Thirty-day all-cause fatality subsequent to MRSA, MSSA and *E. coli* bacteraemia and *C. difficile* infection, 2015/16

Data to March 2016
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Contents

Executive summary 4
Introduction 5
  Comparability with previous Office for National Statistics publications on mortality 6
  Interpreting case fatality rates 6
  Supplementary data tables 7
  MRSA bacteraemia 8
  MSSA bacteraemia 11
  Escherichia coli bacteraemia 13
  Clostridium difficile infection 16
Discussion 19
  Limitations 21
Appendix 1: Methods 23
Appendix 2: Summary of differences between Office for National Statistics and PHE mortality outputs 26
References 27
Executive summary

The analysis presented here reports 30-day all-cause fatality following meticillin-resistant *Staphylococcus aureus* (MRSA), meticillin-susceptible *Staphylococcus aureus* (MSSA) and, *Escherichia coli* bacteraemia (ie bloodstream infection) and *Clostridium difficile* infection (CDI). Thirty-day all-cause fatality is a widely used outcome for assessing risk of death, although it should be emphasised that deaths in individual cases may or may not be attributable to these infections. Case fatality rates (CFR) are used as they provide a standard measure of the surviveability of an infection.

There have been large reductions in the numbers of deaths within 30 days following MRSA bacteraemia and CDI since 2007/08, reflecting decreased incidence of these infections over time. In contrast, there have been continued increases in the number of deaths within 30 days following MSSA and *E. coli* bacteraemia since 2011/12 and 2012/13 (the respective time periods when mandatory surveillance was implemented for each pathogen), reflecting the increased incidence of these infections. However, as case fatality rates have fallen, patients are more likely to survive these infections now than in previous years.

In 2015/16, the CFRs following bacteraemia due to MRSA, MSSA, and *E. coli* were 29.4%, 20.0% and 15.3%, respectively. The CFR following CDI was 15.1%. The CFRs for MRSA and MSSA bacteraemia were slightly higher than in the previous financial year (28.9% and 19.9, respectively); however, these increases are not statistically significant. The CFRs for *E. coli* bacteraemia and CDI showed a small but statistically significant decline from the rates seen in 2014/15 (16.1% and 16.5%, respectively). The 30-day CFRs for all four infections have decreased since the start of their surveillance periods.

While MRSA bacteraemia consistently had the highest CFRs over time, the greatest number of deaths was seen following *E. coli* bacteraemia, due to the much higher incidence of this infection. In 2015/16, there were more deaths following *E. coli* bacteraemia (n=5,603) than there were following MRSA bacteraemia (n=232); indeed, the number of deaths following *E. coli* bacteraemia in 2015/16 exceeded the number of deaths following MRSA bacteraemia seen in 2007/08, when the highest mortality (n=1,354) was observed for this pathogen. Although CFRs and deaths appear to be highest in the north of England, confidence intervals often overlap with those of other regions, indicating a low level of statistical significance.
Introduction

Public Health England (PHE) has undertaken mandatory surveillance of key healthcare-associated infections (HCAIs) in England since 2001, when NHS acute trusts were mandated to report cases of bacteraemia (bloodstream infection) due to meticillin-resistant Staphylococcus aureus (MRSA). Since April 2007, trusts have also been required to report all cases of Clostridium difficile infection (CDI) in patients aged two years or over, with the mandatory surveillance programme being expanded to include bacteraemia due to meticillin-susceptible S. aureus (MSSA) and Escherichia coli in January and June 2011, respectively [1]. While E. coli bacteraemia may not typically be viewed as an HCAI, almost 30% of cases have a time of onset two or more days after admission to hospital, which is commonly taken to indicate likely acquisition of infection in hospital [2].

Large declines have been seen in the incidence of MRSA bacteraemia (81.6%) and CDI (74.5%) between the financial years (FYs) 2007/08 and 2015/16.[1] In contrast, MSSA and E. coli bacteraemia have shown year-on-year increases in incidence, which although relatively small as percentage increases, translate to large increases in the number of cases due to the high incidence of both infections [1]. Due to the potential impact of HCAIs on morbidity and mortality, monitoring mortality is an important part of surveillance [3]. Antimicrobial resistance is also a key issue as many HCAIs are associated with high levels of resistance, which has important implications for treatment options and subsequent mortality. For example, MRSA infections are resistant to the recommended first-line therapy for MSSA infection (flucloxacillin), whilst around 19% of E. coli bloodstream isolates are resistant to ciprofloxacin, recommended for use in the UK only for infections caused by laboratory-confirmed susceptible strains or for the treatment of acute kidney or prostate infections [4-6]. Antimicrobial resistance was recently projected to be the largest cause of death globally by 2050 [7].

