REVIEW 10.1111/1469-0691.12195

# Overall burden of bloodstream infection and nosocomial bloodstream infection in North America and Europe

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## Abstract

In this systematic review, we estimated the total number of episodes of bloodstream infection (BSI) and deaths from BSI per year in North America and Europe, using data from population-based settings. Then, we estimated the number of episodes and deaths from nosocomial BSI from population-based studies and nosocomial infection surveillance systems. We estimated 575 000–677 000 episodes of BSI per year in North America (536 000–628 000 in the USA and 40 000–49 000 in Canada) and 79 000–94 000 deaths (72 000–85 000 in the USA and 7000–9000 in Canada), using estimates from three population-based studies. We estimated over 1 200 000 episodes of BSI and 157 000 deaths per year in Europe, using estimates from one population-based study in each of the following countries: Denmark (9100 episodes and 1900 deaths), Finland (8700 episodes and 1100 deaths) and England (96 000 episodes and 12 000–19 000 deaths). There were substantial differences in estimates of nosocomial BSI between population-based and nosocomial infection surveillance data. BSI has a major impact on the morbidity and mortality of the general population, as it ranks among the top seven causes of death in all included countries in North America and Europe. However, it is difficult to obtain precise estimates of nosocomial BSI, owing to the limited number of studies. This review highlights the need for a greater focus on BSI research in order to reduce the overall burden of disease by improving the outcome of patients with BSI. It also emphasizes the role of infection control and prevention methods in reducing the burden of nosocomial BSI.

**Keywords:** Bacteraemia, epidemiology, mortality, outcome, population-based, sepsis
**Article published online:** 26 February 2013
*Clin Microbiol Infect* 2013; **19:** 501–509

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## Introduction

Despite the great advances in medical science in the past century, bloodstream infection (BSI) remains a growing public health concern in the modern world. It is ranked as the 11th leading cause of death in the USA, accounting for nearly 36 000 deaths in 2008 [1]. However, we believe that the burden of BSI as measured by the International Statistical Classification of Diseases and Related Health Problems (ICD) is underestimated. Many cases of BSI may, rather, be coded according to the underlying source of infection. For example, patients with BSI secondary to urinary, respiratory or gastrointestinal tract sources of infection may be assigned diagnostic codes for urinary tract infection, pneumonia, or peritonitis, respectively. Additionally, BSI may be overlooked as a cause of death, particularly in patients with terminal medical conditions, such as advanced malignancy or end-stage kidney or liver disease.

In this systematic review, we aimed to estimate the overall burden of BSI in countries where the incidence rate of BSI has been established in population-based settings. As population-based studies provide data about local residents from all microbiology laboratories within the specified geographical area, we expected those studies to provide more accurate figures than those based on ICD codes. We focused on

nosocomial BSI, because these cases are potentially preventable with adequate infection control measures within local hospitals. We used two different methods to estimate the burden of nosocomial BSI. First, we estimated the burden of nosocomial BSI from population-based studies. Then, we used nosocomial infection surveillance systems to estimate the burden of nosocomial BSI in countries where such systems were available. We limited this report to North America and Europe, because it was difficult to obtain estimates from other parts of the world, owing to a lack of population-based studies that included all cases of BSI from well-defined geographical areas.

## Methods

### Estimates of total burden of BSI from population-based studies

We examined population-based studies that extended beyond the year 2000 and reported the incidence rate of BSI in well-defined geographical areas. The number of episodes of BSI in each country was calculated as the age-adjusted and gender-adjusted incidence rate of BSI per 100 000 person-years × population in millions × 10. We used the average incidence rate of BSI if the incidence rate was stable throughout the study period, or the incidence rate during the most recent interval of the study if there was a temporal change in incidence rate. In order to estimate the total number of episodes of BSI in countries where the incidence rate was reported in a small geographical area within the nation, we used the upper and lower limits of the 95% confidence intervals (CI) of the incidence rate age-adjusted and gender-adjusted to the national population. The population of each country was obtained from the most recent census results or projected population estimates as available.

