The changing epidemiology of *Staphylococcus aureus* bloodstream infection: a multinational population-based surveillance study

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Abstract

Although the epidemiology of *Staphylococcus aureus* bloodstream infection (BSI) has been changing, international comparisons are lacking. We sought to determine the incidence of *S. aureus* BSI and assess trends over time and by region. Population-based surveillance was conducted nationally in Finland and regionally in Canberra, Australia, western Sweden, and three areas in each of Canada and Denmark during 2000–2008. Incidence rates were age-standardized and gender-standardized to the EU 27-country 2007 population. During 83 million person-years of surveillance, 18 430 episodes of *S. aureus* BSI were identified. The overall annual incidence rate for *S. aureus* BSI was 26.1 per 100 000 population, and those for methicillin-sensitive *S. aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA) were 24.2 and 1.9 per 100 000, respectively. Although the overall incidence of community-onset MSSA BSI (15.0 per 100 000) was relatively similar across regions, the incidence rates of hospital-onset MSSA (9.2 per 100 000), community-onset MRSA (1.0 per 100 000) and hospital-onset MRSA (0.8 per 100 000) BSI varied substantially. Whereas the overall incidence of *S. aureus* BSI did not increase over the study period, there was an increase in the incidence of MRSA BSI. Major changes in the occurrence of community-onset and hospital-onset MSSA and MRSA BSI occurred, but these varied significantly among regions, even within the same country. Although major changes in the epidemiology of community-onset and hospital-onset MSSA and MRSA BSIs are occurring, this multinational population-based study did not find that the overall incidence of *S. aureus* BSI is increasing.

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*International Bacteremia Surveillance Collaborative listed in Appendix 1. This study was presented in part at the 21st European Congress of Clinical Microbiology and Infectious Diseases, Milan, Italy, 2011.

Background

Staphylococcus aureus is the second most common cause of bloodstream infection (BSI), and is the most important cause of BSI-associated death [1–3]. Population-based studies conducted in many regions around the world have identified incidence rates of 15–40 per 100 000 population per year,

with case-fatality rates of approximately 15–25% [4–16]. The epidemiology of *S. aureus* BSI appears to be changing. Many regions worldwide have witnessed increases in the overall incidence of *S. aureus* BSI, and there have been increases in the number and severity of BSIs caused by methicillin-resistant *S. aureus* (MRSA), associated with the emergence of community-associated strains in many areas [11,14,15,17–25]. However, it is unclear whether these increases in MRSA BSI may be replacing or adding to the burden of disease caused by methicillin-sensitive *S. aureus* (MSSA) [6,13,22–24,26–28]. In addition, it is not known to what extent changes in the occurrence of both MSSA and MRSA BSI may be attributable to shifts in incidence between community-based and hospital-based patients.

In order to best establish the distribution and determinants of an infectious disease, population-based studies are optimal. This is because, in these designs, selection bias is minimized by inclusion of all cases of disease occurring among residents of a defined population. Furthermore, by virtue of the fact that all cases are identified among a known population, shifts between subpopulations such as community and hospital can be evaluated, and comparisons among different populations and time periods are facilitated. With the exception of one study that specifically compared MRSA incidence rates between the UK and the USA [29], population-based studies investigating the epidemiology of invasive or bacteraemic *S. aureus* disease to date have been limited to single regions or one country. The objective of this study was therefore to define the occurrence of all MSSA and MRSA BSIs within a large multinational population and to evaluate temporal and regional differences. We were specifically interested in determining whether the overall incidence of *S. aureus* BSI has been changing, and whether MRSA may be replacing or adding to the burden of disease caused by MSSA.

