UK Health Security Agency

English surveillance programme for antimicrobial utilisation and resistance (ESPAUR)

Report 2021 to 2022

Contents

Content has been divided into chapters with sub-sections, to allow the reader to navigate to the most relevant topics.

This report is accompanied by an Annexe, infographics, data appendices in the form of spreadsheets, and downloadable slidedecks of the graphs. These can be all accessed from the ESPAUR web page.

Citation

UK Health Security Agency. English surveillance programme for antimicrobial utilisation and resistance (ESPAUR) Report 2021 to 2022. London: UK Health Security Agency, November 2022.

Executive summary

Between 2017 and 2021 there was a slight increase in rate of bloodstream infections (BSI) caused by key pathogens. However, rates of *Escherichia coli* and *Streptococcus pneumoniae* sustained the decline seen in 2020 into 2021; most likely due to the multifactorial effects of the SARS-CoV-2 (COVID-19) pandemic.

The overall burden of antimicrobial resistance (AMR), decreased by 4.2% between 2017 and 2021, although the trend varied by key pathogen. The AMR burden in BSI had been steadily increasing since 2017 before falling in 2020. This decline has been maintained in 2021 and remains predominantly driven by the reduction in the incidence of *E. coli* BSI.

The AMR burden in BSI varies markedly across regions in England. The rate of resistant BSIs was highest in London (55.5 per 100,000 population) followed by the North West (44.5 out of 100,000) and South East (41.1 out of 100,000). The lowest AMR burden in BSI rate was recorded in the East Midlands (32.1 out of 100,000).

Ethnic minorities appear to be disproportionately affected by infections associated with AMR with 33.0% (n = 1,243) of Asian or Asian British ethnic group patients with a key BSI contracting a resistant BSI compared to 20.9% (n = 10,536) of White ethnic group patients.

In *E. coli* BSI, resistance to co-amoxiclav remained high in 2021 (41.2%), there were also significant increases in percentage resistance to piperacillin with tazobactam and carbapenems between 2017 and 2021. Percentage resistance in *Klebsiella pneumoniae* BSI also increased, in particular for ciprofloxacin, third-generation cephalosporins, and piperacillin with tazobactam. Resistance to key antibiotics (excluding penicillin) has increased over the previous 5-years within invasive group A *Streptococcus* (iGAS) infections, creating implications for treatment regimens for patients allergic to penicillin. Tetracycline resistance in meticillin-resistant *Staphylococcus aureus* (MRSA) BSI increased and peaked at 22.5% in 2021. Finally, the overall percentage of *Enterococcus* spp. that were glycopeptide resistant (17.1%) has increased significantly, although resistance to linezolid and daptomycin remain low.

In 2021, the overall crude case fatality rate for 30-day all-cause mortality in patients with key Gram-negative bacterial BSI was 16.7%. Patients infected with a strain resistant to one or more key antibiotics had a higher case fatality rate (18.1%) compared to those with a susceptible strain (16.3%).

In 2021, the most frequent acquired carbapenemases identified in Gram-negative bacteria in England was OXA-48-like (41.8%) followed by New Delhi metallo-β-lactamase (NDM) (25.1%) and *Klebsiella pneumoniae* carbapenemase (KPC) (24.5%). However, frequency and carbapenemase family varied markedly by region. The North West region had the highest rate of KPC notifications, and London the highest rate of NDM notifications, whereas the OXA-48-like notification rate was highest in the West Midlands.

Social deprivation was one of the factors associated with the rate of carbapenemase-producing Gram-negative bacteria notifications. The rate of notification was higher in the most deprived areas compared to the least deprived.

Incidence of candidaemia has increased by 9.7% since 2017. Detection of *Candida auris* remained low in 2021 with sporadic cases occurring primarily following foreign travel. With the exception of *Candida glabrata*, resistance to antifungals remained low within *Candida* species.

Total antibiotic consumption had been decreasing prior to the COVID-19 pandemic (4.3% reduction between 2017 and 2019, from 18.8 to 18.0 defined daily dose (DDD) per 1,000 inhabitants per day). A sharp decrease was seen during the COVID-19 pandemic, with consumption declining by 10.9% between 2019 and 2020 (to 16.02 DDD per 1,000 inhabitants per day). Data remained similar from 2020 to 2021, with only a slight further decline in consumption of 0.5% (to 15.9 DDD per 1,000 inhabitants per day).

Antibiotic prescribing continued to be highest in general practice (72.1%), with a marginal reduction seen in this setting (from 11.65 to 11.49 DDDs per 1,000 inhabitants per day, between 2020 and 2021). Hospital inpatient, hospital outpatient and other community settings have shown an increase in consumption between 2020 and 2021. This may be a result of an increase in routine healthcare activities following the pandemic. Consumption in dental practices has declined (-7.1%) following the large increase seen during 2020, although it has not returned to pre-pandemic levels.

While secondary care antibiotic usage increased slightly in 2021 (as measured by DDDs per 1,000 inhabitants per day), rates by DDDs per 1,000 admissions have declined (from 4,881 to 4,372 per 1,000 admissions), suggesting the reductions seen as measured by admissions rate is reflective of the increase hospital activity out stripping that of antibiotic use. Usage per admission of all antibiotic groups decreased from 2020 to 2021, except for anti-*Clostridioides difficile* agents which increased by 9.2%. In-line with previous years ‘Access’ antibiotics (51.3% out of total DDDs per 1,000 admissions) were prescribed the most in 2021, followed by ‘Watch’ (45.3%), and ‘Reserve’ (3.1%) antibiotics.

Between 2020 and 2021 total antifungal consumption increased to 1.03 DDDs per 1,000 population per day (7.1%), however it remains lower than 2017 by 22.9%.

By the end of the 2021 to 2022 financial year, 50% of Integrated Care Systems had met the National Action Plan target for reducing total antimicrobial prescribing in primary care, and 50% of participating acute trusts had met the reinstated NHS Standard Contract target to reduce total consumption of antimicrobial by 2% (from 2018 baseline). However, it is unclear how greatly the COVID-19 pandemic contributed towards these achievements.

The Treat Antibiotics Responsibly, Guidance, Education and Tools (TARGET) website saw it’s number of views triple in November 2021 compared to the previous month. This coincided with World Antimicrobial Awareness Week and the launch of the redesigned TARGET website. In

addition to the website redesign, all TARGET patient leaflets were redeveloped as accessible webpages so they can be easily accessed during remote consultations.

The TARGET Antibiotic checklist was included as part of the 2021 to 2022 Community Pharmacy Quality Scheme. 74% of pharmacies in England submitted data from patients collecting an antibiotic prescription. The high engagement with this scheme suggests stewardship principles are embedded and the data gives a realistic picture of current community pharmacy antimicrobial stewardship (AMS).

An evidence-based, system-wide intervention has been developed to be part of the TARGET resources to support primary care teams when reviewing the dose and duration of long-term and repeat antimicrobial prescriptions. In addition to this intervention, a UK-wide antimicrobial intravenous-to-oral switch criteria and decision aid tool has been developed for secondary care.

A scoping review of the literature was undertaken to investigate the association between factors commonly known to be associated with health inequalities and the risk of antibiotic resistant infections and antimicrobial prescribing in high income countries. Findings highlighted that there was evidence that ethnicity, income inequality and deprivation status can increase the risk of suffering from an antibiotic-resistant infection. The extent of association between factors of health inequalities and prescribing of antibiotics varied between healthcare settings, antibiotic indications and therapy.

From initiation in 2014 to the end of 2021, 144,446 people have chosen an Antibiotic Guardian pledge to help keep antibiotics working. The Antibiotic Guardian Schools Ambassadors programme continued to connect healthcare professionals with local schools and community groups, to share information about antibiotic use, AMR and IPC. In 2021, the programme aimed to target the most deprived areas, which led to higher engagement especially in North West, Midlands, North East, and Yorkshire.

A redesign and national roll out of the e-Bug resources (a health education programme) is helping to support schools and communities to reinvigorate key infection prevention and control (IPC) and AMR messages. The e-Bug programme aims to push for messaging on these topics in the National Curriculum and increase focus and accessibility for hard-to-reach groups to reduce inequalities.

Two surveys conducted with members of the public, highlighted that restrictions imposed during the pandemic dramatically impacted health-seeking behaviours across England and enabled greater self-management for respiratory tract infections (RTIs). Another public survey identified wider determinants of health that had an impact on antimicrobial use, understanding, and health-seeking, including younger age, urban populations, deprivation, disability, insecure employment and financial vulnerability.

Between 1 October and 31 March 2022, over 51,000 patients in England received treatment requests for neutralising monoclonal antibodies and antivirals against COVID-19. Eleven

mutations, which may help the virus evade treatment, were identified that exhibited a significant change in frequency of mutations between samples obtained from patients before and after treatment, between October 2021 and March 2022.

A wide range of new and ongoing research projects were undertaken in the field of healthcare-associated infections (HCAI) and AMR in the last year covering many of the major themes of the UK National Action Plan (NAP) for AMR, including stronger laboratory capacity and surveillance in AMR, human infection prevention and control and optimal use of antimicrobials.

The full set of infographics visualising the main findings from the report is available on the ESPAUR report web page.

1. Introduction

This is the ninth annual English Surveillance Programme for Antimicrobial Use and Resistance (ESPAUR) report.

During the coronavirus (COVID-19) pandemic, we saw significant decreases in the incidence of bloodstream infections (BSI), antibiotic resistant infections, and the burden of resistant infection. The reasons for this are complex and multifactorial but likely, at least in part, due to changes in healthcare delivery and healthcare seeking behaviour. As healthcare systems return to pre-pandemic ways of working, now is a pivotal moment to ensure focus remains on what is often referred to as the 'silent pandemic': antimicrobial resistance (AMR).

The ESPAUR programme and oversight group has continued to work across the healthcare system and with external stakeholders to bring together relevant information to inform on trends and the impact of external forces on antimicrobial prescribing, and progress towards the 5-year AMR National Action Plan (NAP). Collaboration between the ESPAUR programme and oversight group and external stakeholders has continued to ensure optimal surveillance of antimicrobial consumption and resistance, and to ensure antimicrobial stewardship interventions such as public and professional education and training continues to be delivered.

The UK NAP ambition for AMR is to reduce the (estimated) total number of antibiotic-resistant infections in the UK by 10% from the 2018 baseline by 2025. Progress has been made towards this target, with a 9.1% reduction being achieved between 2018 and 2021 in England, although much of this reduction occurred during the pandemic and are likely to be in part due to interventions in place to at that time. After an initial increase seen between 2018 and 2019, there was a 15.7% decline in the estimated number of severe antibiotic-resistant infections between 2019 and 2020, followed by a slight increase in 2021 (2.2%).

For the first time in this report, we describe deprivation in carbapenemase-producing Gram-negative bacteria cases, and AMR burden by ethnic group. The rate of carbapenemase-producing Gram-negative bacteria notifications varied by indices of multiple deprivation (IMD), with a higher rate of notifications seen in the more deprived deciles (2021: 6.8 per 100,000 population in the most deprived decile compared with 2.8 per 100,000 population in the least deprived). In 2021, 81% (50,329) of BSI episodes (as per AMR burden combinations) were recorded in persons with a White ethnic group, of which 20.9% were resistant to at least 1 key antimicrobial. The highest percentage resistance was noted in the Asian or Asian British ethnic group with 32.8% of key organism BSI resistant to at least one key antimicrobial. Understanding the impact of ethnicity, deprivation, regional divergence, along with potential confounders, remains a crucial avenue of enquiry and essential to the identification of appropriate target interventions. The AMR health inequalities workstream has been developed to embed a systematic approach to reducing health inequalities in AMR.

Chapter 3 highlights that total antibiotic consumption has been decreasing with a sharp decline seen coinciding with the COVID-19 pandemic. There was an overall 10.9% decrease in antibiotic consumption between 2019 and 2020 alone, followed by a further decline of 0.5% from 2020 to 2021. Antibiotic prescribing continues to be highest in the general practice setting in 2021 (72.1%) and it is also here that the largest reductions in antibiotic prescribing have consistently occurred. In 2021, antibiotic prescribing has also decreased in dental practices, following a spike between 2019 and 2020, but has increased in hospital inpatient, outpatient, and other community settings between 2020 and 2021.

Total consumption of systemic antifungals prescribed in the community and NHS hospitals in England decreased by 22.9% between 2017 and 2021. However, between 2020 and 2021, antifungal consumption has increased by 7.1%.

Assessment of the consumption of antiprotozoal drugs is new to this year's report. There doesn't seem to be a major shift in prescribing since 2017.

Whilst improvements and reductions in antibiotic prescribing have been made, continued stewardship and surveillance are needed to sustain progress towards the NAP. Key national primary and secondary care antimicrobial stewardship (AMS) interventions led by the UK Health Security Agency (UKHSA) are summarised in Chapter 4. This year the TARGET antibiotics toolkit hosted on the Royal College of General Practitioners (RCGP) website underwent a major re-design.

The TARGET Antibiotic Checklist, an antimicrobial stewardship tool, was included as a component of the 2021 to 2022 Pharmacy Quality Scheme (PQS), and 74% of pharmacies in England submitted data from over 200,000 individuals collecting an antibiotic prescription. High engagement from pharmacy staff suggested that the AMS principles introduced with the TARGET Antibiotic Checklist may be embedded.

In line with the NAP ambition to "enhance the role of pharmacists in primary care", UKHSA, in collaboration with partners, has developed evidence based, system-wide intervention ('How to...' guides) to support primary care teams to review the dose and duration of long-term and repeat antimicrobial prescriptions. The intervention focuses on toolkits and resource guides, specifically for acne and chronic obstructive pulmonary disease exacerbations (COPD). Acne and COPD were prioritised as Primary Care Network (PCN) data revealed that these are the most common clinical conditions associated with the highest use of long-term or repeat antibiotics.

Within secondary care, AMS interventions included the development of a UK-wide antimicrobial intravenous-to-oral switch (IVOS) criteria and sample tool for hospitalised adult patients. This was developed from localised policies, literature and expert opinion with consensus for switch criteria obtained via a 4-stage Delphi process involving 279 multidisciplinary colleagues from all 4 UK nations.

Chapter 5 outlines improvement and assurance schemes within NHS England and NHS Improvement. For primary care, the NHS System Oversight Framework 2021 to 2022 replaced the NHS Oversight Framework 2019 to 2020, retaining 2 primary care antibiotic prescribing metrics – total items prescribed and proportion broad-spectrum. By the end of 2021 to 2022, 50% of 42 Integrated Care Systems (ICSs) met the NAP reduction target for total antibiotic prescribing and 83% met the reduction target for the proportion of broad-spectrum antibiotics.

For NHS trusts providing acute care, a requirement to reduce antibiotic consumption by 2% from each trust's own 2018 calendar year baseline was reinstated in the NHS Standard Contract for 2021 to 2022, following suspension during the COVID-19 pandemic. By the end of 2021 to 2022, 50% of acute trusts met this ambition to reduce total consumption of antimicrobials by 2%.

UKHSA continues to lead on education and engagement of healthcare professionals and the public. Chapter 6 highlights the renewed vigour for professional and public education, engagement and training. The National Healthcare Students' AMR Conference which has been held annually since 2017 was developed as online modules, and registration included medical and pharmacy students who praised its flexibility.

Engagement with World Antimicrobial Awareness Week (WAAW) and European Antibiotic Awareness Day (EAAD) has continued. WAAW 2021 offered opportunity to engage professionals and the public in AMR through consolidating digital campaigning introduced in 2020. A new WAAW and EAAD toolkit for healthcare professionals in England was developed to provide guidance to support the NHS, local authorities and others to lead activities and encourage responsible use of antibiotics. There was also continued engagement with Antibiotic Guardian Schools Ambassadors providing antibiotic use aand infection prevention and control education to children and young people through schools and community groups.

A redesign and national roll out of the e-Bug resources is helping to meet objectives to support schools and communities to reinvigorate key infection prevention and control (IPC) and AMR messages. Groundwork for national implementation of TARGET and e-Bug professional training and resources has commenced, aiming for consistent education of healthcare professionals (HCP) and the public in the future.

Chapter 7, a new addition to this year's report, outlines how UKHSA's COVID-19 therapeutics programme has supported the deployment of COVID-19 therapies by undertaking genomic, virological and epidemiological surveillance of the 5 COVID-19 therapeutics. Between 1 October 2021 and 31 March 2022, there were over 51,000 treatment requests for neutralising monoclonal antibodies and antivirals against COVID-19 for patients in England. This programme has provided an important evidence base for changes to clinical commissioning policies for COVID-19 therapeutics.

UKHSA continues to undertake a wide range of new and ongoing research projects in the field of healthcare-associated infections (HCAI) and AMR. Some of the key research projects are

highlighted in Chapter 8, which cover many of the major themes of the NAP for AMR. Key research is presented from the 2 National Institute for Health Research (NIHR) Health Protection Research Units (HPRU), led by Imperial College London and Oxford University in partnership with UKHSA.

As ever, we couldn’t deliver our activities, progress towards our objectives or develop this report without active contribution from and collaboration with the ESPAUR oversight group as well as the engagement of our wide range of over 20 stakeholder organisations. Chapter 9 highlights the breadth of work being undertaken by devolved administrations, professional and educational bodies, healthcare providers and regulators to tackle AMR and promote good antimicrobial stewardship.

ESPAUR will continue to deliver annual reports on achievements. We thank all who have contributed to this report and continue to support UKHSA to deliver on the objectives of the UK 5-year NAP.

2. Antimicrobial resistance (AMR)

This chapter presents updates on antimicrobial resistance (AMR) surveillance activities undertaken by the UK Health Security Agency (UKHSA). It reports trends in resistance for key organism and antibiotic combinations, including those recommended for surveillance by the Advisory Committee on Antimicrobial Prescribing, Resistance and Healthcare-Associated Infections (APRHAI) (1), sexually transmitted infections (STIs) and *Mycobacterium tuberculosis* infections, together with genomic indicators of AMR (including acquired carbapenemase-producing Gram-negative bacteria). Data is also presented on antifungal resistance (AFR) and antiviral resistance (AVR).

The estimated burden of AMR in England is calculated to map progress against the UK government's national action plan (NAP) target of reducing antimicrobial-resistant infections by 10% by 2025 in England (2, 3) .

The primary data source used in this chapter is UKHSA's Second Generation Surveillance System (SGSS, described further in the data tables for chapter 2), and covers the period 2017 to 2021 (4, 5). Data is presented as trends in either numbers of patient episodes (defined in the Annexe accompanying this report), percentage resistance or as a rate per 100,000 population. More detailed reviews of key pathogens (defined either as key organisms for monitoring the effectiveness of AMR strategies, or organisms showing notable changes in epidemiology), stratified by patient age group, biological sex, regional location within England, case fatality rate (2021 data only), deprivation index, and ethnicity, are presented within the chapter or its appendices.

The data sources, analytical methods, caveats, and additional resources are described in more detail in the Annexe accompanying this report. Data and figures are presented in the data spreadsheets and downloadable slidedecks, respectively.

Trends in incidence of key pathogen causing bloodstream infection

In 2021, 153,362 patient episodes of bacteraemia and/or fungaemia (bacteria or fungi isolated from blood) were identified through reports received from laboratories in England (see accompanying data tables), 10.8% increase compared to 2017 (n=138,417 episodes). Of these episodes, 88.9% (n=135,174) were monomicrobial (a single pathogen isolated from blood).

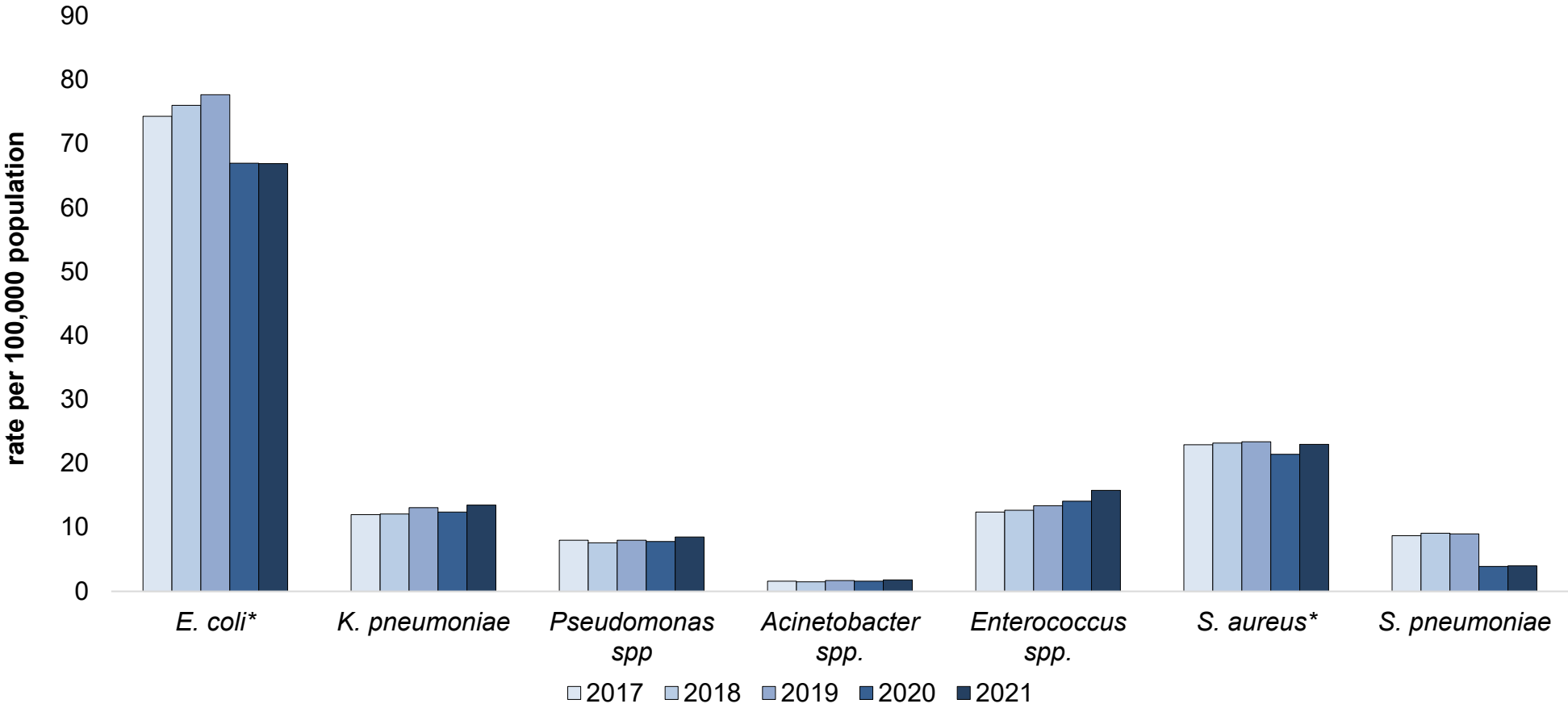
Similar to previous reports (5), the most frequently reported monomicrobial isolates comprised coagulase-negative staphylococci (CoNS; 31%), *Escherichia coli* (22%) and *Staphylococcus aureus* (8%). Among the 11.9% (n=18,188) of episodes that were polymicrobial (more than one bacterial or fungal species identified from the blood sample), the most frequently identified organisms were CoNS (15%), *E. coli* (14%), and unspeciated Gram-negative organisms

(coliforms; 6%). Interpretation of the above data is, however, nuanced as CoNS are common skin commensals and their isolation from blood, in the absence of prosthetic lines or devices, more likely represents contamination during blood culture collection, rather than infection. This issue is discussed in more detail later in this chapter. For more information on species identified from BSIs, refer to the data and figures appendices for chapter 2.

