

Improving Treatment and Outcomes for Melioidosis in Children, Northern Cambodia, 2009–2018

Arjun Chandna,¹ Moritz Bonhoeffer,¹ Thyl Miliya, Keang Suy, Sena Sao, Paul Turner

We report trends in manifestations, treatment, and outcomes of 355 children with culture-confirmed melioidosis over 10 years at a pediatric hospital in northern Cambodia. Bacteremia and presentation with pneumonia were risk factors for death. A total of 39 children recovered after being given only oral antimicrobial drug treatment.

Melioidosis, an infection caused by *Burkholderia pseudomallei*, remains an underrecognized disease, especially in children, in many locations to which it is endemic (1,2). Diverse clinical manifestations and intrinsic resistance to many antimicrobial drugs used for empirical treatment of sepsis contribute to high mortality rates (2–4).

Conventionally, antimicrobial drug therapy for melioidosis comprises 2 phases: intravenous treatment for ≥ 10 days, followed by a prolonged, oral, eradication phase for a minimum of 12 weeks (5,6). Localized cutaneous disease might be treatable with oral agents alone, but adherence with eradication therapy is often difficult to achieve (4,5,7–9). We report trends in management and outcomes of melioidosis over 10 years at a nongovernmental pediatric hospital in northern Cambodia.

The Study

This study was approved by the hospital institutional review board (AHC IRB 979-14; 1044-15) and the Oxford Tropical Medicine Research Ethics Committee (OxTREC 550-14). Data on all culture-confirmed case-patients who had *B. pseudomallei* infection during January 1, 2009–December 31, 2018, were collected

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retrospectively (2009–2013) and prospectively as part of an invasive bacterial infection surveillance study. Retrospective case-patients (the first 173 case-patients) have previously been described and are included to illustrate trends over the decade (2).

Retrospective case-patients were identified by searching laboratory logbooks and databases, which were cross-checked against the hospital electronic patient information system. Data were extracted onto a standardized case report form, which was also adapted for contemporaneous capture of prospective case-patients. Repeat searches of the databases were conducted at the end of the study (Appendix Figure 1, <https://wwwnc.cdc.gov/EID/article/27/4/20-1683-App1.pdf>). The study site, microbiology specimen processing, and case definitions have been described elsewhere (2,8). We provide the statistical methods used (Appendix). Severe undernutrition was defined as a weight-for-age z-score < -3 .

Approximately half (57.5%, 255/355) the children with melioidosis were male, and most (82.8%, 294/355) were brought for treatment during the wet season (Appendix Figure 2). Median age was 5.7 years (interquartile range 3.1–9.5 years). Concurrent conditions were infrequent (14/355, 3.9%). Parotitis was the most common manifestation (27.3%, 97/355) (Table 1).

Hospital guidelines (introduced in 2012) recommend obtaining blood, throat swab and urine specimens for culture for all patients who have suspected melioidosis. However, blood was collected for culture for only 157 (44.2%) of 355 case-patients, a throat swab specimen for 31 (8.7%) of 355, and a urine sample for 16 (4.5%) of 355. Use of microbiological testing improved over time (Appendix Table 5, Figure 3). Of those who had blood cultured, 46.5% (73/157) were

Table 1. Characteristics for 355 children who had culture-confirmed melioidosis, northern Cambodia, 2009–2018*

Characteristic	Value
Median age, y (IQR)	5.7 (3.1–9.5)
Sex	
M	255 (57.5)
F	100 (42.5)
Concurrent condition, n = 355	14 (3.9)
Thalassemia	4
Systemic lupus erythematosus	2
Suspected underlying immunodeficiency	2
Asthma	1
Epilepsy	1
Acute lymphoblastic leukemia	1
Congenital heart disease	1
Chronic kidney disease	1
Pure red cell aplasia	1
Clinical manifestations, n = 355	
Parotitis	97 (27.3)
Skin or soft tissue infection	96 (27.0)
Pneumonia	69 (19.4)
Lymphadenitis	58 (16.3)
Meningitis	1 (0.3)
Multifocal infection	12 (3.4)
Other†	8 (2.3)
Unknown‡	15 (4.5)
Management strategy, n = 355	
Admitted case-patients	212 (59.7)
Case-patients admitted at first presentation	145 (40.8)
Empiric treatment with effective intensive-phase therapy	51
Treatment with effective intensive-phase therapy within 48 h	38
Treatment with effective intensive-phase therapy after 48 h	40
No effective intensive-phase therapy received§	11
Treatment information not available	5
Admitted to intensive care unit, n = 212	52 (24.5)
Surviving patients completing 12 weeks of eradication therapy, n = 306	102 (33.3)
No. patients treated successfully with only oral antimicrobial drugs	39

*Values are no. (%) except as indicated. IQR, interquartile range.