This report presents analysis of 30-day all-cause case fatality rates (CFRs) among patients with bacteraemia due to MRSA, MSSA, or E. coli and CDI, reported by NHS acute trusts to the national mandatory surveillance scheme; these deaths may or may not be related to the infection. Data is presented for each organism by FY, based on the date when positive blood cultures were collected rather than when the patient died; it is, therefore, possible that a death occurred in a different financial year to when the positive blood culture was collected. The counts of infection reports are based on data extracted on 20 April 2016; thus the number of reports presented here may differ from those in other publications. In addition, the methods used for this report differ slightly from those used in the previous report, and therefore, previously reported values may have changed. A full description of the methods can be found in Appendix 1.
Comparability with previous Office for National Statistics publications on mortality

The Office for National Statistics (ONS) previously published data on deaths involving MRSA [8] and C. difficile [9]. The ONS data on MRSA bacteraemia and CDI are not comparable to the data published here for a number of methodological reasons outlined in Appendix 2, Table A1. In summary, the ONS published data from England and Wales by calendar year, based on deaths with mention of MRSA or C. difficile on the death certificate. By contrast this publication includes data from England by FY, with fatality calculated using all deaths occurring within 30 days of MRSA bacteraemia or CDI. In addition, data are presented on fatality following MSSA and E. coli bacteraemia. The two outputs thus differ by geography, time period, source of death information and range of pathogens covered. We have chosen to examine all deaths (all-cause fatality) occurring within 30 days of an infection report because this is a common epidemiological convention. While it is not known if the deaths were attributable to the HCAIs, the use of all-cause fatality is no less robust than the use of data derived from death certification, which is similarly problematic due to its subjective nature [10].

Interpreting case fatality rates

CFRs are a useful statistic to analyse the risk of death per case of a particular infection and are calculated as the number of deaths divided by the number of cases, multiplied by 100. Thus, if the ratio of deaths to cases remains constant over time so will the CFR, even if overall, there has been an increase or decrease in both the number of deaths and cases. By contrast the CFR will increase, for example, if the number of deaths increases but the number of cases remains constant, or if the number of deaths remains constant but the number of cases decreases, ie CFR facilitates comparison between clinical outcomes of diseases with very different incidence. In addition to the CFR we have also provided 95% confidence intervals (CIs). These provide a range of values within which the true CFR is likely to lie. When confidence intervals for two or more different CFRs overlap then the true CFRs could be equal. It must be borne in mind, however, that the CFRs in this report have been derived from all-cause mortality rather than attributable mortality.
Thirty-day all-cause fatality subsequent to MRSA, MSSA, and \textit{E. coli} bacteraemia and \textit{C. difficile} infection

**Supplementary data tables**

All tables accompanying this publication are only available online and can be accessed here, and will be linked throughout the text in maroon:

**MRSA bacteraemia**

- **Table S1.** Thirty-day all-cause case fatality rate following MRSA bacteraemia
- **Table S2.** Thirty-day all-cause case fatality rate by NHS Region following MRSA bacteraemia
- **Table S3.** Thirty-day all-cause case fatality rate by age group following MRSA bacteraemia
- **Table S4.** Thirty-day all-cause fatality rate by gender following MRSA bacteraemia

**MSSA bacteraemia**

- **Table S5.** Thirty-day all-cause case fatality rate following MSSA bacteraemia
- **Table S6.** Thirty-day all-cause case fatality rate by NHS Region following MSSA bacteraemia
- **Table S7.** Thirty-day all-cause case fatality rate by age group following MSSA bacteraemia
- **Table S8.** Thirty-day all-cause case fatality rate by gender following MSSA bacteraemia

**\textit{E. coli} bacteraemia**

- **Table S9.** Thirty-day all-cause case fatality rate following \textit{E. coli} bacteraemia
- **Table S10.** Thirty-day all-cause case fatality rate by NHS Region following \textit{E. coli} bacteraemia
- **Table S11.** Thirty-day all-cause case fatality rate by age group following \textit{E. coli} bacteraemia
- **Table S12.** Thirty-day all-cause case fatality rate by gender following \textit{E. coli} bacteraemia

**\textit{C difficile} infection**

- **Table S13.** Thirty-day all-cause case fatality rate following \textit{C. difficile} infection
- **Table S14.** Thirty-day all-cause case fatality rate by NHS Region following \textit{C. difficile} infection
- **Table S15.** Thirty-day all-cause case fatality rate by age group following \textit{C. difficile} infection
- **Table S16.** Thirty-day all-cause case fatality rate by gender following \textit{C. difficile} infection

**Overall**

- **Table S17.** Thirty-day all cause fatality rate following MRSA, MSSA, \textit{E. coli} bacteraemia or \textit{C. difficile} infection
Results

MRSA bacteraemia

In 2015/16, there were 819 MRSA bacteraemia cases reported to PHE, of which 789 cases (96.3%) could be linked to mortality records (Table S1); of these, 232 cases had a reported death within 30 days of the positive blood culture being taken, giving a 30-day all-cause CFR of 29.4% (95% CI: 26.2-32.7%). This represents a significant decrease (24.4%; p<0.001) when compared to the CFR of 38.9% (95% CI: 37.2-40.5%) seen in 2007/08. Assuming the CFR of 29.4% is representative, the estimated total number of all-cause fatalities following MRSA bacteraemia in 2015/16 would have been 241.

