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The increased risks of death and extra lengths of hospital and ICU stay from hospital-acquired bloodstream infections: a case–control study

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Structured abstract

Objectives: Hospital-acquired bloodstream infections are known to increase the risk of death and prolong hospital stay, but precise estimates of these two important outcomes from well designed studies are rare, particularly for non-ICU patients. We aimed to calculate accurate estimates, which are vital for estimating the economic costs of hospital-acquired bloodstream infections.

Design: Case–control study.

Setting: Nine Australian public hospitals.

Participants: All admitted patients between 2005 and 2010.

Primary and secondary outcome measures: Risk of death and extra length of hospital stay associated with nosocomial infection.

Results: The greatest increase in the risk of death was for a bloodstream infection with Methicillin-resistant *Staphylococcus aureus* (hazard ratio = 4.6, 95% CI: 2.7, 7.6). This infection also had the longest extra length of stay to discharge in a standard bed (12.8 days, 95% CI: 6.2, 26.1 days). All eight bloodstream infections increased the length of stay in the ICU, with longer stays for patients who eventually died (mean increase: 0.7 to 6.0 days) compared with those who were discharged (mean increase: 0.4 to 3.1 days).

Conclusions: Bloodstream infections are associated with an increased risk of death and longer hospital stay. Avoiding infections could save lives and free up valuable bed days.

Article summary

Article focus

- There are few accurate estimates of the increased risk of death and extra length of hospital stay after a hospital-acquired infection because of the frequent use of study designs that ignore the time-dependent bias.
- We used a multi-state approach to overcome the time-dependent bias.

Key messages

- All eight of the bloodstream infections studied were associated with an increased risk of death and longer hospital stay.

Strengths and limitations of this study

- We had an extremely large sample size, but with little detailed individual information. We could not therefore match or control for detailed individual characteristics, which may mean there is some residual confounding in our estimates.
- Our estimates will be useful for economic studies on the costs and health benefits of interventions that reduce hospital-acquired infections.

INTRODUCTION

Hospital-acquired infections increase a patient's risk of death and prolong their hospital stay.[1] Accurate estimates of the increased risk of death and extra length of stay are rare because of the complex statistical analysis needed to avoid the potentially serious biases of ignoring the timing of infection.[2, 3] There are few accurate estimates of the extra length of stay and increased risk of death due to bloodstream infections,[4] with most good estimates only for patients in intensive care. This is an important gap in our understanding of the complete burden of hospital-acquired bloodstream infections, particularly as death and length of stay are vital for estimating the economic costs of hospital-acquired infections.[5-7] Also, financial penalties are applied in some hospitals for any hospital-acquired bloodstream infection (not just central line associated bloodstream infection).

In this paper we used an analysis that accounts for the timing of infection and hence gives accurate estimates of the risk of death and extra length of stay. We examined eight types of hospital-acquired bloodstream infections using data from nine Australian hospitals over six years. We estimated the extra length of stay due to infections for both standard and intensive care unit (ICU) beds.

METHODS

Data

We examined the nine largest public hospitals in Queensland, Australia (see Table 1 for some descriptive statistics). We requested all patient admissions with an admission or discharge date between 1 January 2005 and 31 December 2010 from the Health Statistics Centre of Queensland Health. The infection data came from the Centre for Healthcare Related Infection Surveillance and Prevention (CHRISP), Queensland Health. The admission and infection data

were linked by Queensland Health staff using a unique patient unit record number and infection date.

The data used included the dates of admission, discharge and infection (if any), and the dates (if any) of admissions and discharges from intensive care. Data were also requested on admitting hospital, patient age, principal diagnosis code (ICD-10) and outcome in three categories: discharged alive, died or censored. Censored meant the outcome of the patient was unknown, which occurred when: i) the patient was transferred to another hospital, ii) the patient was discharged to some other facility, such as an aged care facility or medi-hotel. We accounted for this censoring in our analyses using statistical censoring.

CHRISP coordinates a statewide healthcare associated infection surveillance program, which aggregates and assures data quality. The surveillance definitions and processes have been refined and validated over ten years,[8] and are consistent with national and international definitions. Hospitals monitor infections hospital-wide as detailed in the surveillance manual.[9] The data undergo a central quality assurance check every six months, and the observed numbers of infections are regularly compared with expected numbers. Hospitals with numbers that are lower than the state-wide control limit are asked about their surveillance processes.

Bloodstream infections were classified *a priori* into four non-mutually exclusive groups, those due to: (1) *Staphylococcus aureus*, (2) coagulase negative staphylococci, (3) Gram positive organisms and (4) Gram negative organisms. After examining the results from these four groups we added four further subgroups, viz. *Staphylococcus aureus* infections were split into Methicillin-resistant *Staphylococcus aureus* (MRSA) and Methicillin-sensitive *Staphylococcus aureus* (MSSA), and Gram negative organisms were split into *E. coli* and *Pseudomonas aeruginosa*, to examine a lower and higher virulence organism, respectively.

The infection groups are not mutually exclusive, for example, bloodstream infections due to *Staphylococcus aureus* were also classified in the Gram positive organism group.

Community associated infections were excluded. The portal of entry of bloodstream infection (e.g., urinary tract infection, pneumonia, intra-abdominal infection, central line) was not available.

The study was approved by the ethics committees of Queensland Health and Queensland University of Technology. The Research Ethics Governance Unit for Queensland Health approved the data collection and linkage process, number: HREC/10/QPAH/180.

Statistical methods

The basis of our statistical model is shown in Figure 1. A patient's admission over time is modelled using the four states, with all patients eventually dying or being discharged, and some patients being infected. Using this multi-state model we can examine our two key questions:

1. By how much did a hospital-acquired bloodstream infection increase the risk of death?
2. By how much did a hospital-acquired bloodstream infection increase the length of stay?

Incidence density sampling

We created a smaller group of infected and non-infected patients from the complete data using incidence density sampling.[10] The incidence density sampling approach is illustrated in Figure 2. Patient E is the infected case, whose infection occurred four days after their admission. Patient D is not a potential control, as they were discharged alive before day four. The other three patients (A to C) are all eligible controls as they were infection free at the time of the case's infection. This includes patient C, who acquired an infection on a later day.

The days in hospital after the infection (for both cases and controls) were used to estimate the extra length of stay (solid lines in Figure 2). We examined the extra number of days in both standard and intensive care beds (thin and thick lines in Figure 2, respectively). For patients with multiple infections, we only considered their first infection. This was done to simplify the analysis (as multiple infections would require another state in Figure 1), and because there were relatively few admissions with multiple infections.

Matching infected patients to control patients when estimating the extra length of stay due to infection usually gives poor estimates because of the time-dependent bias.[5] This bias occurs because the time before infection is used when estimating the extra length of stay (dashed horizontal lines in Figure 2). However, unlike traditional matching studies, we used incidence density sampling, which also matches on the timing of infection because potential controls must have been infection free at the time of the case's infection.[10]

To make comparable groups of patients in terms of morbidity we matched infected cases to controls who: had the same first letter in the principal diagnosis code (using ICD-10 coding), were of a similar age (within 10 years), were at the same hospital, and were infection free at the time of the case's infection. We randomly selected four controls for each infected patient.

Statistical power

The study had a 90% power to detect an increased hazard ratio of 1.40 (40%) for infected versus uninfected patients using the smallest number of infections of 189 for MRSA, and an increased hazard ratios of 1.18 (18%) for the second smallest number of infections of 744. These calculations assumed a two-sided 5% significance level.

We only examined the risk of in-hospital death, as we had no information on patients after discharge.

Extra length of stay

We estimated the extra length of stay due to infection using the following steps. We calculated the number of days from infection to discharge for cases, and the number of days from the case's infection to discharge for its four matched controls. We then subtracted the case's length of stay from the average length of stay for its matched controls, with separate estimates for stays in standard and ICU beds. We then averaged these individual extra lengths of stay over all cases. These averages were stratified to create separate estimates for patients discharged alive and dead.

There are no parametric equations for calculating confidence intervals for the extra length of stay, hence we used a bootstrap method to generate a 95% confidence interval.[11] We randomly selected sets of cases and matched controls with replacement, creating a random sample with the same sample size as the original data. We repeated this random selection 1,000 times.

All analyses were conducted in R version 2.15.0 using the "survival" library.

