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Population-based burden of bloodstream infections in Finland

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Abstract

Bloodstream infections (BSI) are a major cause of mortality, morbidity and medical cost, but few population-based studies have concomitantly evaluated BSI incidence and mortality. Data on BSI episodes reported to national, population-based surveillance by all clinical microbiology laboratories in Finland during 2004–07 were linked to vital statistics. Age-, sex and microbe-specific incidence and mortality rates were calculated. During 2004–07, 33 473 BSI episodes were identified; BSI incidence increased from 147 to 168 per 100 000 population (average annual increase, 4.4%; p <0.001). Rates were highest among persons ≥65 years and <1 year, and higher among male patients than female patients (166 versus 152 per 100 000). The most common aetiologies were *Escherichia coli* (27%) and *Staphylococcus aureus* (13%). Among male patients, 52% of BSI were caused by gram-positive bacteria compared with 42% among female patients (p <0.001). The overall 30-day case-fatality was 13%. Of the deaths, 32% occurred within 2 days, 70% were among people aged 65 years or more and 33% were caused by *E. coli* or *S. aureus* infections. The BSI mortality rate increased from 19 to 22 per 100 000 (average annual increase: 4.0%, p 0.01). Among people aged 25 years or more, the mortality rate was 1.4-fold higher in men than women (34 versus 25 per 100 000 population). Overall excess annual mortality from BSI in the population was 18 per 100 000. The substantial BSI burden among the elderly and among adult men highlights the need for developing and implementing effective interventions, particularly for BSI caused by *E. coli* and *S. aureus*. One-third of BSI deaths occurred early, emphasizing the importance of early identification and treatment.

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Introduction

Bloodstream infections (BSI) are a major cause of mortality and healthcare cost worldwide. In the USA, septicaemia is the tenth leading cause of death [1]. In previous population-based studies, the incidence of BSI ranged from 123 to 190 per 100 000 population [2–5] and increases in rates have been reported both from European countries and the USA [2,4–7].

Limited population-based information is available on the epidemiology and outcome of BSI [2,3], as most studies report data from single or selected hospitals [8–11]. However, population-based information on both the incidence and mortality are needed to define the public health burden of BSI and to improve treatment and prevention strategies. We used data from a national, population-based laboratory surveillance system to evaluate age-, sex- and microbe-specific incidence and mortality from BSI during 2004–07. We also estimated the excess deaths due to BSI in the Finnish population.

Methods

Population-based surveillance

The Health Care System in Finland (population 5.3 million) is organized into 20 healthcare districts, with catchment populations ranging from 68 000 to 1.4 million. All clinical microbiology laboratories are required to notify all bacterial and

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fungal isolates from blood to the National Infectious Disease Register. More than 95% of laboratories report electronically the following information: specimen date, microbe, date of birth, sex, place of residence, and each individual's unique national identity code. Multiple notifications of the same microbe which contain the same national identity code are merged into a case if they occur within 3 months of each other.

Episode of bloodstream infection

An episode of BSI was defined as bacterial species or fungus isolated from blood culture and reported to the National Infectious Disease Register during 2004–07; 36 268 episodes were included in the analysis and 229 were excluded because of invalid national identity codes or inconsistent dates. Cases with the same national identity code but different microbes isolated within 2 days were merged into a single episode and classified as polymicrobial; the rest of the episodes were monomicrobial BSI.

Outcome

Data on patients who had died (including date of death) up to 90 days after the date of the specimen yielding the first positive blood culture were retrieved from the Population Information System by linkage with the national identity codes.

Analysis and statistics

Population data from Statistics Finland during 2004–07 were used as denominators to calculate age-specific and sex-specific incidence rates of BSI. Average annualized incidence and mortality rates were calculated by using the total number of episodes, deaths, and population during 2004–07. Male-to-female rate ratios with 95% asymptotic CI were calculated. The age-, sex- and microbe-specific case fatality proportions (CFPs) for BSI episodes were calculated within 30 days of the date of blood sample confirming BSI.

