

Review

Length of stay, cost, and mortality of healthcare-acquired bloodstream infections in children and neonates: A systematic review and meta-analysis

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Abstract

Objective: To estimate the attributable mortality, length of stay (LOS), and healthcare cost of pediatric and neonatal healthcare-acquired bloodstream infections (HA-BSIs).

Design: A systematic review and meta-analysis.

Methods: A systematic search (January 2000–September 2018) was conducted in PubMed, Cochrane, and CINAHL databases. Reference lists of selected articles were screened to identify additional studies. Case-control or cohort studies were eligible for inclusion when full text was available in English and data for at least 1 of the following criteria were provided: attributable or excess LOS, healthcare cost, or mortality rate due to HA-BSI. Study quality was evaluated using the Critical Appraisal Skills Programme Tool (CASP). Study selection and quality assessment were conducted by 2 independent researchers, and a third researcher was consulted to resolve any disagreements. Fixed- or random-effect models, as appropriate, were used to synthesize data. Heterogeneity and publication bias were evaluated.

Results: In total, 21 studies were included in the systematic review and 13 studies were included in the meta-analysis. Attributable mean LOS ranged between 4 and 27.8 days; healthcare cost ranged between \$1,642.16 and \$160,804 (2019 USD) per patient with HA-BSI; and mortality rate ranged between 1.43% and 24%. The pooled mean attributable hospital LOS was 16.91 days (95% confidence interval [CI], 13.70–20.11) and the pooled attributable mortality rate was 8% (95% CI, 6–9). A meta-analysis was not conducted for cost due to lack of eligible studies.

Conclusions: Pediatric HA-BSIs have a significant impact on mortality, LOS, and healthcare cost, further highlighting the need for implementation of HA-BSI prevention strategies.

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Healthcare-associated infections (HAIs) have a significant impact on mortality, length of stay (LOS), and healthcare cost worldwide.^{1–3} In the United States, ~2 million patients suffer from HAIs annually, nearly 90,000 are estimated to die due to HAIs, and the overall annual direct cost of HAIs to hospitals ranges from \$28 billion to \$45 billion.⁴ The 2008 Annual Epidemiological Report on Communicable Diseases in Europe of the European Centre for Disease Prevention and Control (ECDC) declared that HAIs caused 16 million extra days of hospital stay and 37,000 attributable deaths annually, while the associated annual cost reached 7 billion euros (2019 USD, 7.75 billion).⁵

Healthcare-acquired bloodstream infections (HA-BSIs) are the most common HAIs in critically ill pediatric patients of all age groups because central venous catheters (CVCs) are commonly used in these patients.^{6–9} In the United States, HA-BSIs are associated with the highest number of preventable deaths among HAIs, as well as the highest costs, ranging from \$960 million to \$18.2 billion annually.¹⁰ Although strong evidence indicates that most HA-BSIs are preventable,^{9,11–16} pediatric and neonatal HA-BSI rates remain far above zero in many countries worldwide, highlighting the need to initiate further national and targeted prevention strategies.^{17–19}

Published data regarding pediatric and neonatal HA-BSI outcomes vary significantly, depending on the country of origin, year of publication, and study design.²⁰ Accurate estimates of LOS, cost, and mortality attributed to HA-BSIs are essential for developing cost-effective infection prevention and infection control measures.²¹ In the present study, we systematically

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reviewed the available evidence and estimate attributable LOS, healthcare costs, and mortality rates for pediatric and neonatal HA-BSIs.

Methods

This study was conducted in accordance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.²² The systematic review protocol is not registered.

Literature search strategy

A systematic search from January 2000 to September 2018 of the PubMed, Cochrane, and CINAHL databases was conducted by 1 researcher (S.K.) using 3 groups of key words related to the terms “bloodstream,” “population,” and “outcome.” These 3 categories were combined using the Boolean “AND” and “OR.” Appendix 1 (online) presents the full search strategy used for MEDLINE, which was adapted for the other databases. Cited references from selected articles were screened to identify additional studies that were not retrieved in the initial search. Conference abstracts were not searched because they do not contain sufficient data for quality assessment.

Selection criteria

Following the literature search, identified studies were checked to exclude duplicates. The remaining articles were independently screened by 2 researchers (S.K. and C.T.) to identify studies that met the predetermined inclusion criteria. The selection process was performed in 2 steps. In the first step, titles and abstracts were evaluated for eligibility against the predetermined criteria. In the second step, the full-text articles were assessed when the information provided in titles/abstracts was insufficient to decide on inclusion or exclusion. Any disagreements between the 2 researchers were discussed and resolved by a third researcher (G.K.).

The study eligibility criteria were selected by applying the PICOS (population, intervention, comparison, outcomes, and setting) question format:

- Population: Studies referring to neonates and children <18 years of age with HA-BSI were eligible, and those that included both adult and pediatric populations were eligible only if stratified results by age group were presented.
- Interventions and comparators: Studies including both a group of children with HA-BSI (BSIs) and a group of children without HA-BSI (non-BSIs) were eligible.
- Outcomes: Studies that provided data on at least 1 of the following factors were included: attributable or excess LOS, or cost, or mortality due to HA-BSIs.
- Study design: Cohorts or case-control studies were selected.

Cohort or case-control study design was set as a criterion because these study types are reported to measure LOS, cost, and mortality more accurately.²¹ Articles that investigated only HA-BSIs caused by specific microorganisms were excluded, as were articles in which the primary outcomes were not the evaluation of attributable or excess LOS, cost, or mortality. Studies that presented mean or median values of the aforementioned attributable outcomes were included in the systematic review; their results are presented separately. However, in the meta-analysis, studies that reported median values of the attributable outcomes were excluded. Finally, only studies with their full text published in English were included.