There was inter-regional variation in all-cause CFRs in 2015/16, although there was considerable overlap between regions and over time in the 95% CIs (Figure 1; Table S2). The highest CFR was in the North of England (36.1%, 95% CI: 29.9-42.7%) and the lowest in the Midlands and East of England (25.9%, 95% CI: 19.8-32.8%). There was also inter-regional variation in the reduction of 30-day all-cause CFRs over time, ranging from a 9.5% reduction in North of England (from 39.9%, 95% CI: 37.1-42.7% to 36.1%, 95% CI: 29.9-42.7%) to a 38.9% reduction in the Midlands and East of England (from 42.4%, 95% CI: 39.0-45.7% to 25.9%, 95% CI: 19.8-32.8%).

In 2015/16, the North of England and South of England experienced the highest number of deaths (n=83 and 56, respectively) while the Midlands and East of England and London had the lowest numbers (n=49 and 44, respectively). All NHS regions saw similar declines in the number of deaths between 2007/08 and 2015/16, ranging from an 80.3% decline in London (from 223 to 44 deaths) to an 86.6% decline the Midlands and East of England (from 366 to 49 deaths).

The highest 30-day all-cause CFRs and greatest number of deaths were observed in patients aged 75 years and over with the CFR falling outside the 95% CI for all other age groups, except in 2014/15 and 2015/16 when there was some overlap (Figure 2; Table S3). The CFRs in patients aged 75 years and over varied over time and ranged between 51.6% (95% CI: 48.9-54.3%, n=676/1,310) in 2008/09 and 40.2% (95% CI: 35.2-45.4%, n=148/368) in 2015/16. The under 1 and 1-14 year age groups had low numbers of deaths since the start of enhanced MRSA surveillance with a cumulative count of 19 and 7 deaths, respectively, between 2007/08 and 2015/16. No deaths have been observed in the 0-1 year age group from 2011/12.

Tests for significant reductions (p-value) of 30-day mortality calculated over financial years assessed using generalised linear models; full methods found in Appendix 1.
Numerically, more deaths and infections were observed among males. In 2015/16 there were 141 deaths among males and 91 among females, however, the 30-day all-cause CFRs among males and females were comparable across all time periods, except 2015/16 (Figure 3; Table S4). The CFRs decreased overall since 2007/08, with an overall 30.1% reduction in CFR from 38.6% (95% CI: 36.5-40.6%) in 2007/08 to 27.0% (95% CI: 23.2-31.0%) in 2015/16 in males and a 11.4% reduction in CFR from 39.6% (95% CI: 36.8-42.4%) in 2007/08 to 35.1 (95% CI: 29.3-41.3%) in 2015/16. An increase from 2014/15 was observed for females, from 29.4% (95% CI: 24.2-34.9%) to 35.1% (95% CI: 29.3-41.3%) in 2015/16. Cases where the gender was reported as ‘unknown’ have been excluded from Figure 3. This data is, however, retained in the accompanying table (Table S4).
Thirty-day all-cause fatality subsequent to MRSA, MSSA, and *E. coli* bacteraemia and *C. difficile* infection

**Figure 2. Thirty-day all-cause case fatality rate by age group following MRSA bacteraemia**

**Figure 3. Thirty-day all-cause fatality rate by gender following MRSA bacteraemia**
MSSA bacteraemia

In 2015/16, there were 10,586 MSSA bacteraemia cases reported to PHE, of which 10,149 (95.9%) could be linked to mortality records (Table S5); of these, 2,028 cases had a death reported within 30 days, giving a 30-day all-cause CFR of 20.0% (95% CI: 19.2-20.8%). Between 2011/12 and 2015/16 the CFR declined by 7% (p<0.001)*, from 21.5% (95% CI: 20.6-22.4%, n=1,777/8,279) to 20.0% (95% CI: 19.2-20.8%). In 2015/16, the estimated total number of all-cause fatalities was 2,111.

In 2015/16, the highest number of deaths was in the North of England (n=718), with the lowest in London (n=208) (Table S6), which saw a 2.8% reduction in the number of deaths from 214 in 2011/12 to 208 in 2015/16. All other regions saw an increase in deaths between 2011/12 and 2015/16, ranging from 14.7% (626 to 718 deaths) in the North of England, to 18.1% (515 to 608 deaths) in the Midlands and East of England. However, the 30-day all-cause CFRs declined in all regions since 2011/12, with the exception of the Midlands and East of England showing no overall change compared to 2011/12. In 2015/16, the CFR ranged from 15.7% (95% CI: 13.8-17.8%) in London to 21.4% (95% CI: 19.9-23.0%) in the Midlands and East of England. Although there was some variation between regions, there was overlap between the confidence intervals for all regions over time and between each region (The 30-day all-cause CFRs and number of deaths varied by age group (Figure 5; Table S7). In 2015/16, the lowest CFR was seen in 1-14 year olds (1.3%, 95% CI: 0.5-2.8%, n=6) with the highest in those aged 75 years and over (36.1%, 95% CI: 34.4-37.7%, n=1,201). In all time periods observed, 1-14 year olds had the lowest CFRs and number of deaths and the CFRs were higher in the under 1 year age group compared to both 1-14 and 15-44 year olds (Figure 5).

