Thirty-day all-cause mortality following MRSA, MSSA and Gram-negative bacteraemia and *C. difficile* infections

2018/19
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Executive summary

In this analysis, we report the 30-day all-cause mortality following meticillin-resistant *Staphylococcus aureus* (MRSA), meticillin-susceptible *S. aureus* (MSSA) bacteraemia, Gram-negative (*Escherichia coli*, *Klebsiella* spp. and *Pseudomonas aeruginosa*) bacteraemia and *Clostridiodes difficile* infections (CDI). Thirty-day all-cause mortality is a widely-used outcome for assessing risk of death. However, it should be emphasised that since it is deaths from all causes, some of the deaths will not be attributable to these infections.

This report presents case fatality rates (CFR) and mortality rates (MR). CFR is the number of deaths as a percentage of cases and provides a measure for comparing survivability of different infections. In contrast, the MR is the number of deaths divided by the population at risk and reflects the incidence of deaths following each type of infection in the population.

In 2018/19, MR of 30-day all-cause deaths per 100,000 population for each infection covered in this report were; *E. coli* bacteraemia (10.4, n= 5,798 deaths), MSSA bacteraemia (4.0, n= 2,220 deaths), *Klebsiella* spp. bacteraemia (3.4, n= 1,916 deaths), CDI (2.9, n= 1,625 deaths), *P. aeruginosa* bacteraemia (1.8, n= 974 deaths) and MRSA bacteraemia (0.3, n= 191 deaths).

In 2018/19, the CFR were; MRSA bacteraemia (24.5%), *P. aeruginosa* bacteraemia (24.0%), MSSA bacteraemia (19.0%), *Klebsiella* spp. bacteraemia (18.6%), *E. coli* bacteraemia (13.8%) and CDI (13.6%). The CFR of all infections declined over time. This means a greater proportion of patients are surviving each type of infection every year; potentially reflecting earlier diagnosis or improved clinical management.

Between 2007/08 and 2018/19, there were significant declines in the number of 30-day all-cause deaths following MRSA bacteraemia (1,354 to 191 deaths) and CDI (13,973 to 1,625 deaths) due to decreased incidence and other factors (e.g. change in virulence and clinical management) of these infections over the same period. In contrast, the number of deaths following infection have increased for MSSA bacteraemia (1,777 deaths in 2011/12 to 2,220 in 2018/19) and *E. coli* bacteraemia (5,163 deaths in 2012/13 to 5,798 in 2018/19), reflecting the continued increase in incidence of these infections.

In 2018/19, the CFR of both hospital-onset and community-onset cases were highest in *P. aeruginosa* bacteraemia cases (27.1% and 22.3% respectively) and MRSA bacteraemia (25.3% and 24.1% respectively).
Thirty-day all-cause mortality following MRSA, MSSA and Gram-negative bacteraemia and *C. difficile* infections

There were declines in CFRs of both hospital-onset and community-onset cases. However, the reduction was greater in community-onset cases except in MRSA and MSSA bacteraemia, where the reduction was greatest in hospital-onset cases. Conversely, the reduction in CFR was greater in community-onset CDI cases (10.7% difference) compared to hospital-onset CDI case (8.8% difference) between 2007/08 and 2018/19. This was despite greater reductions in the reported number of hospital-onset cases (87.4%) compared to community-onset ones (63.4%) over the same period.
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 *Staphylococcus aureus* bacteraemia (bloodstream infection) and the number that were meticillin-resistant *S. aureus* (MRSA). Case-level reporting was introduced for MRSA in 2005, and for *Clostridioides difficile* infections (CDI) in patients ≥2 years-old since April 2007. The mandatory surveillance programme was expanded to include meticillin-susceptible *S. aureus* (MSSA) and *Escherichia coli* bacteraemia in January and July 2011 respectively. In April 2017, *Klebsiella* spp. and *Pseudomonas aeruginosa* bacteraemia were also added to the surveillance programme [1]. Over time, the dominance of hospital-onset MRSA bacteraemia and CDI has declined with increasing proportion of community-onset cases, reflecting changes in healthcare delivery and population structure. Also, an increasing proportion of MSSA and Gram-negative bacteraemia are community-onset [1]. This publication also investigates mortality outcomes by onset of infection, and prior healthcare exposure for CDI. Due to the potential impact of HCAI on morbidity and mortality [2–4], monitoring trends in mortality is an important part of surveillance.

This report presents an analysis of 30-day all-cause mortality among patients following MRSA, MSSA, *E. coli*, *Klebsiella* spp. and *P. aeruginosa* bacteraemia, and CDI.
Method

Data in this report are presented by financial year based on the specimen date (i.e. collection date of first positive specimen) rather than when the patient died. It is therefore possible that a death occurred in a different financial year from the infection if the specimen date is sufficiently close to the end of the previous financial year. When the date of the blood culture or faecal sample was taken is not known, the date when the sample was received in the laboratory for processing is used as the specimen date. The counts of infections are based on data extracted on 17 April 2019 from the HCAI data capture system (HCAI DCS). Patients’ mortality outcomes were traced on 7 July 2019. The number of infections and deaths presented here may differ from those in earlier publications due to data revisions i.e. inclusion of new or late reports since previous publications.

This report uses the same base data as PHE’s 2018/19 Annual HCAI Epidemiological Commentary [1]. Unlike the methodology in the annual report, here 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 infection. The most recent case within a 30-day window period from the date of death is retained, while the others are excluded from mortality figures. Percentage changes have been calculated using the raw data provided in the supplementary tables. A full description of the methods can be found in the Appendix.