Methods

Study protocol

This study utilized a multicentre population-based cohort design. Active surveillance was conducted nationally in Finland and in eight other regions within Australia, Canada, Denmark and Sweden under the auspices of the International Bacteremia Surveillance Collaborative [30]. All incident episodes of *S. aureus* BSI as defined by the growth of this organism from one or more blood cultures from residents of the surveillance populations during 1 January 2000 to 31 December 2008 were identified. Study laboratories were estimated to identify ~99% of all positive blood cultures from residents of the surveillance regions, and were equipped with electronic information systems to allow complete retrieval of recorded data. Patient age and gender were recorded, and isolates were determined to be MSSA or MRSA with standard methodology, according to the protocols established in each of the participating centres. Cases were classified as hospital-onset if the first culture was obtained more than 2 days after admission to hospital or within 2 days of discharge, and as community-onset otherwise. The Conjoint Health Research Ethics Board at the University of Calgary approved this study, and each centre complied with their local specific scientific and ethical review requirements.

Surveillance populations

The Canberra Region (population 370 000) includes the city of Canberra within the Australian Capital Territory and the satellite city of Queanbeyan and several small surrounding rural towns within the state of New South Wales [31]. The three Canadian centres included Sherbrooke (Quebec), Victoria (British Columbia), and Calgary (Alberta). Sherbrooke has a population of 152 000 residents, and is served by a single microbiology laboratory located in the Centre Hospitalier Universitaire de Sherbrooke [13]. Data from the Victoria area included the south local health area of the Vancouver Island Health Authority (population 364 000), and cases were identified at the regional microbiology laboratory [30]. Laboratory-based surveillance in the Calgary Health Region (population 1.2 million) was conducted at Calgary Laboratory Services [32]. The Danish surveillance regions included the North Denmark Region and two areas within the Capital Region of Denmark. The North Denmark Region surveillance was conducted using the previous boundaries of the North Jutland County (population 495 000). Surveillance from the Capital Region of Denmark was conducted within the boundaries of the two prior regions of Copenhagen City (population 640 000) and Copenhagen County (population 620 000). Surveillance data from Finland (population 5.3 million) was obtained from the National Infectious Disease Register, to which all Finnish clinical microbiology laboratories report all bacterial isolations from blood [33]. The Swedish surveillance region included the Skaraborg County Health Region located in western Sweden (population 256 000), where cases occurring in the community and among patients admitted to all four hospitals were identified [8].

Data management and statistical analysis

Data were analysed with Stata 11.2 (StataCorp, College Station, TX, USA). For purposes of analysis, MSSA and MRSA were considered independently. Only the first isolate per type per patient per year was included in analysis. The incidence of *S. aureus* BSI was calculated by dividing the number of incident cases by the surveillance population as deter-

mined by census data from each of the surveillance areas. Incidence rates were reported after age (<1 year, and deciles thereafter) and gender standardization to the 2007 27-country EU (EU27) population (http://epp.eurostat.ec.europa.eu). Variability in incidence rates was assessed with the chi-square test and the Cuzick non-parametric test for trend across ordered groups. Although exact overall age-specific and gender-specific incidence rates for MSSA and MRSA BSI were available for all years, data defining community-onset and hospital-onset BSI were not available for 2002–2003 in Finland, and these were estimated from adjacent years. The gender-specific risk for the development of an *S. aureus* BSI and the incidence rates between the two time periods 2000–2004 and 2005–2008 was determined by calculating an incidence rate ratio (RR) with a 95% confidence interval (CI).

Results

During the 9-year study involving more than 83 million patient-years of observation, a total of 18 430 incident cases of *S. aureus* BSI were identified, of which 17 618 (95.6%) were MSSA and 812 (4.4%) were MRSA. The incidence was highest in the very young and the elderly, as shown in Fig. 1. As compared with females, males were at increased risk for any *S. aureus* BSI (27.6 vs. 16.9 per 100 000; RR 1.63; 95% CI 1.59–1.68; p <0.0001), and this was true for both MSSA BSIs (26.4 vs. 16.2 per 100 000; RR 1.63; 95% CI 1.58–1.68; p <0.0001) and MRSA BSIs (1.2 vs. 0.7 per 100 000; RR 1.72; 95% CI 1.49–1.99; p <0.0001).