RESULTS

Hazard ratios

The hazard ratios (HRs) for the eight bloodstream infections are in Table 2. All eight infections increased the risk of death, with the largest risk for MRSA (HR = 4.6) and the smallest for gram negative BSI (HR = 2.1). The increases were statistically significant for all eight infections, as the lower limits of the 95% confidence intervals were all above 1. The greatest number of infections was 2,141 for gram positive BSI, and the smallest number was 189 for MRSA.

Extra length of stay

The extra lengths of stay for the eight bloodstream infections are in Table 3. For patients that died, there was no extra length of stay in a standard bed (as all the 95% confidence intervals include zero). For patients discharged alive, infection was associated with an extra length of stay in a standard bed for every type of bloodstream infection except the gram negative BSIs. The longest extra length of stay to discharge in a standard bed was 12.8 days for MRSA (95% CI: 6.2, 26.1 days). The 95% confidence intervals are noticeably wider for infections with smaller numbers.

Most of the bloodstream infection types were associated with an extra length of stay in ICU for both patients that lived and died (Table 3). The extra lengths of stay were generally longer for those patients that died. The longest extra length of stay to death in an ICU bed was 6.0 days for a BSI with CNS (95% CI: 3.3, 10.0 days).

CONCLUSION

This is one of the largest studies to estimate the increased length of stay and risk of death due to hospital-acquired infection.[4] All eight bloodstream infection types studied increased the risk of death and most led to extra days in intensive care. Five of the bloodstream infections also prolonged stay in a standard hospital bed by an average of between 9.8 and 12.8 days. The eight hospital-acquired infections studied therefore significantly increased mortality and morbidity.

Gram negative infections had generally shorter extra lengths of stay and lower risks of death compared with the other infection types. The three most common organisms of gram negative infection were *E. Coli*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*. There were no clear differences between patients with a gram positive and gram negative infection in terms of their age or primary diagnosis (data not shown). BSI with CNS had a higher death risk

(HR=2.9) than Gram-negative BSIs (HR=2.1), which could reflect the higher risk of organ failure.[12]

The average extra lengths of stay after infection were shorter for ICU bed days compared with ward bed days for all infections. This is expected as the average extra length of stay is proportional to the average total length of stay,[2] and lengths of stay were generally longer in ward beds compared with ICU beds.

MRSA was associated with the largest increased risk of death (HR = 4.6) and the largest increase in length of stay for a standard bed (12.8 days for those discharged alive). BSI with CNS had the largest increased length of stay in an ICU bed of 6.0 days for patients who died and 1.4 days for patients discharged alive. These estimates of hazard ratio and length of stay are similar to those from related studies that account for the time-dependent bias. A study in European hospitals found hazard ratios of 3.5 due to MRSA BSI and 3.1 for MSSA BSI, with an extra length of stay of 9.2 days for MRSA BSI and 8.6 days for MSSA BSI.[13] Results from ICUs in 10 European countries gave estimated hazard ratios for BSIs ranging from 2.1 to 4.4 depending on the organism, and extra lengths of stay in ICU ranging from –0.1 to 3.7 days.[1] ICUs in France had an estimated odds ratio for death of 3.2 due to a BSI infection, with a lower odds ratio of 2.7 for those who received appropriate treatment.[14] ICUs in Latin America had average excess length of stay due to a central-line association BSI between –1.2 and 4.7 days.[15] A study of ICUs in Germany found an extra length of stay of 2.7 days for BSIs.[3]

Study limitations

We used a large routinely collected data set of all hospital admissions. Larger data sets give more statistical power, but are often not as detailed or error-free as prospectively collected

data. The hospital admission data used here are subject to data checking at the time of entry, and we subjected the data to further logical checks and found no errors.

We matched controls to cases using the first letter of ICD-10 code so that controls and cases were broadly similar in terms of morbidity, and to prevent very different patients being compared (e.g., psychiatric patients with renal patients). We did not adjust for morbidity beyond age and ICD-10 code because no further morbidity data were available. It is possible that even after the matching, the infected cases were sicker than the controls (prior to the infection) and that this somewhat explains the cases' extra length of stay and increased risk of death. However, adjusting for the timing of infection (which we did) is far more important than adjusting for baseline morbidity when estimating the extra length of stay due to infection.[16]

Despite using hospital-wide surveillance, some infections may have been missed. The surveillance relies on clinical testing, so an infected but untested patient would be missed. However, collection of blood cultures is standard for patients with a fever during hospitalisation.

Our results should be generalisable to other settings, but it is possible that differences will occur depending on how infections are managed. For example, some hospitals use hospital in the home schemes, where infected patients can be cared for at home rather than in the hospital.[17] Caring for infected patients in their own home would reduce the extra length of hospital stay due to infection. Unfortunately we did not have data on the use of hospital in the home, and so could not estimate the entire patient journey. If we had this data it could have been added as another state to the multi-state model in Figure 1.

We had no data on why the extra length of stay occurred. For example, the extra lengths of stay may be directly due to the increased morbidity of infection or they could be due to a

change in patient management, such as the use of defined durations of intravenous antibiotics (such as for *Staphylococcus aureus* bloodstream infection). It is also possible that the total extra length of stay after bloodstream infection is not solely due to the infection. For example, a patient's stay is initially extended because of a bloodstream infection, then during this extra stay an unrelated adverse event happens, for example an adverse drug reaction that keeps them in hospital for longer.[18] To further investigate extra length of stay due to infection, we recommend a detailed individual study that follows patients from the time of their infection to discharge, and details the decisions made and resources used.[19] In some hospitals this is already collected using a post-infection review.

Study strengths

This is one of the first studies to accurately estimate the extra length of stay due to bloodstream infection in a standard hospital bed, as most previous good estimates only examined ICU beds. This is important because days in hospital are costly so extra length of stay is key to determining the economic costs of infection,[20] as well as being an important measure of morbidity. ICU beds have a far greater economic cost than standard beds, so it is vital to get separate estimates for ward and ICU beds.[21]

Our results can be used to inform parameters for studies of the cost-effectiveness of interventions that reduce risks of hospital-acquired infection. This is the most useful application of estimates, as only describing the size of the cost does not help decision-makers, although it might get the attention of politicians and the media in the short-term. Also, erroneous estimates of these parameters might have misled decision making in the past.[5] The application of a multi-state modelling approach (Figure 1), which appropriately classifies patient risks over time should become the gold standard method for these studies.[3]

A key parameter in cost-effectiveness models is the extra number of deaths, as the years of life lost have a potentially large economic cost. We found that all eight types of bloodstream infections increased the risk of death. Avoiding infections is therefore likely to both save lives and free up valuable bed days.

What is already known on this subject?

Hospital-acquired bloodstream infections are thought to increase the risk of death and lead to longer stays in hospital. The only previous estimates of the risks to date have been: biased by poor statistical methods, or only applicable to patients in intensive care units.

What this study adds?

This is the first study to accurately estimate the risks of death and extra length of stay in a hospital population. These estimates will be vital for cost-effectiveness analyses of interventions in hospital that aim to reduce infections (e.g., alternative cleaning regimes).

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Competing interests: None.

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Data Sharing

All the data used in this study are available from Queensland Health and the Centre for Healthcare Related Infection Surveillance and Prevention subject to ethical approval. Please contact Adrian Barnett (a.barnett@qut.edu.au) if you are interested in accessing the data.

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Tables

Table 1: Basic characteristics of the nine Queensland hospitals combined, patients with admission or discharge dates between 1 January 2005 and 31 December 2010. Results for all admissions and admissions by infection status.

Admissions	Numbers	Patient age, median (IQR)	LoS in days, median (IQR)	In-hospital deaths (%)
All	2,725,515	53 (32, 69)	1 (1, 4)	1.1
Those with an infection	19,206	61 (44, 74)	15 (6, 31)	7.1
Those without an infection	2,706,309	53 (32, 69)	1 (1, 4)	1.0

IQR = inter-quartile range, LoS = length of stay

Table 2: Risks of in-hospital death due to a hospital-acquired bloodstream infection. Based on nine hospitals with admissions between 1 January 2005 and 31 December 2010.

