UK Health Security Agency

Thirty-day all-cause mortality following MRSA, MSSA and Gram-negative bacteraemia and *C. difficile* infections, 2020 to 2021

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Contents

Executive summary

Here 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 *Clostridioides difficile* infections (CDI). Thirty-day all-cause mortality is a widely used outcome for assessing risk of death. However, it does mean that not all of the deaths reported here will 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 all reported cases. This provides a measure for comparing survivability of different infections. In contrast, the MR is the number of deaths divided by the population at risk. This reflects the incidence of all-cause deaths following these infections in the population.

In 2020/2021, the CFR increased from the previous year (2019/2020) for *E. coli* bacteraemia (14.3% to 16.0%), *Klebsiella* spp. bacteraemia (19.1% to 21.8%), *P. aeruginosa* bacteraemia (24.5% to 27.7%), MRSA bacteraemia (25.7% to 28.2%), MSSA bacteraemia (19.5% to 23.6%), and CDI (13.5% to 14.9%). These recent increases in CFR beginning in 2019 and 2020, go against the downward trends from the previous years. This period also coincides with the COVID-19 pandemic and the nature of the all-cause mortality indicator used means that we cannot distinguish between patients that died from the bacterial infection, COVID-19 or related health system changes.

The MR of 30-day all-cause deaths per 100,000 population for each infection in 2020/2021 compared with the previous year were (2019/2020): *E. coli* bacteraemia (MR=10.7, n=6,015 deaths to MR=10.2, n=5,750 deaths), *Klebsiella* spp. bacteraemia (MR=3.6, n=2,046 deaths to MR=4.2, n= 2,346 deaths), *P. aeruginosa* bacteraemia (MR=1.8, n=1,034 deaths to MR=2.1, n= 1,158 deaths) and MRSA bacteraemia (MR=0.4, n=201 deaths to MR=0.3, n= 190 deaths), MSSA bacteraemia (MR=4.1, n=2,313 deaths to MR=4.8, n= 2,686 deaths) and CDI (MR=3.1, n=1,741 deaths to MR=3.2, n= 1,825 deaths). These increases have been observed despite overall reductions in the number of *E. coli*, MSSA and CDI cases over the same period.

In 2020/2021, the CFR of both hospital-onset (HO) and community-onset (CO) cases were highest in *P. aeruginosa* bacteraemia cases (33.9% and 23.8% respectively) and MRSA bacteraemia (34.1% and 24.3% respectively). When comparing with the previous year, the highest increase in CFR can be found in MSSA from 19.5% to 23.6% and *P. aeruginosa* from 24.5% to 27.7%.

Between 2007/2008 and 2020/2021 there have been significant declines in the number of 30-day all-cause deaths for MRSA bacteraemia (1,354 to 190 deaths) and CDI (13,973 to 1,825 deaths) due to a decrease in incidence of these infections over the same period. In contrast, the number of deaths following MSSA bacteraemia (1,777 deaths in 2011/2012 to 2,686 in

2020/2021) and *E. coli* bacteraemia (5,163 deaths in 2012/2013 to 5,750 in 2020/2021) have increased. Furthermore Klebsiella spp. and P. aeruginosa which started surveillance in financial year 2017/2018 have also increased from 1,895 deaths to 2,346 deaths and decreased from 1,121 deaths to 1,158 deaths respectively.

Since the start of each infections' surveillance period, there were declining trends of CFRs of both HO and CO cases. However, the greatest reductions have been in MRSA (-8.3% and -8.8% in HO and CO cases respectively) and CDI (-6.8% and -9.7% in hospital-onset and community-onset cases respectively). The greater reduction in CFR of HO MRSA cases compared to CO cases could be due to the large reduction in the number of hospital-onset MRSA cases observed over time. Such cases have traditionally been associated with many co-morbidities resulting in poorer health outcomes. Therefore, the large reduction in HO MRSA cases would be accompanied by a considerable reduction in the total number of deaths following these infections. However, despite similarly large reductions in the number of HO CDI cases over time, the reduction in CFR of CO CDI cases was greater than that of HO CDI cases over the same period.

The overall trend in CFR of each infection was a declining one up to 2018/2019, which then appears to deviate up from that trend. In the 2 most recent financial years (2019/2020 and 2020/2021) the CFR increased from 14.3% to 16.0% ($p< 0.01$) for *E. coli,* 19.1% to 21.8% ($p = 0.03$) for *Klebsiella* spp., 24.5% to 27.7% ($p = 0.09$) for *P. aeruginosa,* 25.7% to 28.2% ($p = 0.59$) for MRSA, 19.5% to 23.6% ($p<0.01$) for MSSA and 13.5% to 14.9% ($p = 0.23$) for CDI. Therefore the COVID-19 pandemic which significantly affected health care provision and has resulted in the UK in a large number of SARS-CoV-2 infections during the 2 most recent financial years appears to be a contributory factor for this deviation in trend, as evident from the COVID-19 related CFR of all cases this year (2020/2021) being 127.9% greater than their non-COVID-19 related counterparts. The reduction in elective procedures during the pandemic may have contributed to the increase in CFRs as there was likely to have been a reduction in blood stream infections (BSI) and CDI cases in individuals at lower risk of death (for example, individuals healthy enough to undergo an elective procedure), whereas those individuals with more serious acute or chronic conditions will largely have been unaffected.

Effect of the COVID-19 pandemic on mortality

The SARS-CoV-2 pandemic (COVID-19) was declared on 11 March 2020. The number of COVID-19 cases peaked thrice and resulted in 2 national lockdowns to date. This unprecedented humanitarian crisis has affected broad public behaviour. It has also affected the healthcare systems, straining available resources.

This year's 30-day all-cause mortality report covers the first 2 peaks of the COVID-19 pandemic (first in November 2020 and second in January 2021). The years covering the COVID-19 pandemic (end of 2019/2020 and 2020/2021) have seen a break in the overall downward trends in CFR for all pathogens. Compared with the last non-COVID-19 related financial year in 2018/2019, the CFRs in 2020/2021 for all infections covered in these report increased: *E. coli* from 13.9% to 16.0%; *Klebsiella* spp. from 18.6% to 21.8%; *P. aeruginosa* from 24.1% to 27.7%; MRSA 24.6% to 28.2%; meticillin-susceptible *S. aureus* (MSSA) bacteraemia from 19.1% to 23.6%; and CDI from 13.6% to 14.9%.

Broken down by onset and comparing totalled case to mortality CFR for 2018/2019 and 2020/2021, an increase of 3.2% was observed in HO and increase of 2.4% in CO. The most notable increases are observed in the HO with an increase of 8.4% in MRSA, increase of 6.7% in *P. aeruginosa* and increase of 4.8% in MSSA between 2018/2019 and 2020/2021. Work is ongoing to investigate specific populations affected and develop hypotheses for reasons for these increases.

The rate of mortality between 2018/2019 and 2020/2021 increased in all but MRSA and *E. coli*; *E. coli*: from 10.4 to 10.2, *Klebsiella* species 3.4 to 4.2, *P. aeruginosa* 1.7 to 2.1, MRSA 0.3 to 0.3, MSSA bacteraemia 4.0 to 4.8 and CDI 2.9 to 3.2 per 100,000 population. Broken down by onset and comparing total rate shows an increase of 5.3 per 100,000 population for HO and an increase of 1.0 per 100,000 population. The most notable increases observed are in HO cases with an increase of 1.5 per 100,000 population in *Klebsiella* species and increase of 1.1 per 100,000 population in MSSA and an increase of 0.8 per 100,000 population in CDI.

When comparing totalled case to mortality CFR for 2018/2019 and 2020/2021, an increase of 3.2% was observed in HO and increase of 2.4% in CO. Over the same period the total rate had increased by 5.3 per 100,000 population for HO and 1.0 per 100,000 population for CO.

The trends in CFR were affected by the COVID-19 pandemic: for the most part CFRs increased. An analysis was conducted to quantify how much COVID-19 had influenced the CFR of pathogens covered by the mandatory surveillance. The analysis identified patients with cases of the infections covered in this report and laboratory-confirmed COVID-19 within 28 before or after the specimen or test date of the SARS-CoV-2 case (COVID-19 related). Within 2020/2021 we observed a total percentage difference of 23.4% (percentage difference of all pathogens

totalled: 10,759 non COVID-19 related deaths and 3,284 COVID-19 related deaths) and that an average of 26.5% (lowest - *E. coli* 19.5%, highest - MRSA 36.8%) of all deaths were in patients that had tested positive for COVID-19 in the 28 day window. For 30-day all-cause deaths among HO cases in the mandatory HCAI surveillance, the average COVID-19 related apportionment was 36.4% (lowest – CDI 25.3%, highest – MRSA 47.3%), while the average for CO cases was 19.1% (lowest - *Klebsiella* spp. 14.8%, highest – MRSA 26.8%).

The average difference between the CFR of all COVID-19 related cases and those unrelated was 21.3% higher in COVID-19 related, with the highest difference found in MSSA with 24.8% and lowest in CDI with a 17.3% higher CFR in COVID-19 related. When broken down by age group and sex as a percentage proportion within each group (non-apportioned) we observed generally the same age distribution and sex distribution. The notable exceptions are *Klebsiella* spp. presenting higher proportions in COVID-19 related deaths in the 45 to 64 and 65 to 74 age groups both in males, MRSA in age groups 75 to 84 in Females and *P. aeruginosa* for age groups 45 to 64 in males.

Results would suggest an increased likelihood of deaths in patients with these mandatory infections who also had COVID-19. However, no firm conclusions can be drawn as data analysed is all-cause mortality and therefore the differences are an association not necessarily indicative of a cause of death. When removing COVID-19 related deaths from each mandatory pathogen the mortality number is lower than the 2 previous years and when re-calculating CFR we observe a concurrent decrease in all but *E. coli* and MSSA from 2018/2019 to present.

Introduction

Public Health England (now the UK Health Security Agency (UKHSA)) has undertaken mandatory surveillance of the main 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. Also, a rising proportion of MSSA and Gram-negative bacteraemia are community-onset (1). Since the composition of the patient population from both settings can vary in each setting, this publication reports mortality outcomes by onset of infection, and by prior healthcare exposure for CDI. Due to the impact of HCAI on morbidity and mortality (2, 3, 4), monitoring trends in mortality is an important part of HCAI surveillance. This report presents an analysis of 30-day all-cause mortality among MRSA, MSSA, *E. coli*, *Klebsiella* spp. and *P. aeruginosa* bacteraemia, and CDI patients. A separate report presents an analysis of the incidence of all reported cases of these same infections.

Methods

Data in this report is presented by financial year based on specimen dates (that is, the 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 (bacteraemia) or faecal sample (CDI) was taken is not known, the date when the sample was received in the laboratory for processing is used as a proxy. The counts of infections reported here are based on data extracted from the HCAI data capture system (HCAI DCS) on 9 July 2021. Patients' mortality outcomes were traced on 21 July 2021. The extract covered MRSA bacteraemia and CDI cases between 1 April 2007 and 31 March 2021, MSSA bacteraemia cases between 1 April 2011 and March 2021, *E. coli* bacteraemia cases between 1 April 2012 and 31 March 2021, and *P. aeruginosa* and *Klebsiella* spp. bacteraemia cases between 1 April 2017 and 31 March 2021. The number of infections and deaths presented here may differ from those in earlier publications due to late reports or inclusion of new reports since previous publications.

This report uses the same base data as UKHSA (formerly Public Health England)'s 2020/2021 Annual HCAI Epidemiological Commentary (1). Unlike the annual report, in this publication counts of infections and deaths within 30 days of specimen collection have been deduplicated (separately per infection) to a patient level. This means that a patient positive for 3 different types infection within 30 days of their death is presented 3 times, once per infection). This ensures that a patient's mortality outcome is reflected for each infection. The most recent case in this 30-day window period is retained as the index, while earlier infections within the 30-day window 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 Appendices.

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 is not comparable to the data published here for several methodological reasons outlined in the appendices. 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 mortality calculated using all deaths occurring within 30 days of onset of MRSA bacteraemia or CDI. In addition, data is 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. All deaths (all-cause mortality) occurring within 30 days of an infection report adopted 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. There 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 percentage of people with infections who die within 30 days. This is the risk of death in the wider population. 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 (7). For HO cases, the population estimate used overnight admissions (8). However, for CO: healthcare-associated cases, overnight and day admissions (9) have been used.

Results

In 2020/2021, there was a total of 77,029 cases of *E. coli*, *Klebsiella* spp., *P. aeruginosa*, MRSA and MSSA bacteraemia, and CDI in England. This was a decrease from the previous year (2019/2020)'s total of 84,996. There were 13,955 deaths within 30 days of taking a specimen (blood culture for bacteraemia, faecal sample for CDI). This gave a MR of 24.8 deaths per 100,000 population (see Table S0 in the accompanying data sheet), and a CFR of 18.6% of all reported cases (Figure 2).

The number of deaths has increased from the previous year (2019/2020: 13,350 deaths) to the current year (2020/2021: 13,955 deaths), along with its MR of 24.8 deaths per 100,000 in 2020/2021 (increase of 1.1 deaths per 100,000 from the previous year) and CFR of 18.6% in 2020/2021 (increase of 2.4% of all reported cases from the previous year). The CFR increases were significant (p-value < 0.05) for *E. coli*, MSSA and *Klebsiella* spp. The increases observed in the MR, can be linked to a true increase in deaths and or decrease in bed-days observed through this period (coinciding in time with the SARS-CoV-2 pandemic). Figure 1 shows a relatively large increase in the number of deaths observed in MSSA and *Klebsiella* spp., despite both displaying a decrease in the total number of cases between the current and previous financial year. Noteworthy observations include MSSA, *Klebsiella* spp. and *P. aeruginosa* showing spikes in mortality relative to previous years showing a 16.1%, 14.7% and 12.0% increase in deaths respectively as compared with the previous year. Furthermore, the increases in CFR has occurred for the last 2 years for all infections.

Figure 1. Number of deaths within 30-days of case detection by infection 2007/2008 to 2020/2021

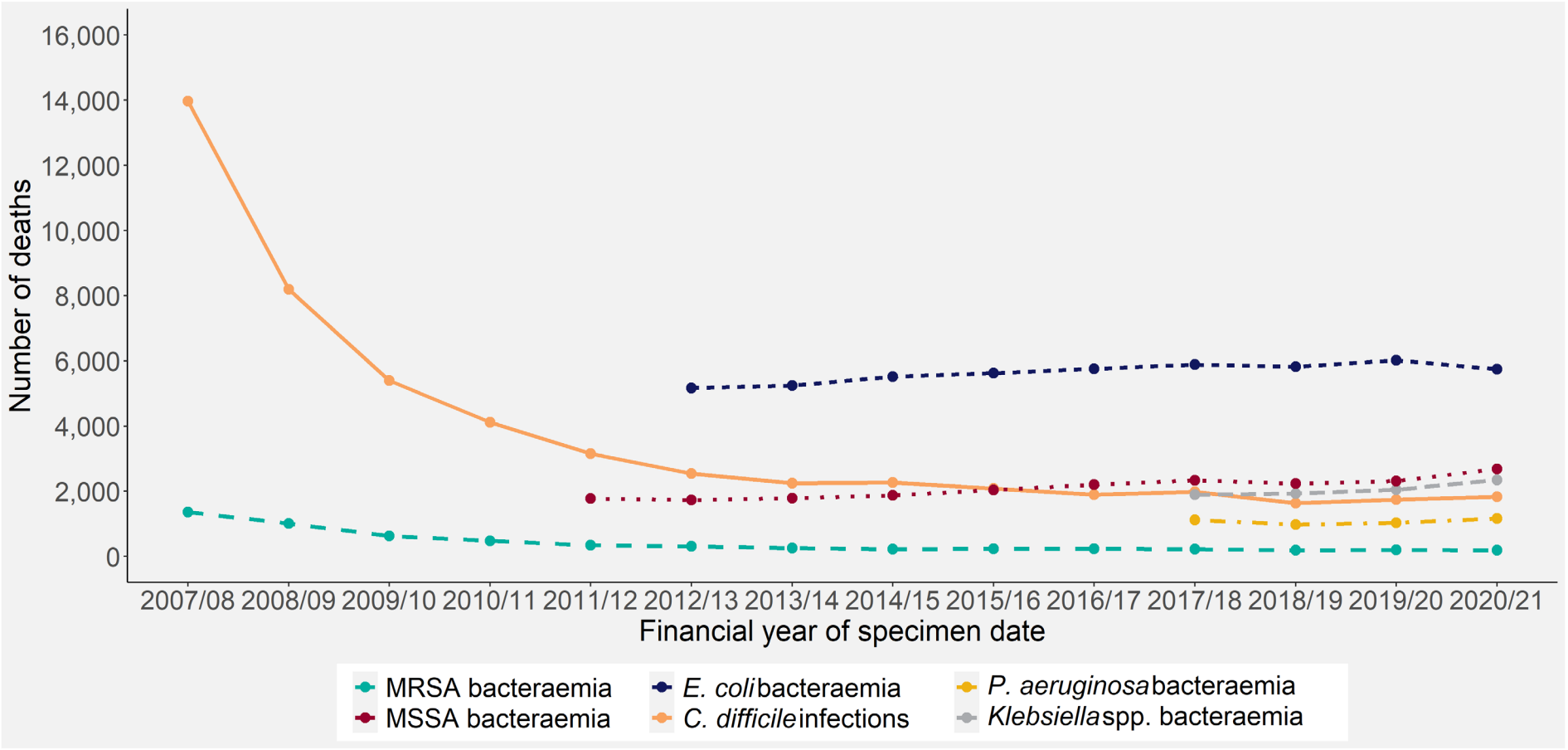
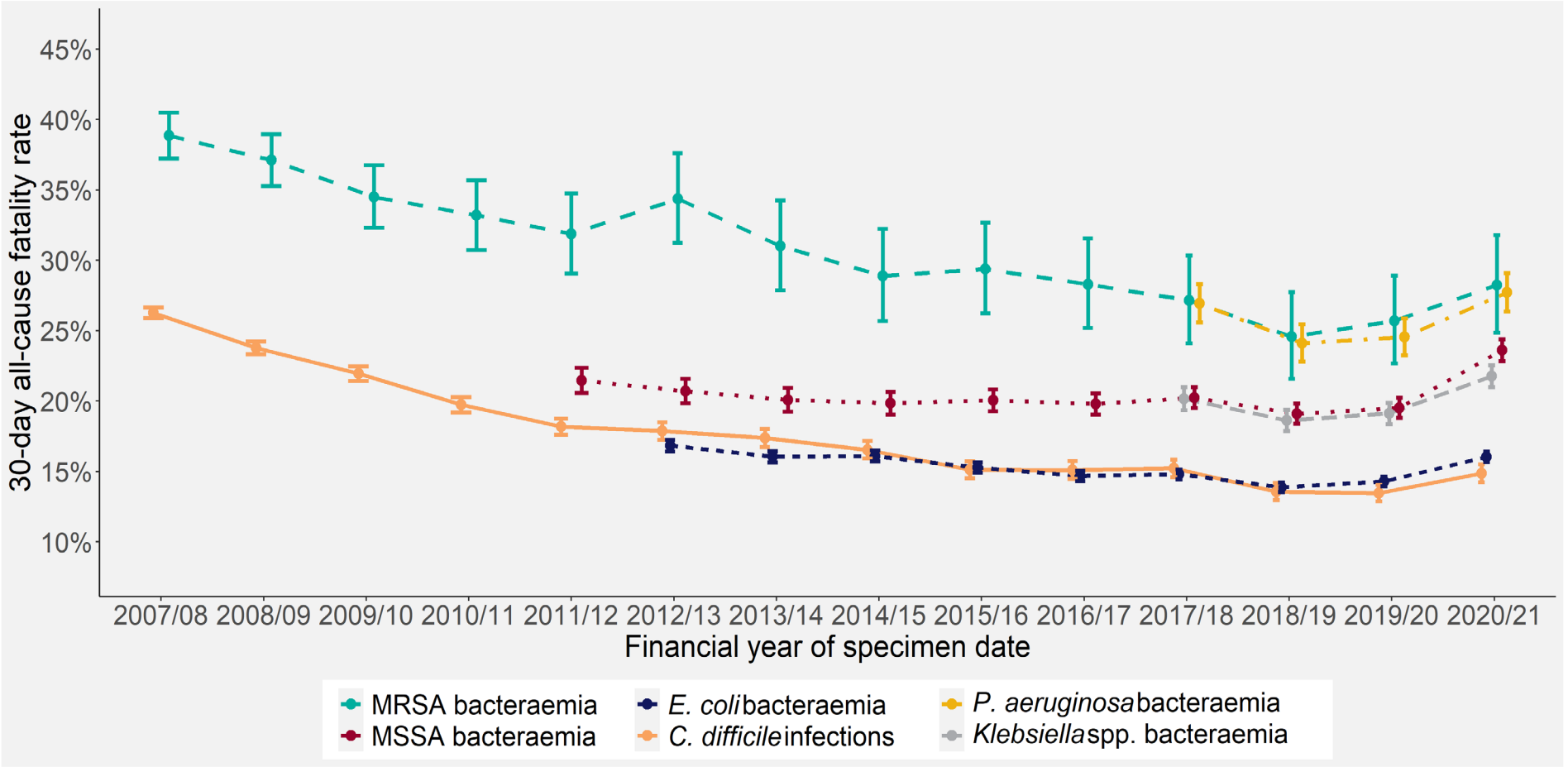


Figure 2. Thirty-day all-cause case fatality rate by infection 2007/2008 to 2020/2021



Gram-negative bacteraemia

Escherichia coli bacteraemia

In 2020/2021, 36,728 *E. coli* bacteraemia cases were reported in England. Information on mortality was available for 98% (n= 35,850) of these cases (see Table S1 in the accompanying data sheet). There were 5,750 deaths within 30 days of an *E. coli* bacteraemia which was a MR of 10.2 deaths per 100,000 population. The CFR was 16.0% of cases.

There was a declining trend in CFR starting from 16.8% in 2012/2013 to 13.9% in 2018/2019 ($p < 0.01$) after which, the CFR then increased each year to 16.0% in the current financial year (2020/2021). The overall trend of MR increased from 9.7 deaths per 100,000 population in 2012/2013 to 10.4 in 2018/2019 before declining to 10.2 in 2020/2021. The overall difference in CFR between 2012/2013 and 2020/2021 was not statistically significant ($p=0.26$).

During the COVID-19 pandemic there was an increase in CFR (14.3% to 16.0%) between the previous 2019/2020 and current 2020/2021 financial years. Additionally, there was a decrease (10.7 to 10.2 deaths per 100,000 population) in MR over the same period.

The different trend during 2019/2020 to 2020/2021 is likely a consequence of the COVID-19 pandemic. The decline in burden of 30-day all-cause death (MR) is due to reduced hospital activity at the height of the pandemic, while the increase CFR over this period was compounded by a considerable proportion of the 30-day all-cause deaths occurring in patients with a COVID-19 infection.

An analysis of patients with *E. coli* cases and a COVID-19 infection within 28 days before or after the infection found that found a CFR of 32.1% (n= 3,515/1,129) compared with 14.4% (n = 4,653 out of 32,413) among cases without a corresponding COVID-19 infection by the same patient within the 28 days before or after the *E. coli* case. This also means that 19.5% of 30-day all-cause deaths were in cases that had a corresponding COVID-19 infection as described above, suggesting that patients with COVID-19 infection were a considerable contribution to the increase in *E. coli* CFR for 2020/2021.

Variation by onset of bacteraemia

The CFR of HO cases declined from 23.6% in 2012/2013 to 22.8% in 2020/2021, and from 14.8% in 2012/2013 to 14.6% in 2020/2021 for CO cases (see Table S2 in the accompanying data sheet and Figure 4). The HO CFR this current year 2020/2021 (22.8%) has not been as high since 2013/2014. Though the CFR in HO and CO has decreased from 2012/2013 to 2020/2021 the decrease was only constant from 2012/2013 until 2019/2020, which coincides with the start of the COVID-19 pandemic.

During the financial years influenced by the COVID-19 pandemic (2019/2020 and 2020/2021) the CFR for HO increased from 21.9% in 2019/2020 to 22.8% in 2020/2021. The same was observed for the CO CFR increasing from 12.6% in 2019/2020 to 14.6% in 2020/2021.

In the same period, the MR of HO cases increased to 5.3 deaths per 100,000 bed-days (n= 1,456 deaths) compared to 4.8 deaths per 100,000 bed-days (n= 1,664 deaths) in the previous financial year (2019/2020) (see Table S2 in the accompanying data sheet and Figure 3). The same trend is observed with CO MR cases decreasing from 7.7 (n= 4,351 deaths, 2019/2020) to 7.6 deaths per 100,000 population (n= 4,294 deaths, 2020/2021) respectively. The increase in HO MR is compounded by an increase in all reported HO seen over the 2020/2021 winter period. There was a declining trend in HO CFR starting from 23.6% in 2012/2013 (pre-COVID-19) to 21.5% in 2018/2019 (pre-COVID-19), the CFR then incrementally increased to 22.8% in the current financial year 2020/2021 (during COVID-19).

The major trends observed pre-COVID-19 and during COVID-19 have shown a declining trend in HO CFR starting from 21.5% in 2018/2019 (pre-COVID-19) to 22.8% in the current financial year 2020/2021 (during COVID-19). The CFR for CO cases showed a similar trend declining from 12.6% in 2018/2019 (pre-COVID-19) to 14.6 in the current financial year 2020/2021 (during COVID-19).

The trend observed in HO MR has increased from 4.6 per 100,000 population in 2018/2019 (pre-COVID-19) to 5.3 per 100,000 population in 2020/2021 (during COVID-19). This pattern is identical for CO MR which has increased from 7.6 per 100,000 population in 2018/2019 (pre-COVID-19) to 7.6 in 2020/2021 (during COVID-19).

Figure 4 shows that the increase in CO *E. coli* CFR has been larger than its HO counterpart. This is worth highlighting due to poorer outcomes historically being expected from HO not CO. This is seemingly compounded by more COVID-19 related cases being observed in the CO (714 COVID-19 related deaths) opposed to HO (415 COVID-19 related deaths) over the 2020/2021 financial year.