The overall standardized annual incidence rate for *S. aureus* BSI was 26.1 per 100 000 population, and those for MSSA and MRSA BSIs were 24.2 and 1.9 per 100 000, respectively. The overall adjusted incidence rates for *S. aureus* BSI were markedly different (p <0.001) among the surveillance regions, as shown in Fig. 2. Whereas the overall incidence of community-onset MSSA BSI (15.0; range 11.9–16.5 per 100 000) was relatively similar across regions, rates of hospital-onset MSSA (9.2; range 3.1–17.0 per 100 000), community-onset MRSA (1.0; range 0.04–2.4 per 100 000) and hospital-onset MRSA (0.8; range 0–2.7 per 100 000) BSIs varied substantially by surveillance area, as shown in Fig. 2.

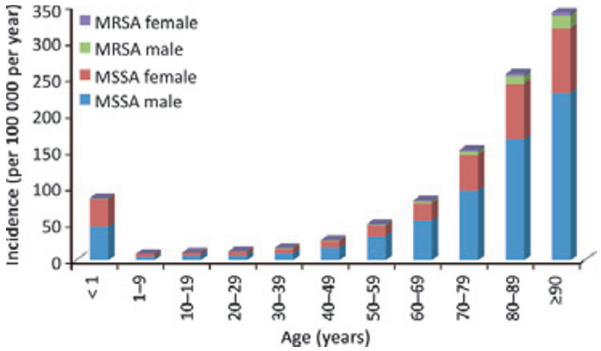

FIG. 1. Age-specific and gender-specific incidence rates of *Staphylococcus aureus* bloodstream infection, 2000–2008. MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-sensitive *S. aureus*.

Although there was evidence for year-to-year variability (p <0.001) during the study period, there was no evidence to support an overall annual change in incidence (p 0.8), as shown in Fig. 3. However, the annual incidence of community-onset *S. aureus* BSI increased significantly (p <0.001). Although there was no evidence to support an overall trend for an annual increase in the incidence of MSSA BSI (p 0.8) or of hospital-onset MSSA BSI (p 0.12), a significant (p 0.005) increase in the incidence of community-onset MSSA BSI was observed (Fig. 3). The overall yearly incidence of MRSA BSI increased (p 0.035), particularly in the second half of the study, and this was principally attributable to increases in the numbers of community-onset MRSA BSIs (p 0.013), as shown in Fig. 3.

The incidence of *S. aureus* BSI showed considerable variability by region (Fig. 4) and over time, even within countries, as shown in Table I and Appendix 2. In western Sweden, there was a significant increase in the incidence of MSSA BSI that was related to an increase in the incidence of community-onset BSI; MRSA BSI was rare. In Finland, an increase in the incidence of BSI overall was observed, with increasing numbers of cases of hospital-onset MSSA BSI and both community-onset and hospital-onset MRSA BSI. In both Canberra and Sherbrooke, the incidence rates of MSSA and MRSA BSIs increased initially and then decreased, such that an overall change was not observed. In Calgary, overall

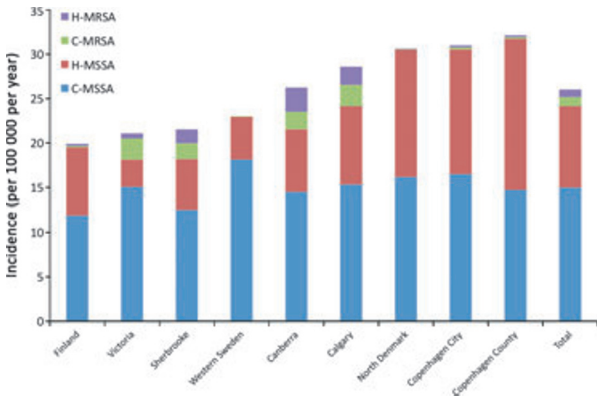

FIG. 2. Age-adjusted and gender-adjusted annual incidence rates of *Staphylococcus aureus* bloodstream infection by region, 2000–2008. H-MRSA, hospital-onset methicillin-resistant *S. aureus*; C-MRSA, community-onset methicillin-resistant *S. aureus*; H-MSSA, hospital-onset methicillin-sensitive *S. aureus*; C-MSSA, community-onset methicillin-sensitive *S. aureus*.