Bloodstream infection	Number of infections	Deaths in infections, n (%)	Controls	Deaths in controls, n (%)	Hazard ratio (95% CI)
BSI and gram positive	2,141	338 (15.8%)	8,512	526 (6.2%)	3.0 (2.6, 3.5)
BSI with SAB					
All	744	124 (16.7%)	2,950	175 (5.9%)	3.5 (2.7, 4.6)
MRSA	189	38 (20.1%)	740	45 (6.1%)	4.6 (2.7, 7.6)
MSSA	555	86 (15.5%)	2,218	121 (5.5%)	3.4 (2.5, 4.7)
BSI with CNS	918	139 (15.1%)	3,640	219 (6.0%)	2.9 (2.3, 3.7)
BSI and gram negative					
All	2,044	285 (13.9%)	8,089	609 (7.5%)	2.1 (1.8, 2.4)
E. coli	465	57 (12.3%)	1,838	130 (7.1%)	2.0 (1.4, 2.8)
Pseudomonas	449	74 (16.5%)	1,771	163 (9.2%)	2.2 (1.6, 3.0)

BSI = bloodstream infection, CI = confidence interval, CNS = coagulase-negative staphylococci, MRSA = Methicillin-resistant *Staphylococcus aureus*, SAB = *Staphylococcus aureus* bacteremia.

Table 3: Extra length of stay (in days) in a standard bed and ICU bed due to a hospital-acquired bloodstream infection. Cells show the mean extra length of stay (in days) with 95% confidence intervals in parentheses. Based on nine hospitals with admissions between 1 January 2005 and 31 December 2010. Separate estimates were made for admissions that ended in death and discharge. The total length of stay is the standard bed time plus the ICU bed time (see Figure 2).

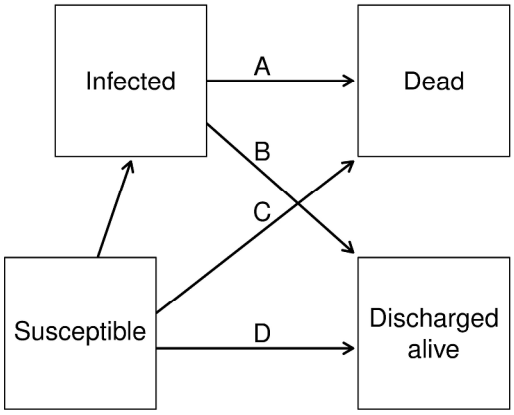
Bloodstream Infection	**Standard bed**		**ICU bed**	
	Died	Discharged	Died	Discharged
BSI and gram positive	1.0 (–3.9, 5.6)	9.8 (7.7, 12.6)	4.0 (2.6, 5.7)	0.9 (0.4, 1.8)
BSI with SAB				
All	–1.5 (–6.8, 6.1)	12.1 (6.7, 15.3)	1.4 (0.5, 3.0)	0.9 (0.1, 2.9)
MRSA	–1.6 (–12.6, 12.6)	12.8 (6.2, 26.1)	3.1 (0.5, 7.2)	3.1 (0.4, 13.2)
MSSA	2.7 (–2.6, 9.7)	11.0 (6.4, 14.9)	0.7 (–0.3, 2.0)	0.4 (0.0, 0.8)
BSI with CNS	3.5 (–4.0, 13.4)	9.8 (3.6, 14.6)	6.0 (3.3, 10.0)	1.4 (0.6, 2.5)
BSI and gram negative				
All	–3.9 (–8.7, –0.4)	2.7 (–4.1, 6.1)	3.0 (1.4, 4.5)	0.6 (0.3, 1.0)
E. coli	–3.3 (–9.3, 7.9)	1.1 (–13.2, 5.7)	2.5 (0.4, 4.7)	0.5 (–0.1, 0.9)
Pseudomonas	–5.4 (–11.6, 9.2)	5.6 (–6.4, 14.3)	3.2 (0.8, 7.1)	0.5 (0.3, 1.2)

BSI = bloodstream infection, CI = confidence interval, CNS = coagulase-negative staphylococci, ICU = intensive care unit, MRSA = Methicillin-resistant *Staphylococcus aureus*, MSSA = Methicillin-sensitive *Staphylococcus aureus,* SAB = *Staphylococcus aureus* bacteremia.

Figure legends

Figure 1: Four-state model to estimate the extra risk of death and extra length of stay due to a hospital-acquired bloodstream infection. The arrows represent hazards in a survival model. The extra risk of death was estimated using the hazard ratio of the hazard of death for infected patients (arrow A) and the hazard for susceptible patients (arrow C). The extra length of stay for those discharged alive was calculated by comparing the time take to discharge for infected patients (arrow B) with the time take to discharge for susceptible patients (arrow D)

Figure 2: Illustration of incidence density sampling for an infected case (patient E) and matched controls (patients A to C). The vertical dotted line shows the timing of infection. The dashed lines show the periods of hospital stay before infection. These times are discarded, as only times after infection are used to estimate the extra length of stay. The thicker solid lines show time spent in ICU. Adapted from Wolkewitz et al (2009).



Four-state model to estimate the extra risk of death and extra length of stay due to a hospital-acquired bloodstream infection. The arrows represent hazards in a survival model. The extra risk of death was estimated using the hazard ratio of the hazard of death for susceptible patients (arrow A) and the hazard for uninfected patients (arrow C). The extra length of stay for those discharged alive was calculated by comparing the time take to discharge for infected patients (arrow B) with the time take to discharge for susceptible patients (arrow D)
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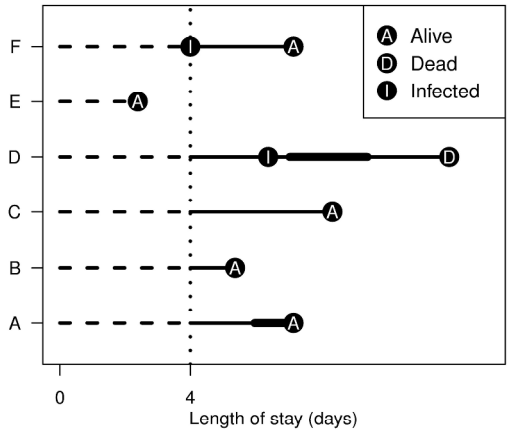

Illustration of incidence density sampling for an infected case (patient E) and matched controls (patients A to C). The vertical dotted line shows the timing of infection. The dashed lines show the periods of hospital stay before infection. These times are discarded, as only times after infection are used to estimate the extra length of stay. The thicker solid lines show time spent in ICU. Adapted from Wolkewitz et al (2009).
279x361mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***case-control studies***

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 4
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 6
Methods			
Study design	4	Present key elements of study design early in the paper	Page 6 & Fig 1
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	Page 7 & Fig 2
		(*b*) For matched studies, give matching criteria and the number of controls per case	Page 7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Pages 4-5
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	Page 7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Pages 6-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Pages 6-8
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how matching of cases and controls was addressed	Page 7
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Tables 1 & 2
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	NA
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	Table 1
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Tables 2 &3
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	Pages 9-12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Pages 10-12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 12
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 13

*Give information separately for cases and controls.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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The increased risks of death and extra lengths of hospital and ICU stay from hospital-acquired bloodstream infections: a case–control study

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The increased risks of death and extra lengths of hospital and ICU stay from hospital-acquired bloodstream infections: a case–control study

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Structured abstract

Objectives: Hospital-acquired bloodstream infections are known to increase the risk of death and prolong hospital stay, but precise estimates of these two important outcomes from well designed studies are rare, particularly for non-ICU patients. We aimed to calculate accurate estimates, which are vital for estimating the economic costs of hospital-acquired bloodstream infections.

Design: Case–control study.

Setting: Nine Australian public hospitals.

Participants: All admitted patients between 2005 and 2010.

Primary and secondary outcome measures: Risk of death and extra length of hospital stay associated with nosocomial infection.

Results: The greatest increase in the risk of death was for a bloodstream infection with Methicillin-resistant *Staphylococcus aureus* (hazard ratio = 4.6, 95% CI: 2.7, 7.6). This infection also had the longest extra length of stay to discharge in a standard bed (12.8 days, 95% CI: 6.2, 26.1 days). All eight bloodstream infections increased the length of stay in the ICU, with longer stays for patients who eventually died (mean increase: 0.7 to 6.0 days) compared with those who were discharged (mean increase: 0.4 to 3.1 days). The three most common organisms associated with gram negative infection were *E. Coli*, *Pseudomonas aeruginosa* and *Klebsiella pneumonia*.

Conclusions: Bloodstream infections are associated with an increased risk of death and longer hospital stay. Avoiding infections could save lives and free up valuable bed days.

Article summary

Article focus

- There are few accurate estimates of the increased risk of death and extra length of hospital stay after a hospital-acquired infection because of the frequent use of study designs that ignore the time-dependent bias.
- We used a multi-state approach to overcome the time-dependent bias.

