Open Forum Infectious Diseases

MAJOR ARTICLE

What Is the Optimal Follow-up Length for Mortality in *Staphylococcus aureus* Bacteremia? Observations From a Systematic Review of Attributable Mortality

Anthony D. Bai,[1,2] Carson K. L. Lo,[3] Adam S. Komorowski,[2,4] Mallika Suresh,[5] Kevin Guo,[6] Akhil Garg,[7] Pranav Tandon,[8] Julien Senecal,[9] Olivier Del Corpo,[10] Isabella Stefanova,[5] Clare Fogarty,[11] Guillaume Butler-Laporte,[12] Emily G. McDonald,[13] Matthew P. Cheng,[14] Andrew M. Morris,[15] Mark Loeb,[3] and Todd C. Lee[13]

[1]Division of Infectious Diseases, Department of Medicine, Queen's University, Kingston, Ontario, Canada, [2]Department of Health Research Methods, Evidence and Impact, Faculty of Health Sciences, McMaster University, Hamilton, Ontario, Canada, [3]Division of Infectious Diseases, Department of Medicine, McMaster University, Hamilton, Ontario, Canada, [4]Division of Medical Microbiology, Department of Pathology and Molecular Medicine, McMaster University, Hamilton, Ontario, Canada, [5]Michael G. DeGroote School of Medicine, McMaster University, Hamilton, Ontario, Canada, [6]Faculty of Health Sciences, McMaster University, Hamilton, Ontario, Canada, [7]Department of Medicine, Queen's University, Kingston, Ontario, Canada, [8]Temerty Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada, [9]Faculty of Medicine and Health Sciences, McGill University, Montreal, Quebec, Canada, [10]Department of Medicine, Division of Experimental Medicine, Division of Infectious Diseases, McGill University, Montreal, Quebec, Canada, [11]McGill University Health Centre, McGill University, Montreal, Quebec, Canada, [12]Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, Canada, [13]Clinical Practice Assessment Unit, Department of Medicine, McGill University, Montreal, Quebec, Canada, [14]Divisions of Infectious Diseases and Medical Microbiology, McGill University Health Centre, Montreal, Quebec, Canada, and [15]Division of Infectious Diseases, Department of Medicine, Sinai Health, University Health Network, and the University of Toronto, Toronto, Ontario, Canada

Background. Deaths following *Staphylococcus aureus* bacteremia (SAB) may be related or unrelated to the infection. In SAB therapeutics research, the length of follow-up should be optimized to capture most attributable deaths and minimize nonattributable deaths. We performed a secondary analysis of a systematic review to describe attributable mortality in SAB over time.

Methods. We systematically searched Medline, Embase, and Cochrane Database of Systematic Reviews from 1 January 1991 to 7 May 2021 for human observational studies of SAB. To be included in this secondary analysis, the study must have reported attributable mortality. Two reviewers extracted study data and assessed risk of bias independently. Pooling of study estimates was not performed due to heterogeneity in the definition of attributable deaths.

Results. Twenty-four observational cohort studies were included. The median proportion of all-cause deaths that were attributable to SAB was 77% (interquartile range [IQR], 72%–89%) at 1 month and 62% (IQR, 58%–75%) at 3 months. At 1 year, this proportion was 57% in 1 study. In 2 studies that described the rate of increase in mortality over time, 2-week follow-up captured 68 of 79 (86%) and 48 of 57 (84%) attributable deaths that occurred by 3 months. By comparison, 1-month follow-up captured 54 of 57 (95%) and 56 of 60 (93%) attributable deaths that occurred by 3 months in 2 studies.

Conclusions. The proportion of deaths that are attributable to SAB decreases as follow-up lengthens. Follow-up duration between 1 and 3 months seems optimal if evaluating processes of care that impact SAB mortality.

Clinical Trials Registration. PROSPERO CRD42021253891.

Keywords. attributable mortality; bacteremia; follow-up; mortality; *Staphylococcus aureus*; systematic review.

Staphylococcus aureus bacteremia (SAB) is a common bloodstream infection with a high mortality rate [1]. The mortality in SAB varies greatly across studies from 10% to 30% [1, 2]. One contributing factor to the wide range of mortality estimates is a lack of consensus on the optimal follow-up duration for SAB, which is reflected by varied length of follow-up across studies ranging from 2 weeks [3, 4] to 1 year [5, 6].

In principle, follow-up should be long enough to capture most deaths attributable to SAB. However, as follow-up lengthens, deaths that are not attributable to SAB will accumulate and, at a certain time point, the ability to determine the impact of processes of care on SAB becomes confounded by the competing risk of death from all other causes. For example, consider an intervention where patients received combination antibiotic therapy in the first 5 days. If the patient dies within the first week, that may have a strong correlation to the treatment whereas if a patient dies of lung cancer in month 11, it is extremely unlikely to be related. In fact, once the bacteremia is cured, outside of a relapse or major irreversible drug toxicity, it is unlikely that any death beyond a certain time point would be related to the initial therapy. Based on the same logic, a study that examines risk factors for mortality over a long period would converge on general predictors of life expectancy that are unrelated to the management of SAB.

Received 1 December 2021; editorial decision 16 February 2022; accepted 19 February 2022; published online 10 April 2022.

Correspondence: Anthony D. Bai, MD, Division of Infectious Diseases, Queen's University, 94 Stuart St, Etherington Hall, Room 3010, Kingston, ON K7L 3N6, Canada (tony.bai@queensu.ca).

Open Forum Infectious Diseases®2022

https://doi.org/10.1093/ofid/ofac096

The ideal follow-up length for studies that evaluate the impact of specific interventions should capture most attributable deaths while minimizing the number of nonattributable deaths. This is especially important for the design of randomized controlled trials (RCTs) that require significant funding, important resources, and meticulous planning. When designing the study, the trialist must decide on the optimal length of follow-up to detect the effect of an intervention in reducing mortality related to SAB or its treatment (signal) while reducing the competing risk of deaths unrelated to SAB or its treatment (noise).