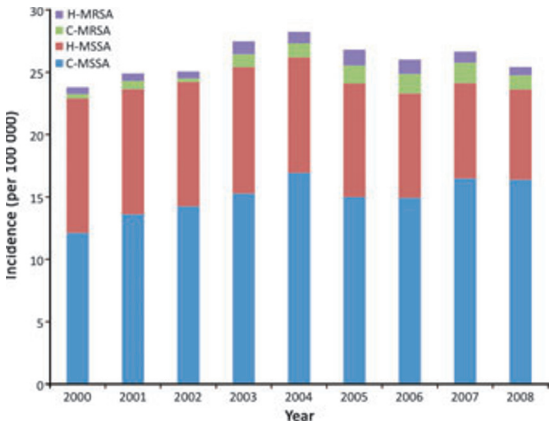

FIG. 3. Age-adjusted and gender-adjusted annual incidence rates for *Staphylococcus aureus* bloodstream infection, 2000–2008. H-MRSA, hospital-onset methicillin-resistant *S. aureus*; C-MRSA, community-onset methicillin-resistant *S. aureus*; H-MSSA, hospital-onset methicillin-sensitive *S. aureus*; C-MSSA, community-onset methicillin-sensitive *S. aureus*.

decreases in the incidence rates of both community-onset and hospital-onset MSSA BSIs were observed, although there were increased incidence rates of MRSA BSI. Although a similar emergence of community-onset MRSA BSI occurred in Victoria, unlike in Calgary this added to the incidence of MSSA BSI, resulting in an overall increase in the burden of disease. Both the North Denmark and Copenhagen City regions witnessed an overall decrease in the incidence rates of BSI, which was attributable to significant decreases in the incidence rates of hospital-onset MSSA BSI. In contrast, in Copenhagen County, a decreasing incidence of hospital-onset MSSA BSI was countered by an increase in the incidence of community-onset MSSA BSI and a low but significant additive incidence of MRSA BSI, particularly in the community.

Discussion

This study has a number of important and novel attributes. First, it is the largest (nearly 20 000 patients) study of *S. aureus* BSI reported to date. Second, it includes all incident cases of MRSA and MSSA BSI occurring in both the community and hospital. As a result, we were able to evaluate overall effects in the population at large and detect shifts within subgroups. Third, we included nine regions from five countries in three continents. Following standardization against a reference population, we were able to conduct regional and international incidence rate comparisons. Fourth, the study duration was 9 years, so year-to-year variability and trends over time could be observed over a long period. Ultimately, this study provides new information on the incidence of all *S. aureus* BSIs occurring in multiple populations around the globe, and highlights major regional differences in the epidemiology of *S. aureus* BSI.

There are only a few contemporary population-based studies that have investigated the incidence of all *S. aureus* BSIs in other populations around the globe for comparison. Asgeirsson *et al.* [14] investigated *S. aureus* BSI among 692 adults in Iceland during 1995–2008, and found decreasing nosocomial infection rates that were countered by increasing rates in the community, giving an overall increasing incidence of 22.7–28.9 per 100 000. El Atrouni *et al.* [15] studied *S. aureus* BSIs among 247 adult residents of Olmsted County

TABLE 1. Changes in the occurrence of *Staphylococcus aureus* bloodstream infection

