%) children had no prescription of antibiotics for the eradication therapy. Of those, one (2.8%) child did not receive any antibiotics recommended for melioidosis, but recovered clinically.

After sending specimens to the microbiology lab, the median time to positive results of bacterial cultures was 4 days (IQR from 3.75 to 4.25 days; range from 3 to 7 days). However, since there was also a delay until specimens were sent to the laboratory after admission, the median time to *B. pseudomallei*-positive culture results after admission was 8 days (IQR from 5 to 11 days; range from 4 to 29 days). Fourteen (63.6%) of the 22 (62.8%) children receiving the appropriate intensive antibiotic therapy were switched immediately to the recommended antibiotics when culture results were available. The remainder (n = 8; 36.4%) received the antibiotics after a median of 2.5 days after culture results were available (IQR from 1 to 8 days; range from 1 to 13 days). Twenty-four (77.4%) of the 31 surviving children were prescribed either trimethoprim-sulfamethoxazole or amoxicillin-clavulanic acid for eradication therapy after hospital discharge.

The median length of hospital stay was 18 days (interquartile range [IQR] from 13 to 28 days; range from 7 to 42 days). One five-year-old boy with septicemia was treated with imipenem and amoxicillin-clavulanic acid but relapsed 5 days after hospital discharge with a swollen left neck, from which *B. pseudomallei* was previously isolated. He finally recovered after treatment with oxacillin (5 days), followed by ceftriaxone (5 days), and was discharged with a prescription of amoxicillin-clavulanic acid. All surviving Vietnamese children (n = 30) were healthy on the follow-up phone call in December 2019.

Laboratory findings

The hematological analysis on admission showed that the white blood cell and neutrophil counts in the group with disseminated disease were significantly higher than those in the group with localized infection, but the red blood cell count and hemoglobin were significantly lower (Table 1). Of the four fatal

cases, three children showed leukopenia (white blood cell counts ranged from 1.6 to 3.0 x 10^9 cells/L), neutropenia (neutrophils range from 0.2 to 2.5 x 10^9 cells/L), lymphopenia (lymphocytes range from 0.2 to 1.2 x 10^9 cells/L), and thrombocytopenia (platelets range from 11.8 to 149.0 x 10^9 cells/L), whereas the child with a head trauma of the right temporal region from which *B. pseudomallei* was isolated from a purulent discharge and who died one month after a traffic accident showed normal blood cell counts.

The biochemical analysis showed no differences in C-reactive protein, aspartate aminotransferase, alanine aminotransferase, and urea between the two groups (Table 1). Significantly elevated median values, in the three fatal cases with abnormal blood cell counts, in comparison to those of the others, were observed in aspartate aminotransferase (155.0 vs. 28.8 U/L, $P < 0.001$), creatinine (87.9 vs. 49.0 µmol/L, $P = 0.019$), and urea (10.1 vs. 4.1 µmol/L, $P = 0.027$), but no differences in alanine aminotransferase (60.0 vs. 22.5 U/L, $P = 0.069$) and C-reactive protein (68.0 vs. 51.5 mg/L, $P = 0.225$).

Geographic distribution

Three (8.6%) children with culture-confirmed melioidosis were Cambodian citizens. Twenty-two (68.7%) of the 32 (91.4%) Vietnamese children were from the southeast region of Vietnam (Fig. 2A). Based on the cases detected in our single referral hospital, the average annual incidence rates per 100,000 children aged < 15 years in this region (Fig. 2C) were 0.314 (in Binh Duong province), 0.279 (in Binh Phuoc province), 0.205 (in Dong Nai province), 0.201 (in Tay Ninh province), 0.09 (in Ba Ria - Vung Tau province), and 0.059 (in Ho Chi Minh City). The other pediatric patients were from the south-central coast (n = 7; 21.8%), central highlands (n = 1; 3.1%), and Mekong river delta (n = 2; 6.2%) (Fig. 2A). Children with melioidosis were detected in 13 of 32 provinces and cities in the four regions. There was a correlation between the annual pediatric inpatients admitted to CH2 from certain provinces and cities (Fig. 2B) and the number of melioidosis cases detected ($r = 0.6218$; $P < 0.001$), as shown in Fig. 3.

