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Estimating attributable fraction of mortality from sepsis to inform clinical trials

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ABSTRACT

Purpose: Nearly all sepsis trials report no statistically significant difference in mortality. The attributable fraction of deaths due to sepsis (AFsepsis) may be an important, yet overlooked consideration. We derived AFsepsis and explored the effect of incorporating AFsepsis into sample size calculations.
Materials and methods: We derived AFsepsis with a matched cohort study using consecutive admissions to adult general intensive care units (ICUs) in England (n = 614,509). Cases were ICU patients with sepsis and the two controls were ICU-non-sepsis controls, matched for propensity to have sepsis and age-sex-matched general population. The primary exposure was sepsis. The primary outcome was hospital mortality. We generated sample size graphs, by varying control group mortality (10%–60%), relative risk reduction (0–1), for 80% power and 5% alpha. We then compared AFsepsis derived sample sizes with sample size calculations from published sepsis trials.
Results: AFsepsis was 15% (95% CI: 14%–16%) compared with propensity matched ICU-non-sepsis controls and 93% (95% CI: 92%–93%) compared with age-sex-matched general population controls. When comparing AFsepsis derived sample sizes with sample size calculations from 18 trials meeting our selection criteria, these calculations assumed very high AFsepsis and/or very effective treatments.
Conclusions: Estimating trial specific AFsepsis to inform sample size calculations could be an additional step in sepsis trial design.

1. Introduction

Sepsis [1] is common and is associated with a hospital mortality of 18% to 33% [2]. Numerous sepsis randomized clinical trials (RCTs) that do not demonstrate a statistically significant difference in the primary end point [3] may be explained by treatment response variations seen within trial populations [4-7] and differences in sepsis pathobiology [3,8]. In addition to identifying novel, more effective therapies, there may be opportunities during design to improve the sensitivity of RCTs [9]. These trial design modifications have generally focused on enrolling sepsis patients at high risk of death, accounting for risk of death in the analysis, excluding patients with, for example, cancer or cirrhosis, whose risk of death is due to their comorbidity, or enriching the population with patients susceptible to the intervention based on its mechanism [6,9].

In this paper, we present a novel analysis of sepsis RCTs using the attributable fraction of deaths due to sepsis (AFsepsis) approach [10,11]. The hypothesis is that risk factors for sepsis including age, sex and comorbidities are also risk factors for death in critically ill patients regardless of the aetiology of their critical illness. If only deaths in the attributable fraction are preventable with a sepsis therapy and this fraction is <100%, larger sample sizes may be needed to detect plausible treatment effects.

2. Materials and methods

2.1. Conceptual approach

The interventions tested in sepsis RCTs are developed based on dominant biological pathways observed in sepsis [3]. The interventions' ability to reduce risk of death is defined using either absolute or relative risk reduction (RRR). The standard approach for sample size estimation in

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RCTs assumes a RRR across 100% of deaths with the disease. If the control group mortality in a sepsis RCT is 40% and we expect the drug to have 20% RRR, then treated patients will have a mortality of 32% and 564 patients per group would be required with typical assumptions of 80% power and 5% alpha to detect this effect. The AFsepsis approach explores the possibility that, for illustration, only 50% of deaths are attributable to sepsis and assumes that only these deaths are affected by treatments for sepsis and that there are no placebo responders [10]. If the RRR of 20% applies only to the attributable deaths, the *effective RRR* would reduce to 10% and will require 2311 patients per group in this RCT. After empiric estimation of AFsepsis, we compared the sample size estimates between the standard and the AFsepsis approach across a range of AFsepsis, control group mortalities and treatment effectiveness amongst attributable deaths (effective RRR) using examples from published sepsis RCTs [12,13]. Although intuitive and often discussed, the attributable mortality from sepsis-related critical illness has not been estimated for Sepsis-3 criteria [1,14], while attributable mortality and morbidity estimates from ICU acquired infections highlight that these may be quite low [15-17].

2.2. Study design and data source

We performed a matched cohort study with cases that met *Sepsis-3* criteria [1] (eTable 1 [18]) and controls that were either non-septic critically ill patients or general population to estimate the range of AFsepsis. For sepsis cases and non-septic critically ill controls, we used the Intensive Care National Audit & Research Centre (ICNARC) Case Mix Programme Database (CMPD) [19] (Further details are reported in eMethods).

