30-day all-cause fatality subsequent to MRSA, MSSA and Gram-negative bacteraemia and *C. difficile* infections, 2017/18

October 2018
30-day all-cause fatality subsequent to MRSA, MSSA, and Gram-negative bacteraemia and *C. difficile* infections

About Public Health England

Public Health England exists to protect and improve the nation’s health and wellbeing, and reduce health inequalities. We do this through world-leading science, knowledge and intelligence, advocacy, partnerships and the delivery of specialist public health services. We are an executive agency of the Department of Health and Social Care, and a distinct delivery organisation with operational autonomy. We provide government, local government, the NHS, Parliament, industry and the public with evidence-based professional, scientific and delivery expertise and support.

Public Health England
Wellington House
133-155 Waterloo Road
London SE1 8UG
Tel: 020 7654 8000
www.gov.uk/phe
Twitter: @PHE_uk
Facebook: www.facebook.com/PublicHealthEngland

Prepared by; Olisaeloka Nsonwu, Graeme Rooney, Simon Thelwall and Russell Hope.
For queries relating to this document, please contact: mandatory.surveillance@phe.gov.uk

© Crown copyright 2018
You may re-use this information (excluding logos) free of charge in any format or medium, under the terms of the Open Government Licence v3.0. To view this licence, visit OGL or email psi@nationalarchives.gsi.gov.uk.

Where we have identified any third party copyright information you will need to obtain permission from the copyright holders concerned. [Citation to PHE department of HCAI & AMR is required. Citation: Public Health England. 30-day all-cause fatality subsequent to MRSA, MSSA and Gram-negative bacteraemia and *C. difficile* infections, 2017/18. London: Public Health England, October 2018].

Published: October 2018
PHE gateway number: 2018510
PHE supports the UN Sustainable Development Goals
Contents

About Public Health England ........................................................................................................... 2
Contents .............................................................................................................................................. 3
Executive summary ............................................................................................................................ 4
Introduction .......................................................................................................................................... 5
  Comparability with previous ONS publications on mortality .......................................................... 6
  Interpreting case fatality rates ......................................................................................................... 6
  Supplementary data tables and graphs ............................................................................................... 7
Results ................................................................................................................................................ 8
  Staphylococcus aureus ..................................................................................................................... 8
    MRSA bacteraemia ........................................................................................................................ 8
    MSSA bacteremia .......................................................................................................................... 11
  Gram-negative bacteraemia ............................................................................................................. 13
    Escherichia coli bacteremia .......................................................................................................... 13
    Klebsiella spp. bacteremia ......................................................................................................... 16
    Pseudomonas aeruginosa bacteremia ............................................................................................ 17
  Clostridium difficile infections ......................................................................................................... 19
Discussion ........................................................................................................................................... 23
Limitations ........................................................................................................................................ 25
Appendix 1: Methods ....................................................................................................................... 27
Appendix 2: Summary of differences between ONS and PHE fatality outputs ................................ 30
References ........................................................................................................................................... 31
Executive summary

The analysis presented here reports 30-day all-cause fatality following meticillin-resistant *Staphylococcus aureus* (MRSA), meticillin-susceptible *S. aureus* (MSSA) bacteraemia, Gram-negative (*Escherichia coli*, *Klebsiella* spp. and *Pseudomonas aeruginosa*) bacteraemia and *Clostridium difficile* infections (CDI). 30-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. This report uses case fatality rates (CFR) - a ratio of deaths to cases, as they provide a standard measure (independent of the incidence of the infection) on the survivability of an infection. Enhanced mandatory surveillance of *Klebsiella* spp. and *P. aeruginosa* bacteraemia began in April 2017 and this is the first publication of this report to include 30-day all-cause deaths and associated CFRs for these infections. Mortality outcome by onset of infections is also included for the first time.

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, reflecting the increased incidence of these infections.

CFRs of MRSA, MSSA and *E. coli* bacteraemia and CDI have declined over time. Thus, patients are more likely to survive these infections now compared to previous years. In 2017/18, the 30-day all-cause CFRs following bacteraemia due to MRSA and MSSA were 27.0% and 20.2% respectively. The CFRs following *E. coli*, *Klebsiella* spp. and *P. aeruginosa* bacteraemia were 14.8%, 20.2% and 27.0% respectively.

MRSA and *P. aeruginosa* bacteraemia had the highest CFRs. However, the greatest number of deaths was seen following *E. coli* bacteraemia due to its higher incidence. For example, in 2017/18, there were many more 30-day all-cause deaths following *E. coli* bacteraemia (n=5,865) than there were following MRSA (n=219) and *P. aeruginosa* (n=1,116) bacteraemia.