Figure 3. Thirty-day all-cause mortality rate of *E. coli* bacteraemia by onset of bacteraemia 2012/2013 to 2020/2021

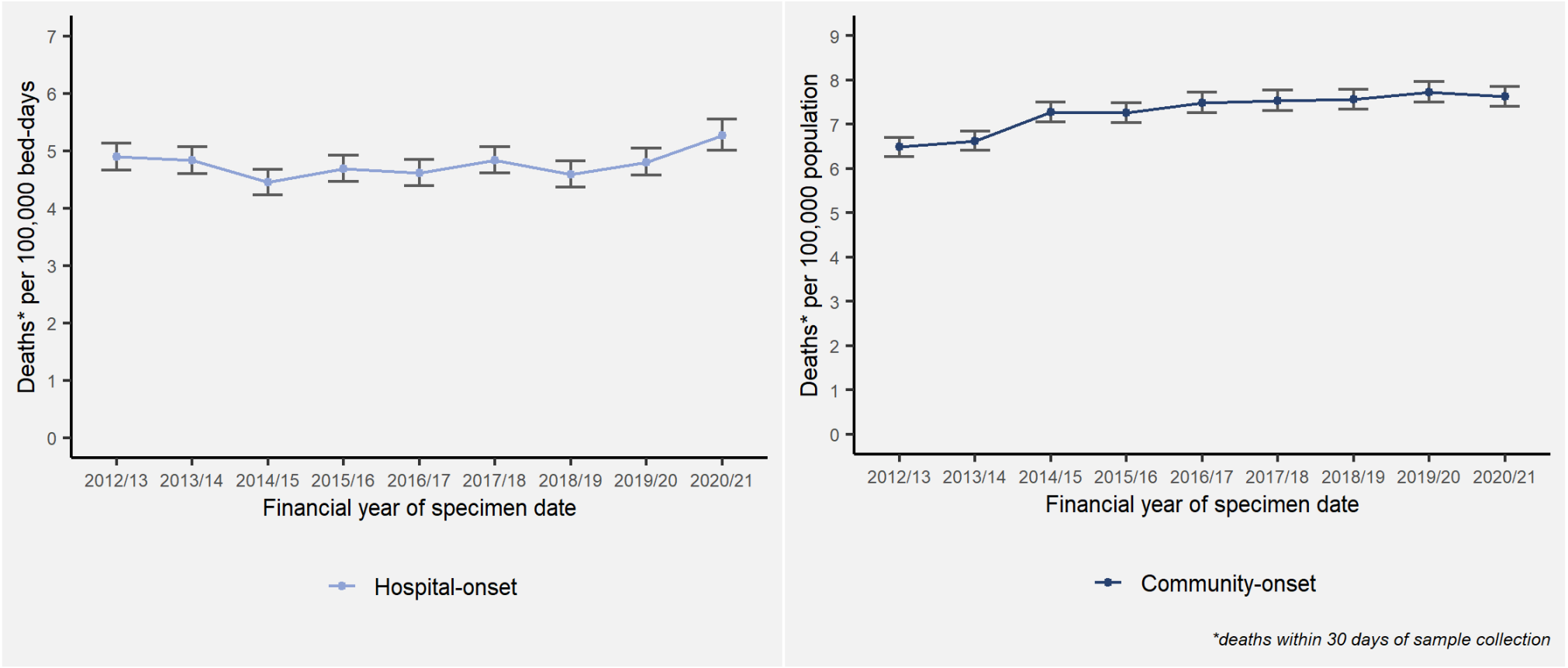
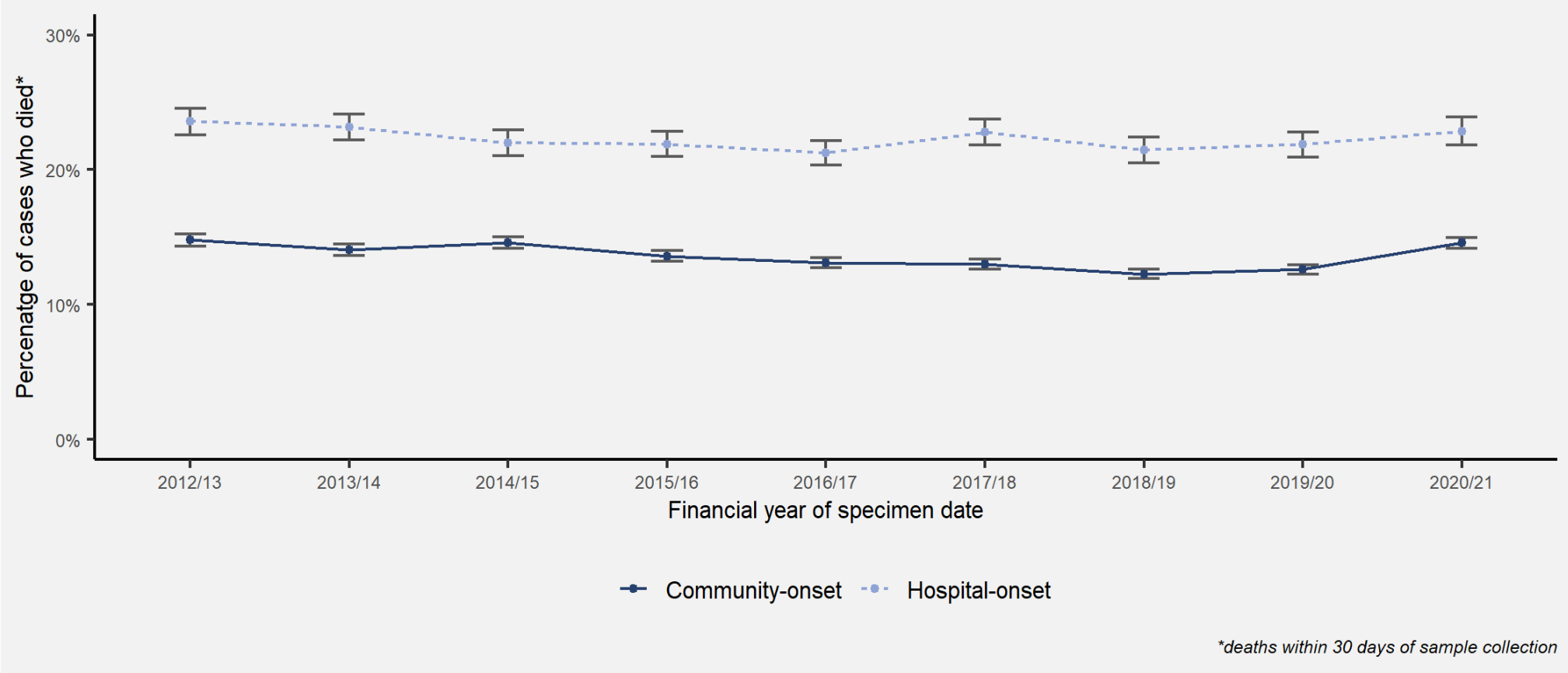


Figure 4. Thirty-day all-cause case fatality rate of *E. coli* bacteraemia by onset of bacteraemia 2012/2013 to 2020/2021



Variation by NHS commissioning region

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

In 2020/2021, regional MR ranged from 7.6 deaths per 100,000 population in London to 12.9 deaths per 100,000 population in the North East and Yorkshire (see Table S3 in the accompanying data sheet and Figure 5). Over the same period, CFRs ranged from 13.1% in the South West to 18.1% in the Midlands (see Table S3 in the accompanying data sheet and Figure 6).

The area with the highest differences in Rate Ratio (RR) are found between the North East and Yorkshire and the South West (RR: 1.68, $p < 0.01$) with the lowest being the inverse (see Appendix 3).

There was no strong evidence[1] to suggest significant differences in regional odds of deaths, except between the East and the South West (OR: 1.28, $p < 0.01$), London and the South West (OR: 1.26, $p < 0.01$) and the South West and the North East and Yorkshire (OR: 0.71, $p < 0.01$), the North West (OR: 0.73, $p < 0.01$) and the Midlands (OR: 0.66, $p < 0.01$) (see Appendix 4).

[1] Strong evidence described as a statistically significant ($p< 0.05$) odds ratio of ≥0.25.

Figure 5. Thirty-day all-cause mortality rate of *E. coli* bacteraemia by NHS commissioning region 2012/2013 to 2020/2021

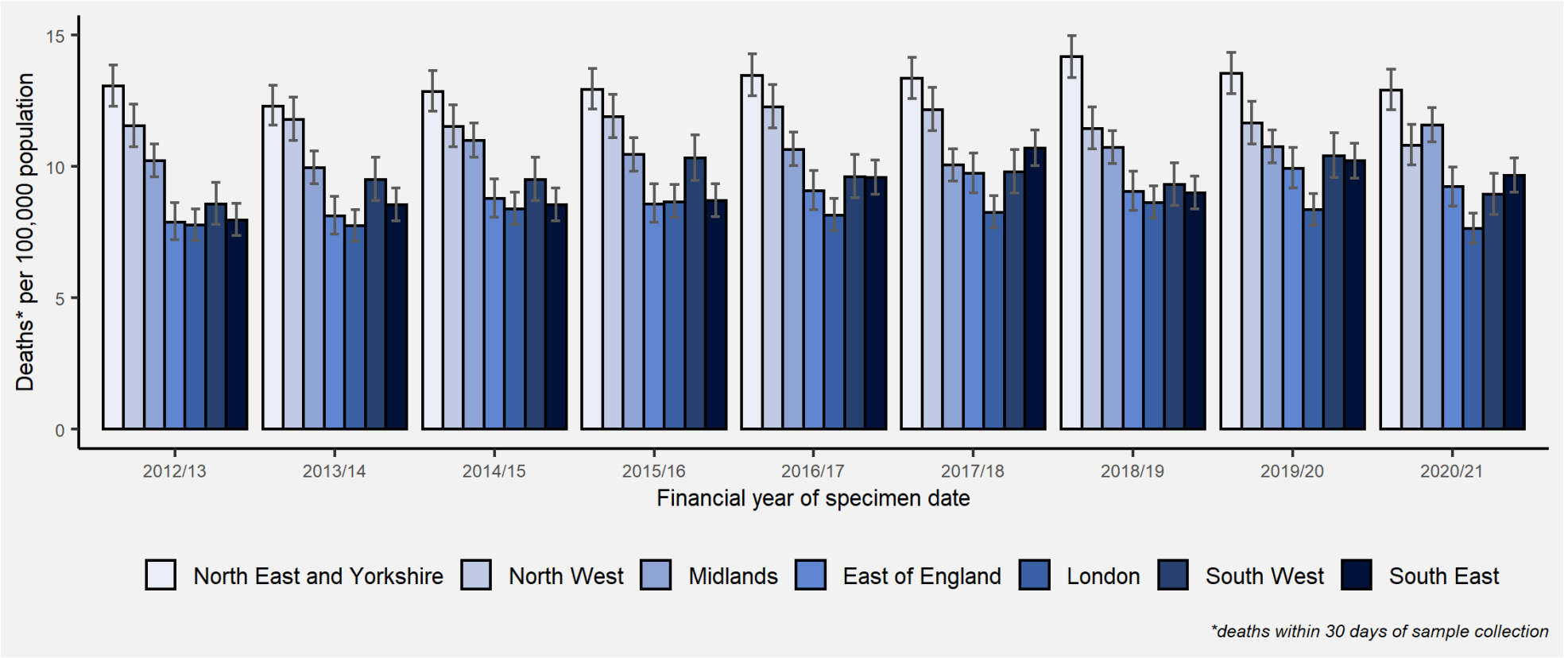
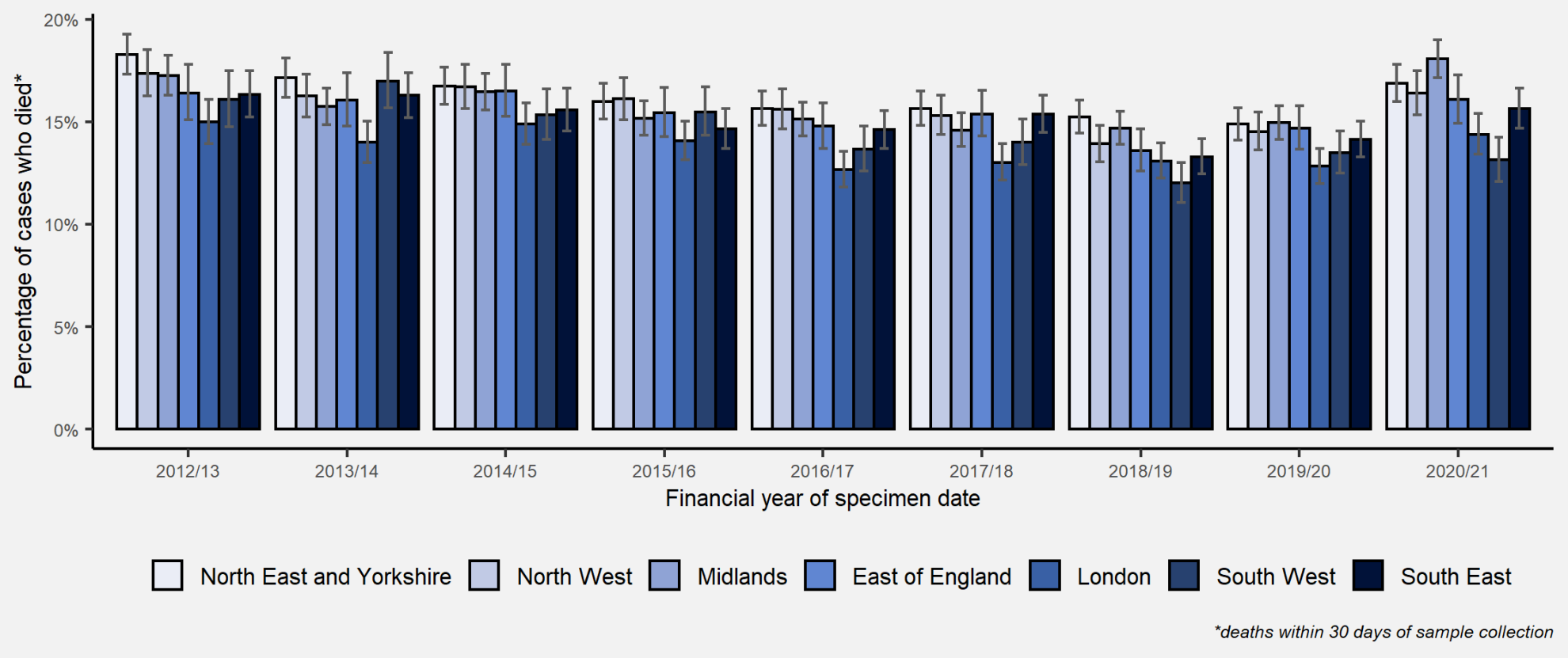


Figure 6. Thirty-day all-cause case fatality rate of *E. coli* bacteraemia by NHS commissioning region 2012/2013 to 2020/2021



Variation by age and sex

MR and CFR increased with age and was greater in male patients than female patients. However, both were greater in patients less than 1 year old compared to those between 1 to 44 years old (see Table S4 in the accompanying data sheet, Figure 7 and Figure 8).

In 2020/2021, among male patients, the highest MRs were in the ≥85 year age group (177.5 deaths per 100,000 population) and 75 to 84 year age group (68.0, Figure 7), which equated to CFRs of 23.6% and 18.8% the cases respectively (Figure 8).

In 2020/2021, among female patients, MR were 99.8 per 100,000 population (≥85 year age group) and 40.4 (75 to 84 year age group). These equated to CFR of 20.2% and 15.9% of cases in respective age groups.

The MR in male patients aged less than one year was 7.9 deaths per 100,000 population (6.7% of cases) compared to 5.3 (7.9% of cases) in female patients.

Figure 7. Thirty-day all-cause mortality rate of *E. coli* bacteraemia by age and sex 2012/2013 to 2020/2021

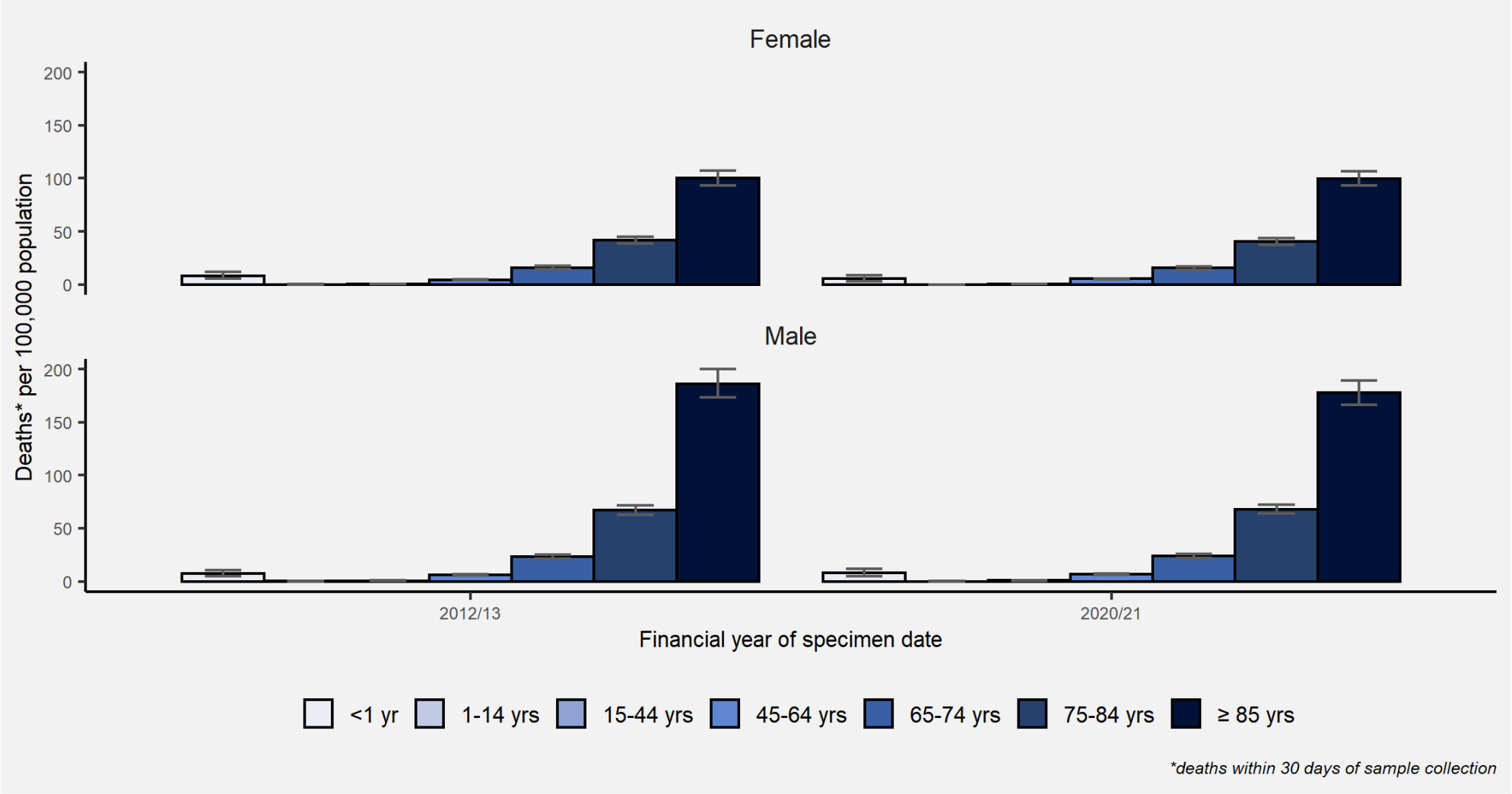
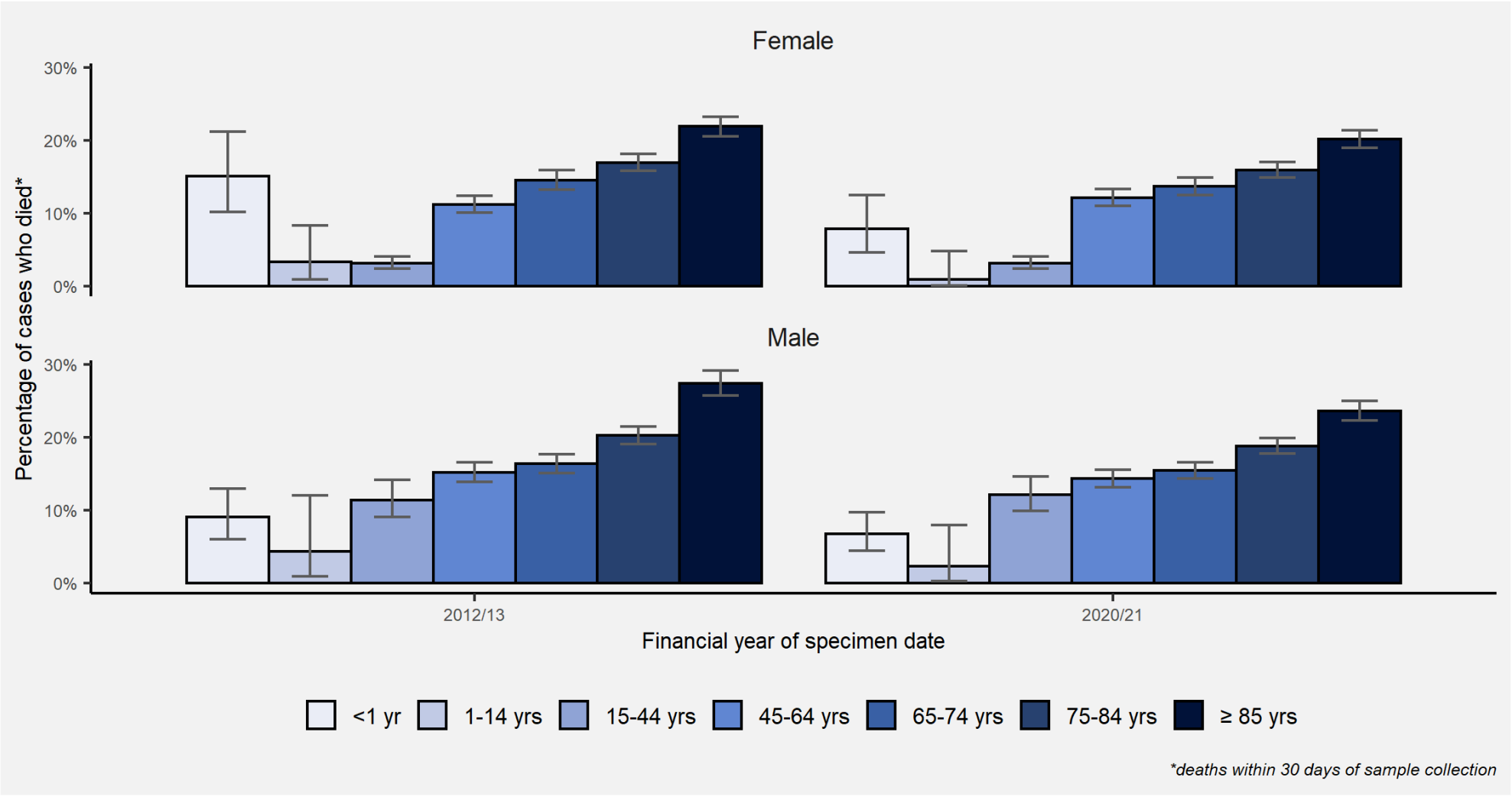


Figure 8. Thirty-day all-cause case fatality rate of *E. coli* bacteraemia by age and sex 2012/2013 to 2020/2021



Klebsiella spp . bacteraemia

In 2020/2021, 11,096 *Klebsiella* spp. bacteraemia cases were reported in England. Information on mortality was available for 97% (n = 10,779) of these cases (see Table S5 in the accompanying data sheet). There were 2,346 deaths within 30 days of a *Klebsiella* spp. bacteraemia giving an MR of 4.2 deaths per 100,000 population. The CFR was 21.8% of cases.

Mandatory surveillance of *Klebsiella* spp. started in financial year 2017/2018, meaning trends are not as established as those in data collections such as MRSA or *E. coli*. The CFR had increased from 20.2% (n = 1,895) in 2017/2018 to 21.8% (n = 2,346) in 2020/2021 (p = 0.2). The MR had also increased from 3.4 per 100,000 population in 2017/2018 to 4.2 per 100,000 population in 2020/2021 (p = 0.2).

A large increase in CFR was observed between 2018/2019 and 2020/2021 coinciding with the COVID-19 pandemic. The CFR increased from 18.6% in 2018/2019 to 21.8% in 2020/2021 (p = 0.01). The MR also increased from 3.4 per 100,000 population 2018/2019 to 4.2 per 100,000 population in 2020/2021.

An analysis of patients with *Klebsiella* spp. and a COVID-19 infection within 28 days before or after the infection found that found a CFR of 38.8% (n= 1,748/647) compared with 18.8% (n = 9,454/1,726) among cases without a corresponding COVID-19 infection by the same patient within the 28 days before or after the *Klebsiella* spp. case. This also means that 27.3% of 30-day all-cause deaths were in cases that had a corresponding COVID-19 infection as described above, suggesting that patients with COVID-19 infection were a considerable contribution to the increase in *Klebsiella* spp. CFR for 2020/2021.

Variation by onset of bacteraemia

The MR of HO cases increased from 1.9 (n= 670 deaths, 2019/2020) to 3.6 deaths per 100,000 bed-days (n= 986 deaths, 2020/2021) (see Table S6 in the accompanying data sheet and Figure 9). This spike is likely compounded by the increase in HO cases seen over the 2020/2021 winter period. Over the same period, the MR in CO cases was 2.4 (n= 1,376 deaths in 2020/2021) and 2.4 deaths per 100,000 population (n= 1,360 deaths in 2019/2020) respectively.

Between the start of surveillance (2017/2018) and the current year (2020/2021) the CFR of HO cases increased from 24.5% (2017/2018) to 27.0% (2020/2021), while for CO cases it increased from 18.1% to 19.1% of cases (see Table S2 in the accompanying data sheet and Figure 4).

When comparing between periods prior, beginning and during the COVID-19 pandemic the following are observed. The MR for HO decreased from 2.0 (n=687 deaths) in 2017/2018, to 1.9 (n=670 deaths) in 2019/2020 (beginning of COVID-19) and then increased to 3.6 (n=986 deaths) deaths per 100,000 population in the current financial year (during COVID-19). The MR for CO increased from 2.2 (n= 1,208 deaths) in 2017/2018 (pre-COVID-19) to 2.4 (n= 1,376

deaths) in 2019/2020 (beginning of COVID-19) and then remained broadly similar at 2.4 (n=1,360 deaths) deaths per 100,000 population in the current financial year (during COVID-19).

During the COVID-19 pandemic the CFR for HO increased from (21.7% to 27.0%) between the previous year (2019/2020, beginning of COVID-19) and current (2020/2021, during COVID-19) financial year. The CO CFR also increased from (18.3% to 19.1%) for the same period.