In 2015/16, the respective CFRs of 1-14 and 15-44 year olds were: 1.3% (95% CI: 0.5-2.8%) and 5.5% (95% CI: 4.5-6.7%), respectively, while CFR of under 1 year age group was 7.2% (95% CI: 4.6-10.6%, n=23).

A greater number of deaths were observed among males, while the CFR was highest among females (Figure 6; Table S8). For example, in 2015/16, there were 1,220 deaths among men and 783 among women while the equivalent CFRs were 19.2% (95% CI: 18.2-20.1%, n=1,220/6,369) and 21.4% (95% CI: 20.1-22.8%, n=783/3,653). Cases where the gender was reported as 'unknown' have been excluded from the Figure 6. This data is, however, retained in the accompanying table (Table S8).

* Tests for significant reductions (p-value) of 30-day mortality calculated over financial years assessed using generalised linear models; full methods found in Appendix 1.
Thirty-day all-cause fatality subsequent to MRSA, MSSA, and *E. coli* bacteraemia and *C. difficile* infection

Figure 4).

The 30-day all-cause CFRs and number of deaths varied by age group (Figure 5; Table S7). In 2015/16, the lowest CFR was seen in 1-14 year olds (1.3%, 95% CI: 0.5-2.8%, n=6) with the highest in those aged 75 years and over (36.1%, 95% CI: 34.4-37.7%, n=1,201). In all time periods observed, 1−14 year olds had the lowest CFRs and number of deaths and the CFRs were higher in the under 1 year age group compared to both 1–14 and 15–44 year olds (Figure 5). In 2015/16, the respective CFRs of 1–14 and 15–44 year olds were: 1.3% (95% CI: 0.5-2.8%) and 5.5% (95% CI: 4.5-6.7%), respectively, while CFR of under 1 year age group was 7.2% (95% CI: 4.6-10.6%, n=23).

A greater number of deaths were observed among males, while the CFR was highest among females (Figure 6; Table S8). For example, in 2015/16, there were 1,220 deaths among men and 783 among women while the equivalent CFRs were 19.2% (95% CI: 18.2-20.1%, n=1,220/6,369) and 21.4% (95% CI: 20.1-22.8%, n=783/3,653). Cases where the gender was reported as ‘unknown’ have been excluded from the Figure 6. This data is, however, retained in the accompanying table (Table S8).
Thirty-day all-cause fatality subsequent to MRSA, MSSA, and *E. coli* bacteraemia and *C. difficile* infection

Figure 4. Thirty-day all-cause case fatality rate by NHS Region following MSSA bacteraemia

![Graph showing fatality rates by NHS Region](image)

- **London**
- **Midlands and East of England**
- **North of England**
- **South of England**

Figure 5. Thirty-day all-cause case fatality rate by age group following MSSA bacteraemia

![Graph showing fatality rates by age group](image)

- **<1 yr**
- **1-14 yrs**
- **15-44 yrs**
- **45-64 yrs**
- **65-74 yrs**
- **75+ yrs**
Thirty-day all-cause fatality subsequent to MRSA, MSSA, and *E. coli* bacteraemia and *C. difficile* infection

**Figure 6. Thirty-day all-cause case fatality rate by gender following MSSA bacteraemia**

![Graph showing 30-day all-cause fatality rate by gender following MSSA bacteraemia]

*Escherichia coli* bacteraemia

There were 38,132 *E. coli* bacteraemia cases reported to PHE in 2015/16, of which 36,620 (96%) could be linked to mortality records (Table S9); of these, 5,603 cases died within 30 days of the positive blood culture being taken, giving a 30-day all-cause CFR of 15.3% (95% CI: 14.9-15.7%). Between 2012/13 and 2015/16 the CFR declined by 8.9% (p<0.001) \(^*\) from 16.8% (95% CI: 16.4-17.3%, n=5,163/30,659) to 15.3% (95% CI: 14.9-15.7%). The estimated total number of all-cause fatalities for 2015/16 was 5,822.

All regions observed an increase in the number of deaths between 2012/13 and 2015/16 (Table S10). In 2015/16, the region with the greatest number of deaths was the North of England (n=1,912); this represented an increase of 2.1% on the number seen in 2012/13 (n=1,873), and was the smallest observed increase among all regions. The South of England saw the largest increase (16.5%) from 1,131 to 1,318.