Centre	C-MSSA	H-MSSA	MSSA	C-MRSA	H-MRSA	MRSA	All SA
North Denmark	16.4 vs. 16.0; 1.02 (0.88–1.18)	11.6 vs. 16.5; 0.70 (0.60–0.83)	28.0 vs. 32.6; 0.86 (0.77–0.96)	0.05 vs. 0.04; 1.23 (0.02–96.91)	Two cases during 2005–2008	0.15 vs. 0.04; 3.70 (0.30–194.4)	28.1 vs. 32.6; 0.86 (0.77–0.96)
Calgary	14.0 vs. 16.4; 0.85 (0.77–0.94)	7.1 vs. 10.1; 0.71 (0.62–0.81)	21.1 vs. 26.5; 0.80 (0.74–0.86)	4.3 vs. 0.9; 4.93 (3.59–6.90)	3.1 vs. 1.2; 2.57 (1.91–3.48)	7.4 vs. 2.1; 3.57 (2.89–4.45)	28.6 vs. 28.6; 1.00 (0.93–1.08)
Copenhagen City	15.9 vs. 17.0; 0.94 (0.82–1.07)	11.5 vs. 16.1; 0.71 (0.61–0.82)	27.4 vs. 33.1; 0.83 (0.75–0.91)	0.2 vs. 0.3; 0.72 (0.19–2.50)	0.01 vs. 0.02; 0.38 (0.07–1.54)	0.3 vs. 0.5; 0.58 (0.21–1.43)	27.7 vs. 33.7; 0.82 (0.75–0.91)
Copenhagen County	16.6 vs. 13.2; 1.25 (1.09–1.44)	14.6 vs. 19.1; 0.76 (0.67–0.87)	31.1 vs. 32.3; 0.96 (0.88–1.06)	0.3 vs. 0.06; 5.01 (1.00–48.44)	0.3 vs. 0.1; 3.34 (0.80–19.55)	0.7 vs. 0.2; 4.00 (1.40–13.99)	31.8 vs. 32.5; 0.98 (0.89–1.08)
Canberra	14.4 vs. 14.6; 0.99 (0.82–1.19)	6.5 vs. 7.6; 0.86 (0.65–1.12)	20.9 vs. 22.1; 0.94 (0.81–1.10)	2.0 vs. 2.0; 0.98 (0.58–1.65)	2.9 vs. 2.6; 1.13 (0.73–1.76)	4.9 vs. 4.6; 1.07 (0.76–1.48)	25.7 vs. 26.7; 0.96 (0.84–1.11)
Finland	11.9 vs. 11.9; 1.00 (0.95–1.05)	9.0 vs. 6.5; 1.38 (1.29–1.48)	21.2 vs. 18.9; 1.13 (1.08–1.17)	0.2 vs. 0.09; 2.67 (1.61–4.52)	0.3 vs. 0.1; 2.95 (1.94–4.57)	0.6 vs. 0.2; 2.83 (2.06–3.93)	21.8 vs. 19.0; 1.15 (1.10–1.19)
Western Sweden	21.6 vs. 15.3; 1.41 (1.16–1.72)	4.4 vs. 5.2; 0.85 (0.57–1.26)	26.1 vs. 20.5; 1.27 (1.07–1.52)	One case during 2005–2008	No cases	No cases during 2000–2004	26.2 vs. 20.5; 1.28 (1.07–1.52)
Victoria	20.6 vs. 18.7; 1.10 (0.87–1.39)	2.5 vs. 3.5; 0.71 (0.46–1.09)	18.5 vs. 17.9; 1.03 (0.87–1.22)	5.4 vs. 1.8; 3.00 (1.61–5.88)	0.9 vs. 0.3; 2.57 (0.91–8.2)	4.7 vs. 1.6; 2.99 (1.89–4.85)	23.2 vs. 19.5; 1.19; (1.02–1.39)
Sherbrooke	14.4 vs. 11.1; 1.30 (0.95–1.78)	5.6 vs. 5.7; 0.99 (0.61–1.60)	20.4 vs. 16.8; 1.19 (0.92–1.55)	1.8 vs. 1.7; 1.09 (0.44–2.71)	1.2 vs. 1.9; 0.60 (0.20–1.58)	3.0 vs. 3.6; 0.83 (0.43–1.56)	23.0 vs. 20.4; 1.13 (0.89–1.43)
Total	15.7 vs. 14.5; 1.09 (1.05–1.13)	8.1 vs. 10.0; 0.81 (0.77–0.84)	23.8 vs. 24.5; 0.97 (0.94–1.00)	1.4 vs. 0.7; 2.09 (1.82–2.41)	1.0 vs. 0.7; 1.35 (1.17–1.58)	2.4 vs. 1.4; 1.71 (1.55–1.90)	26.3 vs. 26.0; 1.01 (0.99–1.04)