†Clinical manifestations for patients classified as Other included mandibular osteomyelitis (2), diarrheal disease (2), vaginitis (2), mastoiditis (1), and septic arthritis (1).

‡Clinical manifestations were unknown for 15 patients: 10 were bacteremic and 5 had *Burkholderia pseudomallei* isolated from pus swabs.

§A total of 9 children died within 24 h (before culture results were available), and 2 were switched directly to oral treatment.

bacteremic. The proportion of bacteremic children remained consistent over the study period (Appendix Figure 4). For 12 children who were evaluated during 2017–2018, the only positive microbiological specimen was a throat swab specimen.

Treatment data were available for 344 (96.9%) of 355 children. Of these, 140 were admitted when care was initially sought; 89 (63.6%) received an intravenous antimicrobial drug (ceftazidime, meropenem, or imipenem) that had activity against *B. pseudomallei* within 48 hours (Table 1). Eleven children did not receive an effective intravenous drug; 9 died within 24 hours (before culture results were available), and 2 were switched directly to an oral treatment. The time to effective antimicrobial drug therapy did not change over the study period.

The in-hospital case-fatality rate (CFR) was 11.5% (41/355). Median time to death was 2.5 days (interquartile range 1–8 days). Two deaths occurred after discharge for children who had completed 14 days of intensive therapy.

Pneumonia, female sex, and age <5 years were risk factors for death. Among children who had a blood culture, bacteremia was strongly associated with death, as was severe undernutrition in children <10 years of age. Adjusted analyses, including only children <10 years of age who had a blood culture (n = 128), confirmed that bacteremia (odds ratio 57.09, 95% CI 10.80–1,063.54; p < 0.001) and pneumonia (odds ratio 3.95, 95% CI 1.22–14.43; p = 0.027) were independently associated with death (Table 2). The annual CFR remained stable, although a nonsignificant decrease was observed for bacteremic children (Appendix Figure 5). This decrease occurred in the context of major reductions in the prevalence of undernutrition (Figure 1).

Of 312 surviving case-patients, postdischarge information was available for 306 (98.1%), of whom 102 (33.3%) completed ≥12 weeks of eradication therapy. The proportion of children completing eradication therapy increased substantially during the study period (Figure 2), and trimethoprim/sulfamethoxazole

Table 2. Risk factors for death of children who had culture-confirmed *Burkholderia pseudomallei* infection, northern Cambodia, 2009–2018*

Characteristic	Survivors	Nonsurvivors	Unadjusted OR (95% CI); p value	Adjusted OR (95% CI); p value
Whole population, n = 355	n = 312	n = 43		
Female sex	126/312 (40.4)	25/43 (58.1)	2.05 (1.07–3.91); 0.03	1.58 (0.71–3.53); 0.26
Age <5 y	126/312 (40.4)	25/43 (58.1)	2.05 (1.07–3.91); 0.03	0.69 (0.28–1.60); 0.39
Pneumonia†	34/312, (10.9)	35/43 (81.4)	35.77 (15.34–83.41); <0.001	38.99 (16.46–104.01); <0.001
Bacteremia‡	31/114 (27.2)	42/43 (97.7)	112.45 (14.83–852.47); <0.001	70.24 (13.73–1,289.14); <0.001
Severe undernutrition§	32/225 (14.2)	12/37 (32.4)	2.90 (1.32–6.34); 0.008	1.36 (0.51–3.52); 0.53
Children ≤10 y of age who had blood culture, n = 128	n = 91	n = 37		
Female sex	39/91 (42.9)	20/37 (54.1)	1.57 (0.73–3.38); 0.25	1.24 (0.44–3.46); 0.679
Age <5 y	54/91 (59.3)	23/37 (62.2)	1.13 (0.51–2.47); 0.77	0.70 (0.21–2.18); 0.542
Pneumonia†	31/91 (34.1)	30/37 (81.1)	8.29 (3.27–21.02); <0.001	3.97 (1.22–14.43); 0.027
Bacteremia	29/91 (31.9)	36/37 (97.3)	76.97 (10.05–589.16); <0.001	57.09 (10.80–1,063.54); <0.001
Severe undernutrition	17/91 (18.7)	12/37 (32.4)	2.09 (0.88–4.97); 0.09	2.08 (0.62–7.72); 0.247

*Values are no. positive/no. tested (%) except as indicated. OR, odds ratio.
 †Pneumonia was defined according to the working diagnosis of the treating clinical team, taking into consideration clinical, laboratory, and radiologic information. A total of 89.9% (62/69) of children who were given a diagnosis of pneumonia had a chest radiograph.
 ‡Risk for bacteremia assessed in children who had a blood culture collected (n = 157).
 §Risk for severe undernutrition (weight-for-age z score <-3) assessed in children <10 y of age (n = 262; a weight measurement was available for 95.6% [262/274] of children <10 y of age). Multivariate analyses adjusted for sex, age <5 years, and pneumonia. Subgroup analysis (n = 128). Includes only children <10 y of age who had a blood culture collected.

was increasingly likely to be selected as the eradication agent of choice (Appendix Figure 6). Thirty-nine children recovered after receiving only oral antimicrobial drug treatment, including 17 who had lymphadenitis, 14 who had with localized cutaneous disease, and 4 who had parotitis. No culture-confirmed relapses have been reported.