Categorical variables were analysed with the chi-square test, using Yates's correction. Statistical significance of the observed trends in annual incidence and mortality rates was assessed using a Poisson regression model. To study the timing of deaths related to BSI episodes, the observed daily hazard of death was calculated using the life-table method. To assess excess (observed – expected) deaths due to BSI, the expected daily hazard of death in the Finnish population, adjusted for age and sex, was calculated by using 2006 data from Statistics Finland and compared with the observed daily hazard following a BSI episode.

Data were analysed using SPSS FOR WINDOWS, version 17.0 (Chicago, IL, USA), PASW, version 17.2 and STATA, version 9.2 (Chicago, IL, USA).

Results

During 2004–07, a total of 33 473 BSI episodes were identified among 30 523 individual patients; median age was 67 years; 51% (17 094) were male. The average annualized incidence was 159 BSI episodes per 100 000 population, with a significant increasing trend from 147 per 100 000 in 2004 to 168 per 100 000 in 2007 (average increase 4.4% per year, $p < 0.001$). Rates were highest among people ≥65 years (528) and <1 year (514) (Table 1). Among infants <1 year and people ≥35 years, the BSI rate was significantly higher for male patients than female patients; for people aged 15–34 years, the BSI rate was significantly higher in female patients than in male patients.

Aetiology of BSI

Gram-positive bacteria caused 48.5% (16 233) of the BSI episodes, gram-negative bacteria caused 43.8% (14 645), other

TABLE 1. Incidence of bloodstream infections by age and gender, Finland, 2004–07

Age group (years)	Rate of bloodstream infections[a] (number of episodes)			Male to female rate ratio	95% CI
	Male	Female	Total		
<1	583 (694)	442 (503)	514 (1197)	1.32	1.18–1.48
1–14	35 (589)	31 (519)	33 (1117)	1.11	0.98–1.24
15–24	33 (440)	39 (495)	36 (935)	0.85	0.75–0.97
25–34	39 (513)	47 (597)	43 (1110)	0.82	0.73–0.92
35–44	70 (1025)	57 (807)	64 (1832)	1.23	1.12–1.35
45–54	128 (1981)	95 (1455)	112 (3436)	1.35	1.26–1.44
55–64	236 (3354)	168 (2440)	201 (5794)	1.41	1.33–1.48
65–74	460 (3832)	291 (2891)	368 (6723)	1.58	1.50–1.66
75–84	782 (3529)	569 (4411)	648 (7940)	1.37	1.31–1.44
≥85	1264 (1128)	824 (2261)	932 (3389)	1.53	1.43–1.65
All	166 (17094)	152 (16379)	159 (33473)	1.09	1.07–1.11

CI, confidence interval.
[a]Average annualized incidence rate (episodes per 100 000 population).

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bacteria (not classifiable by Gram stain) caused 0.1% (22) and fungi caused 1.6% (544). Polymicrobial infections accounted for 6.1% (2029) of episodes. Overall, the four most common BSI aetiologies were *Escherichia coli* (27%), *Staphylococcus aureus* (13%), coagulase-negative staphylococci (10%) and *Streptococcus pneumoniae* (9%); ten microbe categories accounted for 82% of all episodes (Fig. 1). The causative agents for BSI varied by age and gender. Gram-negative bacteria were significantly more common among female patients (51.7%, 8469/16 379 versus 36.1%, 6176/17 094; p <0.001) and gram-positive were more common among male patients (55.1%, 9414/17 094 versus 41.6%, 6819/16 379; p <0.001). The gender difference in BSI caused by polymicrobial infections (6.9% in male patients versus 5.1% in female patients, p <0.001) was less prominent, and for BSI caused by fungi there was no difference (1.8% in male patients versus 1.5% in female patients). *Escherichia coli* caused 37% (6118/16 379) of BSI among female patients and 18% (3072/17 094) among male patients (p <0.001); it was the most frequent cause of BSI among women ≥15 years and among men ≥65 years (Fig. 1). *Staphylococcus aureus* was the causative agent in 15% (2626/17 094) of episodes among male patients compared with 10% (1605/16 379) among female patients (p <0.001); *S. aureus* was a particularly common cause among younger male patients (Fig. 1). *Streptococcus pneumoniae* caused 10% (1655/17 094) of episodes among male patients and 8% (1254/16 379) among female patients (p <0.001). Group B streptococcus was a prominent cause of BSI among infants aged <1 year (17%) and among women aged 25–34 years (9%) (Fig. 1).

