

## Increasing incidence but decreasing in-hospital mortality of adult *Staphylococcus aureus* bacteraemia between 1981 and 2000

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### ABSTRACT

*Staphylococcus aureus* is a leading cause of bacteraemia. This study analysed temporal trends from 18 702 adult cases of *S. aureus* bacteraemia in Denmark between 1981 and 2000. After stratification for mode of acquisition, 57% of cases were hospital-acquired (HA), 28% were community-acquired (CA) and 15% were of undetermined acquisition (UA). Incidence rates increased from 18.2 to 30.5 cases/100 000 population. Annual rates increased by 6.4% for CA, by 2.2% for HA and by 3.6% for UA cases, respectively. Case-mortality associated with HA bacteraemia decreased from 36.2% to 20.7% (43% rate reduction,  $p$  0.0001), compared with a decrease from 34.5% to 26.5% (23% rate reduction,  $p$  0.0001) for CA bacteraemia. Following multivariate analysis, age, pneumonia, endocarditis and chronic illness were associated with increased mortality, regardless of the mode of acquisition. Overall, mortality associated with *S. aureus* bacteraemia declined significantly between 1981 and 2000, but incidence rates doubled, so that the total number of deaths increased. These data emphasise the public health importance of *S. aureus* bacteraemia and the need for further preventive measures and improved care in order to reduce incidence rates and improve outcomes.

**Keywords** Bacteraemia, epidemiology, incidence, mortality, outcome, *Staphylococcus aureus*

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### INTRODUCTION

*Staphylococcus aureus* is an important cause of hospital-acquired (HA) and community-acquired (CA) morbidity and mortality. Recent studies of *S. aureus* bacteraemia have demonstrated high incidence rates worldwide [1–3], but the epidemiology of HA bacteraemia and that of CA bacteraemia differ substantially; for example, HA bacteraemia is related largely to invasive procedures and devices, whereas CA bacteraemia is related to host factors and carrier status. Several predisposing risk-factors for *S. aureus* infection have undergone significant changes during the

past 20 years; for example, changes in demography have shifted the age distribution towards an elderly population; sedentary lifestyles and obesity have increased rates of diabetes; more advanced regimens of chemotherapy and other immunosuppressive treatments are in use; and intravascular devices and invasive procedures are now used widely. However, an increased age, underlying co-morbid disease, and the type and site of infection, continue to be risk-factors associated with an increased risk of death from bacteraemia [4,5].

Although *S. aureus* is the most frequent Gram-positive pathogen isolated from blood, little is known concerning recent temporal changes in the incidence and mortality associated with *S. aureus* bacteraemia. The present study used the ongoing nationwide registration of all Danish cases of bacteraemic *S. aureus* infection to analyse temporal

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trends in mortality and incidence of HA and CA *S. aureus* bacteraemia during a 20-year period [6].

## MATERIALS AND METHODS

### Study population

A continuous, nationwide registration of *S. aureus* infections in Denmark has been carried out at the Staphylococcal Laboratory at the Statens Serum Institut, Copenhagen, since 1956 [6]. More than 90% of strains isolated from blood cultures are referred for typing and antibiotic susceptibility testing. The present study defined a case as an individual with *S. aureus* bacteraemia who was identified via the Statens Serum Institut database between 1981 and 2000. All subsequent episodes of *S. aureus* bacteraemia occurring in an individual patient within 3 months were regarded as a relapse and were excluded from the study. Danish resident population data and hospital admission data were obtained from the Danish National Bureau of Statistics (Danmarks Statistik; <http://www.dst.dk>) and were used to calculate incidence rates nationwide and among specified subgroups. The Ethics Committee for Copenhagen and Frederiksberg Counties approved the study (01-369/93).

### Data collection

Data were extracted from discharge records annually by a qualified clinician. Data extracted included age, gender, reported chronic illness, source of bacteraemia (hospital, community or undetermined), and the site of infection associated with *S. aureus* bacteraemia. Chronic illness included diabetes, chronic liver disease, chronic kidney disease, malignancy, immunosuppression, infection with human immunodeficiency virus 1, intravenous drug use, chronic skin disease and collagenoses. A primary focus was defined as a skin infection, a surgical wound, an intravascular device, a urinary tract infection, or a respiratory tract infection if stated in the discharge record; otherwise, the focus was recorded as unknown. A discharge diagnosis of endocarditis, osteomyelitis/arthritis or meningitis (recorded from 1990 onwards) was classified as a secondary focus. Outcome was registered as alive or dead at discharge, or unknown.