2.2.1. Rationale for controls

Estimating the attributable risk of sepsis requires careful selection of controls and attention to confounding variables. We attempted to estimate the bounds of AFsepsis and AFseptic shock by using general population and non-septic critically ill controls. Population controls will estimate the upper bound of the AFsepsis as they reflect the best-case scenario that a treatment returns patients admitted to the ICU with sepsis to the mortality that patients of similar age and sex would incur. Since unmeasured risk factors for sepsis in the population are also predictors of mortality [20], this assumption is optimistic. The non-septic critically ill controls will estimate the lower bound of the AFsepsis as they reflect a worst-case scenario that a treatment returns patients admitted to the ICU with sepsis to the mortality that non-septic *critically ill* patients of similar age, sex, comorbidity and surgical status would incur. Since non-septic critically ill controls incur mortality risk for unique reasons due to their reason for ICU admission and severity of illness, this estimate of AFsepsis is likely to be an under-estimate. Therefore, while it is unknown whether an effective sepsis therapy will return patients to a mortality trajectory similar to the population at large or to a general ICU population, we believe that the AFsepsis likely falls in this range. This approach to estimate bounds of AFsepsis is similar to that used for estimating the magnitude of cardiovascular events in sepsis survivors [21].

2.3. Analyses

The primary exposure was sepsis. The primary outcome was acute hospital mortality. All analyses presented as 'sepsis' included the subpopulation with septic shock. In Sepsis-3 definitions, as septic shock is considered a subset of sepsis with greater risk of death than sepsis alone [14], we replicated all the analyses for this subpopulation. Amongst the 654,918 ICU admissions, we excluded patients with readmissions (0.05%), patients with missing data on acute illness severity (3.9%), and acute hospital mortality (0.3%), resulting in a cohort of 614,509 ICU admissions for complete case analyses (eFig. 1).

2.3.1. Estimating AFsepsis and rationale for propensity matching

Propensity-score methods can be used in a matched cohort study design, to estimate the causal effects of sepsis by balancing sepsis and non-septic controls on a set of observed baseline covariates [11,22]. To estimate the mortality of non-septic critically ill patients we identified a population similar to sepsis based on a propensity model with age,

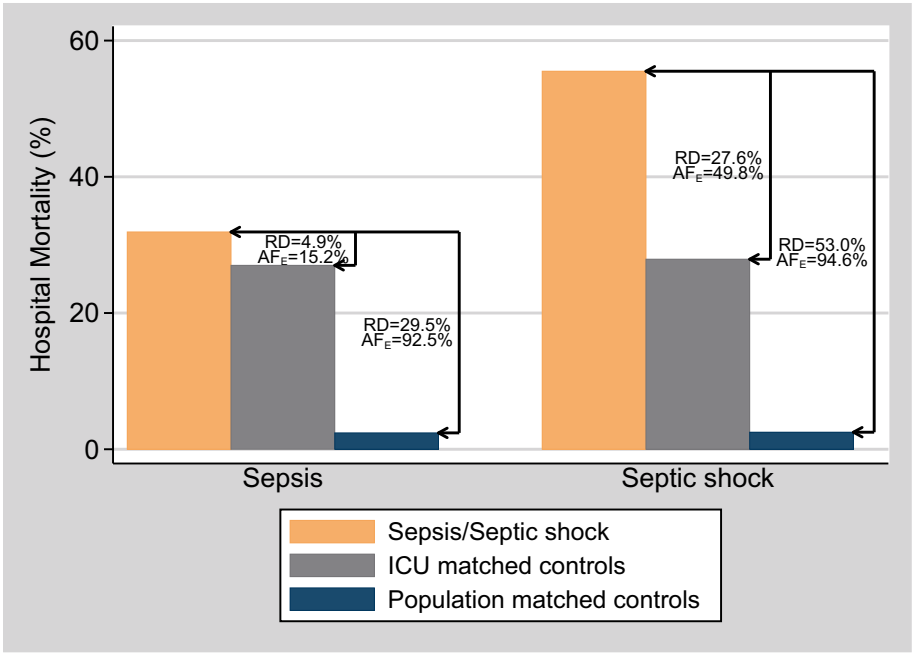


Fig. 1. Range of AFsepsis estimated using control populations. The fraction of deaths attributable to the sepsis exposure (AFsepsis) = [(Deaths in sepsis − Deaths in non-sepsis) / Deaths in sepsis] ascertained using proportions. Propensity for sepsis logistic regression models [22] can be used to derive AFsepsis and AFseptic shock. Bar graphs show the mortality difference between sepsis/septic shock compared first to propensity matched ICU-non-sepsis controls and second to age-sex matched general population controls. AF_E = AFsepsis and AFseptic shock respectively; RD = risk difference. Further details of study population and propensity models are provided in Table 1. Model-1 represents propensity model for sepsis. Model-2 represents propensity model for septic shock.