Key messages

- All eight of the bloodstream infections studied were associated with an increased risk of death and longer hospital stay.

Strengths and limitations of this study

- We had an extremely large sample size, but with little detailed individual information. We could not therefore match or control for detailed individual characteristics, which may mean there is some residual confounding in our estimates.
- Our estimates will be useful for economic studies on the costs and health benefits of interventions that reduce hospital-acquired infections.

INTRODUCTION

Hospital-acquired infections increase a patient's risk of death and prolong their hospital stay.[1] Accurate estimates of the increased risk of death and extra length of stay are rare because of the complex statistical analysis needed to avoid the potentially serious biases of ignoring the timing of infection.[2, 3] There are few accurate estimates of the extra length of stay and increased risk of death due to bloodstream infections,[4] with most good estimates only for patients in intensive care. This is an important gap in our understanding of the complete burden of hospital-acquired bloodstream infections, particularly as death and length of stay are vital for estimating the economic costs of hospital-acquired infections.[5-7] Also, financial penalties are applied in some hospitals for any hospital-acquired bloodstream infection (not just central line associated bloodstream infection).

In this paper we used an analysis that accounts for the timing of infection and hence gives accurate estimates of the risk of death and extra length of stay. We examined eight types of hospital-acquired bloodstream infections using data from nine Australian hospitals over six years. We estimated the extra length of stay due to infections for both standard and intensive care unit (ICU) beds.

METHODS

Data

We examined the nine largest public hospitals in Queensland, Australia (see Table 1 for some descriptive statistics). We requested all patient admissions with an admission or discharge date between 1 January 2005 and 31 December 2010 from the Health Statistics Centre of Queensland Health. The infection data came from the Centre for Healthcare Related Infection Surveillance and Prevention (CHRISP), Queensland Health. The admission and infection data

were linked by Queensland Health staff using a unique patient unit record number and infection date.

The data used included the dates of admission, discharge and infection (if any), and the dates (if any) of admissions and discharges from intensive care. Data were also requested on admitting hospital, patient age, principal diagnosis code (ICD-10) and outcome in three categories: discharged alive, died or censored. Censored meant the outcome of the patient was unknown, which occurred when: i) the patient was transferred to another hospital, ii) the patient was discharged to some other facility, such as an aged care facility or medi-hotel. We accounted for this censoring in our analyses using statistical censoring.

CHRISP coordinates a statewide healthcare associated infection surveillance program, which aggregates and assures data quality. The surveillance definitions and processes have been refined and validated over ten years,[8] and are consistent with national and international definitions. Hospitals monitor infections hospital-wide as detailed in the surveillance manual.[9] The data undergo a central quality assurance check every six months, and the observed numbers of infections are regularly compared with expected numbers. Hospitals with numbers that are lower than the state-wide control limit are asked about their surveillance processes.

Bloodstream infections were classified *a priori* into four non-mutually exclusive groups, those due to: (1) *Staphylococcus aureus*, (2) coagulase negative staphylococci, (3) Gram positive organisms and (4) Gram negative organisms. After examining the results from these four groups we added four further subgroups, viz. *Staphylococcus aureus* infections were split into Methicillin-resistant *Staphylococcus aureus* (MRSA) and Methicillin-sensitive *Staphylococcus aureus* (MSSA), and Gram negative organisms were split into *E. coli* and *Pseudomonas aeruginosa*, to examine a lower and higher virulence organism, respectively.

The infection groups are not mutually exclusive, for example, bloodstream infections due to *Staphylococcus aureus* were also classified in the Gram positive organism group.

Community associated infections were excluded. The portal of entry of bloodstream infection (e.g., urinary tract infection, pneumonia, intra-abdominal infection, central line) was not available.

The study was approved by the ethics committees of Queensland Health and Queensland University of Technology. The Research Ethics Governance Unit for Queensland Health approved the data collection and linkage process, number: HREC/10/QPAH/180.

Statistical methods

The basis of our statistical model is shown in Figure 1. A patient's admission over time is modelled using the four states, with all patients eventually dying or being discharged, and some patients being infected. Using this multi-state model we can examine our two key questions:

1. By how much did a hospital-acquired bloodstream infection increase the risk of death?
2. By how much did a hospital-acquired bloodstream infection increase the length of stay?

Incidence density sampling

We created a smaller group of infected and non-infected patients from the complete data using incidence density sampling.[10] The incidence density sampling approach is illustrated in Figure 2. Patient E is the infected case, whose infection occurred four days after their admission. Patient D is not a potential control, as they were discharged alive before day four. The other three patients (A to C) are all eligible controls as they were infection free at the time of the case's infection. This includes patient C, who acquired an infection on a later day.

The days in hospital after the infection (for both cases and controls) were used to estimate the extra length of stay (solid lines in Figure 2). We examined the extra number of days in both standard and intensive care beds (thin and thick lines in Figure 2, respectively). For patients with multiple infections, we only considered their first infection. This was done to simplify the analysis (as multiple infections would require another state in Figure 1), and because there were relatively few admissions with multiple infections.

Matching infected patients to control patients when estimating the extra length of stay due to infection usually gives poor estimates because of the time-dependent bias.[5] This bias occurs because the time before infection is used when estimating the extra length of stay (dashed horizontal lines in Figure 2). However, unlike traditional matching studies, we used incidence density sampling, which also matches on the timing of infection because potential controls must have been infection free at the time of the case's infection.[10]

To make comparable groups of patients in terms of morbidity we matched infected cases to controls who: had the same first letter in the principal diagnosis code (using ICD-10 coding), were of a similar age (within 10 years), were at the same hospital, and were infection free at the time of the case's infection. We randomly selected four controls for each infected patient.

Statistical power

The study had a 90% power to detect an increased hazard ratio of 1.40 (40%) for infected versus uninfected patients using the smallest number of infections of 189 for MRSA, and an increased hazard ratios of 1.18 (18%) for the second smallest number of infections of 744. These calculations assumed a two-sided 5% significance level.

We only examined the risk of in-hospital death, as we had no information on patients after discharge.

Extra length of stay

We estimated the extra length of stay due to infection using the following steps. We calculated the number of days from infection to discharge for cases, and the number of days from the case's infection to discharge for its four matched controls. We then subtracted the case's length of stay from the average length of stay for its matched controls, with separate estimates for stays in standard and ICU beds. We then averaged these individual extra lengths of stay over all cases. These averages were stratified to create separate estimates for patients discharged alive and dead.

There are no parametric equations for calculating confidence intervals for the extra length of stay, hence we used a bootstrap method to generate a 95% confidence interval.[11] We randomly selected sets of cases and matched controls with replacement, creating a random sample with the same sample size as the original data. We repeated this random selection 1,000 times.

All analyses were conducted in R version 2.15.0 using the "survival" library.

RESULTS

Hazard ratios

The hazard ratios (HRs) for the eight bloodstream infections are in Table 2. All eight infections increased the risk of death, with the largest risk for MRSA (HR = 4.6) and the smallest for gram negative BSI (HR = 2.1). The increases were statistically significant for all eight infections, as the lower limits of the 95% confidence intervals were all above 1. The greatest number of infections was 2,141 for gram positive BSI, and the smallest number was 189 for MRSA.

Extra length of stay

The extra lengths of stay for the eight bloodstream infections are in Table 3. For patients that died, there was no extra length of stay in a standard bed (as all the 95% confidence intervals include zero). For patients discharged alive, infection was associated with an extra length of stay in a standard bed for every type of bloodstream infection except the gram negative BSIs. The longest extra length of stay to discharge in a standard bed was 12.8 days for MRSA (95% CI: 6.2, 26.1 days). The 95% confidence intervals are noticeably wider for infections with smaller numbers.

Most of the bloodstream infection types were associated with an extra length of stay in ICU for both patients that lived and died (Table 3). The extra lengths of stay were generally longer for those patients that died. The longest extra length of stay to death in an ICU bed was 6.0 days for a BSI with CNS (95% CI: 3.3, 10.0 days).

CONCLUSION

This is one of the largest studies to estimate the increased length of stay and risk of death due to hospital-acquired infection.[4] All eight bloodstream infection types studied increased the risk of death and most led to extra days in intensive care. Five of the bloodstream infections also prolonged stay in a standard hospital bed by an average of between 9.8 and 12.8 days. The eight hospital-acquired infections studied therefore significantly increased mortality and morbidity.