### Antibiotic susceptibility

All isolates were tested at the Statens Serum Institut using Neosensitabs (Rosco, Taastrup, Denmark) [7].

### Statistics

Incidences were normalised to the population distribution and to hospital admission rates, and were presented with 95% CIs. Qualitative variables were compared by Fisher's exact test or Pearson's chi-square test. Annual data were divided into four periods (1981–1985, 1986–1990, 1991–1995 and 1996–2000) for the assessment of temporal changes.

Multivariate logistic regression was performed to determine the risk of death after adjusting for possible confounders. Subjects with unknown vital status were classified as alive for analytical purposes. All variables in the multivariate analysis

were analysed using the forced entry procedure. Tests for interaction among variables were performed by the log likelihood test after including an interaction term. The goodness of fit of the model was tested with the Hosmer–Lemeshow test [8], which revealed adequate model fit ( $p > 0.2$ ). All values were two-sided. Analyses were performed using SPSS v.11.5 (SPSS Inc., Chicago, IL, USA).

## RESULTS

### Patient characteristics

Table 1 shows the age and gender of all patients according to the acquisition group. In brief, 57% of cases were HA, 28% were CA, and 15% were of undetermined acquisition (UA); 60% of cases involved male patients in all three acquisition categories. Patients with CA bacteraemia were younger than patients with either HA or UA bacteraemia. A primary focus of either skin or lung was predominant among CA infections, whereas surgery, a vascular device or a lung focus were the predominant primary foci of HA and UA infections. For all three categories, >50% had an unknown primary focus; a secondary focus was detected for 30% of CA bacteraemias, but for <5% of HA and UA infections. The

**Table 1.** Characteristics of patients with hospital acquisition, community acquisition or unknown acquisition of *Staphylococcus aureus* bacteraemia

	Hospital-acquired ( <i>n</i> = 10 558)	Community-acquired ( <i>n</i> = 5302)	Unknown acquisition ( <i>n</i> = 2842)
Males, %	60.0	58.6	59.2
Age, years (%)			
21–30	4.1	7.3	6.4
31–40	6.5	10.6	9.9
41–50	10.4	9.4	13.3
51–60	15.8	12.2	17.7
61–70	23.8	18.4	22.2
71–80	25.5	24.4	20.9
>80	13.9	17.7	9.7
Primary focus, %			
Skin infection	4.1	18.2	6.2
Surgical infection	16.5	0.7	5.9
Vascular device	13.2	1.0	7.8
Dialysis	2.5	0.6	7.0
Urinary tract infection	2.3	0.5	0.6
Pulmonary infection	7.5	17.3	5.2
Other	0.9	0.2	0.1
Unknown	53.0	61.4	67.2
Secondary focus, %			
None	94.3	69.1	87.8
Endocarditis	2.0	12.5	5.3
Osteomyelitis/arthritis	3.5	16.9	6.6
Meningitis	0.1	1.4	0.3
Chronic illness, %			
None	48.0	55.0	47.6
1	42.0	38.6	41.2
>1	10.0	6.4	11.2
MRSA, %	0.4	0.2	0.5

MRSA, methicillin-resistant *Staphylococcus aureus*.

presence of a chronic illness was slightly more frequent in patients with HA or UA infections than in patients with CA infections. Finally, methicillin-resistant *S. aureus* (MRSA) bacteraemia was infrequent (0.3%), but twice as many cases were HA or UA infections than were CA infections.

### Incidence rates

The number of patients with *S. aureus* bacteraemia increased from 571 in 1981 to 1172 in 2000 (an annual increase of 5.3%). After normalisation to population changes, the incidence of *S. aureus* bacteraemia increased 1.7-fold during the 20-year period, from 18.2 cases/100 000 population to 30.5 cases/100 000 population, with an annual increase of 3.4% (Fig. 1a). However, population-adjusted incidence rates increased less for HA and UA bacteraemia (annual increase of 2.2% and 3.6%, respectively) than for CA bacteraemia (6.4% per year) (Fig. 1b). In particular, incidence rates of CA bacteraemia among males increased by 7.2% annually during the study period.