Conclusions

Our study illustrates the challenges associated with providing care for children who have melioidosis at a pediatric hospital in northern Cambodia. Unlike many hospitals in the region, there was access to level

3 care in a pediatric intensive care unit and an on-site diagnostic microbiology laboratory supported by an active clinical microbiology liaison service (10). Nevertheless, 2/10 children admitted because they had melioidosis did not survive to leave the hospital, and only one third of those discharged alive were confirmed as having completed eradication therapy.

Few easily identifiable features exist to alert clinicians to a possible diagnosis of melioidosis. Given the necessity of early and appropriate antimicrobial drug therapy and the intrinsic resistance of *B. pseudomallei* to many first-line antimicrobial drugs, clinicians have the difficult task of maintaining a high index of suspicion while balancing the need for effective antimicrobial stewardship.

Our study might have underestimated the burden associated with melioidosis due to suboptimal

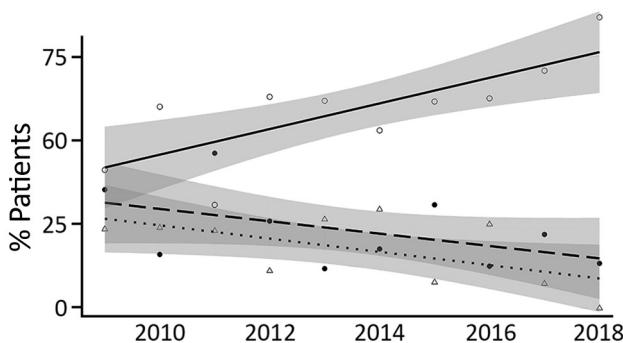


Figure 1. Prevalence of undernutrition for 262 children <10 years of age who had culture-confirmed melioidosis, northern Cambodia, 2009–2018. Linear trend lines indicate nonunderweight children (solid line, open circles: R = 0.76; p = 0.011), children with moderate undernutrition (weight for age z-score [WAZ] <-2) (dashed line, solid circles: R = -0.49; p = 0.150), and children with severe nutrition (WAZ <-3) (dotted line, open triangles: R = -0.59; p = 0.074). Shaded areas indicate 95% CIs for linear trend lines.

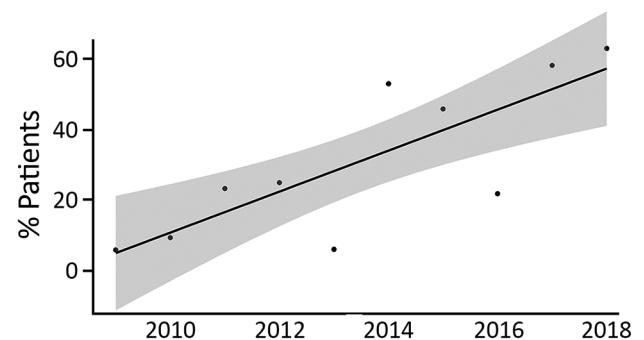


Figure 2. Proportion of 306 surviving children who had culture-confirmed melioidosis and completed ≥12 weeks of eradication therapy, northern Cambodia, 2009–2018. Shaded area indicates 95% CIs for the linear trend line (R = 0.8; p = 0.006).

diagnostic testing, particularly at the beginning of the study period. The hospital's clinical microbiology liaison service has expanded over time and now includes 3 weekly infection rounds, invasive bacterial and hospital-acquired infection surveillance, and antimicrobial drug and diagnostic stewardship training as part of the hospital induction program. During 2015, the antimicrobial treatment guidelines became accessible by a mobile application (10). In the final 2 years of the study period, 12 children received a confirmed diagnosis only because the clinical team sent a throat swab specimen specifically for *B. pseudomallei* culture.

We observed a slight decrease in the CFR for bacteremic children. Although not significant, this trend cannot be explained by changes in case-mix severity (proportion of bacteremic children) or time to effective antimicrobial therapy. However, it did occur in the context of substantial gains in the nutritional status of the population. Malnutrition might potentiate severity of melioidosis in children and is a well-recognized risk factor in other pediatric infections (4,11).

The fact that only one third of children surviving to hospital discharge went on to successfully complete 12 weeks of eradication therapy illustrates both the challenge associated with ambulatory care in resource-constrained settings and the gains that can be achieved over time. During 2009, only 5% of case-patients completed 12 weeks of eradication therapy, compared with 52% during 2018. Furthermore, by the end of the study period, amoxicillin/clavulanic acid had been replaced by trimethoprim/sulfamethoxazole acid as the eradication drug of choice, consistent with current recommendations (5,6).