Gram negative infections had generally shorter extra lengths of stay and lower risks of death compared with the other infection types. The three most common organisms associated with gram negative infection were *E. Coli*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*. There were no clear differences between patients with a gram positive and gram negative infection in terms of their age or primary diagnosis (data not shown). BSI with CNS had a

higher death risk (HR=2.9) than Gram-negative BSIs (HR=2.1), which could reflect the higher risk of organ failure.[12]

The average extra lengths of stay after infection were shorter for ICU bed days compared with ward bed days for all infections, which is expected as the average extra length of stay is proportional to the average total length of stay.[2]

MRSA was associated with the largest increased risk of death (HR = 4.6) and the largest increase in length of stay for a standard bed (12.8 days for those discharged alive). BSI with CNS had the largest increased length of stay in an ICU bed of 6.0 days for patients who died and 1.4 days for patients discharged alive. These estimates of hazard ratio and length of stay are similar to those from related studies that account for the time-dependent bias. A study in European hospitals found hazard ratios of 3.5 due to MRSA BSI and 3.1 for MSSA BSI, with an extra length of stay of 9.2 days for MRSA BSI and 8.6 days for MSSA BSI.[13] Results from ICUs in 10 European countries gave estimated hazard ratios for BSIs ranging from 2.1 to 4.4 depending on the organism, and extra lengths of stay in ICU ranging from –0.1 to 3.7 days.[1] ICUs in France had an estimated odds ratio for death of 3.2 due to a BSI infection, with a lower odds ratio of 2.7 for those who received appropriate treatment.[14]

Study limitations

We used a large routinely collected data set of all hospital admissions. Larger data sets give more statistical power, but are often not as detailed or error-free as prospectively collected data. The hospital admission data used here are subject to data checking at the time of entry, and we subjected the data to further logical checks and found no errors.

We matched controls to cases using the first letter of ICD-10 code so that controls and cases were broadly similar in terms of morbidity. It is possible that even after the matching, the

infected cases were sicker than the controls (prior to the infection) and that this somewhat explains the cases' extra length of stay and increased risk of death. However, adjusting for the timing of infection (which we did) is far more important than adjusting for baseline morbidity when estimating the extra length of stay due to infection.[15]

Despite using hospital-wide surveillance, some infections may have been missed. The surveillance relies on clinical testing, so an infected but untested patient would be missed. However, collection of blood cultures is standard for patients with a fever during hospitalisation.

Our results should be generalisable to other settings, but it is possible that differences will occur depending on how infections are managed. For example, some hospitals use hospital in the home schemes, where infected patients can be cared for at home rather than in the hospital.[16] Caring for infected patients in their own home would reduce the extra length of hospital stay due to infection. Unfortunately we did not have data on the use of hospital in the home, and so could not estimate the entire patient journey. If we had this data it could have been added as another state to the multi-state model in Figure 1.

We had no data on why the extra length of stay occurred. For example, the extra lengths of stay may be directly due to the increased morbidity of infection or they could be due to a change in patient management, such as the use of defined durations of intravenous antibiotics (such as for *Staphylococcus aureus* bloodstream infection). It is also possible that the total extra length of stay after bloodstream infection is not solely due to the infection. For example, a patient's stay is initially extended because of a bloodstream infection, then during this extra stay an unrelated adverse event happens, for example an adverse drug reaction that keeps them in hospital for longer.[17] To further investigate extra length of stay due to infection, we recommend a detailed individual study that follows patients from the time of

their infection to discharge, and details the decisions made and resources used.[18] In some hospitals this is already collected using a post-infection review.

Study strengths

This is one of the first studies to accurately estimate the extra length of stay due to bloodstream infection in a standard hospital bed, as most previous good estimates only examined ICU beds. This is important because days in hospital are costly so extra length of stay is key to determining the economic costs of infection,[19] as well as being an important measure of morbidity. ICU beds have a far greater economic cost than standard beds, so it is vital to get separate estimates for ward and ICU beds.[20]

Our results can be used to inform parameters for studies of the cost-effectiveness of interventions that reduce risks of hospital-acquired infection. This is the most useful application of estimates, as only describing the size of the cost does not help decision-makers, although it might get the attention of politicians and the media in the short-term. Also, erroneous estimates of these parameters might have misled decision making in the past.[5] The application of a multi-state modelling approach (Figure 1), which appropriately classifies patient risks over time should become the gold standard method for these studies.[3]

A key parameter in cost-effectiveness models is the extra number of deaths, as the years of life lost have a potentially large economic cost. We found that all eight types of bloodstream infections increased the risk of death. Avoiding infections is therefore likely to both save lives and free up valuable bed days.

What is already known on this subject?

Hospital-acquired bloodstream infections are thought to increase the risk of death and lead to longer stays in hospital. The only previous estimates of the risks to date have been: biased by

poor statistical methods, or only applicable to patients in intensive care units.

What this study adds?

This is the first study to accurately estimate the risks of death and extra length of stay in a hospital population. These estimates will be vital for cost-effectiveness analyses of interventions in hospital that aim to reduce infections (e.g., alternative cleaning regimes).

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Competing interests: None.

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Contributorship: The study was motivated by an ongoing economic evaluation involving all authors. AGB ran the statistical analysis and wrote the first draft and is the paper's guarantor. KP, MC, LH, DLP and NG gave critical input into the study design. All authors read the first draft and provided edits.

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Tables

Table 1: Basic characteristics of the nine Queensland hospitals combined, patients with admission or discharge dates between 1 January 2005 and 31 December 2010. Results for all admissions and admissions by infection status.

Admissions	Numbers	Patient age, median (IQR)	LoS in days, median (IQR)	In-hospital deaths (%)
All	2,725,515	53 (32, 69)	1 (1, 4)	1.1
Those with an infection	19,206	61 (44, 74)	15 (6, 31)	7.1
Those without an infection	2,706,309	53 (32, 69)	1 (1, 4)	1.0

IQR = inter-quartile range, LoS = length of stay

Table 2: Risks of in-hospital death due to a hospital-acquired bloodstream infection. Based on nine hospitals with admissions between 1 January 2005 and 31 December 2010.

Bloodstream infection	Number of infections	Deaths in infections, n (%)	Controls	Deaths in controls, n (%)	Hazard ratio (95% CI)
BSI and gram positive	2,141	338 (15.8%)	8,512	526 (6.2%)	3.0 (2.6, 3.5)
BSI with SAB					
All	744	124 (16.7%)	2,950	175 (5.9%)	3.5 (2.7, 4.6)
MRSA	189	38 (20.1%)	740	45 (6.1%)	4.6 (2.7, 7.6)
MSSA	555	86 (15.5%)	2,218	121 (5.5%)	3.4 (2.5, 4.7)
BSI with CNS	918	139 (15.1%)	3,640	219 (6.0%)	2.9 (2.3, 3.7)
BSI and gram negative					
All	2,044	285 (13.9%)	8,089	609 (7.5%)	2.1 (1.8, 2.4)
E. coli	465	57 (12.3%)	1,838	130 (7.1%)	2.0 (1.4, 2.8)
Pseudomonas	449	74 (16.5%)	1,771	163 (9.2%)	2.2 (1.6, 3.0)

BSI = bloodstream infection, CI = confidence interval, CNS = coagulase-negative staphylococci, MRSA = Methicillin-resistant *Staphylococcus aureus*, SAB = *Staphylococcus aureus* bacteremia.

Table 3: Extra length of stay (in days) in a standard bed and ICU bed due to a hospital-acquired bloodstream infection. Cells show the mean extra length of stay (in days) with 95% confidence intervals in parentheses. Based on nine hospitals with admissions between 1 January 2005 and 31 December 2010. Separate estimates were made for admissions that ended in death and discharge. The total length of stay is the standard bed time plus the ICU bed time (see Figure 2).