Mortality from BSI

Of the BSI episodes, 4375 were fatal within 30 days after the first positive blood culture was obtained (CFP, 13%). Of the deaths, 70% (3044/4375) occurred in patients ≥65 years (CFP, 17%). The average annualized BSI mortality rate was 20.8 deaths per 100 000 population (range by year 19.2–21.6), with an increasing trend over time (average annual increase 4.0%, p 0.01). As the annual CFP remained stable (12.6–13.2%), the increasing trend in mortality rate was asso-

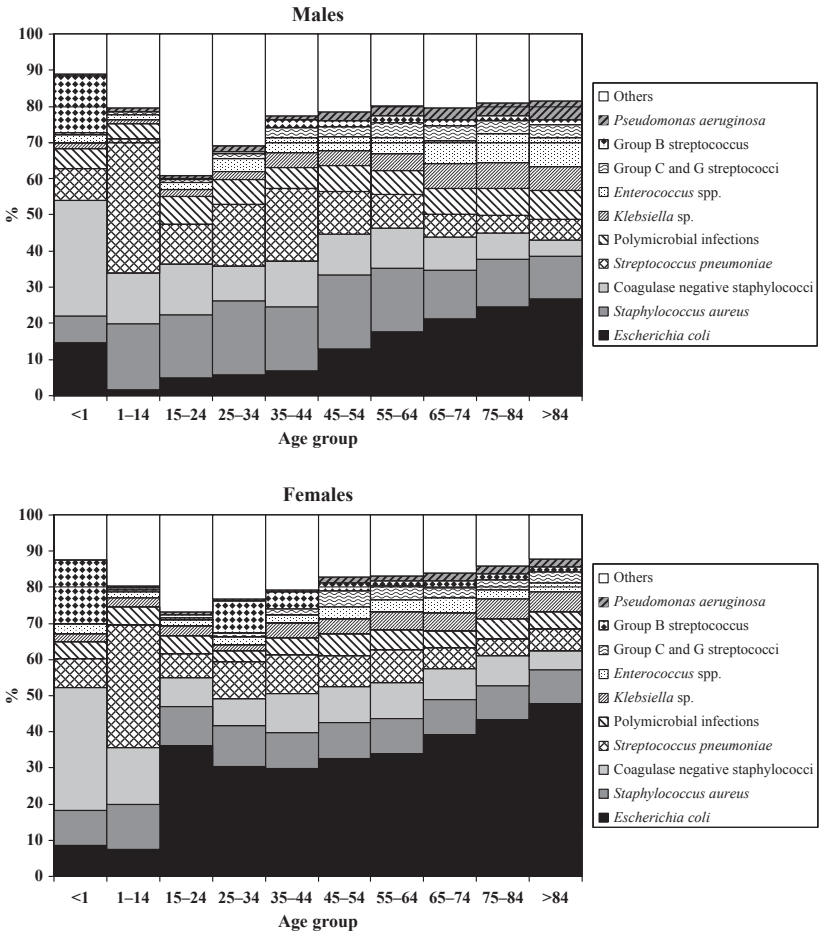

FIG. 1. Distribution of ten commonest categories of microbes causing bloodstream infections by gender and age group, Finland, 2004–07.

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ciated with the increase in incidence. The average annualized mortality rate increased by age, beginning in middle age and was highest among the elderly (Table 2). Among people ≥25 years, mortality rates were 1.4-fold higher among men than women (33.7 versus 24.5 per 100 000 population).