Discussion

Previous reports have shown that melioidosis might not be evenly distributed in endemic countries, but significant differences regarding disease incidence exist [26, 27]. Apart from a variable environmental presence of the causative soil bacterium, other factors, such as occupational risk behavior or the prevalence of underlying diseases, might contribute to this phenomenon [28]. A previous study from 1999 looking only at blood culture results showed a low incidence rate of adult cases of melioidosis and a restricted distribution of *B. pseudomallei* in the environment in southern Vietnam [19]. By contrast, the results of our study indicate a wide distribution of melioidosis in southern Vietnam. This study confirms our previous study that the introduction of the simple laboratory algorithm, including a three-antibiotic disc test for detecting *B. pseudomallei* from clinical samples can increase the number of culture-confirmed cases of melioidosis considerably [3]. Before the introduction of the three-antibiotic disc test, the staff of the microbiology lab of CH2 recalled one or two API 20NE biochemical identification results during the past years indicating possible *B. pseudomallei* strains, although those results were neither confirmed nor was special attention paid to them.

Although the occurrence of *B. pseudomallei* gentamicin-susceptible phenotypes, as described in Sarawak, Malaysia [29], and various proportions of amoxicillin-clavulanic acid-resistant isolates [30] might decrease the sensitivity of this simple algorithm, this procedure is cheap and easy to perform in microbiological laboratories in resource-limited areas where melioidosis is potentially endemic but has not been detected previously.

Compared to the literature on adult melioidosis, studies on the clinical features of pediatric melioidosis are more limited. Our pediatric cases of melioidosis showed that localized infection involving the head and neck regions was the most common clinical presentation, with a majority of the cases presenting unilateral suppurative parotitis, followed by cervical lymph node and soft tissue abscesses. This common clinical feature of suppurative parotitis has also been reported from the neighboring countries of Cambodia and Thailand [8, 9, 27], but it is different from other geographical locations, such as East Malaysia, the Northern Territory of Australia, and North Queensland, where lung, skin and soft tissue involvement are common and neurological manifestations occur [10–13].

The lungs were the second most common site of infection in our study, and children with lung involvement were highly associated with bacteremia. These clinical features are similar to adult melioidosis reported in other endemic areas [3, 4] and pediatric melioidosis in East Malaysia [12, 13]. Central nervous system involvement was lower in our pediatric cases, with only four (11.4%) children presenting with meningitis. Notably, none of the children had primary skin and soft tissue abscesses outside the head and neck regions. This clinical feature differs from other endemic areas where skin and soft tissue abscesses are occasionally observed in the arm, axilla, buttock, thigh, and leg in cutaneous melioidosis [8, 31]. The difference might be explained by the fact that bacterial cultures for pus samples were not commonly performed among patients in our setting who were not critically ill, and empirical antibiotic treatment was the priority choice for skin and soft tissue infections [32].

A limitation of our study is the fact that abdominal ultrasound was not systematically performed in our melioidosis cases to search specifically for liver and spleen abscesses, and none of the children in our study were shown to have liver and spleen abscesses. Previous studies in Malaysia showed that a majority of pediatric melioidosis cases had occult liver and spleen abscesses, although clinical features of the abdomen were silent [12, 13, 33]. Hepatic and splenic abscesses have recently been suggested as predictors for children suspected of having melioidosis in South Thailand [34].

Diabetes is the most predominant predisposing factor in adult melioidosis. Similar to other endemic areas, none of the children in our study had diabetes, and only a few children presented with comorbidities [9, 11]. Thalassemia has been identified as a major risk factor for pediatric melioidosis in Sabah, Malaysia [13]. However, thalassemia was not routinely diagnosed in our hospital, therefore, this potential risk factor might have gone undetected in our patients. In contrast to a previous study [12], our study did not identify malnutrition as a risk factor for pediatric melioidosis because the proportion of malnutrition in the pediatric group with melioidosis was similar to that in the national pediatric

population [35]. Recent observations in Cambodia also showed that malnutrition was reduced over a period of ten years, but the number of pediatric cases of melioidosis remained constant [9].