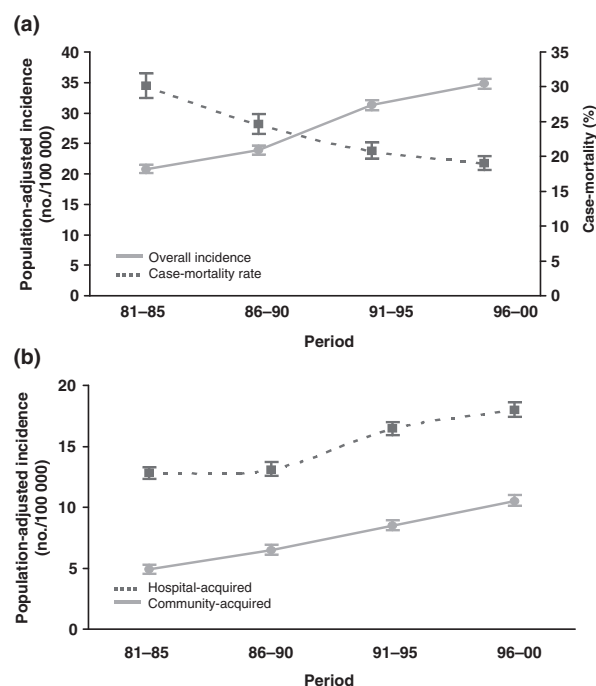


Fig. 1. (a) In-hospital mortality rate and population-adjusted incidence of *Staphylococcus aureus* bacteraemia. (b) Population-adjusted incidence according to acquisition setting, 1981–2000. All values are annual incidence rates with 95% CIs.

Among cases of HA bacteraemia, annual increases in incidence were <2.9% for each age group. The largest increase was detected among individuals aged 21–30 years (2.9% annually) and individuals aged 51–60 years (2.7% annually). Among individuals aged >80 years, the annual rate declined by 1% annually. Annual increases in incidence rates among cases of CA varied between 5.0% and 8.8%. The largest annual increase occurred among the oldest age groups (61–70 years, 7.1%; >80 years, 8.8%), and among individuals aged 31–40 years (7.6%).

During the study period, the Danish adult population (aged >20 years) increased from 3 603 265 in 1981 to 4 027 422 in 2000 (5.9% average annual increase). Hospital admission rates were stable throughout the study period (c. 850 000–900 000 annual adult admissions). After adjustment for admission rates, the increase in incidence of *S. aureus* bacteraemia increased from 108/100 000 admissions between 1981 and 1985 to 172/100 000 admissions between 1996 and 2000, corresponding to an annual increase of 3.0%.

### Mortality

The overall case-mortality rate decreased from 34.5% to 21.7% during the study period (i.e., a 37.1% rate reduction) (Fig. 1a). Despite the improved survival rates, the total number of in-hospital deaths associated with *S. aureus* bacteraemia increased from 1143 in 1981–1985 to 1325 in 1996–2000 (6.3–6.6 deaths/100 000 population, respectively). Among cases of HA bacteraemia, survival rates improved from 63.8% to 79.3% (43% rate reduction) (Table 2). Statistically significant changes occurred in all age groups, but with considerable variation. In the youngest age group, case-mortality rates were reduced by 81%, whereas the reduction was 26% in the oldest age group. Changes in case-mortality rates among males were greater than among females. Case-mortality rates were reduced for all groups of primary foci, but were only statistically significant for surgical, vascular device-associated, pulmonary and other/unknown infections. The decline in mortality from HA endocarditis was statistically significant, but mortality remained high throughout the study period. Although an increase in mortality rates associated with HA osteomyelitis/arthritis was observed during the