We hypothesized that the ideal follow-up duration for SAB could be calibrated based on how attributable and nonattributable deaths increase over time. We recently performed a systematic review and meta-analysis to summarize SAB mortality [7]. The objective of this secondary analysis is to describe the attributable mortality and its relation to all-cause mortality for different lengths of follow-up ranging from 2 weeks to 1 year.

METHODS

This was a secondary analysis of a systematic review. The study protocol for the original systematic review was prospectively registered (International Prospective Register of Systematic Reviews [PROSPERO] CRD42021253891). There were no amendments to the study protocol. This study was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (Supplementary Text 1) [8].

Literature Search

The literature search was performed using Medline, Embase, and the Cochrane Database of Systematic Reviews for dates between 1 January 1991 and 7 May 2021 using Medical Subject Headings (MeSH) terms to capture *S aureus*, bacteremia, and mortality (Supplementary Text 2). There were no language restrictions.

Eligibility Criteria

Studies that described human subjects with SAB based on positive blood culture for *S aureus* were included in the review. The studies needed to include 50 or more patients with SAB and report absolute numbers for mortality.

Studies in which SAB patients were only a subgroup (eg, studies of gram-positive bacteremia where a proportion of cases were SAB) typically do not report SAB-specific mortality, so these studies were excluded from the review. In addition, studies that included select SAB cases based on infectious foci (eg, only line-associated SAB) or patient characteristics (eg, only people who inject drugs) would not be representative of the overall prognosis of the SAB patient population, so these studies were also excluded. Case-control studies with cases defined by deaths would have the number of deaths arbitrarily chosen and were thus excluded. Studies that did not report primary data (commentaries, reviews, conference proceedings, study protocols, trial registrations, or secondary analyses of data that have already been published) were also excluded. Studies that excluded early deaths within any time interval would underestimate the true mortality rate, so they were excluded from the review. Studies that included only patients who received an intervention later in the disease course such as definitive antibiotic therapy or peripherally inserted central catheters were excluded, because these studies were assumed to have excluded patients who died too early to receive this intervention.

To be included in this secondary analysis, studies must have reported attributable mortality, that is, the number of deaths attributed to SAB as defined by the study authors. Attributable mortality could not only be based on in-hospital mortality as follow-up length would then vary across patients within the study.

Data Extraction and Items

Using Covidence [9], 2 reviewers (A. D. B., C. K. L. L., A. S. K., M. S., K. G., A. G., P. T., J. S., O. D. C., I. S., E. G. M., M. P. C., or T. C. L.) independently screened the title and abstracts to identify relevant studies for full text review. Similarly, 2 reviewers (A. D. B., C. K. L. L., A. S. K., M. S., K. G., A. G., P. T., J. S., O. D. C., I. S., or C. F.) independently read and extracted the data in duplicate onto a standardized form. Disagreements between reviewers were resolved by discussion to reach consensus. If consensus could not be reached by discussion, a third reviewer provided adjudication.

The data extraction sheet included author names, year of publication, journal, funding, study location, study period, study design, research question, and sample size. For each study, the reviewers extracted data on patient demographics (age, sex, comorbidities), infectious foci, proportion of methicillin-resistant *S aureus* infections, and mortality.

Risk of Bias

Two reviewers independently assessed the risk of bias for included studies using the Newcastle-Ottawa Scale for observational studies (Supplementary Text 3), which includes reporting bias [10]. Publication bias was assessed based on funnel plot for outcomes with more than a single study, where asymmetry was tested using methods as described by Peters et al [11].

Primary Outcome

The primary outcome was the proportion of all-cause deaths that were attributable to SAB at time intervals of 2 weeks, 1 month, 3 months, 6 months, and 1 year. Follow-up lengths of 28 days, 30 days, and 4 weeks were all considered equivalent to 1-month follow-up. Similarly, follow-up lengths of 90 days and 12 weeks were considered equivalent to 3-month follow-up. There was significant clinical heterogeneity in terms of how attributable mortality was defined in each study (Supplementary Table 1) such that a meta-analysis and pooling attributable mortality rates would not be valid. Therefore, only basic descriptive analysis of individual studies was done.

Simulation of Hypothetical Scenarios

We created 2 hypothetical scenarios to illustrate the ability to detect the signal of a mortality benefit for a new treatment at different lengths of follow-up. In the first scenario, we arbitrarily chose the sample size for the treatment and control group. Both groups had the same number of patients. In the control group, we used the attributable and nonattributable mortality rates reported in studies included within this review. The attributable and nonattributable mortality rates at 2 weeks, 1 month, 3 months, 6 months, and 1 year from studies were used to calculate the daily attributable and nonattributable mortality rate from day 0 to 365 in the control group assuming that the daily attributable and nonattributable mortality rates were constant between the interval of 0 to 2 weeks, 2 weeks to 1 month, 1 month to 3 months, 3 months to 6 months, and 6 months to 1 year. Decimals for number of deaths were allowed.

We then stipulated that the new treatment in the treatment group had a true mortality benefit with a relative risk (RR) of 0.75 at any time when compared to the control group with respect to the attributable deaths only. The treatment had no effect on nonattributable deaths. In the treatment group, the rate of nonattributable mortality over time was the same as the control group.

We then compared the all-cause mortality between the control and treatment group to calculate the observed RR at different lengths of follow-up. A 95% confidence interval (CI) was calculated for the RR using methods as described by Morris and Gardner [12]. The observed RR and the 95% CI were then compared to the known true RR of 0.75.

In the second hypothetical scenario, we arbitrarily chose a sample size for 2 trials (A and B) with the same parameters of nonattributable mortality rate, attributable mortality rate, and the RR of 0.75 for the treatment as the first hypothetical scenario. The only difference was that trial A ended follow-up at 3 months and trial B ended follow-up at 1 month. We then compared the point estimate and CI of the RR of treatment group vs control group in terms of all-cause mortality for these 2 trials.