Figure 9. Thirty-day all-cause mortality rate of Klebsiell*a* spp. bacteraemia by onset of bacteraemia 2017/2018 to 2020/2021

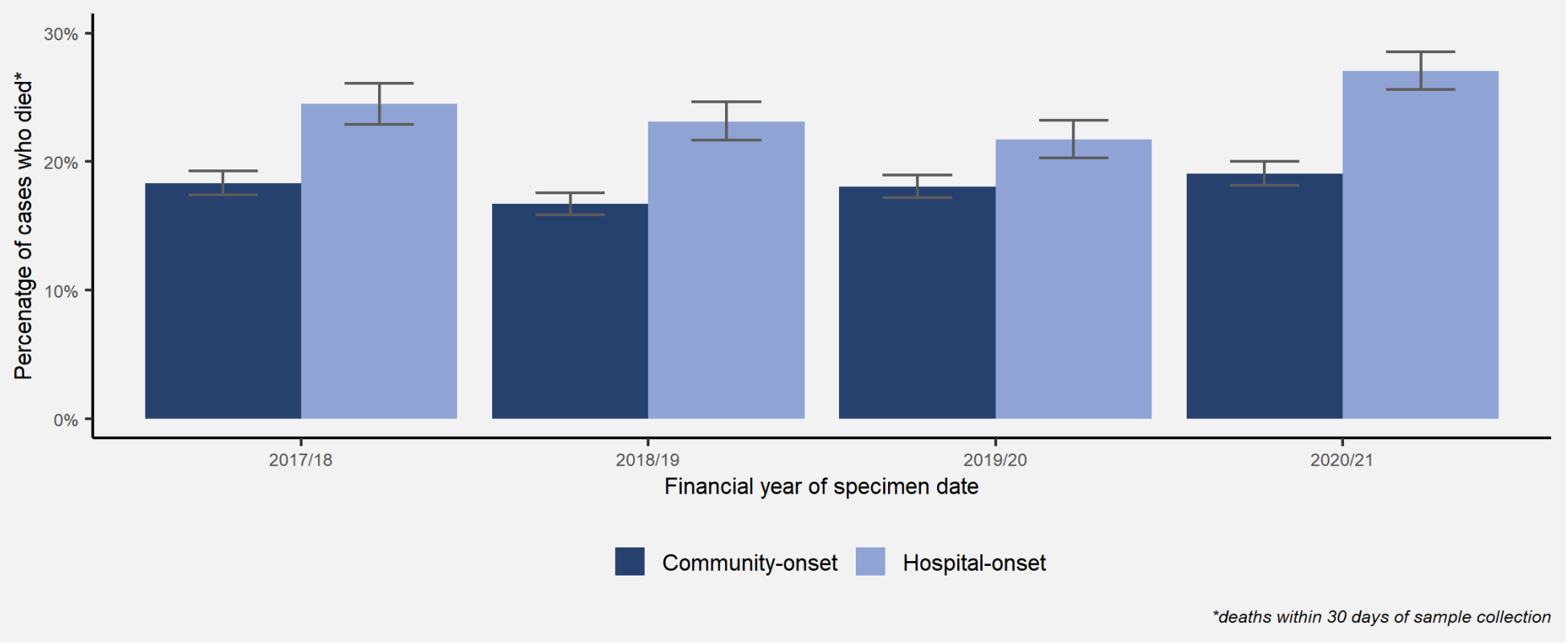
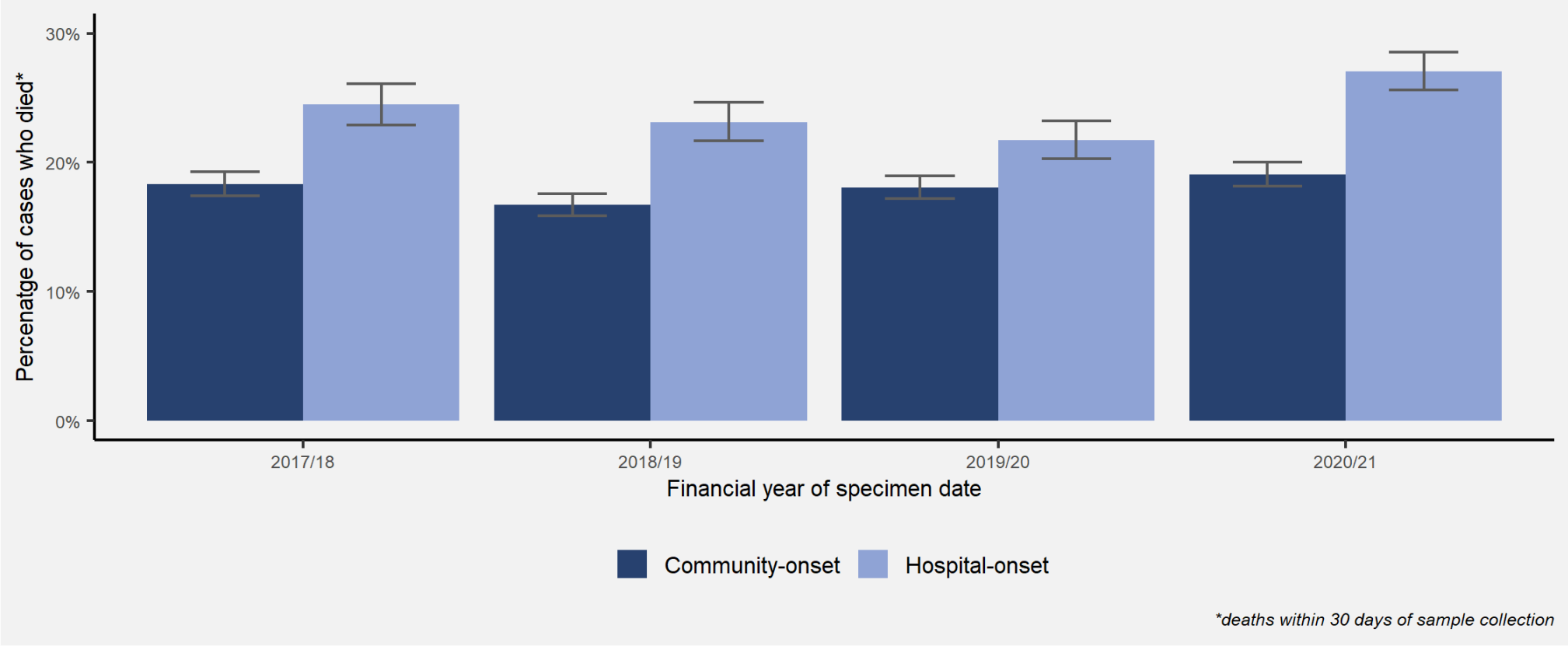


Figure 10. Thirty-day all-cause case fatality rate of *Klebsiella* spp. bacteraemia by onset of bacteraemia 2017/2018 to 2020/2021



Variation by NHS commissioning region

In 2020/2021, regional MR ranged from 3.1 deaths per 100,000 population in the South West to 5.1 deaths per 100,000 population in London (see Table S7 in the accompanying data sheet and Figure 11). Over the same period, CFRs ranged from 17.3% in the South West to 22.6% in the North East and Yorkshire (see Table S7 in the accompanying data sheet and Figure 12).

Between 2017/2018 and 2020/2021 the South East region had the greatest increase in CFR (19.8% to 22.0%) and MR (3.1 to 3.8 deaths per 100,000 population).

The areas with the highest differences in RR are found between London and the East (RR: 2.58, $p < 0.01$) with the lowest being the South West and London (RR: 0.39, $p < 0.01$) (Appendix 3).

There was no strong evidence[2] to suggest significant differences in regional odds of deaths, except between the South East and the South West (OR: 1.39, $p < 0.01$) and the South West and London (OR: 0.64, $p < 0.01$), the North East and Yorkshire (OR: 0.69, $p < 0.01$), the North West (OR: 0.71, $p < 0.01$), the Midlands (OR: 0.71, $p < 0.01$) and the East (OR: 0.70, $p < 0.01$) (Appendix 4).

[2] Strong evidence described as a statistically significant ($p < 0.05$) odds ratio of ≥0.25.

Figure 11. Thirty-day all-cause mortality rate of *Klebsiella* spp. bacteraemia by NHS commissioning region 2017/2018 to 2020/2021

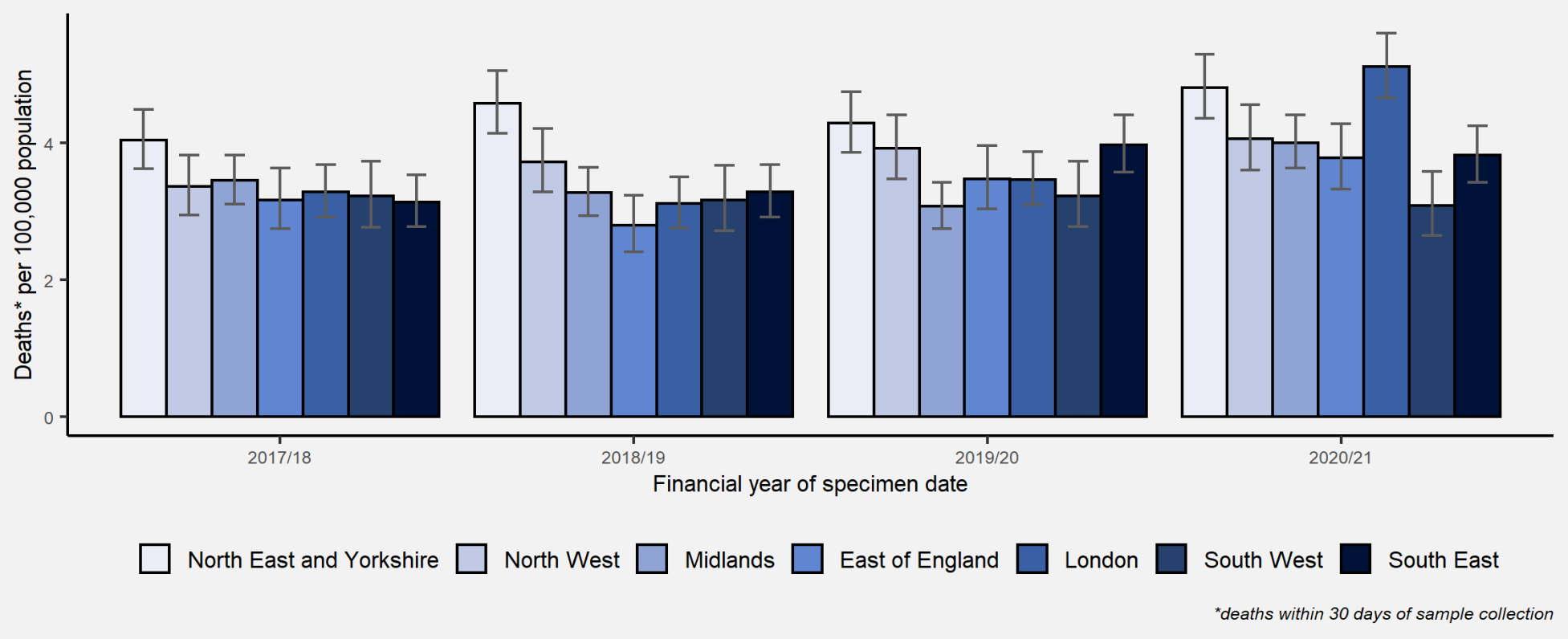
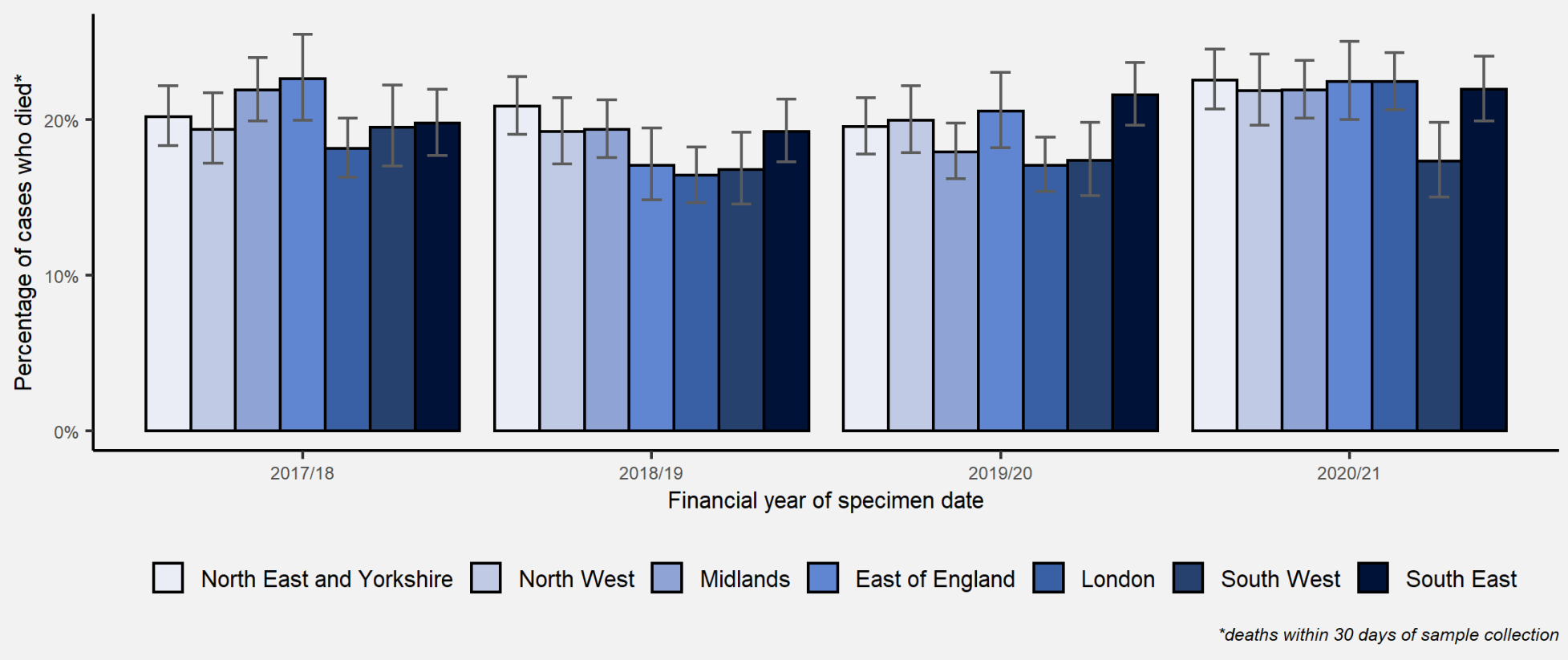


Figure 12. Thirty-day all-cause case fatality rate of *Klebsiella* spp. bacteraemia by NHS commissioning region 2017/2018 to 2020/2021



Variation by age and sex

In 2020/2021, MR and CFR increased with age. The MR was greater in male patients while the CFR was greater in female patients (see Table S8 in the accompanying data sheet, Figure 13 and Figure 14).

Among male patients, the highest MRs were in the ≥85 years age group (65.0 deaths per 100,000 population) and 75 to 84 years age group (25.0 deaths per 100,000 population) age groups, which equated to CFRs of 29.4% and 21.5% respectively.

In female patients of the same age groups the MRs were 21.1 (≥85 years age group) and 10.3 (75 to 84 years age group). These were CFRs of 31.5% and 22.1% of all cases in those respective age groups.

The MR in male patients aged less than one year was 3.5 deaths per 100,000 population (10.6% of cases) compared to 3.7 (13.3% of cases) in female patients.

Figure 13. Thirty-day all-cause mortality rate of *Klebsiella* spp. bacteraemia by age and sex 2017/2018 to 2020/2021

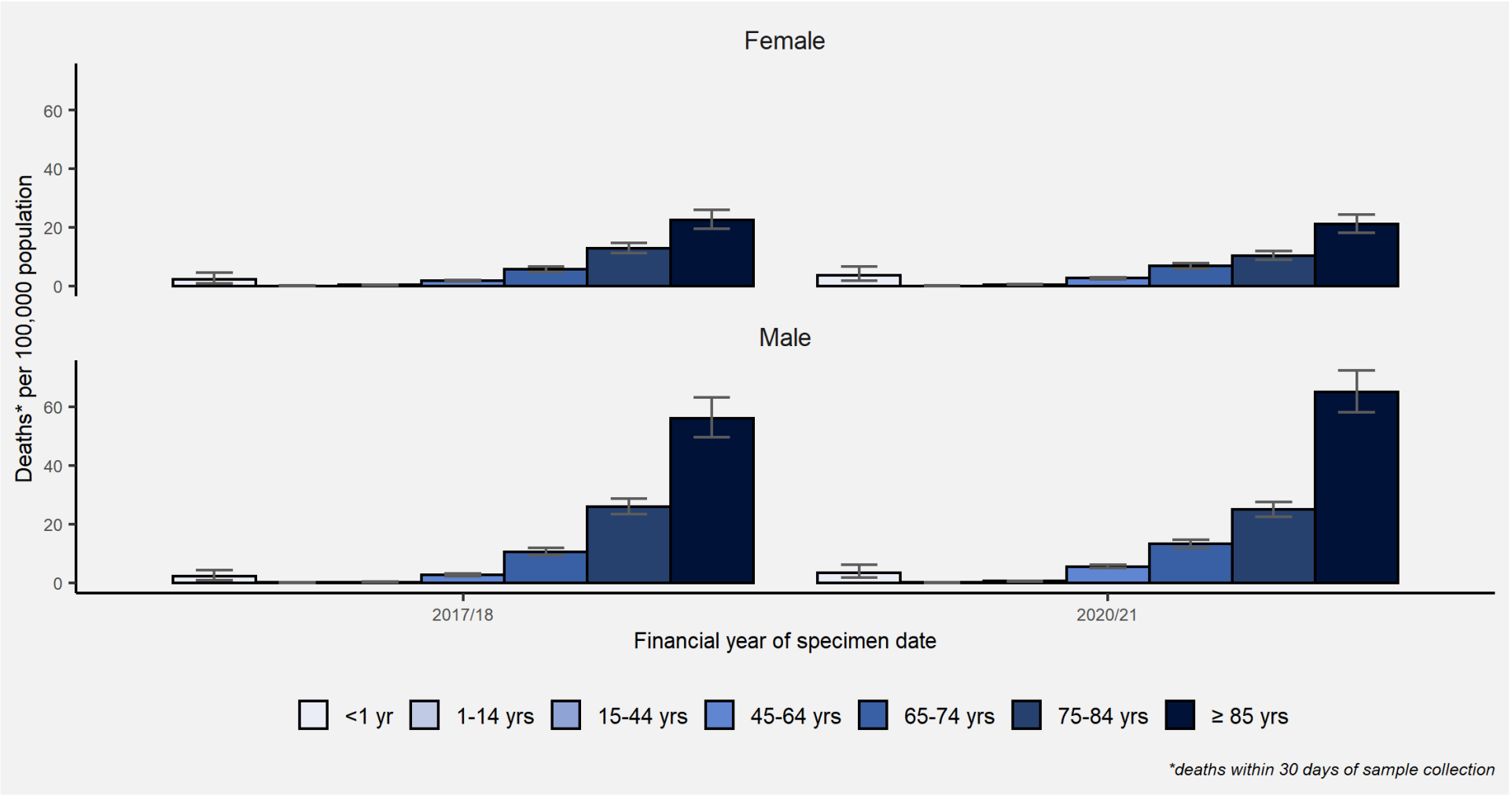
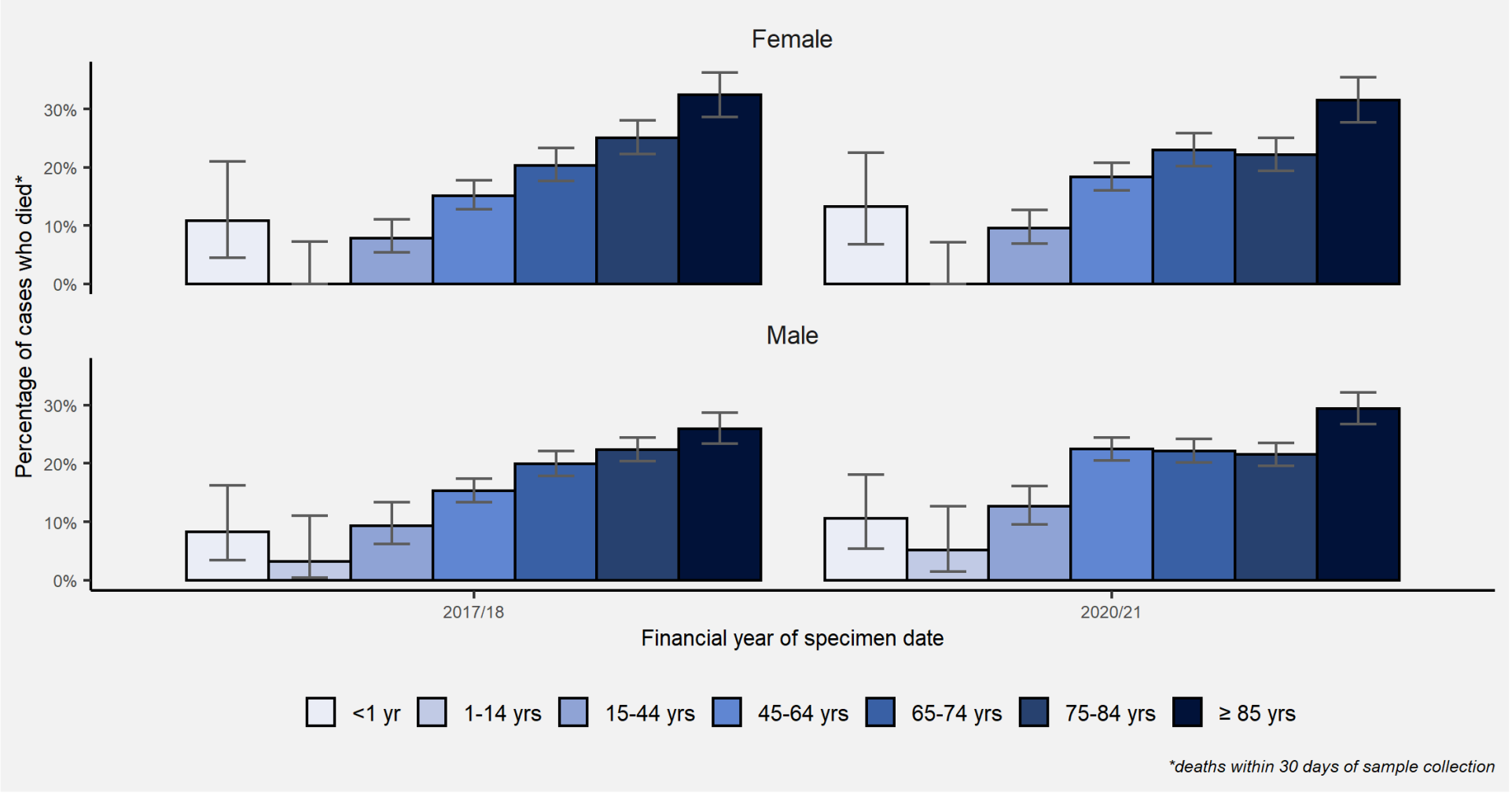


Figure 14. Thirty-day all-cause case fatality rate of *Klebsiella* spp. bacteraemia by age and sex 2017/2018 to 2020/2021



Pseudomonas aeruginosa bacteraemia

In 2020/2021, 4,285 *P. aeruginosa* bacteraemia cases were reported in England. Information on mortality was available for 98% (n= 4,178) of these cases (see Table S9 in the accompanying data sheet). There were 1,158 deaths within 30 days of a *P. aeruginosa* bacteraemia, giving a MR of 2.1 deaths per 100,000 population. The CFR was 27.7% of cases.

Mandatory surveillance of *P. aeruginosa* bacteraemia started in financial year 2017/2018, meaning trends are not as established as those in data collections such as MRSA of *E. coli*. The CFR had increased from 26.9% (n = 1,121 death) in 2017/2018 to 27.7% (n = 1,158 deaths) in 2020/2021. The MR had also increased slightly from 2.0 per 100,000 population in 2017/2018 to 2.1 per 100,000 population in 2020/2021. This difference was observed as not statistically significant (p = 0.69).

The CFR increased from 24.1% in 2018/2019 to 27.7% in 2020/2021. The MR had also increased from 1.7 per 100,000 population in 2018/2019 to 2.1 per 100,000 population in 2020/2021. The difference in CFR between these 2 years was not significant (p = 0.06).

An analysis of patients with *P. aeruginosa* cases and a COVID-19 infection within 28 days before or after the infection found that found a CFR of 47.8% (n= 663/309) compared with 24.1% (n = 3,635 /853) among cases without a corresponding COVID-19 infection by the same patient within the 28 days before or after the *P. aeruginosa* case. This also means that 26.6% of 30-day all-cause deaths were in cases that had a corresponding COVID-19 infection as described above, suggesting that patients COVID-19 infection was a considerable contribution to the increase in *P. aeruginosa* CFR for 2020/2021.

Variation by onset of bacteraemia

In 2020/2021, the MR of HO cases increased to 2.0 deaths per 100,000 bed-days (n= 551 deaths) compared to 1.3 (n= 433 deaths) in the previous financial year (2019/2020) (see Table S10 in the accompanying data sheet and Figure 15). It is to be noted that this increase in all-cause deaths is likely due to the increase in HO cases seen over the 2020/2021 winter period. Over the same period, the MR in CO cases was 1.1 (n= 601 deaths) deaths per 100,000 population and 1.1 (n= 607 deaths) respectively.

Between the start of surveillance (2017/2018) and the current year (2020/2021) the CFR of HO cases increased from 29.9% (2017/2018) to 33.9% (2020/2021), while for CO cases it decreased from 25.2% (2017/2018) to 23.8% (2020/2021) of cases (see Table S2 in the accompanying data sheet and Figure 4).

When comparing between periods prior to, beginning at and during the COVID-19 pandemic, the following are observed. The MR for HO decreased from 1.3 (n=470 deaths) in 2017/2018, to 1.3 (n=433 deaths) in 2019/2020 (beginning of COVID-19) and then increased to 2.0

(n=551 deaths) deaths per 100,000 population in the current financial year (during COVID-19). The MR for CO cases decreased from 1.2 (n= 651 deaths) in 2018/2019 (pre-COVID-19) to 1.1 (n= 601 deaths) in 2019/2020 (beginning of COVID-19) and then increased to 1.1 (n=607 deaths) deaths per 100,000 population in the current financial year (during COVID-19).

During the COVID-19 pandemic the CFR for HO cases increased from 28.5% to 33.9% between the previous year (2019/2020, beginning of COVID-19) and current financial year (2020/2021 during COVID-19). The CO CFR also increased from 22.3% to 23.8% for the same period.

Figure 15. Thirty-day all-cause mortality rate of *P. aeruginosa* bacteraemia by onset of bacteraemia 2017/2018 to 2020/2021

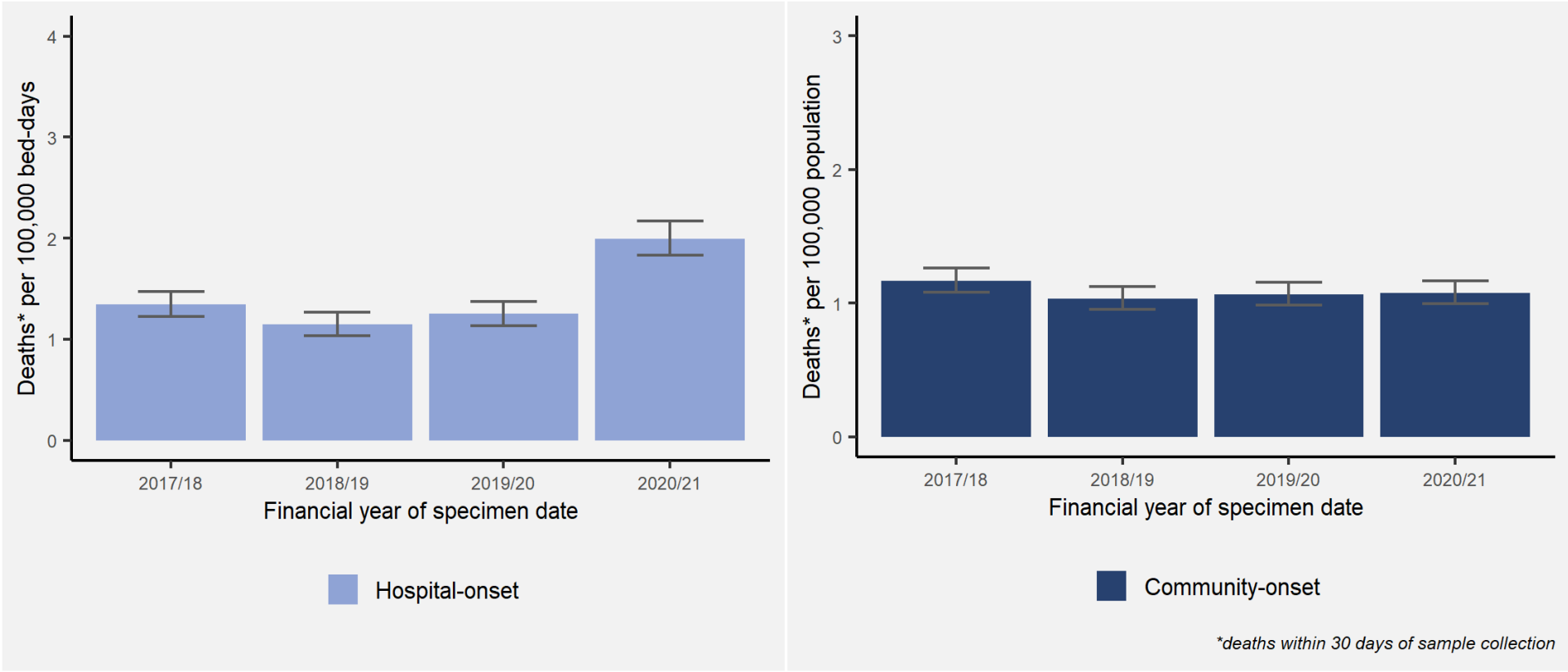
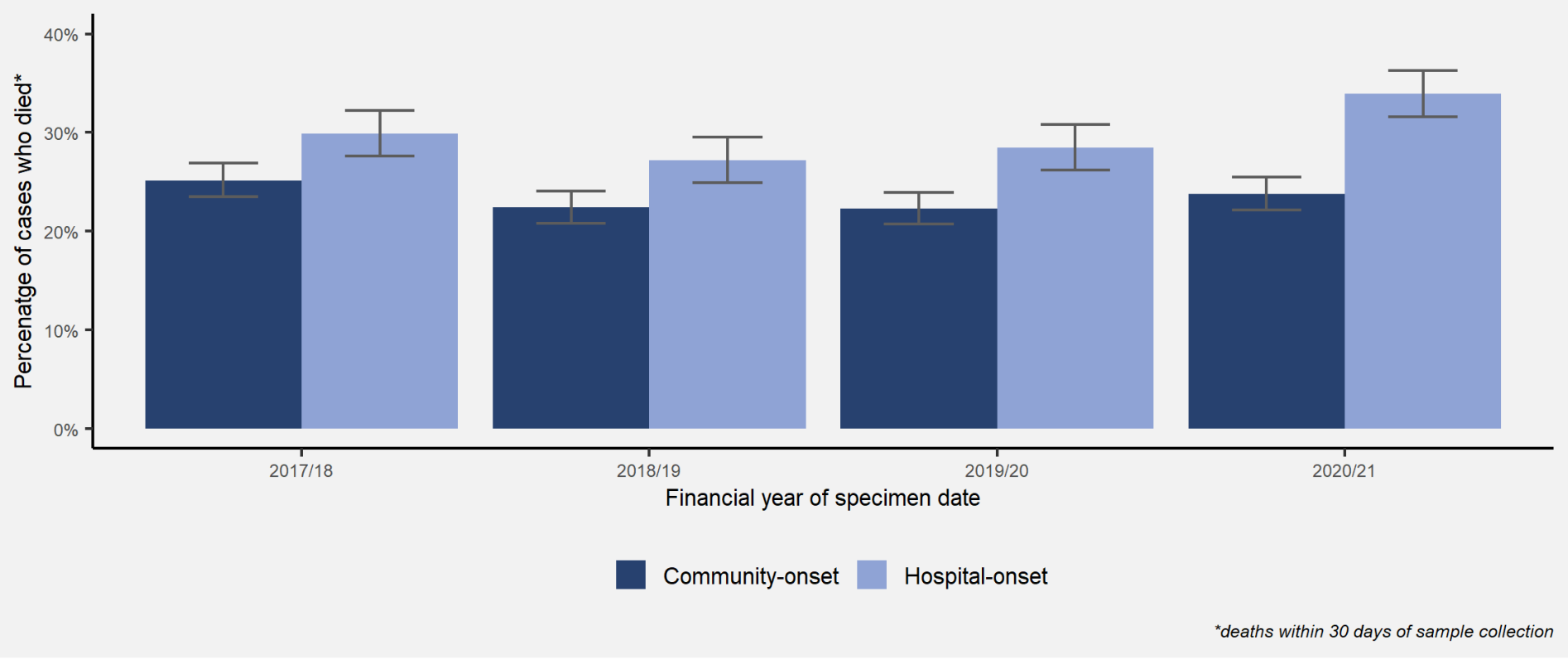


Figure 16. Thirty-day all-cause case fatality rate of *P. aeruginosa* bacteraemia by onset of bacteraemia 2017/2018 to 2020/2021



Variation by NHS commissioning region

In 2020/2021, regional MR ranged from 1.3 deaths per 100,000 population in the South West to 2.6 deaths per 100,000 population in London (see Table S11 in the accompanying data sheet and Figure 17). Over the same period, CFRs ranged from 20.9% in the South West to 32.3% in the North West (see Table S11 in the accompanying data sheet and Figure 18).