For many of the key pathogens (*Klebsiella pneumoniae*, *Pseudomonas* spp., *Acinetobacter* spp., and *Enterococcus* spp.) reviewed within this report, the incidence of BSI showed a slight increase between 2017 and 2021 (Figure 2.1). Over the same time frame, the incidence of *E. coli* and *Streptococcus pneumoniae* BSI decreased, predominantly in 2020 and 2021, most likely due to the multifactorial effects of the SARS-CoV-2 (COVID-19) pandemic commencing in early 2020. More detail on the trends in incidence for *E. coli*, *S. aureus*, *K. pneumoniae* and *Pseudomonas aeruginosa* BSI are available in the annual epidemiological commentary for these mandatory reporting pathogens.

Figure 2.1 Annual incidence rate of key pathogen BSI, per 100,000 population, England 2017 to 2021

Note in this graph, the asterisk denotes that *Escherichia coli* and *Staphylococcus aureus* incidence is based on mandatory surveillance data.



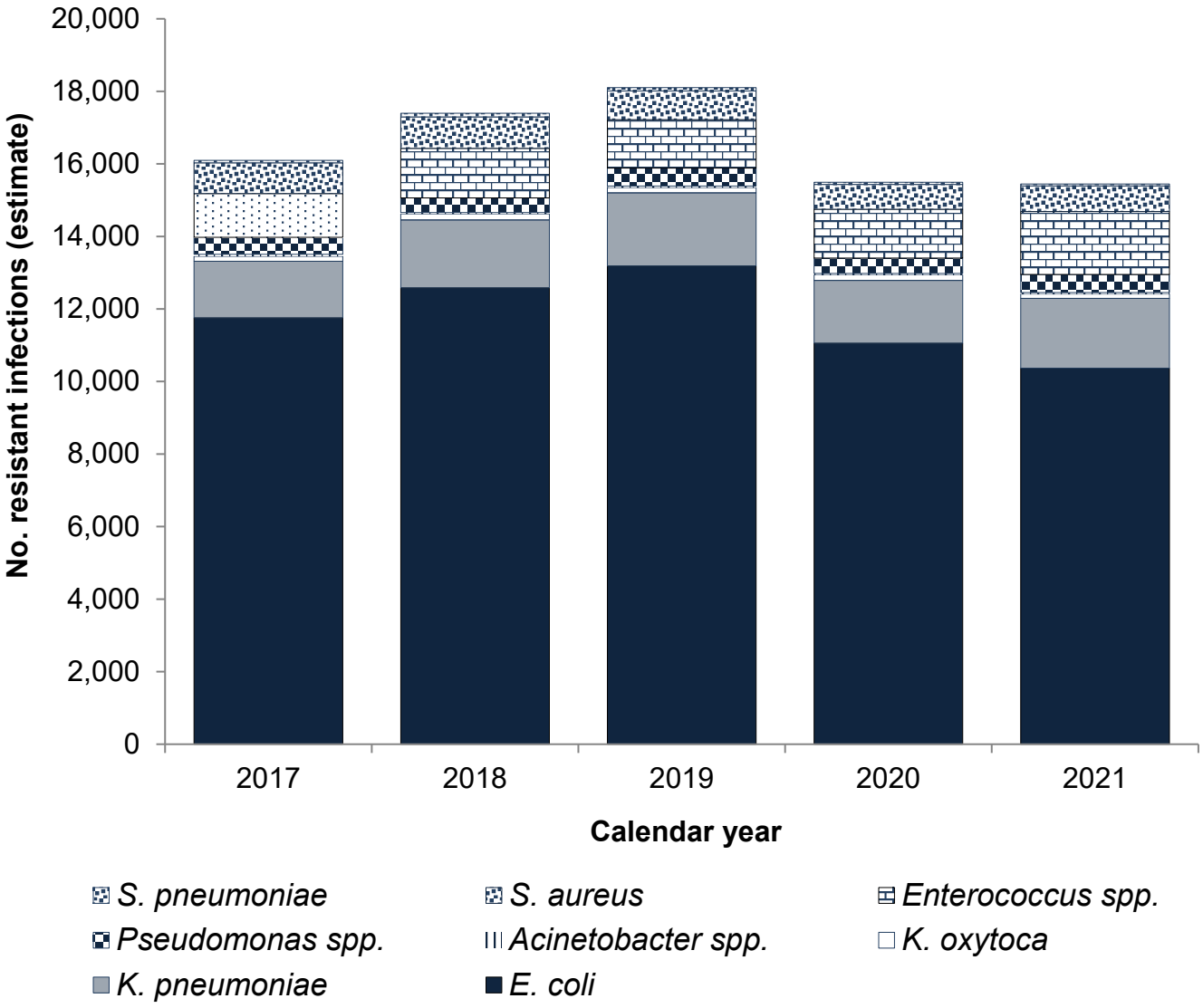
The BSI incidence per 100,000 population for *Enterobacter* spp., *Serratia* spp., and *Citrobacter* spp. increased steadily year-on-year between 2017 and 2021. Incidence was 29.3% higher in 2021 than 2017 for *Citrobacter* spp. (2.5 per 100,000 in 2021), 33.2% higher for *Enterobacter* spp. (4.7 per 100,000 population in 2021), and 40.0% higher for *Serratia* spp. (2.5 per 100,000 in 2021) (see accompanying data tables). Other Gram-negative data is presented in the accompanying data tables.

Antibacterial resistance

AMR burden

The burden of resistance, estimated by the total number of key BSI pathogens resistant to one or more key antibiotics, decreased by 4.2% between 2017 (n=16,099) and 2021 (n=15,446; Figure 2.2). Details on ascertainment factor, AMR burden estimation, pathogen and antibiotic combinations, and obtaining patient's ethnicity are available in the chapter section of the accompanying Annexe.

Figure 2.2 Annual estimated total of (the burden) of antibiotic-resistant bloodstream episodes, England 2017 to 2021



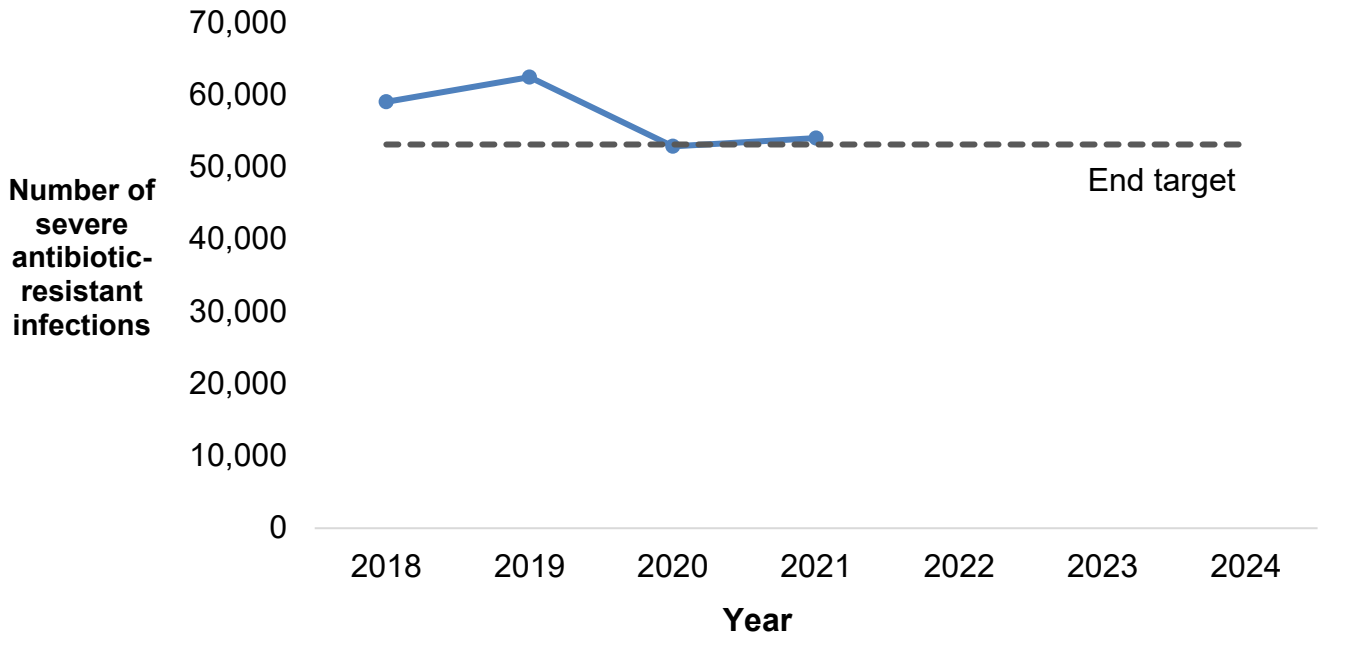
The burden of antibiotic-resistant BSI predominates within the Enterobacterales family (particularly *E. coli*), comprising 80.3% of the total (with the peak in 2019 at 84.8%). The burden of resistant infections remains relatively unchanged for Gram-positive infections (*S. pneumoniae*, *S. aureus* and *Enterococcus* spp.). Further detail is available in the data tables accompanying this report.

2.1 How is England performing against the National Action Plan (NAP)?

In November 2018, the European Centre for Disease Prevention and Control (ECDC) published a methodology for estimating incidence and attributable deaths due to severe antibiotic-resistant bacterial infections (6). This method calculated a ratio relating the number of antibiotic-resistant BSIs to the number of antibiotic-resistant surgical site infections (SSI), antibiotic-resistant urinary tract infections (UTI) and antibiotic-resistant respiratory infections, using point prevalence survey data alongside BSI incidence data reported through ECDC surveillance schemes. A corresponding estimate of mortality is also calculated. Details on the derivation of the ratios are available in the ECDC publication (6).

The UK NAP ambition for AMR is to reduce the (estimated) total number of antibiotic-resistant infections in the UK by 10% from the 2018 baseline by 2025 (2). The method of estimation used to monitor resistance is derived from the ECDC method described above. In England, a 9.1% reduction has been recorded between 2018 and 2021 (from 59,001 to 53,985; Figure 2.1). After an initial increase seen between 2018 and 2019 there was a 15.3% decline in the estimated number of antibiotic-resistant infections between 2019 and 2020, followed by a slight increase in 2021 (2.2%).

Figure 2.1. Estimated number of severe antibiotic resistant infections by year



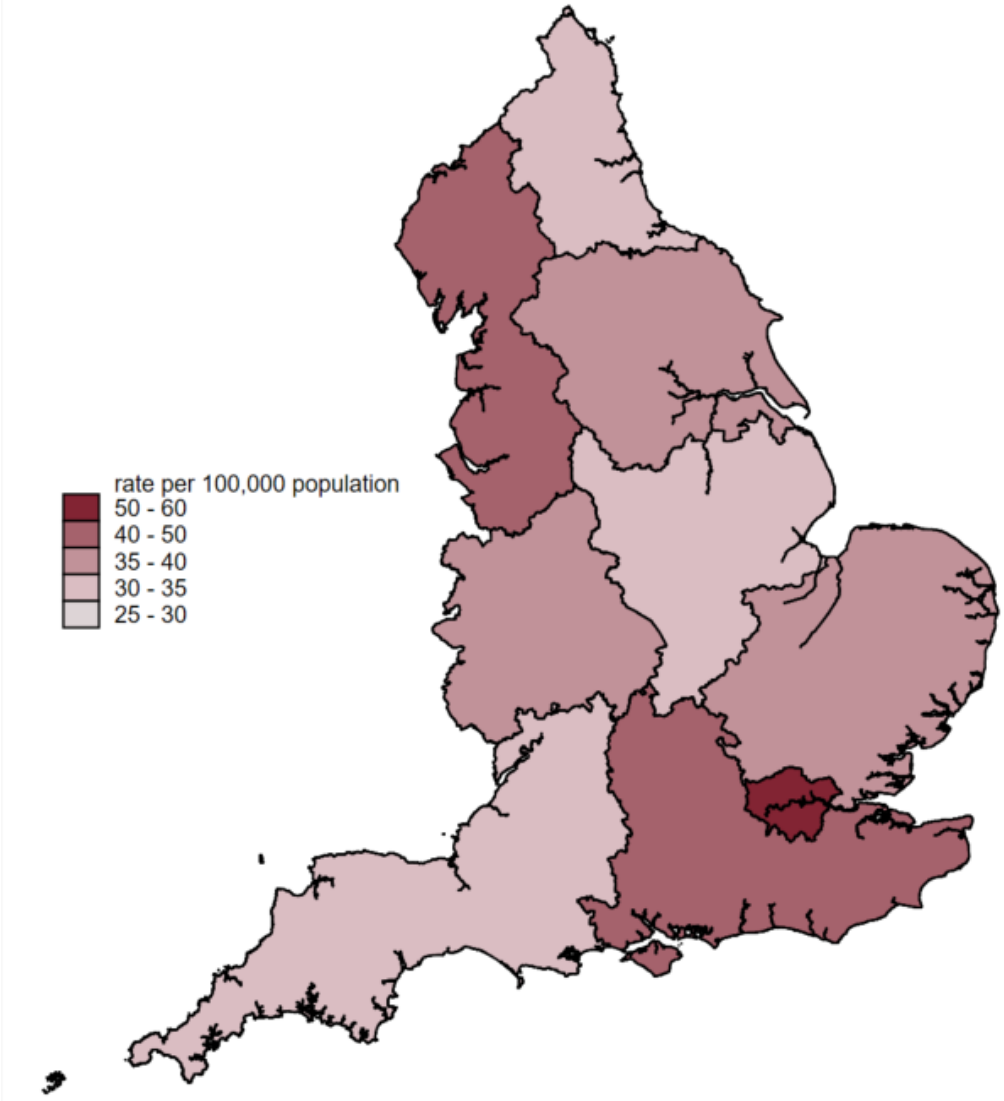
The corresponding estimated number of deaths decreased 8.5% between 2018 and 2021, from 2,419 to 2,213. As AMR estimates rely on the number of BSI, trends analysis should be caveated by the overall reduction in incidence seen due to the COVID-19 pandemic (5).

The regional variation in the burden of AMR in BSI and the incidence of key pathogen BSI is shown in Figure 2.3. The London region reported the highest AMR burden rate per 100,000 population (55.5) followed by the North West (44.5 per 100,000 population) and South East

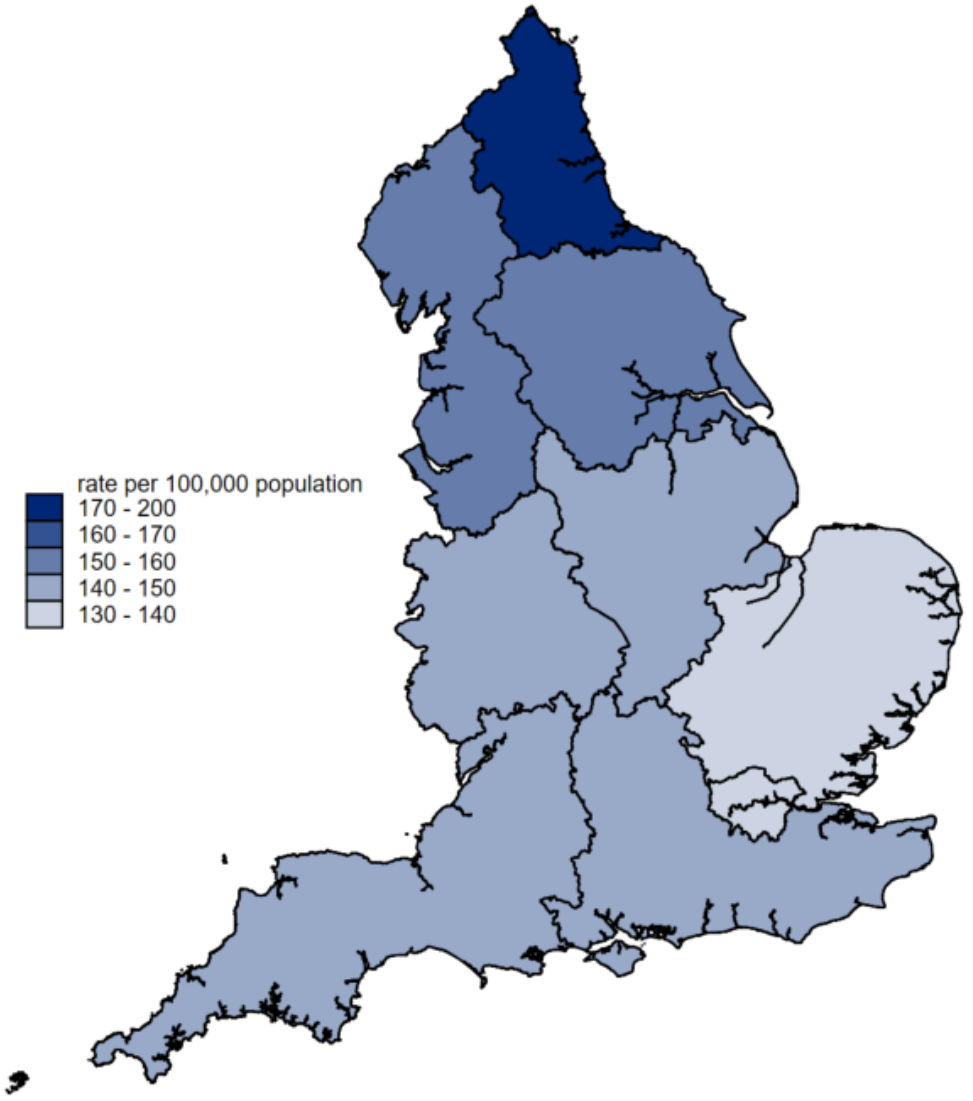
(41.1 per 100,000 population). The lowest AMR burden rate (from BSI) was recorded in the East Midlands (32.1 per 100,000 population). For overall incidence of key BSI pathogens, the lowest estimated rate was recorded in the East of England (130.7 per 100,000 population) and London regions (131.2 per 100,000 population). The highest rate of key species BSI infection was recorded in the North East (176.5 per 100,000 population).

Figure 2.3 Regional variation in rate per 100,000 population of a) the estimated burden of AMR and b) the estimated numbers of BSI in England in 2021

a)



b)



Variation in AMR burden from BSI was noted by ethnic group (Table 2.1). In 2021, the highest number of BSI episodes (as per AMR burden combinations described in the Annexe accompanying this report) as recorded in persons with a White ethnic group (80.8% key BSI episodes; n=50,329), of which 20.9% were recorded as resistant to at least one key antimicrobial. The highest percentage resistant was noted in the Asian or Asian British ethnic group (n=1,243).

Table 2.1. AMR burden from BSI by ethnic group in England in 2021

For this table, 598 (1.0%) BSI episodes could not be linked to obtain ethnic group information. The percentage resistant in this group was 21.6% (n=129; no ascertainment factor adjustment used).

Ethnic group	Number resistant	Number key BSI	Percentage resistant (95% confidence intervals)
White	10,536	50,329	20.9% (20.6 to 21.3)
Asian or Asian British	1,243	3,795	32.8% (31.3 to 34.3)
Black, African, Caribbean or Black British	746	2,348	31.8% (29.9 to 33.7)
Mixed or Multiple ethnic groups	110	454	24.2% (20.4 to 28.4)
Any other ethnic group	322	948	34.0% (31.0 to 37.1)
Not known or Not stated	1,035	3,840	27.0% (25.6 to 28.4)

Key Gram-negative bacterial infections

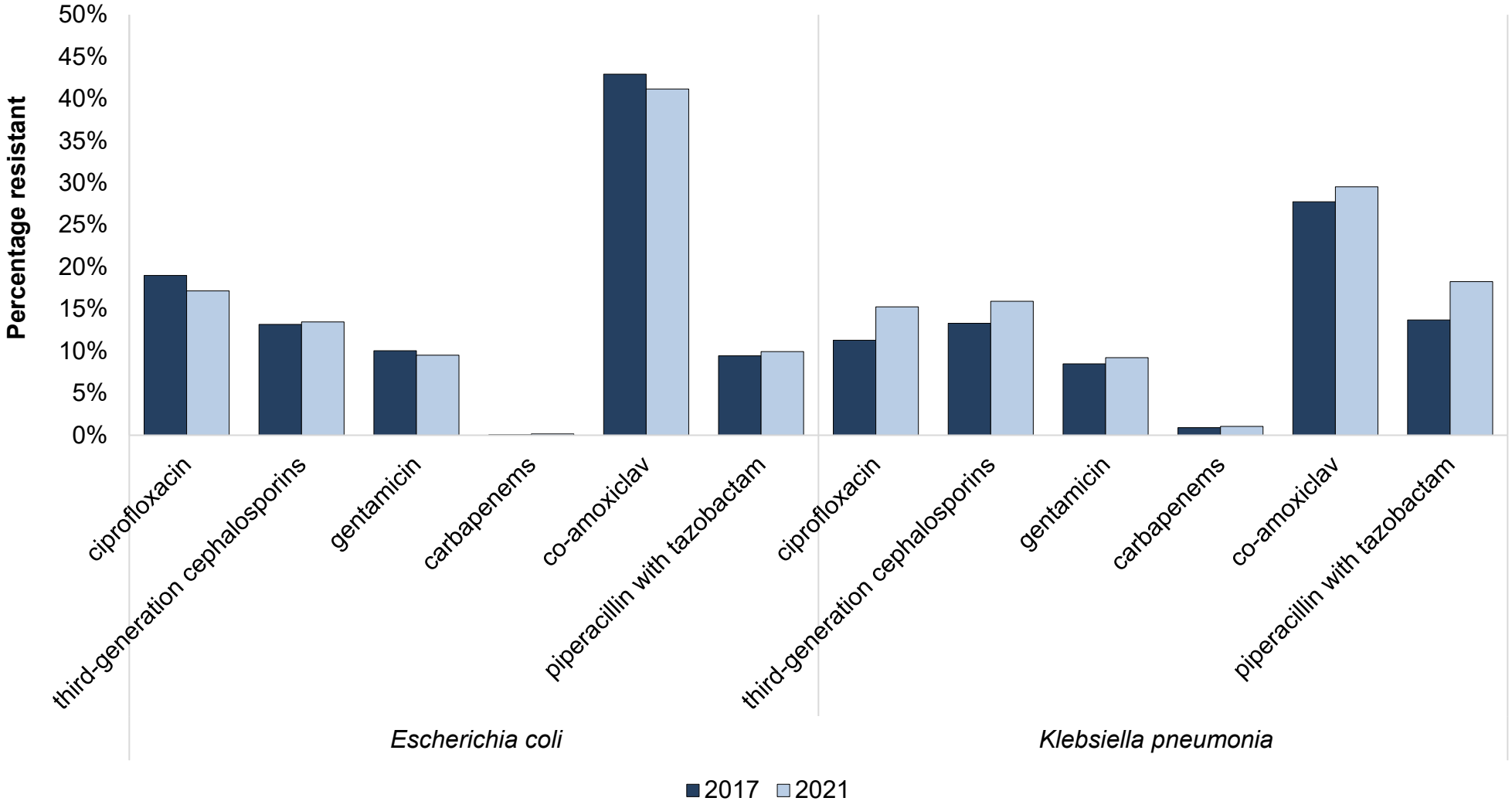
Data presented in this section focuses on a limited number of Gram-negative bacterial pathogens and their phenotypic susceptibility to key antibiotics. More extensive pathogen and antibiotic combination analysis can be found in the data and figure appendices accompanying this report. Data on acquired carbapenemase-producing Gram-negative bacteria is presented later in the chapter.