CFRs of hospital-onset and community-onset cases declined over time. Hospital-onset cases had higher CFRs than community-onset cases, likely reflecting to some extent the difference in patient mix; hospital-onset cases may be expected to have more co-morbidities leading to poorer outcomes compared to community-onset cases. Between 2007/08 and 2017/18, there was a large decline in the CFR of community-onset CDI from 20.2% to 11.1%, while the CFR of hospital-onset cases declined from 30.2% to 22.6%. In 2017/18, MRSA and *P. surveillance* bacteraemia had the highest CFR in both hospital-onset (30.1% and 29.8% respectively) and community-onset cases (25.6% and 25.2% respectively).
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 aggregate counts of bacteraemia (bloodstream infection) due to *Staphylococcus aureus* together with the number of meticillin-resistant *S. aureus* (MRSA); case level MRSA reporting was introduced in 2005. Since April 2007, trusts have also been required to report all cases of *Clostridium difficile* infection (CDI) in patients that are ≥2 years old, with the mandatory surveillance programme expanded to include bacteraemia due to meticillin-susceptible *S. aureus* (MSSA) and *Escherichia coli* in January and July 2011 respectively. Mandatory surveillance of bacteraemia due to *Klebsiella* spp. and *P. aeruginosa* bacteraemia was introduced in April 2017 [1]. Over time, the predominant location of onset of MRSA bacteraemia and CDI infections has changed from hospital-onset to community-onset cases. Also, a greater proportion of all reported MSSA and Gram-negative bacteraemia are community-onset rather than are hospital-onset [1]. As patient mix from these types of cases can be very different, this publication for the first time, investigates mortality outcomes by onset of infection.

There have been large declines in the incidence rates (IR) of MRSA bacteraemia (81%) and CDI (76%) between the financial years (FYs) 2007/08 and 2017/18 [1]. In contrast, there has been a year-on-year increase in IR of MSSA and *E. coli* bacteraemia. Although these are relatively small as percentage increases, they translate to large increases in the number of cases [1]. Due to the potential impact of HCAIs on morbidity and mortality, monitoring mortality is an important part of surveillance [2]. 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 [3]. For example, MRSA are resistant to the recommended first-line therapy for infections suspected to be cause by *S. aureus* infections (flucloxacillin), whilst around 19% of *E. coli* bloodstream isolates are resistant to ciprofloxacin, which in the UK is recommended for use 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 predicted 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 following bacteraemia due to MRSA, MSSA, *E. coli*, *Klebsiella* spp. and *P. aeruginosa* and CDI; these deaths may or may not be related to the infection. Data are presented for each organism by financial year, based on the date of case detection (ie date of first positive specimen) rather than when the patient died; it is therefore possible that a death occurred in a different financial year to the infection. The date of case detection is usually the date the blood culture or faecal sample was taken from the
patient; when this is unknown, the date when the samples were received in the laboratory for processing is used. The counts of infections are based on data extracted on 3 May 2018 from the HCAI data capture system (HCAI DCS), and patients’ mortality outcomes were traced on 26 June 2018. The number of infections and deaths presented here may differ from those in earlier publications due to data revisions from previous extracts or inclusion of new or late reports since the previous publications.

This report uses the same base data as PHE’s 2017/18 Annual Epidemiological Commentary (AEC) [1]. Unlike the AEC methodology, counts of infections and deaths have been deduplicated on a patient level to ensure that each patient can only have a single mortality outcome per HCAI. Percentage changes have been calculated using the raw data provided in the supplementary tables. A full description of the methods can be found in Appendix 1.

Comparability with previous ONS publications on mortality

The Office for National Statistics (ONS) previously published data on deaths involving MRSA and C. difficile [8,9]. 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 which mention MRSA or C. difficile on the death certificate. By contrast, this publication includes data from England by financial year, with fatality calculated using all deaths occurring within 30 days of onset of MRSA bacteraemia or CDI. In addition, data are presented on deaths following MSSA and Gram-negative 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 as 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 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. Thus the CFR facilitates comparison between clinical outcomes of diseases with differing incidence. When comparing the CFRs of these infections, it’s important to compare the CFRs in the different patient population (ie gender and age group). Differences in CFRs may be due to different patient mix with
each infection. In addition to the CFR, this report includes 95% confidence intervals (CIs). These provide a range of values within which the true CFR is likely to lie. When CIs for two or more different CFRs overlap then the true CFRs could be equal. It must be borne in mind that the CFRs in this report have been derived from 30-day all-cause fatality rather than attributable fatality. Attributable fatalities are deaths that were as a result of the infection, hence the attributable fatality rate can be lower than the all-cause fatality rate.

Supplementary data tables and graphs

All tables accompanying this publication are available online and can be accessed here.

**Table T1: Table numbers of accompanying tables data tables**

<table>
<thead>
<tr>
<th>Data</th>
<th>MRSA</th>
<th>MSSA</th>
<th>CDI</th>
<th>E. coli</th>
<th>Klebsiella spp.</th>
<th>P. aeruginosa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary</td>
<td>S0</td>
<td>S0</td>
<td>S0</td>
<td>S0</td>
<td>S0</td>
<td>S0</td>
</tr>
<tr>
<td>Overview</td>
<td>S1</td>
<td>S6</td>
<td>S26</td>
<td>S11</td>
<td>S16</td>
<td>S21</td>
</tr>
<tr>
<td>Onset of infection</td>
<td>S2</td>
<td>S7</td>
<td>S27</td>
<td>S12</td>
<td>S17</td>
<td>S22</td>
</tr>
<tr>
<td>Geographical region</td>
<td>S3</td>
<td>S8</td>
<td>S28</td>
<td>S13</td>
<td>S18</td>
<td>S23</td>
</tr>
<tr>
<td>Age</td>
<td>S4</td>
<td>S9</td>
<td>S29</td>
<td>S14</td>
<td>S19</td>
<td>S24</td>
</tr>
<tr>
<td>Gender</td>
<td>S5</td>
<td>S10</td>
<td>S30</td>
<td>S15</td>
<td>S20</td>
<td>S25</td>
</tr>
</tbody>
</table>