**Table 2.** Case-mortality rates among 10 558 cases of hospital-acquired *Staphylococcus aureus* bacteraemia, 1981–2000

	Case-mortality rate (%), by year				p
	1981–1985 (n = 2100)	1986–1990 (n = 2221)	1991–1995 (n = 2932)	1996–2000 (n = 3305)	
All	36.2	27.8	23.8	20.7	0.0001
Age, years					
21–30	16.9	3.8	8.2	3.2	0.001
31–40	18.0	18.3	10.6	9.4	0.02
41–50	24.7	18.1	12.7	10.2	0.0001
51–60	32.1	27.1	19.9	14.4	0.0001
61–70	38.4	28.8	23.4	18.9	0.0001
71–80	42.5	32.8	27.7	27.7	0.0001
>80	45.3	40.2	43.2	33.5	0.002
Gender					
Male	37.5	27.7	22.4	20.2	0.0001
Female	34.3	28.1	25.9	21.5	0.0001
Primary focus					
Skin infection	29.1	20.4	32.0	18.6	0.06
Surgical infection	29.4	21.2	19.1	12.7	0.0001
Vascular device	13.2	6.7	9.1	6.6	0.021
Dialysis	14.3	5.9	11.7	9.9	6.1
Urinary tract infection	13.1	5.9	5.3	9.7	0.38
Pulmonary infection	57.6	52.8	48.6	41.6	0.01
Other	38.5	20.7	17.9	0.0	0.04
Unknown	40.7	32.7	27.7	26.9	0.0001
Secondary focus					
None	36.2	27.1	23.8	20.7	0.0001
Endocarditis	55.9	61.4	35.3	41.9	0.03
Osteomyelitis/arthritis	15.8	23.1	19.7	13.9	0.38
Meningitis	NA	NA	36.4	25.0	0.68
Chronic illness					
None	31.2	23.9	22.2	21.2	0.0001
1	41.4	30.2	24.7	20.6	0.0001
>1	42.4	36.3	28.1	19.1	0.0001
MRSA					
No	36.2	27.8	23.8	20.7	0.0001
Yes	36.4	33.3	28.6	30.0	0.98

NA, data not available; MRSA, methicillin-resistant *Staphylococcus aureus*.

second and third study periods, the overall rates declined and remained low. Rate reductions were larger among patients with reported chronic illness, and therefore mortality rates during the last study period were similar for patients with or without reported chronic illness. Cases of HA MRSA were few throughout the study period, but the associated mortality rate remained above average.

Among cases of CA bacteraemia, survival rates improved from 65.5% to 73.5% (23% rate reduction) (Table 3). Mortality rates declined for all age groups, but the reductions were only statistically significant in individuals aged 51–80 years. The largest reduction occurred among individuals aged 51–60 years. Among individuals with CA bacteraemia who were aged >80 years, mortality rates remained unchanged (between 46.1% and 50.0%) throughout the study period. Mortality rates among males were significantly reduced by 28%, and a trend towards a significant (15%) reduction was observed among females. The

**Table 3.** Case-mortality rates among 5302 cases of community-acquired *Staphylococcus aureus* bacteraemia, 1981–2000

	Case-mortality rate (%), by year				p
	1981–1985 (n = 768)	1986–1990 (n = 1104)	1991–1995 (n = 1503)	1996–2000 (n = 1927)	
All	34.5	31.7	29.8	26.5	0.0001
Age, years					
21–30	7.8	6.0	3.6	2.3	0.29
31–40	14.3	12.6	15.0	6.8	0.08
41–50	28.6	19.2	18.8	17.8	0.30
51–60	33.0	30.3	18.5	19.3	0.005
61–70	42.0	37.1	32.9	27.5	0.007
71–80	41.1	39.6	37.7	30.0	0.01
>80	46.1	49.1	50.0	46.4	0.79
Gender					
Male	36.0	29.6	28.5	25.8	0.001
Female	32.5	34.3	31.6	27.5	0.07
Primary focus					
Skin infection	20.2	17.6	16.5	10.0	0.008
Surgical infection	0	9.1	28.6	0	0.15
Vascular device	14.3	6.7	31.6	10.0	0.24
Dialysis	25.0	0	0	0	0.17
Urinary tract infection	0	0	0	0	–
Pulmonary infection	50.0	38.0	45.7	44.7	0.16
Other	0	0	0	0	–
Unknown	34.5	35.4	29.2	28.2	0.002
Secondary focus					
None	34.5	33.7	33.3	30.9	0.33
Endocarditis	51.6	44.2	27.2	23.9	0.0001
Osteomyelitis/arthritis	11.6	15.0	14.6	8.3	0.05
Meningitis	NA	NA	58.8	52.0	0.57
Chronic illness					
None	30.8	32.2	31.4	29.8	0.75
1	40.3	30.5	29.2	21.2	0.0001
>1	31.6	35.3	19.6	26.5	0.13
MRSA					
No	34.4	31.8	29.7	26.5	0.0001
Yes	100	0	66.7	33.3	0.31