Trends in antibacterial resistance in bloodstream infections

Between 2017 and 2021, carbapenem resistance in *E. coli* remained at less than 0.5% (albeit with statistical significance doubling from 0.1% to 0.2%, $p<0.05$). Similarly, small but statistically significant rises in resistance to piperacillin with tazobactam (from 9.4% to 10.0%, $p<0.05$), and decreases in resistance to ciprofloxacin (from 19.0% to 17.2%, $p<0.05$) and co-amoxiclav (42.9% to 41.2%, $p<0.05$) were detected in *E. coli* blood isolates (Figure 2.4).

Figure 2.4 Trends in resistance to key antibiotics in *E. coli* and *K. pneumoniae* bacteraemia, 2017 and 2021, England

For this report, 'third-generation cephalosporins' refers to cefotaxime, ceftazidime, cefpodoxime and ceftriaxone. 'Carbapenems' refers to meropenem or imipenem but, where no result is available for either meropenem or imipenem, ertapenem is used.

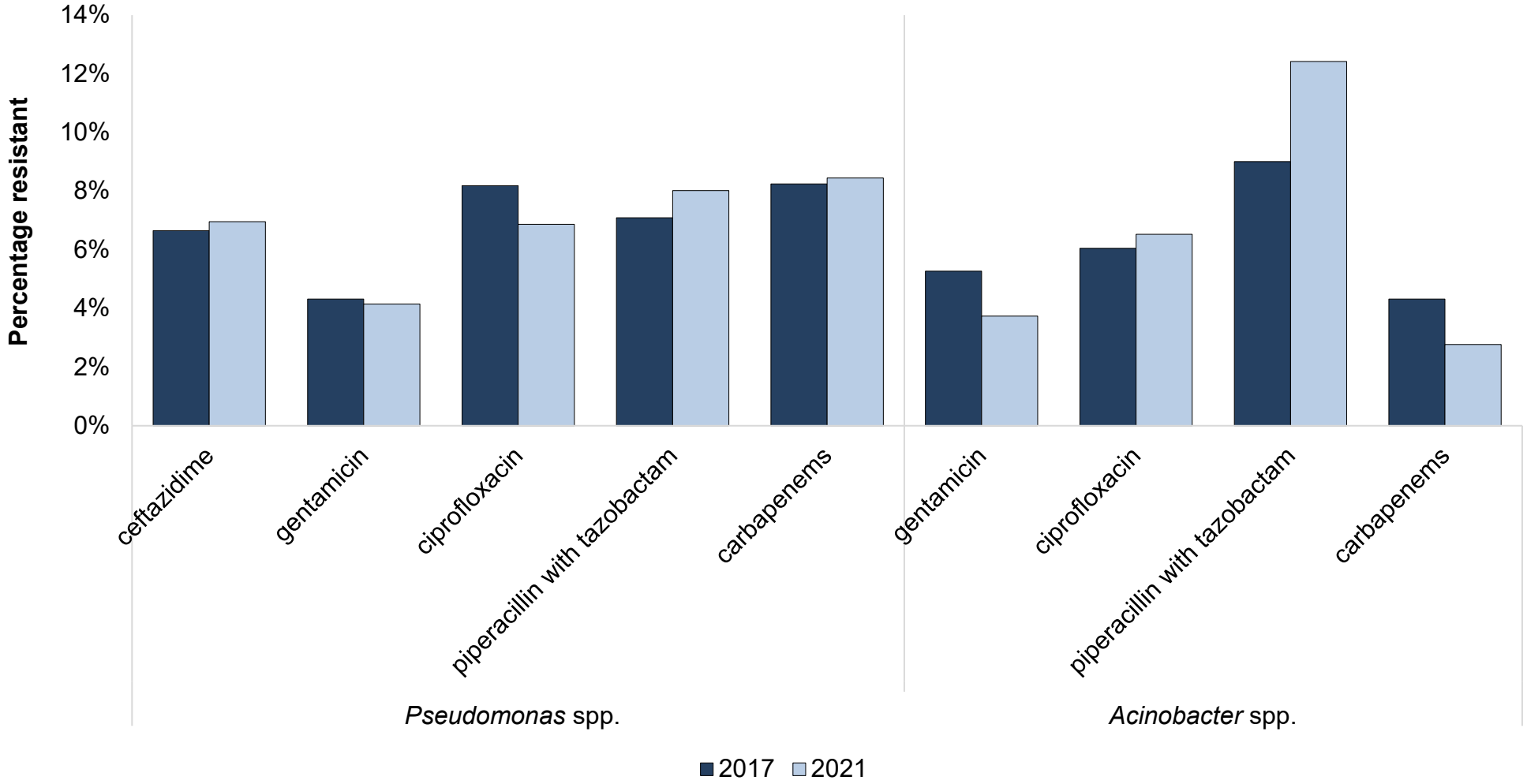


Resistance to multiple key antimicrobials increased in *K. pneumoniae* BSI between 2017 and 2021 (Figure 2.4). Statistically significant increases were seen in resistance to ciprofloxacin (11.3% to 15.3%, $p<0.05$), third-generation cephalosporins (13.3% to 15.9%, $p<0.05$), co-amoxiclav (27.8% to 29.5%, $p<0.05$) and piperacillin with tazobactam (13.7% to 18.3%, $p<0.05$). Resistance to piperacillin with tazobactam has risen in *K. pneumoniae* BSI annually since 2017. Resistance to carbapenems remained low at 1.0% in 2021.

Pseudomonas spp. BSI resistance has remained stable since 2017 for most key antimicrobials. Resistance to ciprofloxacin has decreased significantly from 8.2% in 2017 to 6.9% in 2021 ($p<0.05$) (Figure 2.5, below). Resistance to key antimicrobials in *Acinetobacter* spp. BSI was more fluctuant over the 2017 to 2021 period, however, none of these changes were statistically significant.

Figure 2.5 Trends in resistance to key antibiotics in *Pseudomonas* spp. and *Acinetobacter* spp. bacteraemia, 2017 and 2021, England

Note, in this Figure, 'carbapenems' here refers only to meropenem or imipenem as ertapenem is intrinsically only weakly active against these species.



All-cause mortality in Gram-negative BSI

The overall case fatality rate for 30-day all-cause mortality in patients with key Gram-negative bacterial BSI (*Escherichia* spp., *Klebsiella* spp., *Pseudomonas* spp., *Acinetobacter* spp.) was 16.7% in 2021 (n=7,627); fatality was lowest in children aged 1 to 14 years (1.9%, n=11) and highest in adults aged 85 years and over (21.8%, n=2,053). Patients infected with a strain resistant to 1 or more key AMR burden-defined antibiotics had a statistically significant ($p<0.05$) higher crude case fatality rate (18.1%, n=1,725) compared to those with a susceptible strain (16.3%, n=5,818).

Resistance in less frequently reported Gram-negative pathogens

Following an increase from 2017 to 2019, there was a decrease in the percentage of *Enterobacter* spp. BSI resistant to key antibiotics (gentamicin, ciprofloxacin, and carbapenems) in 2021 (data is available in the data tables accompanying this report).

In contrast, resistance of *Serratia* spp. BSI to key antibiotics (gentamicin, ciprofloxacin, and meropenem) increased between 2020 and 2021. Similarly, resistance of *Citrobacter* spp. BSI increased for most key antibiotics in 2021, the exception being meropenem (0.25% in 2020 and 0.23% in 2021), although the changes were not statistically significant.

There was an increase in the resistance of *Proteus mirabilis* BSI to aminoglycosides (gentamicin (7.4% in 2017 to 11.9% in 2021) and amikacin (0.6% in 2017 to 2.1% in 2021)). All other key antibiotics remained stable for *P. mirabilis* and *Proteus vulgaris* (see the data tables accompanying this report).

2.2 Mobile tigecycline resistance

Tigecycline is a glycylcycline antibiotic and is listed as a ‘critically important antimicrobial’ for use in human medicine by the World Health Organization (WHO), since it is one of few antibiotics with activity remaining against most multidrug-resistant Enterobacterales and *Acinetobacter baumannii*. Resistance is commonly conferred by over-expression of efflux pumps or ribosomal mutations and is not transferable. However, tet(X) gene variants encoding flavin-dependent monooxygenase enzymes that modify tigecycline (and all clinically relevant tetracyclines) and weaken their ability to inhibit protein translation have also been described (7).

Mobile plasmid-mediated resistance is an emerging threat, that can compromise salvage antibiotic regimes due to ease of transmissibility between and across strains. In 2019, the first plasmid-mediated tet(X) genes conferring tigecycline resistance (minimum inhibitory concentration (MIC) 32mg/L) were reported in various *Acinetobacter* spp., Enterobacterales and other Gram-negative bacteria isolated from humans, food-production animals, and meat samples in China (8).

Although subsequent reports of tet(X) variants conferring tigecycline resistance have primarily been in food-production animals and reports in bacteria isolated from humans remain rare (9), these genes have been described in Enterobacterales harbouring acquired carbapenemase and

mobile colistin resistance genes, raising the possibility of infections not treatable with current antibiotic options.

Following the identification of a tet(X4) gene in an *E. coli* isolated from a pooled pig faecal sample by the Animal and Plant Health Agency in 2021, UKHSA screened existing short-read sequencing data to determine whether tet(X4) could be detected in Enterobacterales causing healthcare-associated and gastrointestinal infections in the UK. Among 33,319 *E. coli* and *Shigella* spp. and 58,763 *Salmonella* isolates originating from humans between 2014 and 2020, tet(X4) was identified in only 4 *Salmonella* and 1 *Shigella sonnei* (10). The Antimicrobial Resistance and Healthcare Associated Infections (AMRHAI) Reference Unit are currently developing an in-house real-time PCR to enable surveillance of tet(X) variants conferring tigecycline in Gram-negative bacteria and will amend referral criteria recommending submission of potential isolates in due course.

Acquired carbapenemase-producing Gram-negative bacteria

Acquired carbapenemase-producing Gram-negative bacteria continue to pose a significant public health concern in terms of threat to global health and economic stability (11).

Carbapenems constitute some of the most effective and broadest-spectrum antibiotics available and are typically reserved for severe and multi-drug-resistant infections. Acquired carbapenemases are enzymes which inactivate carbapenems and most other β-lactam antibiotics, including penicillins and cephalosporins, and can result in infections with severely limited treatment options. Many carbapenemase genes are found on mobile genetic elements and are thus easily transferable between species.

The prominent carbapenemase families, termed the ‘big 5’, and constituting >98% overall, are KPC, NDM, OXA-48-like, VIM and IMP, and are increasingly found in species such as *E. coli*, *K. pneumoniae* and *Enterobacter cloacae* complex. However, novel mechanisms of resistance are increasingly being detected (12).

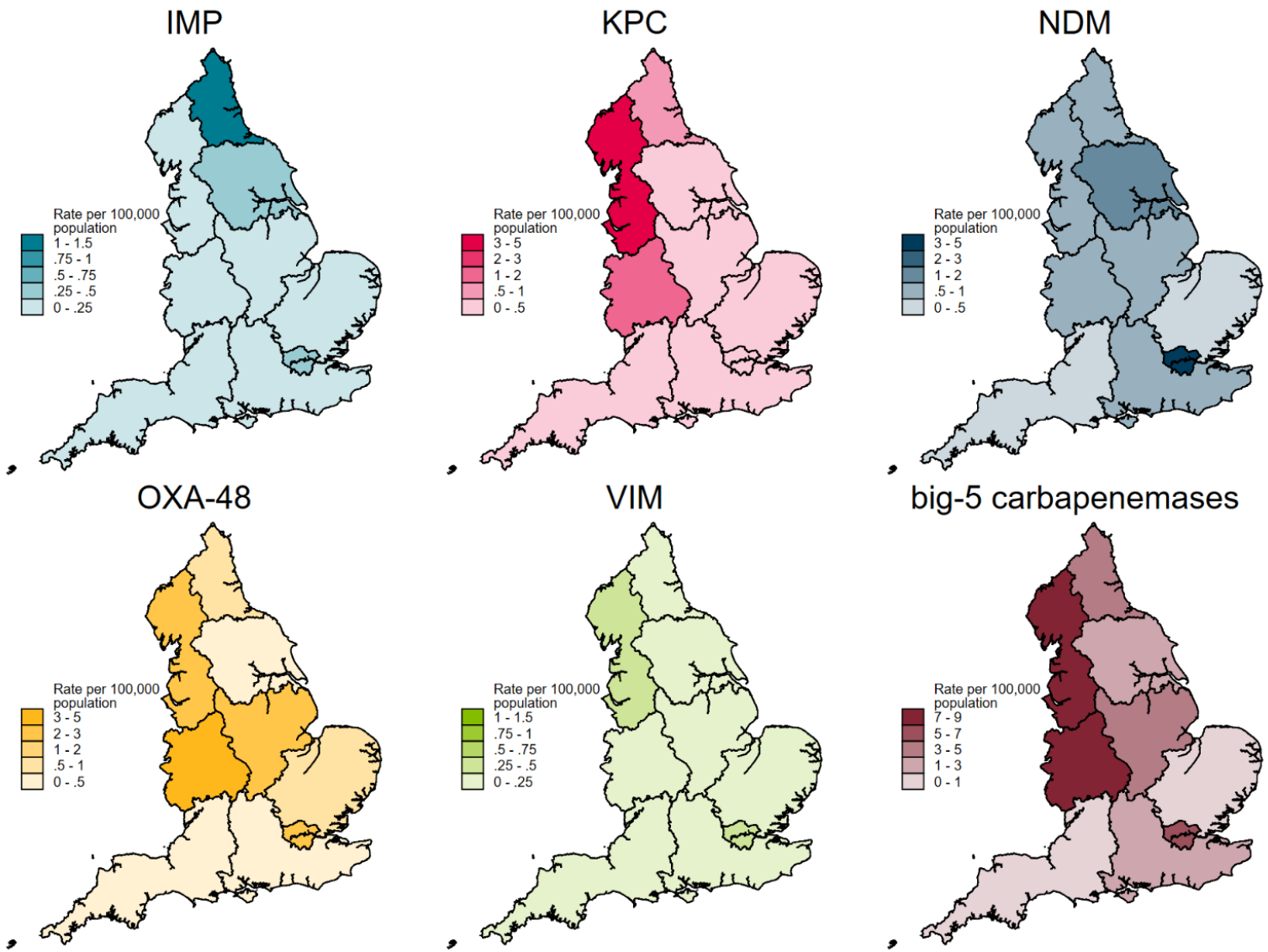
Preventing and controlling the spread of carbapenemase-producing Enterobacterales (CPE) in England, is one of the deliverables of the 5-year NAP introduced in May 2019 (2, 4, 5). Developing local laboratory capacity to detect the ‘big 5’ carbapenemase families has been a key part of the national response, and a change in referral criteria to the Antimicrobial Resistance and Healthcare Associated Infections (AMRHAI) Reference Unit with a focus on invasive isolates and mechanistic uncertainty in the context of certain resistant determinants, has seen a decrease in nationally referred isolates (presented later in the Chapter). In a survey of laboratories completed in 2021 (described in more detail in the ESPAUR report 2020 to 2021), 84% of laboratories in England indicated that they were able to identify the ‘big 5’ carbapenemases ‘in-house’.

Notification data

From 1 October 2020, diagnostic laboratories in England have had a statutory duty to report acquired carbapenemase-producing Gram-negative bacteria isolated from human samples, as well as the results of any antimicrobial susceptibility testing and resistance mechanisms to UKHSA (13). Since October 2020, notifications of acquired carbapenemase-producing Gram-negative bacteria have been published weekly and quarterly at national and regional levels. Details on notification definition and de-duplication are available in Chapter 2 of the Annexe accompanying this report.

In 2021, there were 2,244 notifications of carbapenemase-producing Gram-negative bacteria in England. The majority were identified from screening samples (69.6%), with only 5.6% reported from sterile site specimens; the rest were from 'other' samples (24.9%), such as urine and lower respiratory tract. The most frequent carbapenemase recorded in England was OXA-48-like (915 out of 2,244; 40.8%) followed by NDM (563 out of 2,244; 25.1%) and KPC (550 out of 2,244; 24.5%). In 2021, London and North West regions (Figure 2.6) reported the largest number of acquired carbapenemase-producing Gram-negative bacteria, however, there is considerable regional variation in both the number and type of carbapenemases being recorded (Figure 2.6).

Figure 2.6. Regional notifications per 100,000 population of acquired carbapenemase-producing Gram-negative bacteria by big-5 carbapenemase in England, 2021



The most frequently isolated bacterial species was *K. pneumoniae* (33.1%; n=742 out of 2,244), followed by *E. coli* (25.8%; n=579) and *Enterobacter* spp. (20.6%; n=462). Across these 3 species, the carbapenemase family most frequently identified was OXA-48-like (44.3%, 39.8% and 44.0% in *K. pneumoniae*, *Enterobacter* spp. and *E. coli*, respectively). For *K. pneumoniae* and *Enterobacter* spp., this was followed by KPC and NDM (28.0% and 24.8% in *K. pneumoniae* and 29.0% and 18.8% in *Enterobacter* spp. respectively), and in *E. coli* this was followed by NDM (31.6%) and KPC (21.1%).

Regionally across England in 2021, the highest rate of IMP laboratory notifications were recorded in the North East (1.3 per 100,000 population; 34 notifications) due to a prolonged outbreak within the region, whereas all other regions had a rate of 0.3 or lower (Figure 2.6). The North West had the highest rate of KPC notifications in 2021 (5.0 per 100,000 population; 365 notifications), relating to a previous largescale outbreak in this region. The other regions recorded rates of KPC between 0 and 1.6 per 100,000 population.

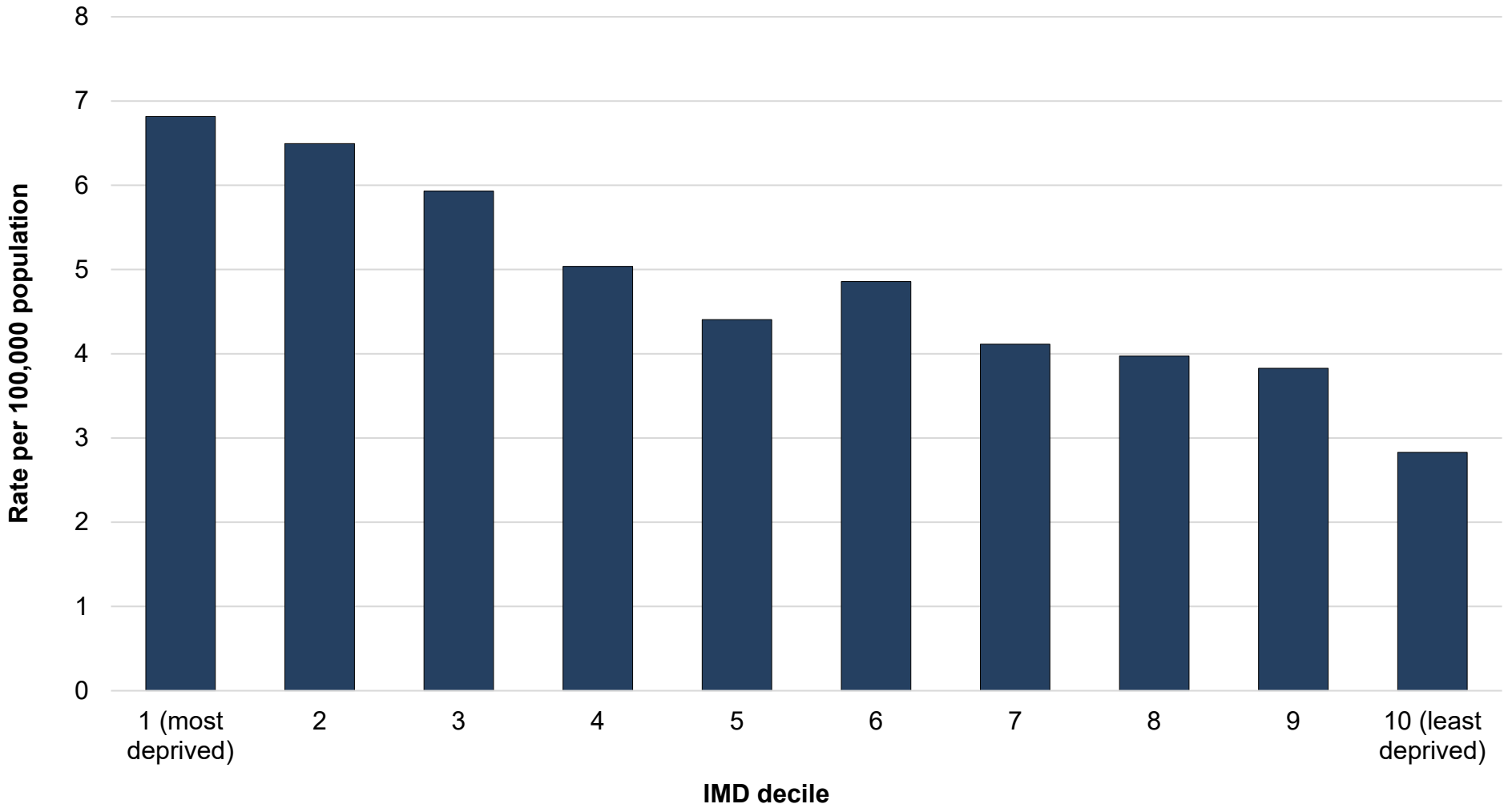
London had the highest rate (3.2 per 100,000 population) of NDM carbapenemases, with all remaining regions recording rates below 1.2 per 100,000 population in 2021.

For OXA-48-like carbapenemases, the West Midlands had the highest rate with 4.5 per 100,000 population, which is in part due to a known outbreak of OXA-48-like *Enterobacter cloacae* complex during 2021. London, East Midlands and North West regions had similar incidence rates of OXA-48-like carbapenemase at 2.6, 2.3 and 2.1 per 100,000 population respectively; the remaining regions had rates of 1.0 per 100,000 population or below.

VIM carbapenemases were comparatively rare in England in 2021, with all regions recording notification rates of 0.3 per 100,000 population or less.

The rate of carbapenemase-producing Gram-negative bacteria notifications varied by indices of multiple deprivation (IMD), measured by decile (where first decile represents the population in the most deprived 10% of areas in England and the tenth decile represents the least deprived 10% of areas) (Figure 2.7). A higher rate of notifications was seen in the more deprived deciles.