**Table T2: Figure numbers for all graphs included in this report**

<table>
<thead>
<tr>
<th>Data</th>
<th>MRSA</th>
<th>MSSA</th>
<th>CDI</th>
<th>E. coli</th>
<th>Klebsiella spp.</th>
<th>P. aeruginosa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of infection</td>
<td>1</td>
<td>5</td>
<td>17</td>
<td>9</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Geographical region</td>
<td>2</td>
<td>6</td>
<td>18</td>
<td>10</td>
<td>13</td>
<td>15</td>
</tr>
<tr>
<td>Age</td>
<td>3</td>
<td>7</td>
<td>19</td>
<td>11</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>Gender</td>
<td>4</td>
<td>8</td>
<td>20</td>
<td>12</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Summary - Deaths</td>
<td>21</td>
<td>21</td>
<td>21</td>
<td>21</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>Summary - CFR</td>
<td>22</td>
<td>22</td>
<td>22</td>
<td>22</td>
<td>22</td>
<td>22</td>
</tr>
</tbody>
</table>
Results

*Staphylococcus aureus*

**MRSA bacteraemia**

In 2017/18, 846 MRSA bacteraemia cases were reported in England, of which 810 (96%) had known fatality outcomes (Table S1). Of these, 219 died within 30 days of the onset of bacteraemia, giving a CFR of 27.0% (95% CI: 24.0-30.2%). This is a decrease of 30% (p<0.001) when compared to the CFR of 38.9% (95% CI: 37.2-40.5%) seen in 2007/08, and a 4% decrease (p>0.2) when compared to that seen in the previous financial year (28.3%; 95% CI: 25.2-31.6% in 2016/17).

**Variation by onset of bacteraemia**

In 2017/18, the CFR in hospital-onset cases was 30.1% (95% CI: 24.6-36.0%) (Figure 1; Table S2) which was a 29% decrease from that seen in 2007/08 (42.4%; 95% CI: 40.3-44.5%). The CFR for community-onset cases was 25.6% (95% CI: 21.9-29.4%) in 2017/18, a 23% decrease from that seen in 2007/08 (33.1%; 95% CI: 30.5-35.7%).

**Variation by region**

CFRs varied geographically by NHS regions, although there was considerable overlap in the 95% CIs of CFRs when comparing between NHS regions and across all time periods (Figure 2; Table S3). The highest CFR was in the Midlands and East of England (32.1%; 95% CI: 25.6-39.2%) while the lowest was in London (24.0%; 95% CI: 17.7-31.2). The CFRs in all regions declined over time, although the magnitude varied; ranging from a 24% reduction in the Midlands and East of England (from 42.4%; 95% CI: 39.0-45.7% in 2007/08 to 32.1%; 95% CI: 25.6-39.2% in 2017/18) to a 35% reduction in London (from 36.7%; 95% CI: 32.9-40.7% in 2007/08 to 24.0%; 95% CI: 17.7-31.2% in 2017/18).

In 2017/18, the Midlands and East of England and North of England experienced the greatest number of deaths (n=62 and 61, respectively) while London and the South of England had the fewest (n=40 and 56, respectively). All NHS regions saw similar declines in the number of deaths between 2007/08 and 2017/18, ranging from an 81% decline the South of England (from 291 to 56 deaths) to an 87% decline in the North of England (from 474 to 61 deaths).

**Variation by age**

The highest CFR and greatest number of deaths were observed in patients aged ≥85 years with the CFR and 95% CIs overlapping with those aged 75-84 years since 2013/14, but separate from all other age groups (Figure 3; Table S4).
Figure 1: 30-day all-cause case fatality rate of MRSA bacteraemia by onset of bacteraemia; 2007/08 - 2017/18

The CFRs in patients aged ≥85 years varied over time ranging between 45.6% (95% CI: 37.9-53.4%) in 2017/18, and 58.9% (95% CI: 51.7-65.8%) in 2012/13. The <1 year and 1-14 year age groups had low numbers of fatalities since the start of enhanced MRSA surveillance with a cumulative count of 21 and 11 deaths respectively, between 2007/08 and 2017/18.

Variation by gender
Numerically, there were more infections and deaths among male patients. For example, in 2017/18, there were 145 deaths among males and 74 among females. However, CFRs among male and female patients were comparable across all time periods (Figure 4; Table S5).
Figure 3: 30-day all-cause case fatality rate of MRSA bacteraemia by age; 2007/08 - 2017/18

CFRs in both genders have generally decreased since 2007/08, with an overall 32% reduction in among male patients, from 38.6% (95% CI: 36.5-40.6%) in 2007/08 to 26.4% (95% CI: 22.7-30.3%) in 2017/18, and a 28% reduction in CFR among female patients from 39.6% (95% CI: 36.8-42.4%) in 2007/08 to 28.5% (95% CI: 23.1-34.4%) in 2017/18. Cases where a patient’s gender was reported as ‘unknown’ have been excluded from Figure 4. These data are, however, included in the accompanying supplementary table (Table S5).