All regions saw a reduction in CFRs compared to those seen in 2012/13. In 2015/16, the 30-day all-cause CFRs ranged from 14.1% (95% CI: 13.1-15.0%) in London to

\(^*\) Tests for significant reductions (p-value) of 30-day mortality calculated over financial years assessed using generalised linear models; full methods found in Appendix 1.
16.1% (95% CI: 15.4-16.7%) in the North of England. There was, however, overlap in the confidence intervals around the CFRs between the regions and over time (Figure 7).

Figure 7. Thirty-day all-cause case fatality rate by NHS Region following *E. coli* bacteraemia

There was variation in the 30-day all-cause CFRs and the number of deaths by age group (
Figure 8; Table S11). In all FYs, the lowest CFRs and fewest deaths were in 1–14 years old (4.3%, 95% CI: 2.0-7.9%, n=9 in 2015/16) and the number of deaths and CFR in the under 1 year old age group (7.7%, 95% CI: 5.6-10.3%, n=43 in 2015/16) were higher than those in 1–14 year olds, although there was overlap in the confidence intervals in 2015/16 with those aged under 45. The highest CFR and number of deaths in all FYs were in the 75+ age group (19.1%, 95% CI: 18.6-19.7%, n=3,560 in 2015/16).

All age groups experienced an overall decrease in CFR between 2012/13 and 2015/16, with the exception of 1-14 year olds who had an increase of 4.9% in CFR (from 4.1%, 95% CI: 1.8-7.9% in 2012/13 to 4.3%, 95% CI: 2.0-7.9% in 2015/16). The largest CFR decrease of 31.3% was observed in the under 1 year age group from 11.2% (95% CI: 8.5-14.3%) in 2012/13 to 7.7% (95% CI: 5.6-10.3%).
There were increases in the number of deaths among both males and females between 2012/13 and 2015/16 (from 2,723 to 2,951 and from 2,316 to 2,570, respectively) ([Table S12](#)). However, due to a greater increase in the number of infections relative to the number of deaths for both genders, the CFR declined slightly over the same time period (   )
Figure 9). In 2015/16, the CFR among men was higher than that among women; 17.1% (95% CI: 16.6-17.7%) versus 13.7% (95% CI: 13.2-14.2%), respectively, an observation made in all years. Cases where the gender was reported as ‘unknown’ have been excluded from Figure 9. This data is, however, retained in the accompanying table (Table S12).
Thirty-day all-cause fatality subsequent to MRSA, MSSA, and *E. coli* bacteraemia and *C. difficile* infection

**Figure 9. Thirty-day all-cause case fatality rate by gender following *E. coli* bacteraemia**

![Graph showing the thirty-day all-cause case fatality rate by gender following *E. coli* bacteraemia.

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**Clostridium difficile** infection

In 2015/16, 14,139 cases of CDI were reported to PHE (Table S13), of which 13,764 (97.3%) could be linked to mortality records; of these cases, 2,072 had a reported death within 30 days of the positive faecal specimen being taken, giving a 30-day all-cause CFR of 15.1% (95% CI: 14.5-15.7%). Between 2007/08 and 2015/16, the CFR declined by 42.4% (p<0.001) from 26.2% (95% CI: 25.9-26.6%, n=13,940/53,145) to 15.1% (95% CI: 14.5-15.7%). The estimated number of all-cause fatalities in 2015/16 was 2,127.

Geographically, there was wide variation in the number of deaths observed in 2015/16. The greatest number of deaths was seen in the North of England (n=761), the number being nearly three times greater than that seen in London (n=256), the region with the lowest number of deaths (Table S14). All regions saw similar trends, with a national decline of 85.1% (regional range 84.0-86.7%) in the number of deaths between 2007/08 and 2015/16. In 2015/16, the CFRs ranged from 13.3% (95% CI: 12.1-14.5%) in the South of England to 16.2% (95% CI: 15.2-17.3%) in the North of England (Figure 10), but with was overlap between regions in the confidence intervals around the CFR.

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* Tests for significant reductions (p-value) of 30-day mortality calculated over financial years assessed using generalised linear models; full methods found in Appendix 1.
Thirty-day all-cause fatality subsequent to MRSA, MSSA, and *E. coli* bacteraemia and *C. difficile* infection

**Figure 10. Thirty-day all-cause case fatality rate by NHS Region following *C. difficile* infection**

![Graph showing the thirty-day all-cause case fatality rate by NHS Region following *C. difficile* infection.](image)

The 30-day all-cause CFRs and number of deaths increased with age (Figure 11; Table S15). In 2015/16, there were three deaths among 2–14 year olds, a CFR of 1.1% (95% CI: 0.2-3.2%, n=3/268), while among those aged 75 years and over there were 1,504 deaths, a CFR of 19.8% (95% CI: 18.9-20.7%, n=1,504/7,610). The CFR in patients aged 75 years and over remained significantly higher than that in all other age groups over time. However, all age groups have seen a decline in the number of deaths and the CFRs from 2007/08 to 2015/16.