Data extraction

Data extraction was performed by 1 researcher (S.K.), and the information was recorded in Microsoft Excel tables (Microsoft, Redmond, WA). The following data were noted: first author, year of publication, country, study design, hospital unit type, definition of HA-BSI, number of children with and without infection (BSIs and non-BSIs), and matching criteria (if used). Moreover, LOS, cost, and mortality (separately for each group), as well as attributable LOS, cost, or mortality, along with the corresponding 95% confidence intervals, were recorded. In studies where confidence intervals were not provided, we followed the recommendations of the Cochrane collaboration for calculating them.²³ In cases in which these calculations were not feasible, the relevant studies were excluded from the meta-analysis.

For studies that provided separate estimates for >1 hospital unit (eg, the neonatal and the pediatric intensive care units, NICU and PICU), estimates were recorded separately. In 3 studies, the number of children without infection (non-BSI) was calculated by subtracting the BSIs from the total number of pediatric patients included in the study^{24,25} or by applying the matching ratio.²⁶

Quality assessment

Study quality was evaluated by 2 researchers (S.K. and C.T.) using the Critical Appraisal Skills Programme Tool (CASP) for case-control and prospective cohort and retrospective cohort studies.²⁷ Disagreements were discussed with a third researcher (G.K.), and all 3 researchers ultimately reached consensus.

Statistical analysis

A meta-analysis was conducted using the STATA commands “metaan” and “metan” to estimate the pooled effect sizes with 95% confidence intervals (CIs) for attributable LOS and attributable mortality, respectively, as well as to graphically present the results in forest plots. The I^2 statistic was used to assess heterogeneity among the included studies. An $I^2 > 75\%$ indicates high heterogeneity among studies, and in such case, a random-effects model was used to obtain the pooled effect sizes. Moreover, sensitivity analysis was conducted by removing 1 study each time to identify the study that most influenced the results. Finally, the Egger test and funnel plots were used to evaluate potential publication bias.

Results

Of the 4,660 papers identified in the literature search, 21 were included in the systematic review^{6,24–26,28–44} and 13 were included in the meta-analysis (Fig. 1).^{29,30,32–36,39–44}

The main characteristics of the participating studies are listed in Table 1. Of the included studies, 4 were conducted in a hematology-oncology unit,^{6,24,25,44} 6 involved NICU patients,^{29,34,38,39,41,42} 6 involved PICU patients,^{30,31,35,37,40,43} and 5 involved a mixed pediatric population.^{26,28,32,33,36} In most of the studies,^{24,26,28–32,34–37,39–44} HA-BSI was defined according to CDC/NHSN criteria.^{45–47} In 1 study³⁸ the Vermont Oxford Network (VON) criteria^{48,49} were used; in another, ICD-9-CM codes were used²⁵; and in 2 other studies, institution-based criteria were considered.^{6,33} These institution-based criteria were reasonably chosen by the authors, and they were very much similar to the CDC/NHSN criteria. In addition, 10 of the participating studies were characterized as prospective cohort studies,^{24,26,28,30,31,35,37,40,41,44} 5 were characterized as retrospective cohort studies,^{25,33,36,38,39} and 6 were

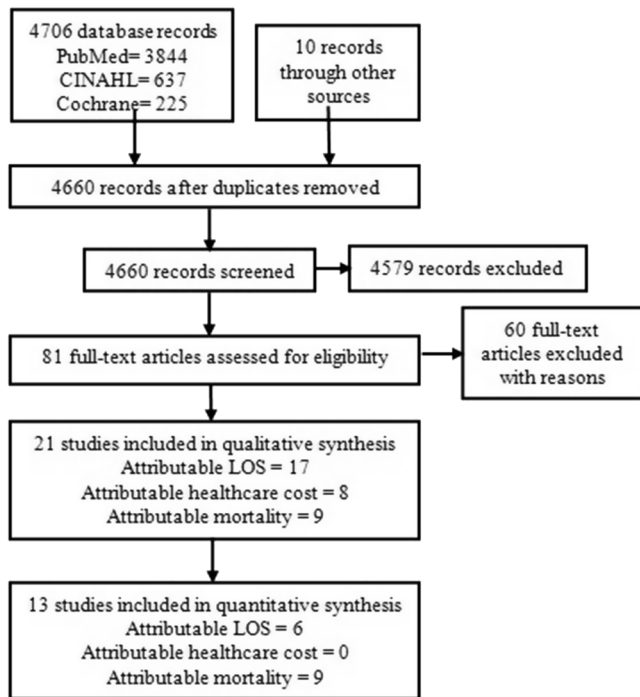


Fig. 1. Flow diagram of included studies. Note. LOS, length of stay.

characterized as case-control studies.^{6,29,32,34,42,43} However, we decided that the included case-control studies should ultimately be classified as either retrospective cohorts^{6,32,34,42} or as prospective cohorts^{29,43} because they actually measured outcomes after prospective or retrospective surveillance of matched BSI and non-BSI children until discharge or death.

Finally, with regard to the methodology of the studies that presented attributable HA-BSI LOS and/or cost, 8 studies used a time-fixed statistical approach^{25,30,32,37,38,41,43,44}; 7 of these studies presented time-matched outcomes of BSI and non-BSI patients^{6,24,26,28,29,36,39} and only 1 study used multistate modeling to estimate attributable HA-BSI LOS.³³

HA-BSI attributable LOS

In the systematic review, attributable LOS was presented in 17 studies.^{6,24–26,28–30,32,33,35–39,41,43,44} As shown in Table 2, the attributable mean LOS ranged from 4 to 27.8 days, and in the studies in which median LOS values were presented, attributable median LOS ranged from 1.57 to 12 days. For hospital unit, the attributable mean LOS ranged from 11.4 to 21.1 days in PICUs, from 4 to 27.8 days in NICUs, and from 14.24 to 25.1 days in hematology-oncology units.

In the meta-analysis, 6 studies were included.^{29,32,35,36,43,44} The pooled mean attributable hospital LOS was 16.91 days (95% CI, 13.70–20.11) (Fig. 2). We detected no heterogeneity among the studies ($I^2 = 27.74\%$) and no publication bias (Egger bias test $P = .705$) (Appendix 2 online). A subanalysis of 4 studies assessing the attributable LOS of central-line-associated bloodstream infections (CLABSIs),^{32,35,36,44} resulted in a pooled mean attributable LOS of 18.82 days (95% CI, 15.11–22.54).

