
T.L. Lamagni*, N. Potz, D. Powell, R. Pebody, J. Wilson, G. Duckworth
Health Protection Agency Centre for Infections, London, UK

Abstract
A population-based study was undertaken to determine the short term risk of death in English patients diagnosed with meticillin-resistant Staphylococcus aureus (MRSA) bacteraemia. All patients with an MRSA-positive blood culture taken in 2004 and 2005 in England identified through routine surveillance were matched to the national registry of deaths. The study found an overall case fatality (all-cause) within 7 days of MRSA-positive blood culture diagnosis of 20%, rising to 38% within 30 days. Risk of death was highest on the day subsequent to the blood specimen being drawn (4%). Seven-day case fatality rates in women were 16% higher than for men (odds ratio: 1.16; 95% confidence interval: 1.04–1.29), although no significant difference was discernable by day 30. Risk of death increased with rising age, with 28% (425/1513) of patients aged ≥85 years dying within 7 days and 57% (859/1513) within 30 days. A seasonal pattern in case fatality rates was evident, highest in the winter and lowest in the summer. The age-standardised mortality ratios within the first week were 180 and 225 times as high for men and women, respectively, as for the general population. This declined rapidly after 10 weeks to approximately 9 for both sexes. An estimated 5.53 deaths per 100 000 population followed MRSA bacteraemia in 2004 and 2005, although no inference on causality or attributable mortality could be made through this study.

Introduction
A number of national surveillance systems exist in England providing data on trends in healthcare-associated infections. Although these programmes provide a measure of changes in incidence, they fail to provide a measure of the changing mortality associated with infections under surveillance. Our estimates of mortality in patients diagnosed with healthcare-associated infections come from ad hoc studies in individual hospitals, or national statistics on death registrations. Although results from single-centre studies can provide some valuable insights into factors influencing patient mortality, they cannot quantify and monitor changes in mortality nationwide. Use of death registration statistics for epidemiological analysis is complicated by inconsistencies in the noting of opportunistic infections and other contributory causes of death on certificates.

An alternative approach to obtaining an estimate of mortality following healthcare-associated infection is to join together surveillance data with death registrations to identify individual patients’ outcome. A feasibility study was undertaken to establish methods of linking these datasets to provide a means for measuring case fatality following meticillin-resistant Staphylococcus aureus (MRSA) infection, as well as to provide a framework for a confidential investigation of deaths following MRSA infection. If successful, such methods could be used for routine monitoring of case fatality following MRSA and other infections of public health importance.

Methods

Data sources and study design
All patients who had a bloodstream MRSA infection reported to the Health Protection Agency through the voluntary laboratory reporting scheme in England during the period 1 January 2004 to...
31 December 2005 were included in the study. Voluntary surveillance data were used because the mandatory MRSA bacteraemia surveillance data during this period were not available at an individual patient level, precluding their linkage to death registrations.

Analyses were restricted to individuals with acute infections during 2004–2005 by excluding those with prior MRSA bacteraemia diagnoses (from 1 January 2003). Duplicate records were identified through finding those with matching demographic and geographical parameters and removed from subsequent analyses. Estimates of the total number of deaths and population mortality rate in England were derived through applying the case fatality rates identified from the voluntary reporting system to the more complete counts derived from the mandatory MRSA bacteraemia surveillance scheme over the same period.4

Records of deaths in England and Wales registered during the period 1 January 2004 to 31 March 2006 were obtained from the Office for National Statistics and linked using probabilistic methods to the records of MRSA bacteraemia to identify individuals who had died from any cause following infection.5

Definitions

A case of MRSA bacteraemia was defined as the isolation of MRSA from a blood culture. Intervals between MRSA bacteraemia diagnosis and death were calculated from the date the subsequently positive blood culture specimen was originally drawn to the date of death.