Figure 4: 30-day all-cause case fatality rate of MRSA bacteraemia by gender; 2007/08 - 2017/18
MSSA bacteremia

In 2017/18, 11,938 MSSA bacteraemia cases were reported in England, of which 11,529 cases (97%) had known fatality outcomes (Table S6). Of these, 2,328 died within 30 days of the onset of bacteraemia, giving a CFR of 20.2% (95% CI: 19.5-20.9%). This was a 6% decrease (p<0.001) from that seen in 2011/12 when the CFR was 21.5% (95% CI: 20.6-22.4%). However, this was a slight increase compared to the previous financial year (2016/17) when the CFR was 19.8% (95% CI: 19.0-20.5%). This increase was not statistically significant (p>0.2).

Variation by onset of bacteraemia

Between 2011/12 and 2017/18, the number of deaths among community-onset cases increased by 54% from 1,053 to 1,618 cases. However, CFRs remained relatively stable, ranging from 18.0% (95% CI: 17.0-18.9% in 2013/14) to 19.1% (95% CI: 18.3-19.9% in 2017/18) (Figure 5; Table S7). Over the same period, deaths of hospital-onset cases decreased by 2% from 724 cases in 2011/12 to 710 in 2017/18, which translated to a 13% decrease in CFR from 26.7% (95% CI: 25.1-28.4%) to 23.2% (95% CI: 21.8-24.8%) respectively.

Figure 5: 30-day all-cause case fatality rate of MSSA bacteraemia by onset of bacteraemia; 2011/12 - 2017/18

Variation by region

In 2017/18, the highest number of deaths occurred in the North of England (n=745) while the lowest was in London (n=274) (Table S8). The increase in the number of deaths between 2011/12 and 2017/18 was also observed in all NHS regions. These increases ranged from 19% (626 to 745) in the North of England, to 41% (422 to 595 deaths) in the South of England. Conversely, over the same period, CFRs declined in
all NHS regions except the Midlands and East of England where the CFR increased by 3% (p>0.2) from 21.4% (95% CI: 19.8-23.1%) to 22.1% (95% CI: 20.7-23.6%). In the most recent financial year (2017/18), the CFR ranged from 17.1% (95% CI: 15.3-19.0%) in London to 22.1% in the Midlands and East of England (Figure 6).

**Variation by age**
The number of deaths and associated CFRs varied by age (Figure 7; Table S9). In 2017/18, the lowest CFR was seen in 1-14 year olds (1.5%; 95% CI: 0.6-3.0%) while the highest was in those aged ≥85 years (44.0%; 95% CI: 41.5-46.5%). In all time periods observed, 1-14 year olds had the number lowest number of deaths and associated CFRs. Furthermore, the greatest reduction (41%) in CFRs between 2011/12 and 2017/18 was observed in patients <1 year old, declining from 6.7% (95% CI: 4.5-9.6%) to 4.0% (95% CI: 2.1-6.7%).

**Variation by gender**
The number of deaths among male patients was greater than those for female patients. However, CFRs were generally higher in females (Figure 8; Table S10). For example in 2017/18 there were 1,426 deaths in males compared to 900 in females, with associated CFRs of 19.7% (95% CI: 18.8-20.6%) and 21.1% (95% CI: 19.8-22.3%) respectively. Furthermore compared to 2011/12, the CFR in both male and female patients were relatively stables with average CFRs of 19% and 22% respectively over the same period. Cases where the gender was reported as ‘unknown’ were excluded from Figure 8. These data are, however, included in the accompanying table (Table S10).

**Figure 6: 30-day all-cause case fatality rate of MSSA bacteraemia by NHS region; 2011/12 - 2017/18**
30-day all-cause fatality subsequent to MRSA, MSSA, and Gram-negative bacteraemia and *C. difficile* infections

---

**Figure 7:** 30-day all-cause case fatality rate of MSSA bacteraemia by age; 2011/12 - 2017/18

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

**Figure 8:** 30-day all-cause case fatality rate of MSSA bacteraemia by gender; 2011/12 - 2017/18

![Graph showing fatality rates by gender](image)

---

Gram-negative bacteraemia

*Escherichia coli* bacteraemia

In 2017/18, 41,060 *E. coli* bacteraemia cases were reported in England, of which 39,707 (97%) had known fatality outcomes (Table S11). Of these, 5,865 died within 30 days of onset of bacteraemia, giving a CFR of 14.8% (95% CI: 14.4-15.1%). This was similar to the CFR of 14.7% (95% CI: 14.3-15.0%) seen in the previous financial year.
Between 2012/13 and 2017/18, the CFR decreased by 12% (p<0.001) from 16.8% (95% CI: 16.4-17.3%) to 14.8%.

**Variation by onset of bacteraemia**
In 2017/18, the CFR in hospital-onset cases was 22.7% (95% CI: 21.8-23.7%) (Figure 9; Table S12), which was a 4% decrease from the CFR in 2012/13; 23.6% (95% CI: 22.6-24.6%). In the same financial year (2017/18), the CFR for community-onset cases was 12.9% (95% CI: 12.6-13.3%) which was a 12% decrease from that seen in 2012/13; 14.8% (95% CI: 14.3-15.2%).

**Figure 9: 30-day all-cause case fatality rate of *E. coli* bacteraemia by onset of bacteraemia; 2012/13 - 2017/18**

**Variation by region**
Between 2012/13 and 2017/18, the number of deaths increased in all NHS regions (Table S13) with the greatest increase (1,131 to 1,483; 31%) seen in the South of England. However, over the same period, CFRs declined in all regions. In 2017/18, CFRs ranged from 13.0% (95% CI: 12.1-13.9%) in London to 15.5% (95% CI: 14.9-16.1%) in the North of England (Figure 10; Table S13).