In countries where the mortality rate of BSI was reported in population-based studies, we calculated the number of deaths as mortality rate per 100 000 person-years × population in millions × 10. When the BSI mortality rate was not reported, we used the short-term (14-day, 28-day, 30-day or in-hospital) case-fatality rate (CFR) of BSI as reported from population-based studies that extended beyond the year 2000 in that nation to calculate the total number of deaths following BSI in each country. In countries where no studies reporting the overall BSI CFR were available, we used a wide range for CFR as estimated from studies in other North American and European counties. The number of deaths was calculated as the number of episodes of BSI × proportion of CFR. We calculated BSI mortality rate by multiplying the incidence rate of BSI by CFR proportion.

### Estimates of burden of nosocomial BSI from population-based studies

Nosocomial BSI was defined as BSI acquired 48 h after hospital admission. The number of episodes of nosocomial BSI was calculated as total number of episodes of BSI × proportion of nosocomial BSI from all cases as reported from population-based studies in each country. Then, we used the CFR of nosocomial BSI as reported from either population-based or institutional studies that extended beyond the year 2000 to calculate the total number of deaths following nosocomial BSI in each country. We used a range for CFR in nations where more than one study was found. The number of deaths was calculated as the number of episodes of nosocomial BSI × proportion of CFR.

### Estimates of burden of nosocomial BSI from nosocomial infection surveillance systems

We used a different approach to evaluate the burden of nosocomial BSI. We estimated the number of episodes of nosocomial BSI annually on the basis of surveillance studies of nosocomial infections. Nationwide surveillance systems that track the incidence rate of nosocomial infections are implemented in many North American and European countries. These surveillance systems estimate attack rates of nosocomial infections, including BSI, in hospitalized patients. The advantages of a nationwide surveillance system over an institutional study of nosocomial BSI include heterogeneity of sampling hospitals, a wide geographical catchment area, and a large number of participating facilities. However, most surveillance programmes are focused on a proportion of nosocomial BSI with more public health interest, such as central-line-associated BSI or infections caused by multidrug-resistant organisms.

The number of episodes of nosocomial BSI was calculated as the incidence rate of nosocomial BSI per 1000 hospital admissions × annual number of hospital admissions in each country as reported by the Organization for Economic Co-operation and Development/1000 [2,3]. Then, we used the same methods as above to calculate the number of deaths from nosocomial BSI.

## Results

### Estimates of total burden of BSI from population-based studies

*North America.* The most recent population-based study of BSI in the USA was conducted in Olmsted County, Minnesota, from 2003 to 2005, and estimated an age-adjusted and gender-adjusted incidence rate of 189 (95% CI 174–204) per 100 000 person-years [4]. Given a USA population of 308 million in

2010 (US Census Bureau (http://quickfacts.census.gov), accessed 1 October 2012), we estimated approximately 582 000 episodes of BSI per year in the USA. The annual number of episodes of BSI in the USA probably fell between 536 000 and 628 000, according to the upper and lower limits of the 95% CI of the age-adjusted and gender-adjusted incidence rate, respectively (Table 1).

The same population-based study reported an in-hospital CFR of BSI of 13.5% [4]. This was similar to the in-hospital CFR of 13% recently reported from a large multicentre study from 59 hospitals in the USA [5] and the in-hospital-attributable CFR of 12% in another recent large multicentre study [6], as summarized in Table 2. On the basis of a CFR of 13.5%, we estimated that 72 000–85 000 individuals die each year in the USA shortly following an episode of BSI. This corresponded to a mortality rate of 23–28 per 100 000 person-years. Accordingly, we concluded that BSI was the seventh most common cause of death and the leading cause of death caused by infections in the USA [1].

In Canada (population of nearly 35 million), the incidence rates of community-onset BSI were 81.6 and 101.2 per 100 000 person-years, in the Calgary and Victoria areas, respectively [7,8]. Accordingly, we estimated nearly 28 000–35 000 episodes per year of community-onset BSI in Canada. However, these estimates represent only 72% of the total episodes of BSI in Canada, as another population-based study performed in Calgary showed that 28% of all episodes of BSI were acquired in the hospital [9]. After accounting for nosocomial cases, we estimated nearly 40 000–49 000 total episodes of BSI per year in Canada. The in-hospital CFR of BSI in Calgary was 18% [9]. Accordingly, we estimated 7000–9000 deaths per year following BSI in Canada, with a mortality rate of 20–25 per 100 000 person-years, making BSI the sixth leading cause of death in Canada and the leading cause of deaths caused by infections (Statistics Canada (www.statcan.gc.ca), accessed 24 January 2013).