Statistical analysis

Case fatality rates were calculated as the proportion of individuals diagnosed with an MRSA bacteraemia who subsequently died (from any cause) within specified time periods. Age- and sex-specific death rates for the population of England and Wales were calculated using the mid-year population estimates for 2004–2005. Age-standardised mortality ratios (SMRs) were calculated by sex per successive week following diagnosis of MRSA bacteraemia.6 Confidence intervals for standardised mortality ratios were calculated as described by Kirkwood and Sterne.7 As the proportional-hazard assumption was violated, logistic rather than Cox regression techniques were used to assess the independent contribution of age, sex, calendar month, and year of diagnosis on risk of death following a single episode of MRSA bacteraemia. Two models were constructed to assess 7- and 30-day all-cause mortality.

Ethical approval

The study was granted ethical approval in June 2005 by the South East Multi-Centre Research Ethics Committee.

Results

Of the 10,408 reports of MRSA bacteraemia from hospital laboratories across England, 103 (1.0%) were identified as being duplicates and removed. Of the remaining 10,305 records, 96% (9,940) had adequate identifiers to permit linkage to death records. From these, 9,001 patients were identified who had had a single episode of MRSA bacteraemia during 2004–2005, the remaining 939 having had multiple episodes. All subsequent analyses were undertaken on these 9,001 records.

Mortality following a single episode of MRSA bacteraemia

The risk of death (all-cause) following MRSA bacteraemia diagnosis was highest one day after the culture-positive specimen

![Figure 1. Daily case fatality according time interval from date meticillin-resistant Staphylococcus aureus blood culture-positive specimen taken and death, England 2004-2005.](image-url)
was taken (4.5% risk of death), gradually declining thereafter (Figure 1). Twenty per cent (1825/9001) of all patients died within 7 days of the specimen being taken and 38% (3450) within 30 days, with the daily risk of death levelling off after day 20. There was no significant change in either the 7-day [odds ratio (OR): 0.98; 95% confidence interval (CI): 0.88–1.09] or 30-day (OR: 1.04; 95% CI: 0.95–1.14) case fatality rate between 2004 and 2005 (Table I).

There was a slight change in case fatality according to calendar month, with the highest 7- and 30-day case fatality rates in January (24% and 44%), falling with each successive month up to August (17% and 32%) before rising again during the Autumn (Table I).

**Mortality according to age and sex**

Risk of death within the first 7 days of microbiological diagnosis was found to be higher in female patients (22%; 750/3422) than male patients (19%; 1075/5575) when adjusted for age and month/year of diagnosis (OR: 1.16; 95% CI: 1.04–1.29), although no significant differences were apparent at 30 days (Table I). Seven-day case fatality rates were higher in women than men in every age group, although only reaching statistical significance in 15–34-year-olds, among whom 1.4% of male patients and 5.6% of female patients died \( \chi^2 (1 \text{ df}) = 5.15; P = 0.023 \). Age was a strong predictor of risk of death, with risk of death increasing progressively with age. Just 2% (2/126) of children aged <15 years died from any cause within 7 days, and 6% within 30 days. With adjustment for sex and month/year of diagnosis, and compared with a baseline age group of 35–44 years, the likelihood of mortality within 30 days was almost four-fold higher in 75–84-year-olds (OR: 3.73; 95% CI: 2.91–4.77) and almost six-fold in patients aged ≥85 years (5.68; 4.39–7.33) (Table I).

**Risk of death following MRSA bacteraemia relative to population risk**

Comparison of risk of death in patients diagnosed with MRSA bacteraemia to age-standardised death rates in the general population indicated that female patients were 225 times more likely to die (SMR: 22 521; 95% CI: 20 966–24 192) within the week following microbiological diagnosis of MRSA bacteraemia than women in the general population, and men 179 (SMR: 17 925; 95% CI: 16 885–19 029) times more likely to die than their population counterparts (Figure 2). This ratio fell sharply after the first week until around week 10, after which the ratio for both sexes gradually declined from around 19 times to 9 times the age-standardised mortality in the general population by the end of the follow-up period.