Figure 2.7. Rate of acquired carbapenemase-producing Gram-negative bacteria notifications per 100,000 population by IMD decile in England, 2021



In the most deprived IMD decile, the rate of carbapenemase-producing Gram-negative bacteria notifications was 6.8 per 100,000 population, compared with 2.8 per 100,000 population in the least deprived. The carbapenemase family identified also varied with deprivation, however, differences may be as a result of regional mechanism variations (Figure 2.6), local screening policies and outbreaks (more information available in the figures and data appendices accompanying this report).

In 2021, the crude 30-day all-cause case fatality rate in people with acquired carbapenemase-producing Gram-negative bacteria with invasive isolates was 24.5% (n=25 out of 102). The case fatality rate varied by age-group with 0% in children, rising to 35 to 45% in patients aged 65 years or more.

CPE screening

During 2021, 121 acute trusts reported 310,411 CPE screens (88% of trusts; see Table 2.5 in the Annexe accompanying this report), of those acute trusts that reported screening data, 3% reported that they conducted zero faecal screens.

Most CPE screening results data was reported by acute trusts in the London region, (31.6%) followed by the North West and West Midlands regions (17.9% and 17.6% respectively) corresponding to areas where the largest numbers of carbapenemase cases have been identified and reported (Figure 2.6). This may have resulted in ascertainment bias as enhanced testing is likely to lead to increased incidence. In addition, the screening of patients remains voluntary and risk-based; large intra- and inter-regional reporting differences are seen between acute trusts in terms of the total screens reported, ranging from 0 to 37,227, where screening data has been submitted for each of the 4 quarters.

The full list of acute trusts reporting by quarter is available in the chapter 2 data tables accompanying this report.

2.3 Resistance and susceptibility testing for newer antibiotics

New antibiotics and inhibitors combinations, such as cefiderocol, ceftolozane with tazobactam and ceftazidime with avibactam, are now available for the treatment of patients with multi-drug-resistant pathogens. While still uncommon, usage of such drugs is increasing (Chapter 3). Susceptibility testing for these newer antibiotics is not routine, and often limited to specific circumstances, such as resistance to first and second line options. Therefore, resistance prevalence is likely not to be representative.

In 2021, 2,373 *E. coli*, 562 *K. pneumoniae* and 570 *Pseudomonas* spp. isolates from blood were tested for ceftazidime with avibactam susceptibility in NHS laboratories, and 5 (0.2%), 19 (3.4%) and 40 (7.0%) were reported as resistant, respectively; 13 *E. coli*, 15 *K. pneumoniae* and 24 *Pseudomonas* spp. were tested for cefiderocol (available since September 2020) susceptibility in 2021, and 2 (15.4%), 0 (0%) and 2 (8.3%) were reported as resistant, respectively.

As testing and usage of these newer agents is adopted more widely, future ESPAUR reports will integrate assessment of the susceptibility results with additional data on the carbapenemase family presence to enable improved interpretation of the results.

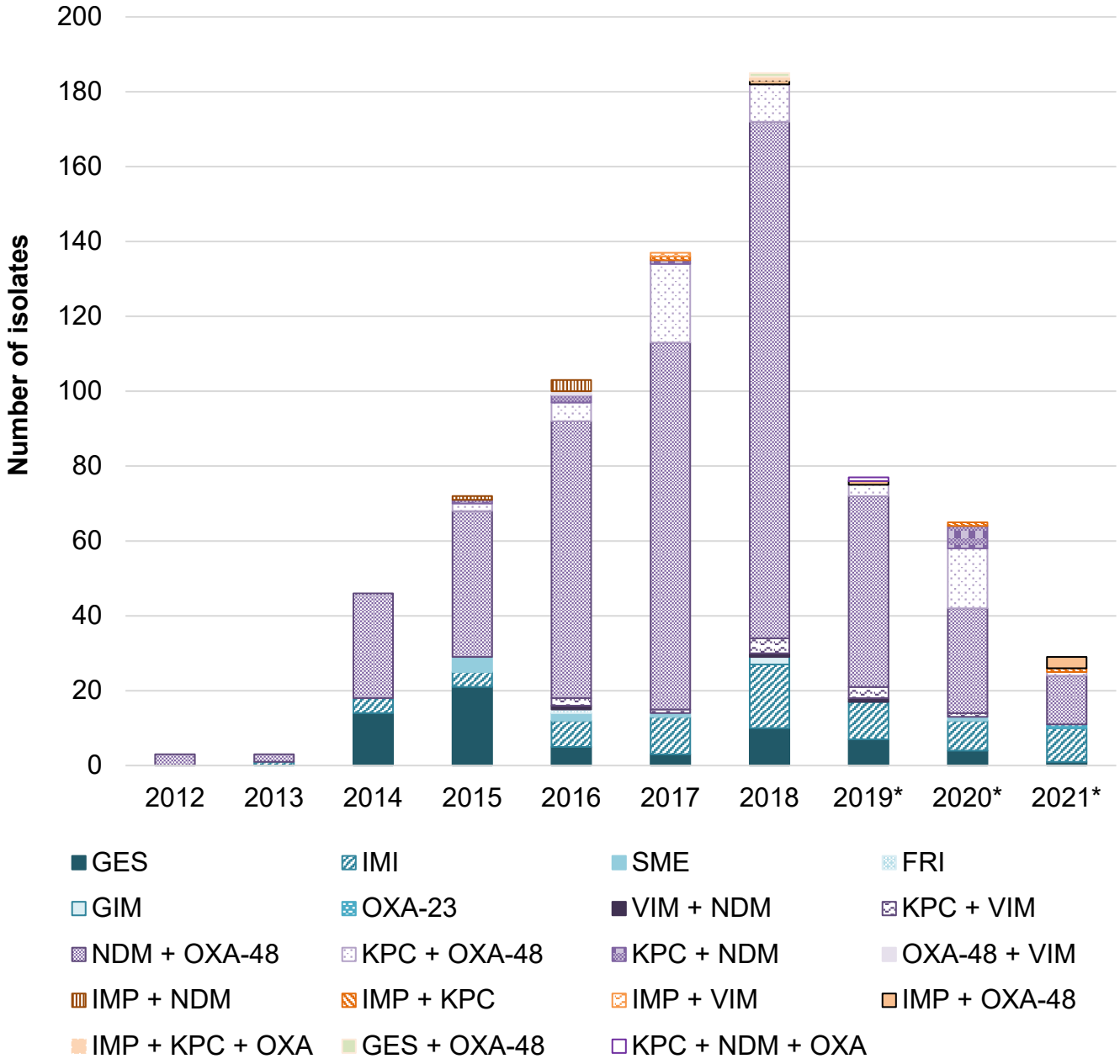
Reference laboratory

In 2021, 654 (78 from BSI) Enterobacterales referred to the AMRHAI Reference Unit were confirmed as positive for at least one carbapenemase. The 'big 5' carbapenemase families (KPC, OXA-48-like, NDM, VIM and IMP) and combinations thereof, continue to dominate and account for >98% of CPE. Of the referred isolates, 3.7% were positive for more than one carbapenemase (Figure 2.8a). There has been a slight increase in the percentage of CPE originating from blood (11.9% in 2021 compared to 10.4% in 2020) (Figure 2.8b).

AMRHAI have been screening all Enterobacterales sent for investigation of carbapenem resistance with a multiplex PCR targeting all carbapenemase gene families that have been identified amongst submissions (see the Annexe accompanying this report). Since 2020, this includes the OXA-23-like, OXA-40-like and OXA-58-like acquired carbapenemase genes consistently associated with resistance in *Acinetobacter* spp..

In 2021, the AMRHAI Reference Unit detected the first instance of an Enterobacterales isolate (*P. mirabilis*) harbouring a gene encoding for OXA-23 carbapenemase amongst referrals. OXA-23 carbapenemase has been previously reported in the chromosome of *P. mirabilis* belonging to a single lineage associated with human and animal sources in France and Belgium since 1996 (14). Despite harbouring the OXA-23 carbapenemase gene these isolates are susceptible to most antibiotics but with meropenem above the European Committee on Antimicrobial Susceptibility Testing (EUCAST) meropenem screening cut-off. Detection at a local level remains difficult, although the elevated meropenem screening cut-off should trigger carbapenemase gene screening. Suspicious isolates will remain negative for the 'big 5' carbapenemase families after local testing, with a meropenem MIC in the range of 1mg/L, and observed resistance to imipenem (imipenem MIC = 8mg/L, although reduced susceptibility to imipenem is expected in *Proteus* spp.). The clinical significance of such isolates remains uncertain. As genes encoding for OXA carbapenemases other than OXA-48-like are seldomly included in carbapenemase detection assays for Enterobacterales it is likely that the prevalence of such isolates is underestimated.

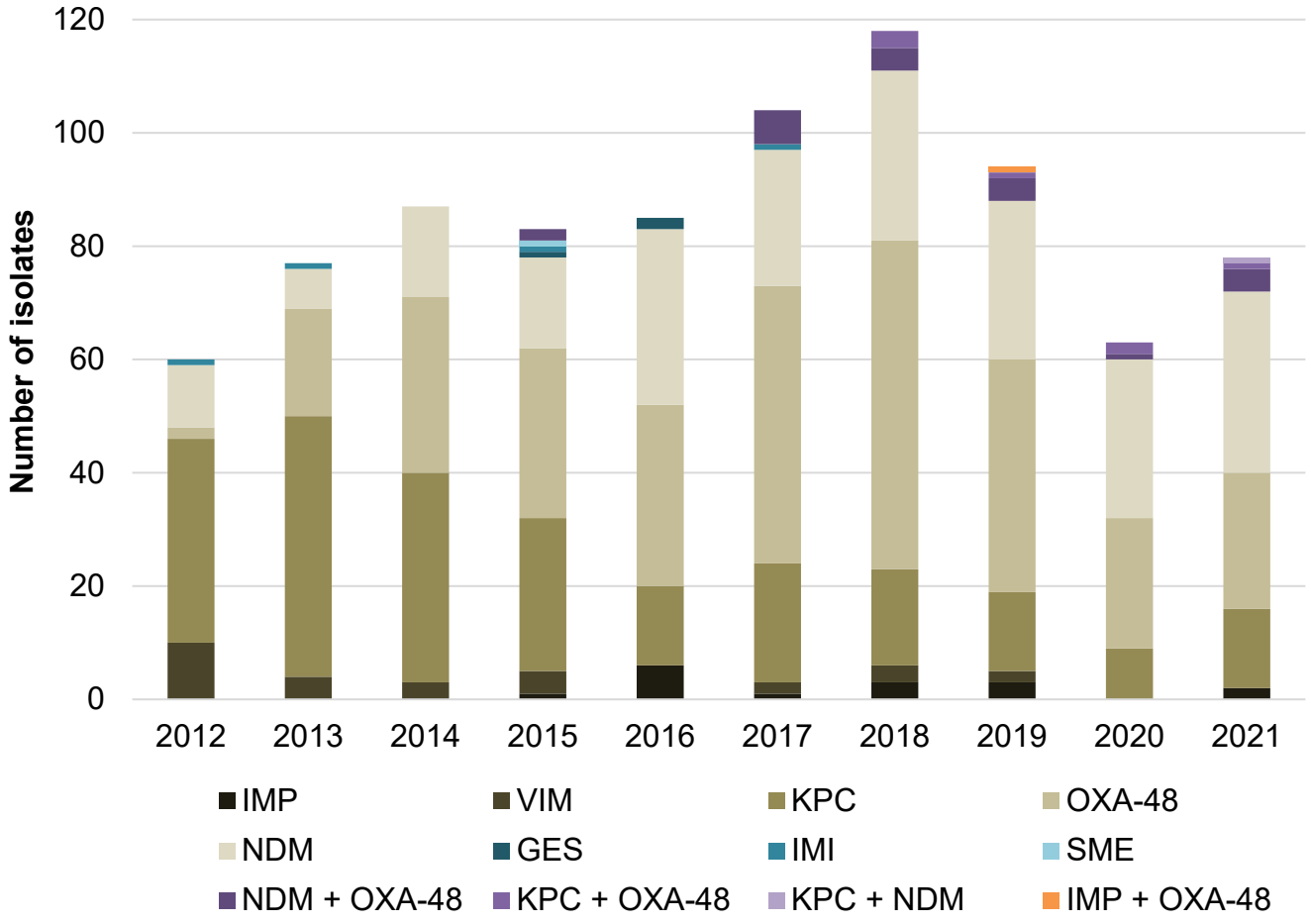
Figure 2.8 (a) Number of confirmed non-'big 5' (unless in combination) CPE isolates referred to UKHSA's AMRHAI Reference Unit (excluding blood cultures), 2012 to 2021
Note that this graph only includes the 'big 5' mechanisms when they are in combination.



* Following a change to the referral criteria in 2019, submission of confirmed CPE from colonised patients to the AMRHAI Reference Unit was no longer encouraged.

Data behind the graph is available in the chapter 2 data table accompanying this report.

Figure 2.8 (b) Number of confirmed CPE blood culture isolates referred to UKHSA's AMRHAI Reference Unit, 2012 to 2021



For *Pseudomonas* spp., the metallo-carbapenemase enzymes VIM, IMP and NDM continue to predominate but other metallo-carbapenemase enzymes (DIM and SIM) as well as non-metallo carbapenemase families (GES, KPC and OXA-48-like) have been identified (Table 2.2).

Table 2.2. Distribution of carbapenemase gene families amongst *Pseudomonas* spp. referred to UKHSA's AMRHAI Reference Unit from all sources

Year	Carbapenemase gene family				
	VIM	IMP	NDM	GES	Other (number)
2017	111	22	19	8	DIM (1); OXA-48-like (2)
2018	99	17	41	9	DIM (2); KPC (3); OXA-48-like (2)
2019	86	11	27	11	DIM (1); KPC (1); OXA-48-like (1); SIM (1)
2020	33	10	19	8	DIM (2); KPC (1)
2021	33	4	13	9	-

Critical antibiotic resistance in foodborne bacteria

In 2021, UKHSA's Gastrointestinal Bacterial Reference Unit sequenced isolates of 5,220 *Salmonella* spp., 2,098 *E. coli* and 519 *Shigella* spp. from England. The AMR determinants were predicted using a validated bioinformatics tool 'Genefinder'. Carbapenemase genes blaOXA-48 were identified in 1 blood and 3 faecal isolates in cases with Salmonellosis (*S.* Typhimurium monophasic, n=3 and *S.* Kottbus n=1). Additionally, blaNDM-5 was detected in *E. coli* isolates from 2 patients, one was infected with a Shiga-toxin producing *E. coli* (STEC) O157:H7 while the other was a non-STEC O102:H6. No carbapenemase genes were identified among the *Shigella* spp. from England.

Transmissible colistin resistance was predicted by the detection of mobile colistin resistance (MCR) genes. In 2021, MCR genes were identified in 6 *Salmonella entrica* isolates, of which 5 were from human cases and 1 was from a food sample. MCR-1 genes were detected in 4 isolates and MCR-9 were detected in the remaining 2 (one each of *S.* Blockley, *S.* Bredeney, *S.* Java, *S.* Kentucky, *S.* Takoradi and *S.* Typhimurium). MCR-10 gene was identified in 2 patients with STEC (O9:H25 and O148:H30). No MCR genes were identified among the *Shigella* spp. from England.

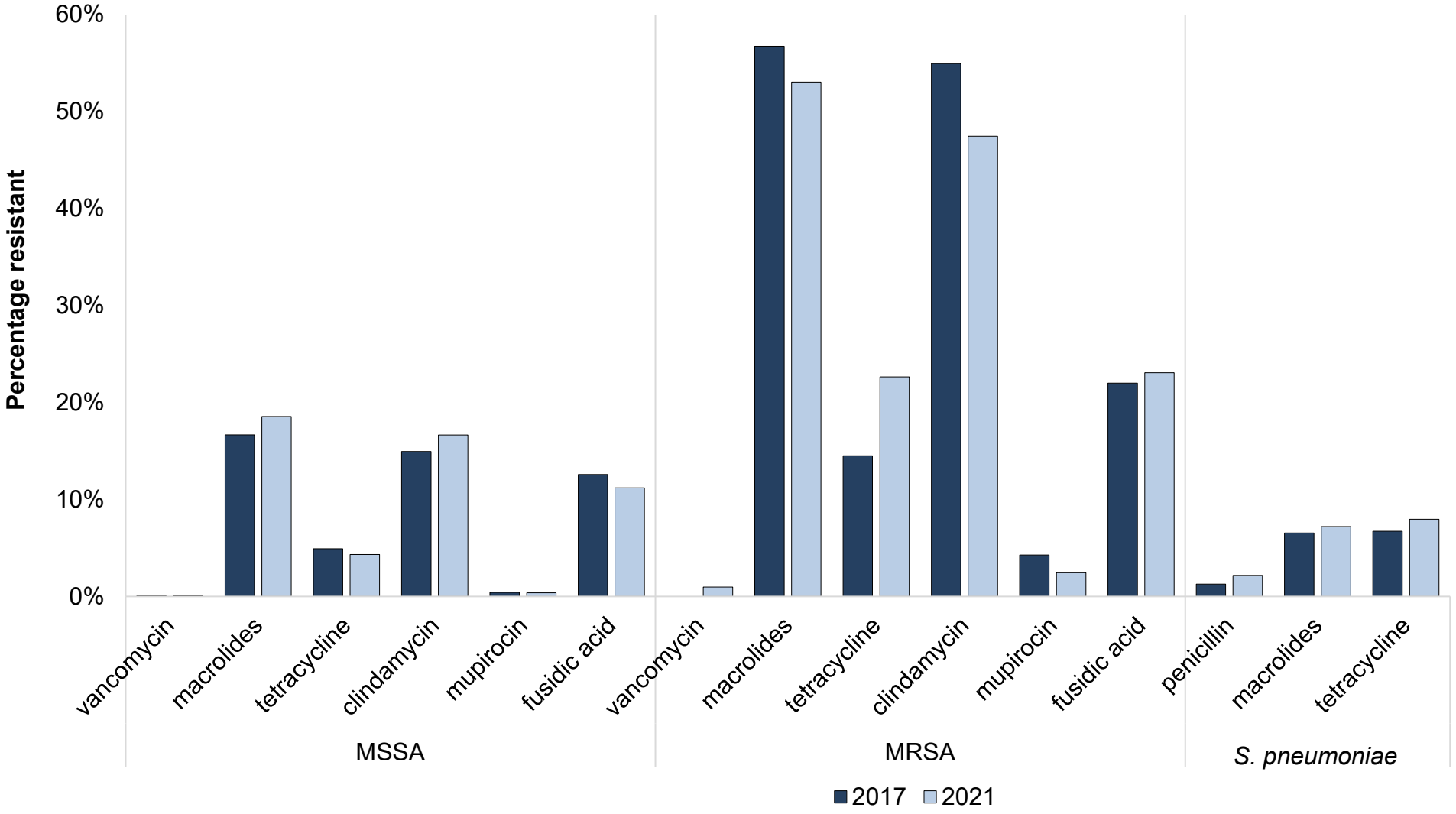
Gram-positive bacterial infections

Trends in antibacterial resistance in bloodstream infections

In 2021, methicillin-resistant strains of *S. aureus* comprise 5.7% of the total number of *S. aureus* strains isolated from blood. Figure 2.9 highlights the difference in resistances to key antibiotics between meticillin-susceptible *S. aureus* (MSSA) and meticillin-resistant *S. aureus* (MRSA) BSI. Resistance to key antibiotics is higher in MRSA compared with MSSA, particularly for macrolides, tetracycline, and clindamycin (53.0% versus 18.6%, 22.5% versus 4.4% and 47.4% versus 16.7% in 2021 respectively).

Figure 2.9 Antibiotic resistance in meticillin-susceptible *S. aureus* (MSSA), meticillin-resistant *S. aureus* (MRSA) (Note), and *Streptococcus pneumoniae* BSI to key antibiotics, England 2017 and 2021

Note: The *S. aureus* data in this chart is based on voluntary reports of meticillin resistance.



Whilst flucloxacillin remains the drug of choice for MSSA infections, second line options are frequently required. Between 2017 and 2021 resistance of MSSA BSI increased to clindamycin (14.9% to 16.7% resistance, p<0.05) and macrolides (16.7% to 18.6%; p<0.05) (Figure 2.9), with small decreases in resistance to tetracycline (4.9% to 4.4%, p=0.058), fusidic acid (12.6% to 11.2%, p<0.05) and mupirocin (4.3% to 2.4%, p=0.08); However, the inverse was observed for MRSA, resistance decreased to clindamycin (55.0% to 47.4%, p<0.05), but rose to tetracycline (14.4% to 22.5, p<0.05).

Data on susceptibility of *S. pneumoniae* BSI is shown in Figure 2.9. The percentages of isolates resistant to penicillin, tetracycline and to macrolides increased slightly between 2017 and 2021, from 1.2% to 2.2% (p<0.05), 6.6% to 7.2% (p=0.09) and 6.7% to 8.0% (p=0.305), respectively. Full 5-year trend graphs and Tables are available in the chapter 2 data tables accompanying this report.

2.4 Trends in antibiotic resistance in invasive group A Streptococcus (iGAS)

In England to-date, penicillin resistance in group A *Streptococcus* (GAS) has not been detected; however, the percentage of iGAS laboratory notifications that are resistant to other key antibiotics has been increasing over the last 5 years Figure 2.4. Between 2017 and 2021, erythromycin resistance more than doubled (121%), from 6.8% to 15.0%, clindamycin increased by 116%, from 6.0% to 12.9%, and tetracycline resistance increased by 237%, from 11.6% to 39.3%.