C-MRSA, community-onset methicillin-resistant *S. aureus*; C-MSSA, community-onset methicillin-sensitive *S. aureus*; H-MRSA, hospital-onset methicillin-resistant *S. aureus*; H-MSSA, hospital-onset methicillin-sensitive *S. aureus*; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-sensitive *S. aureus*; SA, *S. aureus*. Data are shown as age-adjusted and gender-adjusted annualized incidence per 100 000 population during 2005–2008 vs. 2000–2004, incidence rate ratio, and 95% confidence interval.

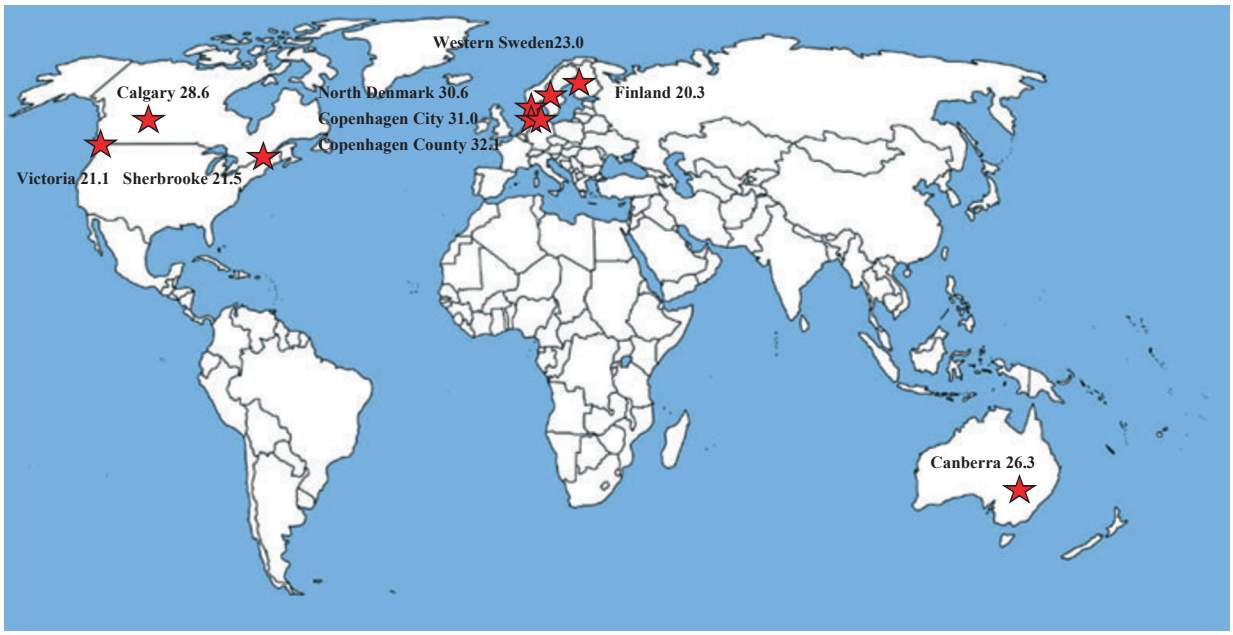

FIG. 4. Annualized age-adjusted and gender-adjusted incidence rates (per 100 000 population) of *Staphylococcus aureus* bacteraemia in nine surveillance populations during 2000–2008.