On the basis of these calculations from the USA and Canada, we estimated nearly 575 000–677 000 episodes of BSI

**TABLE 1. Overall burden of bloodstream infection (BSI) in North America and Europe**

| Country/Region | Population (in millions) | Incidence rate of BSI (per 100 000 person-years) | Estimated annual number of episodes of BSI | Short-term case-fatality rate following BSI (%) | Estimated mortality rate of BSI (per 100 000 person-years) | Estimated annual number of deaths following BSI |
|---|---|---|---|---|---|---|
| USA | 308.0 | 174–204[a] | 535 920–628 320 | 13.5 | 23.5–27.5 | 72 349–84 823 |
| Canada | 34.9 | 113.3–140.6[b] | 39 542–49 069 | 18 | 20.4–25.3 | 7117–8832 |
| North America | 342.9 | – | 575 462–677 389[c] | – | – | 79 466–93 655[c] |
| Denmark | 5.5 | 166 | 9130 | 20.6 | 34.2 | 1881 |
| Finland | 5.2 | 168 | 8736 | 13 | 22 | 1144 |
| England | 50.8 | 189 | 96 012 | 13–20[d] | 24.6–37.8 | 12 482–19 202 |
| Europe | 731.0 | 166–189[d] | 1 213 460–1 381 590 | 13–20[d] | 21.6–37.8 | 157 750–276 318 |

[a]Ninety-five per cent CIs of the incidence rate age-adjusted and gender-adjusted from Olmsted County, Minnesota to the US white population.
[b]The incidence rate was calculated on the basis of incidence rates of community-onset BSI of 81.6 and 101.2 per 100 000 person-years in the Calgary and Victoria regions, respectively, on the assumption that 28% of all episodes were nosocomial.
[c]The annual number of episodes and deaths from BSI in North America were calculated by adding the numbers from the USA and Canada.
[d]Estimates are based on results from population-based studies in other European countries.

**TABLE 2. Summary of recent studies reporting case-fatality rates of bloodstream infection (BSI) in North America and Europe**

| Country | Years | Type of study | Setting | Number of participating hospitals | Number of episodes of BSI | Case-fatality rate (%) | Type of case fatality | First author [reference] |
|---|---|---|---|---|---|---|---|---|
| USA | 2003–2005 | Population-based | Regional (Olmsted County, Minnesota) | 2 | 650 | 13.5 | In-hospital, all-cause (crude) | Uslan [4] |
| USA | 2002–2003 | Multicentre, retrospective | Multiple settings | 59 | 6697 | 13 | In-hospital, all-cause (crude) | Shorr [5] |
| USA | 2004 | Multicentre, retrospective | Academic medical centres | 3 | 1225 | 12 | In-hospital, attributable | Pien [6] |
| Canada | 2000–2007 | Population-based | Regional (Calgary) | 3 | 7712 | 18 | In-hospital, all-cause (crude) | Lenz [9] |
| Denmark | 1992–2006 | Population-based | Regional (northern Denmark) | 8–11 | 14 303 | 20.6[a] | 30-day all-cause (crude) | Sogaard [10] |
| Finland | 2004–2007 | Population-based | Nationwide | NA | 33 473 | 13 | 30-day all-cause (crude) | Skogberg [11] |
| Spain | 2003–2004 | Multicentre, prospective, observational | Academic medical centres | 3 | 1157 | 18.5 | 30-day all-cause (crude) | Vallés [20] |

NA, not available.
[a]Case-fatality rate during the 2002–2006 period of the study.

and 79 000–94 000 deaths per year shortly following BSI in North America.

*Europe.* In Denmark (population of 5.5 million in 2006), the incidence rate of BSI increased over a period of 15 years to reach an age-adjusted and gender-adjusted incidence rate of 166 per 100 000 person-years in 2006 in a population-based study in northern Denmark [10]. This corresponded to a total of nearly 9000 episodes of BSI in Denmark in 2006. The 30-day CFR following BSI was 20.6% during the 2002–2006 period of the same study [10]. Therefore, we estimated nearly 1900 deaths from BSI per year in Denmark. BSI was the seventh leading cause of death in Denmark in 2006 (StatBank Denmark (http://statbank.dk), accessed 1 October 2012).