The area with the highest differences in RR were between London and the South West (RR: 3.20, $p < 0.01$) with the lowest being the inverse (see Appendix 3).

There was no strong evidence[3] to suggest significant differences in regional odds of deaths, except between the East and the North East and Yorkshire (OR: 0.74, $p = 0.05$) and the North West (OR: 0.68, $p = 0.02$), the Midlands and East (OR: 1.32, $p = 0.05$), the South East and the South West (OR: 1.60, $p < 0.01$) and the South West and London (OR: 0.68, $p = 0.01$), the North East and Yorkshire (OR: 0.59, $p < 0.01$), the North West (OR: 0.54, $p < 0.01$) and the Midlands (OR: 0.60, $p < 0.01$) (see Appendix 4).

[3] Strong evidence described as a statistically significant ($p< 0.05$) odds ratio of ≥0.25.

Figure 17. Thirty-day all-cause mortality rate of *P. aeruginosa* bacteraemia by NHS commissioning region 2017/2018 to 2020/2021

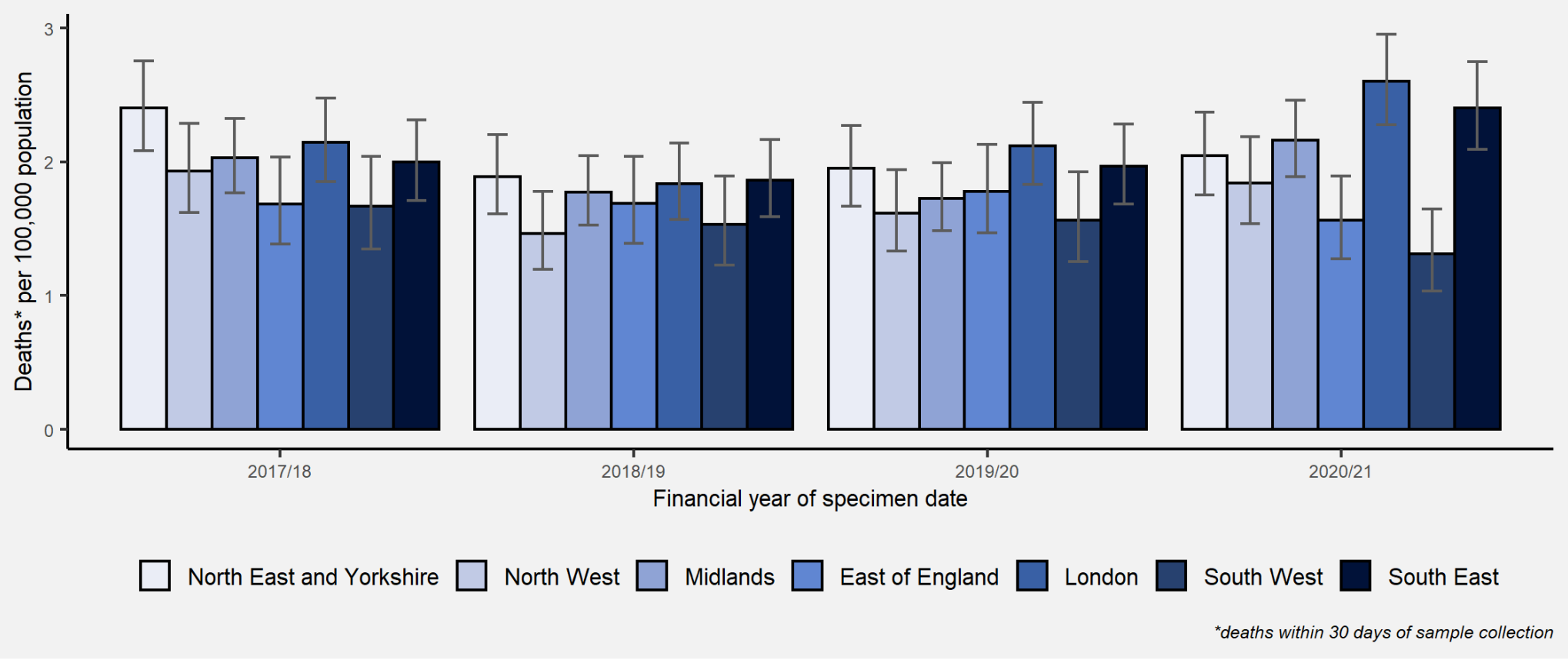
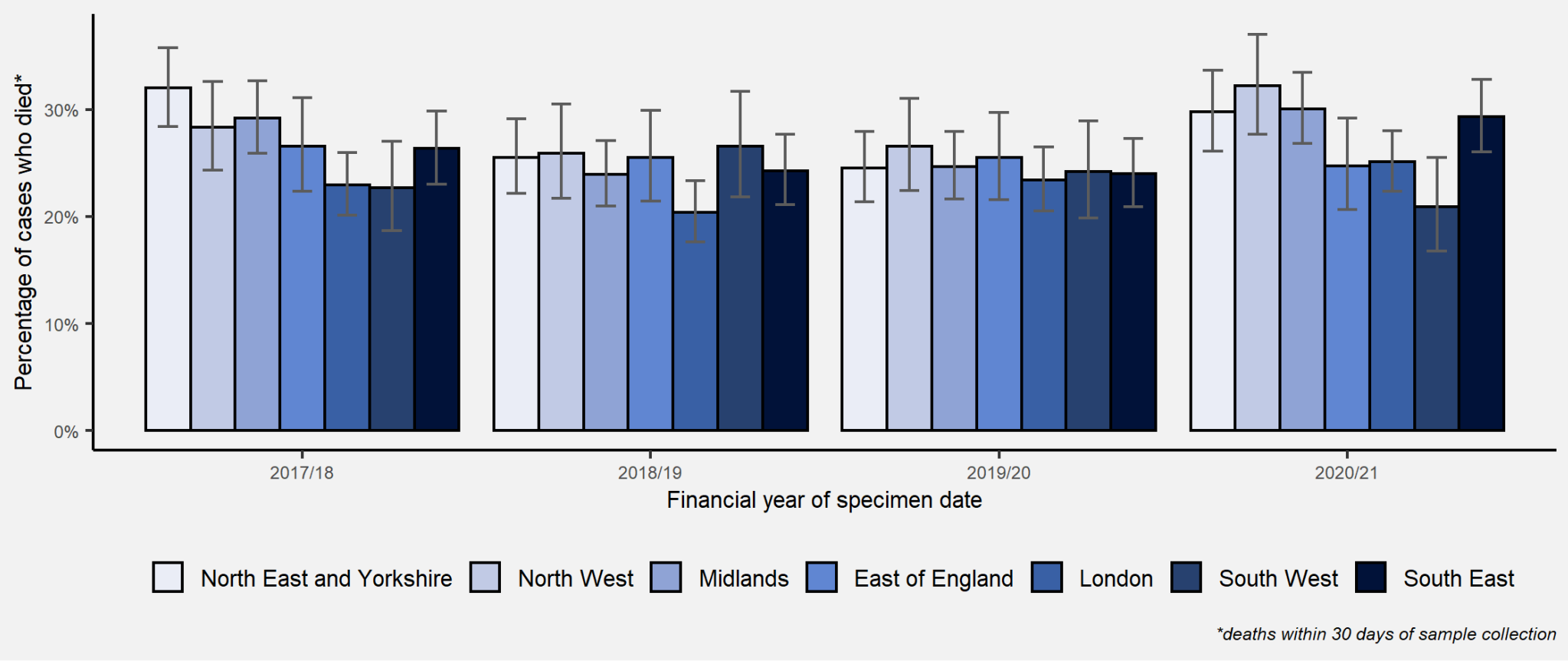


Figure 18. Thirty-day all-cause case fatality rate of *P. aeruginosa* bacteraemia by NHS commissioning region 2017/2018 to 2020/2021



Variation by age and sex

In 2020/2021, MR and CFR increased with age. The MR was greater in male patients while the CFR was greater in female patients. However, the MR and CFR of patients under 1 year old were higher than those between 1 to 64 years old (see Table S12 in the accompanying data sheet, Figure 19 and Figure 20).

In 2020/2021, among male patients, the highest mortality rates were in the ≥85 years old (28.2 deaths per 100,000 population) and 75 to 84 years old (13.0) age groups, which were CFRs of 31.9% and 28.0% cases respectively.

In female patients of the same age groups, the MRs were far lower than their male counterparts, 10.3 (≥85 years old) and 5.9 (75 to 84 years old) deaths per 100,000 population. These equated to CFRs of 41.0% and 34.5% of all cases in those respective age groups.

The MR in male patients aged less than one year was 1.6 deaths per 100,000 population (25.0% of cases) compared to 1.0 (16.7% of cases) in female patients. Although, caution is required in interpreting this data, as the number of deaths were relatively small in both groups.

Figure 19. Thirty-day all-cause mortality rate of *P. aeruginosa* bacteraemia by age and sex 2017/2018 to 2020/2021

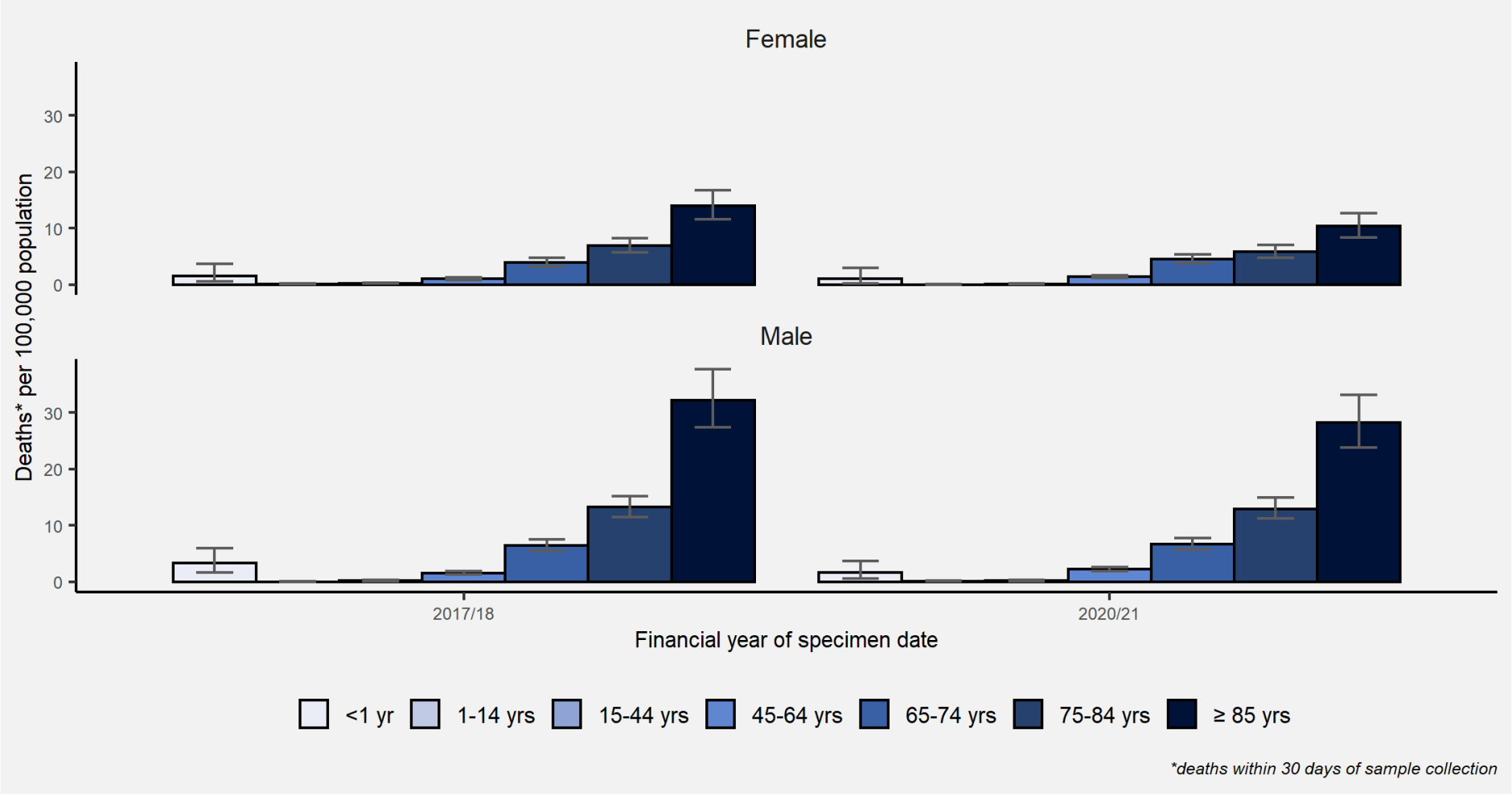
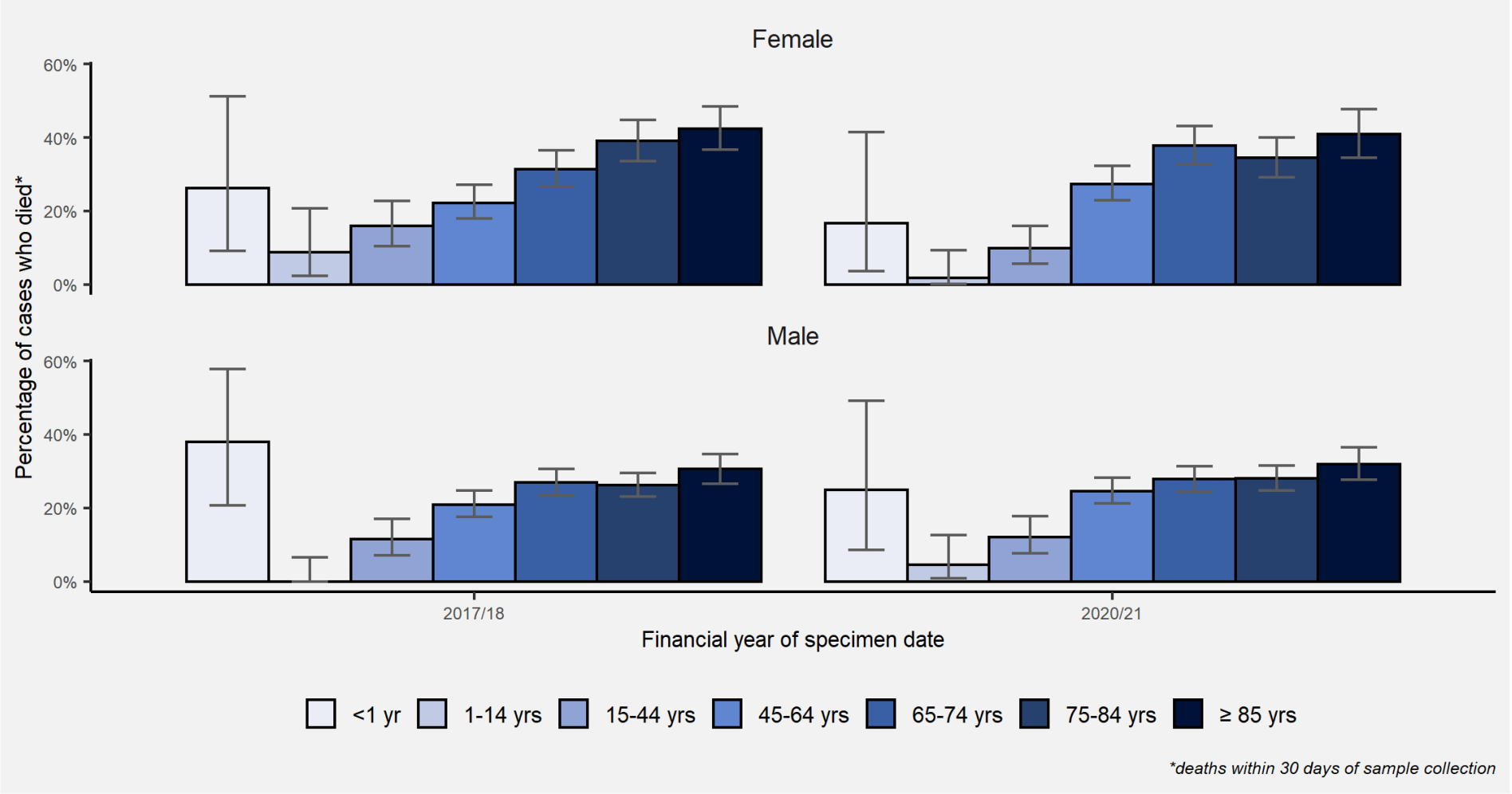


Figure 20. Thirty-day all-cause case fatality rate of *P. aeruginosa* bacteraemia by age and sex 2017/2018 to 2020/2021



Staphylococcus aureus bacteraemia

MRSA bacteraemia

In 2020/2021, 694 MRSA bacteraemia cases were reported in England. Information on mortality was available for 97% (n= 673) of these cases (see Table S13 in the accompanying data sheet). There were 190 deaths within 30 days of an MRSA bacteraemia which was a MR of 0.3 deaths per 100,000 population. The CFR was 28.2% of cases.

There was a consistent declining trend in CFR starting from 38.9% in 2007/2008 to 24.6% in 2018/2019 ($p<0.01$) after which, the CFR then increased each year to 28.2% in the current financial year 2020/2021. The overall trend of MR decreased from 2.6 deaths per 100,000 population in 2007/2008 to 0.3 in 2018/2019 keeping at 0.3 in 2020/2021. The overall difference in CFR between 2007/2008 and 2020/2021 was statistically significant ($p<0.01$).

During the COVID-19 pandemic there was an increase in CFR from 25.7% to 28.2% from 2019/2020 (post-COVID-19) to 2020/2021 (post-COVID-19) financial years. Additionally, there was a decrease (0.4 to 0.3 deaths per 100,000 population) in MR over the same period. The different trend between 2019/2020 and 2020/2021 is likely a consequence of the COVID-19 pandemic. The decline in burden of 30-day all-cause death (MR) is likely due to reduced hospital activity at the height of the pandemic, while the increase CFR over this period was compounded by a considerable proportion of the 30-day all-cause deaths occurring in patients with a COVID-19 infection.

An analysis of patients with MRSA and a COVID-19 infection within 28 days before or after the infection found that a CFR of 46.7% (n= 70/150) compared with 22.5% (n = 120/533) among cases without a corresponding COVID-19 infection by the same patient within the 28 days before or after the *Klebsiella* spp case. This also means that 36.8% of 30-day all-cause deaths were in cases that had a corresponding COVID-19 infection as described above, suggesting that patients with a COVID-19 infection were a considerable contribution to the increase in *Klebsiella* spp CFR for 2020/2021.

Further statistical analysis is required. However, given that 36.8% of overall mortality was COVID-19 related, there is enough evidence to speculate that the presence of COVID-19 may be responsible for the unprecedented spike in CFR in 2020/2021.

Variation by onset of bacteraemia

The CFR of HO cases decreased from 42.4% in 2007/2008 to 34.1% in 2020/2021, while for CO cases it decreased from 33.1% in 2007/2008 to 24.3% in 2020/2021 of cases (see Table S2 in the accompanying data sheet and Figure 4). The HO CFR this current year 2020/2021, (34.1%) is the highest recorded since 2011/2012.

During the financial years influenced by the COVID-19 pandemic (2019/2020 and 2020/2021) the CFR for HO increased from 29.2% in 2019/2020 to 34.1% in 2020/2021. The same large

increase was not observed for the CO CFR increasing from 24.1% in 2019/2020 to 24.3% in 2020/2021.

In the same period, the MR of HO cases increased from 0.21 deaths per 100,000 bed-days (n= 73 deaths, 2019/2020) to 0.33 deaths per 100,000 bed-days (n= 93 deaths, 2020/2021) (see Table S2 in the accompanying data sheet and Figure 3). The same trend is observed with CO MR cases decreasing from 0.23 (n= 128 deaths, 2019/2020) to 0.17 deaths per 100,000 population (n= 97 deaths, 2020/2021) respectively.

The major trends observed pre-COVID-19 and during COVID-19 have shown the following for HO and CO. There was an increasing trend in HO CFR starting from 25.7% in 2018/2019 (pre-COVID-19) rising to 34.1% in the current financial year 2020/2021 (during COVID-19). The CFR for CO cases showed a similar trend increasing from 24.0% in 2018/2019 (pre-COVID-19) to 24.3% in the current financial year 2020/2021 (during COVID-19).

The trend observed in HO MR has increased from 0.2 per 100,000 population in 2018/2019 (pre-COVID-19) to 0.3 per 100,000 population in 2020/2021 (during COVID-19). This pattern differs from CO MR which remained at 0.22 per 100,000 population in 2018/2019 (pre-COVID-19) and in 2020/2021 (during COVID-19).

Figure 21. Thirty-day all-cause mortality rate of MRSA bacteraemia by onset of bacteraemia 2007/2008 to 2020/2021

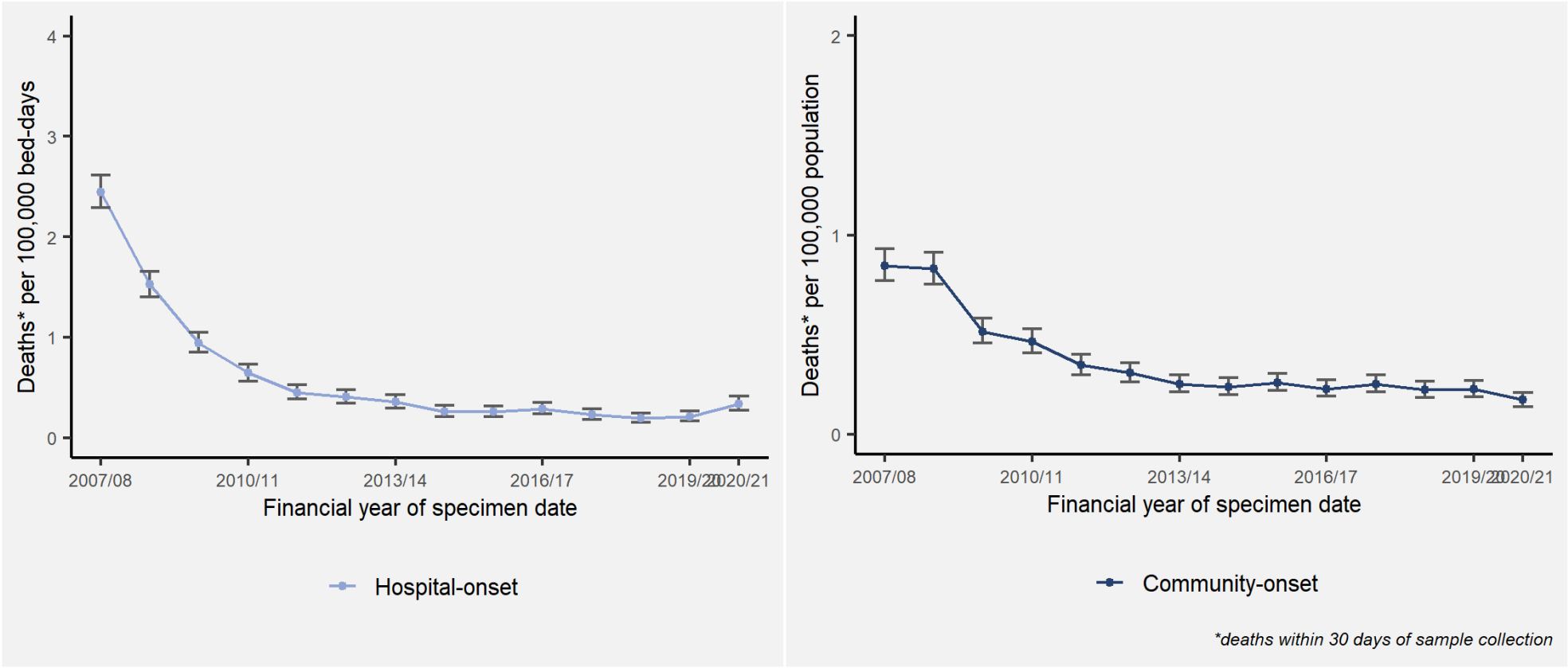
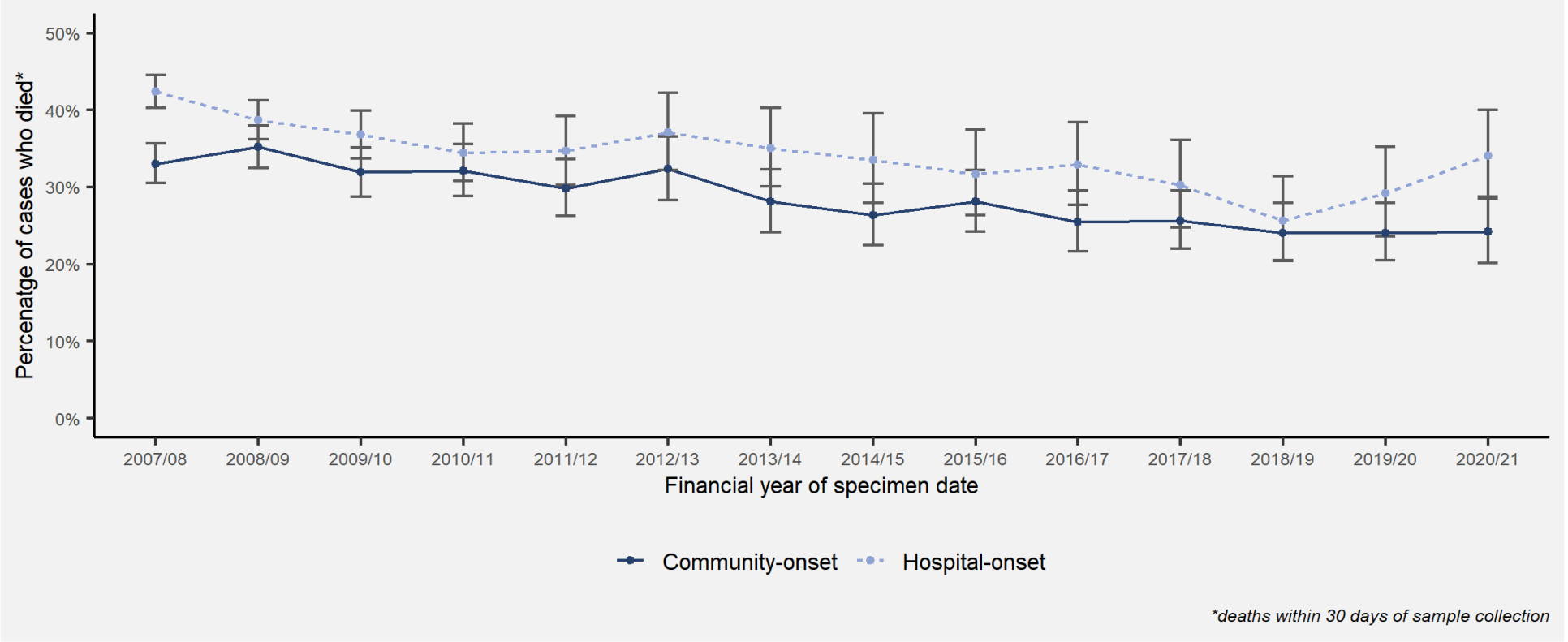


Figure 22. Thirty-day all-cause case fatality rate of MRSA bacteraemia by onset of bacteraemia 2007/2008 to 2020/2021



Variation by NHS commissioning region

Like the national trend, both regional MRs and CFRs declined between 2007/2008 and 2020/2021.