This study lends support to the idea that certain *B. pseudomallei* infections might be treatable with oral agents alone (5). The 39 cases described herein add to ≥ 26 previously reported case-patients for whom successful outcomes have been achieved in the absence of parenteral therapy (4,8,9).

In summary, melioidosis remains a major disease in children in Cambodia. Proactive microbiological specimen collection is critical to confirming the diagnosis. Although adherence with prolonged eradication therapy is challenging, over time, improvements can be realized. Adherence will become increasingly essential if outpatient oral treatment regimens are to be considered in resource-limited settings, as they are in some high-income, disease-endemic locations (4).

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About the Author

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Appendix

Statistical Methods

Data were analyzed by using R software version 3.6.1 (<https://www.r-project.org>). For children <10 years of age, weight-for-age z-scores were calculated according to World Health Organization Child Growth Standards (<https://www.who.int/toolkits/child-growth-standards>) and the “anthro” package in R. Descriptive statistics were used to describe relevant characteristics of the cohort. Medians and interquartile ranges were used to report non-normally distributed variables (age and time to death).

Variables for univariable analysis were selected according to clinical relevance and biologic plausibility (sex, age <5 years, clinical diagnosis of pneumonia, severe undernutrition, and presence of bacteremia) to determine their association with death. Unadjusted odds ratios and 95% CIs were calculated. The denominator for analysis of sex, age, and clinical presentation was the entire study population (n = 355). The analysis for bacteremia was restricted to the number of children that had a blood culture collected (n = 157) and for undernutrition to children <10 years of age (n = 274) because the World Health Organization Child Growth Standards are only validated up until this age. An α of 0.05 was defined as being statistically significant.

For the purposes of these analyses, the 12 children (12/274, 4.4%) <10 years of age for whom a weight measurement was not available were excluded. The 15 case-patients for whom clinical presentation was unknown were classified as not having presented with pneumonia: 10 of these 15 case-patients were bacteremic and assumed to have presented with undifferentiated sepsis, and the remaining 5 had *Burkholderia pseudomallei* isolated from pus swabs and were therefore believed unlikely to have had a pneumonic presentation.

Multivariable logistic regression was used to identify any variables that were independently associated with death. All variables that were biologically plausible (i.e., all

variables selected for univariable analyses) were included in the multivariable analysis. Variables were not formally assessed for collinearity or interactions. Analysis of residuals confirmed the assumptions of linearity. Adjusted odds ratios and 95% CIs were calculated. Regression equations, coefficients of each explanatory variable, and goodness-of-fit of models assessed by the Hosmer and Lemeshow test (χ^2) are indicated (Appendix Tables 1–5).

Correlation analyses were used to determine the trend over time for explanatory and outcome variables (explanatory: undernutrition and bacteremia; outcome: in-hospital case fatality rates, blood culture collection rate, choice of antimicrobial agent for eradication therapy, and successful completion of eradication therapy). The value of the Pearson correlation coefficient (R) was reported. An α of 0.05 was defined as being statistically significant.

Appendix Table 1. Multivariable logistic regression model to identify risk factors for death for children who had culture-confirmed *Burkholderia pseudomallei* infection (n = 355), northern Cambodia, 2009-2018*

Variable	Coefficient (95% CI)	p value
Intercept	-0.11 (-0.76 to -0.52)	0.73
Age<5 years	-0.38 (-1.26 to -0.47)	0.39
Pneumonia	3.66 (2.80–4.64)	<0.001
Female sex	0.45 (-0.34 to 1.26)	0.72

*Mortality rate = $-0.11 + (-0.38 \times \text{age} < 5 \text{ years}) + (3.66 \times \text{pneumonia}) + (0.45 \times \text{female})$.
Hosmer and Lemeshow goodness of fit: $\chi^2 = 1.19$; p = 1.00.

Appendix Table 2. Multivariable logistic regression model to identify risk factors for death for children who had culture-confirmed *Burkholderia pseudomallei* infection and had a blood culture collected (n = 157), northern Cambodia, 2009-2018*

Variable	Coefficient (95% CI)	p value
Intercept	-0.77 (-1.60 to 0.00)	0.06
Bacteremia	4.25 (2.62–7.16)	<0.001
Age <5 years	-0.57 (-1.75 to -0.49)	0.30
Pneumonia	1.73 (0.62–2.97)	0.003
Female sex	0.31 (0.67–1.29)	0.53

*Mortality rate = $-0.77 + (-0.57 \times \text{age} < 5 \text{ years}) + (1.73 \times \text{pneumonia}) + (0.31 \times \text{female})$.
Hosmer and Lemeshow goodness of fit: $\chi^2 = 7.77$; p = 0.46.