sex, severe comorbidity defined using Acute Physiology And Chronic Health Evaluation (APACHE II method), and surgical status, assuming AFsepsis is constant across different baseline risks [10,11]. Since the overall goal was to estimate the independent risk of death attributable to sepsis, we did not incorporate acute physiologic derangement which likely mediates the effects of sepsis on hospital mortality. Further details of propensity methods and rationale for sensitivity analysis to estimate AFsepsis and AFseptic shock are reported in e-methods.

For population controls, age- and sex-specific expected probabilities of death for the general population of England in 2014 were obtained from the Office for National Statistics [23]. We used the shortest timeframe available, one-year risk of death, to estimate the hospital mortality that could be expected by a treatment that reduced AFsepsis to age- and sex-matched population norms.

2.3.2. Comparing AFsepsis based sample size estimates to standard approach

In sepsis RCTs, as all patients have the exposure sepsis, AFsepsis could be used for sample size estimations [10]. We derived sample sizes for the estimated range of AFsepsis [10], by varying the expected control group mortality between 10% and 60%, the effective RRR between 0 and 1, for typical assumptions of 80% power, 5% alpha and their corresponding constants from normal distribution.

For illustrating how change in AFsepsis within a trial population could influence power and sample size calculation of trials, we identified parallel group sepsis RCTs, published since 2007, testing a single intervention, with mortality as the primary outcome and included in two recent meta-analyses [12,13]. We chose parallel group RCTs, as there are additional assumptions involved in other RCT designs for sample size calculations [24]. We explored patters of inclusion and exclusion criteria used in these RCTs. We then extracted control group mortality, RRR, power and alpha that informed standard sample size calculations from these RCTs for exploring the impact of AFsepsis estimations. If trials used absolute risk reduction, then the corresponding RRR was derived.

Reported p values are two-sided and p values < 0.05 were considered statistically significant. All analyses were performed using Stata/SE version 14 (StataCorp LP, College Station, TX).

3. Results

3.1. Patient characteristics

Amongst 614,509 ICU admissions with 179,717 sepsis and 36,838 septic shock cases, we matched 179,704 sepsis and 36,833 septic shock cases to ICU-non-sepsis controls, propensity score balanced on age, sex, severe comorbidity and surgical status. Sepsis patients had a greater risk of death compared to propensity matched non-sepsis ICU controls (hospital mortality 32% vs 27%; risk ratio 1.18; 95% CI (1.17%–1.19%); p < 0.001). Similarly, septic shock patients had a greater risk of death compared to propensity matched non-sepsis ICU controls (hospital mortality 56% vs 28%; risk ratio 1.99; 95% CI (1.95–2.03); p < 0.001) (Fig. 1 and Table 1).

3.2. Range of AFsepsis and AFseptic shock

Using ICU-non-sepsis controls, AFsepsis was 15.2% (95% CI 14.4%–16.1%) and AFseptic shock was 49.8% (95% CI 48.8%–50.7%). Compared with age- and sex-matched general population controls, AFsepsis was 92.5% (95% CI 92.3%–92.7%) and AFseptic shock was 94.6% (95% CI 94.3%–94.9%) (Fig. 1).

Sepsis patients without comorbidities had a greater risk of death compared to propensity matched non-sepsis ICU controls without comorbidities (hospital mortality 29% vs 24%; risk ratio 1.18; 95% CI (1.16–1.19); p < 0.001) and the AFsepsis was similar to the overall

Table 1
Baseline characteristics of sepsis, septic shock, and corresponding non-sepsis propensity matched control populations to derive sepsis/septic shock attributable fraction.