Statistical Analysis

Descriptive analysis included median and interquartile range (IQR) for continuous variables as well as number with frequency for categorical variables. The 95% CI for mortality rate in individual studies was estimated using the Wilson method [13]. All statistical analyses used R version 3.6.3 software.

Certainty Assessment

The *Grading* of Recommendations Assessment, Development, and Evaluation (GRADE) approach specific for prognosis studies was used to assess the certainty for each outcome [14]. Using this approach, certainty of evidence was rated as high, moderate, low, or very low for each outcome after consideration for study design, risk of bias, imprecision, inconsistency, indirectness, and publication bias [14].

RESULTS

Study Characteristics

From the original systematic review, 24 observational cohort studies were ultimately included in this secondary analysis (Figure 1) [15–38]. The excluded studies with reasons for exclusion are listed in Supplementary Table 2. Each study is described in detail in Supplementary Table 3. Of these studies, the

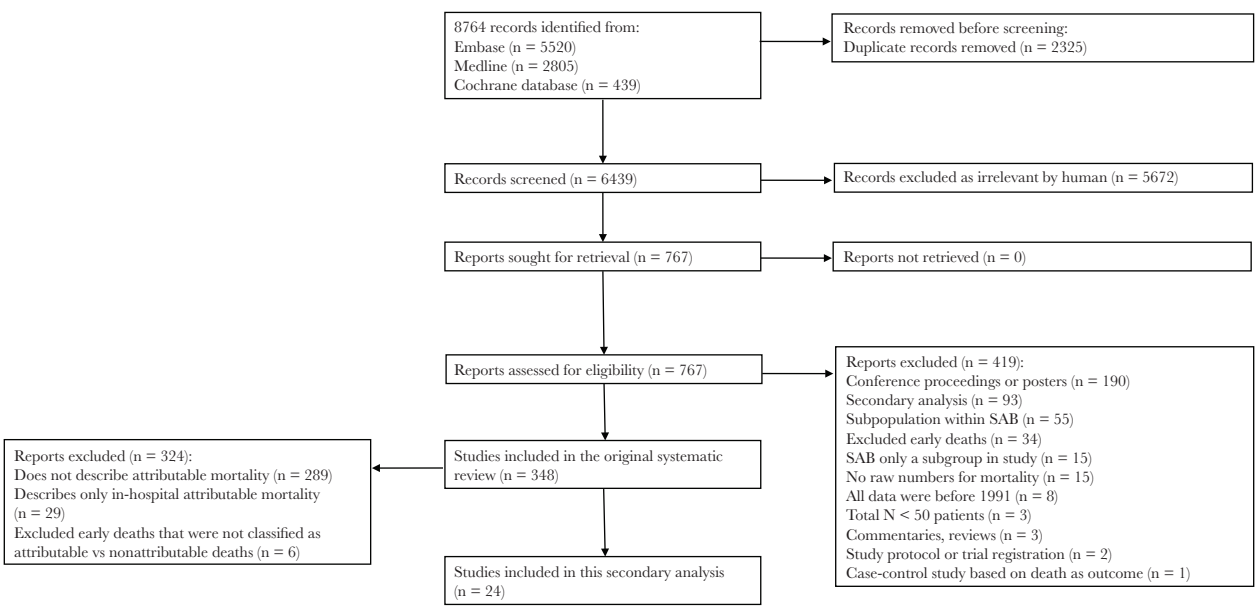

Figure 1. Flow diagram. Abbreviation: SAB, *Staphylococcus aureus* bacteremia.

Table 1. Study Characteristics

Characteristic	No. of Studies (%) N = 24
Total No. of patients in study, median (IQR)	189.5 (98.0–333.75)
Research question	
Basic description of patients	5 (21)
Antibiotic therapy	2 (8)
Vancomycin MIC and outcomes	3 (13)
MRSA vs MSSA	4 (17)
Predictors of mortality	3 (13)
Other	7 (29)
Funding	
Not funded	5 (21)
Research grants	10 (42)
Government	1 (4)
Pharmaceutical industry	1 (4)
Not specified	7 (29)
Center	
Single center	18 (75)
Multicenter	6 (25)
Setting	
Academic and tertiary centers	21 (88)
Academic and community centers	1 (4)
Community centers	0 (0)
Not specified	2 (8)
Continent that the study was conducted in	
North America	4 (17)
Europe	8 (33)
Asia	10 (42)
South America	1 (4)
Africa	1 (4)
Resistance profile	
All SAB (MSSA and MRSA)	15 (63)
MRSA only	6 (25)
MSSA only	3 (13)
Attributable mortality rate reported	
2-week	4 (17)
1-month	12 (50)
3-month	12 (50)
6-month	1 (4)
1-year	1 (4)

Abbreviations: IQR, interquartile range; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; SAB, *Staphylococcus aureus* bacteremia.

most common reported attributable mortality time point was 1 month in 12 (50%) studies and 3 months in 12 (50%) studies (Table 1).

Risk of Bias Assessment

Risk of bias assessment can be found in Supplementary Table 4. Out of a maximum of 9 stars, the median number of stars for all studies was 7 (IQR, 6–8). Funnel plots for 2-week, 1-month, and 3-month attributable mortality are presented in Supplementary Figures 1–3, respectively. Tests for asymmetry were not statistically significant.

Attributable Mortality

The attributable mortality as a proportion of all patients and all-cause deaths are presented in Table 2. At 2 weeks, 98% of all deaths were attributable to SAB in a single study [26]. The median proportion of all-cause deaths that were attributable to SAB was 77% (IQR, 72%–89%) at 1 month and 62% (IQR, 58%–75%) at 3 months. In a single study that provided attributable mortality at 1 year, this proportion was only 57% [18].