For hospital unit, the pooled adjusted mean attributable PICU LOS was 16.4 days (95% CI, 10.1–22.71; $I^2 = 0$) (Fig. 3a) and the pooled mean attributable NICU LOS was 11.37 days (95% CI,

4.85–17.89) (Fig. 3b). No heterogeneity was detected between the PICU studies ($I^2 = 0\%$) and NICU studies ($I^2 = 68.96\%$). No publication bias was detected either for the PICU studies or the NICU studies: the Egger bias test P statistic was .76 for PICU studies and .07 for NICU studies.

HA-BSI attributable cost

Attributable healthcare cost was presented in 8 studies,^{6,25,29,31,32,36,43,44} and ranged from \$1,642.16 to \$160,804 (2019 USD) per patient with HA-BSI. This range refers to the 7 studies that estimated mean (and not median) attributable healthcare cost (Table 3). At this point, providing specific data around cost per hospital unit would be inaccurate because of the small number of referring studies: only 3 studies measured PICU HA-BSI cost,^{31,36,43} 2 studies estimated NICU costs,^{29,36} and 4 studies assessed costs for hematology-oncology patients.^{6,25,36,44} All of these studies differ with regard to the corresponding currency and year.

Meta-analysis was not conducted for the attributable HA-BSI cost due to the lack of eligible studies; only 3 of the participating studies estimated standard error of attributable HA-BSI cost, and their study populations presented heterogeneity.^{32,36,44}

HA-BSI attributable mortality

Attributable mortality was reported in 8 studies^{30,34,35,39–43} and was calculated in 1 study, using estimates that were provided separately for BSI and non-BSI patients.³³ The attributable mortality rate ranged between 0.01 and 0.24 (Table 4). The attributable mortality rate for the NICU was between 0.01 and 0.24, and for the PICU it was between 0.11 and 0.24.

In the meta-analysis, 9 studies were included.^{30,33–35,39–43} The pooled mortality rate was 0.08 (95% CI, 0.06–0.09) (Fig. 4). We detected no statistically significant heterogeneity among the studies ($I^2 = 45.3\%$; $P = .067$). A subanalysis of 4 studies assessing the attributable mortality of CLABSIs^{30,35,40,41} resulted in a pooled mean attributable mortality rate of 0.14 (95% CI, 0.08–0.20).

Finally, meta-analysis showed that the pooled attributable mortality rate in NICUs was 0.08 (95% CI, 0.03–0.13) (Fig. 5) and in PICUs this rate was 0.13 (95% CI, 0.07–0.19) (Fig. 5). No statistically significant heterogeneity was detected in either NICUs ($I^2 = 58.1\%$; $P = .067$) or PICUs ($I^2 = 0\%$; $P = .76$). As mentioned, no publication bias was detected for either for PICUs or NICUs.

Discussion

The goal of this systematic review and meta-analysis was to provide evidence around HA-BSI attributable LOS, cost, and mortality among pediatric and neonatal patients, targeting the design and implementation of appropriate and cost-effective prevention strategies. As far as we know, this is the first attempt to synthesize all existing data around HA-BSI outcomes in the pediatric and neonatal population.

The HA-BSI mean attributable LOS ranged from 4 to 27.80 days, and the pooled mean attributable hospital LOS was 16.90 days (95% CI, 13.70–20.11). Stratified results by type of unit revealed a higher impact of HA-BSIs in PICUs (pooled mean attributable LOS, 16.40 days) compared to NICUs (pooled mean attributable LOS, 11.40 days). The results were more consistent in PICUs, with the mean attributable LOS ranging from 11.40 to 21.10 days, whereas in NICUs it ranged between 4 and

Table 1. Main Characteristics of the Included Studies

Author (Year)	Country	Study Design	Unit Type	Matching Criteria	BSI Definition	No. of BSIs	No. of Non-BSIs	Outcome
Aiken (2011) ²⁸	Kenya	Prospective cohort	Pediatric ward in 1 hospital, except for inpatients with minor trauma or undergoing elective surgery	1:4; age, nutritional status, and LOS at least as long as the index patient at the point he or she developed bacteremia	HA bacteremia, CDC/NHSN 2008	89 survivors	353 survivors	LOS
Allareddy (2012) ²⁵	United States	Retrospective cohort	Hematology-oncology unit, children under leukemia treatment, Nationwide Inpatient Sample database, Healthcare and Utilization Project	N/A	Septicemia, identified using ICD-9-CM codes	787	5,433	LOS, cost
Atif (2008) ²⁹	Algeria	Prospective, nested case-control	NICU	1:2; sex, birth weight, length of NICU stay ≥ 7 d, hospital admission year	Nosocomial BSI, CDC 1988	83	166	LOS, cost
Aviles-Robles (2014) ²⁴	Mexico	Prospective cohort	Pediatric hematology-oncology unit, children with febrile neutropenia	N/A	LCBI, CDC/NHSN 2008	24	193	LOS
Biwersi (2009) ⁶	Germany	Case-control	Pediatric hematology-oncology unit	1:1; age, gender, underlying malignancy, chemotherapy, exact date of event	Institution-based criteria	43	43	LOS, cost
Dramowski (2016) ²⁶	South Africa	Prospective cohort	General pediatrics, pediatric surgery, pediatric infectious diseases/gastroenterology/ cardiology, and PICU	1:3; Age- and ward-matched controls per HCAI event, hospitalized for at least as long as the index patient	LCBI, CDC/NHSN 2013	41	123	LOS
Duenas (2011) ³⁰	INICC, El Salvador	Prospective cohort	PICU	N/A	CLABSI, CDC/NHSN 2008	40	994	LOS, mortality
Elward (2005) ³¹	United States	Prospective cohort	PICU	N/A	Nosocomial primary BSI, CDC/NHSN 1996	57	854	Cost
Goudie (2014) ³²	United States	Case-control	Children with inpatient discharges in the Nationwide Inpatient Sample databases, Healthcare and Utilization Project	1:2; age, discharge year, and propensity score	CLABSI, CDC/NHSN 2012	1,339	2,678	LOS, cost
Green (2014) ³³	England	Retrospective cohort	National laboratory surveillance database (LabBase2), including NICUs, PICUs, General and Specialist Pediatric Medical/Surgical wards	N/A	Institution- based criteria	214	333,391	LOS, mortality
Grisaru-Soen (2012) ³⁴	Israel	Retrospective matched case-control	NICU	1:1; gestational age, birth weight, and duration of NICU hospitalization prior to the onset of late-onset sepsis.	Nosocomial late-onset BSI, CDC/NHSN 2008	101	101	Mortality
Gupta (2011) ³⁵	India	Prospective surveillance	PICU	N/A	HA-BSI, CVC-BSI, CDC/ NHSN 2008	11 HA-BSI; 11 CVC-BSI	176 no HA-BSI; 120 no CVC-BSI	LOS, mortality
Karagiannidou (2018) ³⁶	Greece	Retrospective cohort	PICU, NICU, hematology-oncology unit, and bone marrow transplantation unit	1:1; hospital, unit, and length of stay prior to study enrollment	CLABSI, CDC/NHSN 2014	94	94	LOS, cost