**Variation by age**
The number of deaths and CFRs varied by age group (Figure 11; Table S14) in each financial year. However, all age groups experienced an overall decrease in CFR across all financial years (2012/13 - 2017/18). Over this period, the greatest decrease (44%) in CFR was observed in patients aged 1-14 years, declining from 4.1% (95% CI: 1.8-7.9%; 2012/13) to 2.3% (95% CI: 0.7-5.2%; 2017/18).

In all financial years the lowest CFR and fewest fatalities were observed in patients aged 1-14 years, while the highest were in those aged ≥85 years. In 2017/18, CFRs of
these two age groups were 2.3% (95% CI: 0.7-5.2%) and 22.1% (95% CI: 21.2-22.9%) respectively.

Figure 10: 30-day all-cause case fatality rate of *E. coli* bacteraemia by NHS region; 2012/13 - 2017/18

In the same financial year, the CFRs in patients <1 year old was 8.6% (95% CI: 6.4-11.3%) and those aged 15-44 years was 3.4% (95% CI: 2.8-4.2%) respectively.

Figure 11: 30-day all-cause case fatality rate of *E. coli* bacteraemia by age; 2012/13 - 2017/18

Variation by gender
There was an increase in the number of deaths among male and female patients between 2012/13 and 2017/18; from 2,723 to 3,216 and from 2,316 to 2,646, respectively. (Table S15). However, due to a greater increase in the number of infections relative to the number of deaths for both genders, the CFR declined over the
same time period (Figure 12). In 2017/18, the CFR among men was higher than that among women; 16.8% (95% CI: 16.3-17.4%) versus 12.9% (95% CI: 12.4-13.3%) respectively, an observation made in all years. Cases where the gender was reported as ‘unknown’ have been excluded from Figure 12. These data are, however, included in the accompanying table (Table S15).

Figure 12: 30-day all-cause case fatality rate of *E. coli* bacteraemia by gender; 2012/13 - 2017/18

![Graph showing fatality rate by gender and financial year]

*Klebsiella* spp. bacteraemia

In 2017/18, 9,617 cases of *Klebsiella* spp. bacteraemia cases were reported in England, of which 9,245 (96%) had known fatality outcomes (Table S16). Of these, 1,863 died within 30 days of onset of bacteraemia, giving a CFR of 20.2% (95% CI: 19.3-21.0%).

Variation by onset of bacteraemia

In 2017/18 there were 1,193 deaths among community-onset cases compared to 670 in hospital-onset cases. However, CFRs were greater in hospital-onset cases (24.4%; 95% CI: 22.8-26.1% versus 18.3%; 95% CI: 17.4-19.3%) (Table S17).

Variation by region

Regional CFRs ranged from 18.0% (95% CI: 16.1-20.0%) in London to 22.2% (95% CI: 20.6-23.9%) in the Midlands and East of England (Figure 13; Table S18). Numerically, the highest number of deaths occurred in the North of England (560).

Variation by age

The number of deaths and the CFRs varied by age (Figure 14; Table S19). The greatest CFR was observed in patients aged ≥85 years at 28.4% (95% CI: 26.2-30.6%) while the lowest was in those aged 1-14 years at 1.8% (95% CI: 0.2-6.4%). The CFR in patients <1 year old was 8.8% (95% CI: 4.8-14.6%) which was higher than those aged 1-14 years and 15-44 years (8.5%; 95% CI: 6.4-10.9%).
Variation by gender
In 2017/18, CFR for males and female patients were similar; 19.9% (95% CI: 18.8-20.9%) and 20.6% (95% CI: 19.3-22.0%) respectively (Table S20). Cases where gender was reported as ‘unknown’ are included in the accompanying table (Table S20).

Figure 13: 30-day all-cause case fatality rate of *Klebsiella* spp. bacteraemia by NHS region; 2017/18

Figure 14: 30-day all-cause case fatality rate of *Klebsiella* spp. bacteraemia by age; 2017/18

*Pseudomonas aeruginosa* bacteraemia
In 2017/18, 4,286 cases of *P. aeruginosa* bacteraemia cases were reported in England, of which 4,140 (97%) had known fatality outcomes (Table S24). Of those, 1,116 died within 30 days of onset of bacteraemia, giving a CFR of 27.0% (95% CI: 25.6-28.3%).
Variation by onset of bacteraemia
In 2017/18 there were 649 deaths among community-onset cases compared to 467 in hospital-onset cases (Table S22). However, CFRs were similar in both hospital-onset cases (29.8%; 95% CI: 27.5-32.1%) and community-onset cases (25.2%; 95% CI: 23.6-26.9%).

Variation by region
In 2017/18, regional CFRs ranged from 22.9% (95% CI: 20.1-25.9%) in London to 30.4% (95% CI: 27.7-33.2%) in the North of England. Numerically, the highest number of deaths occurred in the North of England (n=336.0) (Figure 15; Table S23).

Variation by age
The number of deaths and the CFRs varied by age (Figure 16; Table S24). The greatest CFR was observed in patients aged ≥85 years (34.8%; 95% CI: 31.4-38.2%) followed by those aged <1 year (33.3%; 95% CI: 20.4-48.4%), while the lowest was in those aged 1-14 years at (4.0%; 95% CI: 1.1-9.9%).