Figure 2.4. Trends in resistance to key antibiotics in invasive group A Streptococcal infections, England 2017 to 2021

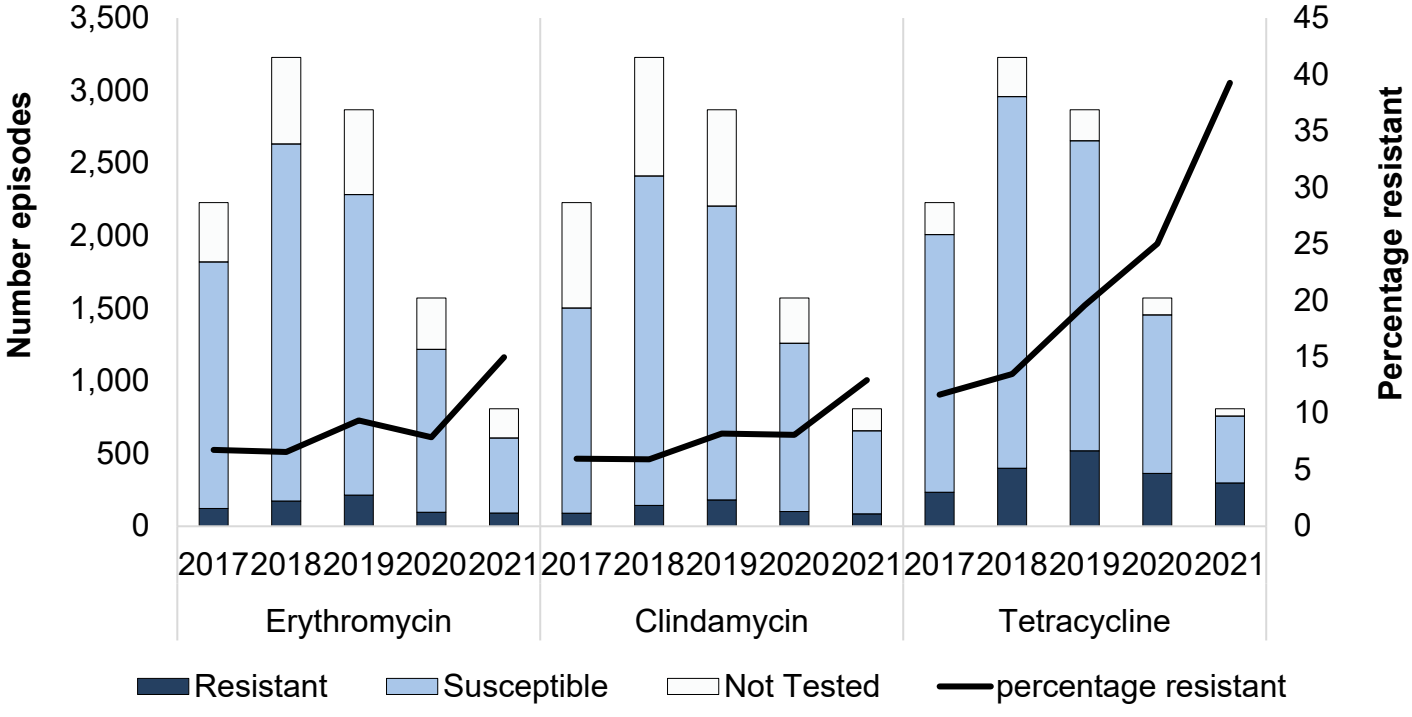


Figure 2.4 also shows that the incidence of iGAS increased to more than 3,000 notifications in 2018 and then declined, reaching lowest levels in 2020 to 2021, coinciding with the COVID-19 pandemic, lock-down effect, and increased social distancing.

Trends and demographics of GAS are discussed in more detail in the seasonal and annual reports.

Group B *Streptococcus* (GBS) resistance to penicillin remains exceedingly rare. An invasive GBS isolate (initially reported in 2016), has subsequently been confirmed as harbouring resistance to penicillin, the first in the UK. Laboratories are requested to send any group A, B, C or G streptococcal isolates exhibiting resistance to penicillin, cephalosporins, daptomycin, quinupristin-dalfopristin, fluoroquinolones or tigecycline to the AMRHAI Reference Unit for confirmation. Guidance on how to do this is in the Bacteriology Reference Department user manual.

2.5 *Staphylococcus capitis* in hospitalised infants, England, 2015 to 2021

During Summer 2020, UKHSA was alerted to a perceived increase in invasive infections caused by *Staphylococcus capitis* (a CoNS species) in hospitalised infants in London over the prior year. The use of whole-genome sequencing (WGS) was employed to investigate the increase, confirmed that most of the neonatal sepsis cases were caused by the NRCS-A clone, known to be multi-drug-resistant and with known environmental persistence in neonatal units (15).

To assess the distribution of the NRCS-A clone, laboratories across England were asked to speciate any CoNS recovered from blood or CSF in an infant (aged <90 days) and refer those identified as *S. capitis* to the AMRHAI Reference Unit for WGS. Between February 2021 and October 2021 more than 300 isolates were referred, and along with additional routine (dating back to 2015) and environmental isolates, >800 isolates were sequenced. WGS results demonstrated widespread geographic dispersal of the NRCS-A clone across England, with evidence of inter- and intra-hospital transmission. Positive specimens being identified within the neonatal environment, predominantly on the surfaces and door ports, dedicated stethoscopes and incubator blankets. This led to the publication of infection prevention guidance, highlighting the importance of decontamination of incubators on neonatal units.

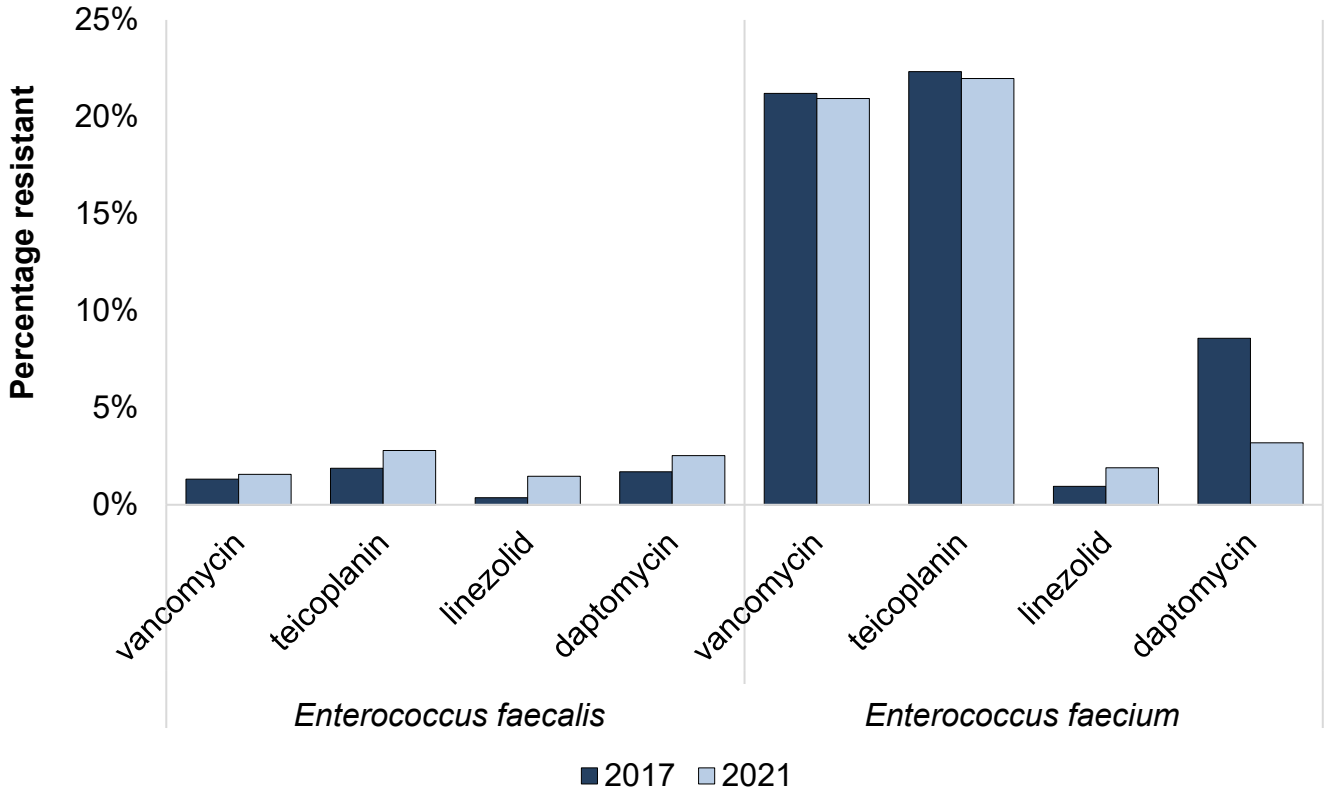
Increased dispersion of multi-drug resistant clones of these common opportunistic pathogens is a concern; particularly when, as with the NRCS-A clone, they can survive for long periods on surfaces with minimal losses in viability. This reinforces the need for thorough (and effective) terminal disinfection of infant incubators, as well as highlights the utility of WGS in investigating the scope of outbreaks to inform infection-prevention practice.

The key *Enterococcus* species split in 2021 has shifted slightly, with *E. faecalis* accounting for 41.1% (down from 43.7% in 2017; $p<0.05$) and *E. faecium* 45.0% (up from 37.3% in 2017; $p<0.05$), with most of this change occurring during the pandemic period.

In 2021, the overall percentage of *Enterococcus* spp. that were glycopeptide resistant was 17.1% (1,427 out of 8,347), a significant increase from 14.7% (1,014 out of 6,907) in 2017 ($p<0.05$). This resistance pattern was largely driven by changes in the species identified. Of the episodes in 2021 that were reported as glycopeptide resistant, 93.1% (1,329 out of 1,427) were also tested for linezolid susceptibility and 5.0% (66 out of 1,329) were found to be resistant.

Resistance to vancomycin and daptomycin remained stable in both *E. faecalis* and *E. faecium* over this period (Figure 2.10). Resistance of *E. faecalis* to linezolid increased significantly 0.4% to 1.5% ($p<0.05$) between 2017 and 2021, respectively. *E. faecium* linezolid resistance also increased significantly from 0.9% to 1.9% ($p<0.05$), whereas daptomycin resistance decreased significantly from 8.6% to 3.2% ($p<0.05$).

Figure 2.10 Antibiotic resistance in *Enterococcus faecalis* and *Enterococcus faecium* BSI to key antibiotics, England 2017 and 2021



2.6 Mobile linezolid resistance update

Oxazolidinones such as linezolid and tedizolid are one of few remaining treatment options for glycopeptide-resistant enterococci (GRE), particularly *E. faecium* that is inherently resistant to β-lactams.

Resistance to linezolid is mostly attributed to mutations within chromosomal genes, primarily genes encoding for 23S ribosomal RNA but also more rarely due to plasmid-mediated cfr, optrA and poxtA genes. Although resistance to linezolid remains rare, the detection of transferable genes such as cfr, optrA and poxtA genes and distinction from chromosomal resistance is of

public health importance, allowing implementation of effective infection prevention and control (IPC) measures to minimise spread and preserve linezolid activity (16).

From 2020 to 2021, using an in-house real-time PCR for the detection of the G2576T 23S ribosomal RNA mutation and acquired plasmid-mediated cfr, optrA and poxtA genes, AMRHAI screened 92 enterococci (52 *E. faecium*, 20 *E. faecalis* and 20 *Enterococcus* spp.) and 28 staphylococci isolates referred by NHS laboratories due to phenotypic resistance to linezolid.

The G2576T mutation remained the most common resistance mechanism and was found in 66.6% of linezolid-resistant isolates (61 enterococci and 19 staphylococci).

Plasmid-mediated resistance gene optrA was detected on its own in 17.5% (n=21) or in combination with poxtA in 1.6% (n=2) of linezolid-resistant enterococci.

The cfr gene was detected in 3.3% (n=4) of the linezolid-resistant staphylococci and was associated with the G2576T mutation in one coagulase-negative staphylococcus.

Antibacterial resistance topics

Surveillance of antibiotic resistance in *Neisseria gonorrhoeae*

Between 2020 and 2021, no instances of ceftriaxone resistance (MIC >0.125mg/L) were observed in the Gonococcal Resistance to Antimicrobials Surveillance Programme (GRASP; Figure 2.11); however, 11 cases of ceftriaxone resistance were reported between September 2021 and June 2022 upon direct referral from primary diagnostic laboratories, compared to a total of 9 between 2015 and 2020. Reassuringly, all cases were successfully treated.

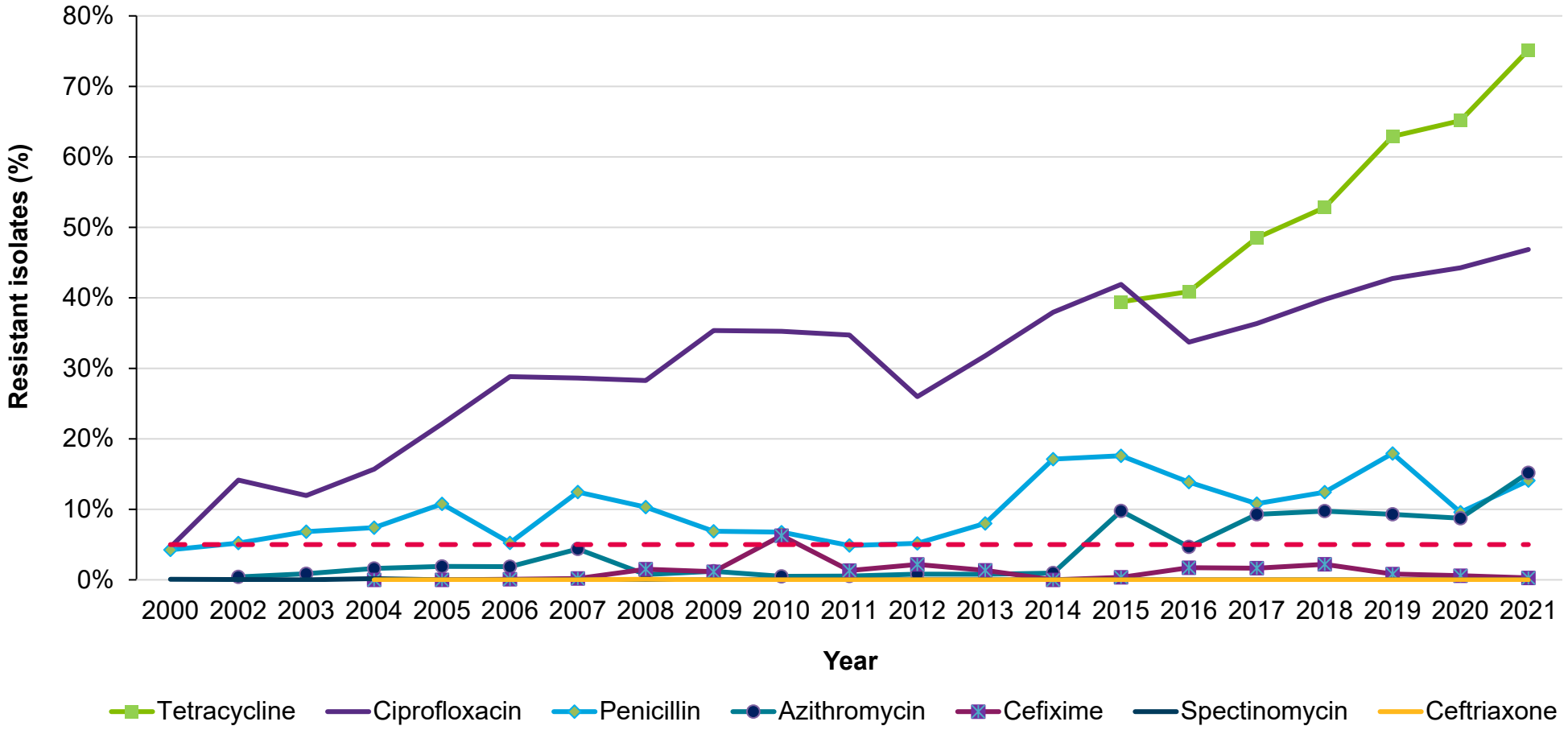
Figure 2.11 also describes the trends in tetracycline, ciprofloxacin, penicillin and spectinomycin resistance from 2000, as well as trends in azithromycin resistance from 2001 and cefixime resistance from 2004. The increase in azithromycin resistance (MIC >0.5mg/L, previous EUCAST breakpoint used for continuity) in 2021 was driven by an increase in isolates with MICs at 1.0mg/L as the proportion of isolates with azithromycin MIC >1.0mg/L remained stable at 4.2% in 2020 and 5.0% in 2021. Penicillin resistance remained stable with some fluctuation over recent years. Tetracycline and ciprofloxacin resistance, on the other hand, have continued to increase rapidly since 2016. As in previous years, no spectinomycin resistance (MIC >64mg/L) was detected in 2021.

Prescribing data collected through the sentinel surveillance system demonstrates excellent compliance with the UK guidelines, with 97.1% of individuals receiving the recommended first-line therapy of ceftriaxone 1g IM monotherapy. The update to UK guidelines in 2019, which replaced dual therapy (ceftriaxone 500mg IM and azithromycin 1g) with a higher dose ceftriaxone 1g IM monotherapy as the recommend first-line treatment, appears to coincide with improving susceptibility to ceftriaxone and cefixime and the overall effectiveness of treatment as no treatment failures were reported in 2021.

Results of the GRASP sentinel surveillance data are described in full in the annual GRASP report.

Figure 2.11. Percentage of *N. gonorrhoeae* isolates in the GRASP sentinel surveillance system that were resistant to selected antimicrobials, England and Wales, 2000 to 2021

Note: Due to changes in the diagnostic sensitivity medium used to test antimicrobial susceptibility of sentinel surveillance isolates, MICs for the 2015 to 2021 collections are not directly comparable with those from previous years. Trends from 2000 to 2014 compared to 2015 to 2021 must be interpreted with caution, particularly for azithromycin and tetracycline (data for tetracycline is only included from 2015 onwards due to this issue) (17). The 5% threshold (≥5% of infections resistant to the first-line therapy) at which the WHO recommends that first-line monotherapy guidelines should be changed is indicated by the horizontal dashed red line.



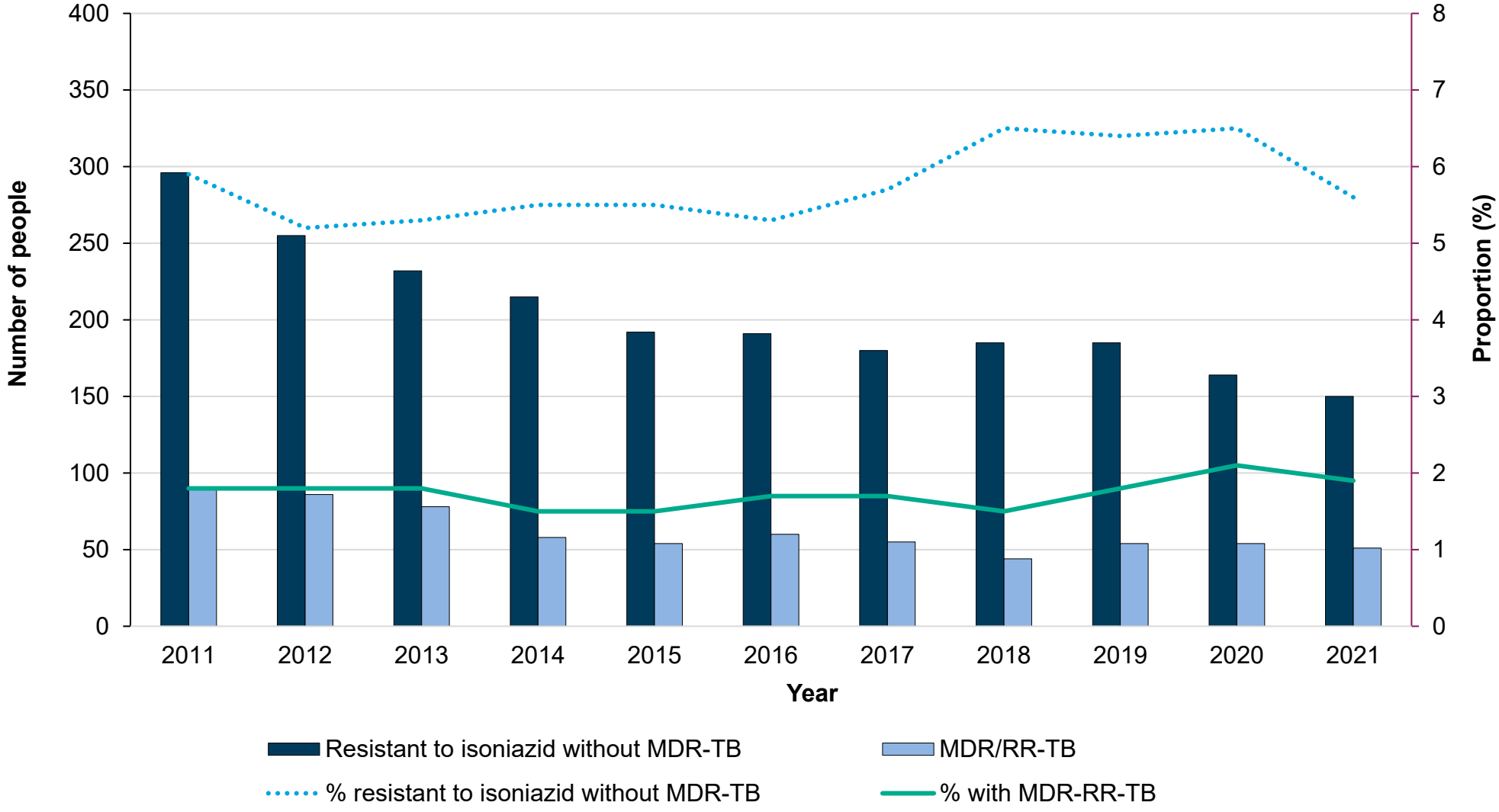
Surveillance of antibiotic resistance in *Mycobacterium tuberculosis* infections

The number of tuberculosis (TB) disease notifications has nearly halved between 2011 and 2021 (8,282 versus 4,425). However, the percentage Isoniazid mono-resistant or multi-drug resistance remained steady over the same time frame.

Isoniazid (INH) monoresistance is the most frequent resistance pattern in Mycobacterium tuberculosis (MTB) complex isolates in England, occurring in between 5.5% to 6.5% of tested cases (Figure 2.12, below). A small reduction in the proportion of INH monoresistance was observed in 2021 compared to the previous 3 years. Multidrug-resistant TB (MDR) and rifampicin-resistant TB (RR) are defined as MTB resistant to both INH and rifampicin or rifampicin alone. Since 2011, MDR/RR-TB cases occur in around 2% of tested cases. A small decrease in the proportion of cases with MDR-RR-TB was observed for 2021 compared to the previous year. Outcomes for patients with MDR-TB are worse than for drug sensitive disease. The drugs used for treatment of MDR-TB are often poorly tolerated and need careful monitoring because of toxicity. More detail on trends in drug resistance and treatment outcomes of MDR-TB is presented in the Tuberculosis in England annual report.

Figure 2.12. Number and proportion of people notified with TB with initial drug resistance, England, 2011 to 2021

Note: People with culture-confirmed TB with a result (DST or WGS) for at least isoniazid and rifampicin



Antifungal resistance

Trends in incidence and antifungal resistance in candidaemia

The incidence of candidaemia was 3.7 per 100,000 population (n=2,090) in 2021, an overall increase of 9.7% since 2017 (3.4 per 100,000).

Prior to 2020, the incidence of *Candida* spp. BSI was decreasing, with a 6.5% decrease between 2017 and 2019 (3.1 per 100,000 population in 2019; n=1,774). However, between 2019 and 2021 the incidence increased by 17.4%; an 11.3% increase from 2019 to 2020 and then a smaller increase of 5.4% from 2020 to 2021. *Candida albicans* was the most frequently isolated *Candida* species across the 5-year period followed by *Candida glabrata*, accounting for 43% and 25% of candidaemia episodes, respectively.

Candida auris, the fluconazole-resistant and sometimes multidrug-resistant yeast which has been responsible for multiple intensive-care unit (ICU) outbreaks globally including several in the UK, continues to cause sporadic infections often in individuals that have recently travelled to areas where it is endemic, most notably India. Four *C. auris* candidaemia were reported to SGSS in 2021.