Bloodstream Infection	**Standard bed**		**ICU bed**	
	Died	Discharged	Died	Discharged
BSI and gram positive	1.0 (–3.9, 5.6)	9.8 (7.7, 12.6)	4.0 (2.6, 5.7)	0.9 (0.4, 1.8)
BSI with SAB				
All	–1.5 (–6.8, 6.1)	12.1 (6.7, 15.3)	1.4 (0.5, 3.0)	0.9 (0.1, 2.9)
MRSA	–1.6 (–12.6, 12.6)	12.8 (6.2, 26.1)	3.1 (0.5, 7.2)	3.1 (0.4, 13.2)
MSSA	2.7 (–2.6, 9.7)	11.0 (6.4, 14.9)	0.7 (–0.3, 2.0)	0.4 (0.0, 0.8)
BSI with CNS	3.5 (–4.0, 13.4)	9.8 (3.6, 14.6)	6.0 (3.3, 10.0)	1.4 (0.6, 2.5)
BSI and gram negative				
All	–3.9 (–8.7, –0.4)	2.7 (–4.1, 6.1)	3.0 (1.4, 4.5)	0.6 (0.3, 1.0)
E. coli	–3.3 (–9.3, 7.9)	1.1 (–13.2, 5.7)	2.5 (0.4, 4.7)	0.5 (–0.1, 0.9)
Pseudomonas	–5.4 (–11.6, 9.2)	5.6 (–6.4, 14.3)	3.2 (0.8, 7.1)	0.5 (0.3, 1.2)

BSI = bloodstream infection, CI = confidence interval, CNS = coagulase-negative staphylococci, ICU = intensive care unit, MRSA = Methicillin-resistant *Staphylococcus aureus*, MSSA = Methicillin-sensitive *Staphylococcus aureus,* SAB = *Staphylococcus aureus* bacteremia.

Figure legends

Figure 1: Four-state model to estimate the extra risk of death and extra length of stay due to a hospital-acquired bloodstream infection. The arrows represent hazards in a survival model. The extra risk of death was estimated using the hazard ratio of the hazard of death for infected patients (arrow A) and the hazard for susceptible patients (arrow C). The extra length of stay for those discharged alive was calculated by comparing the time take to discharge for infected patients (arrow B) with the time take to discharge for susceptible patients (arrow D)

Figure 2: Illustration of incidence density sampling for an infected case (patient E) and matched controls (patients A to C). The vertical dotted line shows the timing of infection. The dashed lines show the periods of hospital stay before infection. These times are discarded, as only times after infection are used to estimate the extra length of stay. The thicker solid lines show time spent in ICU. Adapted from Wolkewitz et al (2009).

The increased risks of death and extra lengths of hospital and ICU stay from hospital-acquired bloodstream infections: a case–control study

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Structured abstract

Objectives: Hospital-acquired bloodstream infections are known to increase the risk of death and prolong hospital stay, but precise estimates of these two important outcomes from well designed studies are rare, particularly for non-ICU patients. We aimed to calculate accurate estimates, which are vital for estimating the economic costs of hospital-acquired bloodstream infections.

Design: Case–control study.

Setting: Nine Australian public hospitals.

Participants: All admitted patients between 2005 and 2010.

Primary and secondary outcome measures: Risk of death and extra length of hospital stay associated with nosocomial infection.

Results: The greatest increase in the risk of death was for a bloodstream infection with Methicillin-resistant *Staphylococcus aureus* (hazard ratio = 4.6, 95% CI: 2.7, 7.6). This infection also had the longest extra length of stay to discharge in a standard bed (12.8 days, 95% CI: 6.2, 26.1 days). All eight bloodstream infections increased the length of stay in the ICU, with longer stays for patients who eventually died (mean increase: 0.7 to 6.0 days) compared with those who were discharged (mean increase: 0.4 to 3.1 days). The three most common organisms associated with gram negative infection were *E. Coli*, *Pseudomonas aeruginosa* and *Klebsiella pneumonia.*

Conclusions: Bloodstream infections are associated with an increased risk of death and longer hospital stay. Avoiding infections could save lives and free up valuable bed days.

Article summary

Article focus

- There are few accurate estimates of the increased risk of death and extra length of hospital stay after a hospital-acquired infection because of the frequent use of study designs that ignore the time-dependent bias.
- We used a multi-state approach to overcome the time-dependent bias.

Key messages

- All eight of the bloodstream infections studied were associated with an increased risk of death and longer hospital stay.

Strengths and limitations of this study

- We had an extremely large sample size, but with little detailed individual information. We could not therefore match or control for detailed individual characteristics, which may mean there is some residual confounding in our estimates.
- Our estimates will be useful for economic studies on the costs and health benefits of interventions that reduce hospital-acquired infections.

INTRODUCTION

Hospital-acquired infections increase a patient's risk of death and prolong their hospital stay.[1] Accurate estimates of the increased risk of death and extra length of stay are rare because of the complex statistical analysis needed to avoid the potentially serious biases of ignoring the timing of infection.[2, 3] There are few accurate estimates of the extra length of stay and increased risk of death due to bloodstream infections,[4] with most good estimates only for patients in intensive care. This is an important gap in our understanding of the complete burden of hospital-acquired bloodstream infections, particularly as death and length of stay are vital for estimating the economic costs of hospital-acquired infections.[5-7] Also, financial penalties are applied in some hospitals for any hospital-acquired bloodstream infection (not just central line associated bloodstream infection).

In this paper we used an analysis that accounts for the timing of infection and hence gives accurate estimates of the risk of death and extra length of stay. We examined eight types of hospital-acquired bloodstream infections using data from nine Australian hospitals over six years. We estimated the extra length of stay due to infections for both standard and intensive care unit (ICU) beds.

METHODS

Data

We examined the nine largest public hospitals in Queensland, Australia (see Table 1 for some descriptive statistics). We requested all patient admissions with an admission or discharge date between 1 January 2005 and 31 December 2010 from the Health Statistics Centre of Queensland Health. The infection data came from the Centre for Healthcare Related Infection Surveillance and Prevention (CHRISP), Queensland Health. The admission and infection data

were linked by Queensland Health staff using a unique patient unit record number and infection date.

The data used included the dates of admission, discharge and infection (if any), and the dates (if any) of admissions and discharges from intensive care. Data were also requested on admitting hospital, patient age, principal diagnosis code (ICD-10) and outcome in three categories: discharged alive, died or censored. Censored meant the outcome of the patient was unknown, which occurred when: i) the patient was transferred to another hospital, ii) the patient was discharged to some other facility, such as an aged care facility or medi-hotel. We accounted for this censoring in our analyses using statistical censoring.

CHRISP coordinates a statewide healthcare associated infection surveillance program, which aggregates and assures data quality. The surveillance definitions and processes have been refined and validated over ten years,[8] and are consistent with national and international definitions. Hospitals monitor infections hospital-wide as detailed in the surveillance manual.[9] The data undergo a central quality assurance check every six months, and the observed numbers of infections are regularly compared with expected numbers. Hospitals with numbers that are lower than the state-wide control limit are asked about their surveillance processes.

Bloodstream infections were classified *a priori* into four non-mutually exclusive groups, those due to: (1) *Staphylococcus aureus*, (2) coagulase negative staphylococci, (3) Gram positive organisms and (4) Gram negative organisms. After examining the results from these four groups we added four further subgroups, viz. *Staphylococcus aureus* infections were split into Methicillin-resistant *Staphylococcus aureus* (MRSA) and Methicillin-sensitive *Staphylococcus aureus* (MSSA), and Gram negative organisms were split into *E. coli* and *Pseudomonas aeruginosa*, to examine a lower and higher virulence organism, respectively.

The infection groups are not mutually exclusive, for example, bloodstream infections due to *Staphylococcus aureus* were also classified in the Gram positive organism group.

Community associated infections were excluded. The portal of entry of bloodstream infection (e.g., urinary tract infection, pneumonia, intra-abdominal infection, central line) was not available.

The study was approved by the ethics committees of Queensland Health and Queensland University of Technology. The Research Ethics Governance Unit for Queensland Health approved the data collection and linkage process, number: HREC/10/QPAH/180.

Statistical methods

The basis of our statistical model is shown in Figure 1. A patient's admission over time is modelled using the four states, with all patients eventually dying or being discharged, and some patients being infected. Using this multi-state model we can examine our two key questions:

1. By how much did a hospital-acquired bloodstream infection increase the risk of death?
2. By how much did a hospital-acquired bloodstream infection increase the length of stay?

Incidence density sampling

We created a smaller group of infected and non-infected patients from the complete data using incidence density sampling.[10] The incidence density sampling approach is illustrated in Figure 2. Patient E is the infected case, whose infection occurred four days after their admission. Patient D is not a potential control, as they were discharged alive before day four. The other three patients (A to C) are all eligible controls as they were infection free at the time of the case's infection. This includes patient C, who acquired an infection on a later day.

The days in hospital after the infection (for both cases and controls) were used to estimate the extra length of stay (solid lines in Figure 2). We examined the extra number of days in both standard and intensive care beds (thin and thick lines in Figure 2, respectively). For patients with multiple infections, we only considered their first infection. This was done to simplify the analysis (as multiple infections would require another state in Figure 1), and because there were relatively few admissions with multiple infections.