Variation by gender
In 2017/18, CFR for males and female patients were similar 24.8% (95% CI: 23.2-26.5%) and 30.7% (95% CI: 28.4-33.1%) respectively (Table S25). Cases where the gender was reported as ‘unknown’ are included in the accompanying table (Table S25).

Figure 15: 30-day all-cause case fatality rate of P. aeruginosa bacteraemia by NHS region; 2017/18
30-day all-cause fatality subsequent to MRSA, MSSA, and Gram-negative bacteraemia and *C. difficile* infections

Figure 16: 30-day all-cause case fatality rate of *P. aeruginosa* bacteraemia by age; 2017/18

![Figure 16: 30-day all-cause case fatality rate of *P. aeruginosa* bacteraemia by age; 2017/18](image)

**Clostridium difficile** infections

In 2017/18, 13,286 cases of CDI were reported in England (Table S26), of which 12,980 (98%) had known fatality outcomes. Of these, 1,977 died within 30 days of onset of CDI, giving a CFR of 15.2% (95% CI: 14.6-15.9%).

The CFR in 2017/18 (15.2%) has decreased significantly (42%; p<0.001) compared to that seen in 2007/08 (26.3%; 95% CI: 25.9-26.7%) however, there was little difference (<1%; p>0.2) when compared to the previous financial year (15.1%; 95% CI: 14.5-15.7% in 2016/17).

**Variation by onset of infection**

Between 2007/08 and 2017/18, the number of deaths was consistently greater in hospital-onset cases but the CFRs in community-onset cases declined at a faster rate compared to hospital-onset cases (Figure 17; Table S27). During the same period, the CFR in hospital-onset cases decreased by 25% from 30.2% (95% CI: 29.7-30.7%) to 22.6% (95% CI: 21.4-23.8%), while the CFR in community-onset cases declined by 45% from 20.2% (95% CI: 19.7-20.8%) to 11.1% (95% CI: 10.5-11.8%).

**Variation by region**

In 2017/18, there was a wide variation in the number of deaths by NHS regions. The greatest number of deaths were seen in the North of England NHS region (n=653), the number being nearly three times greater than that seen in London (n=222), the NHS region with the lowest number of deaths (Table S28). All NHS regions saw similar trends to the national decline of 86% in the number of deaths between 2007/08 and 2017/18; regional range 85-87%.
In 2017/18, the CFRs ranged from 13.0% (95% CI: 11.5-14.7%) in London to 16.9% (95% CI: 15.8-18.2%) in the Midlands and East of England (Figure 18; Table S28).

Variation by age
The number of deaths and associated CFRs increased with age (Figure 19; Table S29). In 2017/18, there was one death among 2-14 year olds giving a CFR of 0.4% (95% CI: 0-2.2%), while among those aged ≥85 years, there were 820 deaths; a CFR of 24.5% (95% CI: 23.1-26.0%). The CFR in patients aged ≥85 years remained (p<0.001) 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 between 2007/08 and 2017/18.

Variation by gender
Between 2007/08 and 2017/18, the number of deaths was higher among female patients compared to male patients. However, over the same period, the CFR remained higher in male patients. For example, in 2017/18 the CFR among male patients was 16.8% (95% CI: 15.9-17.9%) while it was 14.1% (95% CI: 13.3-14.9%) in female patients (Figure 20; Table S30). Between 2007/08 and 2017/18, the CFRs in female patients declined by 45% from 25.7% (95% CI: 25.2-26.1%) to 14.1%, while among male patients it declined by 38% from 27.1% (95% CI: 26.5-27.7%) to 16.8% in males. Cases where the gender was reported as ‘unknown’ have been excluded from Figure 20; Table S29. These data are, however, retained in the accompanying table (Table S30).
Figure 18: 30-day all-cause case fatality rate of *C. difficile* infections by NHS region; 2007/08 - 2017/18

Figure 19: 30-day all-cause case fatality rate of *C. difficile* infections by age; 2007/08 - 2017/18
Figure 20: 30-day all-cause case fatality rate of *C. difficile* infections by gender; 2007/08 - 2017/18
Discussion

There was a significant decrease in the CFRs of MRSA, MSSA and *E. coli* bacteraemia and CDI over the surveillance period. The small changes in the patient age distributions over time did not significantly affect CFR trends. The large reductions in the CFR of MRSA bacteraemia (Figure 23; Table S1) and CDI (Figure 24; Table S26) shows that; in addition to large decline in incidence rates of reported cases, the proportion of these where patients died following the infections has also greatly reduced over time. Furthermore, the large reductions in CFRs of all reported MRSA bacteraemia and CDI are indicative of the change in their epidemiology over the years. Between 2007/08 and 2017/18 both infections have changed from predominantly hospital-onset infections to community-onset infections. Since CFRs are generally higher in hospital-onset cases compared to community-onset cases, large reductions in hospital-onset cases would also translate to large reductions in the overall CFR of these infections (Figure 1, Figure 17; Table S2, Table S27). The reduction in CFR of CDI was further magnified due to the larger decline in CFR of community-onset CDI (45%) compared to community-onset cases of all other infections covered in this report. In 2017/18, MRSA and *P. aeruginosa* bacteraemia had the highest CFR in hospital-onset (30.1% and 29.8%) and community-onset cases (25.6% and 25.2%) respectively.