**Estimates of MRSA mortality in England**

A total of 7329 and 7168 cases of MRSA bacteraemia were reported through the mandatory healthcare-associated infection surveillance programme for 2004 and 2005. Extrapolating our 30-day case fatality rate to these cases, an estimated 2758 (5.51 per 100 000 population) and 2798 (5.54 per 100 000) deaths would have been associated with, although not necessarily attributable to, MRSA bacteraemia in 2004 and 2005.

**Discussion**

This study pioneered a novel application of sophisticated data linkage techniques, allowing national estimates of case fatality following MRSA infection to be ascertained for the first time in England. The study was undertaken as part of a wider research

---

**Table I**

Factors associated with 7- and 30-day mortality (all-cause) following meticillin-resistant *Staphylococcus aureus* bacteraemia, England 2004–2005

<table>
<thead>
<tr>
<th></th>
<th>No. patients</th>
<th>No. of deaths (%)</th>
<th>7-day mortality</th>
<th>30-day mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>5575</td>
<td>1075 (19%)</td>
<td>b</td>
<td>2105 (38%)</td>
</tr>
<tr>
<td>Female</td>
<td>3422</td>
<td>750 (22%)</td>
<td>1.16 (1.04–1.29)</td>
<td>1345 (39%) 1.03</td>
</tr>
<tr>
<td>Age group (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;15</td>
<td>126</td>
<td>2 (2%)</td>
<td>0.16 (0.04–0.67)</td>
<td>8 (6%) 0.29 (0.14–0.63)</td>
</tr>
<tr>
<td>15–34</td>
<td>377</td>
<td>12 (3%)</td>
<td>0.32 (0.17–0.63)</td>
<td>29 (8%) 0.36 (0.23–0.56)</td>
</tr>
<tr>
<td>35–44</td>
<td>462</td>
<td>42 (9%)</td>
<td>1.54 (1.05–2.26)</td>
<td>86 (19%)</td>
</tr>
<tr>
<td>45–54</td>
<td>696</td>
<td>94 (14%)</td>
<td>1.92 (1.35–2.74)</td>
<td>182 (26%) 1.54 (1.15–2.05)</td>
</tr>
<tr>
<td>55–64</td>
<td>1189</td>
<td>193 (16%)</td>
<td>2.34 (1.67–3.28)</td>
<td>323 (27%) 1.60 (1.23–2.09)</td>
</tr>
<tr>
<td>65–74</td>
<td>1900</td>
<td>360 (19%)</td>
<td>3.40 (2.45–4.73)</td>
<td>697 (37%) 2.51 (1.95–3.24)</td>
</tr>
<tr>
<td>75–84</td>
<td>2738</td>
<td>697 (25%)</td>
<td>3.83 (2.73–5.36)</td>
<td>1266 (46%) 3.73 (2.91–4.77)</td>
</tr>
<tr>
<td>≥85</td>
<td>1513</td>
<td>425 (28%)</td>
<td></td>
<td>859 (57%) 5.68 (4.39–7.33)</td>
</tr>
<tr>
<td>Year</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>4528</td>
<td>919 (20%)</td>
<td>b</td>
<td>1704 (38%) b</td>
</tr>
<tr>
<td>2005</td>
<td>4473</td>
<td>906 (20%)</td>
<td>0.98 (0.88–1.09)</td>
<td>1746 (39%) 1.04 (0.95–1.14)</td>
</tr>
<tr>
<td>Month</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jan</td>
<td>872</td>
<td>207 (24%)</td>
<td>b</td>
<td>385 (44%) b</td>
</tr>
<tr>
<td>Feb</td>
<td>758</td>
<td>176 (23%)</td>
<td>0.98 (0.78–1.24)</td>
<td>318 (42%) 0.91 (0.74–1.11)</td>
</tr>
<tr>
<td>Mar</td>
<td>808</td>
<td>184 (23%)</td>
<td>0.98 (0.78–1.24)</td>
<td>332 (41%) 0.91 (0.74–1.11)</td>
</tr>
<tr>
<td>Apr</td>
<td>789</td>
<td>162 (21%)</td>
<td>0.86 (0.68–1.09)</td>
<td>299 (38%) 0.79 (0.65–0.97)</td>
</tr>
<tr>
<td>May</td>
<td>757</td>
<td>148 (20%)</td>
<td>0.81 (0.64–1.03)</td>
<td>287 (36%) 0.79 (0.65–0.98)</td>
</tr>
<tr>
<td>Jun</td>
<td>741</td>
<td>143 (19%)</td>
<td>0.76 (0.60–0.97)</td>
<td>292 (39%) 0.80 (0.65–0.98)</td>
</tr>
<tr>
<td>Jul</td>
<td>785</td>
<td>147 (19%)</td>
<td>0.75 (0.59–0.95)</td>
<td>281 (30%) 0.69 (0.56–0.85)</td>
</tr>
<tr>
<td>Aug</td>
<td>731</td>
<td>123 (17%)</td>
<td>0.66 (0.52–0.85)</td>
<td>235 (32%) 0.60 (0.48–0.74)</td>
</tr>
<tr>
<td>Sep</td>
<td>650</td>
<td>115 (18%)</td>
<td>0.71 (0.54–0.91)</td>
<td>231 (36%) 0.70 (0.57–0.87)</td>
</tr>
<tr>
<td>Oct</td>
<td>681</td>
<td>133 (20%)</td>
<td>0.79 (0.61–1.01)</td>
<td>259 (38%) 0.77 (0.62–0.95)</td>
</tr>
<tr>
<td>Nov</td>
<td>708</td>
<td>139 (20%)</td>
<td>0.80 (0.62–1.02)</td>
<td>253 (36%) 0.69 (0.56–0.86)</td>
</tr>
<tr>
<td>Dec</td>
<td>721</td>
<td>148 (21%)</td>
<td>0.84 (0.66–1.07)</td>
<td>278 (39%) 0.77 (0.63–0.96)</td>
</tr>
</tbody>
</table>