There were consistently more deaths among females compared to males over time; for example in 2015/16 there were 1,115 and 933 deaths, respectively (Table S16). However, due to differences in the number of infection reports, the CFR remained higher among males (16.8%, 95% CI: 15.8-17.8%, n=933/5,550 in 2015/16) compared to females (13.9%, 95% CI: 13.2-14.7%, n=1,115/8,018 in 2015/16) (Figure 12). Both females and males experienced a decline in CFR between 2007/08 and 2015/16, declining by 45.7% from 25.6% (95% CI: 25.1-26.1%, n=7,822/30,550) to 13.9% (95% CI: 13.2-14.7%, n=1,115/8,018) in females and by 38.0% from 27.1% (95% CI: 26.5-27.7%, n=5,942/21,959) to 16.8% (95% CI: 15.8-17.8%, n=933/5,550) in males, respectively. Cases where the gender was reported as ‘unknown’ have been excluded from Figure 12. This data is, however, retained in the accompanying table (Table S16).
Thirty-day all-cause fatality subsequent to MRSA, MSSA, and *E. coli* bacteraemia and *C. difficile* infection

**Figure 11.** Thirty-day all-cause case fatality rate by age group following *C. difficile* infection

**Figure 12.** Thirty-day all-cause case fatality rate by gender following *C. difficile* infection
Discussion

There was a significant decrease over the study period in the 30-day all-cause CFRs for all four infections reported here. The small changes over time in the patient age distributions did not significantly impact on CFR trends. The decline in the CFRs for MRSA bacteraemia and CDI, coupled with reductions in infection rates, was reflected in rapid declines in the number of deaths following these infections since 2007/08 (Figure 13; Table S17). The declines in the CFRs show how for MRSA bacteraemia and CDI, the number of deaths decreased more rapidly than the number of infections while for MSSA and E. coli bacteraemia the increase in deaths was slower than the increase in the numbers of infections. The largest reduction (42.4%) in 30-day all-cause CFR was seen in CDI. This may be associated with declines in infections caused by C. difficile ribotype 027, which historically predominated in England and has been associated with higher mortality compared to other strains.[11] Additionally, there has been a shift in CDI epidemiology in England where the majority of cases were attributed to hospital onset in 2007/08 compared to a majority of cases being non-hospital-onset from 2011/12 onwards.[1] Nonetheless, mortality among CDI patients remains a concern; an English study published in 2013 found around 15% of patients with CDI died in hospital compared to around 2% of uninfected patients. Notably, in the aforementioned study, where the ribotype was known (72% of cases), none of the patients within the study had infection caused by 027.[12]

With regard to the increase in the MRSA bacteraemia CFR in 2012/13 (Figure 14; Table S17), this may be related to an excess in all-cause fatality associated with respiratory causes noted during the winter of 2012/13.[13] This is, however, set against the general downward trend observed in CFR. Furthermore, the confidence intervals for the CFR in 2012/13 overlap with those of the surrounding years; thus, the CFR is not significantly different from other years.

The declines observed over time in the CFRs following MSSA and E. coli bacteraemia are relatively small in proportion compared to those for MRSA bacteraemia and CDI. Notably, while the CFR following E. coli bacteraemia was lower than MRSA and MSSA bacteraemias, the relatively high incidence of this bloodstream infection equates to a greater number of deaths. As an indication of the public health burden of mortality following E. coli bacteraemia, the number of deaths observed for E. coli bacteraemia in 2015/16 (n=5,603) was still higher than that seen for MRSA bacteraemia in 2007/08 (n=1,354), the time period with the highest CFR since the start of mandatory surveillance.

The decline over time in the CFR following CDI has continued a downward trend, and has the lowest CFR of the four infections reported in 2015/16, however, there is overlap between the confidence intervals with E. coli.
Thirty-day all-cause fatality subsequent to MRSA, MSSA, and *E. coli* bacteraemia and *C. difficile* infection

**Figure 13.** Number of deaths within 30-days of specimen collection by infection

**Figure 14.** Thirty-day all-cause case fatality rate by infection
The most striking patterns in the 30-day all-cause CFRs were by age, with a general increase in CFR by age. For all four infections, patients aged 75 years and over had a significantly higher CFR compared to other age groups (except in one instance; MRSA bacteraemia in 2015/16). Among patients aged 0–1 year with MSSA and E. coli bacteraemia, the CFR was higher than that for 1–14 and 15–44 year olds, which is similar to the pattern observed for the incidence of these bacteraemias.[14, 15] There were no deaths in the 0–1 age group for MRSA bacteraemia in 2015/16 (nor in the previous four years) despite there being infections reported; however, it is possible that a small number of deaths will be observed in future years due to normal fluctuation in the number of cases and subsequent number of deaths. It is not possible to assess mortality rates in patients less than two years old with CDI due to infections in this age group not being reported to PHE (see Appendix 1).