Additional data on *Candida* species, including recent taxonomic revisions, and regional data on incidence, can be found in the Annexe accompanying this report.

Routine laboratory surveillance reports submitted to UKHSA's SGSS showed that in 2021, 83.5% (1,745 out of 2,090) of *Candida* isolated from blood were subjected to susceptibility testing. This section will focus on susceptibility test results for 3 key antifungals (amphotericin B, caspofungin and fluconazole, see Figure 2.13, below).

More detailed trend data, including numbers reported as susceptible or resistant, is available in the chapter 2 data table accompanying this report.

Figure 2.13. Percentage of all *Candida* species combined, and *C. albicans* and *C. glabrata* isolates from blood assessed separately, displaying resistance to key antifungals in England, 2017 and 2021

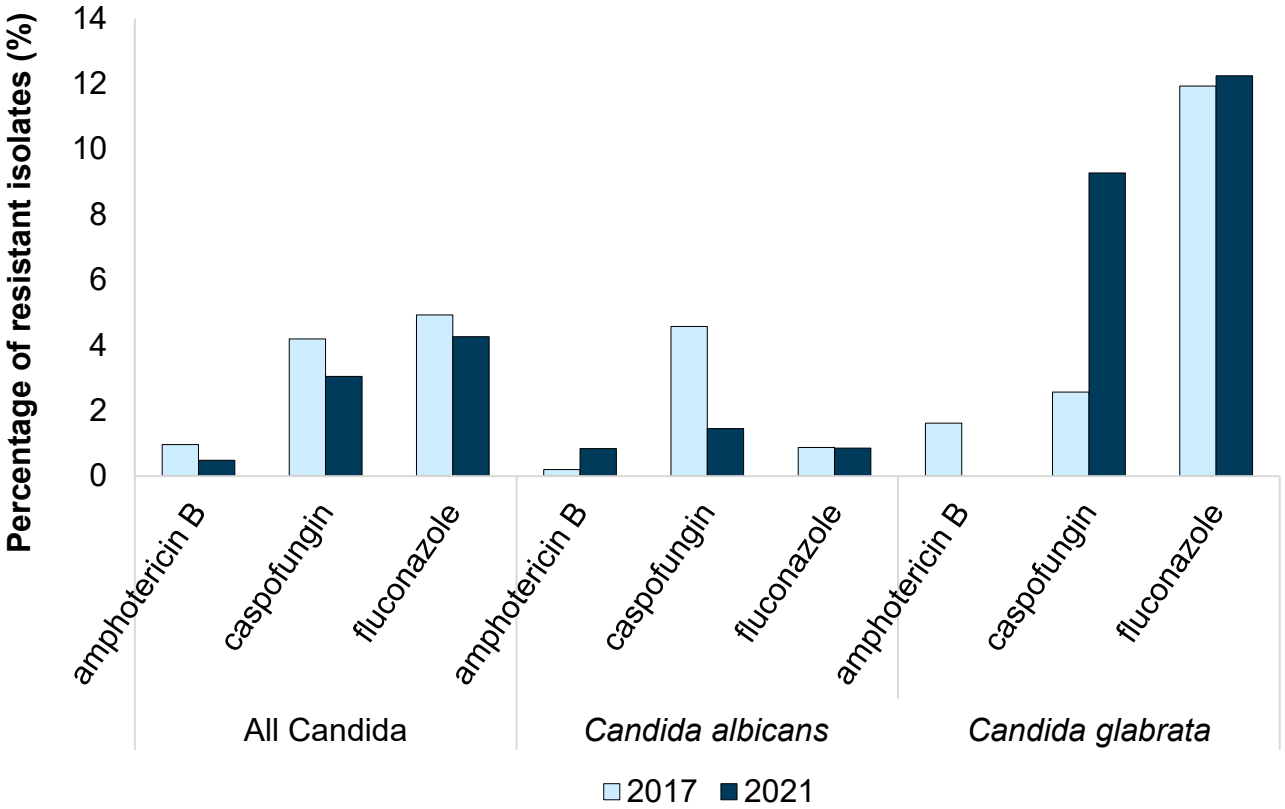


Figure 2.13. depicts the percentage of isolates resistant to 3 key antifungals, comparing 2021 with 2017, for all *Candida* species, *C. albicans* and *C. glabrata*. In 2021, resistance to fluconazole was detected in 0.9% of *C. albicans* and 12.2% of *C. glabrata* isolates.

Caspofungin resistance decreased (4.6% to 1.5%; $p<0.05$) in *C. albicans*, but increased in *C. glabrata* BSI (2.6% in 2017 to 9.3% in 2021; $p<0.05$). Other observed fluctuations were not statistically significant.

Supplementary analyses on candidaemia cases are available in the chapter 2 data tables, along with an update from the UKHSA National Mycology Reference Laboratory (MRL) on antifungal susceptibilities in less frequently reported fungal pathogens, and antifungal drug resistance in 2021, a perspective from the Mycology Reference Centre Manchester.

Antiviral resistance

Information on SARS-CoV-2 and key COVID-19 therapeutics are presented in Chapter 7.

Influenza virus

During the 2021 to 2022 flu season (period between week 40 of 2021 and week 10 of 2022) no Influenza viruses with known markers of resistance to neuraminidase inhibitors in 309 A(H3N2),

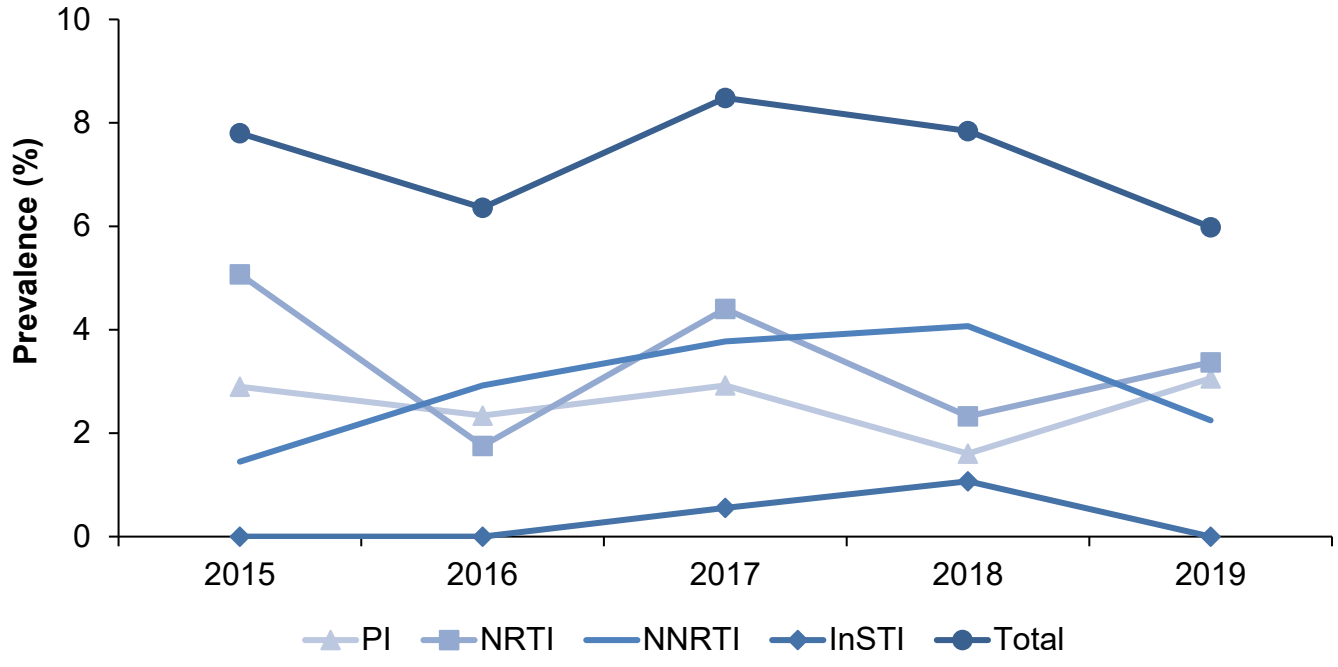
17 A(H1N1) pdm09 and 11 B/Victoria-lineage neuraminidase gene sequences were detected through UKHSA influenza virus surveillance systems (see the Methods and caveats section of the Annexe accompanying this report). This continues the ongoing trend of very low resistance to neuraminidase inhibitors in the UK (2016 to 2021) (5).

In addition, no viruses with known markers of resistance to baloxavir marboxil (a new class of influenza polymerase inhibitor licensed for use in the UK in 2020) were detected (out of 14 A(H1N1) pdm09 and 10 B/Victoria-lineage PA gene sequences (cap-dependent endonuclease)). Of 277 A(H3N2) PA gene sequences, 275 had no markers of resistance to baloxavir, however, 2 sequences were identified with an E199G amino acid substitution. Further information of Influenza virus trends and antiviral resistance testing for the 2021 to 2022 season can be found in the annual influenza report.

Human immunodeficiency virus (HIV)

In the INITIO (an open randomised trial to evaluate different therapeutic strategies of combination therapy for HIV-1 infection) study, samples from approximately 1,000 randomly selected patients with recently-acquired (<4 months) HIV and no history of antiretroviral drug treatment were submitted for HIV WGS in the Antiviral Unit. Results are shown in Figure 2.14. In 2019, drug resistance prevalence in this drug-naïve population was 6.0% overall with 3.4% nucleos(t)ide reverse transcriptase inhibitors (NRTI), 3.1% protease inhibitors (PI) and 2.2% non-nucleoside reverse transcriptase inhibitors (NNRTI) resistance. Drug resistance prevalence declined between 2015 and 2019 from 7.8 to 6.0%, driven by the decline in NRTI resistance from 5.1% to 3.4%. With regard to potential resistance against current pre-exposure prophylaxis (PrEP) agents, there were only 2 cases of M184I/V in reverse transcriptase (RT), and no cases of K65R within drug-naïve individuals between 2015 to 2019.

Figure 2.14. Prevalence of resistance to antiretrovirals within the INITiO study – antiretroviral-naïve individuals with recently-acquired HIV

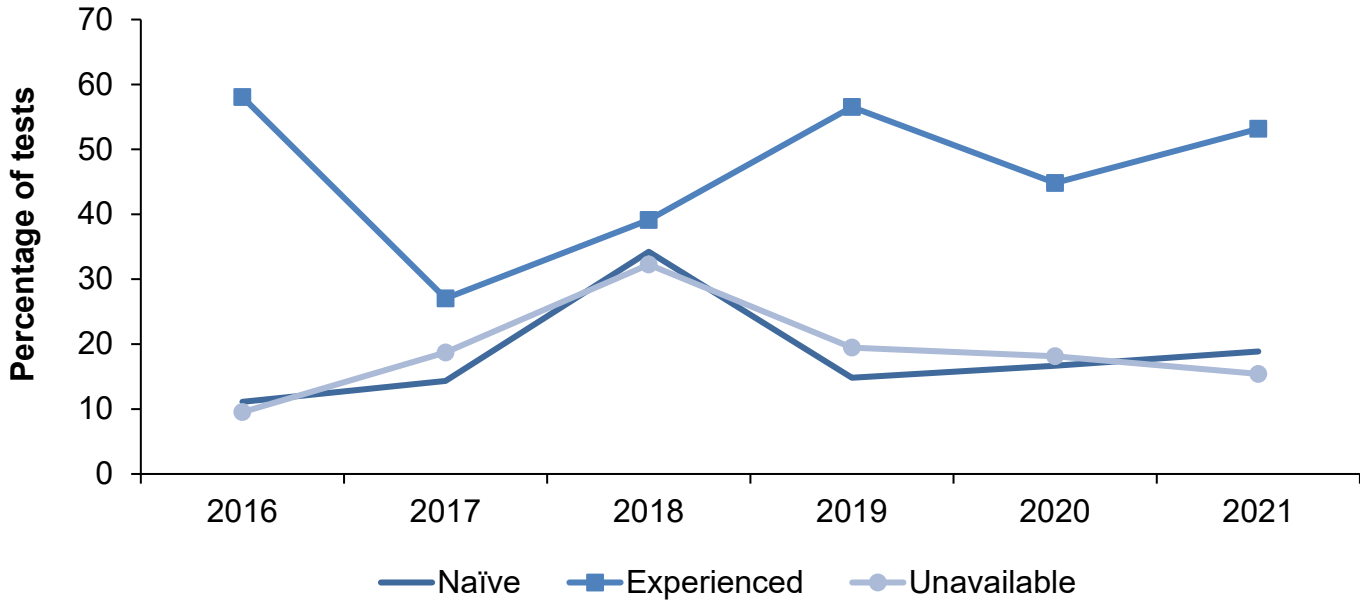


Hepatitis C virus (HCV)

Figure 2.15 shows the prevalence of resistance to HCV direct-acting antiviral (DAA) drugs where resistance-associated substitutions were detected in the NS5A gene of subtype 1a samples from 2,449 patients with HCV between 2016 and 2021 in England, Wales and Northern Ireland (as reported by the UKHSA's Anti-viral Unit).

Resistance in drug-naïve individuals increased from 11.1% to 18.9% from 2016 to 2021, likely reflecting the widespread adoption of NS5A inhibitor-containing regimens in conjunction with the selection and subsequent transmission of NS5A inhibitor resistant variants. In drug-experienced individuals, there is a high prevalence of NS5A resistance.

Figure 2.15. The percentage of tests where resistance-associated substitutions were detected in the NS5A gene for HCV subtype 1a (source Antiviral Unit, UKHSA)

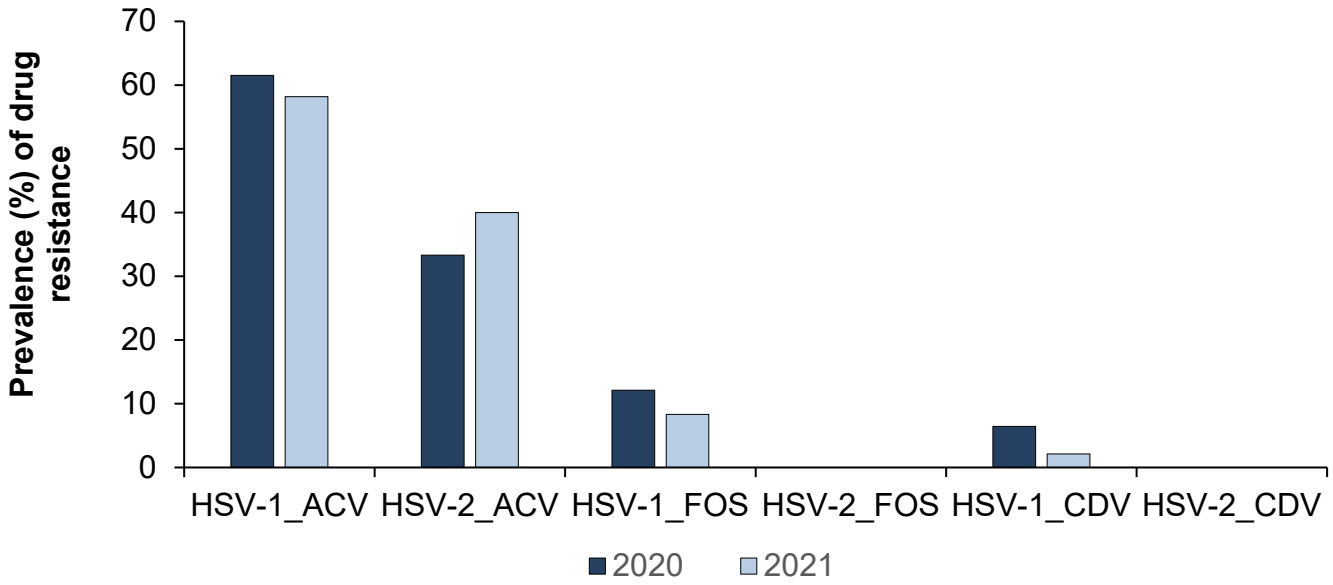


Herpes simplex virus (HSV)

The prevalence of drug-resistant HSV-1 or HSV-2 in 2020 to 2021 in samples from patients with known disease received in UKHSA's Antiviral Unit is shown in Figure 2.16. In total, 79 and 121 samples were received in 2020 and 2021, respectively, with most samples coming from individuals with underlying immunosuppression. Aciclovir resistance was detected in the majority (60%) of samples with HSV-1 and in a significant minority (33 to 40%) with HSV-2 infection.

Foscarnet resistance was detectable in approximately 10% of HSV-1 samples and in none of the HSV-2 samples. Cidofovir resistance was detected in 2 to 6% of HSV-1 samples and none detected for HSV-2. However, these cases were immunosuppressed and likely to have received multiple courses of antivirals and therefore do not represent the majority of clinical cases treated with antivirals.

Figure 2.16. Prevalence of drug resistant HSV-1 or HSV-2 in patients with known HSV disease, from samples received in UKHSA's Antiviral Unit, 2020 to 2021



Hepatitis B virus (HBV)

Between 2019 and 2021, <5% of samples sequenced as part of the characterisation service had evidence of motifs associated with HBV resistance. Within these, there was evidence of cross resistance with 79% of samples harbouring resistance profiles for lamivudine and telbivudine, 21% of samples with resistance profiles for adefovir and lamivudine and 63% harbouring resistance profiles for lamivudine and entecavir. Of these drugs, only entecavir is currently used for HBV treatment in England; lamivudine may still be commonly used globally, particularly in lower-middle income countries. A review of enhanced acute hepatitis B surveillance data (from 2009) has shown little evidence of transmission of mutations associated with antiviral resistance.

UK participation in international surveillance of AMR

The fourth WHO global antimicrobial resistance and use surveillance system (GLASS) report was published in June 2021, and included data from the UK, covering blood and urine isolates from 2019, and a description of the current status of AMR surveillance nationally.

Long-term goals of GLASS include supporting the development of surveillance approaches that include epidemiological, clinical, and population-level data to allow calculation of AMR rates in the population, and the coordination of global surveillance systems on AMR in animals, food, and the environment for the investigation of drivers of AMR development.

Replacing the ECDC European antimicrobial resistance surveillance network (Ears-Net) submission for the UK for 2020 antimicrobial resistance data, was a submission to the WHO Central Asian and European Surveillance of Antimicrobial Resistance (CAESAR) network for inclusion in the report in 2022.

Main AMR resources and reports

UKHSA works to produce and publish reports on AMR and infections as part of many routine outputs. Here we list a few key reports, for a longer list of AMR resources and reports please refer to the 'Methods and caveats' section of the Annexe accompanying this report. Research-based outputs using much of the data referred to in this report and the listed resources are documented in the Research chapter (Chapter 8) and include:

- carbapenemase-producing Gram-negative bacteria laboratory surveillance quarterly reports
- weekly carbapenemase Notifications of Infectious Diseases (NOIDs) reports
- MRSA, MSSA, Gram-negative bacteraemia and *C. difficile* infections quarterly report
- pyogenic and non-pyogenic Streptococcal bacteraemia annual data from voluntary surveillance
- Fingertips: AMR local indicators
- UK One Health report: Antibiotic use and antibiotic resistance in animals and humans
- Tuberculosis in England: national quarterly reports

A more comprehensive list of relevant reports is available in Chapter 2 of the Annexe accompanying this report.

Discussion

As we emerge from the COVID-19 pandemic, it will take time to assess the resulting impact on bacterial trends and AMR burden. Between 2018 (baseline) and 2021, there has been a 9.1% reduction in (estimated) antibiotic-resistant infections in England, with the equivalent of an estimated 148 'severe' resistant infections, on average, occurring each day (in 2021). As it currently stands, England appears on track to meet the NAP ambition, to achieve a 10% reduction against the 2018 baseline by 2025. However, as AMR estimates rely on the number of BSI, trends analysis should be caveated by the overall reduction in incidence of BSI seen in 2020 due to the pandemic associated with changes in healthcare activity.

The burden of resistance, estimated by the total number of key BSI pathogens resistant to one or more key antibiotics, decreased by 4.2% between 2017 and 2021. Antibiotic-resistant BSI are predominately caused by bacteria from the Enterobacterales family, comprising 80.3% of the total resistant episodes, with *E. coli* resistance dominating at 67.1% across all species within this family.

There were marked regional variations in the burden of BSI AMR, with the London region reporting the highest rate per 100,000 population. This is likely due to a combination of factors, including patient referrals to specialist centres concentrated in certain regions. A more detailed analysis is planned that will also consider the effects of ethnicity and deprivation. In preliminary analysis, the highest percentage resistant BSI in England in 2021 was seen in the Asian or

Asian British ethnic group (32.8%), followed by Black, African, Caribbean, Black British (31.8%), with the lowest rates (but highest burden of incidence) in the white ethnic group (20.9%).

The crude 30-day all-cause case fatality rate in patients with key Gram-negative bacterial BSI susceptible to AMR burden-defined antibiotics was 16.3%, 2% lower than patients infected with a strain resistant to one or more key AMR burden-defined antibiotics. For patients with invasive acquired carbapenemase-producing Gram-negative isolates, the crude case fatality rate was 24.5%. The true picture is more nuanced than resistance alone, and will be affected for example, by population demographics, case mix, time to effective treatment, and pathogenicity. However, the diverging case fatality rates have been noted and require further monitoring and investigation.

The incidence of *E. coli* BSI decreased between 2017 and 2021. A more mixed picture is seen across the other reported Gram-negatives species, with rises in BSI incidence per 100,000 population seen in *K. pneumoniae* and *Pseudomonas* spp., and year-on-year increases in *Enterobacter* spp., *Serratia* spp., and *Citrobacter* spp. Reasons for this are mixed and include the multifactorial effects of the COVID-19 pandemic, with a resulting change in case mix, and increased rates of HCAI, particularly in high dependency and critical care units.

Resistance to co-amoxiclav remains high in *E. coli* (41.2%). The use of co-amoxiclav as monotherapy for empirical sepsis regimes is not recommended unless hospitals have robust epidemiology and outcome measures available to guide prescribing guidelines. Piperacillin with tazobactam resistance in *K. pneumoniae* BSI has risen annually since 2017 and now peaks at 18.3% ($p<0.05$). This species remains the most frequent harbourer of acquired carbapenemase genes in England.

Ciprofloxacin resistance in isolates from BSI remains elevated across all species and varies between 17.2% in *E. coli*, 15.3% in *K. pneumoniae*, to 6.9% in *Pseudomonas* spp. Ciprofloxacin resistance can severely limit the number of effective oral treatment options, with an increasing reliance on parental agents regardless of clinical severity. *Pseudomonas* spp. BSI resistance has remained stable since 2017 for most key antimicrobials, with carbapenem resistance at 8.4% in 2021.

Similar to what was reported in last year's report, the majority of CPE laboratory notifications originate from screening samples, with just over 5% derived from invasive and sterile sites. Whilst the 'big 5' carbapenemase families continue to dominate, there remains marked regional variation in both the number of screens performed, and the frequency and type of carbapenemase being reported, with a higher rate of notifications reported in more deprived areas.