Parameter	Model-1			Model-2		
	Sepsis	Non-sepsis	Std diff	Septic shock	Non-sepsis	Std diff
Matched (N; %)	179,704/179,717 (99.9%)			36,833/36,838 (99.9%)		
Age (years; mean (SD))	63.7 (16.4)	63.8 (16.5)	−0.004	65.5 (14.9)	65.5 (14.9)	0.000
Sex female N (%)	81,553 (45.4%)	81,460 (45.3%)	−0.001	16,556 (45.0%)	16,556 (45.0%)	−0.000
Ethnicity N (%)						
White	162,147 (90.2%)	159,792 (88.9%)	NMV	32,906 (89.3%)	33,069 (89.8%)	NMV
Asian	6718 (3.7%)	7213 (4.0%)		1539 (4.2%)	1414 (3.8%)	
Black	3988 (2.2%)	4625 (2.6%)		813 (2.2%)	853 (2.3%)	
Other	2082 (1.2%)	2383 (1.3%)		507 (1.4%)	433 (1.2%)	
Mixed	822 (0.5%)	843 (0.5%)		177 (0.5%)	152 (0.4%)	
Not stated	3947 (2.2%)	4848 (2.7%)		891 (2.4%)	912 (2.5%)	
PMH present N (%)	35,988 (20.0%)	35,286 (19.6)	0.010	7527 (20.4%)	7527 (20.4%)	−0.000
Comorbidity N (%)						
Cardiovascular	3097 (1.7%)	4319 (2.4%)	NMV	662 (1.8%)	769 (2.1%)	NMV
Respiratory	7777 (4.3%)	4575 (2.6%)		1038 (2.8%)	1259 (3.4%)	
Liver	4160 (2.3%)	7454 (4.2%)		1183 (3.2%)	1334 (3.6%)	
Renal	3754 (2.1%)	5619 (3.1%)		731 (2.0%)	1037 (2.8%)	
Metastatic disease	4407 (2.5%)	5243 (2.9%)		1000 (2.7%)	1067 (2.9%)	
Hematologic	6628 (3.7%)	3923 (2.2%)		1558 (4.2%)	1040 (2.8%)	
Immunosuppressed	14,947 (8.3%)	11,072 (6.2%)		3241 (8.8%)	2660 (7.2%)	
Surgical status N (%)						
Medical	135,760 (75.5%)	135,626 (75.5%)	−0.002	27,475 (74.6%)	27,475 (74.6%)	0.000
Elective surgical	7591 (4.2%)	7591 (4.2%)		773 (2.1%)	773 (2.1%)	
Emergency surgical	36,353 (20.3%)	36,487 (20.3%)		8585 (23.3%)	8585 (23.3%)	
APACHE II physiology score	13.7 (6.0)	12.2 (6.5)	NMV	17.1 (6.6)	12.5 (6.2)	NMV
APACHE II score	18.5 (6.9)	16.9 (7.4)	NMV	22.1 (7.2)	18.5 (6.9)	NMV
Hospital mortality N (%)	57,319 (31.8%)	48,587 (27.0%)	–	20,439 (55.5%)	10,261 (27.9%)	–
RD (95% CI)	4.9% (4.6%–5.2%)		–	27.6% (26.9%–28.3%)		–
RR (95% CI)	1.18 (1.17–1.19)			1.99 (1.95–2.03)		
AFsepsis or septic shock (%)	15.2% (14.4%–16.1%)			49.8% (48.8%–50.7%)		
p-Value	<0.001			<0.001		

PMH = past medical history of severe comorbidities; N = number; % = proportion; SD = standard deviation; APACHE II = Acute Physiology And Chronic Health Evaluation II method and score; RD = risk difference; RR = relative risk; 95% CI = 95% confidence interval; Attribution fraction (AFsepsis and AFseptic shock); p = p value; Std diff = standardized difference between the treated and not treated in propensity models used for balance checking; NMV = not matched variable.