Finland has a similar population as Denmark (5.2 million). The age-adjusted and gender-adjusted incidence rate of BSI was 168 per 100 000 person-years in a population-based study that included all cases of BSI in Finland in 2007 [11]. From that, we estimated a total of nearly 8700 episodes of BSI per year in Finland. The study provided direct examination of the mortality rate within 30 days of BSI in the Finish population, which was 22 per 100 000 person-years [11]. As a result, we estimated nearly 1100 deaths from BSI per year in Finland. On the basis of these estimates, BSI would be the seventh leading cause of death in Finland (Statistics Finland (http://stat.fi), accessed 1 October 2012).

In England (population of 50.8 million), the incidence rate of BSI in 2008 was 189 per 100 000 person-years [12]. We estimated a total of nearly 96 000 episodes of BSI per year. There was no direct examination of the CFR of BSI in England in population-based settings. Therefore, we used a wide range for the CFR of 13–20%, which yielded 12 000–19 000 deaths following BSI each year in England. This made BSI the fifth leading cause of death in England, and the leading cause of death caused by infections, according to the most conservative estimates (Office for National Statistics (www.ons.gov.uk), accessed 1 October 2012).

Estimation of the total number of episodes of BSI in Europe was difficult, owing to the lack of population-based studies in most other European countries. However, when we applied a range for the incidence rate of 166–189 per 100 000 person-years extrapolated from population-based studies in Denmark, Finland and England [10–12] to the entire population of Europe of 731 million as estimated in 2007 (United Nations, World Population Prospects (www.un.org), accessed 1 October 2012), we estimated 1.2–1.4 million episodes of BSI per year in Europe. The use of a CFR range of 13–20% derived from population-based studies in Europe [10,11] yielded 158 000–276 000 deaths following BSI per year in Europe.

### Estimates of the burden of nosocomial BSI from population-based studies

*North America.* In the USA, 19.1% of the total episodes of BSI were nosocomial in population-based settings [4]. On the basis of this, we estimated 102 000–120 000 episodes of nosocomial BSI per year in the USA (Table 3). To our knowledge, the CFR of nosocomial BSI has not been reported from population-based studies in the USA that examined all episodes of BSI. Recent multicentre studies from the USA have reported a CFR of 15–30%, as summarized in Table 4 [5,13,14]. On the basis of this wide range, we estimated 15 000–36 000 deaths following nosocomial BSI in the USA per year.

Population-based studies in Canada demonstrated that 28% of BSI episodes were nosocomial [9]. This corresponded to 11 000–14 000 episodes of nosocomial BSI per year, based on estimates from the Calgary and Victoria areas [7,8]. On the basis of a CFR of 26% that was recently reported in a population-based study in Calgary [9], we estimated 2900–3600 deaths following nosocomial BSI in Canada per year.

On the basis of the above figures in the USA and Canada, we estimated 113 000–134 000 episodes of nosocomial BSI and 18 000–40 000 deaths per year in North America.

**TABLE 3. Burden of nosocomial bloodstream infection (BSI) in North America and Europe as estimated from population-based studies**

| Country/Region | Estimated annual number of episodes of BSI | Proportion of nosocomial episodes (%) | Estimated annual number of episodes of nosocomial BSI | Case-fatality rate following nosocomial BSI (%) | Estimated annual number of deaths following nosocomial BSI |
|---|---|---|---|---|---|
| USA | 535 920–628 320 | 19.1 | 102 361–120 009 | 15–30 | 15 354–36 003 |
| Canada | 39 542–49 069 | 28 | 11 072–13 739 | 26 | 2879–3572 |
| North America | 575 462–677 389[a] | – | 113 433–133 748[a] | – | 18 233–39 575[a] |
| Denmark | 9130 | 35 | 3196 | 27.6 | 882 |
| Finland | 8736 | 20–30[b] | 1747–2621 | 16 | 280–419 |
| England | 96 012 | 20–30[b] | 19 202–28 804 | 12–32[b] | 2304–9217 |
| Europe | 1 213 460–1 381 590 | 20–30[b] | 242 692–414 477 | 12–32[b] | 29 123–132 633 |

[a]The annual number of episodes and deaths following nosocomial BSI in North America was calculated by adding the numbers from the USA and Canada.
[b]Estimates are based on results from studies in other countries in North America and Europe.