The largest reduction (42%) 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 was historically the predominant strain in England between 2007 and 2012 and has been associated with higher mortality compared to other strains [11]. Reductions in CFR among the community-onset CDI cases may have been greater than that seen in the hospital-onset cases due to patients in the former group being more likely to have less co-morbidities than the latter and thus the outcomes for this group are likely more sensitive to difference is the predominant strain. There has been a shift in the epidemiology of CDI in England from predominantly hospital-onset cases in 2007/08 to mostly community-onset from 2011/12 onwards (Figure 17). It is important to note, however, that a substantial proportion of community-onset case would have healthcare interactions. Nonetheless, mortality among CDI patients remains a concern; with an English study published in 2013 reporting that around 15% of patients with CDI died in hospital compared to around 2% of patients without CDI. Notably, where the ribotype was known (72% of cases), none of the patients had infection caused by 027 [12].

With regard to the observed increase in CFR of MRSA bacteraemia in 2012/13, this may be related to an excess in all-cause deaths 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 over time in the CFRs of MSSA and *E. coli* bacteraemia was relatively small compared to those for MRSA bacteraemia and CDI. It is worth noting that, while the CFR of *E. coli* bacteraemia was lower than those for MRSA and MSSA bacteraemias, the relatively high incidence of this infection equates to a greater number of fatalities compared to MRSA and CDI. As an indication of the public health burden of fatality following *E. coli* bacteraemia, the number of 30-day all-cause fatalities following *E. coli* bacteraemia in a single financial year (n=5,865, 2017/18) was higher than the cumulative number of 30-day all-cause fatalities following MRSA bacteraemia over ten financial years (n=5,263, 2007/08 and 2017/18).

Mandatory surveillance of *Klebsiella* spp. and *P. aeruginosa* bacteraemia only began in April 2017. In the initial 12 months of study (2017/18), the CFR of *P. aeruginosa* bacteraemia was equal to that due to MRSA (27.0%), the highest CFR seen among the infections covered in this report.

**Figure 21: Number of deaths within 30-days of case detection by infection**

The trend in age specific CFRs were similar for all infections. CFRs generally increased with age, with the exception of those <1 year old; where CFRs were usually higher than patients aged 1-14 years old, and in some cases those aged 15-44. Of note, the CFR in patients with *P. aeruginosa* bacteraemia aged <1 year old was greater than that in all other age groups except those ≥85 year. However, it should also be noted that only 1% (n=59) of *P. aeruginosa* cases were from this age group. Conversely, compared to the trend above, the CFR of MRSA bacteraemia in patients aged <1 year was relatively low with only two deaths in this age group since 2011/12 and 19 deaths between then and 2017/18. It is not possible to assess fatality rates in patients less than two years old with CDI as infections in this age group are not reported to PHE (see Appendix 1).
Case fatality was consistently and significantly higher among males than females for CDI and *E. coli* bacteraemia. Among MSSA and *P. aeruginosa* bacteraemia cases the CFR was consistently higher among females. MRSA (past six financial years) and *Klebsiella* spp. bacteraemia (past financial year) had CFRs that were broadly similar by gender, although in 2015/16, the CFR for MRSA bacteraemia among females patients was higher. However, the confidence intervals overlapped suggesting this may not be a true deviation from the trend.

**Figure 22: 30-day all-cause case fatality rate by infection**

There were large regional differences in the number of deaths following all infections. This reflected the different regional trends in the incidence of these infections. Regional CFRs for all infections also varied but in most instances these had overlapping 95% confidence intervals, suggesting that regional CFRs were not statistically significantly different. Use of generalised linear models adjusted for age, sex and region demonstrated that for all infections, no single NHS region was significantly different from each of the other three.

**Limitations**

The ONS has historically published statistics on deaths involving MRSA and *C. difficile*; these statistics are not comparable 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 with a different likelihood of death. 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, between regions and onset setting. However the use of generalised linear models to provide estimates of the adjusted odds ratios of CFR for each infection by controlling for age and gender, found that the crude CFR and adjusted CFR were similar, implying that the crude CFRs provide an appropriate estimate. Pairwise estimates following regression were used to test if changes in CFR were significant. Finally, while analysis of 30-day all-cause fatality enumerates the risk of death following an infection within a fixed time frame it does not provide insight into attributable mortality. However, 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, *E. coli*, *Klebsiella* spp. and *P. aeruginosa* bacteraemia and CDI were extracted on 3 May 2018 from the HCAI Data Capture System (DCS). Reports of CDI from patients aged <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 [14] with little evidence for disease [15]. Fatality estimates cover the first complete financial year after the start of the surveillance for each data collection 2007/08 for MRSA bacteraemia and CDI, 2011/12 for MSSA bacteraemia, 2012/13 for *E. coli* bacteraemia and 2017/18 for *Klebsiella* spp. and *Pseudomonas aeruginosa* bacteraemia.