Three studies reported attributable mortality at multiple time points [18, 25, 26], such that the increase in attributable mortality relative to all-cause mortality could be examined over time (Table 3). In 2 studies, 2-week follow-up captured 86% (68/79) [25] and 84% (48/57) [26] of all attributable deaths that would have occurred by 3 months. In comparison, 1-month follow-up captured 54 of 57 (95%) [26] and 56 of 60 (93%) [18] attributable deaths that would have occurred by 3 months in 2 studies. One study followed patients at 6 months and 1 year [18]. In this study, 3-month follow-up captured 95% (60/63) of attributable deaths and omitted 27 of 47 (57%) nonattributable deaths that would have occurred by 1 year [18].

Certainty Assessment

Certainty assessment using the GRADE approach is presented in Supplementary Table 5. The certainty for the estimate of attributable mortality was moderate at 2-week follow-up and low for 1-month, 3-month, 6-month, and 1-year follow-up.

Notable Excluded Studies

There were 2 RCTs that described attributable mortality [39, 40]. However, both trials were excluded from this review because they excluded early deaths. In the trial by Cheng et al, 32 patients who were moribund, palliative, or dead at screening were excluded [39]. For patients who were included in the study, the 3-month all-cause mortality was 19 of 104 (18%) [39]. Of the 19 deaths at 3 months, 7 of 19 (37%) were attributable to SAB [39]. The trial by Thwaites et al excluded 49 patients who died before they could be randomized [40]. For patients included in the study, the 3-month all-cause mortality was 112 of 758 (15%) [40]. Of the 109 reported deaths, 68 (62%) deaths were attributable to SAB [40].

Hypothetical Scenarios

Figure 2 illustrates the first hypothetical scenario of an RCT of 1000 patients with SAB in the treatment and control group. In the control group, the rate of attributable and nonattributable mortality over time is the same as the rates described in Kim et al [26] for 2 weeks and Eskesen et al [18] for 1 month, 3 months, 6 months, and 1 year. In the treatment group, the treatment has a true mortality benefit with an RR of 0.75. Therefore, the attributable deaths will be lowered by an RR of 0.75 in the treatment group compared to the control group, whereas the

Table 2. Attributable Relative to All-Cause Mortality

Time Point	Study	MRSA or MSSA	Attributable Deaths/Total No. of Patients in the Study		Attributable Deaths/All-Cause Deaths	
			No.	% (95% CI)	No.	% (95% CI)
2-week	Kim 2006 [25]	All SAB	68/238	28.6% (23.2%–34.6%)	…	…
	Lin 2004 [29]	All SAB	22/86	25.6% (17.5%–35.7%)	…	…
	Talon 2002 [37]	All SAB	27/99	27.3% (19.5%–36.8%)	…	…
	Kim 2008 [26]	MSSA	48/294	16.3% (12.5%–20.9%)	48/49	98.0% (89.3%–99.6%)
1-month	Eskesen 2018 [18]	All SAB	56/303	18.5% (14.5%–23.2%)	56/63	88.9% (78.8%–94.5%)
	Guembe 2018 [21]	All SAB	55/485	11.3% (8.8%–14.5%)	…	…
	Kang 2018 [23]	All SAB	423/1974	21.4% (19.7%–23.3%)	…	…
	Kim 2020 [24]	All SAB	10/59	16.9% (9.5%–28.5%)	…	…
	Kim 2003 [27]	All SAB	79/238	33.2% (27.5%–39.4%)	…	…
	Park 2019 [31]	All SAB	24/152	15.8% (10.9%–22.4%)	24/26	92.3% (75.9%–97.9%)
	Seas 2018 [33]	All SAB	126/675	18.7% (15.9%–21.8%)	126/255	49.4% (43.3%–55.5%)
	Forstner 2013 [19]	MRSA	29/124	23.4% (16.8%–31.6%)	29/38	76.3% (60.8%–87.0%)
	Jang 2012 [22]	MRSA	76/303	25.1% (20.5%–30.3%)	76/98	77.6% (68.3%–84.7%)
	Park 2013 [32]	MRSA	13/94	13.8% (8.3%–22.2%)	13/21	61.9% (40.9%–79.3%)
	Soriano 2008 [35]	MRSA	88/414	21.3% (17.6%–25.5%)	88/116	75.9% (67.3%–82.7%)
	Kim 2008 [26]	MSSA	54/294	18.4% (14.4%–23.2%)	54/58	93.1% (83.6%–97.3%)
3-month	Eskesen 2018 [18]	All SAB	60/303	19.8% (15.7%–24.7%)	60/80	75.0% (64.5%–83.2%)
	Fowler 2003 [20]	All SAB	86/722	11.9% (9.8%–14.5%)	86/157	54.8% (47.0%–62.4%)
	Kim 2006 [25]	All SAB	79/238	33.2% (27.5%–39.4%)	79/103	76.7% (67.7%–83.8%)
	Lesens 2004 [28]	All SAB	21/104	20.2% (13.6%–28.9%)	21/35	60.0% (43.6%–74.5%)
	Nickerson 2009 [30]	All SAB	43/98	43.9% (34.5%–53.8%)	43/51	84.3% (72.0%–91.8%)
	Steinhaus 2018 [36]	All SAB	30/100	30.0% (21.9%–39.6%)	30/47	63.8% (49.5%–76.0%)
	Shurland 2007 [34]	All SAB	114/438	26.0% (22.1%–30.3%)	114/250	45.6% (39.5%–51.8%)
	Beeston 2009 [15]	MRSA	24/62	38.7% (27.6%–51.2%)	24/30	80.0% (62.7%–90.5%)
	Dupper 2019 [17]	MRSA	33/227	14.5% (10.5%–19.7%)	33/61	54.1% (41.7%–66.0%)
	Kim 2008 [26]	MSSA	57/294	19.4% (15.3%–24.3%)	57/76	75.0% (64.2%–83.4%)
	Chia 2008 [16]	MSSA	11/100	11.0% (6.3%–18.6%)	11/18	61.1% (38.6%–79.7%)
	Verhagen 2003 [38]	MSSA	10/75	13.3% (7.4%–22.8%)	10/17	58.8% (36.0%–78.4%)
6-month	Eskesen 2018 [18]	All SAB	62/303	20.5% (16.3%–25.4%)	62/94	66.0% (55.9%–74.7%)
1-year	Eskesen 2018 [18]	All SAB	63/303	20.8% (16.6%–25.7%)	63/110	57.3% (47.9%–66.1%)