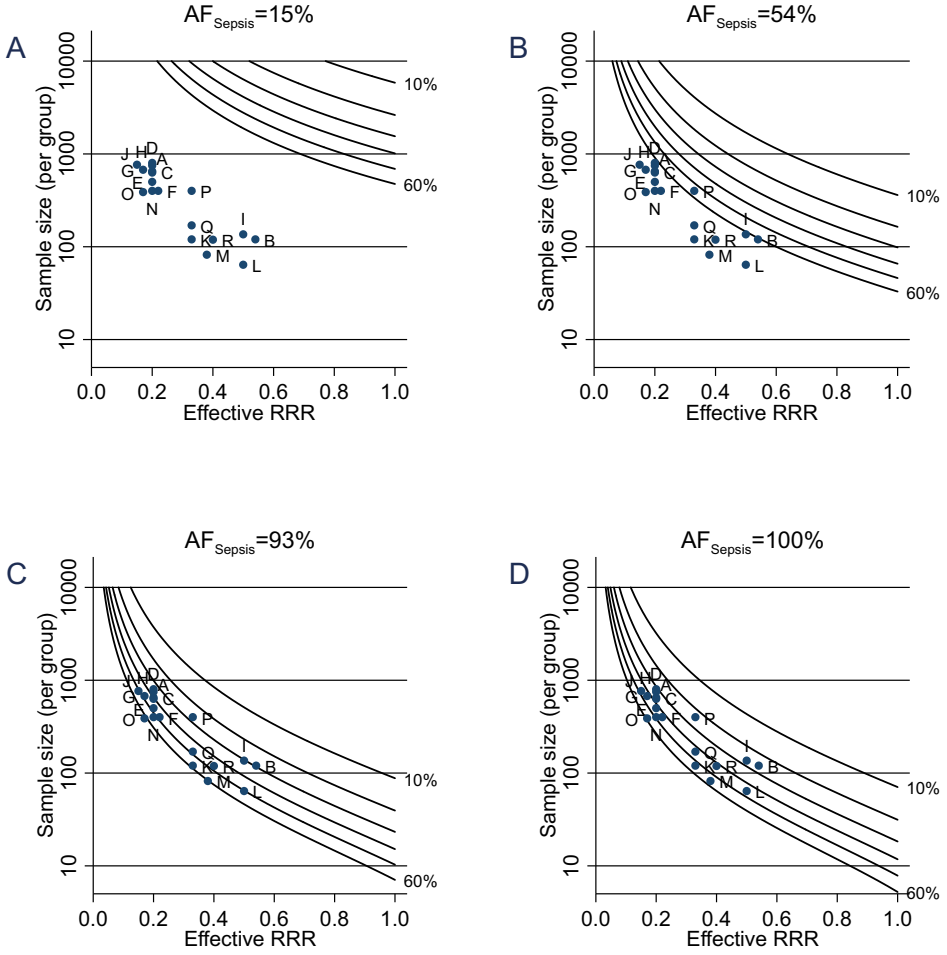
sepsis population 15.0% (95% CI 13.9%–15.9%). Septic shock patients without comorbidities had a greater risk of death compared to propensity matched non-sepsis ICU controls without comorbidities (hospital mortality 52% vs 25%; risk ratio 2.12; 95% CI (2.07–2.17); $p < 0.001$) and the AFseptic shock was also was similar to the overall septic shock population 52.8% (95% CI 51.7%–53.9%). In the posthoc sensitivity analysis estimating AFSepsis and AFseptic shock excluding patients with active treatment withdrawn 12 h of ICU admission, we observed a small increase in AFsepsis to 17.2% (95% CI: 15.7%–18.9%) and small decrease in AFseptic shock to 44.5% (95% CI 42.6%–46.4%), when compared to primary analysis (eTable 2).

3.3. Comparing AFsepsis based sample size estimates to standard approach

Amongst the trials included in the two systematic reviews [12,13], 18 RCTs met our inclusion criteria (eTables 3 and 4). Trial inclusion criteria had infection, two or more systemic inflammatory response syndrome and organ dysfunction as key inclusion criteria. The exclusion criteria varied in trials and could be categorized into generic (such as unlikely to survive beyond 24 h) and intervention specific (such as coagulopathy) (eTable 3). For sample size calculations in these RCTs, the median (interquartile range) control group mortality used was 44% (37%–50%) and RRR was 20% (20%–38%). Most trials aimed for 80% power and 5% alpha. The sample size per group varied between 64 and 800 patients (eFig. 2 and eTable 4). At AFsepsis = 93%, the effective RRR is very similar to the RRR used in the sample size calculations. At AFsepsis = 15% and AFsepsis = 54%, the effective RRR is reduced to that fraction of the RRR used for sample size estimates and significantly reduces the statistical power of these trials (Fig. 2). For any fixed combinations of control group mortality and effective RRR, the sample size will decrease with increase in AFsepsis (Fig. 3). Similarly, for any AFsepsis value, the sample size will decrease with increase in effective RRR (Fig. 3). Higher the control group mortality, lower will be the sample size for any combination of AFsepsis and effective RRR (Fig. 3).