Appendix Table 3. Multivariable logistic regression model to identify risk factors for death for children who had culture-confirmed *Burkholderia pseudomallei* infection and were <10 years of age (n = 262), northern Cambodia, 2009-2018*

Variable	Coefficient (95% CI)	p value
Intercept	-1.10 (-1.06 to -0.85)	0.82
Age <5 years	-0.38 (-1.32 to -0.53)	0.41
Pneumonia	3.23 (2.32–4.27)	<0.001
Severe acute malnutrition	0.30 (-0.68 to 1.26)	0.53
Female sex	0.23 (-0.63 to 1.08)	0.60

*Mortality rate = $-1.10 + (-0.38 \times \text{age} < 5 \text{ years}) + (3.23 \times \text{pneumonia}) + (0.30 \times \text{severe acute malnutrition}) + (0.23 \times \text{female})$. Hosmer and Lemeshow goodness of fit: $\chi^2 = 0.53$; p = 1.00.

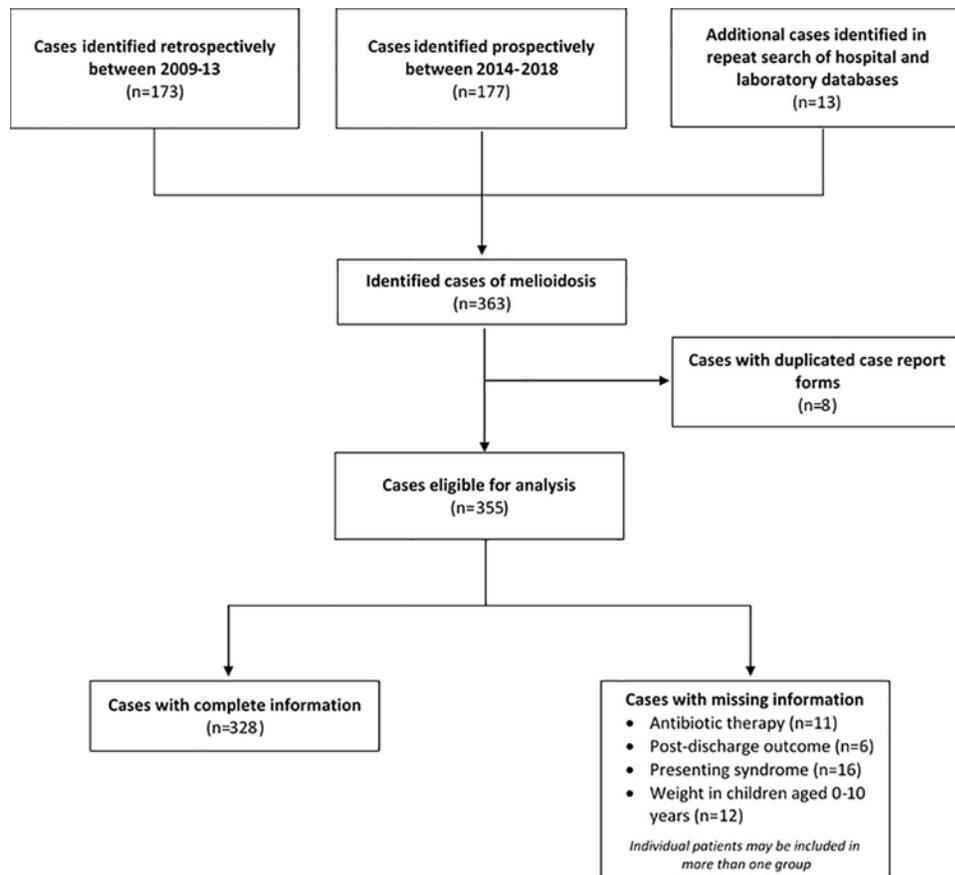
Appendix Table 4. Multivariable logistic regression model to identify risk factors for death for children who had culture-confirmed *Burkholderia pseudomallei* infection, had a blood culture collected and were <10 years of age (n = 128), northern Cambodia, 2009–2018*

Variable	Coefficient (95% CI)	p value
Intercept	-1.19 (-2.57 to -0.04)	0.07
Bacteremia	4.04 (2.38–6.97)	<0.001
Age <5 years	-0.36 (-1.58 to -0.78)	0.54
Pneumonia	1.38 (0.20–2.67)	0.03
Severe acute malnutrition	0.73 (-0.48 to 2.04)	0.25
Female sex	0.21 (-0.82 to 1.24)	0.68