In 2020/2021, regional MR ranged from 0.3 deaths per 100,000 population in the Midlands to 0.5 deaths per 100,000 population in the North West (see Table S15 in the accompanying data sheet and Figure 23). Over the same period, CFRs ranged from 21.1% in the South West to 36.5% in the North West (see Table S15 in the accompanying data sheet and Figure 24).

The area with the highest differences in RR are between London and the South West (RR: 2.17, $p < 0.03$) with the lowest being the inverse (see Appendix 3).

There was no strong evidence[4] to suggest a significant difference in regional odds of deaths after infection (see Appendix 4).

[4] Strong evidence described as a statistically significant ($p< 0.05$) odds ratio of ≥0.25.

Figure 23. Thirty-day all-cause mortality rate of MRSA bacteraemia by NHS commissioning region 2007/2008 to 2020/2021

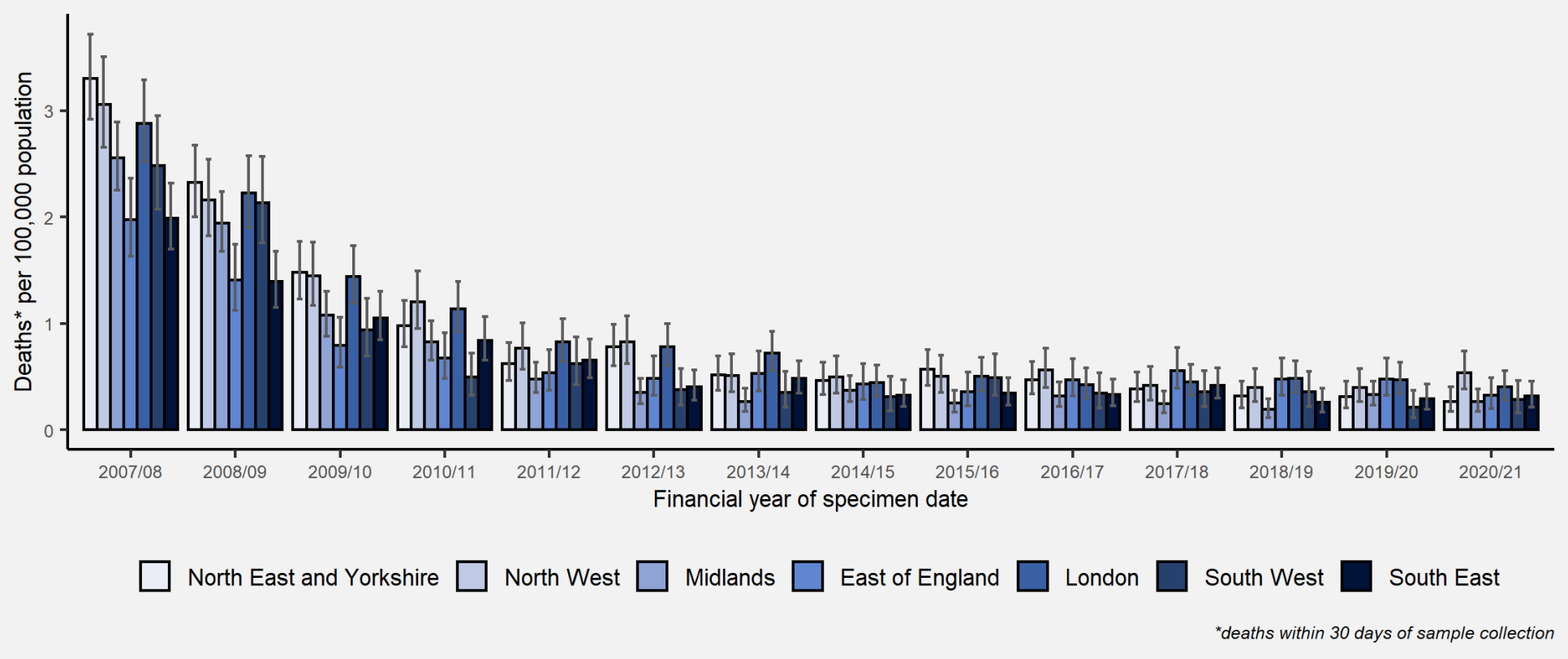
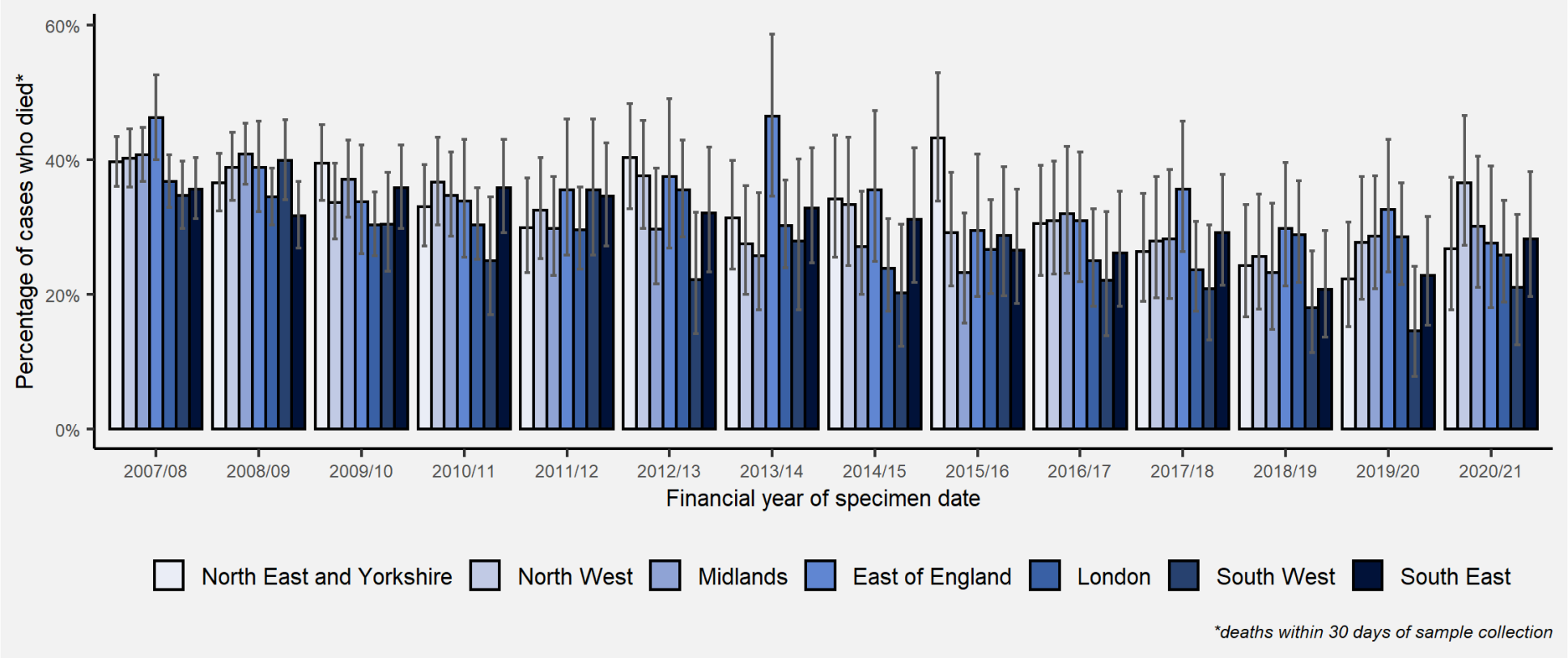


Figure 24. Thirty-day all-cause case fatality rate of MRSA bacteraemia by NHS commissioning region 2007/2008 to 2020/2021



Variation by age and sex

In 2020/2021, MR and CFR increased with age. Over the same period the MR was greater in females while CFR was near equal in both genders (see Table S16 in the accompanying data sheet, Figure 25 and Figure 26). It is to be noted that the CFR was greater in males for the age group 75 to 84.

Among male patients, the highest MR was in the ≥85 year age group (4.3 deaths per 100,000 population) and 75 to 84 year age group (2.3) age groups, CFRs 41.5% and 36.5% respectively.

In female patients, the mortality rates were also higher in older age groups, 3.5 (≥85 year age group) and 0.7 (75 to 84 year age group). These equated to CFRs of 60.8% and 33.3% of all cases in those respective age groups.

Compared to other infections covered in this report, there were relatively fewer deaths in patients aged less than one year compared to other age groups. In 2020/2021, there were 2 deaths within 30 days following MRSA bacteraemia in male and female patients aged less than one year.

Figure 25. Thirty-day all-cause mortality rate of MRSA bacteraemia by age and sex 2007/2008 to 2020/2021

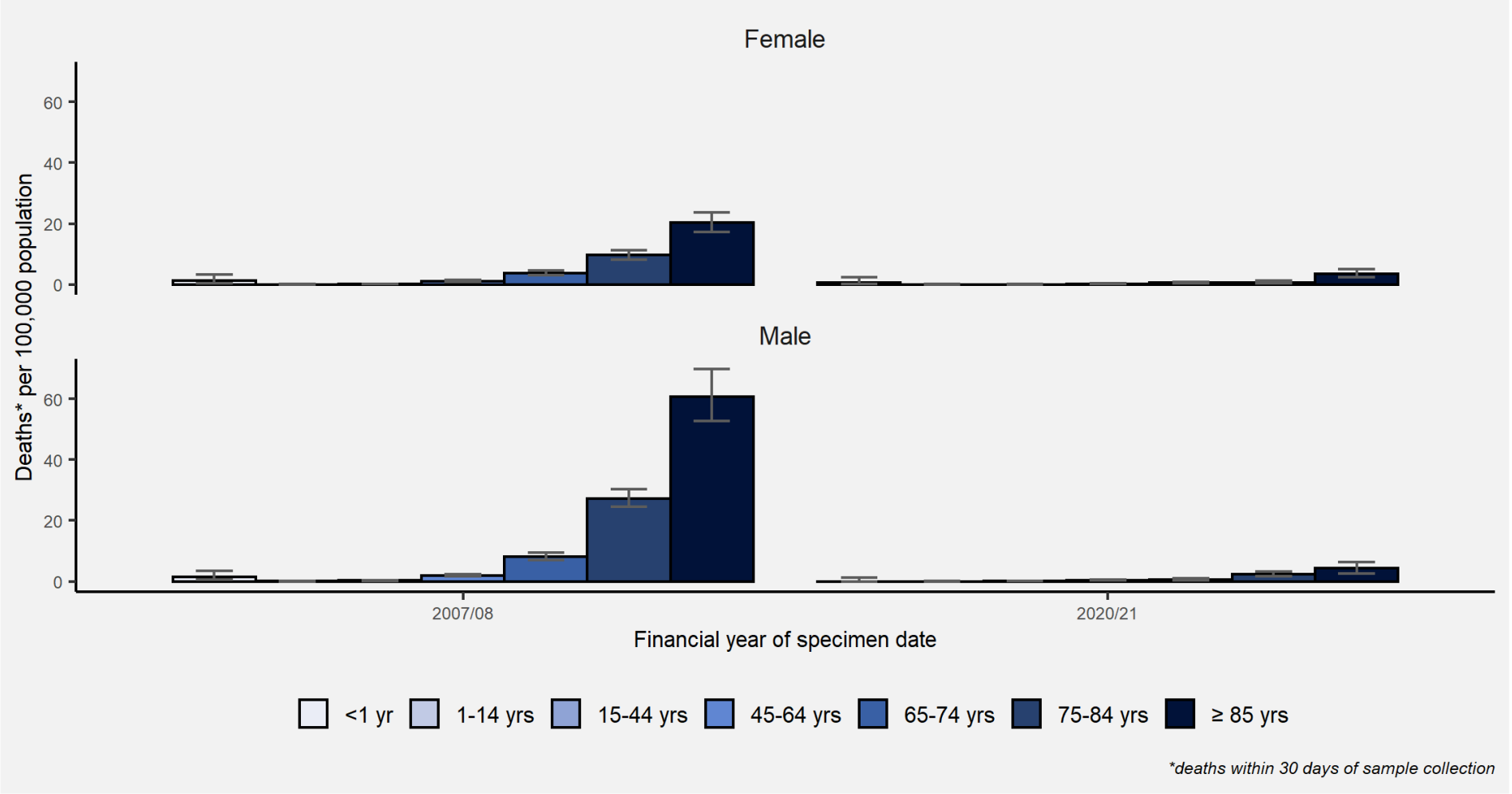
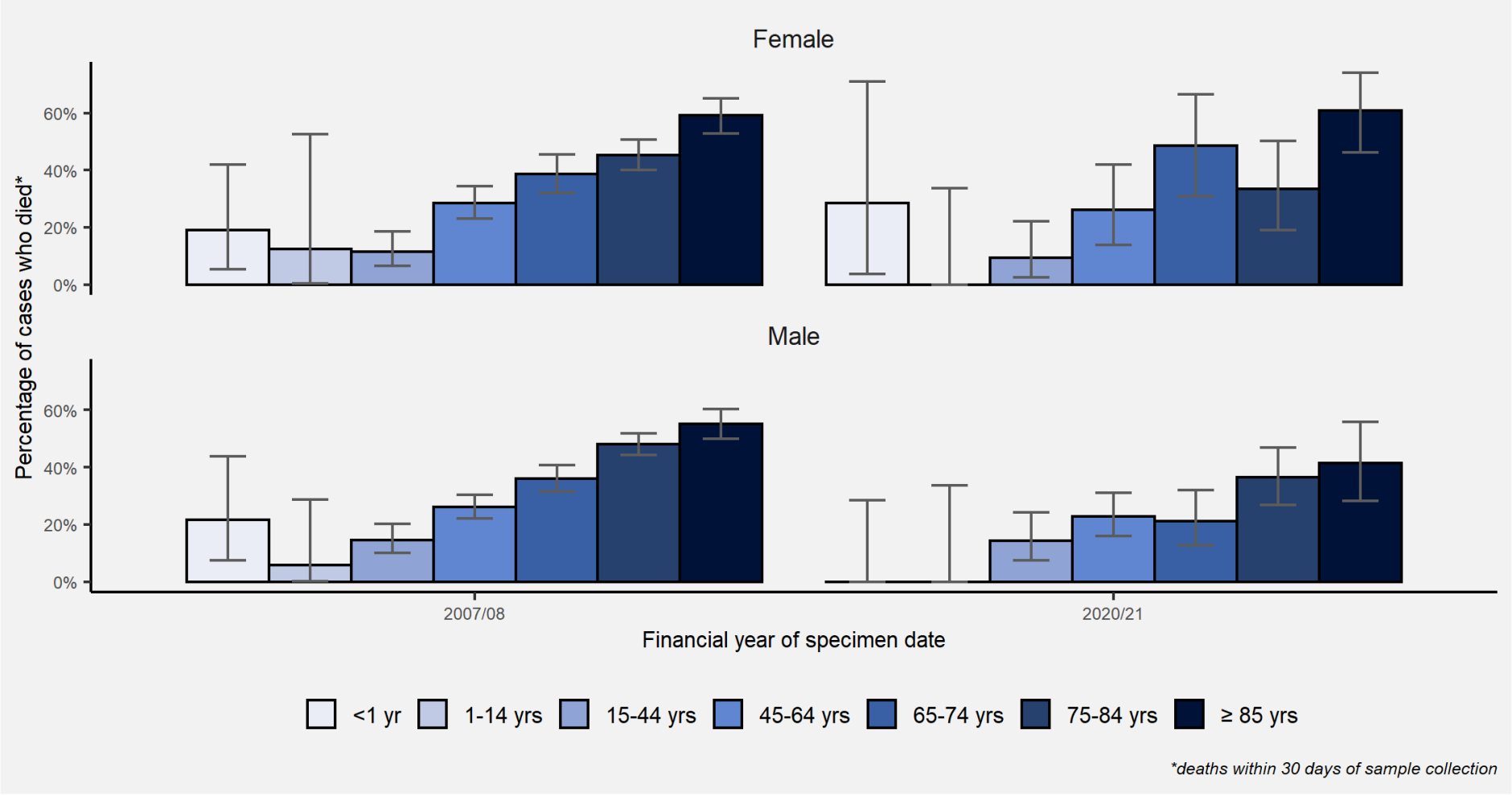


Figure 26. Thirty-day all-cause case fatality rate of MRSA bacteraemia by age and sex 2007/2008 to 2020/2021



MSSA bacteraemia

In 2020/2021, 11,696 MSSA bacteraemia cases were reported in England. Information on mortality was available for 97% (n= 11,374) of these cases (see Table S17 in the accompanying data sheet). There were 2,686 deaths within 30 days of an MSSA bacteraemia which gave an MR of 4.8 deaths per 100,000 population. The CFR was 23.6% of cases.

There was a declining trend in CFR starting from 21.5% in 2011/2012 to 19.1% in 2018/2019 (p=0.06) after which, the CFR then increased each year to 23.6% in the current financial year 2020/2021. The overall trend of MR increased from 3.3 deaths per 100,000 population in 2011/2012 to 4.0 in 2018/2019 to 4.8 in 2020/2021 (the highest MR since the start of mandatory surveillance). The overall difference in CFR between 2011/2012 and 2020/2021 was not statistically significant (p=0.09).

During the COVID-19 pandemic there was an increase in CFR (19.5% to 23.6%) in CFR between the previous financial year 2019/2020 (beginning-of-COVID-19) and the current financial year 2020/2021 (during COVID-19). Additionally, there was an increase (4.1 to 4.8 deaths per 100,000 population) in MR over the same period.

The different trend between 2019/2020 and 2020/2021 is likely a consequence of the COVID-19 pandemic. The increase CFR over this period was compounded by a considerable proportion of the 30-day all-cause deaths occurring in patients with a COVID-19 infection.

An analysis of patients with MSSA and a COVID-19 infection within 28 days before or after the infection found that a CFR of 45.0% (n= 741/1,648) compared with 20.1% (n = 1,965/9,764) among cases without a corresponding COVID-19 infection by the same patient within the 28 days before or after the MSSA case. This also means that 27.4% of 30-day all-cause deaths were in cases that had a corresponding COVID-19 infection as described above, suggesting that patients with COVID-19 infection were a considerable contribution to the increase in MSSA CFR for 2020/2021.

Variation by onset of bacteraemia

The CFR of HO cases increased from 26.7% in 2011/2012 to 28.2% in 2020/2021, while for CO cases it increased from 18.9% of cases in 2012/2013 to 21.8% in 2020/2021 (see Table S2 in the accompanying data sheet and Figure 4). The HO and CO CFR for this current year 2020/2021 (28.2% and 21.8%) is the highest recorded since its mandatory surveillance began. Though the CFR in HO and CO has shown a slow decrease from 2012/2013 to 2020/2021 the decrease was only constant from 2012/2013 until 2019/2020, which coincides with the start of the COVID-19 pandemic.

During the financial years influenced by the COVID-19 pandemic (2019/2020 and 2020/2021) the CFR for HO increased from 22.0% in 2019/2020 to 28.2% in 2020/2021. The same large increase was observed for the CO CFR increasing from 18.6% in 2019/2020 to 21.8% in 2020/2021.

In the same period, the MR of hospital-onset (HO) cases increased from 2.0 deaths per 100,000 bed-days (n= 708 deaths, 2019/2020) to 3.3 deaths per 100,000 bed-days (n= 916 deaths, 2020/2021) (see Table S2 in the accompanying data sheet and Figure 3). The same trend is observed with CO MR cases decreasing from 2.9 (n= 1,605 deaths, 2019/2020) to 3.1 deaths per 100,000 population (n= 1,770 deaths, 2020/2021) respectively.

The major trends observed pre-COVID-19 and during COVID-19 has shown the following for HO and CO. There was an increasing trend in HO CFR starting from 23.3% in 2018/2019 (pre-COVID-19) to 28.6% in the current financial year 2020/2021 (during COVID-19). The CFR for CO cases showed a similar trend increasing from 17.5% in 2018/2019 (pre-COVID-19) to 21.8% in the current financial year 2020/2021 (during COVID-19).

The trend observed in HO MR has increased from to 2.2 per 100,000 population in 2018/2019 (pre-COVID-19) to 3.3 per 100,000 population in 2020/2021 (during COVID-19). This pattern is identical for CO MR which has increased from 2.7 per 100,000 population in 2018/2019 (pre-COVID-19) to 3.1 in 2020/2021 (during COVID-19).

Notable observations for MSSA include the CFR HO increase from 22.0% (2019/202020) to 28.2% (2020/2021). This can be associated with the large CFR observed in the COVID-19 related cases (337 COVID-19 related deaths, and 690 COVID-19 related cases, CFR of 50.4%, difference of 27.4% as compared with the CFR of non-COVID-19 related deaths). The CO saw a less pronounced increase in CFR yet still increased from 18.6% (2019/2020) to 21.8% (2020/2021) difference of 3.2%. This increase in HO (6.1% increase) is nearly double that of CO (3.2% increase), with similar CFR in both COVID-19 related cases, suggesting that the increase in HO is not entirely explained by the introduction of COVID-19.

Figure 27. Thirty-day all-cause mortality rate of MSSA bacteraemia by onset of bacteraemia 2011/2012 to 2020/2021

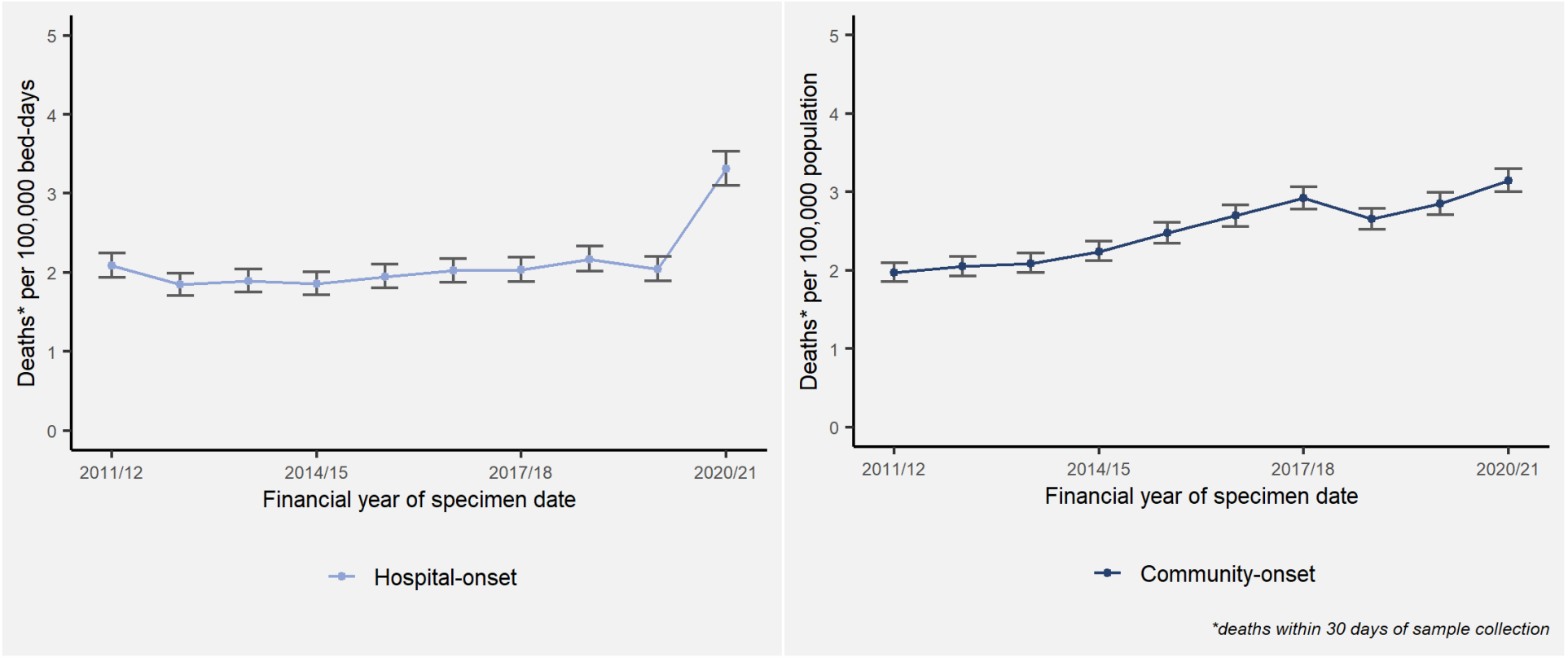
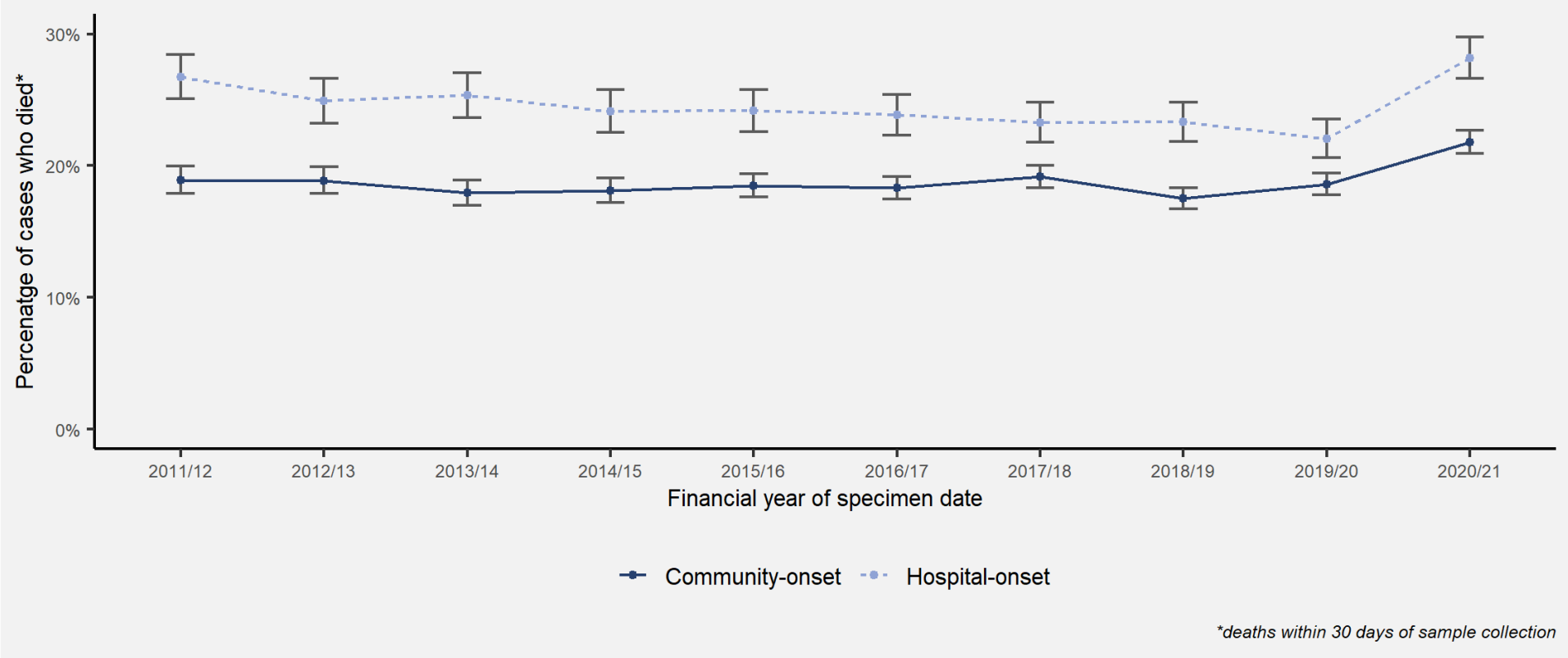


Figure 28. Thirty-day all-cause case fatality rate of MSSA bacteraemia by onset of bacteraemia 2011/2012 to 2020/2021



Variation by NHS commissioning region

In 2020/2021, regional MR ranged from 3.5 deaths per 100,000 population in London to 6.1 deaths per 100,000 population in the North East and Yorkshire (see Table S19 in the accompanying data sheet and Figure 29). Over the same period, CFRs ranged from 20.3% in London to 24.7% in the Midlands (see Table S19 in the accompanying data sheet and Figure 30).