Comparability with previous ONS publications on mortality

The Office for National Statistics (ONS) previously published data on deaths involving MRSA and C. difficile [5,6]. The ONS data on MRSA bacteraemia and CDI are not comparable to the data published here for several methodological reasons outlined in the Appendix. In summary, the ONS published data from England and Wales by calendar year, based on registered death records where MRSA or C. difficile was mentioned. By contrast, this publication includes data from England by financial year, with mortality 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 2 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 provides a consistent methodology to determine the temporal trends and reduces the subjectivity of cause of death or changes in priorities for death certification.
Interpreting case fatality rates

Case fatality rates (CFR) 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.

In addition to the CFR, this report includes 95% confidence intervals. These provide a range of values within which the true CFR is likely to lie. When confidence intervals for 2 or more different CFRs overlap then the true CFRs could be equal.

Interpreting mortality rates

Mortality rates (MR) are a measure of deaths in the population at risk. This contrasts with the CFR which shows the risk of death per case. The MR is calculated as the number of deaths divided by a population estimate. The population estimate is based on England’s mid-year estimates. For MR in Hospital-onset and Community-onset: healthcare associated cases where patients in hospital are those at risk of infection and consequently death following infection, the number of overnight inpatient bed-days.

Regression analysis

When comparing MR and CFR between infections, it is important to consider the patient-mix that different infections may have. Although we have presented crude CFRs and MRs by onset of infection and NHS commissioning regions, differences in mortality rates may be due to varying patient demographics (such as age and sex), and other uncontrolled factors for these infections. Regression models controlled for age groups and patient sex as categorical variables were used to assess regional differences in MR and odds of death used to analysis. P values <0.05 were taken as statistical evidence of non-random regional variation. For each model cases where the patient’s sex was reported as “unknown” were excluded.

An accompanying data table for this report can be found here.
Results

In 2018/19, 83,218 cases of *E. coli*, *Klebsiella* spp., *P. aeruginosa*, MRSA and MSSA bacteraemia, and CDI from 73,574 patients were reported in England. After case deduplication as described in the method section, there were 12,724 deaths within 30 days of taking a specimen (blood culture for bacteraemia, faecal sample for CDI). The mortality rate (MR) was 22.9 deaths per 100,000 population, and the case fatality rate (CFR) was 16%. Figure 1 and Figure 2 show the MR and CFR of each infection over their surveillance periods.

**Figure 1. Number of deaths within 30-days of case detection by infection, 2007/08 to 2018/19**
Thirty-day all-cause mortality following MRSA, MSSA and Gram-negative bacteraemia and *C. difficile* infections

**Figure 2. Thirty-day all-cause case fatality rate by infection, 2007/08 to 2018/19**

**Gram-negative bacteraemia**

*Escherichia coli* bacteraemia

In 2018/19, 43,242 *E. coli* bacteraemia cases were reported in England. Information on mortality was available for 97% (n= 41,970) of these cases (Table S1). There were 5,798 deaths within 30 days of an *E. coli* bacteraemia which was a MR of 10.4 deaths per 100,000 population. The CFR was 13.8% of cases.

The CFR decreased each financial year beginning from 16.8% in 2012/13 to 13.8% in the current financial year (2018/19), while the overall trend of MR increased from 9.7 per 100,000 population to 10.4 over the same period.

**Variation by onset of bacteraemia**

In 2018/19, the MR of hospital-onset cases was 4.6 deaths per 100,000 bed-days (n= 1,576 deaths) compared to 4.9 (n= 1,689 deaths) in the previous financial year (2017/18) (Table S2 and Figure 3). In the same financial year, the MR in community-onset cases was 7.6 deaths per 100,000 population (n= 4,222 deaths) and 7.5 (n= 4,189 deaths) respectively.

Between 2012/13 and 2018/19, there was an overall decreasing trend of CFR in both hospital-onset and community-onset cases. In this period, the CFR of hospital-onset cases declined from 23.6% to 21.3%, while for community-onset cases it declined from 14.8% to 12.2% of cases (Table S2 and Figure 4). CFR of hospital-onset cases in 2017/18 (22.8%) was on average 1% higher than that of the 3 preceding financial years.
Thirty-day all-cause mortality following MRSA, MSSA and Gram-negative bacteraemia and *C. difficile* infections

Figure 3. Thirty-day all-cause mortality rate of *E. coli* bacteraemia by onset of bacteraemia, 2012/13 to 2018/19

![Figure 3](image)

Figure 4. Thirty-day all-cause case fatality rate of *E. coli* bacteraemia by onset of bacteraemia, 2012/13 to 2018/19

![Figure 4](image)

Variation by NHS commissioning region

Like the national trends, regional MR increased over time while regional CFR declined over the same period.

The highest and lowest MRs were observed in the North of England and London respectively. In 2018/19, these were highest at 13.0 deaths per 100,000 population in the North of England versus the lowest of 8.6 in London (Table S3 and Figure 5). These gave CFRs of 14.6% North of England and 13.0% in London respectively (Table S3 and Figure 6).
Regression analysis controlled for age and sex showed strong evidence\(^3\) that the differences in regional mortality rates were not due to random variation (Appendix 3). However, there was little statistical evidence of non-random variation in regional odds of deaths, except in the South West of England compared to North of England (OR: 0.76, \(p< 0.01\)), Midlands and East (OR: 0.80, \(p< 0.01\)) and London (OR: 0.84, \(p= 0.01\)) (Appendix 4).