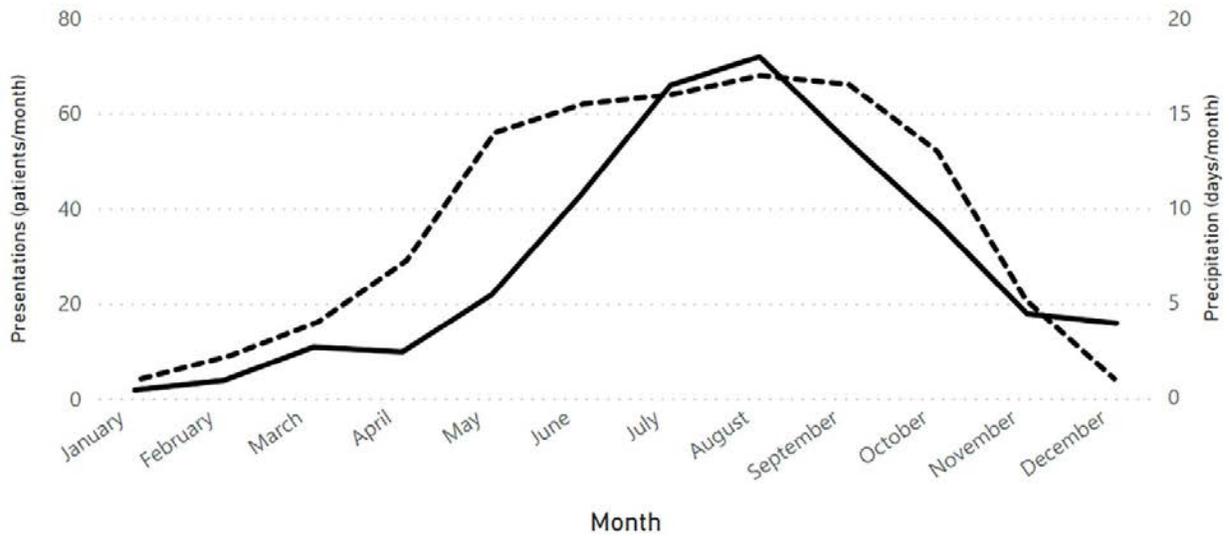
*Mortality rate = $-1.19 + (4.04 \times \text{bacteremia}) + (-0.36 \times \text{age} < 5 \text{ y}) + (1.38 \times \text{pneumonia}) + (0.73 \times \text{severe acute malnutrition}) + (0.21 \times \text{female})$. Hosmer and Lemeshow goodness of fit: $\chi^2 = 7.03$; $p = 0.53$.

Appendix Table 5. Children who provided a throat swab specimen or urine sample for *Burkholderia pseudomallei* culture by year (n = 355), northern Cambodia, 2009–2018

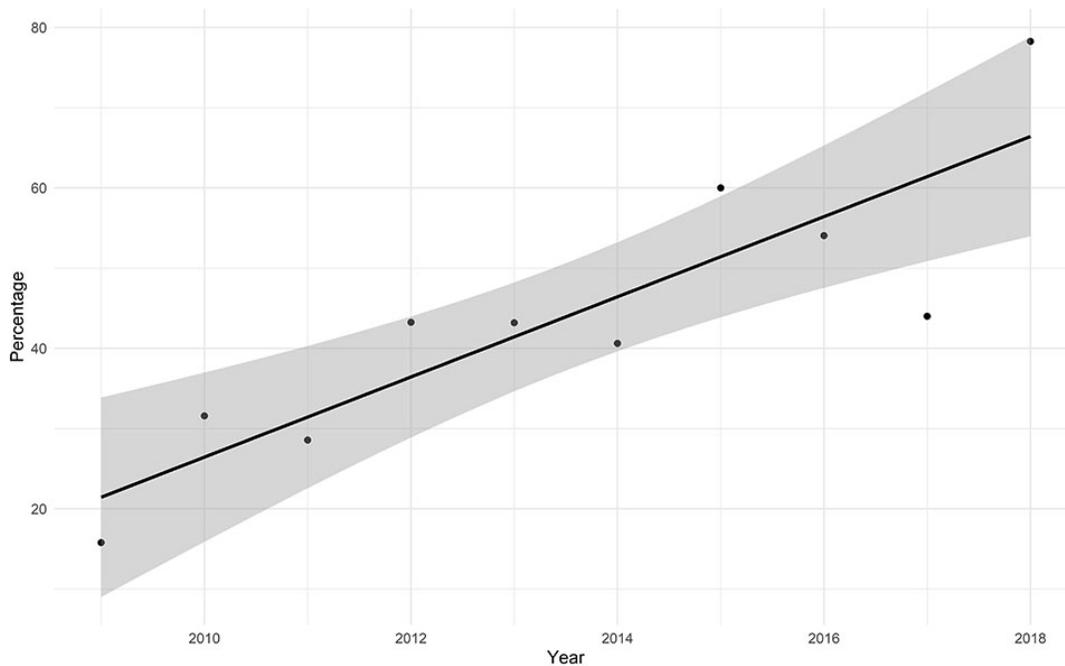
Sample	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Throat swab specimen	1	1	1	0	0	0	1	2	15	10
Urine culture	0	0	0	0	0	0	0	1	5	10