Matching infected patients to control patients when estimating the extra length of stay due to infection usually gives poor estimates because of the time-dependent bias.[5] This bias occurs because the time before infection is used when estimating the extra length of stay (dashed horizontal lines in Figure 2). However, unlike traditional matching studies, we used incidence density sampling, which also matches on the timing of infection because potential controls must have been infection free at the time of the case's infection.[10]

To make comparable groups of patients in terms of morbidity we matched infected cases to controls who: had the same first letter in the principal diagnosis code (using ICD-10 coding), were of a similar age (within 10 years), were at the same hospital, and were infection free at the time of the case's infection. We randomly selected four controls for each infected patient.

Statistical power

The study had a 90% power to detect an increased hazard ratio of 1.40 (40%) for infected versus uninfected patients using the smallest number of infections of 189 for MRSA, and an increased hazard ratios of 1.18 (18%) for the second smallest number of infections of 744. These calculations assumed a two-sided 5% significance level.

We only examined the risk of in-hospital death, as we had no information on patients after discharge.

Extra length of stay

We estimated the extra length of stay due to infection using the following steps. We calculated the number of days from infection to discharge for cases, and the number of days from the case's infection to discharge for its four matched controls. We then subtracted the case's length of stay from the average length of stay for its matched controls, with separate estimates for stays in standard and ICU beds. We then averaged these individual extra lengths of stay over all cases. These averages were stratified to create separate estimates for patients discharged alive and dead.

There are no parametric equations for calculating confidence intervals for the extra length of stay, hence we used a bootstrap method to generate a 95% confidence interval.[11] We randomly selected sets of cases and matched controls with replacement, creating a random sample with the same sample size as the original data. We repeated this random selection 1,000 times.

All analyses were conducted in R version 2.15.0 using the "survival" library.

RESULTS

Hazard ratios

The hazard ratios (HRs) for the eight bloodstream infections are in Table 2. All eight infections increased the risk of death, with the largest risk for MRSA (HR = 4.6) and the smallest for gram negative BSI (HR = 2.1). The increases were statistically significant for all eight infections, as the lower limits of the 95% confidence intervals were all above 1. The greatest number of infections was 2,141 for gram positive BSI, and the smallest number was 189 for MRSA.

Extra length of stay

The extra lengths of stay for the eight bloodstream infections are in Table 3. For patients that died, there was no extra length of stay in a standard bed (as all the 95% confidence intervals include zero). For patients discharged alive, infection was associated with an extra length of stay in a standard bed for every type of bloodstream infection except the gram negative BSIs. The longest extra length of stay to discharge in a standard bed was 12.8 days for MRSA (95% CI: 6.2, 26.1 days). The 95% confidence intervals are noticeably wider for infections with smaller numbers.

Most of the bloodstream infection types were associated with an extra length of stay in ICU for both patients that lived and died (Table 3). The extra lengths of stay were generally longer for those patients that died. The longest extra length of stay to death in an ICU bed was 6.0 days for a BSI with CNS (95% CI: 3.3, 10.0 days).

CONCLUSION

This is one of the largest studies to estimate the increased length of stay and risk of death due to hospital-acquired infection.[4] All eight bloodstream infection types studied increased the risk of death and most led to extra days in intensive care. Five of the bloodstream infections also prolonged stay in a standard hospital bed by an average of between 9.8 and 12.8 days. The eight hospital-acquired infections studied therefore significantly increased mortality and morbidity.

Gram negative infections had generally shorter extra lengths of stay and lower risks of death compared with the other infection types. The three most common organisms ~~of~~ associated with gram negative infection were *E. Coli*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*. There were no clear differences between patients with a gram positive and gram negative infection in terms of their age or primary diagnosis (data not shown). BSI with CNS

had a higher death risk (HR=2.9) than Gram-negative BSIs (HR=2.1), which could reflect the higher risk of organ failure.[12]

The average extra lengths of stay after infection were shorter for ICU bed days compared with ward bed days for all infections, which~~. This~~ is expected as the average extra length of stay is proportional to the average total length of stay.~~,~~[2] ~~and lengths of stay were generally longer in ward beds compared with ICU beds.~~

MRSA was associated with the largest increased risk of death (HR = 4.6) and the largest increase in length of stay for a standard bed (12.8 days for those discharged alive). BSI with CNS had the largest increased length of stay in an ICU bed of 6.0 days for patients who died and 1.4 days for patients discharged alive. These estimates of hazard ratio and length of stay are similar to those from related studies that account for the time-dependent bias. A study in European hospitals found hazard ratios of 3.5 due to MRSA BSI and 3.1 for MSSA BSI, with an extra length of stay of 9.2 days for MRSA BSI and 8.6 days for MSSA BSI.[13] Results from ICUs in 10 European countries gave estimated hazard ratios for BSIs ranging from 2.1 to 4.4 depending on the organism, and extra lengths of stay in ICU ranging from –0.1 to 3.7 days.[1] ICUs in France had an estimated odds ratio for death of 3.2 due to a BSI infection, with a lower odds ratio of 2.7 for those who received appropriate treatment.[14] ~~ICUs in Latin America had average excess length of stay due to a central line association BSI between 1.2 and 4.7 days.[15] A study of ICUs in Germany found an extra length of stay of 2.7 days for BSIs.[3]~~

Study limitations

We used a large routinely collected data set of all hospital admissions. Larger data sets give more statistical power, but are often not as detailed or error-free as prospectively collected

data. The hospital admission data used here are subject to data checking at the time of entry, and we subjected the data to further logical checks and found no errors.

We matched controls to cases using the first letter of ICD-10 code so that controls and cases were broadly similar in terms of morbidity~~, and to prevent very different patients being compared (e.g., psychiatric patients with renal patients). We did not adjust for morbidity beyond age and ICD-10 code because no further morbidity data were available~~. It is possible that even after the matching, the infected cases were sicker than the controls (prior to the infection) and that this somewhat explains the cases' extra length of stay and increased risk of death. However, adjusting for the timing of infection (which we did) is far more important than adjusting for baseline morbidity when estimating the extra length of stay due to infection.[15]

Despite using hospital-wide surveillance, some infections may have been missed. The surveillance relies on clinical testing, so an infected but untested patient would be missed. However, collection of blood cultures is standard for patients with a fever during hospitalisation.

Our results should be generalisable to other settings, but it is possible that differences will occur depending on how infections are managed. For example, some hospitals use hospital in the home schemes, where infected patients can be cared for at home rather than in the hospital.[16] Caring for infected patients in their own home would reduce the extra length of hospital stay due to infection. Unfortunately we did not have data on the use of hospital in the home, and so could not estimate the entire patient journey. If we had this data it could have been added as another state to the multi-state model in Figure 1.

We had no data on why the extra length of stay occurred. For example, the extra lengths of stay may be directly due to the increased morbidity of infection or they could be due to a

change in patient management, such as the use of defined durations of intravenous antibiotics (such as for *Staphylococcus aureus* bloodstream infection). It is also possible that the total extra length of stay after bloodstream infection is not solely due to the infection. For example, a patient's stay is initially extended because of a bloodstream infection, then during this extra stay an unrelated adverse event happens, for example an adverse drug reaction that keeps them in hospital for longer.[17] To further investigate extra length of stay due to infection, we recommend a detailed individual study that follows patients from the time of their infection to discharge, and details the decisions made and resources used.[18] In some hospitals this is already collected using a post-infection review.

Study strengths

This is one of the first studies to accurately estimate the extra length of stay due to bloodstream infection in a standard hospital bed, as most previous good estimates only examined ICU beds. This is important because days in hospital are costly so extra length of stay is key to determining the economic costs of infection,[19] as well as being an important measure of morbidity. ICU beds have a far greater economic cost than standard beds, so it is vital to get separate estimates for ward and ICU beds.[20]

Our results can be used to inform parameters for studies of the cost-effectiveness of interventions that reduce risks of hospital-acquired infection. This is the most useful application of estimates, as only describing the size of the cost does not help decision-makers, although it might get the attention of politicians and the media in the short-term. Also, erroneous estimates of these parameters might have misled decision making in the past.[5] The application of a multi-state modelling approach (Figure 1), which appropriately classifies patient risks over time should become the gold standard method for these studies.[3]

A key parameter in cost-effectiveness models is the extra number of deaths, as the years of life lost have a potentially large economic cost. We found that all eight types of bloodstream infections increased the risk of death. Avoiding infections is therefore likely to both save lives and free up valuable bed days.