**Figure 5. Thirty-day all-cause mortality rate of *E. coli* bacteraemia by NHS commissioning region, 2012/13 to 2018/19**

Variation by age and sex

MR and CFR increased with age and was greater in male patients compared to female patients. However, both were greater in patients <1-year-old compared to those between 1-44 years-old (Table S4, Figure 7 and Figure 8).

Among male patients, the highest MRs were in the ≥85 years-old (189.7 deaths per 100,000 population) and 75-84 years-old (68.7) age groups, which equated to CFRs 20.9% and 16.2% the cases respectively.

In female patients, MR were; 123.2 (≥85 years-old) and 43.0 (75-84 years-old). These equated to CFR of 20.2% and 13.2% of all cases in those respective age groups.

---

3 Statistical significance taken as \(p< 0.05\).
Thirty-day all-cause mortality following MRSA, MSSA and Gram-negative bacteraemia and *C. difficile* infections

Figure 6. Thirty-day all-cause case fatality rate of *E. coli* bacteraemia by NHS commissioning region, 2012/13 to 2018/19

The MR in male patients <1-years-old was 10.7 deaths per 100,000 population (10.4% of cases) compared to 4.4 (6.4% of cases) in female patients.

Figure 7. Thirty-day all-cause mortality rate of *E. coli* bacteraemia by age and sex, 2012/13 and 2018/19
Thirty-day mortality following MRSA, MSSA and Gram-negative bacteraemia and *C. difficile* infections

**Figure 8. Thirty-day all-cause case fatality rate of *E. coli* bacteraemia by age and sex, 2012/13 and 2018/19**

![Graph showing the case fatality rate of *E. coli* bacteraemia by age and sex for 2012/13 and 2018/19.](image)

*Klebsiella* spp. bacteraemia

In 2018/19, 10,638 *Klebsiella* spp. bacteraemia cases were reported in England. Information on mortality was available for ~97% (n = 10,307) of these cases (Table S5). There were 1,916 deaths within 30 days of a *Klebsiella* spp. bacteraemia which was a MR of 3.4 deaths per 100,000 population. The CFR was 18.6% of cases.

The CFR decreased between 2017/18 and 2018/19. The lack of longer term data makes it difficult to be certain whether this is part of a long-term reduction or variation around an average rate. These data will be monitored with interest in future reports.

**Variation by onset of bacteraemia**

In 2018/19, the MR of hospital-onset cases was 2.1 deaths per 100,000 bed-days (n= 713 deaths) similar to the previous year with a rate of 2.0 (n= 685 deaths) (2017/18, Table S6). Over the same period, the MR in community-onset cases was 2.2 (n= 1,203 deaths) and 2.2 (n= 1,206 deaths) deaths per 100,000 population respectively.

Between 2017/18 and 2018/19, there were small reductions in the CFR of both community-onset cases and hospital-onset cases. In this period, the CFR of hospital-onset cases stayed roughly the same from 24.5% to 23.2%, while for community-onset cases it declined from 18.4% to 16.6% of cases (Table S6). Again, without longer-term
data it is difficult to know whether these reductions are part of a longer-term trend or whether they are likely to continue.

Variation by NHS commissioning region
MRs for *Klebsiella* spp. were greatest in the North of England for both years (Figure 9).

Between 2017/18 and 2018/19, the MR in the North of England rose from 3.7 deaths per 100,000 population to 4.2.

In contrast to the MRs, the CFRs for the regions were more evenly distributed (Figure 10).

**Figure 9. Thirty-day all-cause case mortality rate of *Klebsiella* spp. bacteraemia by NHS commissioning region, 2017/18 to 2018/19**

*Variation by age and sex*
In 2018/19, MR and CFR increased with age however, MR was generally greater in male patients while CFR was generally greater in female patients. (Table S8, Figure 11 and Figure 12). The CFR of patients <1-year-old were higher than those between 1-44 years-old. A similarly trend is observed in the MRs.

Among male patients, the highest MRs were in the ≥85 years-old (61.3 deaths per 100,000 population) and 75-84 years-old (23.5) age groups, which equated to CFRs of 25.0% and 19.2% respectively.

In female patients of the same age groups the MRs were; 22.6 (≥85 years-old) and 11.7 (75-84 years-old). These were CFRs of 28.2% and 23.5% of all cases in those respective age groups.
Thirty-day all-cause mortality following MRSA, MSSA and Gram-negative bacteraemia and *C. difficile* infections

Figure 10. Thirty-day all-cause case fatality rate of *Klebsiella* spp. bacteraemia by NHS commissioning region, 2017/18 to 2018/19

The mortality rates in male patients <1-year-old was 2.1 deaths per 100,000 population (8.4% of cases) compared to 2.5 (11.0% of cases) in female patients.

Figure 11. Thirty-day all-cause mortality rate of *Klebsiella* spp. bacteraemia by age and sex, 2017/18 and 2018/19
Thirty-day all-cause all-cause mortality following MRSA, MSSA and Gram-negative bacteraemia and *C. difficile* infections

**Figure 12. Thirty-day all-cause case fatality rate of *Klebsiella* spp. bacteraemia by age and sex, 2017/18 and 2018/19**

*Pseudomonas aeruginosa* bacteraemia

In 2018/19, 4,185 *P. aeruginosa* bacteraemia cases were reported in England. Information on mortality was available for ~97% (n= 4,050) of these cases (Table S9). There were 974 deaths within 30 days of a *P. aeruginosa* bacteraemia, giving a MR of 1.8 deaths per 100,000 population. The CFR was 24.0% of cases.