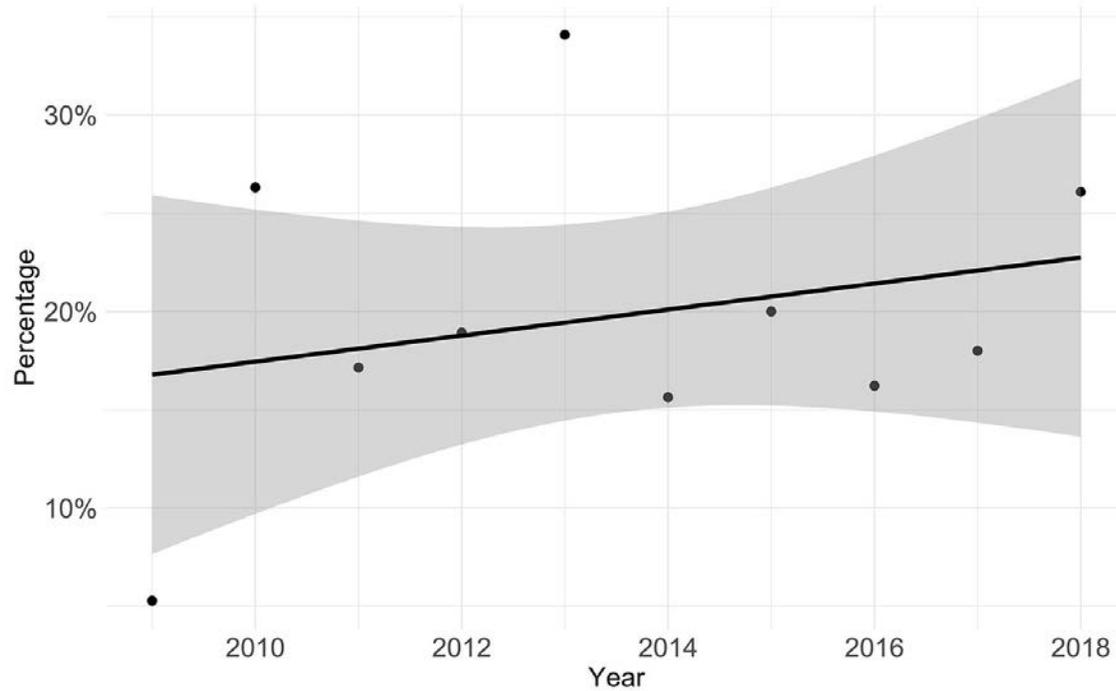
Appendix Figure 1. Identification of children who had *Burkholderia pseudomallei* infection, northern Cambodia, 2009–2018.



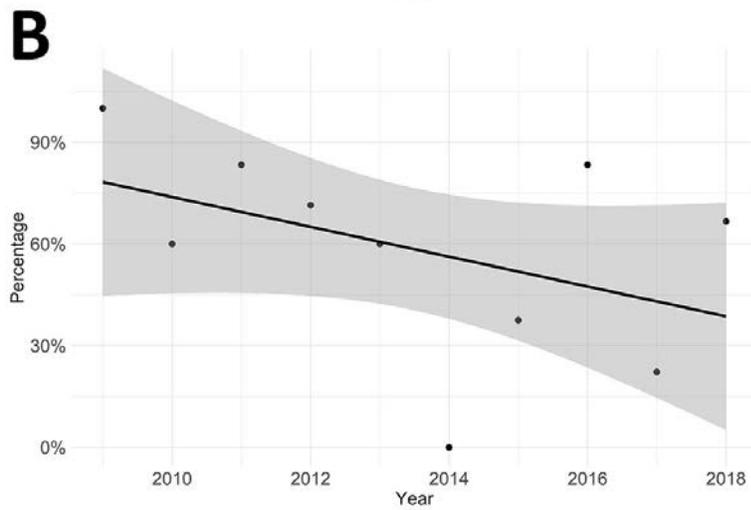
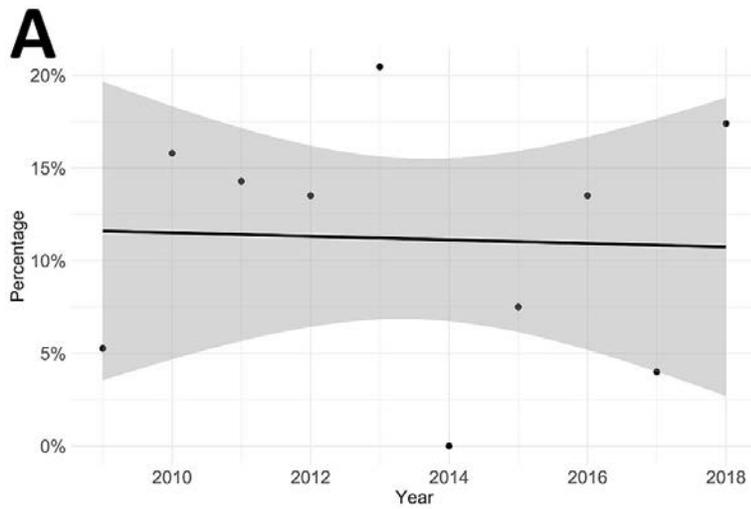
Appendix Figure 2. Seasonality for presentation of children with culture-confirmed melioidosis, northern Cambodia, 2009–2018. Solid line indicates no. cases per calendar month. Dashed line indicates average number of days of rain per calendar month (climate data were obtained from <https://en.tutiempo.net/climate/ws-489660.html>).