4. Discussion

We show that AFsepsis in critically ill patients varies between 15% and 93% and the higher AFseptic shock is consistent with greater risk of death subset highlighted by Sepsis-3 definitions [14]. As AFsepsis is likely to be <100% even with the best case-scenario, our analyses illustrate that existing RCTs could be considered as underpowered except when most deaths are attributable to sepsis, and the treatment is extremely effective, under the key assumption that only AFsepsis deaths are affected by treatments for sepsis. The key interpretation and value



	Trial	Mortality	RRR
A	Mouncey PR et al (2015)	40%	20%
B	Payen DM et al (2015)	37%	54%
C	Yealy DM et al (2014)	30%	20%
D	Peake SL et al (2014)	38%	20%
E	Holst LB et al (2014)	45%	20%
F	Asfar P at al (2014)	45%	22%
G	Caironi O et al (2014)	45%	17%
H	Ranieri VM et al (2012)	35%	20%
I	Huh JW et al (2011)	35%	50%
J	De Backer D et al (2010)	43%	15%
K	Patel GP et al (2010)	60%	33%
L	Palizas F et al (2009)	40%	50%
M	Stephens DP et al (2008)	60%	38%
N	Sprung CL et al (2008)	50%	20%
O	Russell JA et al (2008)	60%	17%
P	Werdan K et al (2007)	30%	33%
Q	Annane D et al (2007)	60%	33%
R	Angstwurm MWA et al (2007)	50%	40%

Fig. 2. Sample size estimations based on different AFsepsis, effective RRR and control group mortality for sepsis RCTs. The figure shows the sample size estimations for different treatment effectiveness amongst attributable deaths (effective RRR) and different control group mortality for 80% power and 5% alpha. The dot plots are placed at a *fixed* point on all four graphs based on actual RRR used for sample size estimation and sample size per group reported in trials (see eTable 4). Each curve represents a different control group mortality and sample sizes above the curve are adequately powered for the corresponding control group mortality. Each graph represents a different AFsepsis ranging from our lowest estimate of 15% (panel A), median estimate of 54% (panel B) and the highest estimate of 93% (panel C). The maximum overall RRR that is observable if the intervention prevented *all sepsis deaths* in panel A is 15%, in panel B is 54% and in panel C is 93%, which is equivalent to an effective RRR of 1.0, that is, the treatment is perfect (effective RRR = 1). It is important to highlight using panel D (100% AFsepsis plot) that all these trials were adequately powered across a range of expected mortality under, standard sample size estimation approaches. These graphs also highlight that the sample size requirements will vary by AFsepsis for the same control group mortality.