**Variation by onset of bacteraemia**

In 2018/19, the MR of hospital-onset cases was 1.1 deaths per 100,000 bed-days (n= 395 deaths) compared to 1.4 (n= 470 deaths) in the previous financial year (2017/18) (Table S10). Over the same period, the MR in community-onset cases was 1.0 (n= 579 deaths) and 1.2 (n= 649 deaths) deaths per 100,000 population respectively.

The CFR of hospital-onset cases was 29.9% of cases in 2017/18% and 27.1% in 2018/19. For community-onset cases, this was 25.1% in 2017/18% and 22.3% in 2018/19 (Table S10).

**Variation by NHS commissioning region**

MRs decreased in all regions between 2017/18 and 2018/19. In 2018/19, there was little variation in regional MRs, with rates ranging from 1.5 deaths per 100,000 population in the South West of England to 1.9 in London (Table S11 and Figure 13).
Conversely, in the same financial year, the lowest case fatality rate was observed in London (20.5%) while the highest was in the South West (26.2%) (Table S1 and Figure 14).

**Figure 13. Thirty-day all-cause mortality rate of *P. aeruginosa* bacteraemia by NHS commissioning region, 2017/18 to 2018/19**

![Diagram showing mortality rate by region and year](image)

*deaths within 30 days of sample collection*

**Variation by age and sex**

In 2018/19, MR and CFR increased with age however, CFR was greater in female patients compared to male patients while MR was greater in male patients compared to female patients. The MR and CFR of male and female patients <1-year-old were higher than those between 1-64 years-old (Table S12, Figure 15 and Figure 16).

In 2018/19, among male patients, the highest mortality rates were in the ≥85 years-old (21.5 deaths per 100,000 population) and 75-84 years-old (10.2) age groups, which were CFRs of 22.1% and 20.4% cases respectively.

In female patients of the same age groups, the MRs were; 12.1 (≥85 years-old) and 6.0 (75-84 years-old). These equated to CFRs of 41.7% and 32.8% of all cases in those respective age groups.

The MR in male patients <1-years-old was 3.3 deaths per 100,000 population (42.3% of cases) compared to 2.2 (36.8% of cases) in female patients.
Thirty-day all-cause mortality following MRSA, MSSA and Gram-negative bacteraemia and \textit{C. difficile} infections

Figure 14. Thirty-day all-cause case fatality rate of \textit{P. aeruginosa} bacteraemia by NHS commissioning region, 2017/18 to 2018/19

Figure 15. Thirty-day all-cause mortality rate of \textit{P. aeruginosa} bacteraemia by age and sex, 2017/18 and 2018/19
Thirty-day all-cause mortality following MRSA, MSSA and Gram-negative bacteraemia and *C. difficile* infections

**Figure 16. Thirty-day all-cause case fatality rate of *P. aeruginosa* bacteraemia by age and sex, 2017/18 and 2018/19**

![Graph showing case fatality rate by age and sex for 2017/18 and 2018/19.](image)

**Staphylococcus aureus** bacteraemia

In 2018/19, 805 MRSA bacteraemia cases were reported in England. Information on mortality was available for ~97% (*n* = 779) of these cases (Table S13). There were 191 deaths within 30 days of an MRSA bacteraemia which was a MR of 0.3 deaths per 100,000 population. The CFR was 24.5% of cases.

There was a trend of declining MR beginning from 2.6 deaths per 100,000 population (*n* = 1,354) in 2007/08 to 0.3 in 2018/19. A similar trend is observed for the CFR which was 38.9% in 2007/08.

**Variation by onset of bacteraemia**

Between 2007/08 and 2018/19, the MR and CFR declined in both hospital-onset and community-onset cases.

In 2018/19, the MR in hospital-onset cases was 0.2 deaths per 100,000 bed-days (*n* = 66 deaths) which was the same as that in the previous financial year (2017/18, Table S14 and Figure 17). Similarly, the MR in community-onset cases did not change between 2017/18 and 2018/19 - 0.2 deaths per 100,000 population in both.
Thirty-day all-cause mortality following MRSA, MSSA and Gram-negative bacteraemia and *C. difficile* infections

Between 2007/08 and 2018/19, the CFR of hospital-onset cases declined from 42.4% to 25.3% respectively, while for community-onset cases it declined from 33.1% to 24.1% of cases (Table S14 and Figure 18) over the same period.

**Figure 17. Thirty-day all-cause mortality rate of MRSA bacteraemia by onset of bacteraemia, 2007/08 to 2018/19**

**Figure 18. Thirty-day all-cause case fatality rate of MRSA bacteraemia by onset of bacteraemia, 2007/08 to 2018/19**

Variation by NHS commissioning region

Like the national trend, both regional MRs and CFRs declined between 2007/08 and 2018/19.
In 2018/19, regional MRs ranged from 0.3 deaths per 100,000 population in South East, South West and Midlands & East of England to 0.5 in London (Table S15 and Figure 19). Regression analysis controlling for age and sex, showed no evidence\(^4\) of non-random variation in the differences between regional MR except in London compared to the other regions (Appendix 3).