Abbreviations: CI, confidence interval; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; SAB, *Staphylococcus aureus* bacteremia.

nonattributable death rate will be the same in both groups. Figure 2D illustrates the observed RR when the follow-up cutoff increases up to 1 year. At the end of 1 year, the observed RR would be 0.86 with a 95% CI that excludes the true RR of 0.75, because the increase in nonattributable deaths that is identical between the 2 groups pushes the RR toward the null.

The second hypothetical scenario uses the same parameters for rate of attributable deaths, rate of nonattributable deaths, and a true RR of 0.75 for the treatment as the first scenario. In this second scenario, consider 2 trials, A and B (Supplementary Table 6). In trial A, the trialist chooses to follow 550 patients in each arm for 3 months. In this trial, the observed RR for all-cause mortality at the end of follow-up is 0.813 (95% CI, .657–1.005). In trial B, the trialist chooses to follow 550 patients in each arm for 1 month only. The observed RR is 0.778 with 95% CI of .605 to .999. Both trials have the same number of patients. Technically, trial A should have more power, because it has more events during the longer follow-up. However, trial B with the shorter follow-up has an RR that is closer to the truth and a CI that excludes 1. This is because extending the follow-up from 1 to 3 months captures mainly nonattributable deaths that occur at the same rate in both groups, which biases the estimated RR toward the null.

DISCUSSION

In this secondary analysis of our systematic review on SAB, we found that the proportion of all deaths that were attributable to SAB became lower as length of follow-up increased. Follow-up at 2 weeks was not long enough to adequately capture deaths attributable to SAB, as approximately 1 in 6 attributable deaths by 3 months would be missed. At 3-month follow-up, the median percentage of deaths attributable to SAB was only around 60%. In a single study, 3-month follow-up captured 95% of attributable deaths while omitting 37% of the nonattributable deaths that would have occurred by 1 year. Therefore, extending follow-up beyond 3 months is unlikely to add useful information on mortality related to SAB. Extending follow-up from 1 to 3 months only added a few attributable deaths while the proportion of deaths that were attributable to SAB dropped from

Table 3. Attributable and All-Cause Mortality Over Time for Longitudinal Studies

	Kim 2006 [25] All SAB	Kim 2008 [26] MSSA	Eskesen 2018 [18] All SAB
Mortality	No. (%) (95% CI)	No. (%) (95% CI)	No. (%) (95% CI)
Attributable deaths			
2-week	68/238 (28.6%) (23.2%–34.6%)	48/294 (16.3%) (12.5%–21.0%)	…
1-month	…	54/294 (18.4%) (14.4%–23.2%)	56/303 (18.5%) (14.5%–23.2%)
3-month	79/238 (33.2%) (27.5%–39.4%)	57/294 (19.4%) (15.3%–24.3%)	60/303 (19.8%) (15.7%–24.7%)
6-month	…	…	62/303 (20.5%) (16.3%–25.4%)
1-year	…	…	63/303 (20.8%) (16.6%–25.7%)
All-cause deaths			
2-week	…	49/294 (16.7%) (12.8%–21.4%)	…
1-month	…	58/294 (19.7%) 15.6%–24.7%	63/303 (20.8%) (16.6%–25.7%)
3-month	103/238 (43.3%) (37.1%–49.6%)	76/294 (25.9%) (21.2%–31.1%)	80/303 (26.4%) (21.8%–31.6%)
6-month	…	…	94/303 (31.0%) (26.1%–36.4%)
1-year	…	…	110/303 (36.3%) (31.1%–41.9%)
Attributable/all-cause deaths			
2-week	…	48/49 (98.0%) 89.3%–99.6%	…
1-month	…	54/58 (93.1%) (83.6%–97.3%)	56/63 (88.9%) (78.8%–94.5%)
3-month	79/103 (76.7%) (67.7%–83.8%)	57/76 (75.0%) (64.2%–83.4%)	60/80 (75.0%) (64.5%–83.2%)
6-month	…	…	62/94 (66.0%) (55.9%–74.7%)
1-year	…	…	63/110 (57.3%) (47.9%–66.1%)

Abbreviations: CI, confidence interval; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; SAB, *Staphylococcus aureus* bacteremia.

a median of 77% to 62%. As illustrated by our hypothetical scenarios, 1-month follow-up is likely the most efficient as it captures most attributable deaths while reducing confounding due to other competing causes of mortality.

To our knowledge, this is the first systematic review on attributable mortality in SAB. A prior narrative review focused on all-cause mortality and predictors of mortality [2] instead of attributable mortality. Studies that report attributable mortality differ in the length of follow-up used, so it is difficult to assess the trend and differences by reading each individual study. This systematic review summarizes and organizes the attributable mortality by length of follow-up to present a comprehensive picture of change in attributable mortality over time.