Except for one child death who had a traffic accident prior to hospital admission, the other three deaths had septicemia with leukopenia, neutropenia, lymphopenia, thrombocytopenia, and liver and kidney dysfunction. The clinical features were similar to those of recent child deaths who had no suppurative parotitis reported in the northern part of the country [36]. This hematological and biochemical information may aid clinicians in the early recognition of illness severity and improve the patient outcome in children, although further studies are needed. A previous study reported lymphopenia to be a risk factor for mortality in a small cohort of adult melioidosis [37].

We note that a large number of children (n = 22; 62.8%) did not receive the recommended antibiotic treatment for melioidosis or had delayed therapy with appropriate antibiotics when culture results were available. This indicates insufficient medical attention to melioidosis in this part of the country. Other studies showed that 39 children recovered successfully after receiving only oral antibiotic treatment [9], and nine (16%) patients with primary skin melioidosis recovered successfully after receiving oral antibiotics alone, including one 9-year-old girl who received no antibiotic therapy [6].

Here, we found a wide distribution of pediatric melioidosis cases in all four regions of South Vietnam. Our calculated incidence rates varied between the regions, but most probably reflect the big differences in the number of inpatients admitted from the various regions, since the number of cases detected from certain geographical regions correlated with the number of patients admitted to CH2 (Fig. 3). Our calculated incidence rates are likely to be much higher, since the numbers are only based on the cases detected in a single hospital. Moreover, it seems probably that the true number of cases in our tertiary hospital is also much higher because: (i) no active screening for pediatric melioidosis by, for example, collecting throat swabs for microbiological culture [9] was performed, and ii) no selective culture media were used for non-sterile clinical specimens. In conclusion, our study indicates that a substantial burden of melioidosis might be underrecognized in South Vietnam. Awareness raising and laboratory capacity strengthening are needed to speed up early detection, improve patient outcomes, and reinvestigate the true burden of the disease in this part of the country.

Declarations

Author contributions

TTT, IS, and PTS designed the study. PTS, BTT, NTN, and DVC collected clinical and microbiological data. BNHL and VTNA characterized the bacterial strains. TTT, PTS, VTNA, EU, and SL analyzed the data. TTT, PTS, and IS wrote the manuscript. All authors read and approved the final version of the manuscript.

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Ethics approval This study was approved by the ethical review board of Children's Hospital 2 (reference no. CS/ND2/20/01).

Consent to participate This was a retrospective study. Informed consent was not needed because the clinical data for analysis were anonymized, and no interventions were undertaken.

Consent for publication Not applicable. No individual images and videos are shown.

Competing interests The authors declare no conflicts of interests.