(Continued)

Table 1. (Continued)

Author (Year)	Country	Study Design	Unit Type	Matching Criteria	BSI Definition	No. of BSIs	No. of Non-BSIs	Outcome
Navoa-Ng (2011) ³⁷	INICC, Philippines	Prospective cohort	PICU	N/A	CLABSI, CDC/NHSN 2008	4	240	LOS
Payne (2004) ³⁸	United States	Retrospective cohort	NICU	N/A	Nosocomial BSI (NBI), Vermont Oxford Network (VON) criteria 1998 and 1999	553; CONS, 372; other bacteria, 232; fungemia, 85	2,256	LOS
Pessoa-Silva (2001) ³⁹	Brazil	Retrospective matched cohort	NICU	1:1; sex, birth weight, gestational age, secondary diagnosis, hospitalization for at least as long as the matched case before the LO-BSI event	Nosocomial Late-onset BSI, CDC/NHSN 1988	50	50	LOS, mortality
Rosenthal (2014) ⁴¹	INICC, 43 countries	Prospective cohort	NICU	N/A	CLABSI, CDC/NHSN 2008	51	7,447	LOS, mortality
Rosenthal (2012) ⁴⁰	INICC, 16 limited-resource countries	Prospective cohort	PICU	N/A	CLABSI, CDC/NHSN 2008	95	3,285	Mortality
Schwab (2015) ⁴²	Germany	Retrospective cohort and case-control	NICU, very low birth weight infants (VLBW)	Case-control study, 1:1; department, gestational age, length of stay of the control \geq length of stay to the start of infection of the case, start of surveillance, sex, mode of delivery	BSI and laboratory confirmed (LC-BSI, no CoNS) CDC/ NHSN 2008	Cohort: 6,911 BSIs; 1,806 LC-BSIs Case-control: 5,187 BSIs; 1,511 LC-BSIs	Cohort: 36,205 no BSIs; 41,310 no LC-BSIs; Case-control: 5,187 non-BSIs; 1,511 non-LC-BSIs	Mortality
Slonim (2001) ⁴³	United States	Case-control	PICU	1:1; age, severity of illness, primary diagnosis, and admission date	Nosocomial BSI, CDC/ NHSN 1988	38	38	LOS, cost, mortality
Wilson (2014) ⁴⁴	United States	Prospective cohort	Pediatric hematology-oncology unit	1:1; propensity score	CLABSI, CDC/NHSN 2014	59	59	LOS, cost

Note. N/A, not available; BSI, bloodstream infection; CLABSI, central line-associated BSI; HA-BSI, healthcare-acquired BSI; HA-Bacteremia, healthcare-associated bacteremia; CVC-BSI, central venous catheter BSI; LC-BSI or LCBI, laboratory-confirmed BSI; HCAI, healthcare-acquired infection; CVC, central venous catheter; LOS, length of stay; NICU, neonatal intensive care unit; PICU, pediatric intensive care unit; CoNS, coagulase-negative staphylococci; INICC, International Nosocomial Infection Control Consortium; CDC, Centers for Disease Control and Prevention; NHSN, National Healthcare Safety Network.

Table 2. Outcome Data of Included Studies With Regard to Length of Stay (LOS)