These study findings have implications for future research studies on SAB, particularly RCTs related to the treatment of the first episode. The decrease in the proportion of all-cause deaths that are attributable to SAB as follow-up lengthens demonstrates that deaths occurring early and late in the follow-up period are not the same. Most attributable deaths occur early, so early events give the most useful information to detect a signal that an intervention provides a mortality benefit. In contrast, most nonattributable deaths occur later, so later events provide less useful information as it is more likely to be noise as illustrated by Figure 2. Moving forward, the length of follow-up for all-cause mortality should be standardized across studies to make mortality results comparable. Based on this exploratory analysis, the recommended follow-up length should be between 1 and 3 months. Our hypothetical scenario of the 2 trials illustrates that 1-month follow-up may be slightly better than 3-month follow-up because it excludes many nonattributable deaths occurring beyond 1 month that would bias the results toward the null. Therefore, to increase power (ie, number of deaths), it is better to increase sample size with 1 month follow-up than to extend follow-up from 1 to 3 months. Pragmatically, shorter follow-up also saves time, effort, and cost while minimizing loss to follow-up. For these reasons, we prefer 1-month follow-up over 3-month follow-up for all-cause mortality as a primary outcome.

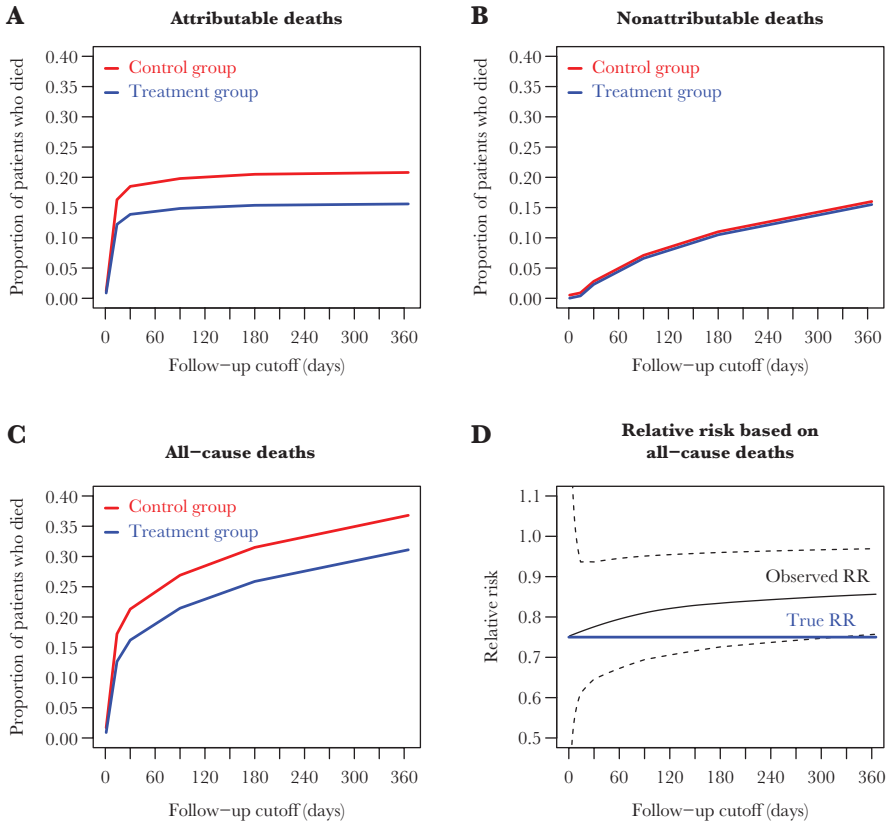

Figure 2. Hypothetical scenario illustrating how nonattributable deaths skew relative risk (RR) of all-cause mortality toward the null over time. *A*, Attributable deaths. *B*, Nonattributable deaths. *C*, All-cause deaths (sum of attributable deaths in *A* and nonattributable deaths in *B*). *D*, Relative risk based on all-cause deaths. Dotted lines represent the 95% confidence interval for the observed RR. The true RR refers to attributable deaths whereas the observed RR refers to all-cause deaths.

It should be noted that our recommended follow-up duration was meant for all-cause mortality only and does not apply to other outcomes in SAB. As an example, relapse of bacteremia as an outcome likely would require longer follow-up as the median time to relapse was 32 days following end of treatment in a study [41]. Similarly, metastatic foci occur later in complicated SAB, so morbidity from metastatic infectious foci may require a longer follow-up period for better characterization. Metastatic foci leading to death would still be considered attributable to SAB based on the definitions used in many studies included within our review, because any death with persistent symptoms/signs of ongoing infection or without any other definitive causes was considered attributable to SAB in most studies (Supplementary Table 1). Interestingly, the fact that there was minimal increase in attributable deaths beyond 30 days suggests that most deaths due to metastatic foci would have occurred by day 30.

There are several limitations to this study. There is significant clinical heterogeneity in the definition of what is considered an attributable death across studies, preventing pooling of the estimates. Unlike all-cause mortality, attributable deaths always require interpretation, which increases the risk for ascertainment bias. Furthermore, misclassification of attributable and nonattributable deaths may increase with longer follow-up period in studies. It is possible that the frequency and thoroughness of clinical monitoring decreases with longer follow-up, especially after hospital discharge, so it would be more difficult to ascertain the exact cause of death in longer follow-up. This could underestimate the proportion of attributable mortality later in the disease course. However, acceptable alternatives to determine attributable mortality do not exist. While imperfect, attributable mortality is still clinically important and should not be disregarded while acknowledging these flaws. The certainty for each outcome was appropriately moderate to low based on the GRADE approach. As a result of these limitations, our exploratory analysis should be interpreted with caution. That said, we are not proposing to use attributable mortality as a primary outcome, but rather to keep all-cause mortality as the primary outcome as it is not subject to ascertainment bias and to reduce the timeframe of follow-up to a duration that captures mostly attributable deaths.

There is a lack of rigorously conducted large studies on attributable mortality in SAB. For future studies, we recommend a blinded assessor to determine attributable deaths based on specific criteria that are consistently applied to all patients. Autopsy should be incorporated in the criteria where feasible for better validity. As well, future studies should report both the attributable and all-cause mortality at multiple time points such as at 2

weeks, 1 month, and 3 months to better characterize the changing rate of attributable and nonattributable deaths over time. From this information, the optimal follow-up duration can be further refined.