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Figures

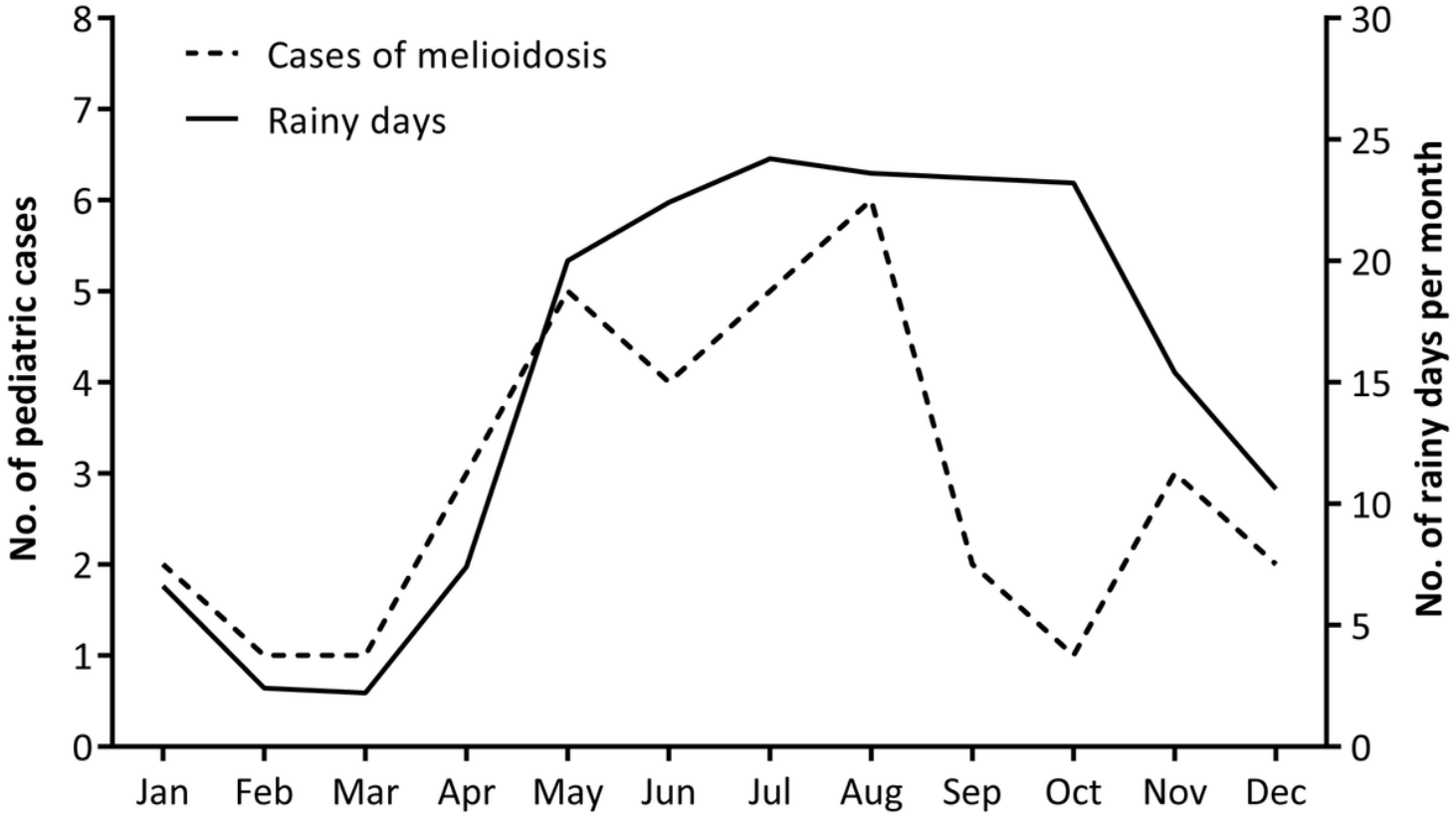

Figure 1

Seasonal distribution of culture-confirmed cases with melioidosis aged < 15 years at Children's Hospital 2 (CH2), Ho Chi Minh City, between July 2015 and August 2019. The solid line indicates the average number of rainy days per month from 2015 to 2019 in Ho Chi Minh City. The climate data were obtained from https://en.tutiempo.net/climate/ws-489000.html, accessed on 12 August 2022. The dashed line indicates the collective cases with melioidosis each month.