For cases reported in 2020/2021, regression analysis as described in the method section of this report showed strong evidence of a significant difference[5] in regional mortality rates (see Appendix 3). There was no strong evidence[6] to suggest a significant difference in regional odds of deaths after infection (see Appendix 4).

[5] Strong evidence described as a statistically significant ($p < 0.05$) mortality rate ratio of ≥0.5.
[6] Strong evidence described as a statistically significant ($p < 0.05$) odds ratio of ≥0.25.

Figure 29. Thirty-day all-cause mortality rate of MSSA bacteraemia by NHS commissioning region 2011/2012 to 2020/2021

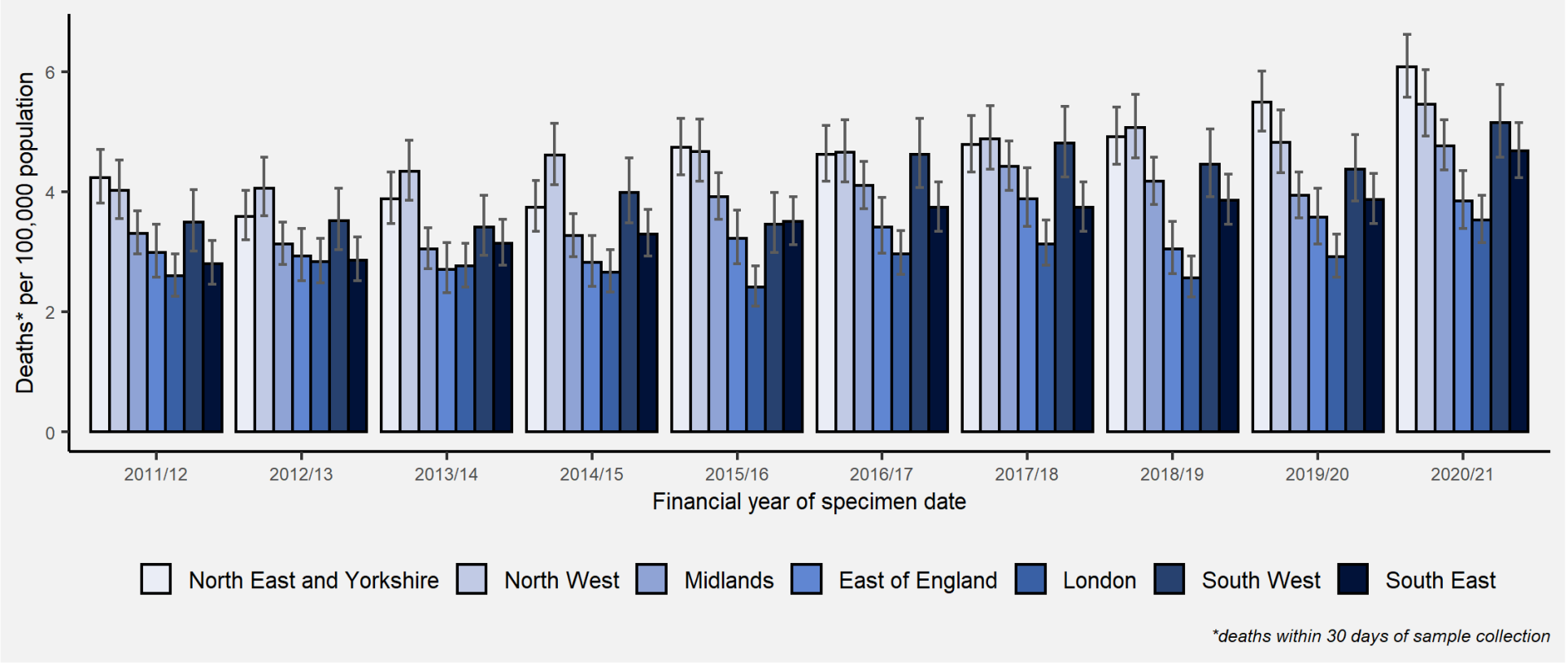
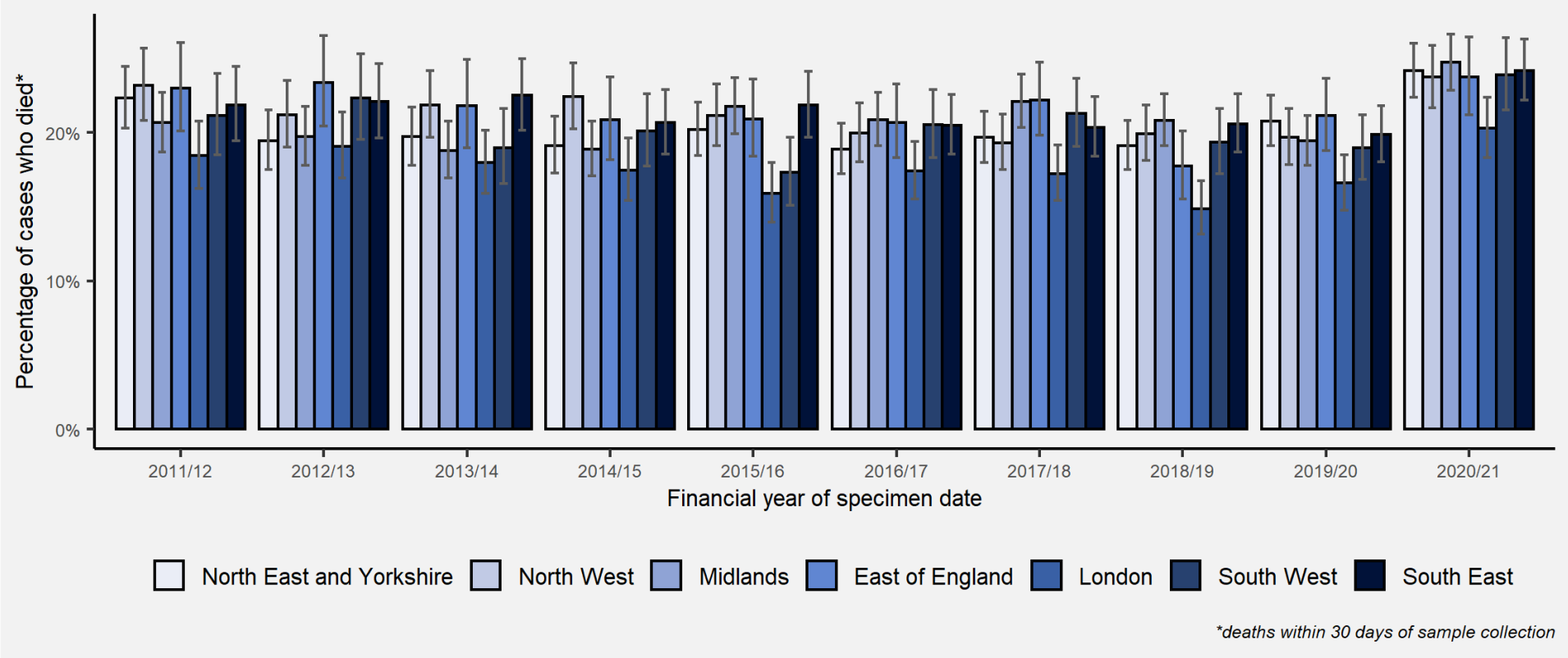


Figure 30. Thirty-day all-cause case fatality rate of MSSA bacteraeia by NHS commissioning region 2011/2012 to 2020/2021



Variation by age and sex

In 2020/2021, the MR and CFR increased with age. MR was greater in male patients while CFR was close to equal in both genders. (see Table S20 in the accompanying data sheet, Figure 31 and Figure 32).

Among male patients, the highest MRs were in the ≥85 year age group (82.2 deaths per 100,000 population) and the 75 to 84 year age group (30.2 deaths per 100,000 population) with CFRs of 45.1% and 34.2% respectively.

In female patients, the MRs were also higher in older age groups, 36.7 (≥85 year age group) and 15.4 (75 to 84 year age group). These equated to CFR of 44.7% and 34.8% of all cases in those respective age groups.

The MR in male patients under 1 year old was 3.1 deaths per 100,000 population (5.0% of cases) compared to 1.3 (4.0% of cases) in female patients.

Figure 31. Thirty-day all-cause mortality rate of MSSA bacteraemia by age and sex 2011/2012 to 2020/2021

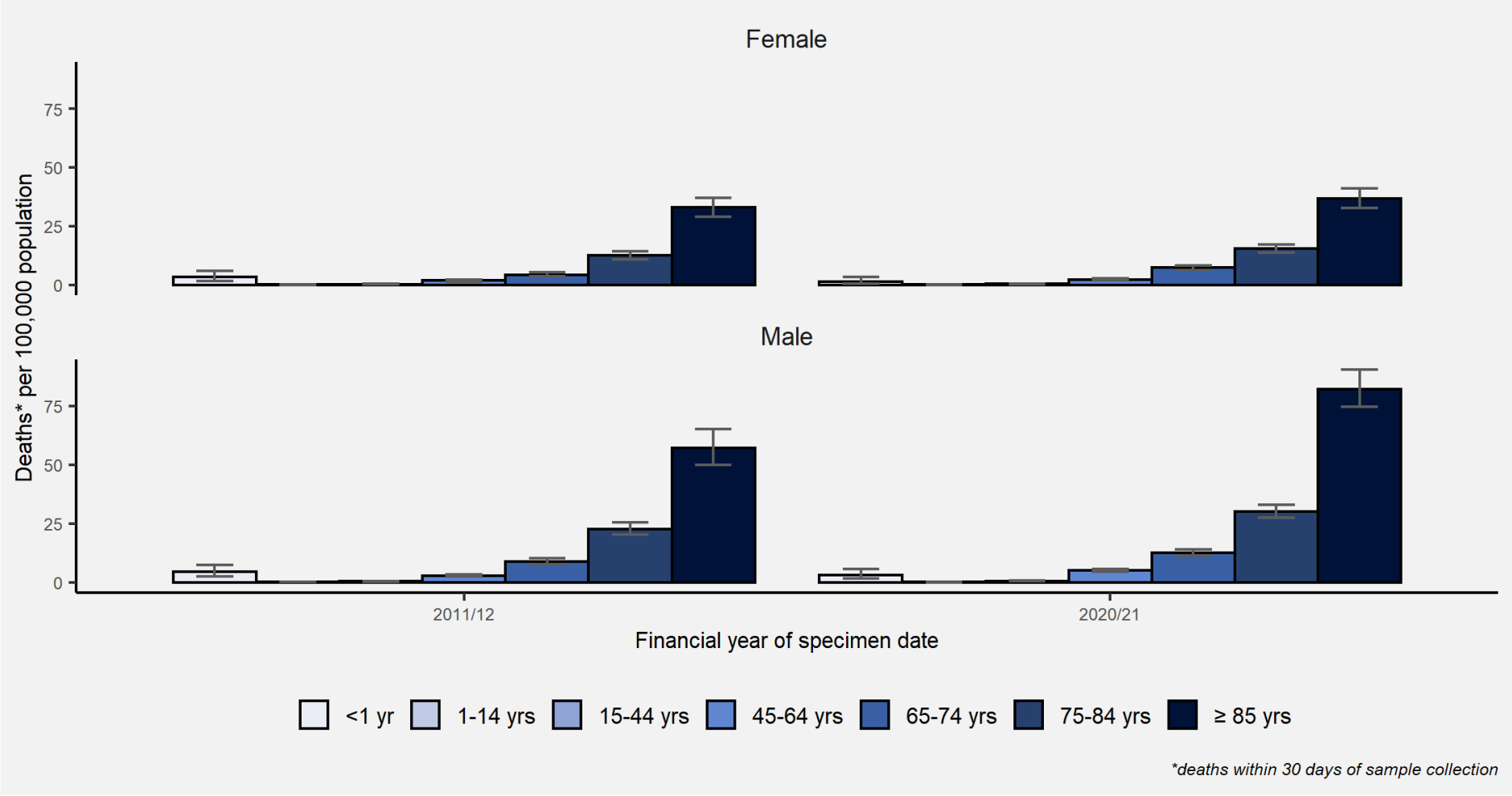
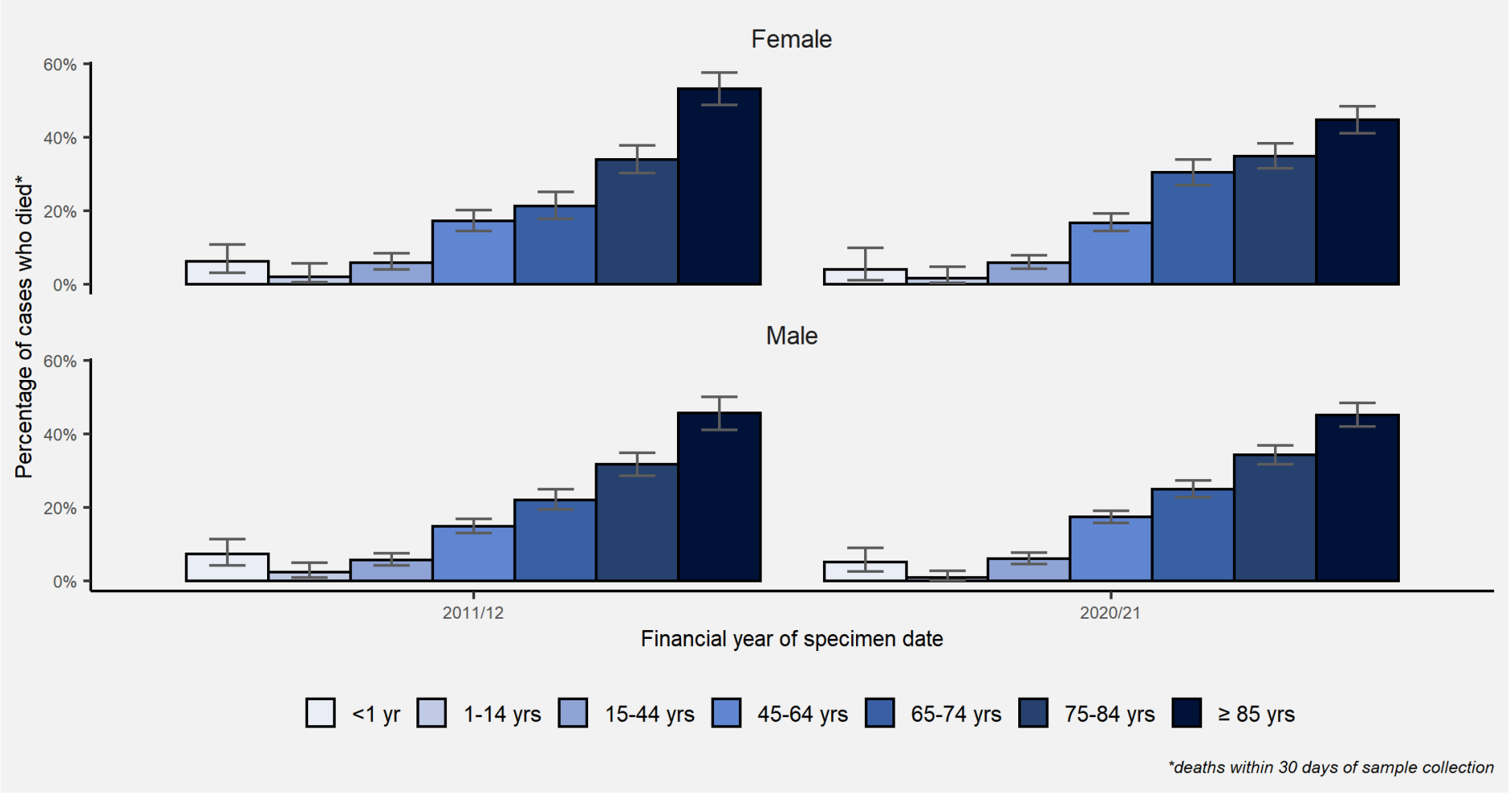


Figure 32. Thirty-day all-cause case fatality rate of MSSA bacteraemia by age and sex 2011/2012 to 2020/2021



Clostridioides difficile infection

In 2020/2021, 12,503 CDI cases were reported in England. Information on mortality was available for 98% (n= 12,273) of these cases (see Table S21 in the accompanying data sheet). There were 1,825 deaths within 30 days of a CDI case giving an MR of 3.2 deaths per 100,000 population. The CFR was 14.9% of cases.

There was a declining trend in CFR starting from 26.3% in 2007/2008 to 13.6% in 2018/2019 ($p<0.01$) after which, the CFR then increased to 14.9% in the current financial year 2020/2021. The overall trend of MR decreased from 27.1 deaths per 100,000 population in 2007/2008 to 2.9 deaths per 100,000 population in 2018/2019 before increasing to 3.2 in 2020/2021. The overall difference in CFR between 2007/2008 and 2020/2021 was statistically significant ($p<0.01$).

During the COVID-19 pandemic there was an increase in CFR (13.5% to 14.9%) in CFR between the previous financial year 2019/2020 (start of COVID-19) and the current financial year 2020/2021 (post COVID-19). Additionally, there was an increase (3.1 to 3.2 deaths per 100,000 population) in MR over the same period.

The different trend between 2019/2020 and 2020/2021 is likely a consequence of the COVID-19 pandemic. The increase CFR over this period was compounded by a considerable proportion of the 30-day all-cause deaths occurring in patients with a COVID-19 infection.

An analysis of patients with CDI and a COVID-19 infection within 28 days before or after the infection found that a CFR of 30.3% (n= 388/1,282) compared with 13.0% (n = 1,442 /11,094) among cases without a corresponding COVID-19 infection by the same patient within the 28 days before or after the CDI case. This also means that 21.2% of 30-day all-cause deaths were in cases that had a corresponding COVID-19 infection as described above, suggesting that patients with COVID-19 infection were a considerable contribution to the increase in CDI CFR for 2020/2021.

Variation by onset of bacteraemia

The CFR of HO cases decreased from 30.2% in 2007/2008 to 23.4% in 2020/2021, with CO cases also decreasing from 20.2% in 2007/2008 to 10.5% in 2020/2021 of cases (see Table S2 in the accompanying data sheet and Figure 4). The HO CFR this current year 2020/2021 (23.4%) is the highest recorded since 2013/2014. Though the CFR in HO and CO has shown a slow decrease from 2007/2008 to 2020/2021 the decrease was only constant from 2007/2008 until 2019/2020, which coincides with the start of the COVID-19 pandemic.

During the financial years influenced by the COVID-19 pandemic (2019/2020 and 2020/2021) the CFR for HO increased from 20.5% in 2019/2020 to 23.4% in 2020/2021. The increase was observed for the CO CFR increasing from 9.6% in 2019/2020 to 10.5% in 2020/2021. In the same period, the MR of hospital-onset (HO) cases increased from 1.4 deaths per 100,000 bed-days (n= 794 deaths, 2019/2020) to 1.5 deaths per 100,000 bed-days (n= 851

deaths, 2020/2021) (see Table S2 in the accompanying data sheet and Figure 3). The same trend is observed with CO MR cases increasing from 1.4 (n= 794 deaths, 2019/2020) to 1.5 deaths per 100,000 population (n= 851 deaths, 2020/2021) respectively.

The major trends observed pre-COVID-19 and during COVID-19 have shown the following for HO and CO. There was a declining trend in HO CFR starting from 21.4% in 2018/2019 (pre-COVID-19) to 23.4% in the current financial year 2020/2021 (during COVID-19). The CFR for CO cases showed a similar trend increasing from 9.5% in 2018/2019 (pre-COVID-19), to 10.5% in the current financial year 2020/2021 (during COVID-19).

The trend observed in HO MR has increased from 2.5 per 100,000 population in 2018/2019 (pre-COVID-19) to 3.5 per 100,000 population in 2020/2021 (during COVID-19). This pattern is identical for CO MR which has increased from 1.3 2018/2019 (pre-COVID-19) to 1.5 per 100,000 population in 2020/2021 (during COVID-19).

Figure 33. Thirty-day all-cause mortality rate of CDI by onset of infections 2007/2008 to 2020/2021

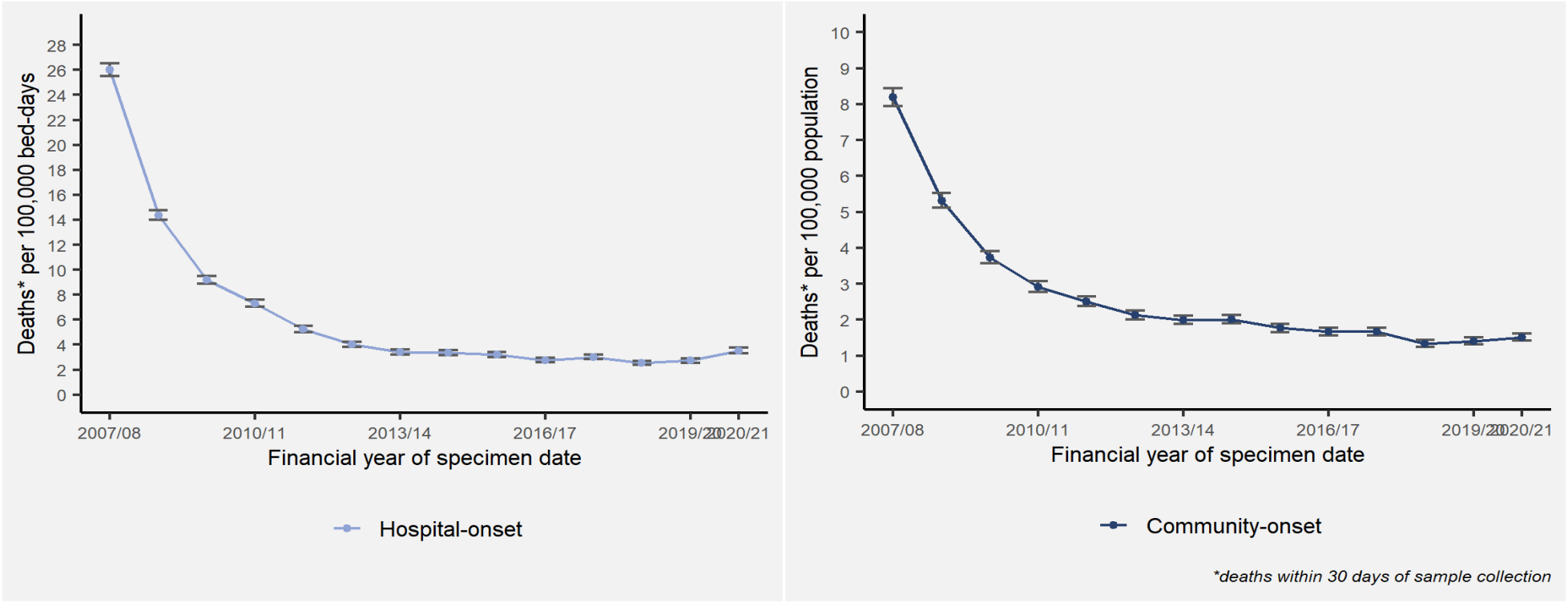
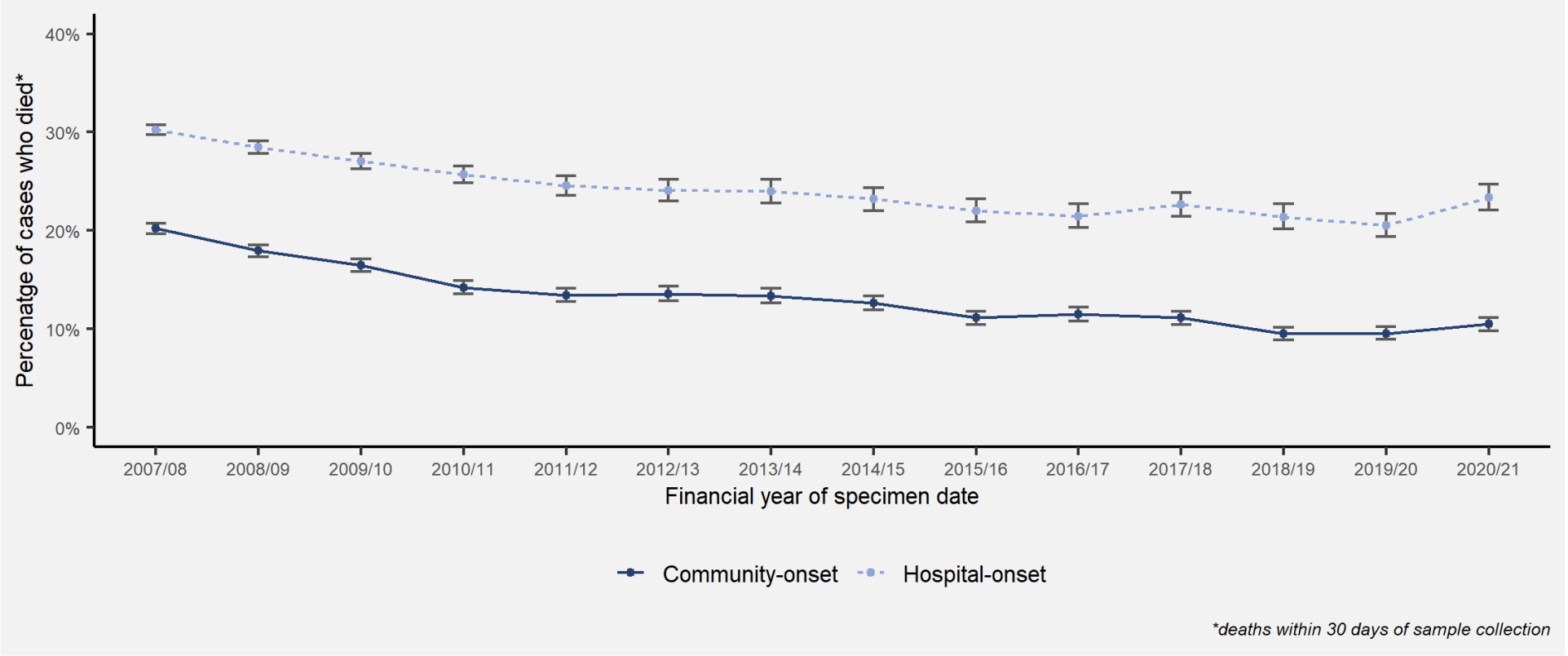


Figure 34. Thirty-day all-cause case fatality rate of CDI by onset of infections 2007/2008 to 2020/2021

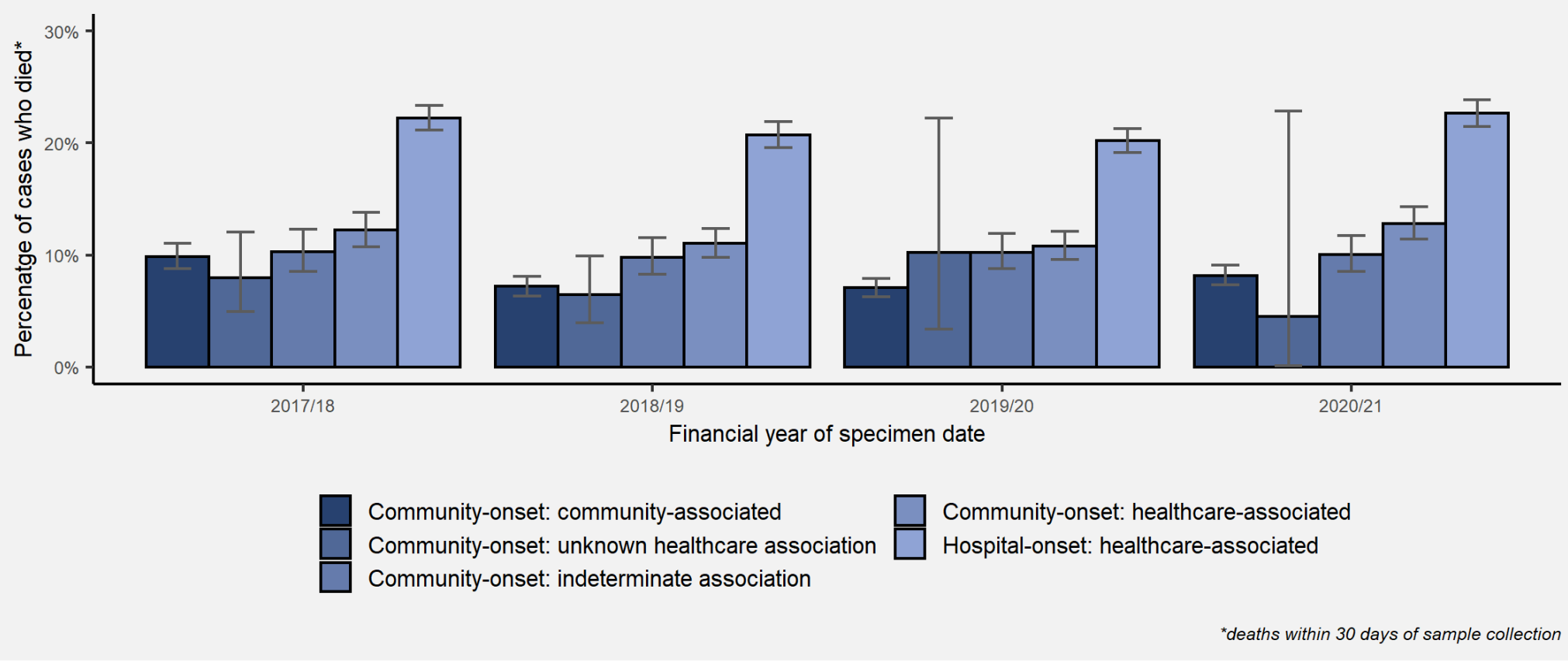


Variation by prior healthcare exposure

The categorisation of CDI cases based on prior healthcare exposure began in 2017/2018. In 2020/2021, the MRs were 3.9 deaths per 100,000 bed-days for HO: healthcare-associated cases and 0.9 deaths per 100,000 bed-days plus day-admissions for CO: healthcare-associated cases. In the same financial year it was 0.6 deaths per 100,000 population for CO: community-associated cases, 0.3 for CO: indeterminate association cases and <0.1 for CO onset: unknown healthcare association cases (see Table S23 in the accompanying data sheet).