Author (Year)	Adjustment	BSI LOS, d	Non-BSI LOS, d	Attributable LOS, d
Aiken (2011) ²⁸	A confounder and time matching approach	Median LOS of matched survivors, 28.9 (IQR, 13–41.6)	Median LOS of matched survivors, 18.8 (IQR, 8.1–30.9)	Additional attributable LOS, 10.1
Allareddy (2012) ²⁵	Presence of septicemia, age, gender, patient disposition, insurance status, leukemia type, admission type, presence of comorbid conditions, and hospital teaching status, location, geographic region, and bed size.	Average (crude), 33.18	Average (crude), 13.79	Estimated adjusted increase in LOS, 14.24
Atif (2008) ²⁹	N/A	Mean in NICU, 24.3 (SD, ±18.7)	Mean in NICU, 15.1 (SD, ±11.3)	Mean attributable extra LOS, 9.2
Aviles-Robles (2014) ²⁴	Age at admission, sex, cancer type, and antimicrobial prophylaxis	Crude median, 19	Crude median, 10	Patients with BSIs had a 100% longer relative LOS, compared with patients for whom no pathogen was identified
Biwarsi (2009) ⁶	N/A	Median inpatient antimicrobial treatment, 12 (IQR, 11–18; range, 7–59)	Median inpatient antimicrobial treatment, 0 (IQR, 0–7; range, 0–34)	Median additional length of inpatient antimicrobial treatment, 12 (IQR, 8.5–16)
Dramowski (2016) ²⁶	A confounder and time-matching approach was used, after excluding patient admission episodes with outcome of death or transfer	Crude median, 20 (IQR, 11–32)	Crude median, 11 (IQR, 7–23)	Median excess LOS, 9
Duenas (2011) ³⁰	N/A	Average, 19.1	Average, 6.2	Extra LOS, 12.9
Goudie (2014) ³²	CLABSI status, age, discharge year, gender, race/ethnicity, insurance status, propensity score, and interactions for CLABSI by age, gender, race/ethnicity, insurance category and year	Mean adjusted, 37.2	Mean adjusted, 18.2	Mean adjusted attributable, 19 (95% CI, 14.3–23.8)
Green (2014) ³³	Time-adjusted estimate of excess LOS, weighted relative to the frequency of transitions to HA-BSI, discharge alive or in-hospital death on each day.	Crude mean, 56.55; median, 30 (IQR, 10–66)	Crude mean, 1.35; median, 0.5 (IQR, 0.5–1)	Adjusted excess LOS, 1.57 (95% CI, 0.20–2.95)
Gupta (2011) ³⁵	N/A	Mean, 25.6 (SE, 7.2)	Mean, 9.6 (SE, 0.87)	Mean attributable LOS, 16 (SE, 4.3)
Karagiannidou (2018) ³⁶	Age, gender, matching characteristics, central line management after study enrollment, and propensity score for predicting the risk of acquiring a CLABSI.	Mean crude, 55.2 (95% CI, 44.8–66.5) Mean adjusted, 58.7 Mean adjusted by unit: PICU, 55; NICU, 75.5; hematology-oncology, 71; BMTU, 33.9	Mean crude, 39.7 (95% CI, 31.4–49.6) Mean adjusted, 37.6 Mean adjusted by unit: PICU, 35.2; NICU, 48.3; hematology-oncology unit, 45.5; BMTU, 21.7	Mean adjusted attributable, 21.3 (95% CI, 6.8–35.8) Mean adjusted attributable by unit: PICU, 20 (95% CI, 3.9–36.2); NICU, 27.8 (95% CI, 8–47.5); hematology-oncology unit, 25.1 (95% CI, 7.9–42.3); BMTU, 12.3 (95% CI, 4.5–20.1)
Navoa-Ng (2011) ³⁷	N/A	Average, 17	Average, 5.6	Crude extra LOS, 11.4 (95% CI, 6.9–62.5)

(Continued)

Table 2. (Continued)

Author (Year)	Adjustment	BSI LOS, d	Non-BSI LOS, d	Attributable LOS, d
Payne (2004) ³⁸	Birth weight, small for gestational age, birth location, gender, maternal race, prenatal care, antenatal steroids, multiple birth, 5-min APGAR score, respiratory distress syndrome, chronic lung disease, necrotizing enterocolitis (NEC), NEC surgery, other surgery, and any ventilation	Crude mean LOS per BW category: BW 401–750 g, 101 BW 751–1,000 g, 83 BW 1,001–1,250 g, 60 BW 1,251–1,500 g, 48 Adjusted mean LOS: BW 401–750 g, 94 BW 751–1,000 g, 75 BW 1,001–1,250 g, 51 BW 1,251–1,500 g, 36	Crude mean LOS per BW category: BW 401–750 g, 85 BW 751–1,000 g, 66 BW 1,001–1,250 g, 47 BW 1,251–1,500 g, 32 Adjusted mean LOS: BW 401–750 g, 88 BW 751–1,000 g, 68 BW 1,001–1,250 g, 47 BW 1,251–1,500 g, 31	Crude mean excess LOS per BW category: BW 401–750 g, 16 BW 751–1,000 g, 17 BW 1,001–1,250 g, 13 BW 1,251–1,500 g, 16 Adjusted mean excess LOS: BW 401–750 g, 6 BW 751–1,000 g, 7 BW 1,001–1,251 g, 4 BW 1,251–1,500 g, 5
Pessoa-Silva (2001) ³⁹	Nasogastric/tracheal tube, lumbar/arterial puncture, thoracic drains, blood and/or blood components transfusion, umbilical catheter, parenteral nutrition, duration of peripheral/central venous catheters, and antibiotics	Mean, 57.6; In 32 pairs where both subjects survived: mean, 53.2	Mean, 43.6 In 32 pairs where both subjects survived: mean, 28.1	In 32 pairs where both subjects survived: prolongation of LOS, 25.1
Rosenthal (2014) ⁴¹	N/A	Pooled average, 23.22 (95% CI, 17.78–31.03)	Pooled average, 10.75 (95% CI, 10.53–10.99)	Pooled average extra, 12.46
Slonim (2001) ⁴³	N/A	Mean PICU LOS, 19.3 (SEM, ±2.3) Mean hospital LOS, 46.7 (SEM, ±4.9)	Mean PICU LOS, 4.6 (SEM, ±6.5) Mean hospital LOS, 24.4 (SEM, ±6.5)	Attributable PICU LOS, 14.6 Attributable hospital LOS, 21.1
Wilson (2014) ⁴⁴	Age, sex, central venous catheter type, total no. of line days, the no. of times the CVC was accessed by hospital personnel other than those on the pediatric hematology-oncology ward, no. of blood cultures and the total no. of excessive blood cultures	Mean, 33.9	Mean, 12.7	Attributable, 21.2 (95% CI, 10.4–32)

Note. N/A, not available; CI, confidence interval; IQR, interquartile range; SEM, standard error of the mean; BSI, bloodstream infection; CLABSI, central line-associated BSI; HA-BSI, healthcare-acquired BSI; CVC, central venous catheter; BW, birth weight; LOS, length of stay; NICU, neonatal intensive care unit; PICU, pediatric intensive care unit; BMTU, bone marrow transplantation unit.