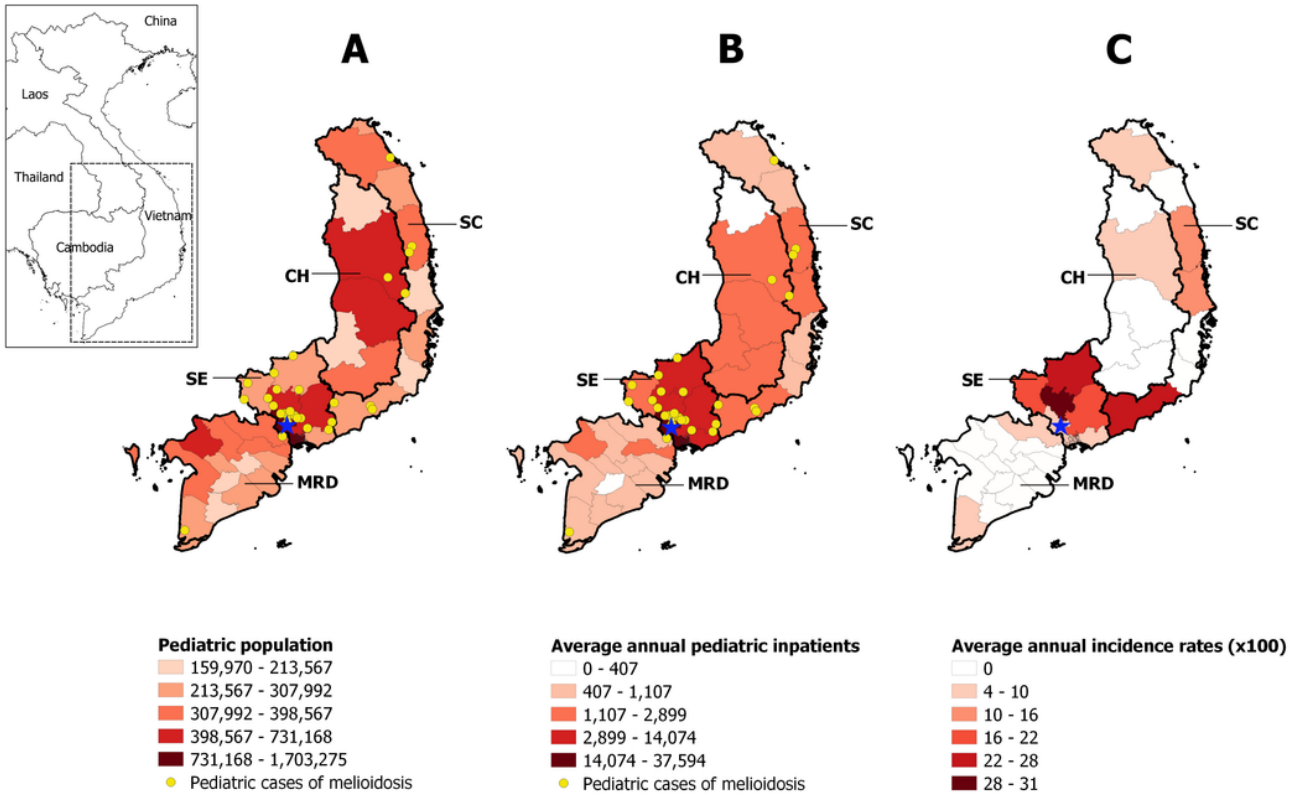

Figure 2

Geographical distribution of culture-confirmed cases with melioidosis aged < 15 years at CH2, Ho Chi Minh City, between July 2015 and August 2019. A, The pediatric population in each province in South Vietnam was obtained from the 2019 Vietnam Population and Housing Census. B, Average pediatric inpatients admitted annually to CH2 from 2015 to 2019. C, Average annual incidence rates (x100) of pediatric melioidosis in each province in South Vietnam. Black lines are the borders of the Central Highlands (CH), South-Central (SC), South-East (SE), and Mekong River Delta (MRD) regions. Blue asterisk shows the location of CH2. The upper insert map shows Vietnam and the neighboring countries, with South Vietnam in the dashed line rectangle.