* Adjusted for variables given in the table.

b Reference group.
Mortality in patients diagnosed with MRSA bacteraemia in England during 2004–2005 was found to be high, with 38% of individuals dying within 30 days of diagnosis, rising to 57% in patients aged ≥85 years. There are few comparable estimates from other countries, as most studies are confined to single centres, specific specialties or particular age groups. A study in Australia estimated a 9% 7-day case fatality rate (all-cause) among patients with MRSA bacteraemia, substantially lower than the 20% found among English patients, although based on sentinel sites across Australia which may not represent the country as a whole. We estimated a mortality rate associated with MRSA bacteraemia of 5.5 per 100 000 population over the study period, slightly lower than estimates from the USA which included non-bacteraemic invasive infections (6.3 per 100 000). Although rates of MRSA bacteraemia in the male population are generally found to be higher than for the female population, we found women to have a slightly elevated risk of death over men within 7 days of diagnosis (16% higher), especially pronounced among young adult patients (aged 15–34 years). The reasons for this short-term elevated risk of death in women over men are unclear, and may be explainable through differences in the nature of the underlying illnesses for which men and women are being treated. A recent study in Canada also found a higher risk of death in women, even with adjustment for comorbidity. As such, the reason behind this elevated risk of death remains unclear and warrants further study.

An interesting finding from our study was the change in case fatality rates throughout the year, being highest in the late winter months and falling to a lowest point in August. Seasonal influxes in MRSA infection have been previously noted, with ecological analyses suggesting that seasonal patterns in consumption of antimicrobials and bed occupancy rates could each play a role in driving these seasonal patterns. Seasonal influxes in viral respiratory infections predisposing to secondary MRSA pneumonia may explain the slight increase in case fatality rates, with S. aureus and MRSA bacteraemia from respiratory sources associated with increased mortality.