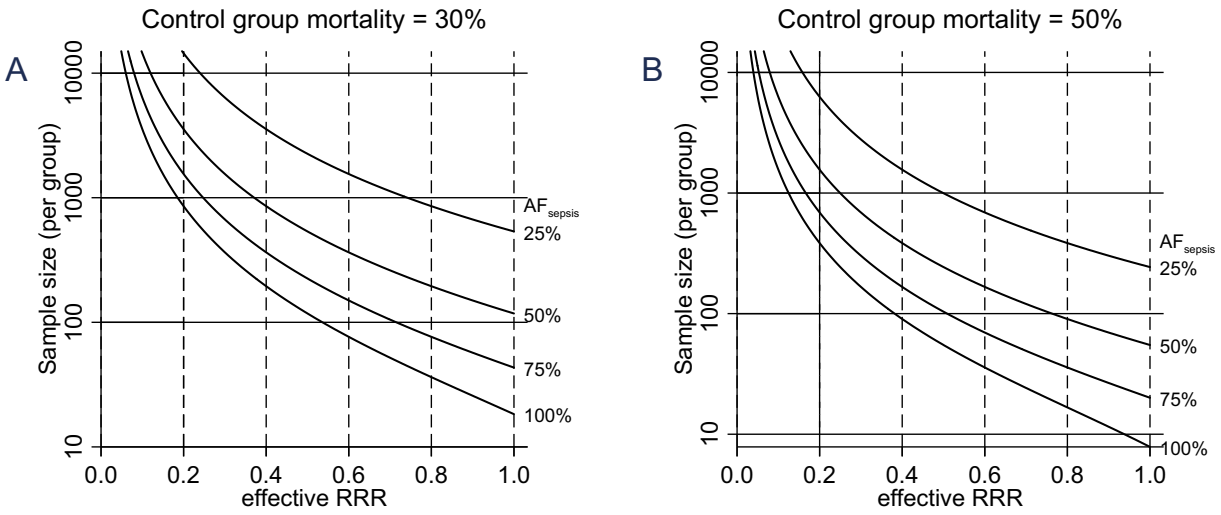


Fig. 3. Illustrating the utility of AFsepsis estimation. The figure shows the sample size estimations for a fixed control arm mortality (panel A = 30% and panel B = 50%). X-axis refers to different treatment effectiveness amongst the attributable deaths (effective RRR). Y-axis is sample size estimation as a function of changing AFsepsis and effective RRR. Two key principles are highlighted by this figure. First, if we have a fixed control group mortality and a fixed effective RRR, the sample size will increase with decrease in AFsepsis. For example, in a trial with control group mortality of 30% with RRR of 20%, the sample size per group would be 859, 1554, 3554 and 14,437 as AFsepsis in the trial population changes from 100%, to 75%, to 50% and 25% respectively. Second, data from a completed trial and a control population registry can be used to estimate a trial specific AFsepsis to determine the what effective RRR might have been missed. The reason being, with AFsepsis approach, patients' risks of target outcome specifically attributed to sepsis are identified. The notion that there is likely to be trial specific AFsepsis is supported by the higher AFseptic shock shown in Fig. 1, explained by differences in septic shock criteria. Abbreviation = relative risk reduction (RRR).

of our methodological study is that, accounting for AFsepsis in trial populations could to improve the sensitivity of future sepsis RCTs.

All RCTs have inclusion and exclusion criteria, which serves to identify patients with the illness and specifically exclude patients who are either unlikely to benefit or have a greater likelihood of harm from the trial treatment [9,25]. The sepsis RCTs mainly differ in terms of their exclusion criteria (eTable 3) [26], with similar inclusion criteria [27]. Therefore, we do not suggest that these principles are completely ignored in published sepsis trials where, for example, patients with metastatic cancer and cirrhosis are frequently excluded presumably

Table 2
Control populations and rationale.

Control description	Comment on control group	Advantages and limitations of control group	Trial design implication for AFsepis estimate for the control group
ICU non-sepsis controls	This control group represents a broader patient population without sepsis. These patients therefore will have a risk of death that is determined by their illness and risk due to being managed in critical care.	Accounts for the risk of critical care management. Conservative estimate of AFsepsis due to 'risk of death from primary illness that required admission' – provides lower boundary of likely risk reduction, irrespective of the potency of the intervention	Intervention is expected to reduce the risk of death to 'non-sepsis critical illness'. This represents worst case scenario for a new intervention tested in a trial.
Hospitalised infected controls	This control group represents a patient population who have infection but without sepsis. These patients represent, those with either in an earlier stage of illness or do not develop organ dysfunction during the entire hospital stay following an infection.	Accounts for the 'all the dysregulated host response to infection related organ dysfunction' and the risk of death associated with hospitalisation but without the critical care related and infection related risks of death Conceptually elegant model for trial design Probability of any single intervention reducing this magnitude of illness specific risk by altering a single biological mechanism is low	Intervention is expected to reduce the risk of death to that expected in hospitalised infected patients.
Hospitalised non-infected controls	This control group represents a broader patient population who are hospitalised for non-infection reason. These patients therefore will have a risk of death that is determined by their illness and risk due to being managed in hospital.	Accounts for the 'all the dysregulated host response to infection related organ dysfunction, risk of death due to infection and the risk of death associated with hospitalisation but without the critical care related risk of death Probability of any single intervention reducing this magnitude of illness specific risk by altering a single biological mechanism is low	Intervention is expected to reduce the risk of death to that expected in hospitalised non-infected patients
Age and sex matched general population controls	This control group represents general population risk.	Liberal estimate of AFsepsis as these controls only account for age and sex effects on outcome. As comorbidities are not accounted for, this would be an overestimate of the intervention effect.	Intervention is expected to reduce the risk of death to 'general population, matched on age and sex'. This represents best case scenario for a new intervention tested in a trial.

because of the high non-sepsis attributable mortality of critical illness in these subsets (eTable 3).

Our analysis highlights the need for explicitly estimating trial specific AFsepsis to inform sample size calculations. The challenge is to determine the comparator population for these estimations. For example, the intervention could *either* reduce the risk of death from sepsis to those experienced by similar patients with the same site of infection but without organ dysfunction (such as uncomplicated urinary tract infection) *or* the intervention would counteract all the effects of the sepsis state, returning the patient their pre-sepsis health state. The control group chosen should match the target state of the treated patient population the intervention is expected to achieve and the trial objectives (Table 2).