The ten most frequent categories of microbes were associated with 78% of all BSI deaths (Table 3). *Escherichia coli* and *S. aureus* were associated with 736 (17%) and 715 (16%) of fatal episodes. The CFPs were 13% for gram-positive, 11% for gram-negative, 14% for other bacterial and 35% for fungal infections. The CFPs were highest for BSI caused by *Pseudomonas aeruginosa* (26%), polymicrobial episodes (21%), *Enterococcus* spp. (19%), and *S. aureus* (17%). Among patients ≥65 years, CFP was significantly higher for BSI caused by gram-positive bacteria compared with those caused by gram-negative bacteria (1415/7301, 19% versus 1210/9357, 13%, p <0.001); no difference was observed among patients <65 years (718/8932, 8% versus 412/5288, 8%). For BSI caused by gram-negative bacteria, CFP was significantly larger for male patients than female patients (862/6176, 14% versus 760/8469, 9%, p <0.001), but not in BSI caused by gram-positive bacteria (1246/9414, 13% versus 887/6819, 13%).

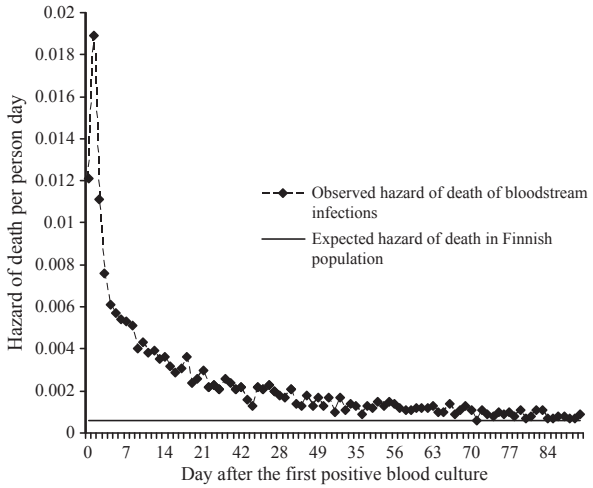

FIG. 2. Timing of deaths related to bloodstream infections, Finland, 2004–07. Observed and expected* daily hazard of death within 90 days. *Age-adjusted and sex-adjusted expected daily hazard of death among the general Finnish population.

To study timing of death, the daily hazard of death following BSI was estimated (Fig. 2); it was highest at day 1 (0.019/person per day), and reached the expected hazard of death

TABLE 2. Mortality rate of bloodstream infections at 30 days by age and gender, Finland, 2004–07

Age group (years)	Mortality of bloodstream infections[a] (number of deaths)			Male to female rate ratio	95% CI
	Male	Female	Total		
<1	22.7 (27)	14.1 (16)	18.5 (43)	1.6	0.9–3.0
1–14	0.3 (5)	0.8 (14)	0.6 (19)	0.3	0.1–1.0
15–24	1.0 (13)	0.6 (7)	0.8 (20)	1.8	0.7–4.5
25–34	1.7 (22)	0.6 (8)	1.2 (30)	2.6	1.2–5.9
35–44	6.6 (96)	2.7 (38)	4.7 (134)	2.4	1.7–3.6
45–54	15.5 (240)	7.2 (111)	11.4 (351)	2.1	1.7–2.7
55–64	33.9 (482)	17.3 (252)	25.5 (734)	2.0	1.7–2.3
65–74	71.5 (596)	37.5 (372)	53.0 (968)	1.9	1.7–2.2
75–84	150.7 (680)	86.6 (671)	110.2 (1351)	1.7	1.6–1.9
≥85	323.8 (289)	158.9 (436)	199.3 (725)	2.0	1.8–2.4
All	23.8 (2450)	17.9 (1925)	20.8 (4375)	1.3	1.2–1.3

CI, confidence interval.
[a]Average annualized mortality rate (deaths per 100 000 population).