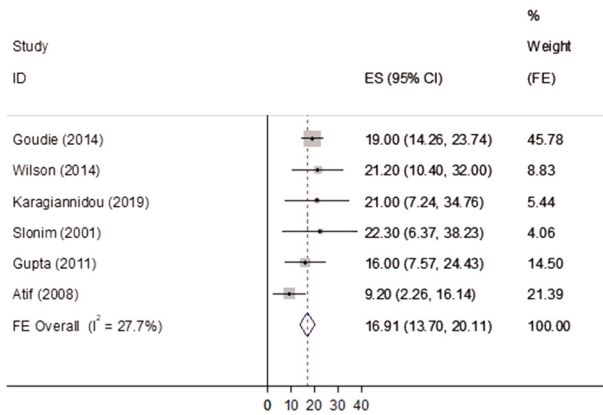


Fig. 2. Pooled mean of attributable hospital length of stay (LOS), forest plot. Note. ES, effect size; FE, fixed effects.

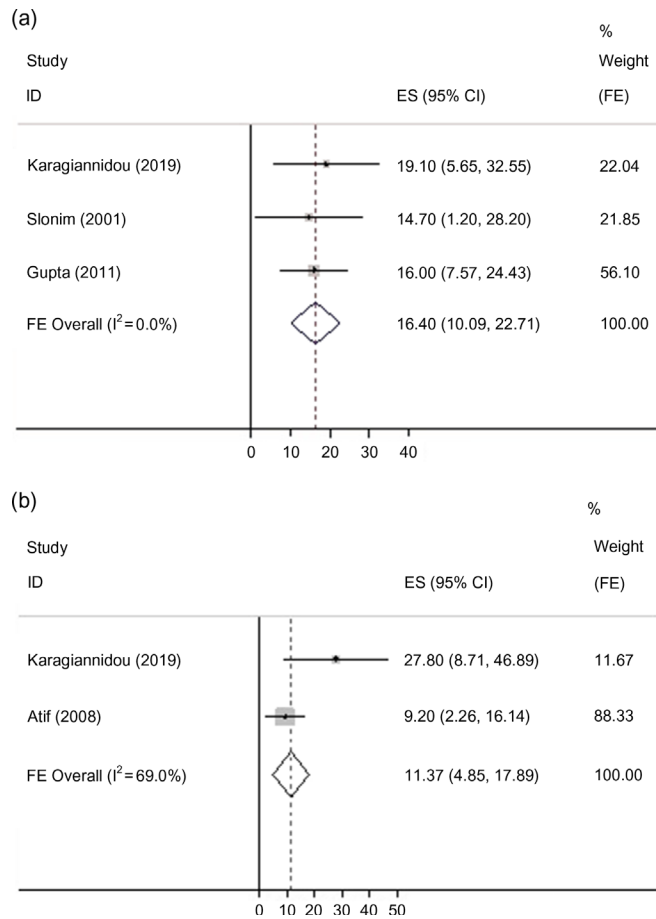


Fig. 3. (a) Pooled mean of attributable hospital length of stay (LOS) in the pediatric intensive care unit (PICU), forest plot; (b) Pooled mean of attributable hospital length of stay (LOS) in the neonatal intensive care unit (NICU), forest plot. Note. ES, effect size; FE, fixed effects.

27.80 days. However, no statistically significant heterogeneity was observed in PICUs or in NICUs.

As described in the previous section, 7 of the studies that participated in the meta-analysis presented time-matched outcomes

of BSI and non-BSI patients with regard to LOS, and only one used a multistate modeling approach to estimate attributable HA-BSI LOS. Previous work by Manoukian et al²¹ has suggested that excess LOS associated with HA-BSIs in adult populations presents significant variations according to the statistical method employed. More specifically, Manoukian et al suggest that studies using time-fixed methods overestimate the attributable LOS compared to time-varying methods,²¹ because they do not take into account the time-dependent bias. Multistate modeling is considered the most accurate statistical method of attributable LOS estimation.^{20,50} This hypothesis can only be partially confirmed by our study because the only study using multistate modeling among those included in our review provided the lower estimation of excess LOS (1.57 days).³³

Attributable mean healthcare cost ranged from \$1,642.16 to \$160,804 (2019 USD) per patient with HA-BSI. Previous work by Umscheid et al¹⁰ assessed attributable cost of catheter-associated BSIs (CA-BSIs) in the adult ICU and reported costs from \$41,900 to \$123,600 (2009 USD).

In general, the large difference observed between reported attributable cost estimates for several HAI types is due to differences in the perspective of cost analysis (ie, hospital or societal), the costing methodology (ie, microcosting approach or not), and the year of costing, as well as differences in clinical practice patterns and healthcare systems among countries (ie, use of novel and expensive technologies in high-income countries, etc).²⁰

Attributable mortality rate ranged between 0.01 and 0.24, and pooled mortality was 0.08 (95% CI, 0.06–0.09). Stratified analysis by type of unit revealed that the pooled mortality rate was higher in PICUs (0.13) compared to NICUs (0.08).

Previous systematic reviews and meta-analyses have presented data indicating that the odds ratio for in-hospital death associated with HA-BSIs in adult patients ranges between 1.96 and 2.75.^{51,52} However, attributable HA-BSI mortality rates present significant variations, according to several causative microorganisms and susceptibility patterns.^{51,53}

Quantifying excess HA-BSI outcomes is essential for both healthcare providers and policy makers. Improving efficiency with regard to resources and bed days by implementing targeted prevention strategies is crucial to increasing a hospital's capacity to provide high-quality care to the highest number of patients. Precise measurements of HA-BSI outcomes could guide decision making around investments in infection control.

This study has several limitations. First, we acknowledge the possibility of language bias due to the fact that only studies written in English were incorporated in this review. Practical reasons, namely the difficulty of translating from a variety of languages, led us to the decision to include only English-language studies. Moreover, restricting the search strategy to only electronic databases may have introduced publication bias because this approach is unlikely to identify studies that have not been published in peer-reviewed journals. Because we did not include unpublished studies in our review, it was impossible to assess the potential publication bias by comparing the results of published and unpublished studies. However, we applied the Egger test, which revealed that no publication bias exists in HA-BSI-attributable LOS and mortality studies. We should underscore that the Egger test is inappropriate where there is heterogeneity; the test has low power and is of little use in analyses with few studies.