Case fatality was consistently and significantly higher among males than females following CDI and E. coli bacteraemia. Among MSSA bacteraemia cases the CFR was consistently higher among females, although in 2015/16 the CFR confidence intervals converged. MRSA bacteraemia had CFRs that were broadly similar by gender in the past five years, although in 2015/16, females exhibited a higher CFR than males; however, the confidence intervals overlapped suggesting this may not be a true deviation from the trend.

While there were some large differences in the number of deaths and CFRs by region, there was overlap in the confidence intervals associated with the CFRs, suggesting there may be no significant differences between the regions in outcome following infection with MRSA, MSSA, and E. coli bacteraemia and CDI.

Limitations

The ONS has historically published statistics on deaths involving MRSA and C. difficile; these statistics are incomparable with those presented here for the reasons highlighted in the Introduction.

The analyses presented here are based on infections reported to PHE that could be linked to the NHS Spine to obtain mortality information. While the majority of infection reports had complete NHS numbers (required for linkage), for occasional reports the NHS Spine was not able to return patient information, for reasons such as the NHS number and date of birth not matching a record on the NHS Spine. Thus, there may be bias in the records with available mortality information, which may over- or under-estimate the number of deaths and associated CFRs, if the records without mortality information were for patients more or less likely to have died. Additionally, crude CFRs are presented and as such have not been adjusted for potential confounders such as age, gender or co-morbidities, which may affect comparisons over time and between regions. To assess this, generalised linear models were used to provide estimates of the adjusted odds ratios of the CFRs for each infection, controlling for age and gender.
These models found that the crude and adjusted odds ratios were similar, implying that the crude CFRs provide an appropriate estimate.

Finally, analysis of 30-day all-cause fatality enumerates the number of deaths following an infection within a fixed time frame but does not provide insight into attributable mortality. It is difficult to ascertain attributable mortality in practice, due to clinical and diagnostic uncertainty encountered when trying to determine the exact cause of death in patients, particularly in those with multiple co-morbidities.
Appendix 1: Methods

Data on MRSA, MSSA, and *E. coli* bacteraemia and CDI were extracted on 20 April 2016 from the HCAI Data Capture System (DCS). Reports of CDI made in patients aged under 2 years at the time of specimen collection were excluded from all analyses because this data is not mandatorily collected as carriage rates are high [16] with little evidence for disease [17]. Mortality estimates cover the period 2007/08 to 2015/16 for MRSA bacteraemia and CDI; 2011/12 to 2015/16 for MSSA bacteraemia; and, 2012/13 to 2015/16 for *E. coli* bacteraemia.

Mortality information was obtained by batch tracing the extracted MRSA, MSSA, and *E. coli* bacteraemia and CDI data against the NHS Spine, a central repository of patient demographic and medical information managed by the Health and Social Care Information Centre. Records were traced using the NHS number and date of birth (DoB). Only records that match on both the NHS number and the DoB can be successfully traced and have the potential for mortality information to be returned. Within the HCAI DCS, NHS number and DoB are mandatory fields for entering and saving a case onto the surveillance system; users can enter "9"s in place of a valid NHS number if the NHS number is unknown, while 01/01/1900 is used for DoB if it is unknown. Only traced reports are considered when calculating CFR (see footnote 2).

Records between 2007/08 and 2014/15 were originally traced on 04 July 2015; a secondary trace was conducted on all records from financial years' 2013/14 to 2015/16 on 08 August 2016. A retrace of the previous two financial years was undertaken to capture updated reports, including the addition of new reports or updates of existing reports, entered into NHS Spine during the current financial year, resulting in minor changes to previous years final counts (see footnote 3).

For infection reports with a death reported in the NHS Spine, the time in days between specimen date (the date upon which the specimen was collected) and date of death was calculated to identify whether it was within the 30-day window included in the case fatality calculations. Reports where the date of death was 2 or more days before the specimen date for bacteraemias, or 3 or more days before the specimen date for CDI were excluded from the analysis. Where multiple records had the same NHS number and date of birth (within each bacteraemia or CDI) within the 30-day mortality window, some records had valid a NHS numbers and date of birth but failed to trace to the NHS Spine; this involved the following number of records across all reported financial years (and percentage of total records) for each infection: MRSA bacteraemia, 641 (4.2%); MSSA bacteraemia, 1247 (2.6%); *E. coli* bacteraemia, 3844 (2.7%); CDI 5959 (2.8%).

This involved the following number of new/updated reports (and count of updated reports with a death within the 30-day mortality window) for each infection: MRSA bacteraemia, 2 (0); MSSA bacteraemia, 18 (14); *E. coli* bacteraemia, 99 (26); CDI 34 (11).
only the final specimen date was used to calculate 30-day all-cause CFR. Bacteraemia or CDI reports where the date of death was one-day or two-days, respectively, before the specimen date, were included in the 30-day fatality group (see footnote 4); however, these records were only retained in the mortality calculations if the patient did not have a sample taken 30-days prior to their date of death. These data were deduplicated for when a patient (by NHS number and DoB) had more than one record flagged for death (within the 30-day window), per organism. Where this occurs, only the record with specimen date closest to the date of death is associated with 30-day all-cause mortality. This deduplication algorithm was applied to both the 30-day mortality, traced and total number of reports to prevent an inflated count of deaths and reports (see footnote 5).