The CFRs were 22.7% for HO: healthcare-associated cases, 12.8% for CO: healthcare-associated cases, 8.2% for CO: community-associated cases, 10.0% for CO: indeterminate association cases and 4.5% for CO: unknown healthcare association cases (see Table S23 in the accompanying data sheet).

Figure 35. Thirty-day all-cause case fatality rate of CDI by prior healthcare exposure 2007/2008 to 2020/2021



Variation by NHS commissioning region

In 2020/2021, regional MR ranged from 2.3 deaths per 100,000 population in London to 4.8 deaths per 100,000 population in the North West (see Table S24 in the accompanying data sheet and Figure 36). Over the same period, CFRs ranged 12.9% in the South West to 17.0% in the North West (see Table S24 in the accompanying data sheet and Figure 37).

The area with the highest differences in RR are found between the North West and the South East (RR: 2.10, $p < 0.01$) with the lowest being the inverse (see Appendix 3).

There was no strong evidence[7] to suggest significant differences in regional odds of deaths, except between the Midlands and the North West (OR: 1.26, $p = 0.01$), the North West and the South West (OR: 0.72, $p < 0.01$) and the South East (OR: 0.74, $p < 0.01$), the South East and the North East and Yorkshire (OR: 1.25, $p = 0.02$) and the East (OR: 1.29, $p = 0.01$) and the South West and the North East and Yorkshire (OR: 1.29, $p = 0.01$), London (OR: 1.27, $p = 0.04$) and the East (OR: 1.33, $p = 0.01$) (see Appendix 4).

[7] Strong evidence described as a statistically significant ($p< 0.05$) odds ratio of ≥0.25.

Figure 36. Thirty-day all-cause mortality rate of CDI by NHS commissioning region 2007/2008 to 2020/2021

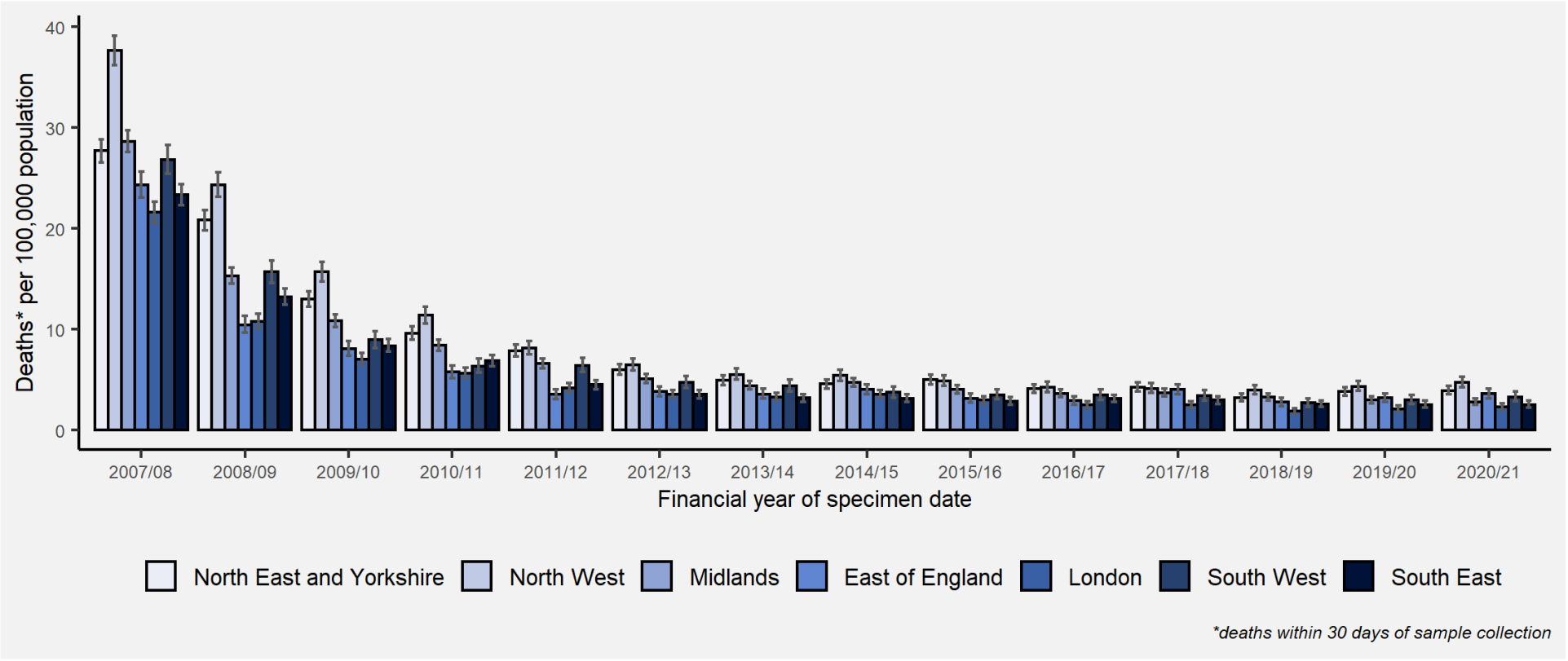
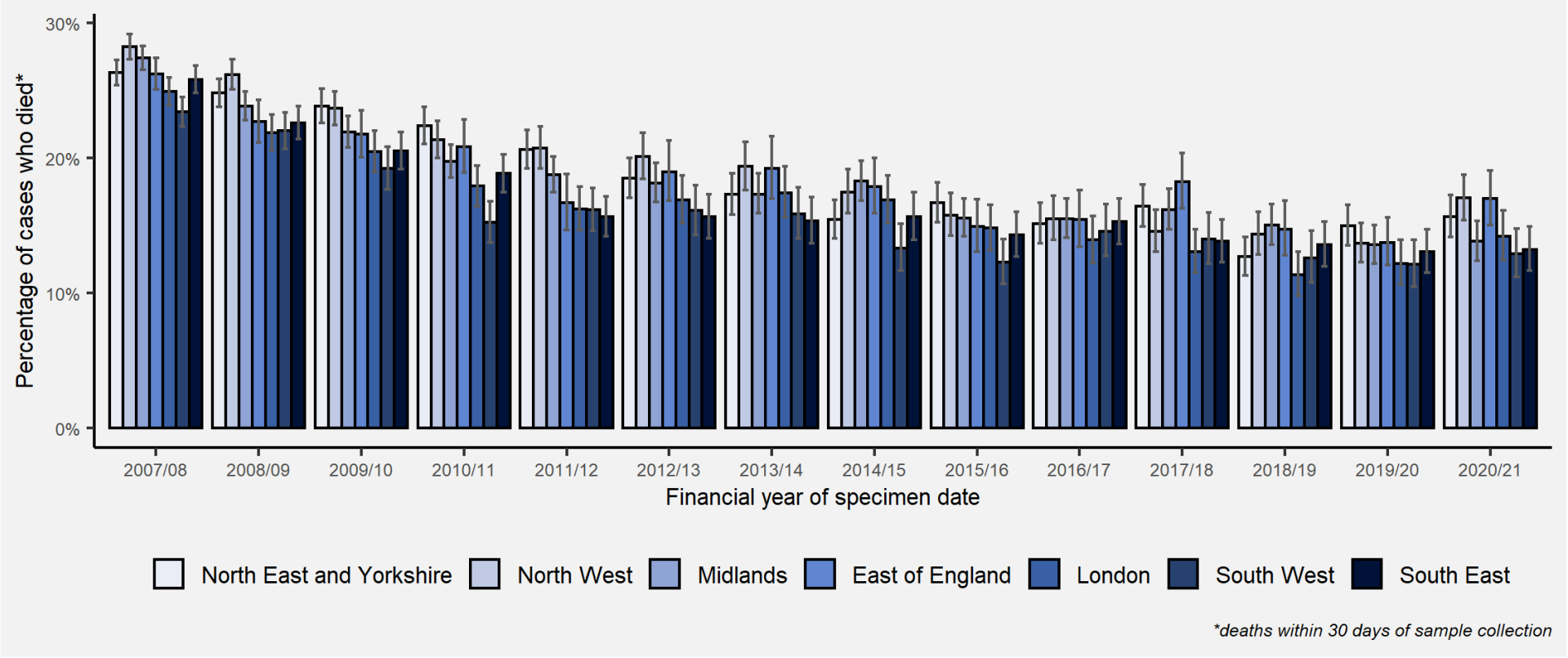


Figure 37. Thirty-day all-cause case fatality rate of CDI by NHS commissioning region 2007/2008 to 2020/2021



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. (see Table S25 in the accompanying data sheet, Figure 38 and Figure 39).

Among male patients, the highest MRs were in the ≥85 year age group (56.5 deaths per 100,000 population) and the 75 to 84 year age group (20.4 deaths per 100,000 population), linked to 26.8% and 20.2% respectively.

In female patients, the MRs were also higher in older age groups, 47.8 (≥85 year age group) and 14.2 (75 to 84 year age group). These equated to CFRs of 23.3% and 13.9% of all cases in those respective age groups.

Figure 38. Thirty-day all-cause mortality rate of CDI by age and sex 2007/2008 to 2020/2021

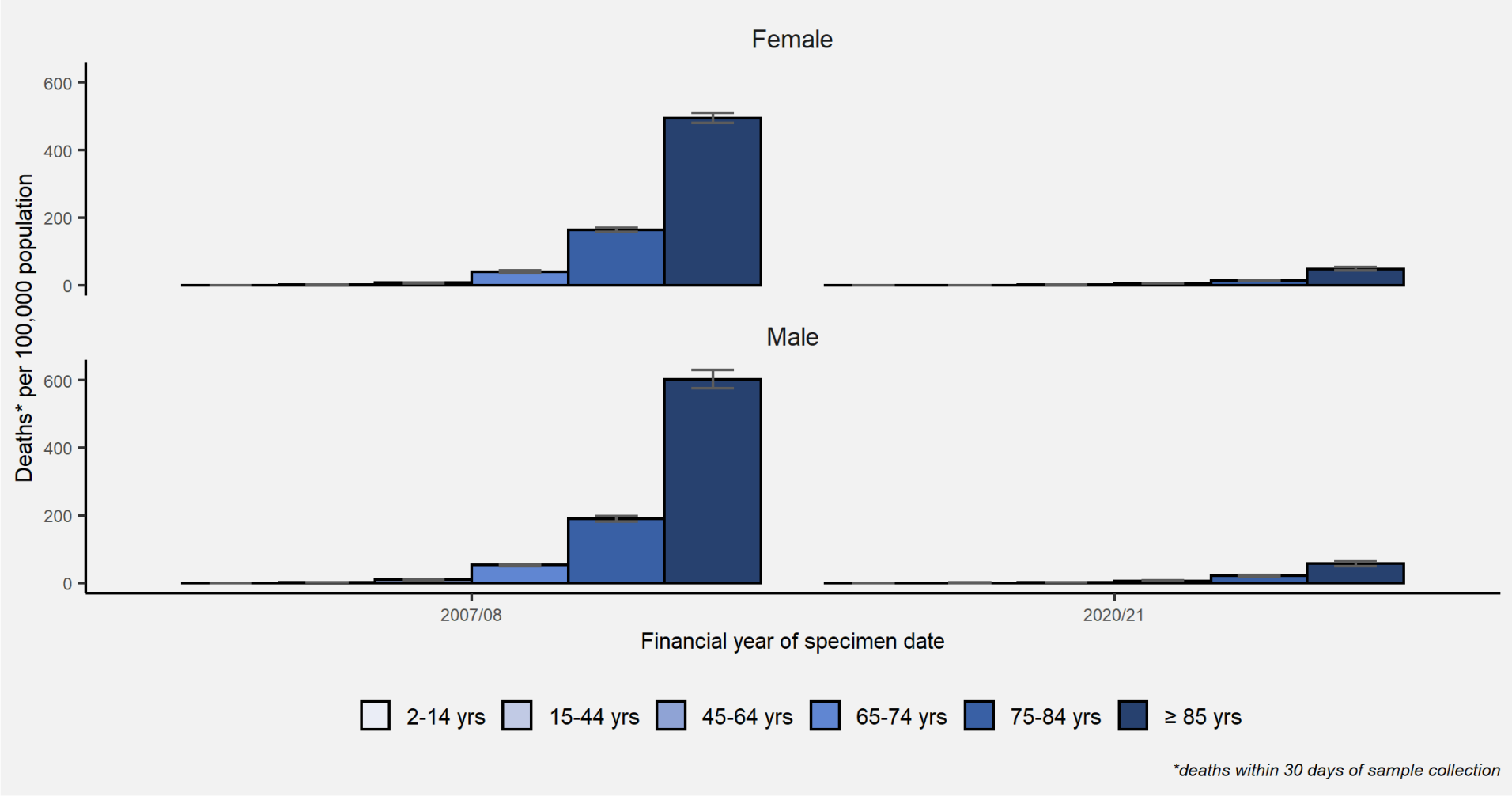
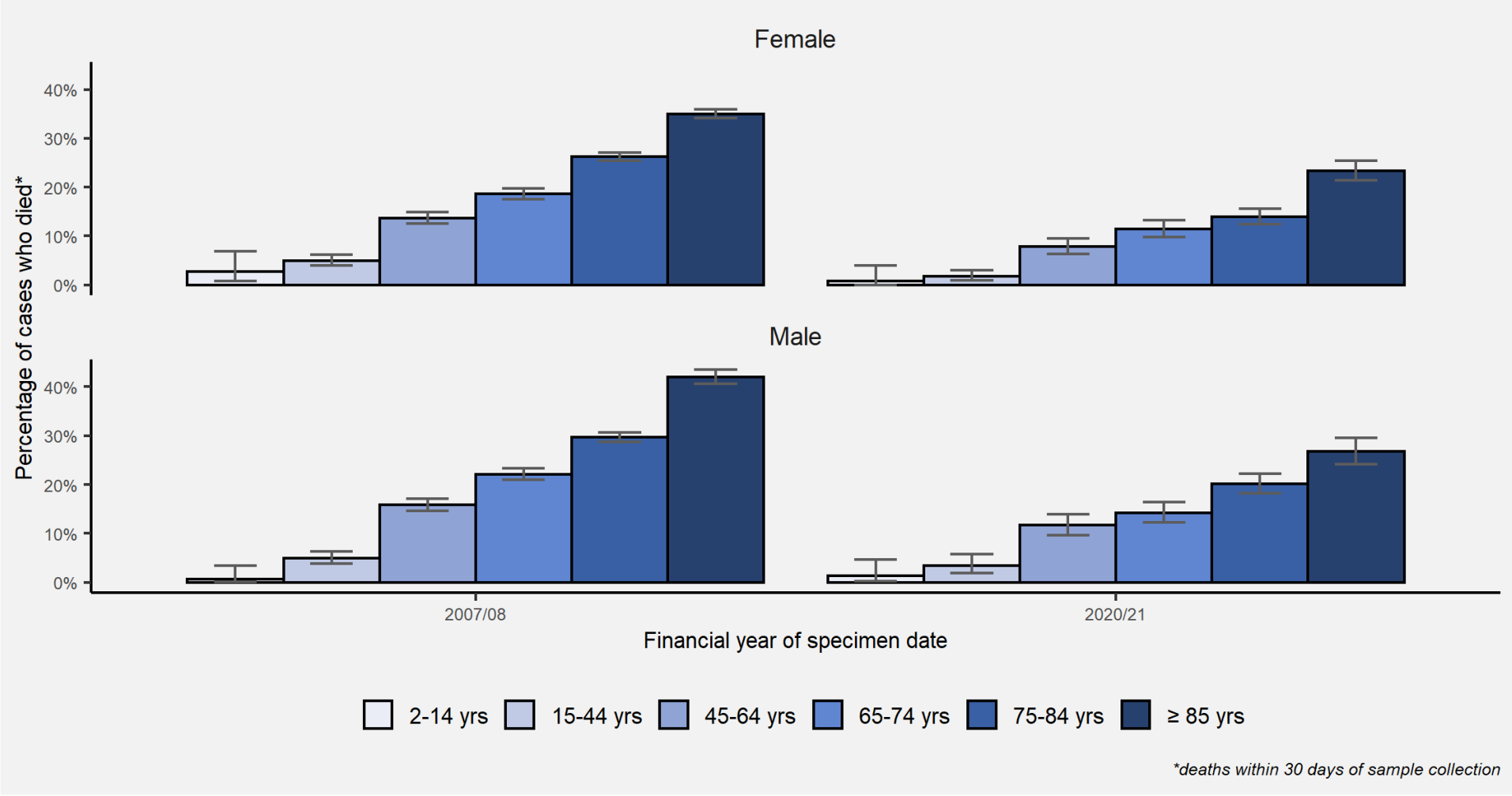


Figure 39. Thirty-day all-cause case fatality rate of CDI by age and sex 2007/2008 to 2020/2021



Discussion

Overall, the percentage of patients that died (CFR) following each infection-bearing MSSA covered by this report has declined over time until 2019/2020 (Figure 2) despite instances of increasing incidence of deaths (MR) in infections like *E. coli* bacteraemia (Figure 1). However, there have been increases in CFR in 2019/2020 and 2020/2021, particularly among HO cases.

These changes in CFR for all reported cases of *E. coli* and *Klebsiella* spp. cases were statistically significant ($p < 0.05$). Supplementary analysis has shown that these increases are in part due to a considerable proportion of all-cause deaths among patients with HO BSI or CD I who also had a COVID-19 infection within 28 days either side of the onset of bacterial infections.

In total we found that 19.5% (*E. coli*) to 36.8% (MRSA) of the all-cause deaths in these infections were from patients that had a positive COVID-19 infection within 28 days prior to or after the BSI or CDI's specimen date during January 2020 to March 2021. In total 11.8% of all cases also had a COVID-19 infection, while 23.4% of all deaths also has COVID-19 infection. For each infection, this ranged from 9.7% of all E.coli cases to 22.0% of all MRSA cases, and 19.5% of all E.coli deaths to 36.8% of all MRSA deaths. To put these percentages in perspective the number of patients admitted for COVID-19 during this period was 373,486 out of 3,767,207 (9.9%) COVID-19 cases (15). Also, as there were 5,034,746 emergency admissions during this period, COVID-19 cases would have accounted for roughly 7.4% of these admissions. Note this is an approximation based on the difference between unlinked aggregate admission counts and the assumption that most COVID-19 admissions would have been via accident and emergency.

The HO cases and deaths that had a COVID-19 episode within 28 days of bacterial specimen date were as follows: Total CDI 247 deaths of 786 cases associated with COVID-19 (CFR: 31.4%) as compared with 730 deaths of 3,474 non COVID-19 related cases (CFR: 21.0%), *E. coli* 415 deaths of 1,105 cases associated with COVID-19 (CFR: 37.6%) as compared with 1,052 deaths of 5,292 non COVID-19 related cases (CFR: 19.9%), *Klebsiella* spp. 444 deaths of 1,014 cases associated with COVID-19 (CFR: 43.8%) as compared with 556 deaths of 2,763 non COVID-19 related cases (CFR: 20.9%), MRSA 44 deaths of 88 cases associated with COVID-19 (CFR: 50.0%) as compared with 49 deaths of 191 non COVID-19 related cases (CFR: 25.7%), MSSA 337 deaths of 669 cases associated with COVID-19 (CFR: 50.4%) as compared with 597 deaths of 2,604 non COVID-19 related cases (CFR: 22.9%), *Pseudomonas* spp. 204 deaths of 386 cases associated with COVID-19 (CFR: 52.8%) as compared with 349 deaths of 1,245 non COVID-19 related cases (CFR: 28.0%).

The overall declining trend of CFRs for CDI and MRSA bacteraemia is indicative of the change in their epidemiology over the years. During this period, the incidence of these

infections declined, and both have shown a shift from predominantly HO infections to CO cases. Since mortality and morbidity are often higher in HO (a proxy for healthcare-acquired) cases compared to CO 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, see Table S14 and Table S22 in the accompanying data sheet).

The large decline in CFR following CDI may also 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 ribotype (10).

A substantial proportion of CO CDI cases will have had prior healthcare interactions (with emphasis on older cases), and thus more likely to have a higher CFR associated with healthcare associated infection, although greater likelihood of underlying conditions predisposing this group to increased risk of death cannot be discounted. CFR analysis showed higher CFR in the healthcare-associated cases HO: healthcare-associated (22.7%) and CO: healthcare-associated (12.8%) and CO: community-associated (8.2%) in 2020/2021 (see Table S23 in the accompanying data sheet and Figure 35).

There was a noticeable increase in the CFR of MRSA bacteraemia in 2012/2013. This may be related to an excess in all-cause deaths associated with respiratory causes noted during the winter of 2012/2013 (11). However, this was set against the general downward trend observed in CFR. Furthermore, the confidence intervals for the CFR in 2012/2013 overlap with those of the surrounding years, thus suggesting that differences between 2012/2013 and surrounding years could have occurred by chance.

In general, for all pathogens, CFRs increased with age except in patients aged less than one year, where CFRs were usually higher than patients aged 1 to 14 years old, and in some cases compared to patients aged 15 to 44 years old. 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 UKHSA (see Appendix 1).

CFRs for CDI and *E. coli* bacteraemia were generally higher in male patients compared to female patients, while MRSA, MSSA and *P. aeruginosa* bacteraemia were generally higher in female patients compared to male patients.

In 2020/2021, the largest CFR, were in MRSA (28.2%) and *P. aeruginosa* bacteraemia (27.7%). The CFR of *E. coli* bacteraemia (16.0%) was relatively small compared to those for MRSA and *P. aeruginosa* bacteraemia. However, its higher incidence of infection, and deaths following infection (MR: 10.2 deaths per 100,000 population) compared to MRSA (MR: 0.3 deaths per 100,000 population) and *P. aeruginosa* bacteraemia (MR: 2.1 deaths per 100,000 population) highlights the public health burden of this infection. Thus, the continued increase in mortality rates following *E. coli* bacteraemia is of particular concern. In 2020/2021, there

were 5,750 deaths within 30 days of *E. coli* bacteraemia, over 4 times the number of deaths following MRSA bacteraemia at the start of mandatory surveillance (2007/2008, 1,354) when MRSA bacteraemia cases were at its highest levels. Despite the high mortality rates, the CFR for *E. coli* bacteraemia remains low.

In 2020/2021, all CFR have increased as compared with the previous financial year, especially in MSSA, *Klebsiella* spp. and *P. aeruginosa*. CFRs were the highest ever observed for these species.

The cumulative impact of the COVID-19 pandemic on the health sector has been extensive, affecting all areas, from direct acute care and admissions to mental health and policy. COVID-19, due to its severity, particularly prior to the vaccine roll-out, will have drastically increased hospitalisations and thus increased the likelihood of HO BSI and CDI cases arising. It is noted that severe viral infections reduce the reaction of the host innate immunity against bacterial infections and enhanced susceptibility to secondary infections. SARS-CoV-2 being a severe respiratory disease is thought to contribute to poor patient outcomes, particularly in vulnerable patients such as those with pre-existing conditions or co-morbidities. To explore this, we conducted supplementary analysis on the mortality, which showed cases occurring within 27 days after or before a COVID-19 infection had a higher CFR than cases where no COVID-19 infection was reported. Among bacteraemia and CDI cases the CFR is on average 26.5% greater than their non-related counterparts (highest being MSSA being 24.8% greater and lowest CDI being 17.2% greater).

A separate analysis not included in the report, found that the age and sex distribution of 30-day-all cause mortality deaths were similar among cases covered in this report, where the patient also had a COVID-19 infection within 28 days before or after the HCAI case's specimen date. Please note that this is analysis of all-cause mortality and cause of death can't be attributed to a particular causative agent.

Limitations

The analyses presented here are based on infections reported to UKHSA 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 some reports the NHS Spine was not able to return patient information. This was due to, 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, this effect on reported outcomes is likely to be low, since the linkage had a high degree of completeness, at around 96% of all cases.

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.

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.

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.