The general teaching in trial design has been that it is always better to have longer follow-up to collect more events and increase power. In this paper, we are arguing that this is not necessarily the case when examining the impact of early interventions on mortality in SAB as longer follow-up can introduce more noise and risks obscuring the signal. A proposal that 1-month follow-up may be better than 3-month follow-up for mortality in SAB may be controversial to many. We hope that this work will spark further discussions and efforts toward standardizing outcome measurement in SAB among researchers. The same principles likely apply to other acute infections where most of the attributable risk of death is upfront, and we look forward to discourse in this area as well.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. Conception and design: A. D. B., A. M. M., M. L., T. C. L. Abstract screening and data extraction: A. D. B., C. K. L. L., A. S. K., M. S., K. G., A. G., P. T., J. S., O. D. C., I. S., C. F., E. G. M., M. P. C., T. C. L. Data analysis: A. D. B., G. B.-L. Writing of the article: A. D. B. Revision of the manuscript: A. D. B., C. K. L. L., A. S. K., M. S., K. G., A. G., P. T., J. S., O. D. C., I. S., C. F., G. B.-L., E. G. M., M. P. C., A. M. M., M. L., T. C. L.

Acknowledgments. The authors thank Neera Bhatnagar for her guidance on search strategy.

Data sharing. The study protocol, data set, and statistical analysis R code are available upon request from the corresponding author (tony.bai@queensu.ca).

Disclaimer. The funding body had no role in the design of the study, data collection, analysis, interpretation of data, or writing of the manuscript.

Financial support. This project was supported by the McMaster Medicine Specialty Resident and Fellows Research Grant.

Potential conflicts of interest. M. P. C. reports grants from the McGill Interdisciplinary Initiative in Infection and Immunity and the Canadian Institutes of Health Research during the conduct of the study; has received personal fees from GEn1E Lifesciences and nplex biosciences for scientific advisory board membership, outside the submitted work; is the co-founder of Kanvas Biosciences and owns equity in the company; and has patents pending (Methods for detecting tissue damage, graft versus host disease, and infections using cell-free DNA profiling; and Methods for assessing the severity and progression of SARS-CoV-2 infections using cell-free DNA). T. C. L. and E. G. M. receive research salary support from the Fonds de recherche du Québec–Santé. M. L. has served on advisory boards for Sanofi, Pfizer, Medicago, Merck, Seqirus, and Paladin Labs; and data safety and monitoring committees for Medicago, CanSino Biologics, the National Institutes of Health, and the World Health Organization Essential Medicines List Antibiotic Working Group.

References

1. Holland TL, Arnold C, Fowler VG. Clinical management of *Staphylococcus aureus* bacteremia: a review. JAMA **2014**; 312:1330–41.
2. Van Hal SJ, Jensen SO, Vaska VL, Espedido BA, Paterson DL, Gosbell IB. Predictors of mortality in *Staphylococcus aureus* bacteremia. Clin Microbiol Rev **2012**; 25:362–86.
3. Shime N, Kosaka T, Fujita N. The importance of a judicious and early empiric choice of antimicrobial for methicillin-resistant *Staphylococcus aureus* bacteraemia. Eur J Clin Microbiol Infect Dis **2010**; 29:1475–9.
4. Lesens O, Brannigan E, Bergin C, Christmann D, Hansmann Y. Impact of the use of aminoglycosides in combination antibiotic therapy on septic shock and mortality due to *Staphylococcus aureus* bacteremia. Eur J Intern Med **2006**; 17:276–80.
5. Asgeirsson H, Gudlaugsson O, Kristinsson KG, Heiddal S, Kristjansson M. *Staphylococcus aureus* bacteraemia in Iceland, 1995-2008: changing incidence and mortality. Clin Microbiol Infect **2011**; 17:513–8.
6. Yahav D, Yassin S, Shaked H, et al. Risk factors for long-term mortality of *Staphylococcus aureus* bacteremia. Eur J Clin Microbiol Infect Dis **2016**; 35:785–90.
7. Bai AD, Lo CKL, Komorowski AS, et al. Staphylococcus aureus bacteremia mortality: a systematic review and meta-analysis. Clin Microbiol Infect **In press**.
8. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ **2021**; 372:n71.
9. Covidence. Covidence: better systematic review management. **2021**. https://www.covidence.org/about-us/. Accessed 1 November 2021.
10. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. **2013**. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed 1 November 2021.
11. Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Comparison of two methods to detect publication bias in meta-analysis. JAMA **2006**; 295:676–80.
12. Morris JA, Gardner MJ. Calculating confidence intervals for relative risks (odds ratios) and standardised ratios and rates. Br Med J (Clin Res Ed) **1988**; 296:1313–6.
13. Wilson EB. Probable inference, the law of succession, and statistical inference. J Am Stat Assoc **1927**; 22:209–12.
14. Iorio A, Spencer FA, Falavigna M, et al. Use of GRADE for assessment of evidence about prognosis: rating confidence in estimates of event rates in broad categories of patients. BMJ **2015**; 350:h870.
15. Beeston CJ, Gupta R, Chadwick PR, Young RJ. Methicillin-resistant *Staphylococcus aureus* bacteraemia and mortality in a teaching hospital. Eur J Clin Microbiol Infect Dis **2009**; 28:585–90.
16. Chia JW, Hsu LY, Chai LY, Tambyah PA. Epidemiology and outcomes of community-onset methicillin-susceptible *Staphylococcus aureus* bacteraemia in a university hospital in Singapore. BMC Infect Dis **2008**; 8:14.
17. Dupper AC, Sullivan MJ, Chacko KI, et al. Blurred molecular epidemiological lines between the two dominant methicillin-resistant *Staphylococcus aureus* clones. Open Forum Infect Dis **2019**; 6:ofz302.
18. Eskesen AN, Belle MA, Blomfeldt A. Predictors of one-year all-cause mortality and infection-related mortality in patients with *Staphylococcus aureus* bacteraemia. Infect Dis (Lond) **2018**; 50:743–8.
19. Forstner C, Dungl C, Tobudic S, Mitteregger D, Lagler H, Burgmann H. Predictors of clinical and microbiological treatment failure in patients with methicillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia: a retrospective cohort study in a region with low MRSA prevalence. Clin Microbiol Infect **2013**; 19:E291–7.
20. Fowler VG Jr, Olsen MK, Corey GR, et al. Clinical identifiers of complicated *Staphylococcus aureus* bacteremia. Arch Intern Med **2003**; 163:2066–72.
21. Guembe M, Alonso B, Lucio J, et al. Biofilm production is not associated with poor clinical outcome in 485 patients with *Staphylococcus aureus* bacteraemia. Clin Microbiol Infect **2018**; 24:659.e1–3.
22. Jang HC, Kang SJ, Choi SM, et al. Difference in agr dysfunction and reduced vancomycin susceptibility between MRSA bacteremia involving SCCmec types IV/IVa and I-III. PLoS One **2012**; 7:e49136.
23. Kang CK, Kwak YG, Park Y, et al; Korea INfectious Diseases (KIND) Study Group. Gender affects prognosis of methicillin-resistant *Staphylococcus aureus* bacteremia differently depending on the severity of underlying disease. Eur J Clin Microbiol Infect Dis **2018**; 37:1119–23.
24. Kim NH, Sung JY, Choi YJ, et al. Toll-like receptor 2 downregulation and cytokine dysregulation predict mortality in patients with *Staphylococcus aureus* bacteremia. BMC Infect Dis **2020**; 20:901.
25. Kim SH, Park WB, Lee CS, et al. Outcome of inappropriate empirical antibiotic therapy in patients with *Staphylococcus aureus* bacteraemia: analytical strategy using propensity scores. Clin Microbiol Infect **2006**; 12:13–21.
26. Kim SH, Kim KH, Kim HB, et al. Outcome of vancomycin treatment in patients with methicillin-susceptible *Staphylococcus aureus* bacteremia. Antimicrob Agents Chemother **2008**; 52:192–7.
27. Kim SH, Park WB, Lee KD, et al. Outcome of *Staphylococcus aureus* bacteremia in patients with eradicable foci versus noneradicable foci. Clin Infect Dis **2003**; 37:794–9.