Regional CFRs also varied with the highest CFR observed in London (28.9%, Table S15 and Figure 20). However, there was little statistical evidence that the difference in regional odds of death was not due to random variation (Appendix 4). The possible exception to this was in South West of England compared to London (OR: 0.54, \(p= 0.04\); Appendix 4) for which there was evidence of non-random variation.

**Figure 19. Thirty-day all-cause mortality rate of MRSA bacteraemia by NHS commissioning region, 2007/08 to 2018/19**

**Variation by age and sex**
In 2018/19, MR and CFR increased with age and was greater in male patients compared to female patients. (Table S16, Figure 21 and Figure 22).

Among male patients, the highest MR were in the ≥85 years-old (10.3 deaths per 100,000 population) and 75-84 years-old (2.0) age groups, which were CFRs of 46.7% and 26.2% respectively.

In female patients, the mortality rates were also higher in older age groups; 2.8 (≥85 years-old) and 0.8 (75-84 years-old). These equated to CFRs of 38.7% and 24.6% of all cases in those respective age groups.

\(^4\) Statistical significance taken as \(p < 0.05\).
In most financial years, the MR and CFR in patients <1-year-old were higher than those between 1-44 years-old. However, in 2018/19, there were no deaths within 30-days following MRSA bacteraemia from patients in this age group.

Figure 21. Thirty-day all-cause mortality rate of MRSA bacteraemia by age and sex, 2007/08 and 2018/19
Figure 22. Thirty-day all-cause case fatality rate of MRSA bacteraemia by age and sex; 2007/08 to 2018/19

MSSA bacteraemia

In 2018/19, 12,073 MSSA bacteraemia cases were reported in England. Information on mortality was available for ~97% (n= 11,689) of these cases (Table S17). There were 2,220 deaths within 30 days of an MSSA bacteraemia which gave an MR of 4.0 deaths per 100,000 population. The CFR was 19.0% of cases.

Overall, there was an increasing trend in mortality rates from 3.3 deaths per 100,000 population in 2011/12 to 4.0 in 2018/19. However, the MR in 2018/19 was less than that from previous financial year; 4.2 in 2018/19.

Variation by onset of bacteraemia

The MR in hospital-onset cases was relatively stable (1.9-2.0 deaths per 100,000 bed-days) between 2012/2013 and 2017/18 but increased to 2.2 deaths per 100,000 bed-days in 2018/19 (Table S18 and Figure 23). For community-onset cases, the MR increased in each financial year from 2.0 deaths per 100,000 population in 2011/12 to 2.9 in 2017/18. This fell to 2.7 deaths per 100,000 population in 2018/19.

Between 2011/12 and 2018/19, the CFR of hospital-onset cases declined from 26.7% to 23.2%, while for community-onset cases it declined from 18.9% to 17.4% of cases (Table S18 and Figure 23).
Thirty-day all-cause mortality following MRSA, MSSA and Gram-negative bacteraemia and *C. difficile* infections

**Figure 23.** Thirty-day all-cause mortality rate of MSSA bacteraemia by onset of bacteraemia, 2011/12 to 2018/19

**Figure 24.** Thirty-day all-cause case fatality rate of MSSA bacteraemia by onset of bacteraemia, 2011/12 to 2018/19

**Variation by NHS commissioning region**

In 2018/19, regional MR ranged from 2.6 deaths per 100,000 population in London to 4.9 in North of England (Table S19 and Figure 25). Regression analysis controlled for age and sex, showed strong evidence\(^5\) to suggest that this variation in MR was not merely due to random variation (Appendix 3).

In 2018/19, the lowest CFR was also observed in London (14.8%) (Table S19 and Figure 26). There was statistical evidence to suggest that some of the difference in regional odds of death was not due to random variation (Appendix 4).

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\(^5\) Statistical significance taken as \(p < 0.05\).
Variation by age and sex

In 2018/19, MR and CFR increased with age however, MR was greater in male patients while CFR was greater in female patients. (Table S20, Figure 27 and Figure 28).

Among male patients, the highest MRs were in those ≥85 years-old (73.0 deaths per 100,000 population) and 75-84 years-old (26.0) age groups, which were CFRs of 40.1% and 28.1% respectively.

In female patients, the MRs were also higher in older age groups; 35.6 (≥85 years-old) and 13.4 (75-84 years-old). These equated to CFR of 47.2% and 30.3% of all cases in those respective age groups.

Figure 25. Thirty-day all-cause mortality rate of MSSA bacteraemia by NHS commissioning region, 2011/12 to 2018/19
Thirty-day all-cause mortality following MRSA, MSSA and Gram-negative bacteraemia and *C. difficile* infections

The MR in male patients <1-years-old was 3.9 deaths per 100,000 population (7.1% of cases) compared to 3.1 (7.8% of cases) in female patients.

**Figure 26. Thirty-day all-cause case fatality rate of MSSA bacteraemia by NHS commissioning region, 2011/12 to 2018/19**

![Graph showing the percentage of cases who died within 30 days of sample collection](image)

**Figure 27. Thirty-day all-cause mortality rate of MSSA bacteraemia by age and sex, 2011/12 and 2018/19**

![Graph showing deaths per 100,000 population by age and sex](image)
Thirty-day all-cause mortality following MRSA, MSSA and Gram-negative bacteraemia and *C. difficile* infections

*Clostridioides difficile* infection

In 2018/19, 12,275 CDI cases were reported in England. Information on mortality was available for ~98% (n= 11,986) of these cases (Table S21). There were 1,625 deaths within 30 days of a CDI case which was a MR of 2.9 deaths per 100,000 population. The CFR was 13.6% of cases.