Whilst the majority (81%) of trusts report CPE screening data, differences are seen intra-and-inter-regionally. Longstanding institutional outbreaks, and differences in local screening approaches impact regional reporting data. Appreciating differences in screening strategy across both acute trust and region, is important for the understanding and interpretation of CPE

incidence and distribution, and to ensure it remains representative of the national picture. The results of the 2022 UKHSA coordinated national point prevalence survey of CPE in ICUs and ICU screening policies will help assess this.

The detected regional differences in AMR burden, and carbapenemase gene prevalence requires local and regional knowledge, context, and strategies. Additionally, the effect of deprivation on CPE incidence, and the effect of AMR burden across ethnic groups has been described for the first time in this chapter.

Understanding the impact of ethnicity, deprivation, regional divergence, along with potential confounders, remains a crucial avenue of enquiry, and essential to the identification of appropriate target interventions. These investigations are currently underway using data linkage and form one of the future actions of this report.

Over the last 5 years local capacity to detect the most frequent carbapenemase families, along with the introduction of statutory reporting of acquired carbapenemase-producing Gram-negative bacteria, their antimicrobial susceptibility testing and resistance mechanisms, has improved our national surveillance capabilities. However, vigilance must be maintained against the introduction of rarer or novel carbapenemases. Investment in national capacity to detect novel drug resistance, both phenotypically and genotypically and particularly our ability to detect and differentiate mobile resistance, will be essential. Improved detection and understanding of AMR and its vectors will allow the implementation of effective IPC measures, to reduce transmission, and maintain our antimicrobial armamentarium.

We have seen how the use of WGS has been used successfully to investigate invasive S. capitis infections in hospitalised infants in London, revealing the spread of a multi-drug-resistant clone (NRCS-A), persistent in the environment, with widespread geographic dispersal. WGS, and other molecular typing methodologies, have an increasingly important role to play in outbreak detection and the understanding of transmission dynamics within healthcare organisations and the wider community, informing IPC measures to reduce hospital transmission of this nosocomial pathogen.

The incidence of BSI caused by Gram-positive bacteria has remained relatively stable since 2017.

The burden of resistant infections remains relatively unchanged for Gram-positive infections (*S. pneumoniae*, *S. aureus* (5.7% MRSA) and *Enterococcus* spp.). Penicillin resistance in *S. pneumoniae* BSI has increased slightly between 2017 and 2021, but remains at less than 2.5%. However, it has been reported in GBS in England from an isolate dating back to 2016.

In England to date, penicillin resistance in GAS has not been detected. However, the percentage of iGAS laboratory notifications that are resistant to other key antibiotics has been increasing over the last 5 years. Since 2017, resistance to erythromycin, clindamycin and tetracycline has more than doubled (to 15%, 13% and approximately 40%, respectively). The

use of clindamycin in empirical life-threatening iGAS regimes as a single agent in penicillin allergy requires caution. With treatment options for GAS in penicillin-allergic patients becoming more challenging, it is important that penicillin allergy labels are correctly applied. Approximately 6% of UK adults have a label of penicillin allergy in their general medical records; however, when evaluated fewer than 1% have IgE-mediated reactions (18). The use of broad-spectrum antibiotics in patients labelled as 'penicillin-allergic' is associated with increased health costs, risk of AMR and suboptimal antibiotic therapy (19). Efforts should be made to review drug allergies, with de-escalation or consideration for drug allergy testing where appropriate (20).

In 2021, glycopeptide resistance in *Enterococcus* spp. was 17.1% (1,427 out of 8,347), a significant increase from 14.7% (1,014 out of 6,907) in 2017 ($p<0.05$). This pattern is likely due to a slight shift in species, with *E. faecium* now predominating at 45% (up from 37.3% in 2017; $p<0.05$), with *E. faecalis* accounting for 41.1% (down from 43.7% in 2017; $p<0.05$), with most of this change occurring during the pandemic period. Linezolid resistance remains low in both *E. faecium* and *E. faecalis* at 1.9% and 1.5% in 2021.

Of the detected ceftriaxone-resistant *N. gonorrheae* cases, most had travel links with the Asia Pacific region, which has been shown to have the highest prevalence of ceftriaxone-resistant *N. gonorrhoeae* globally (21). However, as not all partners could be contacted in addition to some cases having no travel links, ongoing transmission within the UK cannot be excluded.

Prior to 2020 incidence of candidaemia had been decreasing, but for the last 2 years incidence increased; this is likely to have been influenced by the COVID-19 pandemic and the large number of ICU patients experiencing candidaemia as described in last year's ESPAUR report.

C. albicans has remained the most frequently isolated species for the last 5 years (43% of all isolates in 2021), followed by *C. glabrata* (25%). Whilst there has been little change in the frequency of isolating *C. albicans* and *C. glabrata* from 2017 to 2021, there was an increase in the number of isolates of *C. parapsilosis* in 2021 with a 43.1% increase from the numbers reported in 2017 (see the 'Methods and caveats' section of the Annexe accompanying this report).

Detection of *C. auris* has remained low over the past 5 years, with only sporadic introductions occurring predominantly from international repatriations. However, reports have emerged that agricultural use of antifungals may be helping to drive antifungal resistance. A study on stored apples treated with fungicides to prevent spoilage detected isolates of *C. auris* with reduced sensitivity to the fungicides the apples were treated with (22). Other research has suggested that agricultural use of fungicides, specifically azoles, is helping to produce azole-resistant A. fumigatus in the environment (23). Reports have emerged of mechanisms of resistance in agricultural environments leading to cross-resistance of clinical azoles in isolates from patients, suggesting an agricultural origin of *A. fumigatus* strains infecting patients (22, 23, 24).

Ongoing surveillance is needed to detect any emergence of infections due to fungi with resistance acquired in the environment to raise awareness and inform mitigating strategies.

For antiviral resistance, there is continued very low resistance detected for influenza viruses and HBV, whereas resistance has increased in drug-naïve patients with HCV (18.9% in 2021). For patients with HSV, the data highlight that resistance to first line antiviral therapy frequently emerges in immunosuppressed patients, with the potential for emergent resistance to both second-line agents.

For the first time HIV antiviral resistance data is presented in the AMR report. Resistance in drug-naïve patients with HIV has reduced by 2 percentage points since 2015 to 6.0% in 2019. However, HIV resistance data is limited as the UK national HIV drug resistance database is no longer active, due to the end of the funding stream by the Medical Research Council.

Future actions

ESPAUR will continue to:

- emphasise the importance of IPC with the objective of reducing the numbers of (antibiotic-resistant) infections
- collaborate with veterinary and international colleagues to promote a global one health approach to surveillance of AMR
- integrate phenotypic and genotypic data on carbapenemase-producing bacteria derived from local testing into SGSS
- link microbiology data in SGSS with patient-level clinical, epidemiological and risk factor data in HES

Antibacterial resistance

- investigate in more detail the impact that health inequalities have on AMR infections
- identify further surveillance opportunities on plasmid-mediated resistance
- promote recognition to fund the provision of WGS for referred isolates to AMRHAI to enhance outbreak and surveillance of AMR and carbapenemase-producing mechanisms
- complete the analysis on the 2022 point prevalence survey for CPE in ICUs
- investigate CoNS AMR and clinical significance of those patients who are immunocompromised (including neonates) and/or have medical implants
- complete a CPE specific detailed descriptive analysis, incorporating inequalities and mortality analyses
- undertake a deeper investigation into the increases in resistance to key treatment options for GAS infections

Antifungal resistance

- undertake a review of fungal infections and antifungal resistance in specimens that aren’t from blood

- utilise the ESPAUR antifungal sub-group to evaluate and recommend the next steps to improve fungal disease reporting and antifungal prescribing and resistance surveillance

Antiviral resistance

- update national HIV drug resistance surveillance database and ensure continued maintenance
- develop tools for novel HBV biomarkers to monitor responses to the new drugs and develop amplicon based and sequence capture methods for whole genome sequencing to better characterise potentially resistance motifs

3. Antimicrobial consumption

The UK's 5-year National Action Plan (NAP) has an ambition to reduce total UK antimicrobial consumption in humans by 15% by 2024, from a 2014 baseline (25). It also highlights the need for surveillance and 'information for action' to inform and ensure progression towards this, and other, national measures. This chapter exemplifies the importance of data access and active monitoring of trends in antimicrobial usage, over time (including unusual periods, such as the COVID-19 pandemic), and across different prescribing settings.

This chapter presents data on antibiotic and antifungal consumption in England in 2017 to 2021, in primary and secondary care, and includes 2 years since the COVID-19 pandemic was declared. Antibiotic prescribing settings include general practice (GP), dental practice, out-of-hours services, and hospital inpatient and outpatient services (see Chapter 3 of the Annexe accompanying this report for more details).

Methods, research activities and further detailed analyses can be found in the Annexe. Data and figures presented in this chapter are available in the chapter 3 data table spreadsheet and the downloadable figures slidedeck.

Antibiotic consumption

Total antibiotic consumption

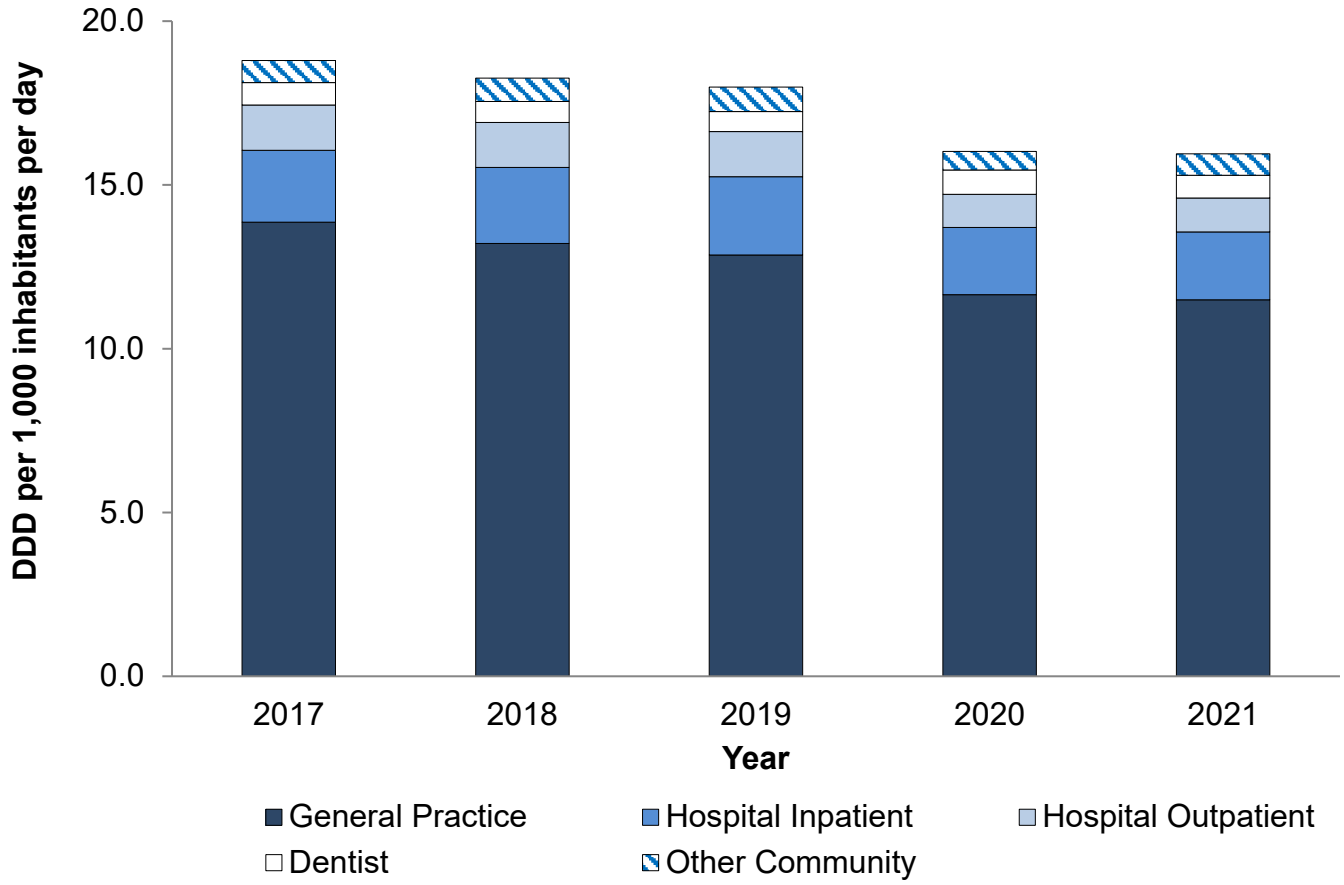
In England, total antibiotic consumption declined by 15.1% between 2017 to 2021, from 18.8 Daily Defined Dose (DDD) per 1,000 inhabitants per day (DID) to 15.9 DID (Figure 3.1). The 2021 DID of 15.9 was 4.7% lower than the set UK target for total antibiotic use, a target of 15% reduction from 2014 baseline. Although a previously decreasing trend was evident pre-COVID-19 (reduction of 4.3% between 2017 to 2019), the decline accelerated, correlating with the start of the pandemic (reduction of 10.9% between 2019 to 2020 alone), with a further decline of 0.5% between 2020 to 2021.

Over the past 5 years, the majority of antibiotics in England were prescribed within general practice, with this trend continuing in 2021 (72.1% of overall prescribing, 11.5 DID). The subsequent percentages of prescribing in 2021 occurred in hospital inpatients 13.0% (2.1 DID), hospital outpatient 6.5% rounding) (1.0 DID), dental practices 4.3% (0.69 DID) and other community settings 4.1% (0.66 DID) (Figure 3.1). During the initial pandemic period (2019 compared to 2020) consumption rates decreased across all settings apart from dental practices.

In 2021, consumption in dental practices did see a reduction (-7.1%, from 0.75 to 0.69 DID in 2020 and 2021, respectively). This is still above the pre-2019 levels and a slight year-on-year decline had been observed up to this point. Hospital inpatient (1.2%, 2.05 DID in 2020 to 2.07 DID in 2021), hospital outpatient (2.4%, 1.01 DID in 2020 to 1.03 DID in 2021), and other

community settings (15.9%, 0.57 DID in 2020 to 0.66 DID in 2021) have all shown increases in consumption between 2020 and 2021.

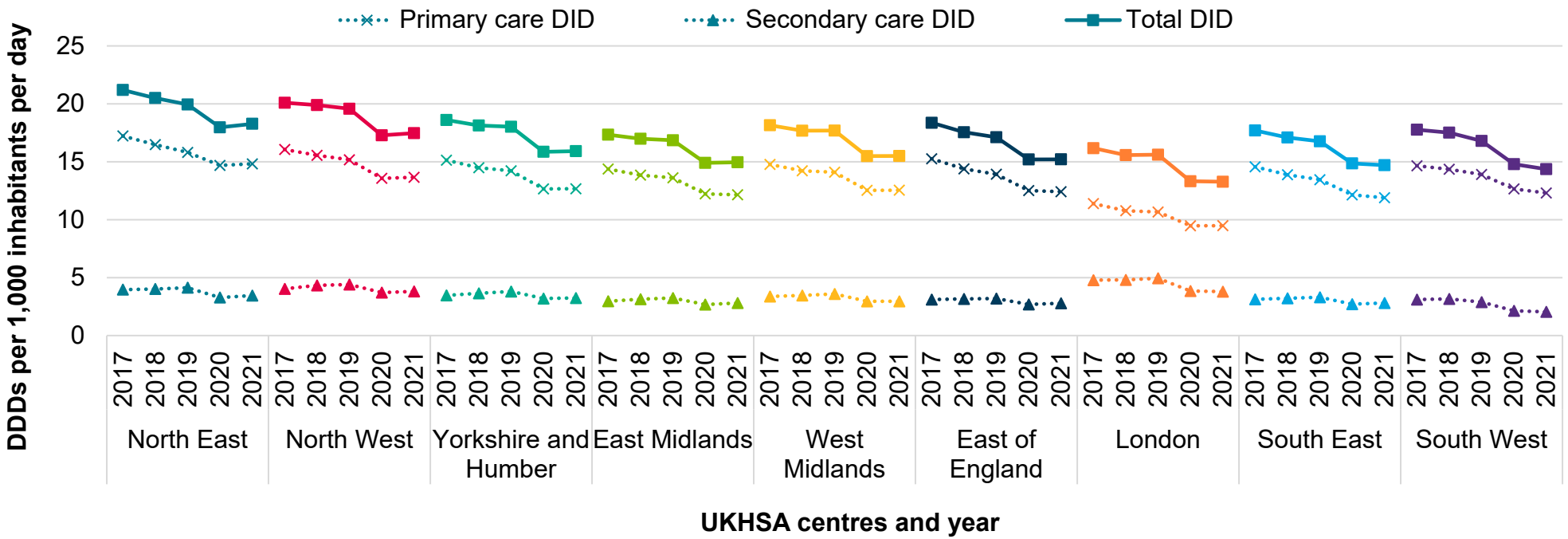
Figure 3.1 Total antibiotic consumption by setting, expressed as DDDs per 1,000 inhabitants per day, England, 2017 to 2021



3.1. Regional variation in antibiotic consumption in England

The DID has consistently been greatest within the North East and North West of England, and lowest in London (Figure 3.1.1, below). From 2017 to 2019, total antibiotic prescribing trends have shown year-on-year decreases across all the UKHSA centres in England, predominantly driven by reductions in the primary care setting. Primary care data did not include dental care prescribing as dental data at the UKHSA region-level were not available. Prior to 2020, the primary care prescribing rate was consistently highest in the North East of England and lowest in London, whilst secondary care consumption was highest within London, and lowest in the South West and East Midlands (Figure 3.1.1).

Figure 3.1.1. Total, primary and secondary care antibiotic consumption in UKHSA centres, expressed as DDDs per 1,000 inhabitants per day, 2016 to 2020 (excludes dental practice data)



The COVID-19 pandemic saw regional reductions in the rate of total antibiotic consumption (DID) as well as across settings (primary and secondary care DIDs).

Since the vast reductions previously noted correlating to the COVID-19 pandemic, increases have since been seen in secondary care between 2020 and 2021 for all regions apart from London, where there was a 1.2% decrease (from 3.61 to 3.57 DID). The analysis has not taken into consideration the change in the number of patients and hospital episodes of care, or the change in case-mix over this time period (with elective surgeries being postponed during the early parts of the COVID-19 pandemic).

Consumption levels for all UKHSA regions and across both primary and secondary care remain lower than pre-COVID-19 levels (that is, sustained lower antibiotic consumption compared to 2019).

Antibiotic group

As can be seen in Table 3.1, below, the antibiotic group with the highest total consumption in England in 2021 were penicillins excluding β-lactamase inhibitor combinations (BLI) (30.4%, 4.84 DID), followed by tetracyclines (27.1%, 4.33 DID), and 'macrolides, lincosamides and streptogramins' (13.8%, 2.19 DID).

There were continued reductions in consumption of most antibiotic groups between 2020 and 2021. However, increases occurred in penicillins (excluding BLIs: 2.1% increase ($p<0.05$), penicillin and BLI combinations: 1.5%), first and second generation cephalosporins (4.3%), carbapenems (1.2%, $p<0.05$), anti-*Clostridioides difficile* agents (20.3%, $p<0.05$), and 'other antibacterials' (see Chapter 3 of the Annexe accompanying this report for full definitions) (1.6%, $p<0.05$). Metronidazole consumption increased between 2019 and 2020 (1.8%, 0.298 DID in 2019, 0.304 DID in 2020), oral metronidazole consumption has now reduced below 2019 levels (-6.1%, 0.285 DID in 2021) (see Table 3.1, below).

Further detailed assessment of antibiotic consumption by antibiotic classes can be found in Chapter 3 of the Annexe accompanying this report.

Table 3.1 Total antibiotic consumption by antibiotic groups, expressed as DDDs per 1,000 inhabitants per day, 2017 to 2021

Antibiotic Group	2017	2018	2019	2020	2021	Trend	p-value
Penicillins (excluding β-lactamase inhibitors)	6.090	5.889	5.711	4.740	4.839		0.023+
Penicillins (β-lactamase inhibitor combinations only)	1.102	1.118	1.106	0.997	1.012		0.084
First and second-generation cephalosporins	0.257	0.243	0.238	0.237	0.247		0.367
Third, fourth and fifth-generation cephalosporins	0.063	0.071	0.077	0.067	0.065		0.996
Carbapenems	0.056	0.052	0.052	0.045	0.046		0.015+
Tetracyclines	4.702	4.617	4.752	4.350	4.326		0.097
Macrolides, lincosamides and streptogramins	3.081	2.871	2.729	2.347	2.198		0.002+
Sulfonamides and trimethoprim	1.056	0.851	0.777	0.749	0.734		0.042+
Quinolone antibacterials	0.531	0.558	0.509	0.459	0.442		0.037+
Anti-*Clostridioides difficile* agents^	0.004	0.004	0.004	0.004	0.005		0.026+
Oral metronidazole	0.323	0.306	0.298	0.304	0.285		0.035+
Other antibacterials*	1.398	1.549	1.603	1.616	1.643		0.037+

+ Statistically significant p-value for trend from 2017 to 2021
^ Anti-*Clostridioides difficile* agents: oral vancomycin and fidaxomicin
* Other antibacterials (ATC 3rd level pharmacological subgroup 'J01X') include: glycopeptide antibacterials, polymyxin, steroid antibacterials, imidazole derivatives, nitrofuran derivatives, other antibacterials (full list in chapter 3 of the Annexe accompanying this report).