28. Lesens O, Hansmann Y, Brannigan E, et al. Positive surveillance blood culture is a predictive factor for secondary metastatic infection in patients with *Staphylococcus aureus* bacteraemia. J Infect **2004**; 48:245–52.
29. Lin JC, Yeh KM, Peng MY, Chang FY. Community-acquired methicillin-resistant *Staphylococcus aureus* bacteremia in Taiwan: risk factors for acquisition, clinical features and outcome. J Microbiol Immunol Infect **2004**; 37:24–8.
30. Nickerson EK, Hongsuwan M, Limmathurotsakul D, et al. *Staphylococcus aureus* bacteraemia in a tropical setting: patient outcome and impact of antibiotic resistance. PLoS One **2009**; 4:e4308.
31. Park KH, Greenwood-Quaintance KE, Cunningham SA, et al. Lack of correlation of virulence gene profiles of *Staphylococcus aureus* bacteremia isolates with mortality. Microb Pathog **2019**; 133:103543.
32. Park SY, Oh IH, Lee HJ, et al. Impact of reduced vancomycin MIC on clinical outcomes of methicillin-resistant *Staphylococcus aureus* bacteremia. Antimicrob Agents Chemother **2013**; 57:5536–42.
33. Seas C, Garcia C, Salles MJ, et al; Latin America Working Group on Bacterial Resistance. *Staphylococcus aureus* bloodstream infections in Latin America: results of a multinational prospective cohort study. J Antimicrob Chemother **2018**; 73:212–22.
34. Shurland S, Zhan M, Bradham DD, Roghmann MC. Comparison of mortality risk associated with bacteremia due to methicillin-resistant and methicillin-susceptible *Staphylococcus aureus*. Infect Control Hosp Epidemiol **2007**; 28:273–9.
35. Soriano A, Marco F, Martínez JA, et al. Influence of vancomycin minimum inhibitory concentration on the treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. Clin Infect Dis **2008**; 46:193–200.
36. Steinhaus N, Al-Talib M, Ive P, et al. The management and outcomes of *Staphylococcus aureus* bacteraemia at a South African referral hospital: a prospective observational study. Int J Infect Dis **2018**; 73:78–84.
37. Talon D, Woronoff-Lemsi MC, Limat S, et al. The impact of resistance to methicillin in *Staphylococcus aureus* bacteremia on mortality. Eur J Intern Med **2002**; 13:31–6.
38. Verhagen DW, van der Meer JT, Hamming T, de Jong MD, Speelman P. Management of patients with *Staphylococcus aureus* bacteraemia in a university hospital: a retrospective study. Scand J Infect Dis **2003**; 35:459–63.
39. Cheng MP, Lawandi A, Butler-Laporte G, De l'Étoile-Morel S, Paquette K, Lee TC. Adjunctive daptomycin in the treatment of methicillin-susceptible *Staphylococcus aureus* bacteremia: a randomized, controlled trial. Clin Infect Dis **2021**; 72:e196–203.
40. Thwaites GE, Scarborough M, Szubert A, et al. Adjunctive rifampicin for *Staphylococcus aureus* bacteraemia (ARREST): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet **2018**; 391:668–78.
41. Chang FY, MacDonald BB, Peacock JE Jr, et al. A prospective multicenter study of *Staphylococcus aureus* bacteremia: incidence of endocarditis, risk factors for mortality, and clinical impact of methicillin resistance. Medicine (Baltim) **2003**; 82:322–32.