There was a trend of declining MR beginning from 27.1 deaths per 100,000 population (n= 13,973) in 2007/08 to 2.9 in 2018/19. A similar trend was observed for the CFR from 26.3% in 2007/08 to 13.6% in 2018/19.

**Variation by onset of infection**

Between 2007/08 and 2018/19, MR and CFR declined in both hospital-onset and community-onset cases.

In 2018/19, the MR of hospital-onset cases was 2.5 deaths per 100,000 bed-days (n= 876 deaths) which was a decline from the previous financial year (3.0, n= 1,048 deaths; 2017/18) (Table S22 and Figure 29). Similarly, in community-onset cases, the MR fell from 26.1 deaths per 100,000 population in 2007/08 to 2.5 in 2018/19.
Between 2007/08 and 2018/19, the CFR of hospital-onset cases declined from 30.2% to 21.4%, while for community-onset cases it declined from 20.2% to 9.5% of cases (Table S22 and Figure 30).

**Figure 29. Thirty-day all-cause mortality rate of CDI by onset of infection, 2007/08 to 2018/19**

![Graph showing the mortality rate of CDI by onset of infection from 2007/08 to 2018/19](image)

*deaths within 30 days of sample collection

**Figure 30. Thirty-day all-cause case fatality rate of CDI by onset of infection, 2007/08 to 2018/19**

![Graph showing the case fatality rate of CDI by onset of infection from 2007/08 to 2018/19](image)

*deaths within 30 days of sample collection

**Variation by prior healthcare exposure**

The categorisation of CDI cases based on prior healthcare exposure began in 2017/18. In 2018/19, the MRs were; 2.9 deaths per 100,000 bed-days for Hospital-onset: healthcare-associated cases and 0.7 for Community-onset: healthcare-associated cases. In the same financial year, it was; 0.4 deaths per 100,000 population for
Community-onset: community-associated cases and 0.2 for Community-onset: indeterminate association cases (Table S23; Figure 31).

The CFRs were; 20.7% for Hospital-onset: healthcare-associated cases, 10.9% for Community-onset: Healthcare-associated cases, 7.3% for Community-onset: community-associated cases, 9.8% for Community-onset: indeterminate association cases and 6.6% for Community-onset: unknown healthcare association cases (Table S23; Figure 32).

**Variation by region**

In 2018/19, regional MRs ranged from 1.9 deaths per 100,000 population in London to 3.6 in North of England (Table S24 and Figure 33). In regression analysis controlled for age and sex, there was evidence\(^6\) to suggest that the differences in regional MRs were not merely due to random variation (Appendix 3).

**Figure 31. Thirty-day all-cause case fatality rate of *C. difficile* infections by prior healthcare exposure, 2007/08 to 2018/19**

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\(^6\) Statistical significance taken as p< 0.05.
Regional CFR also varied with the highest CFR observed in Midlands and East of England (14.9%) (Table S24 and Figure 34). However, there was little statistical evidence to suggest that the regional differences in odds of death were not due to random variation. The exception to this was in the difference between London and Midlands and East (OR: 0.82, p= 0.05; Appendix 4) for which there was evidence of non-random variation.

Figure 33. Thirty-day all-cause mortality rate of CDI by NHS commissioning region, 2007/08 to 2018/19
Thirty-day all-cause mortality following MRSA, MSSA and Gram-negative bacteraemia and *C. difficile* infections

**Variation by age and sex**

The CDI surveillance only covers patients ≥2 years-old. The CFR following *C. difficile* infections increased with age. MR and CFR increased with age and was greater in male patients compared to female patients. (Table S25, Figure 35 and Figure 36). In addition, both MRs and CFR have decreased over time.

Among male patients, the highest MRs were in those ≥85 years-old (52.5 deaths per 100,000 population) and 75-84 years-old (17.3) age groups, which were CFRs of 24.7% and 17.9% respectively. In female patients, the MRs were also higher in older age groups; 45.0 (≥85 years-old) and 15.4 (75-84 years-old). These equated to CFRs of 20.8% and 13.9% of all cases in those respective age groups.
Thirty-day all-cause mortality following MRSA, MSSA and Gram-negative bacteraemia and *C. difficile* infections

**Figure 35. Thirty-day all-cause mortality rate of CDI by age and sex, 2007/08 and 2018/19**

*deaths within 30 days of sample collection

**Figure 36. Thirty-day all-cause case fatality rate of CDI by age and sex, 2007/08 and 2018/19**

*deaths within 30 days of sample collection*
Discussion

Over the surveillance period, the CFR of each infection covered by this report has declined (Figure 2). This is contrasts with the increasing number of deaths following *E. coli* and MSSA bacteraemia (Figure 1).

The largest reductions in CFR were in MRSA bacteraemia (difference of 14.3%) and CDI (difference of 12.7%) which are indicative of the change in their epidemiology over the years. Between 2007/08 and 2018/19, the incidence of both these infections declined, and both have shown a shift from predominantly hospital-onset infections to predominantly community-onset. Since mortality and morbidity are often higher in hospital-onset than the community-onset cases, reductions in the former would be accompanied by reductions in the overall CFR of the infection as seen in MRSA bacteraemia cases (Figure 22, Figure 34; Table S14, Table S22).

The large decline in CFR coinciding with reductions in CDI incidence may be associated with reductions in infections caused by *C. difficile* ribotype 027, which was historically the predominant ribotype in England between 2007 and 2012, and has been associated with higher mortality compared to other ribotypes [7].