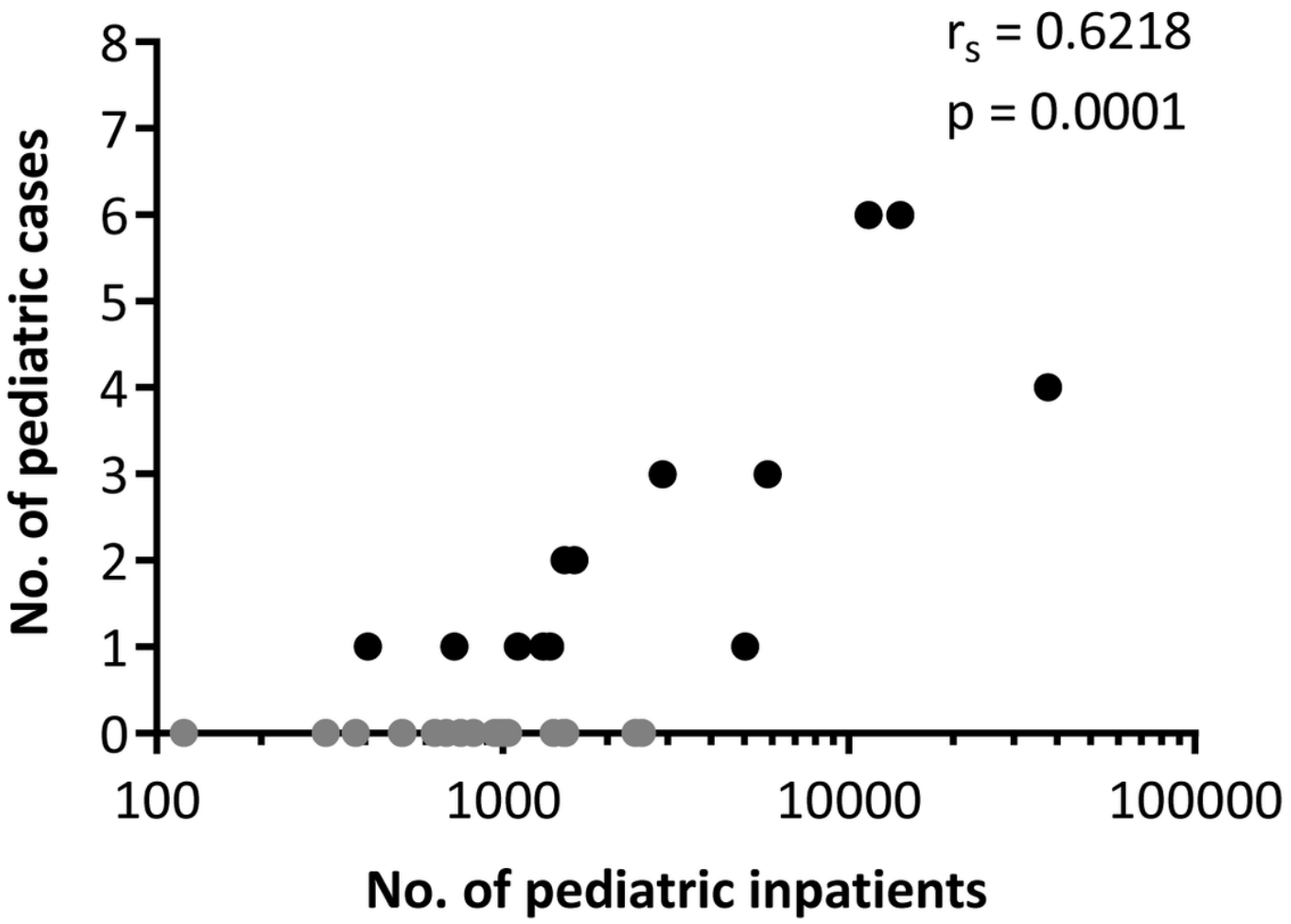

Figure 3

Correlation between the number of pediatric melioidosis cases and the number of pediatric inpatients. Chart of pediatric inpatient numbers (abscissa) versus pediatric melioidosis case numbers (ordinate) submitted to CH2 in Ho Chi Minh City. Each dot represents a province in South Vietnam. Black dots indicate melioidosis positive provinces. Grey dots indicate melioidosis negative provinces. r_S represents the Spearman correlation coefficient.

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