**TABLE 4. Summary of recent reports of case-fatality rates of nosocomial bloodstream infection (BSI) in North America and Europe.**

| Country | Years | Type of study | Setting | Number of participating hospitals | Number of episodes of nosocomial BSI | Case-fatality rate (%) | Type of case fatality | First author [reference] |
|---|---|---|---|---|---|---|---|---|
| USA | 1995–2002 | Multicentre, prospective, observational | Multiple settings | 49 | 24 179 | 27 | In-hospital, all-cause (crude) | Wisplinghoff [13] |
| USA | 2000–2001 | Multicentre, prospective, observational | Multiple settings | 3 | 175 | 30 | In-hospital, all-cause (crude) | Freedman [14] |
| USA | 2002–2003 | Multicentre, retrospective | Multiple settings | 59 | 468 | 15 | In-hospital, all-cause (crude) | Shorr [5] |
| Canada | 2000–2007 | Population-based, surveillance | Regional (Calgary) | 3 | 2132 | 26 | 28-day all-cause (crude) | Lenz [9] |
| Belgium | 2003 | Surveillance | Nationwide | 19 | 1839 | 31.8 | In-hospital, all-cause (crude) | Vrijens [16] |
| Estonia | 2004–2005 | Multicentre, prospective observational | Multiple settings | 3 | 549 | 31 | In-hospital, all-cause (crude) | Mitt [17] |
| Finland | 1999–2000 | Multicenter, prospective, observational | Multiple settings | 4 | 1477 | 16 | 30-day all-cause (crude) | Lyytikainen [15] |
| France | 2004 | Surveillance report | Nationwide | 286 | 4548 | 12 | 7-day all-cause (crude) | RAISIN [18] |
| Spain | 2006–2007 | Multicentre, prospective, surveillance | Regional (Andalusia) | 15 | 476 | 24 | 30-day all-cause (crude) | Rodriguez-Bano [19] |
| Spain | 2003–2004 | Multicentre, prospective, observational | Academic medical centres | 3 | 576 | 27.3 | 30-day all-cause (crude) | Vallés [20] |

RAISIN, Réseau d'alerte d'investigation et de surveillance des infections nosocomiales (a national programme for early warning, investigation and surveillance of healthcare-associated infection in France).

*Europe.* In Denmark, 35% of episodes of BSI were hospital-acquired between 2002 and 2006 [10]. Accordingly, we estimated 3200 episodes of nosocomial BSI per year during that period. On the basis of a 30-day CFR of 27.6% [10], we estimated nearly 900 deaths per year from nosocomial BSI.

The proportions of episodes of nosocomial BSI were not reported in population-based studies from Finland and England. Therefore, we used a 20–30% estimate for the proportion of nosocomial BSI among all episodes. Accordingly, we estimated 1700–2600 and 19 000–29 000 episodes of nosocomial BSI per year in Finland and England, respectively. On the basis of a CFR of nosocomial BSI in Finland of 16% [15], we estimated 300–400 deaths following nosocomial BSI per year in Finland. There were no direct estimates of the CFR of nosocomial BSI from England; therefore, we used a wide range of 12–32%, based on results from other European countries, as summarized in Table 4 [15–20]. This yielded a wide range of 2000–9000 deaths per year.

When we applied the same figures (20–30% of nosocomial BSI among all episodes and 12–32% CFR) to the entire population of Europe, we estimated over 240 000 episodes of nosocomial BSI and 29 000 deaths per year.

### Estimates of burden of nosocomial BSI from nosocomial infection surveillance systems

*North America.* To estimate the nationwide incidence of nosocomial BSI, the Surveillance and Control of Pathogens of Epidemiological Importance (SCOPE) study was conducted from 1995 to 2002 [13]. The study enrolled 49 hospitals of various sizes with a wide geographical distribution, and detected 24 179 cases of nosocomial BSI (approximately 6.0 cases per 1000 hospital admissions or 0.8 cases per 1000 patient-days). On the basis of nationwide hospital discharge data of 37 804 021 discharges in the USA in 2002 (US Department of Health and Human Services (http://hcupnet.ahrq.gov), accessed 20 September 2012), we estimated approximately 227 000 episodes of nosocomial BSI per year in the USA (Table 5). We estimated 34 000–68 000 deaths per year from nosocomial BSI in the USA, based on a CFR of 15–30% as derived from other nosocomial BSI studies in the USA (Table 4).