Fatality information was obtained by batch tracing the extracted MRSA, MSSA, and *E. coli*, *Klebsiella* spp. and *Pseudomonas aeruginosa* 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 fatality 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.¹

Records between 2007/08 and 2014/15 were originally traced on 4 July 2015; a secondary trace was conducted on all records from financial years’ 2013/14 to 2016/17 on 3 July 2017. In addition to records from the most recent financial year (2017/18), records from the two previous financial years (2015/16 and 2016/17) or records prior to this but have not been traced before (late reports) were traced on 26 June 2018. The retrace and/or addition of late reports may result in minor changes to previously published counts.²

For infection reports with a death reported in the NHS Spine, the time in days between specimen date and date of death was calculated to identify whether it was within the 30-day window included in the case fatality calculations. Bacteraemia reports with a date of death ≥2 days prior to the specimen date were excluded from the analysis. In

¹ 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, 660 (4%); MSSA bacteraemia, 1,657 (2%); *E. coli* bacteraemia, 5,536 (2%); *Klebsiella* spp. bacteraemia, 233 (2%); *P. aeruginosa* bacteraemia, 96 (2%); CDI 6,264 (3%)

² This involved the following number of new/updated reports for each infection in previous years’ where 30-day fatality status was updated from “yes” to from “no”: MRSA bacteraemia, 2 (<0.1%); MSSA bacteraemia, 9 (<0.1%); *E. coli* bacteraemia, 20 (<0.1%); CDI 3 (<0.1%)
30-day all-cause fatality subsequent to MRSA, MSSA, and Gram-negative bacteraemia and *C. difficile* infections

publications prior to September 2018, CDI cases with dates of death ≥3 days were excluded however, since then, such cases have been included and are considered a 30-day all-cause deaths. On the HCAI DCS, MRSA, MSSA, *E. coli*, *Klebsiella* spp. and *Pseudomonas aeruginosa* bacteraemia episode lengths are 14-days, and CDI is 28-days, therefore it is possible to have multiple cases within 30 days of a death. Where multiple records had the same NHS number and date of birth (within each bacteraemia or CDI) within the 30-day fatality window, only the record with the specimen date closest to the date of death was used to calculate 30-day all-cause CFR. This was done to prevent estimate bias by overestimating of the numbers of deaths. This deduplication algorithm was applied to both the 30-day fatality, traced and total number of reports to prevent an inflated count of deaths and reports.

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

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

The total numbers of reports were de-duplicated in two stages on; first by traced records where individuals had multiple specimen dates within the 30-day fatality window. Only the records with specimen date closest to the date of death while all records outside the 30-day window are retained regardless of episode length. The second stage was in records with a valid NHS number and date of birth that were not successfully traced. Among these cases, duplicates within a 30-day window period were excluded, retaining only the most recent case. Both stages of deduplications were done to ensure each patient (traced/not-traced) had only one fatality outcome.

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 deduplicated 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 estimated total number of 30-day all-cause deaths was calculated as follows:

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

3 There were 102 cases (<0.1%) of CDI with dates of death ≥3 day prior to their specimen dates. These were included in the analysis and considered 30-day all-cause fatalities.

4 The following number of cases were excluded to ensure each patient had only one 30-day fatality: MRSA bacteraemia, 52 (<1%); MSSA bacteraemia, 140 (<1%); *E. coli* bacteraemia, 508 (<1%); *Klebsiella* spp. bacteraemia, 23 (<1); *P. aeruginosa* bacteraemia, 13 (<1%); CDI 362 (<1%).
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 fatality 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:

\[ v_c = \text{value (deaths or CFR) from the current financial year (2017/18), and;} \]
\[ v_f = \text{value (deaths or CFR) from the first financial year of surveillance} \]

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

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.

Sample calculations for CFR (not including 95% CI), estimated total number of 30-day
all-cause deaths, and percentage change for MRSA in 2017/18. Note that all
calculations within the report use the raw figures found in the supplementary tables,
figures in the report will be rounded to one decimal place:

30 day all cause CFR\text{MRSA 2017/18} = \frac{219 \text{ deaths}}{810 \text{ deduplicated traced reports}} \times 100 = 27%

Est. total number of deaths\text{MRSA 2017/18} = (845 \text{ mortality deduplicated DCS reports}) \times (0.27) = 228

Percentage change in CFR\text{MRSA 2007/08 to 2017/18} = \frac{(27.0 - 38.9)}{38.9} \times 100 = 30%

Percentage change deaths\text{MRSA 2007/08 to 2017/18} = \frac{(219 - 1,354)}{219} \times 100 = 84%
### Appendix 2: Summary of differences between ONS and PHE fatality outputs

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

<table>
<thead>
<tr>
<th>Information</th>
<th>ONS</th>
<th>PHE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geography</td>
<td>England and Wales</td>
<td>England</td>
</tr>
<tr>
<td>Time period covered</td>
<td>Calendar year</td>
<td>Financial year</td>
</tr>
<tr>
<td>Mortality data source</td>
<td>Death registrations</td>
<td>NHS Spine reports of death</td>
</tr>
<tr>
<td>Deaths relating to</td>
<td>MRSA bacteraemia and <em>C. difficile</em></td>
<td>MRSA, MSSA, <em>E. coli</em> bacteraemia and <em>C. difficile</em> infection</td>
</tr>
<tr>
<td>Deaths determined by</td>
<td>Mention of MRSA or <em>C. difficile</em> on the death certificate (where the patient need not have died from MRSA or <em>C. difficile</em>) and where MRSA or <em>C. difficile</em> were the underlying cause of death.</td>
<td>Deaths within 30 days of positive specimen of MRSA, MSSA or <em>E. coli</em> bacteraemia or <em>C. difficile</em> infections determined using data matched with the NHS Spine.</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, <em>E. coli</em> bacteraemia or CDI in the given time period</td>
</tr>
</tbody>
</table>
30-day all-cause fatality subsequent to MRSA, MSSA, and Gram-negative bacteraemia and *C. difficile* infections

**References**