What is already known on this subject?

Hospital-acquired bloodstream infections are thought to increase the risk of death and lead to longer stays in hospital. The only previous estimates of the risks to date have been: biased by poor statistical methods, or only applicable to patients in intensive care units.

What this study adds?

This is the first study to accurately estimate the risks of death and extra length of stay in a hospital population. These estimates will be vital for cost-effectiveness analyses of interventions in hospital that aim to reduce infections (e.g., alternative cleaning regimes).

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Competing interests: None.

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Tables

Table 1: Basic characteristics of the nine Queensland hospitals combined, patients with admission or discharge dates between 1 January 2005 and 31 December 2010. Results for all admissions and admissions by infection status.

Admissions	Numbers	Patient age, median (IQR)	LoS in days, median (IQR)	In-hospital deaths (%)
All	2,725,515	53 (32, 69)	1 (1, 4)	1.1
Those with an infection	19,206	61 (44, 74)	15 (6, 31)	7.1
Those without an infection	2,706,309	53 (32, 69)	1 (1, 4)	1.0

IQR = inter-quartile range, LoS = length of stay

Table 2: Risks of in-hospital death due to a hospital-acquired bloodstream infection. Based on nine hospitals with admissions between 1 January 2005 and 31 December 2010.

Bloodstream infection	**Number of infections**	**Deaths in infections, n (%)**	**Controls**	**Deaths in controls, n (%)**	**Hazard ratio (95% CI)**
BSI and gram positive	2,141	338 (15.8%)	8,512	526 (6.2%)	3.0 (2.6, 3.5)
BSI with SAB					
All	744	124 (16.7%)	2,950	175 (5.9%)	3.5 (2.7, 4.6)
MRSA	189	38 (20.1%)	740	45 (6.1%)	4.6 (2.7, 7.6)
MSSA	555	86 (15.5%)	2,218	121 (5.5%)	3.4 (2.5, 4.7)
BSI with CNS	918	139 (15.1%)	3,640	219 (6.0%)	2.9 (2.3, 3.7)
BSI and gram negative					
All	2,044	285 (13.9%)	8,089	609 (7.5%)	2.1 (1.8, 2.4)
E. coli	465	57 (12.3%)	1,838	130 (7.1%)	2.0 (1.4, 2.8)
Pseudomonas	449	74 (16.5%)	1,771	163 (9.2%)	2.2 (1.6, 3.0)

BSI = bloodstream infection, CI = confidence interval, CNS = coagulase-negative staphylococci, MRSA = Methicillin-resistant *Staphylococcus aureus*, SAB = *Staphylococcus aureus* bacteremia.

Table 3: Extra length of stay (in days) in a standard bed and ICU bed due to a hospital-acquired bloodstream infection. Cells show the mean extra length of stay (in days) with 95% confidence intervals in parentheses. Based on nine hospitals with admissions between 1 January 2005 and 31 December 2010. Separate estimates were made for admissions that ended in death and discharge. The total length of stay is the standard bed time plus the ICU bed time (see Figure 2).

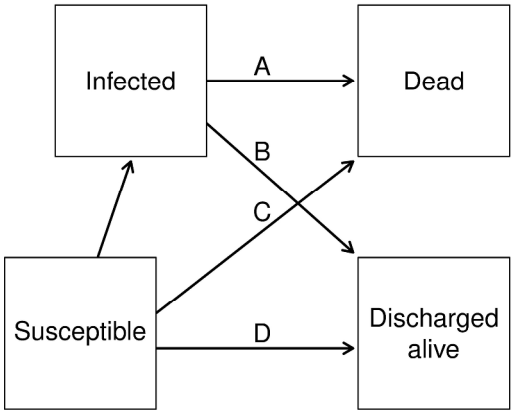
Bloodstream Infection	**Standard bed**		**ICU bed**	
	Died	Discharged	Died	Discharged
BSI and gram positive	1.0 (–3.9, 5.6)	9.8 (7.7, 12.6)	4.0 (2.6, 5.7)	0.9 (0.4, 1.8)
BSI with SAB				
All	–1.5 (–6.8, 6.1)	12.1 (6.7, 15.3)	1.4 (0.5, 3.0)	0.9 (0.1, 2.9)
MRSA	–1.6 (–12.6, 12.6)	12.8 (6.2, 26.1)	3.1 (0.5, 7.2)	3.1 (0.4, 13.2)
MSSA	2.7 (–2.6, 9.7)	11.0 (6.4, 14.9)	0.7 (–0.3, 2.0)	0.4 (0.0, 0.8)
BSI with CNS	3.5 (–4.0, 13.4)	9.8 (3.6, 14.6)	6.0 (3.3, 10.0)	1.4 (0.6, 2.5)
BSI and gram negative				
All	–3.9 (–8.7, –0.4)	2.7 (–4.1, 6.1)	3.0 (1.4, 4.5)	0.6 (0.3, 1.0)
E. coli	–3.3 (–9.3, 7.9)	1.1 (–13.2, 5.7)	2.5 (0.4, 4.7)	0.5 (–0.1, 0.9)
Pseudomonas	–5.4 (–11.6, 9.2)	5.6 (–6.4, 14.3)	3.2 (0.8, 7.1)	0.5 (0.3, 1.2)

BSI = bloodstream infection, CI = confidence interval, CNS = coagulase-negative staphylococci, ICU = intensive care unit, MRSA = Methicillin-resistant *Staphylococcus aureus*, MSSA = Methicillin-sensitive *Staphylococcus aureus,* SAB = *Staphylococcus aureus* bacteremia.

Figure legends

Figure 1: Four-state model to estimate the extra risk of death and extra length of stay due to a hospital-acquired bloodstream infection. The arrows represent hazards in a survival model. The extra risk of death was estimated using the hazard ratio of the hazard of death for infected patients (arrow A) and the hazard for susceptible patients (arrow C). The extra length of stay for those discharged alive was calculated by comparing the time take to discharge for infected patients (arrow B) with the time take to discharge for susceptible patients (arrow D)

Figure 2: Illustration of incidence density sampling for an infected case (patient E) and matched controls (patients A to C). The vertical dotted line shows the timing of infection. The dashed lines show the periods of hospital stay before infection. These times are discarded, as only times after infection are used to estimate the extra length of stay. The thicker solid lines show time spent in ICU. Adapted from Wolkewitz et al (2009).



Four-state model to estimate the extra risk of death and extra length of stay due to a hospital-acquired bloodstream infection. The arrows represent hazards in a survival model. The extra risk of death was estimated using the hazard ratio of the hazard of death for susceptible patients (arrow A) and the hazard for uninfected patients (arrow C). The extra length of stay for those discharged alive was calculated by comparing the time take to discharge for infected patients (arrow B) with the time take to discharge for susceptible patients (arrow D)
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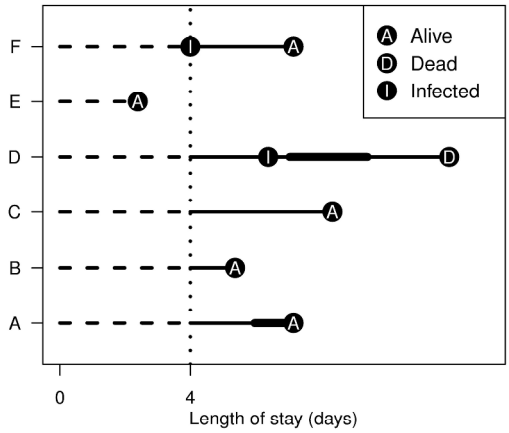

Illustration of incidence density sampling for an infected case (patient E) and matched controls (patients A to C). The vertical dotted line shows the timing of infection. The dashed lines show the periods of hospital stay before infection. These times are discarded, as only times after infection are used to estimate the extra length of stay. The thicker solid lines show time spent in ICU. Adapted from Wolkewitz et al (2009).
279x361mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***case-control studies***

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 4
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 6
Methods			
Study design	4	Present key elements of study design early in the paper	Page 6 & Fig 1
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	Page 7 & Fig 2
		(*b*) For matched studies, give matching criteria and the number of controls per case	Page 7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Pages 4-5
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	Page 7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Pages 6-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Pages 6-8
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how matching of cases and controls was addressed	Page 7
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Tables 1 & 2
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	NA
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	Table 1
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Tables 2 &3
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	Pages 9-12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Pages 10-12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 12
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 13

*Give information separately for cases and controls.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.