A substantial proportion of community-onset CDI cases will have had prior healthcare interactions, from which one would expect a higher CFR. This was reflected in the difference between the CFR of Community-onset: healthcare-associated cases (12.2%) and those that were Community-onset: community-associated (9.9%) in 2018/19 (Table S23; Figure 36).

Regarding 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 [8]. 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, it is not significantly different from other years.

In general, for all pathogens, CFRs increased with age except in patients <1-years-old; where CFRs were usually higher than patients aged 1-14 years old, and in some cases, those aged 15-44 years-old. Of note, is the relatively high CFR of *P. aeruginosa* bacteraemia in <1-year-old patients; 42.3% (n= 11/26, MR: 3.3) and 36.8% (n= 7/19, MR: 2.2) for male and female patients. It is not possible to assess fatality rates in patients less than 2 years old with CDI as infections in this age group are not reported to PHE (see Appendix 1)
CFRs following CDI and *E. coli* bacteraemia were generally higher in male patients compared to female patients, while those following *Klebsiella* spp., MRSA, MSSA and *P. aeruginosa* bacteraemia were generally higher in female patients compared to male patients. Among MSSA and *P. aeruginosa* bacteraemia cases the CFR was consistently higher among females.

There were considerable regional differences in the mortality and case fatality rates of each infection covered in this report. However, regression analysis adjusted for regional age and sex distributions, showed that; in most instances, there was no evidence that such differences could not have occurred by random variation. This suggests that observed regional variations in risk of deaths following each type of infection is primarily due to the age and sex of the populations in those regions.

In 2018/19, the largest CFR of these infections were in MRSA and *P. aeruginosa* bacteraemia. The CFR of *E. coli* bacteraemia was relatively small compared to those for MRSA and *P. aeruginosa* bacteraemia. However, its higher incidence of infection, and deaths following infection (MR: 10.4 deaths per 100,000 population) compared to MRSA (MR: 0.3) and *P. aeruginosa* bacteraemia (MR: 1.8) highlights the public health burden of this infection. In 2018/19, there were 5,798 deaths within 30 days of *E. coli* bacteraemia, over 4 times the number of deaths following MRSA bacteraemia at the start of mandatory surveillance (2007/08; 1,354) when MRSA bacteraemia was at its highest rate of incidence. Despite the CFR for *E. coli* bacteraemia being low, the burden is high due to the high incidence of infection and thus large gains could be realised if the number of infections can be reduced.

**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 most 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. However, any effect this is likely to have on the analyses presented is likely to be low, since the linkage had a high degree of completeness — 96% of all cases. 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
Thirty-day all-cause mortality following MRSA, MSSA and Gram-negative bacteraemia and *C. difficile* infections

setting. Finally, while analysis of 30-day all-cause fatality estimates 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: Figures included in this report

Figure 1: Number of deaths within 30-days of case detection by infection
Figure 2: Thirty-day all-cause case fatality rate by infection
Figure 3: Thirty-day all-cause mortality rate of *E. coli* bacteraemia by onset of bacteraemia
Figure 4: Thirty-day all-cause case fatality rate of *E. coli* bacteraemia by onset of bacteraemia
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Figure 10: Thirty-day all-cause case fatality rate of *Klebsiella* spp. bacteraemia by NHS commissioning region
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Figure 19: Thirty-day all-cause mortality rate of MRSA bacteraemia by NHS commissioning region
Figure 20: Thirty-day all-cause case fatality rate of MRSA bacteraemia by NHS commissioning region
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Thirty-day all-cause mortality following MRSA, MSSA and Gram-negative bacteraemia and *C. difficile* infections

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Figure 29: Thirty-day all-cause mortality rate of CDI by onset of infection
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Table S2: Thirty-day all-cause case fatality rate of *E. coli* bacteraemia by onset of bacteraemia
Table S3: Thirty-day all-cause case fatality rate of *E. coli* bacteraemia by NHS commissioning region
Table S4: Thirty-day all-cause case fatality rate of *E. coli* bacteraemia by age and sex
Table S5: Thirty-day all-cause case fatality rate of *Klebsiella* spp. bacteraemia
Table S6: Thirty-day all-cause case fatality rate of *Klebsiella* spp. bacteraemia by onset of bacteraemia
Table S7: Thirty-day all-cause case fatality rate of *Klebsiella* spp. bacteraemia by NHS commissioning region
Table S8: Thirty-day all-cause case fatality rate of *Klebsiella* spp. bacteraemia by age and sex
Table S9: Thirty-day all-cause case fatality rate of *P. aeruginosa* bacteraemia
Table S10: Thirty-day all-cause case fatality rate of *P. aeruginosa* bacteraemia by onset of bacteraemia
Table S11: Thirty-day all-cause case fatality rate of *P. aeruginosa* bacteraemia by NHS commissioning region
Table S12: Thirty-day all-cause case fatality rate of *P. aeruginosa* bacteraemia by age and sex
Table S13: Thirty-day all-cause case fatality rate of MRSA bacteraemia
Table S14: Thirty-day all-cause case fatality rate of MRSA bacteraemia by onset of bacteraemia
Table S15: Thirty-day all-cause case fatality rate of MRSA bacteraemia by NHS commissioning region
Table S16: Thirty-day all-cause case fatality rate of MRSA bacteraemia by age and sex
Table S17: Thirty-day all-cause case fatality rate of MSSA bacteraemia
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Table S19: Thirty-day all-cause case fatality rate of MSSA bacteraemia by NHS commissioning region
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Table S21: Thirty-day all-cause case fatality rate of *C. difficile* infections
Table S22: Thirty-day all-cause case fatality rate of *C. difficile* infections by onset of infection
Table S23: Thirty-day all-cause case fatality rate of *C. difficile* infections by prior healthcare exposure
### Thirty-day all-cause mortality following MRSA, MSSA and Gram-negative bacteraemia and *C. difficile* infections