Finally, another important limitation of this study is the inclusion of studies that used a variety of HA-BSI definitions, and

Table 3. Outcome Data of Included Studies With Regard to Cost

Author (Year)	Adjustment	BSI Costs	Non-BSI Costs	Attributable Costs
Allareddy (2012) ²⁵	Presence of septicemia, age, gender, patient disposition, insurance status, leukemia type, admission type, presence of comorbid conditions, and hospital teaching status, location, geographic region, and bed size	Mean (crude) hospitalization charges, \$279,137 (2019 USD: \$334,276.74)	Mean (crude) hospitalization charges, \$113,530 (2019 USD, \$135,956.32)	Estimated adjusted increase in hospitalization charges (2008 USD), \$134,279 (2019 USD, \$160,804)
Atif (2008) ²⁹	N/A	Mean cumulative, \$2584 (2019 USD, \$3,226.89)	Mean cumulative, \$1,269 (2019 USD, \$1584.72)	Mean cumulative attributable extra, \$1,315 (2019 USD, \$1,642.16)
Bwersi (2009) ⁶	N/A	N/A	N/A	Median additional expenses, €4,400 (IQR, 3,145–5,920) or \$6,970 (IQR, 4,938–9,294) (2019 USD, \$8,304)
Elward (2005) ³¹	Nosocomial primary BSI, age, severity of illness, underlying disease (congenital heart disease/transplant), and ventilator days	Adjusted mean direct costs of PICU admission, \$45,615 (2019 USD, \$67,728)	Adjusted mean direct costs of PICU admission, \$6,396 (2019 USD, \$9,496)	Adjusted attributable mean direct cost of PICU admission (1999 and 2000 USD), \$39,219 (2019 USD, \$58,231)
Goudie (2014) ³²	CLABSI status, age, discharge year, gender, race/ethnicity, insurance status, propensity score and interactions for CLABSI by age, gender, race/ethnicity, insurance category and year	Mean adjusted, \$103,949 (2019 USD, \$119,314.57)	Mean adjusted, \$48,303 (2019 USD, \$55,443.07)	Mean adjusted attributable (2011 USD), \$55,646 (95% CI, 38,785–72,507) [2019 USD, \$63,871.5 (SE, 9,874)]
Karagiannidou (2018) ³⁶	Age, gender, matching characteristics, central line management after study enrollment, and propensity score for predicting the risk of acquiring a CLABSI.	Mean adjusted, €31,944 Mean adjusted cost by unit: PICU, €31,192; NICU, €36,791; Hematology-oncology unit, €39,431; BMTU, €21,157 (2019 USD: Overall adjusted, \$56,490; PICU, \$53,830; NICU, \$66,019; hematology-oncology unit, \$69,486; BMTU, \$38,198)	Mean adjusted, €18,072 Mean adjusted cost by unit: PICU, €17,646; NICU, €20814; hematology-oncology unit, €22307; BMTU, €11,969 (2019 USD: Overall adjusted, \$17,788; PICU, \$16,951; NICU, \$20,788; hematology-oncology unit, \$21,881; BMTU, \$12,028)	Mean adjusted attributable, €14,099 (95% CI, 5,631–22,568) Mean adjusted attributable by unit (2017 €): PICU, €13,852 (95% CI, 5,409–22,296); NICU, €16,493 (95% CI, 5,623–27,363) hematology-oncology unit, €16,934 (95% CI, 5,599–28,269); BMTU, €9,320 (95% CI, 4,099–14,541) [2019 USD: Overall, \$24,773 (SE, 7337); PICU, \$23,748 (SE, 7,842); NICU, \$29,371 (SE, 9,282); hematology-oncology unit, \$29,673 (SE, 9,940); BMTU, \$16,733 (SE, 5,166)]
Slonim (2001) ⁴³	N/A	Mean total operational costs, \$78,272 (SEM, ±8,202) [2019 USD, \$117,211.39 (SE, 12,282.40)]	Mean total operational costs, \$35,005 (SEM, ±9,865) [2019 USD, \$52,419.57 (SE, 14,772.72)]	Attributable total operating costs, (2000 USD), \$46,133 (2019 USD, \$69,083.62)
Wilson (2014) ⁴⁴	Age, sex, CVC type, total number of line-days, the number of times the CVC was accessed by hospital personnel other than those on the pediatric hematology/oncology ward, number of blood cultures and the total number of excessive blood cultures.	Average, \$107,007 (2019 USD, \$122,824.60)	Average, \$37,675 (2019 USD, \$43,244.06)	Attributable (USD 2011), \$69,332 (95% CI, 35,144–103,521) [2019 USD, \$79,580.54 (SE, 20,021)]

Note. N/A, not available; CI, confidence interval; IQR, interquartile range; SEM, standard error of the mean; SE, standard error, BSI, bloodstream infection; CLABSI, central-line-associated BSI; CVC, central venous catheter; BW, birth weight; LOS, length of stay; ICU, intensive care unit; NICU, neonatal ICU; PICU, pediatric ICU; BMTU, bone marrow transplantation unit.