*Europe.* France conducted a nationwide surveillance of nosocomial BSI from 2002 to 2004, as a part of the RAISIN (Réseau d'alerte, d'investigation et de surveillance des infections nosocomiales) network [18]. In 2004, the programme reported an incidence rate of 0.45 per 1000 patient-days. As the average hospital stay for all causes in France has been stable at approximately 6 days throughout the 2000s [2], these data were converted to 2.7 per 1000 hospital admissions. On the basis of the total population of 62.7 million (World Bank (http://www.worldbank.org), accessed 24 October 2012) and annual hospital discharges of 263 per 1000 population in 2004 [2], we estimated approximately 45 000 episodes of nosocomial BSI per year. When we utilized a CFR of 12% [18], the annual number of deaths from nosocomial BSI in France was nearly 5500.

The Nosocomial Infection National Surveillance Service of the UK also conducted a surveillance of nosocomial BSI

**TABLE 5. Burden of nosocomial bloodstream infection (BSI) in North America and Europe as estimated from surveillance studies of nosocomial infections**

| Country | Time period | Incidence rate of nosocomial BSI (per 1000 patient-days) | Incidence rate of nosocomial BSI (per 1000 hospital admissions) | Nationwide epidemiology | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | Population (in millions) | Annual number of hospital discharges (in millions) | Estimated number of episodes of nosocomial BSI | Case-fatality rate following nosocomial BSI (%) | Estimated number of deaths following nosocomial BSI |
| USA | 1995–2002 | 0.8 | 6.0 | 287.6 | 37.8 | 226 800 | 15–30 | 34 020–68 040 |
| France | 2004 | 0.45 | 2.7[a] | 62.7 | 16.8 | 45 360 | 12 | 5443 |
| England | 1997–2002 | 0.6 | 3.5 | 49.6 | 11.1 | 38 850 | 12–32[b] | 4662–12 432 |
| Finland | 1999–2000 | 0.8 | 2.7 | 5.2 | 1.3 | 3510 | 16 | 562 |
| Spain | 2006–2007 | 1.3[a] | 8.4 | 45.2 | 4.8 | 40 320 | 24–27 | 9677–11 007 |

[a]Incidence rates are estimated on the basis of average length of hospital stay in each country.
[b]Case-fatality rates are estimated from studies of nosocomial BSI in other European countries.

(Surveillance of hospital-acquired bacteraemia in English hospitals 1997–2002 (http://www.hpa.org.uk), accessed 22 October 2012). From 102 participating National Health Service hospitals in England, the study collected data on nearly 3 million hospital admissions. A total of 10 871 episodes of nosocomial BSI were found, with incidence rates of 3.5 episodes per 1000 hospital admissions and 0.6 episodes per 1000 patient-days. On the basis of nearly 11 million hospital discharges annually in England [2], we estimated approximately 39 000 episodes of nosocomial BSI with 4700–12 500 deaths per year, assuming a CFR of 12–32%.

From 1999 to 2000, a surveillance project on nosocomial BSI was performed in southern Finland [15]. The study reported incidence rates of nosocomial BSI of 0.8 per 1000 patient-days and 2.7 per 1000 hospital admissions. When we applied these rates to the entire population of Finland of 5.2 million and annual hospital discharges of 1.3 million in 2000 [2], we estimated approximately 3500 episodes of nosocomial BSI per year. The same surveillance study reported a 30-day CFR of 16% following nosocomial BSI [15]. Accordingly, we estimated approximately 560 deaths from nosocomial BSI per year in Finland.

More recently, the Andalusian Society of Infectious Diseases conducted a prospective cohort study of BSI in Spain from 2006 to 2007 [19]. Over 5 months of the survey period, the study enrolled 476 episodes of nosocomial BSI. Interestingly, the incidence rate of nosocomial BSI was 8.4 episodes per 1000 hospital admissions (1.3 episodes per 1000 patient-days), which was significantly higher than previously reported incidence rates of nosocomial BSI from other geographical areas in Europe. When this incidence rate was applied to the entire nation of Spain with over 4.8 million annual hospital discharges in 2007 [2], we estimated approximately 40 000 episodes of nosocomial BSI per year and 9700–11 000 deaths, assuming a CFR of 24–27% [19,20].