NA, data not available; MRSA, methicillin-resistant *Staphylococcus aureus*.

dominant primary foci were skin, lung and unknown infections. Significantly reduced mortality rates were observed in each group. Mortality rates associated with endocarditis declined significantly, whereas mortality rates associated with osteomyelitis/arthritis increased significantly initially, but then declined and remained unchanged during the study period. There was a reduction in mortality rates among individuals with and without chronic illness. Mortality rates associated with CA MRSA remained high. Among cases of UA bacteraemia, survival rates improved from 73.7% to 84.9% (43% rate reduction).

### Multivariate analysis

Multivariate logistic regression analysis was used to assess the risk of death in each acquisition group. Because a significant interaction between mode of acquisition and infection focus was detected, the analysis was stratified

**Table 4.** Multivariate analysis of factors associated with mortality among cases of hospital- and community-acquired *Staphylococcus aureus* bacteraemia, 1981–2000

	Multivariate OR (95% CI)	
	Hospital-acquired	Community-acquired
Year		
1981–1985	1.0	1.0
1986–1990	0.70 (0.61–0.80)	0.96 (0.77–1.19)
1991–1995	0.60 (0.52–0.68)	0.82 (0.67–1.04)
1996–2000	0.48 (0.42–0.54)	0.65 (0.53–0.79)
Age (per 10-year increment)	1.38 (1.34–1.43)	1.55 (1.48–1.61)
Gender		
Male	1.0	1.0
Female	1.02 (0.93–1.12)	0.98 (0.86–1.12)
Primary focus		
Skin infection	1.0	1.0
Surgical infection	0.89 (0.69–1.15)	0.98 (0.36–2.65)
Vascular device	0.34 (0.26–0.46)	1.14 (0.53–2.45)
Dialysis	0.40 (0.25–0.64)	0.74 (0.22–2.58)
Urinary tract infection	0.26 (0.15–0.42)	–
Pulmonary infection	3.22 (2.47–4.21)	4.20 (3.32–5.32)
Other	0.95 (0.55–1.64)	–
Unknown	1.53 (1.21–1.92)	2.45 (2.00–3.02)
Secondary focus		
None	1.0	1.0
Endocarditis	2.95 (2.19–3.97)	1.58 (1.29–1.92)
Osteomyelitis/arthritis	0.68 (0.52–0.91)	0.33 (0.26–0.41)
Meningitis	2.24 (0.71–7.05)	3.09 (1.87–5.08)
Chronic illness		
None	1.0	1.0
1	1.45 (1.31–1.60)	1.34 (1.16–1.55)
>1	1.76 (1.50–2.07)	1.14 (0.86–1.50)
MRSA		
No	1.0	1.0
Yes	1.78 (0.89–3.56)	1.19 (0.25–5.62)

MRSA, methicillin-resistant *Staphylococcus aureus*.

by mode of acquisition. For each acquisition group, increasing age, a diagnosis of pulmonary infection, endocarditis and the presence of comorbidity were associated independently with an increased risk of death; a diagnosis of osteomyelitis/arthritis was associated with a decreased risk of death compared to bacteraemia without a secondary focus. Among cases of HA bacteraemia, a vascular device, dialysis or a urinary tract infection were associated with a decreased risk of death. The model variables for each acquisition group, with associated ORs, are shown in Table 4.

## DISCUSSION

The results of this investigation of 18 702 adult cases of *S. aureus* bacteraemia documented a 37% decrease in mortality during the past 20 years, while incidence rates during the same period nearly doubled. Marked differences were observed between cases of HA and CA bacteraemia. Rates of CA bacteraemia increased the most, and CA bacteraemia now has the highest overall mortality rate.