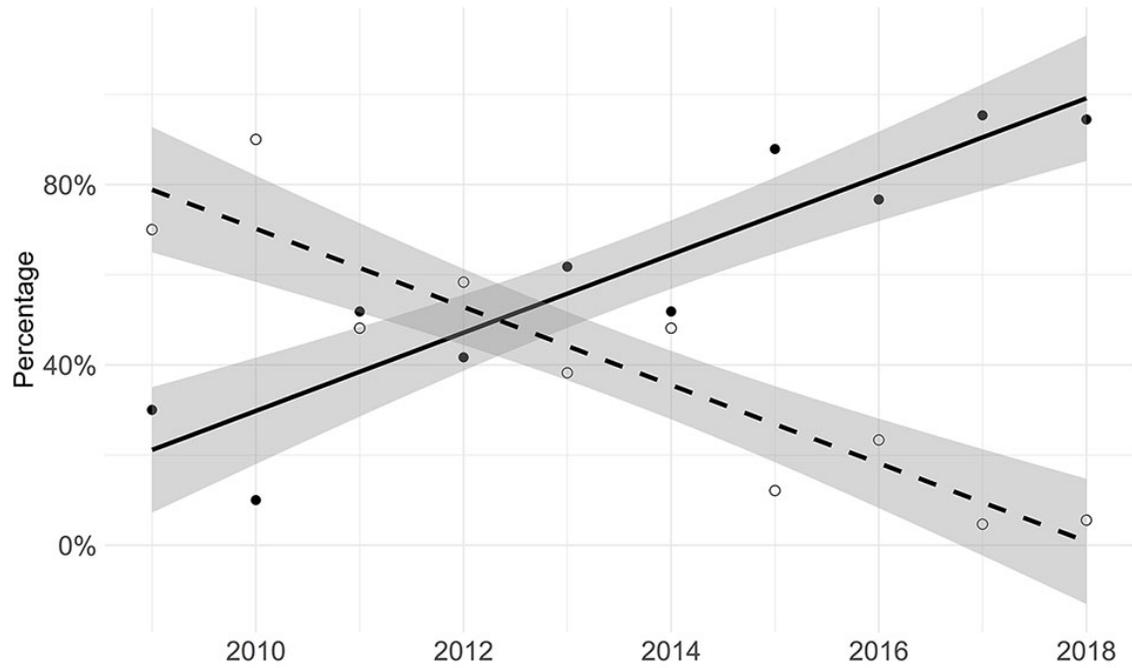
Appendix Figure 3. Trend in proportion of children who had melioidosis and for whom blood was collected for *Burkholderia pseudomallei* culture (n = 355), northern Cambodia, 2009–2018. Blue indicates 95% CI of linear trend line (R = 0.870; p = 0.001). R, Pearson coefficient reported for correlation.



Appendix Figure 4. Trend in proportion of children with *Burkholderia pseudomallei* isolated from blood cultures (n = 355) for children who had melioidosis, northern Cambodia, 2009–2018. Blue indicates 95% CI of linear trend line (R = 0.260, p = 0.47). R, Pearson coefficient for correlation.



Appendix Figure 5. A) Annual in-hospital case-fatality rate for 355 children with melioidosis, northern Cambodia, 2009–2018. Blue indicates 95% CI of linear trend line ($R = -0.044$; $p = 0.9$). R, Pearson coefficient for correlation. B) Annual in-hospital case-fatality rate for children with *Burkholderia pseudomallei* isolated from blood culture ($n = 73$). Blue indicates 95% CI confidence interval of linear trend line ($R = -0.44$; $p = 0.21$). R, Pearson coefficient for correlation.



Appendix Figure 6. Change in selection of oral antimicrobial drug for eradication therapy for 276 children who had melioidosis and were given either trimethoprim/sulfamethoxazole or amoxicillin/clavulanic acid, northern Cambodia, 2009–2018. Solid line and solid circles ($R = 0.92$; $p < 0.001$) indicate trimethoprim/sulfamethoxazole, and dashed line and open circles indicate amoxicillin/clavulanic acid. Blue area indicate 95% CIs of linear trend lines. R, Pearson coefficient for correlation.