(USA) during 1998–2005, and found an overall annual incidence of 38.2 per 100 000. Huggan *et al.* [16] identified 779 patients with *S. aureus* BSI in Christchurch (New Zealand) during 1998–2005, and found an overall incidence of 21.6 per 100 000. Tong *et al.* [7], in Darwin (northern Australia), reported on a 1-year study of 110 cases of *S. aureus* BSI, and found an overall incidence of 65 per 100 000. However, this high incidence was attributable to a dramatically increased risk in the Aboriginal population (172 per 100 000), with the incidence observed in the non-Aboriginal population (30 per 100 000) being similar to that observed in our surveillance regions. Although these studies provide important information, it must be recognized that, because some only included adults [14,15], and age and gender profiles of populations and study time frames were different, caution must be exercised in attempts to directly compare results.

It is important to establish the incidence of infectious disease, in order to define the burden of disease for the setting of healthcare service, preventive and research priorities. There are a number of factors that may influence the incidence of *S. aureus* BSI in populations, and these are not limited to differences in demographics, healthcare systems and practice variability among clinicians and laboratorians. We (Fig. 1), like others [14–16], have observed that older age and male gender significantly increase the risk for *S. aureus* BSI. Populations that are older or that have higher proportions of males may therefore be expected to have higher crude incidence rates. Similarly, comorbid medical conditions, ethnicity and socio-economic status influence the risk of disease, and their distribution in a population will influence the incidence of *S. aureus* BSI [6,7,16]. In our present study, we employed age and gender standardization to a common population structure in order to minimize the influence of demographic differences. In addition, all of our centres are in high-income countries with extensive or completely publicly funded healthcare and laboratory systems, such that there are no financial barriers to high-quality blood culture testing. Therefore, the observed differences among our surveillance regions probably reflect non-demographic population differences, variations in practice, and possibly different approaches to infection prevention and control.

Although MSSA incidence, and in particular community-onset BSI, was relatively similar among the study sites, the epidemiology of MRSA BSI was vastly different. Incidence rates in the Scandinavian centres were low, as expected, although these were rising significantly in Finland and in Copenhagen County. Recent years have seen rising incidence rates of MRSA BSI in many regions around the globe, especially with the emergence of community-onset BSI [20]. The issue of whether the emergence of MRSA has added to or replaced the burden of MSSA BSI has been a topic of controversy. Mostofsky *et al.* [25] recently reported a review of published studies on *S. aureus* BSIs, and concluded that the emergence of MRSA has greatly added to the burden of MSSA disease. However, it must be recognized that most of the studies that they included were performed in selected patients, wards, or hospitals, such that shifts into the community or the population at large could not be detected. In our study, which included all cases occurring in the entire population, we observed evidence for replacement in

some centres and additive effects in others. Most of the differences in the overall incidence of *S. aureus* BSI in our study were related to changes in disease caused by MSSA.

Although we utilized a population-based design, there are some limitations that merit discussion. First, we did not further categorize our community-onset cases into community-acquired or healthcare-associated BSI [34]. Second, we did not utilize a central laboratory for species confirmation [30]. Third, we did not include comorbidity, strain typing and treatment data, which would have been helpful to explain observed differences in incidence over time and among regions. Finally, our study regions were all in high-income industrialized countries with extensive publicly funded health systems, and this may limit generalization to other regions.

In summary, this major study defines the contemporary occurrence of *S. aureus* BSI in nine regions around the globe. Although major changes in the epidemiology of community-onset and hospital-onset MSSA and MRSA BSIs are occurring, there is no evidence to suggest that the overall incidence of *S. aureus* BSI is increasing. Given that there are significant regional differences in the population incidence of *S. aureus* BSI, care should be exercised in generalizing results about the epidemiology of *S. aureus* BSIs on the basis of previous studies conducted in selected populations or single regions.