CFR was calculated by financial year (of the bacteraemia or CDI), region, age and gender; these were calculated for each organism as follows:

\[
30\text{-day all-cause CFR} = \left( \frac{\sum 30\text{-day mortality traced reports}}{\sum \text{traced reports}} \right) \times 100
\]

A crude estimate of the total number of deaths within 30 days of the infection report was calculated for each organism by multiplying the total number of infection reports submitted to the HCAI DCS for a given financial year by the 30-day CFR (expressed as a proportion) rounded to the nearest whole number. The total number of reports were deduplicated in two stages on a bacteraemia or CDI level; first by traced records to where individuals had multiple specimen dates within the 30-day mortality window, only the final specimen date, and dates outside the 30-day window were retained; and second, where records which had a valid NHS number and date of birth, but did not successfully trace, deduplicating any records which occurred within 30-days of the final specimen date, retaining the final specimen date and those outside the 30-day window. The estimated total number of 30-day all-cause deaths was calculated as follows:

\[
\text{Estimated total number 30-day all-cause deaths} = (\text{Mortality deduplicated reports}) \times (30\text{-day all-cause CFR})
\]

This provides an estimate of the number of deaths that might be observed in a given time period if all infection reports could have been linked to mortality records, assuming the risk of death was the same for those records that could and could not be linked.

Percentage changes were calculated for reported deaths and CFRs by financial year (of the bacteraemia or CDI), region, age and gender; these were calculated for each organism as follows:

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4 This involved the following number of reports (and percentage of deaths reported) for each infection: MRSA bacteraemia, 11 (0.23%); MSSA bacteraemia, 20 (0.22%); E. coli bacteraemia, 50 (0.23%); CDI, 173 (0.39%).

5 This involved the following number of deduplicated mortality reports (and percentage of deaths reported) for each infection: MRSA bacteraemia, 46 (0.95%); MSSA bacteraemia, 101 (1.09%); E. coli bacteraemia, 337 (1.54%); CDI, 326 (0.74%).
Thirty-day all-cause fatality subsequent to MRSA, MSSA, and *E. coli* bacteraemia and *C. difficile* infection

\[ v_c = \text{value (deaths or CFR) from the current financial year (2015/16), and;} \]
\[ v_f = \text{value (deaths or CFR) from the first financial year of surveillance} \]

\[
\text{Percentage change} = \left( \frac{v_c - v_f}{v_f} \right) \times 100
\]

The CFR includes 95% confidence intervals calculated using a binomial distribution. Z-tests comparing two proportions were used to determine significant differences in the 30-day all-cause CFR over time, controlling for age, gender and region, assessed using multivariate regression. For the analysis, we have assumed independence between mortality events.

Sample calculations for CFR (not including 95% CI), estimated total number of 30-day all-cause deaths, and percentage change for MRSA in 2015/16:

30-day all-cause CFR\(_{\text{MRSA 2015/16}}\) = \( \frac{232 \text{ deaths}}{789 \text{ traced reports}} \times 100 = 29.4\% \)

Est. total number 30-day all-cause deaths\(_{\text{MRSA 2015/16}}\) = \( 819 \text{ mortality deduplicated DCS reports} \times (0.294) = 241 \)

CFR percentage change\(_{\text{MRSA 2007/08 to 2015/16}}\) = \( \frac{(29.4 - 38.9)}{38.9} \times 100 = 24.0\% \text{ decrease} \)

Deaths percentage change\(_{\text{MRSA 2007/08 to 2015/16}}\) = \( \frac{(232 - 1,354)}{1,354} \times 100 = 82.9\% \text{ decrease} \)
Appendix 2: Summary of differences between Office for National Statistics and PHE mortality outputs

Table A1: Summary of differences in methodology between the ONS and PHE mortality publications

<table>
<thead>
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<th>ONS</th>
<th>PHE</th>
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<td>England</td>
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<td>Calendar year</td>
<td>Financial year</td>
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<td>Mortality data source</td>
<td>Death registrations</td>
<td>NHS Spine reports of death</td>
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<tr>
<td>Deaths relating to</td>
<td>Mentions of MRSA or Clostridium</td>
<td>Deaths within 30 days of positive</td>
</tr>
<tr>
<td></td>
<td>difficile on the death certificate (where the patient need not have died from MRSA or C. difficile) and where MRSA or C. difficile were the underlying cause of death.</td>
<td>specimen of MRSA bacteremia or CDI. Additionally the PHE report includes deaths within 30 days of infection report of MSSA or E. coli bacteremia.</td>
</tr>
<tr>
<td>Denominator</td>
<td>All deaths in the given time period and population in the given time period (two different denominators used)</td>
<td>All traced reports of MRSA, MSSA, E. coli bacteremia or CDI in the given time period</td>
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References