## Discussion

In this systematic review, we estimate nearly 2 million episodes and one-quarter of a million deaths from BSI annually in North America and Europe combined. As the incidence rate of BSI increases with age [4], the burden of BSI will probably increase over the next decade, owing to the increase in life-expectancy in the populations of most industrialized countries, including the USA [1]. As the population of North America and Europe constitutes only one-seventh of the entire world population (World Bank (http://www.worldbank.org), accessed 29 January 2013), it is conceivable that the annual number of deaths from BSI may be comparable to the number caused by the three big infectious disease killers in the world: human immunodeficiency virus (1.8 million deaths in 2010), tuberculosis (1.4 million deaths in 2011), and malaria (660 000 deaths in 2010) (WHO (www.who.int), accessed 29 January 2013). With the advancement of science and research in China, India, and Brazil, it would be interesting to see population-based studies that estimate the incidence rates of BSI in these large nations.

As hypothesized, data from ICD codes severely underestimate the burden of BSI. For example, it has been estimated that 36 000 deaths occur per year in the USA from BSI/septicaemia, according to ICD codes [1]. However, population-based data from Olmsted County, Minnesota indicate nearly double that number (72 000–79 000 deaths per year). This is probably a conservative estimate, as the incidence rate of BSI is probably higher in other geographical areas in the USA where intravenous drug use is more prevalent than in Olmsted County, Minnesota [21].

Our estimates suggest that BSI is among the top seven causes of death in many European and North American countries. Estimates of a BSI mortality rate of 23.5–27.5 per 100 000 person-years in the USA indicate that BSI contributes

to more deaths than any other infection, including influenza and pneumonia combined (16.2 per 100 000 population in 2010), diabetes mellitus (22.4 per 100 000), heart failure (18.7 per 100 000), kidney disease (16.3 per 100 000), chronic liver disease (10.3 per 100 000), suicide (12.4 per 100 000), motor vehicle accidents (11.4 per 100 000), colorectal cancer (17.0 per 100 000), breast cancer (13.3 per 100 000), prostate cancer (9.3 per 100 000), or cancer of any individual solid organ, with the exception of the lungs. The mortality rate of BSI is comparable to that of Alzheimer's disease (27.0 per 100 000), the sixth leading cause of death in the USA in 2010 (CDC (www.cdc.gov), accessed 31 January 2013). Obviously, BSI has not received as much attention as many of the above diseases, which have less impact on the morbidity and mortality of the general population. This highlights the need for more organized efforts to facilitate basic, translational and clinical research in this field that could lead to a better understanding of the pathophysiology and improvement of the outcome of BSI. Despite the decline in the CFR following BSI over the past two decades [6], which is mostly attributable to advances in critical care and antimicrobial management, there is still much room for improvement. It is alarming that 30% of patients with BSI receive inappropriate empirical antimicrobial therapy [10], which is independently associated with poor outcome [6,22]. This also emphasizes the need for national guidelines for the management of BSI. Such guidelines should have as much emphasis on de-escalation of antimicrobial therapy as on optimizing empirical therapy.

This review also highlights the difficulty in obtaining precise estimates of the burden of BSI in the developed world, particularly in the USA, where only one population-based study of the overall incidence rate of BSI was conducted during the past decade [4]. Generalizing the results from the relatively small population of Olmsted County (124 000) to the entire USA population of >300 million may not be optimal, given some differences in population characteristics [21]. However, the incidence rate in Olmsted County was similar to that reported from other developed countries [10–12].

It is interesting to see a difference in the reported CFR of BSI in population-based studies from North America and Europe (range: 13–21%). Some of this difference may be explained by the different methods used. Our previous work has demonstrated that the in-hospital CFR underestimates the number of deaths as compared with the 28-day or 30-day CFR, as some patients may die at home or in nursing hospices soon after discharge from the hospital (M. N. Al-Hasan, L. M. Baddour, Unpublished). Although all-cause, non-attributable mortality was used to estimate the number of deaths, BSI was certainly a contributory factor to deaths occurring shortly after BSI. Additionally, exclusion of all potential skin contaminants in blood cultures, such as coagulase-negative staphylococci and *Corynebacterium* species, without clinical verification may falsely lower the incidence rate of BSI and increase the overall CFR, as BSI caused by these low-virulence organisms is associated with a favourable outcome. Finally, it remains possible that this difference in CFR may be a result of different proportions of patients receiving inadequate empirical antimicrobial therapy, as these data have not been reported in most studies.