#### Table S24: Thirty-day all-cause case fatality rate of *C. difficile* infections by NHS commissioning region

#### Table S25: Thirty-day all-cause case fatality rate of *C. difficile* infections by age and sex

### Appendix 3: Age-sex adjusted regional mortality rate ratios, 2018/19

#### *E. coli* bacteraemia

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#### *Klebsiella* spp. bacteraemia

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#### *P. aeruginosa* bacteraemia

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Thirty-day all-cause mortality following MRSA, MSSA and Gram-negative bacteraemia and *C. difficile* infections

### MSSA bacteraemia

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### CDI

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Thirty-day all-cause mortality following MRSA, MSSA and Gram-negative bacteraemia and *C. difficile* infections

Appendix 4: Age-sex adjusted regional odds ratios, 2018/19

**E. coli** bacteraemia

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**Klebsiella** spp. bacteraemia

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**P. aeruginosa** bacteraemia

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**MRSA** bacteraemia

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### MSSA bacteraemia

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### CDI

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Appendix 5: Methods

Data on MRSA, MSSA, *E. coli*, *Klebsiella* spp. and *P. aeruginosa* bacteraemia, and CDI were extracted on 17 April 2019 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 [9] with little evidence for disease [10]. 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.

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 2016/17 on 03 July 2017. In addition to records from the most recent financial year (2018/19), records from the 2 previous financial years (2016/17 and 2017/18) or records prior to this but have not been traced before (late reports) were traced on 7 July 2019. The retrace and/or addition of late reports may result in minor changes to previously published counts.

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 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, 675 (3.8%); MSSA bacteraemia, 1,861 (2.2%); *E. coli* bacteraemia, 6,303 (2.4%); *Klebsiella* spp. bacteraemia, 431 (2.1); *P. aeruginosa* bacteraemia, 170 (2.0%); CDI 6,448 (2.6%).

8 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, 0 (0%); MSSA bacteraemia, 10 (< 1%); *E. coli* bacteraemia, 13 (< 1%); CDI 1 (< 1%).
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 30-day all-cause deaths\(^9\). 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 closed 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.\(^{10}\) 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 deduplicated in 2 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 trace. 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. This is included in the accompanying datasheet.

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

Estimated total number of 30 day all cause deaths = (Deduplicated total reports)×(30 day all cause CFR)

---

\(^9\) There were 104 cases (< 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.

\(^{10}\) The following number of cases were excluded to ensure each patient had only one 30-day fatality: MRSA bacteraemia, 53 (< 1%); MSSA bacteraemia, 171 (< 1%); *E. coli* bacteraemia, 585 (< 1%); *Klebsiella* spp. bacteraemia, 55 (< 1%); *P. aeruginosa* bacteraemia, 24 (< 1%); CDI 366 (< 1%)
Thirty-day all-cause mortality following MRSA, MSSA and Gram-negative bacteraemia and \textit{C. difficile} infections

This provides an estimate of the number of deaths that might be observed in each 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 differences in CFR were calculated by financial year (of the bacteraemia or CDI); these were calculated for each organism as follows:

\[
\begin{align*}
\nu_{c} & = \text{CFR from the current financial year (2018/19), and;} \\
\nu_{f} & = \text{CFR from the first financial year of surveillance}
\end{align*}
\]

Percentage change = \((\nu_{f} - \nu_{c})\)

The CFR includes 95% confidence intervals calculated using a binomial distribution. \(Z\)-tests comparing 2 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. This is included in the accompanying datasheet.

Sample calculations for CFR (not including 95% CI), estimated total number of 30-day all-cause deaths, and percentage difference for MRSA in 2018/19 as shown below. 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\(_{\text{MRSA 2018/19}}\) = \(\frac{191 \text{ deaths}}{779 \text{ deduplicated traced reports}} \times 100 = 24.5\%\)

Est. total number of deaths\(_{\text{MRSA 2018/19}}\) = \((804 \text{ mortality deduplicated DCS reports}) \times (0.245) = 198\)

Percentage difference in CFR\(_{\text{MRSA 2007/08 to 2018/19}}\) = \(38.9 - 24.5 = 14.3\%\) difference
Thirty-day all-cause mortality following MRSA, MSSA and Gram-negative bacteraemia and *C. difficile* infections

Appendix 6: Summary of differences between Office for National Statistics and PHE fatality outputs

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

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<td>Deaths determined by</td>
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<td>Deaths within 30 days of positive specimen of MRSA, MSSA or <em>E. coli</em> bacteraemia or <em>C. difficile</em> infection determined using data matched with the NHS Spine.</td>
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<td>Denominator</td>
<td>All deaths in the given time period and population in the given time period (2 different denominators used)</td>
<td>All traced reports of MRSA, MSSA, <em>E. coli</em> bacteraemia or CDI in the given time period</td>
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Thirty-day all-cause mortality following MRSA, MSSA and Gram-negative bacteraemia and C. difficile infections

References