Table 4. Outcome Data of Included Studies With Regard to Mortality

Author (Year)	Adjustment	Mortality, BSIs	Mortality, Non-BSIs	Attributable Mortality
Duenas (2011) ³⁰	N/A	Crude, 25.0%	Crude, 13.6%	Crude extra, 11.4%
Green (2014) ³³	N/A	Crude, 13 of 214 (61 per 1,000)	Crude, 157 of 333,391 (0.5 per 1,000)	N/A
Grisaru-Soen (2012) ³⁴	N/A	Crude, 6.9%	Crude, 3%	Crude attributable, 3.9%
Gupta (2011) ³⁵	N/A	HA-BSI crude fatality rate, 55% CVC-BSIs crude fatality rate, 55%	No HA-BSIs crude case-fatality rate, 30% No CVC-BSIs crude case-fatality rate, 41%	HA-BSI crude excess mortality, 24% CVC-BSI crude excess mortality, 14%
Pessoa-Silva (2001) ³⁹	Nasogastric/tracheal tube, lumbar/arterial puncture, thoracic drains, blood and/or blood components transfusion, umbilical catheter, parenteral nutrition, duration of peripheral and central venous catheters, and antibiotics	Crude, 32%	Crude, 8%	Attributable mortality, 24% (95% CI, 9–39)
Rosenthal (2014) ⁴¹	N/A	Pooled crude, 17.6%	Pooled crude, 6.2%	Pooled crude extra, 11.4%
Rosenthal (2012) ⁴⁰	N/A	Pooled crude, 26.3% (95% CI, 17.8–36.4)	Pooled crude, 10% (95% CI, 9–11.1)	Pooled crude excess, 16.3% (95% CI, 8.8–25.3)
Schwab (2015) ⁴²	Case-control BSI, adjusted by birth weight; LC-BSI, no confounders/risk factors by the conditional logistic regression	Cohort (crude): BSIs, 5.64%; LC-BSIs, 10.47% Case-control study (crude): BSIs, 4.95%; LC-BSIs, 9.53%	Cohort (crude): No BSIs, 6.81%; No LC-BSIs, 6.46% Case-control study (crude): No BSIs, 3.53%; No LC-BSIs, 3.04%	Cohort (crude), N/A Case-control study (crude): Attributable mortality of BSI, 1.43% (95% CI, 0.69–2.17) Attributable mortality of LC-BSI, 6.49% (95% CI, 4.86–8.12)
Slonim (2001) ⁴³	N/A	Crude, 23.7%	Crude, 10.5%	Attributable crude, 13.1%

Note. N/A, not available; CI, confidence interval; BSI, bloodstream infection; HA-BSI, healthcare-acquired BSI; CVC-BSI, central venous catheter BSI; LC-BSI, laboratory confirmed BSI.

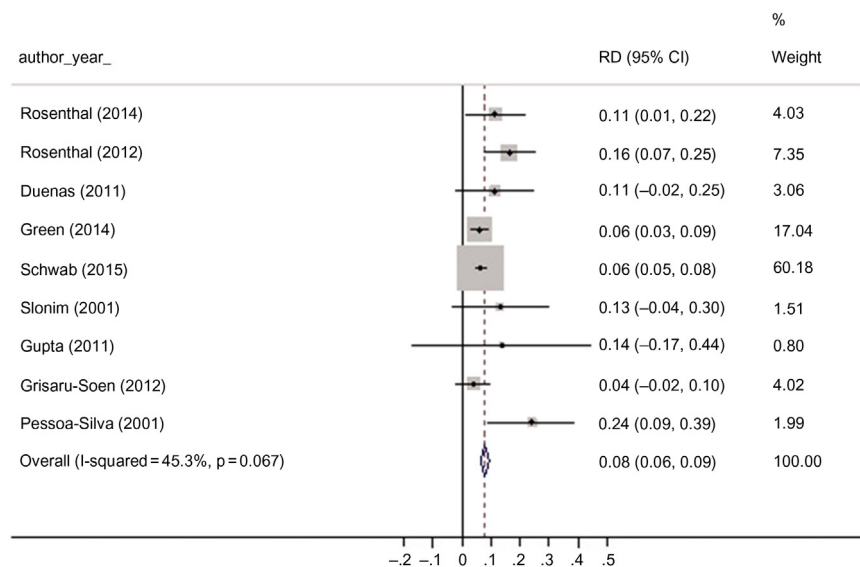


Fig. 4. Pooled overall attributable mortality rate, forest plot. Note. RD, risk difference.

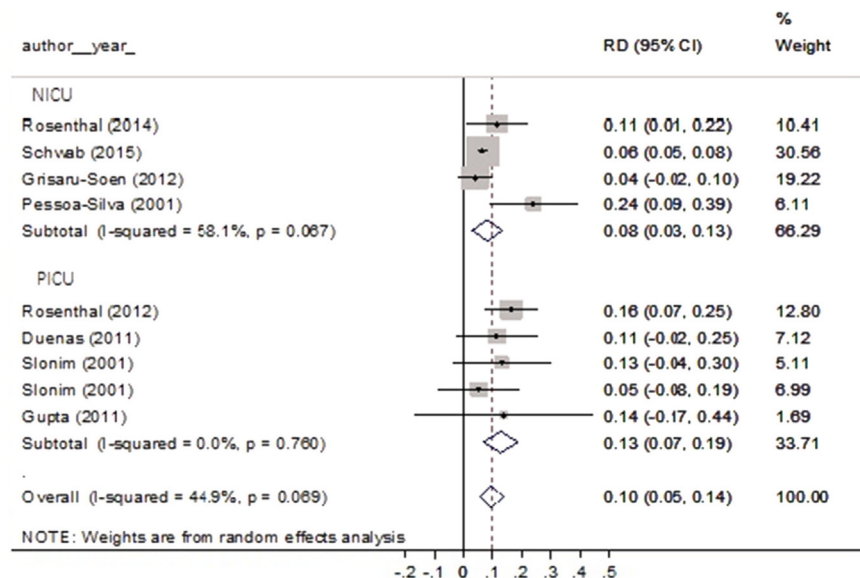


Fig. 5. Pooled attributable mortality rate by unit, forest plot. Note. RD, risk difference.

although all of these BSIs were nosocomial, this could result in outcome differences. We tried to overcome this problem by conducting a subanalysis in studies assessing the attributable LOS and mortality of CLABSIs, and the outcomes were presented separately. The heterogeneity in the HAI definitions used by several authors in the literature is a major problem when trying to conduct a qualitative or quantitative synthesis of the available literature data on HAI outcomes.

In conclusion, HA-BSIs in children and neonates are associated with higher mortality, LOS, and healthcare costs than in children and neonates without HA-BSIs. This finding justifies and may enhance efforts to implement HA-BSI prevention strategies. Future research efforts could make better use of existing HAI definitions and evolving statistical methodologies, presenting more accurate, high-quality, and comparable outcome results globally.

Supplementary material. To view supplementary material for this article, please visit <https://doi.org/10.1017/ice.2019.353>

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