TABLE 3. Incidence and case fatality proportion of bloodstream infections caused by ten commonest categories of microbes at day 30, Finland, 2004–07

Categories of microbes	Incidence[a] (number of cases)	CFP, % (number of deaths)	Proportion of all fatal episodes caused by the category
Escherichia coli	44 (9190)	8.0 (736)	16.8
Staphylococcus aureus	20 (4231)	16.9 (715)	16.3
Coagulase-negative staphylococci	16 (3336)	11.1 (371)	8.5
Streptococcus pneumoniae	14 (2909)	10.0 (291)	6.7
Polymicrobial infections	10 (2029)	21.0 (426)	9.7
Klebsiella sp.	8 (1667)	14.0 (234)	5.3
Enterococcus spp.	7 (1418)	19.3 (274)	6.3
Group C and G streptococci	5 (1004)	9.2 (92)	2.1
Group B streptococcus	4 (791)	7.3 (58)	1.3
Pseudomonas aeruginosa	4 (759)	26.4 (200)	4.6
Other	29 (6139)	15.9 (978)	22.4
Total	159 (33473)	13.1 (4375)	

CFP, case fatality proportion.
[a]Average annualized incidence rate (episodes per 100 000 population).

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among an age-adjusted and sex-adjusted Finnish population (0.00064/person per day) at approximately 60 days. The early peak in the hazard of death was most pronounced among middle aged and older patients (the hazard of death at day 1 was 0.008/person-day among patients aged <1 year, 0.003 in age group 1–34 years, 0.018 in 35–64 years, 0.022 in 65–84 years and 0.027 in patients aged >85 years). Of all deaths, 32% (1380/4375) occurred during days 0–2. Among patients aged <1 years, 49% of deaths within 30 days occurred during days 0–2, whereas this was the case in 30–35% among the other age groups. The proportion of early deaths (days 0–2) was similar among female and male patients (32% versus 31%). Of the deaths associated with *Streptococcus pneumoniae*, 48% occurred early, of those related to *E. coli* 36% were early, for *S. aureus* 23% were early and for coagulase-negative staphylococci this value was 23%.

An estimated 934 average annual excess deaths within 30 days due to BSI were observed compared with the expected 160 deaths among an age-adjusted and sex-adjusted Finnish reference population, indicating an excess mortality rate of 17.7 per 100 000 population.

Discussion

The data from this nationwide, population-based study indicate that both incidence and mortality from BSI increased significantly during 2004–07. Considerable excess mortality was attributable to BSI, particularly among the growing population of older adults, underlining the importance of improving interventions to reduce risk and implementing specific preventive measures such as preventing healthcare-associated BSI and using available vaccines, such as pneumococcal vaccine against the major causes of BSI. Most BSI-related mortality occurred within the first month of infection. One-third of deaths occurred within the first few days after the diagnosis, emphasizing the importance of early identification and treatment of BSI.

The BSI rate increased by 14.3% during the 4-year study period (from 147 to 168 per 100 000 population). Rates were also substantially higher compared with our previous study during 1995–2002 (125 per 100 000) which used data from the same surveillance system [4]. Among the few previous population-based studies, higher rates have been reported from Denmark [2] (153 per 100 000 in 1994), USA [3] (190 per 100 000) and from England (189 per 100 000 in 2008) [5]. Differences in population demographics, healthcare-seeking behaviour and clinical practice, such as blood culture sampling rate, may contribute to the reported differences. In our previous study, the increasing trend and regional differences in BSI rates in Finland were associated with changes in blood-culturing activity, but not with changes in causative agents of BSI [4]. Changes in blood-culturing methodology may also play a role [12].

Over half of all BSI cases in our study and in previous studies were 65 years or older [5,6]. We observed slightly higher rates in male patients than female patients. Larger gender differences have been reported in the USA and in England in BSI [3,5] and in sepsis studies [13], especially among patients aged over 60 years and among black persons. In our study, rates were higher among working-age men compared with women. Differences in prevalence of chronic medical conditions and risk behaviours may contribute to the observed gender differences. For example, smoking-related chronic lung diseases and heavy alcohol use, which are important risk factors for severe sepsis and invasive pneumococcal infections, are more common among men [14,15].

Escherichia coli and *S. aureus* were the most common aetiologies of BSI in our study, consistent with other population-based reports [3,5,6]. The incidence of *E. coli* was 44 per 100 000 in our study compared with 30–48 per 100 000 in the previous population-based studies [3,5,16]. The incidence of *S. aureus* was 20 per 100 000 in our study compared with 20–32 in previous studies) [3,17]. Consistent with previous studies, the proportion of BSI due to *E. coli* was higher among female patients [3,16]. The proportions of *S. aureus* and *Streptococcus pneumoniae* were higher among male patients in both our study and in previous studies [3,17,18].