Future plans for analysis following this report include:

- understanding the additional burden COVID-19 has on mortality for *E.coli*, *Klebsiella* spp., Pseudomonas bacteraemia, MRSA, MSSA and *C. difficile*
- understanding the mix of cases of *E.coli*, *Klebsiella* spp., *Pseudomonas* bacteraemia, MRSA, MSSA and *C. difficile* during the COVID-19 pandemic

Appendices

Appendix 1. Figures included in this report

Appendix 2. List of tables

This is a list of tables which can found in the accompanying data sheet:

Appendix 3. Age-sex adjusted regional mortality rate ratios

***E. coli* bacteraemia**

Region	Reference						
Region	**East**	**London**	**Midlands**	**North East and Yorkshire**	**North West**	**South East**	**South West**
East	1	1.23, p = 0.01	1.31, p < 0.01	1.46, p < 0.01	1.27, p < 0.01	1.03, p = 0.66	0.87, p = 0.08
London	0.82, p = 0.01	1	1.07, p = 0.30	1.19, p = 0.01	1.03, p = 0.63	0.84, p = 0.01	0.71, p < 0.01
Midlands	0.76, p < 0.01	0.94, p = 0.30	1	1.12, p = 0.04	0.97, p = 0.60	0.79, p < 0.01	0.66, p < 0.01
North East and Yorkshire	0.68, p < 0.01	0.84, p = 0.01	0.90, p = 0.04	1	0.87, p = 0.02	0.71, p < 0.01	0.59, p < 0.01
North West	0.79, p < 0.01	0.97, p = 0.63	1.03, p = 0.60	1.15, p = 0.02	1	0.81, p < 0.01	0.68, p < 0.01
South East	0.97, p = 0.66	1.19, p = 0.01	1.27, p < 0.01	1.42, p < 0.01	1.23, p < 0.01	1	0.84, p = 0.02
South West	1.15, p = 0.08	1.41, p < 0.01	1.51, p < 0.01	1.68, p < 0.01	1.46, p < 0.01	1.19, p = 0.02	1

***Klebsiella* spp. bacteraemia**

Region	Reference						
Region	**East**	**London**	**Midlands**	**North East and Yorkshire**	**North West**	**South East**	**South West**
East	1	1.92, p < 0.01	1.10, p = 0.41	1.31, p = 0.02	1.15, p = 0.26	1.00, p = 0.97	0.74, p = 0.04
London	0.52, p < 0.01	1	0.57, p < 0.01	0.68, p < 0.01	0.60, p < 0.01	0.52, p < 0.01	0.39, p < 0.01

Region	Reference						
Region	**East**	**London**	**Midlands**	**North East and Yorkshire**	**North West**	**South East**	**South West**
Midlands	0.91, p = 0.41	1.75, p < 0.01	1	1.20, p = 0.07	1.05, p = 0.67	0.91, p = 0.35	0.68, p < 0.01
North East and Yorkshire	0.76, p = 0.02	1.46, p < 0.01	0.84, p = 0.07	1	0.87, p = 0.22	0.76, p = 0.01	0.57, p < 0.01
North West	0.87, p = 0.26	1.67, p < 0.01	0.95, p = 0.67	1.14, p = 0.22	1	0.87, p = 0.21	0.65, p < 0.01
South East	1.00, p = 0.97	1.93, p < 0.01	1.10, p = 0.35	1.32, p = 0.01	1.15, p = 0.21	1	0.75, p = 0.03
South West	1.34, p = 0.04	2.58, p < 0.01	1.47, p < 0.01	1.77, p < 0.01	1.54, p < 0.01	1.34, p = 0.03	1

***P. aeruginosa* bacteraemia**

Region	Reference						
	East	**London**	**Midlands**	**North East and Yorkshire**	**North West**	**South East**	**South West**
East	1	2.41, p < 0.01	1.41, p = 0.03	1.33, p = 0.09	1.23, p = 0.23	1.52, p = 0.01	0.75, p = 0.16
London	0.42, p < 0.01	1	0.59, p < 0.01	0.55, p < 0.01	0.51, p < 0.01	0.63, p < 0.01	0.31, p < 0.01
Midlands	0.71, p = 0.03	1.71, p < 0.01	1	0.94, p = 0.65	0.87, p = 0.36	1.08, p = 0.55	0.53, p < 0.01
North East and Yorkshire	0.75, p = 0.09	1.81, p < 0.01	1.06, p = 0.65	1	0.93, p = 0.62	1.14, p = 0.32	0.57, p < 0.01
North West	0.81, p = 0.23	1.95, p < 0.01	1.14, p = 0.36	1.08, p = 0.62	1	1.23, p = 0.16	0.61, p = 0.01
South East	0.66, p = 0.01	1.58, p < 0.01	0.93, p = 0.55	0.87, p = 0.32	0.81, p = 0.16	1	0.49, p < 0.01

Region	Reference						
	East	London	Midlands	North East and Yorkshire	North West	South East	South West
South West	1.33, p = 0.16	3.20, p < 0.01	1.88, p < 0.01	1.77, p < 0.01	1.64, p = 0.01	2.02, p < 0.01	1

MRSA bacteraemia

Region	Reference						
	East	London	Midlands	North East and Yorkshire	North West	South East	South West
East	1	1.71, p = 0.09	0.86, p = 0.64	0.86, p = 0.66	1.74, p = 0.08	0.97, p = 0.91	0.80, p = 0.57
London	0.58, p = 0.09	1	0.50, p = 0.02	0.50, p = 0.03	1.02, p = 0.95	0.56, p = 0.05	0.47, p = 0.03
Midlands	1.17, p = 0.64	2.00, p = 0.02	1	1.01, p = 0.99	2.04, p = 0.02	1.13, p = 0.69	0.94, p = 0.86
North East and Yorkshire	1.16, p = 0.66	1.99, p = 0.03	0.99, p = 0.99	1	2.03, p = 0.02	1.12, p = 0.72	0.93, p = 0.86
North West	0.57, p = 0.08	0.98, p = 0.95	0.49, p = 0.02	0.49, p = 0.02	1	0.55, p = 0.04	0.46, p = 0.03
South East	1.04, p = 0.91	1.78, p = 0.05	0.89, p = 0.69	0.89, p = 0.72	1.81, p = 0.04	1	0.83, p = 0.61
South West	1.24, p = 0.57	2.13, p = 0.03	1.06, p = 0.86	1.07, p = 0.86	2.17, p = 0.03	1.20, p = 0.61	1

MSSA bacteraemia

Region	Reference						
	East	London	Midlands	North East and Yorkshire	North West	South East	South West
East	1	1.34, p < 0.01	1.29, p = 0.01	1.65, p < 0.01	1.52, p < 0.01	1.20, p = 0.05	1.22, p = 0.05
London	0.74, p < 0.01	1	0.96, p = 0.62	1.22, p = 0.02	1.13, p = 0.17	0.89, p = 0.19	0.90, p = 0.28
Midlands	0.77, p = 0.01	1.04, p = 0.62	1	1.27, p < 0.01	1.18, p = 0.04	0.93, p = 0.35	0.94, p = 0.48
North East and Yorkshire	0.61, p < 0.01	0.82, p = 0.02	0.78, p < 0.01	1	0.92, p = 0.30	0.73, p < 0.01	0.74, p < 0.01
North West	0.66, p < 0.01	0.89, p = 0.17	0.85, p = 0.04	1.08, p = 0.30	1	0.79, p = 0.01	0.80, p = 0.02
South East	0.83, p = 0.05	1.12, p = 0.19	1.07, p = 0.35	1.37, p < 0.01	1.26, p = 0.01	1	1.01, p = 0.89
South West	0.82, p = 0.05	1.11, p = 0.28	1.06, p = 0.48	1.35, p < 0.01	1.25, p = 0.02	0.99, p = 0.89	1

CDI

Region	Reference						
	East	London	Midlands	North East and Yorkshire	North West	South East	South West
East	1	0.98, p = 0.85	0.82, p = 0.05	1.14, p = 0.18	1.44, p < 0.01	0.68, p < 0.01	0.81, p = 0.06
London	1.02, p = 0.85	1	0.84, p = 0.09	1.16, p = 0.14	1.47, p < 0.01	0.70, p < 0.01	0.83, p = 0.10
Midlands	1.22, p = 0.05	1.19, p = 0.09	1	1.38, p < 0.01	1.75, p < 0.01	0.83, p = 0.07	0.99, p = 0.89

Region	**Reference**						
	East	**London**	**Midlands**	**North East and Yorkshire**	**North West**	**South East**	**South West**
North East and Yorkshire	0.88, p = 0.18	0.86, p = 0.14	0.72, p < 0.01	1	1.26, p = 0.01	0.60, p < 0.01	0.71, p < 0.01
North West	0.70, p < 0.01	0.68, p < 0.01	0.57, p < 0.01	0.79, p = 0.01	1	0.48, p < 0.01	0.56, p < 0.01
South East	1.46, p < 0.01	1.43, p < 0.01	1.20, p = 0.07	1.66, p < 0.01	2.10, p < 0.01	1	1.19, p = 0.13
South West	1.23, p = 0.06	1.21, p = 0.10	1.01, p = 0.89	1.40, p < 0.01	1.77, p < 0.01	0.84, p = 0.13	1

Appendix 4. Age-sex adjusted regional odds ratios

***E. coli* bacteraemia**

Region	Reference						
	East	London	Midlands	North East and Yorkshire	North West	South East	South West
East	1	0.98, p = 0.76	1.17, p < 0.01	1.10, p = 0.09	1.07, p = 0.29	0.97, p = 0.59	0.78, p < 0.01
London	1.02, p = 0.76	1	1.20, p < 0.01	1.12, p = 0.04	1.08, p = 0.16	0.99, p = 0.82	0.79, p < 0.01
Midlands	0.85, p < 0.01	0.84, p < 0.01	1	0.94, p = 0.15	0.91, p = 0.06	0.83, p < 0.01	0.66, p < 0.01
North East and Yorkshire	0.91, p = 0.09	0.89, p = 0.04	1.07, p = 0.15	1	0.97, p = 0.56	0.88, p = 0.01	0.71, p < 0.01
North West	0.94, p = 0.29	0.92, p = 0.16	1.10, p = 0.06	1.03, p = 0.56	1	0.91, p = 0.08	0.73, p < 0.01
South East	1.03, p = 0.59	1.01, p = 0.82	1.21, p < 0.01	1.13, p = 0.01	1.10, p = 0.08	1	0.80, p < 0.01
South West	1.28, p < 0.01	1.26, p < 0.01	1.51, p < 0.01	1.41, p < 0.01	1.37, p < 0.01	1.25, p < 0.01	1

***Klebsiella* spp. bacteraemia**

Region	Reference						
	East	London	Midlands	North East and Yorkshire	North West	South East	South West
East	1	1.09, p = 0.36	0.98, p = 0.84	1.02, p = 0.87	0.99, p = 0.90	0.97, p = 0.74	0.70, p < 0.01
London	0.92, p = 0.36	1	0.90, p = 0.19	0.93, p = 0.39	0.91, p = 0.27	0.89, p = 0.16	0.64, p < 0.01

Region	Reference						
	East	**London**	**Midlands**	**North East and Yorkshire**	**North West**	**South East**	**South West**
Midlands	1.02, p = 0.84	1.11, p = 0.19	1	1.03, p = 0.67	1.01, p = 0.95	0.99, p = 0.87	0.71, p < 0.01
North East and Yorkshire	0.98, p = 0.87	1.07, p = 0.39	0.97, p = 0.67	1	0.97, p = 0.75	0.95, p = 0.57	0.69, p < 0.01
North West	1.01, p = 0.90	1.10, p = 0.27	0.99, p = 0.95	1.03, p = 0.75	1	0.98, p = 0.83	0.71, p < 0.01
South East	1.03, p = 0.74	1.12, p = 0.16	1.01, p = 0.87	1.05, p = 0.57	1.02, p = 0.83	1	0.72, p < 0.01
South West	1.43, p < 0.01	1.56, p < 0.01	1.41, p < 0.01	1.46, p < 0.01	1.42, p < 0.01	1.39, p < 0.01	1

***P. aeruginosa* bacteraemia**

Region	Reference						
	East	**London**	**Midlands**	**North East and Yorkshire**	**North West**	**South East**	**South West**
East	1	1.16, p = 0.29	1.32, p = 0.05	1.34, p = 0.05	1.47, p = 0.02	1.27, p = 0.10	0.79, p = 0.19
London	0.86, p = 0.29	1	1.14, p = 0.26	1.16, p = 0.23	1.26, p = 0.08	1.09, p = 0.44	0.68, p = 0.01
Midlands	0.76, p = 0.05	0.88, p = 0.26	1	1.02, p = 0.88	1.11, p = 0.43	0.96, p = 0.73	0.60, p < 0.01
North East and Yorkshire	0.74, p = 0.05	0.86, p = 0.23	0.98, p = 0.88	1	1.09, p = 0.54	0.94, p = 0.64	0.59, p < 0.01
North West	0.68, p = 0.02	0.79, p = 0.08	0.90, p = 0.43	0.92, p = 0.54	1	0.86, p = 0.29	0.54, p < 0.01
South East	0.79, p = 0.10	0.92, p = 0.44	1.04, p = 0.73	1.06, p = 0.64	1.16, p = 0.29	1	0.63, p < 0.01

Region	Reference						
	East	London	Midlands	North East and Yorkshire	North West	South East	South West
South West	1.26, p = 0.19	1.46, p = 0.01	1.66, p < 0.01	1.69, p < 0.01	1.85, p < 0.01	1.60, p < 0.01	1

MRSA bacteraemia

Region	Reference						
	East	London	Midlands	North East and Yorkshire	North West	South East	South West
East	1	1.12, p = 0.74	1.31, p = 0.45	1.07, p = 0.87	1.59, p = 0.18	1.16, p = 0.68	0.86, p = 0.71
London	0.89, p = 0.74	1	1.17, p = 0.61	0.95, p = 0.88	1.43, p = 0.23	1.04, p = 0.91	0.77, p = 0.47
Midlands	0.76, p = 0.45	0.85, p = 0.61	1	0.81, p = 0.55	1.21, p = 0.55	0.88, p = 0.71	0.66, p = 0.27
North East and Yorkshire	0.94, p = 0.87	1.05, p = 0.88	1.23, p = 0.55	1	1.50, p = 0.23	1.09, p = 0.81	0.81, p = 0.59
North West	0.63, p = 0.18	0.70, p = 0.23	0.82, p = 0.55	0.67, p = 0.23	1	0.73, p = 0.32	0.54, p = 0.09
South East	0.86, p = 0.68	0.96, p = 0.91	1.13, p = 0.71	0.92, p = 0.81	1.37, p = 0.32	1	0.74, p = 0.43
South West	1.16, p = 0.71	1.30, p = 0.47	1.52, p = 0.27	1.24, p = 0.59	1.85, p = 0.09	1.35, p = 0.43	1

MSSA bacteraemia

Region	Reference						
	East	London	Midlands	North East and Yorkshire	North West	South East	South West
East	1	1.04, p = 0.69	1.18, p = 0.07	1.17, p = 0.09	1.22, p = 0.04	1.09, p = 0.39	0.98, p = 0.88
London	0.96, p = 0.69	1	1.13, p = 0.14	1.13, p = 0.17	1.17, p = 0.08	1.04, p = 0.64	0.95, p = 0.56
Midlands	0.85, p = 0.07	0.88, p = 0.14	1	0.99, p = 0.91	1.04, p = 0.67	0.92, p = 0.29	0.83, p = 0.04
North East and Yorkshire	0.85, p = 0.09	0.89, p = 0.17	1.01, p = 0.91	1	1.04, p = 0.60	0.93, p = 0.34	0.84, p = 0.05
North West	0.82, p = 0.04	0.85, p = 0.08	0.97, p = 0.67	0.96, p = 0.60	1	0.89, p = 0.16	0.80, p = 0.02
South East	0.92, p = 0.39	0.96, p = 0.64	1.09, p = 0.29	1.08, p = 0.34	1.13, p = 0.16	1	0.91, p = 0.29
South West	1.02, p = 0.88	1.06, p = 0.56	1.20, p = 0.04	1.19, p = 0.05	1.24, p = 0.02	1.10, p = 0.29	1

CDI

Region	Reference						
	East	London	Midlands	North East and Yorkshire	North West	South East	South West
East	1	0.95, p = 0.64	0.83, p = 0.06	0.97, p = 0.72	1.04, p = 0.66	0.77, p = 0.01	0.75, p = 0.01
London	1.05, p = 0.64	1	0.87, p = 0.18	1.02, p = 0.87	1.10, p = 0.35	0.81, p = 0.05	0.79, p = 0.04
Midlands	1.20, p = 0.06	1.14, p = 0.18	1	1.16, p = 0.09	1.26, p = 0.01	0.93, p = 0.45	0.90, p = 0.33

Region	Reference						
	East	London	Midlands	North East and Yorkshire	North West	South East	South West
North East and Yorkshire	1.03, p = 0.72	0.98, p = 0.87	0.86, p = 0.09	1	1.08, p = 0.37	0.80, p = 0.02	0.78, p = 0.01
North West	0.96, p = 0.66	0.91, p = 0.35	0.80, p = 0.01	0.93, p = 0.37	1	0.74, p < 0.01	0.72, p < 0.01
South East	1.29, p = 0.01	1.23, p = 0.05	1.08, p = 0.45	1.25, p = 0.02	1.35, p < 0.01	1	0.97, p = 0.80
South West	1.33, p = 0.01	1.27, p = 0.04	1.11, p = 0.33	1.29, p = 0.01	1.39, p < 0.01	1.03, p = 0.80	1

Appendix 5. Detailed descriptions of methods

Data extraction, case reports and mortality outcomes

Data on MRSA, MSSA, *E. coli*, *Klebsiella* spp. and *P. aeruginosa* bacteraemia, and CDI was extracted on 9 July 2021 from the HCAI Data Capture System (DCS). Reports of CDI from patients aged under 2 years at the time of specimen collection were excluded from all analyses because this data is not subject to mandatory surveillance, as carriage rates are high (12) with little evidence for disease (13). Mortality estimates cover the first complete financial year after the start of the surveillance for each data collection: 2007/2008 for MRSA bacteraemia and CDI, 2011/2012 for MSSA bacteraemia, 2012/2013 for *E. coli* bacteraemia and 2017/2018 for *Klebsiella* spp. and *Pseudomonas aeruginosa* bacteraemia.

Mortality 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. These are referred to as 'linked or traced reports' in this document and the accompanying datasheet. 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.[8]

Records between 2007/2008 and 2014/2015 were originally traced on 4 July 2015. A secondary trace was conducted on all records from financial years 2013/2014 to 2016/2017 on 3 July 2017. Records after 2016/2017 were traced in the same financial year they were published. Records from the most recent 3 financial years (2018/2019, 2019/2020 and 2020/2021) and retrospective reports prior to these years which have not been included in previous reports were collectively traced on 21 July 2021. Where applicable, data revisions are made to previously traced records from 2018/2019 and 2019/2020 using the outcome of this re-trace. This retrace and/or addition of late reports may result in minor changes to previously published counts.[9]

[8] 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, 703 (3.6%); MSSA bacteraemia, 2,259 (2.1%); *E. coli* bacteraemia, 7,656 (2.2%); *Klebsiella* spp. bacteraemia, 803 (1.9); *P. aeruginosa* bacteraemia, 302 (1.8%); CDI 6,831 (2.5%)

[9] This involved the following number of new or updated reports for each infection in previous years' where thirty-day fatality status was updated from "yes" to from "no": MRSA bacteraemia, 0 (0%); MSSA bacteraemia, 4 (< 1%); *E. coli* bacteraemia, 3 (< 1%); CDI 1 (< 1%)

Thirty-day all-cause deaths

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 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 death[10]. 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 from the data collection (bacteraemia or CDI) had the same NHS number and date of birth 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 case fatality rates (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.[11]

Deduplication algorithm

Blood (faecal for CDI) sample with the earliest specimen date before the patient's date of death was considered the index sample. However, if there was a bacteraemia positive post-mortem sample within one day after a patient's date of death, and no other case was reported within 30-day prior to the patient's date of death, that post-mortem sample is taken as the index sample and considered a 30-day all-cause death. This short period of allowance is included to account for the possibility of late reports and data entry errors. Post-mortem bacteraemia samples after this period of allowance are excluded and not included in either the denominator (linked cases) or numerator (30-day all-cause deaths) of CFR analyses.

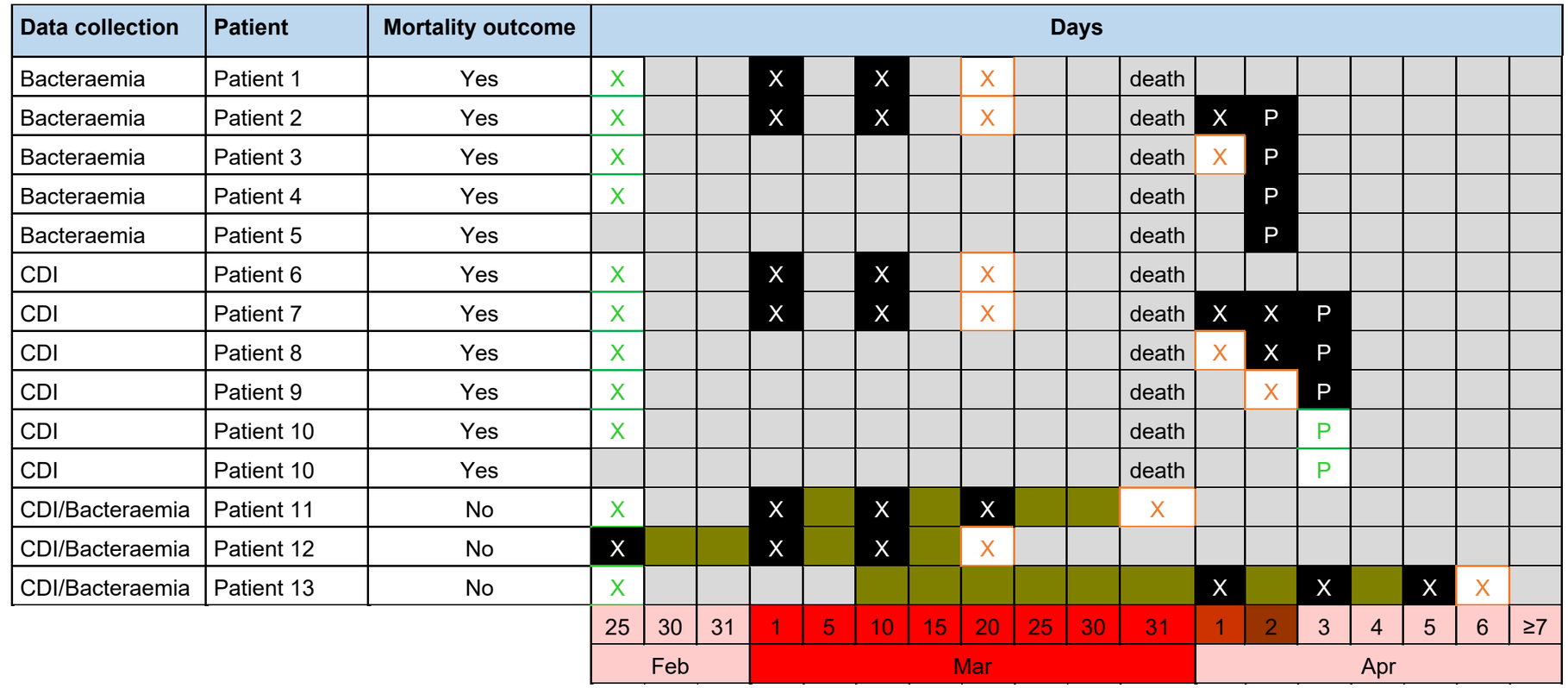
In contrast, CDI positive post-mortem samples are included in CFR where applicable since they are subject to mandatory surveillance (1). For the purpose of this report, patients with a post-mortem CDI faecal sample are assumed to have died to on the same date as their most recent sample. If no other CDI positive sample was reported within 30 days prior to the patient's date of death, these CDI positive post-mortem samples are taken as index cases and considered 30-day all-cause deaths

For bacteraemia and CDI samples which could be linked to fatality records, the most recent sample was taken as an index sample. Bacteraemia and CDI positive samples with specimen dates before index samples but within a 30-day window period prior to the patient's date of death are excluded as duplicates.

[10] There were 105 cases (< 1%) of CDI with dates of death ≥3 day prior to their specimen dates. These were included in the analysis and considered thirty-day all-cause fatalities.
[11] The following number of cases were excluded to ensure each patient had only one thirty-day fatality: MRSA bacteraemia, 58 (< 1%); MSSA bacteraemia, 231 (< 1%); *E. coli* bacteraemia, 741 (< 1%); *Klebsiella* spp. bacteraemia, 109 (< 1); *P. aeruginosa* bacteraemia, 47 (< 1%); CDI 372 (< 1%)

Deduplication is done at a data collection-level. This means that each data collection will have its own index sample if a patient tests positive for multiple infections covered in this report. Additionally, only duplicates of the same type of infection are excluded. For example, if a patient tests positive for MRSA, *E. coli* and CDI samples within 30-days of each other, they will be included in CFR calculation 3 times, once for each data collection.

Figure 40. Visualization of the 30-day mortality de-duplication methodology



X	=>	**Index sample**
X	=>	**Retained sample**
X	=>	**Excluded sample**
P	=>	**Retained post-mortem sample**
P	=>	**Excluded post-mortem sample**
death	=>	**Date of death**
	=>	**30-day all-cause mortality window period**
	=>	**1 day allowance for late report or date entry error (Bacteraemia and CDI)**
	=>	**2 day allowance for late report or data entry error (CDI only)**
	=>	**30-day deduplication window for cases with unknown mortality outcomes**

Case fatality rates (CFR)

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

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

95% CIs for CFR were calculated using the Pearson-Klopper method for a binomial distribution. These are included in the accompanying datasheet.

Estimated total number of 30-day all-cause deaths

An estimate of the number of deaths that might be observed in each period if all infection reports could have been linked to mortality records was calculated. This was done 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) and rounded to the nearest whole number. Care should be taken with interpretation of this data as it assumes the risk of death for those cases that could and could not be linked are the same. This information is included in the accompanying datasheet.

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

$$Estimated\ total\ number\ of\ 30\ day\ all\ cause\ deaths = (Deduplicated\ total\ reports) \times (30\ day\ all\ cause\ CFR)$$

Change in CFR

Changes in CFR were presented as percentage differences. For example, yearly changes in CFR of each infection are calculated as follows:

$$Percentage\ change = (v_p - v_c)$$

where:

v_p = CFR in financial year 1
v_c = CFR in financial year 2

The p-values for these differences were calculated using the method described by Altman and thers (14).

95% confidence intervals for the difference in CFR were calculated using the Standard Error of the difference between 2 proportions.

$$SE(p_1 - p_2) = \sqrt{\frac{p_1(1-p_1)}{n_1} + \frac{p_2(1-p_2)}{n_2}}$$

$$95\%\ CI = (p_1 - p_2) \pm 1.96 * SE(p_1 - p_2)$$

Regression analysis

Statistically significant differences in regional odds of death and mortality rates were assessed by multivariate regression analyses controlled for age and gender.

Sample calculation

Sample calculations for CFR (not including 95% CI) estimated total number of 30-day all-cause deaths and percentage difference for MRSA in 2020/2021 as shown below. Note that all calculations in the report use the raw figures found in the accompanying data sheet. Figures in this report are rounded to one decimal place:

$$30\ day\ all\ cause\ CFR_{MRSA\ 2020/2021} = \frac{190\ deaths}{673\ deduplicated\ traced\ reports} \times 100 = 28.2\%$$

$$Est.\ total\ number\ of\ deaths_{MRSA\ 2020/2021} = (692\ mortality\ deduplicated\ DCS\ reports) \times (0.282) = 196$$

$$Percentage\ difference\ in\ CFR_{MRSA\ 2007/08\ to\ 2020/2021} = 38.9 - 28.2 = 10.6\%\ difference$$

COVID-related bacteraemia and CDI

All laboratory confirmed cases of positive SARS-CoV-2 where extracted from UKHSA's voluntary laboratory surveillance data base, the Second Generations Surveillance System (SGSS). Cases were deterministically linked to the bacteraemia and CDI cases using patient's identifiable details. Bacteraemia and CDI cases whose specimen dates where within 28 days before or after the SARS-CoV-2's specimen date where defined as a COVID-related case. Such cases that were also identified as 30-day call cause death as already described, where defined as a COVID-related CDI or BSI 30-day all-cause death.

Appendix 6. Summary of differences between Office for National Statistics and UKHSA fatality outputs

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

Information	ONS	UKHSA
Geography	England and Wales	England
Time period covered	Calendar year	Financial year
Mortality data source	Death registrations	NHS Spine reports of death
Deaths relating to	MRSA bacteraemia and *C. difficile*	MRSA, MSSA, *E. coli* bacteraemia and *C. difficile* infection
Deaths determined by	Mention of MRSA or C. difficile on the death certificate (where the patient need not have died from MRSA or *C. difficile*) and where MRSA or *C. difficile* were the underlying cause of death.	Deaths within 30 days of positive specimen of MRSA, MSSA or *E. coli* bacteraemia or *C. difficile* infection determined using data matched with the NHS Spine.
Denominator	All deaths in the given time period and population in the given time period (2 different denominators used).	All traced reports of MRSA, MSSA, *E. coli* bacteraemia or CDI in the given time period.

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