Nosocomial BSI has particular importance from the public health standpoint. Optimizing the management and empirical antimicrobial therapy may reduce the burden of nosocomial BSI, but prevention is the key element. Many cases of nosocomial BSI are potentially preventable with proper access techniques and earlier discontinuation of central venous and urinary catheters in hospitalized patients.

We used two different methods in this review to estimate the burden of nosocomial BSI: estimates from population-based studies, and nosocomial infection surveillance systems. The difference in the results between the two methods was substantial. For example, we estimated 102 000–120 00 episodes of nosocomial BSI per year in the USA, using data from population-based studies, and 227 000 episodes using nosocomial infection surveillance systems. Estimates of nosocomial BSI in England and Finland also demonstrated the same pattern; higher estimates from nosocomial infection surveillance systems than from population-based studies. We believe that nosocomial infection surveillance systems overestimate the burden of nosocomial BSI, probably because of referral bias. Despite efforts to include a diverse sample of hospitals in such surveillance systems, most participating institutions remain tertiary-care hospitals that receive referrals of patients with very complex or advanced diseases, which probably increases the risk of complications, including nosocomial BSI. In addition, the participating centres in such surveillance studies are not randomly selected, and therefore do not fairly represent the entire country. Estimates from population-based studies are probably more accurate, owing to lack of referral bias [23]. In addition, the overall incidence rates of BSI reported from population-based studies were similar between the four countries where such data were directly provided (the USA, Denmark, Finland, and England), with only a 12% difference between the highest and lowest incidence rates of 189 and 166 per 100 000 person-years, respectively [4,10–12]. In contrast, the difference in incidence rates of nosocomial BSI reported from nosocomial infection surveillance systems in different countries was substantial. The 65% difference between the highest and lowest incidence rates of 1.3 and 0.45 per 1000 patient-days, respectively, is unlikely to be explained by a temporal change in incidence rate over a

relatively short period of time (Table 5). Additionally, there were wide variations in the number of hospital discharges per 1000 population between different countries, probably because of differences in the structure of the healthcare systems between the countries. This has substantially influenced the estimates of nosocomial BSI obtained with nosocomial surveillance systems. Moreover, the difference in the CFR of nosocomial BSI between studies was also substantial (range: 12–32%). This was probably caused by differences in the methods used to report the CFR (7 days vs. 30 days vs. in-hospital) and differences in the complexity of cases and other host-related factors that influenced the outcome of hospitalized patients.

This further emphasizes the importance of population-based studies in estimating the burden of not only community-onset BSI, but also nosocomial BSI. Population-based studies using laboratory surveillance of BSI with clinical validation and consistent exclusion criteria for potential skin contaminants in blood cultures, preferably from multiple geographical locations in the same country or the entire nation, if feasible, would yield very informative data. In addition to demographics and site of infection acquisition, it would be beneficial to report other variables that are independently associated with mortality, in order to allow meaningful comparison across different geographical areas. These include acute severity of illness as indicated by the Pitt bacteraemia score [24], receipt of adequate antimicrobial regimens [22], primary source of infection, and the presence or absence of malignancy and liver cirrhosis [25]. Recently, a major step has been taken in the right direction with the development of a multinational population-based BSI surveillance collaboration between six geographical regions in four countries and three continents [26]. We are hoping that such collaboration will generate large-scale data regarding the epidemiology, temporal trends and outcome of BSI, and encourage other nations to follow this direction by investing in high-quality research in population-based settings.

## Transparency Declaration

M. Goto wrote the introduction, parts of the methods and results sections related to nosocomial infection surveillance systems, and summarized mortality data. M. N. Al-Hasan wrote the introduction, discussion, and parts of the methods and results sections related to population-based studies. Both authors take responsibility for the integrity of the data and the accuracy of the analysis. There is no funding source for the study. Both authors declare that there are no conflicts of interest.

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