To our knowledge, this is the first study to report nationwide estimates of case fatality (13%) and mortality (20.8 per 100 000) for BSI within 30 days, describing the overall disease burden of BSI in the population. We found considerable excess mortality from BSI (17.7 per 100 000) in the population. Excess deaths were observed until approximately 60 days after BSI diagnosis, suggesting the need for standardization regarding the time-point to record outcome. In our study, as in others, the mortality rate began to increase in the middle aged, and 70% of fatal cases occurred in patients aged 65 years or older [3,8,9]. Overall, we observed 1.4-fold higher mortality rates in adult men than women, which may be associated with a higher frequency of gram-positive BSI, especially *S. aureus*. However, the difference may also reflect different predisposing factors and care-seeking behaviour.

Escherichia coli and *S. aureus* caused an equal number of the deaths and were associated with one-third of all fatal outcomes. Whereas the rate of *E. coli* BSI was twice as high as the rate of *S. aureus* BSI, the CFP of *S. aureus* BSI was two-fold (8% in *E. coli* BSI versus 17% in *S. aureus*). Changes

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in overall rates of *S. aureus* BSI have been associated with rates of methicillin-resistant *S. aureus* (MRSA) in England [5,19], but not in Canada [17]. Significant mortality and morbidity was associated both with methicillin-susceptible *S. aureus* (MSSA) and MRSA BSI in a recent European multicentre study [20]. As only 2.7% of *S. aureus* BSI cases were caused by MRSA in Finland in 2007 (National Infectious Disease Register, unpublished data), it is unlikely that MRSA contributes to the overall increase in BSI.

About one-third of the deaths occurred during the first 2 days after the blood culture specimen confirming BSI. Some of the early deaths may be associated with delays in seeking care, inaccurate initial diagnosis, or delay in or inappropriate treatment; others may be the result of severity of disease at presentation in patients with predisposing factors or virulent causative agents. The importance of delays in administering antimicrobial therapy on the outcome of septic shock is well established [21,22]. Although the choice of empiric antibiotic therapy for blood-culture-confirmed severe sepsis was considered appropriate in 90% of cases in a recent Finnish multicentre trial [14], inappropriate therapy may be an important risk factor among nosocomial and healthcare-associated BSI [23,24]. The choice of empiric antibiotic may be even more important in the future, if resistance increases among common causes of BSI, such as extended spectrum β-lactamase-producing *E. coli* strains.

Several limitations should be considered in interpreting our findings. First, we did not have information on the patients' underlying medical conditions, including type and severity of underlying illness or immunosuppression, which may have influenced the observed gender differences and are risk factors for fatal outcome. Second, we did not have information on whether infection was the primary, immediate or contributing factor of death. However, deaths occurring shortly after the diagnosis of BSI are likely to be associated with infection. Third, our database did not contain information on whether the BSI was healthcare-associated or community-acquired, or clinical information such as the source of infection and whether antimicrobial therapy was delayed or inappropriate [8,9,22].

Our study documents the considerable burden of BSI, and increasing incidence and mortality. To reduce this burden, both general and microbe-specific interventions should be developed. For *E. coli* and *S. aureus*, the most common causative agents for fatal BSI, infection control protocols are available for prevention of healthcare-associated BSI, especially those related to surgery and devices. Studies by the US CDC have shown that prevention of central line-associated BSI has a profound impact on mortality [25]. In Finland, enhanced surveillance of healthcare-associated BSI has been conducted in selected hospitals since 1999, enabling identification of the source of infection (primary or secondary) and monitoring of outcomes [26]. Only a few preventive measures, such as pneumococcal and influenza vaccinations, are available for community-acquired BSI. Many deaths occurred within the first few days after the diagnosis, highlighting the importance of improving access to health services, and implementing treatment guidelines to identify and treat patients with sepsis and BSI without delay.

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Transparency Declaration

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