There were several limitations to our study. We did not have any information about patients’ underlying illness or health status prior to MRSA bacteraemia, the reasons they were admitted to hospital, their comorbidities or their treatment. We could not therefore estimate how many deaths may have been attributable to the MRSA bacteraemia. Most patients who develop MRSA bacteraemia already have a limited life expectancy prior to the infection as a result of poor underlying health or serious acute illness. Although our comparison of the risk of death in the period following infection in patients with MRSA bacteraemia to the general population identified a very high, short peak in the first week, it is likely that other life-threatening events related to the illness or injury for which the patients were being treated were also clustered around the same point in time as the MRSA bacteraemia diagnosis. As such, this initial peak probably overestimates the mortality due to the bacteraemia itself. We found that the standardised mortality ratios fell rapidly over the next 20 weeks, after which they stabilised to around 900. If it could be assumed that this plateau reflects the risk of death prior to the development of MRSA bacteraemia then it might be estimated that the underlying risk of death in these patients was about nine times that in the general population. However, epidemiological studies comparing mortality in patients with and without MRSA bacteraemia, adjusted for comorbidity and all other factors known to affect risk of death, would need to be undertaken to robustly estimate the excess mortality attributable to MRSA bacteraemia. Comparisons to patients with meticillin-susceptible S. aureus bacteraemia adjusted for known confounders would also provide a valuable insight into the impact of the emergence of MRSA.

Although using all-cause mortality rather than cause-specific mortality may be considered a limitation of this study, it does overcome problems of subjectivity of reporting of contributory...

Figure 2. Standardised mortality ratios in successive weeks post meticillin-resistant Staphylococcus aureus-positive blood culture, England 2004–2005.
causes of death, and as such offers a more objective means of monitoring changes in mortality over time. A further advantage over analyses based on certified cause of death is that it overcomes the problem of laboratory diagnostic information being unavailable at the time of the certificate being issued and therefore not being precisely specified. The approach taken in this study, monitoring all-cause fatality post MRSA infection, has similarly been adopted by other countries as a reasonable measure for public health surveillance purposes.\textsuperscript{8,9,12,17–19} We chose a 30-day cut-off to estimate the total mortality associated with MRSA bacteraemia, given the substantial tail-off in mortality after 30 days. Others have used death at discharge, although this will potentially incorporate even more deaths for which the infection did not contribute than using a time-limited cut-off.\textsuperscript{20,21}

Although the outcome for a small proportion of our cases (4%) could not be determined, since this leaves only a limited possibility for bias in the cases whose outcome could be determined, extrapolating our case fatality rate to all diagnosed MRSA bacteraemia as a means of estimating the total number of deaths potentially associated with MRSA bacteraemia would seem reasonable. Our estimated mortality rate associated with MRSA bacteraemia, 5.5 per 100,000 population, was derived through applying the case fatality rate calculated from the voluntary reporting scheme to the mandatory reporting scheme, owing to the incomplete nature of the voluntary surveillance data.\textsuperscript{20} The mandatory scheme does contain some contaminants, as these are to be reported alongside clinically significant isolates.\textsuperscript{21} However, analysis of clinical information submitted within the mandatory system in 2006, the nearest year available to the data presented here, only identified 5% of the isolates as contaminants and, as such, the derived mortality rate provides a reasonable estimate.\textsuperscript{22}

Integrating death registration statistics into national surveillance programmes will provide a means to evaluate changes in case fatality and mortality, not just for healthcare-associated infections but for a host of other potentially life-threatening infectious diseases, providing a valuable early alert of epidemiological changes. Utilising already existing national data sets for public health benefit is an important next step towards maximising the use of data already collected and thus minimising excessive research and surveillance demands on healthcare professionals.

Acknowledgements

We would like to extend our thanks to the following members of the Project Board and Steering Group for their input into the study: A. Chronias, C. Griffiths, N. Hoveyda, C. Rooney, L. Wheller, P. Goldblatt, A. Phillips, S. Scobie, R. Spencer. We also thank A. Charlett for his statistical advice, Office for National Statistics staff for their assistance in interpreting death registrations and our microbiology colleagues in laboratories across England, Wales and Northern Ireland for their continued reporting of infection data.

Conflict of interest statement

None declared. The views expressed in the publication are those of the authors and not necessarily those of the Department of Health.

Funding source

This work was undertaken by the Health Protection Agency who received funding from the Department of Health.

References