A two-fold increase in the incidence of *S. aureus* bacteraemia is consistent with a recent report from Finland [9] and other reports on all-cause sepsis [10–13]. Incidence rates changed differentially, depending on the mode of acquisition. Cases of CA bacteraemia increased at a two- to three-fold higher rate than did HA infections. Incidence rates of CA bacteraemia increased more among the oldest individuals, but this was not the case for HA bacteraemia, where the changes were more uniform among age groups. The reasons for these changes may be multifactorial. Culture techniques have become more sensitive, but do not explain a continuing, but differential, increase in incidence across acquisition and age groups. Higher culture activity or increased hospital admission rates are other possible explanations, but this was not the case in a previous study [14]. Changes in age distribution, leading to a growing and increasingly frail population of elderly individuals, may account, in part, for the larger increase in the incidence of CA compared with HA cases of bacteraemia. Certainly, older age is a risk associated with invasive disease [12,15]. Furthermore, a higher proportion of cases was found to have more than one underlying comorbidity, and chronic illness was a strong predisposing factor for invasive infection [12,15]. Hospital-related procedures and wider use of immunosuppressive therapy may also have contributed, but the design of the study did not permit detailed analysis of this and other potential risk-factors. Further studies are required to investigate the detailed epidemiology behind the increase in incidence.

Few studies have provided longitudinal data concerning mortality rates resulting from *S. aureus* bacteraemia, which were believed to have been stable for several decades [13,16]. However, mortality rates from all-cause sepsis have declined moderately during the past decades [13,17]. Interestingly, Martin *et al.* [13] found that the decline in mortality rates occurred in sepsis caused by Gram-negative, but not Gram-positive, organisms. This contrasts with the results of the present study, and the reason for the discrepancy is not immediately clear. Differences in study populations (e.g., age and race), geographical region and healthcare provision and practice may have contributed. However, an overall mortality rate of 22% is comparable with the results of other recent studies [3,18–20]. Mortality rates from HA and

CA endocarditis decreased, but remained high. A recent study of a large number of cases of *S. aureus* endocarditis revealed mortality rates of 15–30% [21]. The present study did not permit a detailed analysis of the discrepancy. Meningitis and pulmonary infections were also associated with the highest mortality rates throughout the study period, which is consistent with previous reports [12,22]. Mortality rates associated with dialysis and vascular devices were low throughout the study period, which is in contrast to the study of Engemann *et al.* [23], but in line with the findings of Jernigan and Farr [24]. In order to improve survival rates in cases of endocarditis, meningitis and pulmonary infections, further research into pathogenesis, antibiotic and surgical treatment, as well as prevention, is warranted.

Rates of MRSA infection were low throughout the study period, probably because of control policies in Denmark, based on the prompt isolation of MRSA cases [25]. Low MRSA rates are unique to Denmark, the rest of Scandinavia and The Netherlands [26,27]. Unfortunately, increasing numbers of cases of MRSA infections are now being detected in Denmark (DANMAP 2004; [http://www.dfvf.dk/files/filer/zoonosecentret/publikationer/Danmap/Danmap\\_2004.pdf](http://www.dfvf.dk/files/filer/zoonosecentret/publikationer/Danmap/Danmap_2004.pdf)). This is a major concern, since invasive infections caused by MRSA are associated with increased morbidity, mortality and cost [28,29]. Further studies and initiatives are currently underway to control the spread of MRSA in Denmark.

The present study has certain limitations. The study used a prospective registry of a very large number of *S. aureus* bacteraemias over a continuous 20-year study period to analyse temporal trends. The dataset was representative of different settings, because it included all microbiology departments in Denmark. However, the use of discharge records limits the quality of some of the data; e.g., detailed information concerning diagnostic procedures was not available, and thus it was not always possible to determine the primary focus of infection or to rule out secondary infectious complications. Furthermore, a severity index score to assess the severity of bacteraemia could not be calculated from the dataset, so that changes in disease severity over time could be neither assessed nor analysed. Only cases with positive blood cultures were studied. Thus, the true incidence of invasive *S. aureus* disease was probably underestimated. However, *S. aureus*

bacteraemia provides an easily identifiable indicator of invasive *S. aureus* disease incidence. Finally, although discharge records were examined carefully to ascertain variables, records were not always complete, and case patients were not always interviewed.

In conclusion, this study revealed that mortality rates associated with *S. aureus* bacteraemia have declined significantly during the past 20 years. This may be a result of changes in epidemiology, as well as better and improved treatments. However, incidence rates doubled, resulting in an increase in the total number of deaths. These data emphasise the public health importance of *S. aureus* bacteraemia and the need for further preventive measures and improved care in order to reduce incidence rates and further improve outcomes. Particular attention should be given to CA bacteraemia because of the higher overall mortality rate.

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