The AFsepsis approach complements other recent recommendations about trial design including susceptibility to tested treatment and likelihood of outcome [6,9], by identifying, empirically, patients at the greatest risk of dying from sepsis. Identifying patients with a mechanism that is responsive to the tested intervention is referred as predictive enrichment, with the assumption that the target biological effect of sepsis is a major contributor for death. This principle has been demonstrated using the association between mortality and response to PEEP in Acute Respiratory Distress Syndrome patients [28] and for corticosteroid responsiveness in septic shock [29]. These methods are particularly challenging in critical care, as markers of treatment response that are in the causal biological network [30] of the tested intervention and independently associated with higher mortality, are difficult to ascertain. For example, intravenous immunoglobulin (IVIg) trials test effects of immunomodulation and normalisation of low immunoglobulin levels in sepsis, with no consistent benefits [31]. However, enriching on low immunoglobulins alone may not overcome this [32], but enriching a sepsis population with combination of low immunoglobulin levels alongside raised free light chains implying impaired immunoglobulin production, might [33]. Prognostic enrichment, which uses the risk of the study outcome as predicted by baseline covariates, relies on the observation that treatment effects usually exert a fixed relative risk of benefit regardless of the individual patient's risk of the outcome. Patients at the greatest risk of the outcome derive the greatest, and therefore, the easiest to measure, benefit [34]. This method was tried, unsuccessfully, in the evaluation of activated protein C in patients with both low [35] and high risk of death [36]. More sophisticated approaches to incorporating baseline risk of outcome in to trial design have been proposed [37]. We also show how the baseline risk of death is also important as patients at the highest risk of death also have the highest AFsepsis (see Fig. 3).

Our study has strengths and limitations. We estimate AFsepsis for the first time using the Sepsis-3 criteria. We report an AFsepsis range using two control populations. The upper limit of the range highlights that AFsepsis is unlikely to be 100% as similarly ill patients have high mortality even when not septic because sepsis, unlike, say myocardial infarction, does not usually occur in previously healthy patients. We used a high-quality representative national database that had enough patients to use a strict 1:1 matching criteria and matched >99% of the sepsis cohort to non-sepsis ICU controls to reduce confounding in the sepsis and mortality association. We then used AFsepsis to generate isopleths of control group mortality for different RRR to illustrate the impact of knowing AFsepsis during trial design, which is novel. Although we have highlighted the AFsepsis conceptual principles using original data, with two different controls and propensity methods, we have not formally tested this in a completed trial. Despite our use of a multivariate propensity model, residual confounding is certainly a concern. Failure to account for residual confounders might make the estimated AFsepsis even smaller than estimated in this study. Our analysis uses ICU controls and these controls might have higher mortality than hospital based non-septic controls, due to their underlying illness. Our analysis is relatively robust to this concern as we did not incorporate acute physiologic derangement in our propensity score, however, a theoretic sepsis therapy that might avoid ICU admission entirely would need an AFsepsis analysis using hospital non-septic controls (Table 2). Despite this limitation, our analyses are consistent with the AFsepsis estimates of ICU acquired secondary sepsis that yielded attributable fractions between 10.9% and 21.1% [15], and ventilator associated pneumonia attributable fraction between 4.4% and 13% [16,38].

Our analysis raises a number of important future studies. First, as magnitude of sepsis-related mortality is influenced by the site of infection, organ dysfunction characteristics and the end point chosen in trials (such as 28-days or 90-days), the trial specific AFsepsis is also likely to vary [14,39]. Like baseline risk of death, there is likely to be a heterogeneity of AFsepsis within any given trial population and lends itself to similar analytic solutions [5]. Our analysis highlights the need to reconsider the expected magnitude of RRR chosen for sample size calculations in sepsis trials. Given the potentially large sample size requirements, when either the AFsepsis is low or the likely RRR in a trial population is low, we illustrate the need for efficient trial designs in critically ill patients to prioritize finding effective treatments over evaluating single therapy [40].

5. Conclusions

Using AFsepsis principles, we illustrate the impact of AFsepsis on sample size estimations in sepsis trials. Given that AFsepsis could be substantially <100%, estimating AFsepsis based on trial specific eligibility criteria to inform sample size calculations could be another useful additional step in designing sepsis trials. Our results are best considered as proof of concept that requires validation.

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Author contributions

Drs Harrison and Rowan had full access to all the data in the study and take responsibility for integrity of data and the accuracy of the data analyses.

Concept and design: Shankar-Hari, Rubenfeld
Statistical analysis: Shankar-Hari, Harrison
Drafting of manuscript: Shankar-Hari, Rubenfeld
Acquisition, analysis and interpretation of data: All authors
Critical revision of the manuscript for important intellectual content: All authors
Obtained funding: Harrison, Rowan
Administrative, technical, or material support: Rowan, Harrison
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Conflict of interest statement

No conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2018.01.018.

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