Funding

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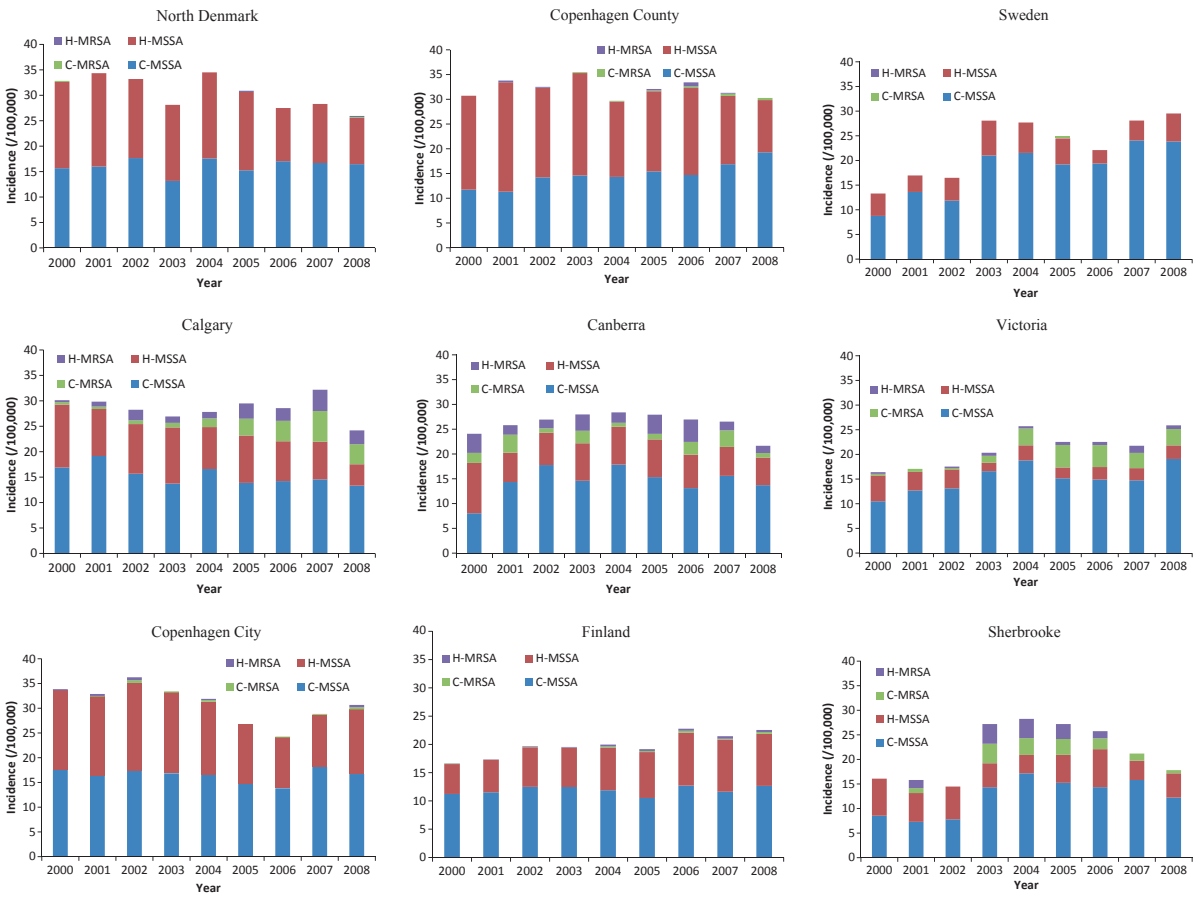
Transparency Declaration

None of the authors have professional or financial conflicts of interest that would influence the conduct or reporting of this study.

Appendix 1

The International Bacteremia Surveillance Collaborative includes K. J. Kennedy, P. Collignon (Canberra, Australia),

Appendix 2



APPENDIX. 2.

K. B. Laupland, D. L. Church, D. B. Gregson (Calgary, Canada), L. Valiquette (Sherbrooke, Canada), J. Galbraith, P. Kibsey (Victoria, Canada), H. C. Schønheyder, M. Søgaard (Aalborg, Denmark), J. D. Knudsen, C. Østergaard, U. S. Jensen, M. Arpi (Copenhagen, Denmark), K. O. Gradel (Odense, Denmark), G. Jacobsson (Skövde, Sweden), and O. Lyytikäinen (Helsinki, Finland).

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