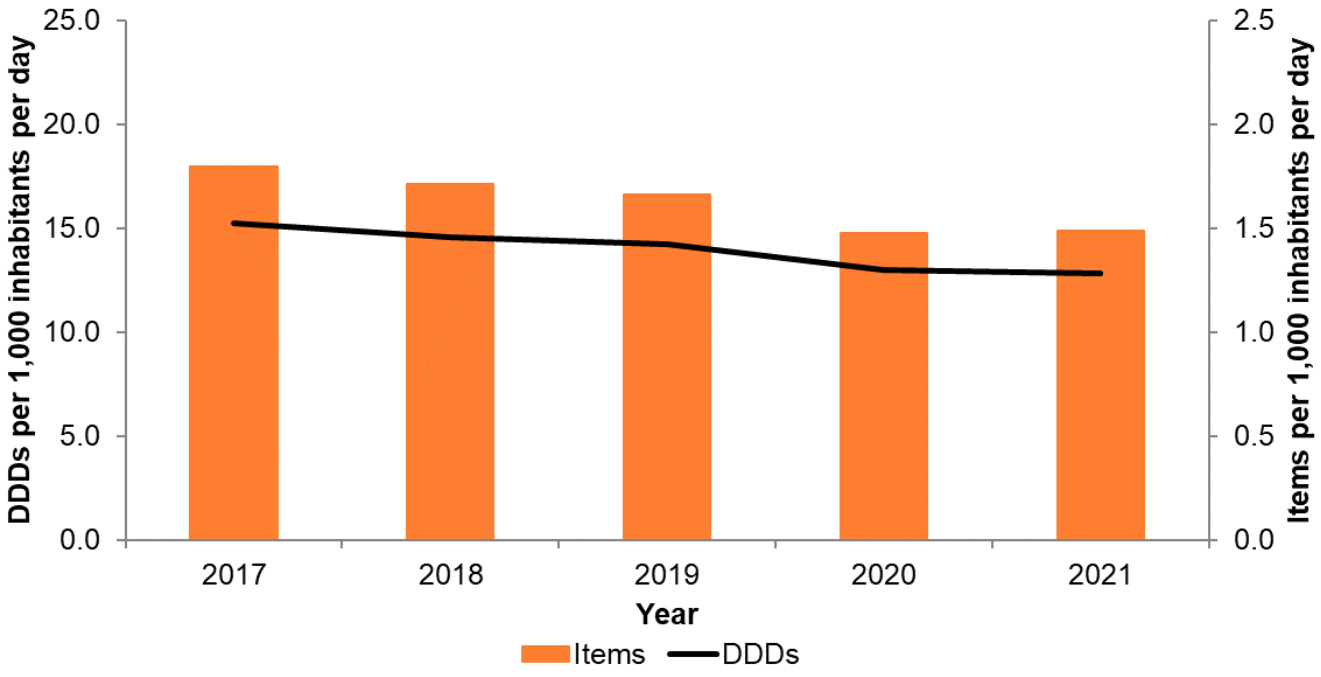
Antibiotic prescribing in primary care (items by population)

Total antibiotic use in primary care

Prescribing within the primary care setting accounted for 80.5% of all antibiotics prescribed in 2021. Antibiotic prescribing within the primary care settings, measured by antibiotic items, declined from 1.80 items per 1,000 inhabitants per day in 2017 to 1.49 items per 1,000 inhabitants per day in 2021, a decrease of 17.2% over 5 years (Figure 3.2, below). Although there have been reductions in items prescribed over the past 5 years, there was a substantial decline between the COVID-19 period of 2019 and 2020 (11.1% in the one year alone, from 1.66 to 1.48 items per 1,000 inhabitants per day).

However, primary care antibiotic consumption between 2020 and 2021 demonstrated an increase of 0.6% (1.48 to 1.49 items per 1,000 inhabitants per day), although this is still below the preceding 3 years pre-COVID-19 rates. With a return towards pre-pandemic level of activity between 2020 and 2021, increases were noted in general practice and other community setting prescribing (increase of 0.5% from 1.245 to 1.251 items per 1,000 inhabitants per day, and 18% from 0.081 to 0.096 items per 1,000 inhabitants per day, respectively), although these rates remained lower than those of 2019. A decrease was observed in dental practice prescribing between 2020 and 2021 (-7.1%, from 0.15 to 0.14 items per 1,000 inhabitants per day), though this comes after a 17.6% (0.13 to 0.15 items per 1,000 inhabitants per day) increase seen within this setting between 2019 and 2020; the only setting to have exhibited an increase during the initial COVID-19 time period and when national social restrictions were applied.

Figure 3.2 Total antibiotic consumption in primary care, expressed as DDDs and items per 1,000 inhabitants per day, England, 2017 to 2021



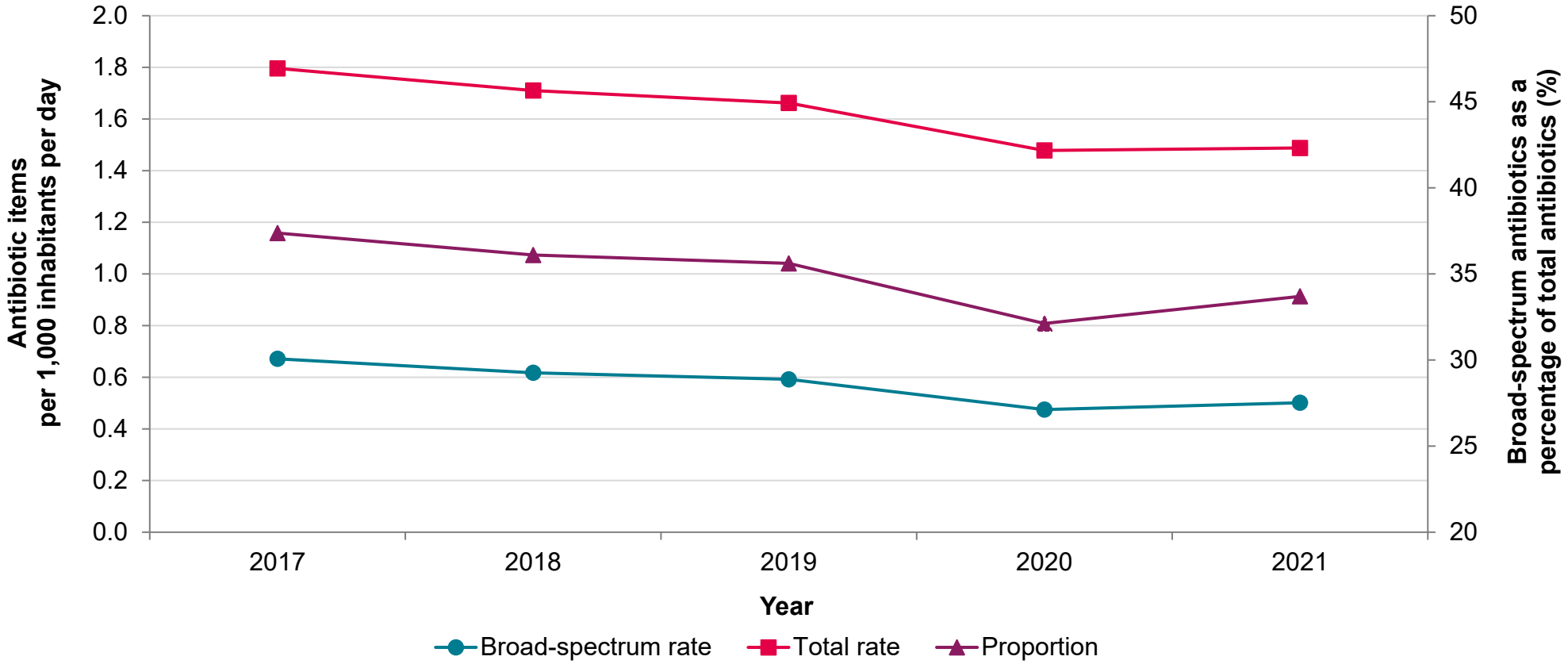
3.2. Primary care proportion and rate of broad-spectrum antibiotic consumption

Antibiotic stewardship and campaigns encourage prudent prescribing; that is, avoiding overuse and unnecessary prescriptions, optimal drug choice, dose and duration; and favouring narrow-spectrum over broad-spectrum antibiotics where clinically reasonable (26, 27). Broad-spectrum antibiotics are effective against a wider range of bacteria than narrow-spectrum antibiotics, however, they are likely to lead to resistance in a wider range of bacteria and have the potential to cause adverse events, for example *Clostridioides difficile* infections and associated diarrhoea (27). In primary care, these antibiotics are commonly used to treat acute respiratory infections (including bronchitis, rhinitis, sinusitis and their sequelae) (28).

Over the past 5 years, there was a decrease in broad-spectrum antibiotic (includes amoxicillin with clavulanate, cephalosporins and quinolones) use within primary care (-25.3%, from 0.67 to 0.50 items per 1,000 inhabitants per day, compared with -17.2% in total primary care antibiotic use) (Figure 3.2.1, below).

Declines in broad-spectrum antibiotic consumption, although small and steady over the years, had a slightly larger reduction coinciding with the COVID-19 pandemic (-19.8% between 2019 and 2020 alone, from 0.59 to 0.48 broad-spectrum items per 1,000 inhabitants per day). Similarly, total consumption, as discussed previously, saw a substantial drop between 2019 and 2020 (-11.1%, 1.66 to 1.48 items per 1,000 inhabitants per day) (Figure 3.2.1, below). Both total and broad-spectrum antibiotic use have increased since the first year of COVID-19 declines, an increase of 0.6% and 5.6%, respectively, from 2020 to 2021 (Figure 3.2.1, below). Broad-spectrum antibiotic use as a percentage of total antibiotic use increased between 2020 and 2021 (from 32.1% to 33.7%), this, however, still remained lower than pre-COVID-19 levels (Figure 3.2.1, below).

Figure 3.2.1. Total and broad-spectrum antibiotic consumption in primary care, expressed as items per 1,000 population, as well as percentage of broad-spectrum over total antibiotics



Changes in services once again in 2021, with the partial recommencement of face-to-face consultations, lifting of social restrictions, increased social mixing and travelling, resulting in increased infections and appointments, may have contributed to the slightly higher proportion of broad-spectrum antibiotics being prescribed after the first COVID-19 pandemic year in England, albeit rates of broad-spectrum antibiotic consumption have remained lower than pre-pandemic levels.

General practice prescribing

Over the past 5 years, there has been a general decrease (19.2%) in total antibiotic items prescribed in the GP setting from 2017 to 2021, from 1.55 to 1.25 items per 1,000 inhabitants per day (with a large decrease of 12.5% between 2019 and 2020 as the country entered the COVID-19 period, and an increase of 0.5% since, from 2020 to 2021).

Penicillin use within the general practice setting has decreased by 25% between 2017 and 2021. However, penicillins remain the most commonly prescribed antibiotic group within this setting and account for 45.2% of all antibiotic prescriptions in 2021 (Table 3.2).

Penicillins contribute the greatest proportion of the antibiotic use reductions seen in GP practices. Their use declined by 9.4% between 2017 to 2019, 21.9% during the first COVID-19 year alone (between 2019 and 2020). However, a subsequent increase of 5.2% was observed between 2020 and 2021, although still lower than pre-2020 levels (Table 3.2).

Table 3.2. Antibiotic items prescribed by GP, expressed as items per 1,000 inhabitants per day, England, 2017 to 2021

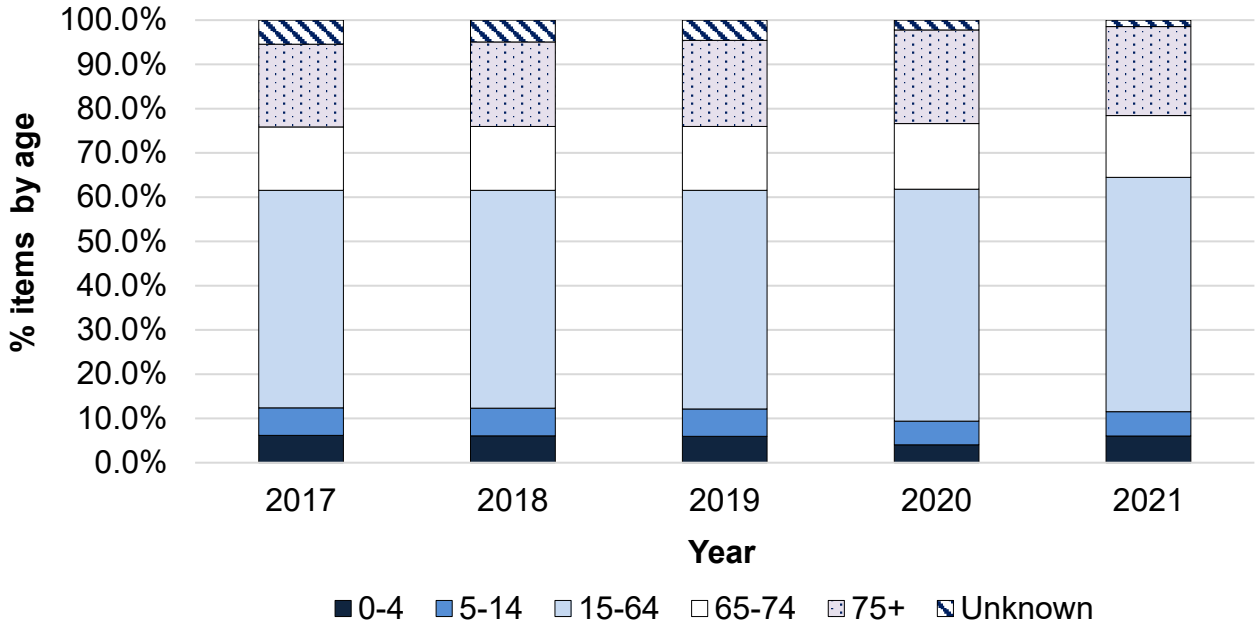
Antibiotic Group	2017	2018	2019	2020	2021	Trend	p-value
Penicillins (excluding β-lactamase inhibitors)	0.687	0.649	0.623	0.487	0.512		0.025+
Penicillins (β-lactamase inhibitor combinations only)	0.066	0.061	0.056	0.055	0.053		0.006+
First and second-generation cephalosporins	0.040	0.037	0.035	0.037	0.038		0.529
Third, fourth and fifth-generation cephalosporins	0.000	0.000	0.000	0.000	0.000		0.004+
Carbapenems	0.000	0.000	0.000	0.000	0.000		0.086
Tetracyclines	0.210	0.205	0.212	0.195	0.197		0.135
Macrolides, lincosamides and streptogramins	0.190	0.174	0.165	0.141	0.134		0.002+
Sulfonamides and trimethoprim	0.134	0.097	0.084	0.081	0.077		0.046+
Quinolone antibacterials	0.030	0.030	0.025	0.024	0.022		0.004+
Anti-Clostridioides difficileagents^	0.000	0.000	0.000	0.000	0.000		0.049+
Oral metronidazole	0.029	0.027	0.026	0.025	0.023		<0.001+
Other antibacterials*	0.159	0.187	0.194	0.200	0.193		0.103

+ Statistically significant p-value for trend from 2017 to 2021.
^ Anti-*Clostridioides difficile* agents include: oral vancomycin and fidaxomicin.
* Other antibacterials (ATC third level pharmacological subgroup 'J01X') include: glycopeptide antibacterials, polymyxin, steroid antibacterials, imidazole derivatives, nitrofuran derivatives, other antibacterials.

GP practice antibiotic items prescribed generally decrease over the past 5 years across all age groups (see the Annexe accompanying this report for age information and the accompanying figure).

Between 2019 and 2020, prescribing reduced across all ages to a greater extend in the one year compared to the 3 years prior. Between 2019 and 2020, the reductions were most evident in children aged 0 to 4 years and 5 to 14 years; -39.9% (from 1.56 to 0.94 items per 1,000 inhabitants per day) and -25.9% (0.78 to 0.57 items per 1,000 inhabitants per day), respectively. This reduction may have been related to declines in amoxicillin prescribed in children aged 0 to 9 years. This trend subsequently increased in 2021 for children aged 0 to 4 years by 51.8% (to 1.42 items per 1,000 inhabitants per day). Increases between 2020 to 2021 were also noted amongst the 5 to 14 (4.6%) and 15 to 64 (2.7%) age groups (see the Annexe accompanying this report). The age groups 65 to 74 and 75 years and above both saw continued reductions in items prescribed (-4.3% and -3.3%, respectively between 2020 and 2021). Percentage of prescriptions across the age groups were greatest within the 15 to 64 age category (52.9% in 2021), and lowest across the 0 to 4 and 5 to 14 (6% and 5.5% in 2021, respectively) (Figure 3.3).

Figure 3.3 Percentage of items in general practices by age group, England, 2017 to 2021



Other community prescribing

Following a slight increasing trend pre-COVID-19 (7.7%, from 0.102 to 0.11 items per 1,000 inhabitant per day between 2017 and 2019) 'other community' prescribing has shown a decline of 26% (0.11 to 0.81 items per 1,000 inhabitants per day) between 2019 and 2020 and an increase from that in 2021(18%, to 0.096 items per 1,000 inhabitants per day) (see Chapter 3 of the Annexe accompanying this report). Items prescribed in out-of-hours primary care centres accounted for 52.6% of 'other community' prescribing and exhibited the same trend (decreased by 3.5% between 2017 and 19, with a substantial drop of 17.9% between 2019 and 2020, and an increase of 11.5% in 2021).

Dental prescribing

A Dental Prescribing Dashboard has been developed by NHS Business Services Authority (NHSBSA) which includes dental practice prescribing data from NHS dental practices. Prescribed dental items decreased by 11.9% between 2017 and 2019 (from 0.146 to 0.129 items per 1,000 inhabitants per day). This reversed into a 17.6% increase between 2019 and 2020 (0.129 to 0.152 items per 1,000 inhabitants per day), coinciding with the COVID-19 pandemic and national restrictions implemented, but has since declined by 7.1% (to 0.141 items per 1,000 inhabitants per day in 2021); this is still higher than 2019 rates.

The predominant antibiotics prescribed in the dental setting in 2021 were amoxicillin (66.4%), metronidazole (28.5%) and erythromycin (2.4%) (Table 3.3). All antibiotics prescribed in this setting had a stable or declining trend pre-2019. There was an increase in the use of amoxicillin and metronidazole between 2019 and 2020 (17.3% and 19.5%, from 0.85 to 0.1 and 0.037 to 0.044 items per 1,000 inhabitants per day, respectively). In 2021 compared with 2020, there was a slight decrease in items prescribed (-6.7% for amoxicillins and -9.5% for metronidazoles).

Table 3.3 Dental antibiotic consumption for the most commonly used antibiotics, expressed as DDDs and items per 1,000 inhabitants per day, 2017 to 2021

Antibiotic		2017	2018	2019	2020	2021	Trend	p-value
Amoxicillin	Items	0.096	0.090	0.085	0.100	0.094		0.837
	DDDs	0.512	0.480	0.460	0.558	0.521		0.505
Amoxicillin with clavulanate	Items	0.001	0.001	0.001	0.001	0.001		0.213
	DDDs	0.002	0.002	0.002	0.002	0.002		0.150
Clarithromycin	Items	0.000	0.000	0.000	0.001	0.001		0.091
	DDDs	0.004	0.004	0.004	0.006	0.006		0.096
Clindamycin	Items	0.001	0.001	0.001	0.001	0.001		0.216
	DDDs	0.002	0.002	0.002	0.003	0.003		0.258
Erythromycin	Items	0.005	0.004	0.004	0.004	0.003		0.020+
	DDDs	0.041	0.036	0.031	0.034	0.028		0.044+
Oral Metronidazole	Items	0.042	0.039	0.037	0.044	0.040		0.824
	DDDs	0.114	0.109	0.106	0.136	0.124		0.280

Antibiotic prescribing in secondary care (DDDs by admissions)

Total antibiotic use in secondary care

Total antibiotic use in NHS acute hospital trusts, measured using hospital admissions as the denominator, decreased by 5.2% between 2017 and 2021 (from 4,613 to 4,372 DDDs per 1,000 admissions). This was driven by reductions in outpatient prescribing which decreased by 18.3% (from 1,782 to 1,456 DDDs per 1,000 admissions) during that period, whereas inpatient prescribing increased by 3.0% (from 2,832 to 2,916 DDDs per 1,000 admissions).

Total antibiotic use in secondary care declined by 10.4% in 2021 compared to 2020 (from 4,881 to 4,372 DDDs per 1,000 admissions). However, COVID-19 had a pronounced impact on the antibiotic prescribing rate, which sharply increased among hospital in-patients in 2020. The

increase in prescribing rate in 2020 masks a reduction in total DDDs prescribed, and an even greater decrease in hospital admissions between 2019 and 2020 (-18.4% and -22.0% respectively). This reflects the changes in hospitalised populations since the start of the pandemic; a higher proportion of acutely ill patients with respiratory infections were admitted while elective procedures were cancelled. In 2021, total DDDs and hospital admissions both increased compared to 2020, by 2% and 13%, respectively, yet they remain lower than 2019 levels (by -17% and -12%, respectively).

The rate of total antibiotic prescribing decreased in all acute trust types over the past 5 years, particularly in acute large (-11.5%), and acute multiservice (-8.2%) trusts (Figure 3.4). In 2020, there were large increases across all trust types corresponding with the first waves of COVID-19. By comparison, in 2021 there were decreases across all trust types compared to the previous year. Reductions were particularly pronounced among acute large (-16.5%) and acute specialist (-13.7%) trusts. (Definitions of trust types can be found in Chapter 3 of the Annexe accompanying this report.)

Figure 3.4. Antibiotic prescribing, by trust type, expressed as DDDs per 1,000 admissions, England, 2017 to 2021

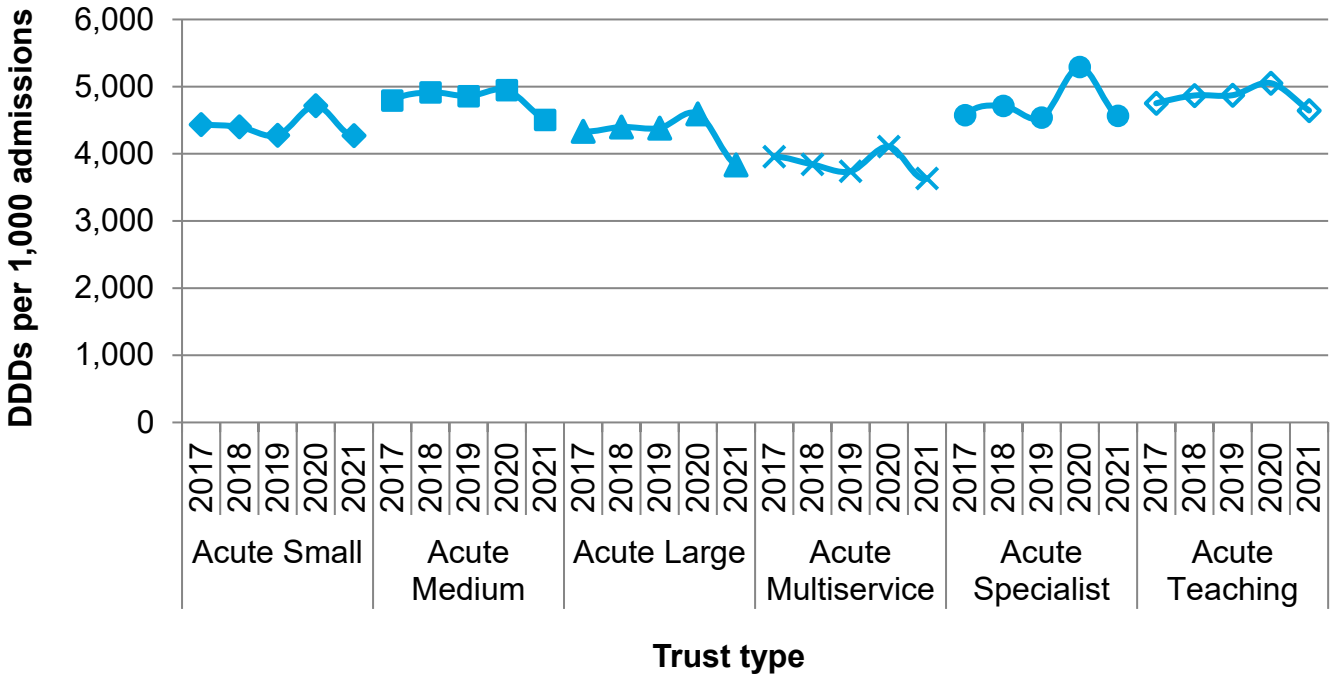


Table 3.4 shows antibiotic usage (DDDs per 1,000 admissions) by antibiotic group from 2017 to 2021. In 2021, penicillins (BLI combinations only) and penicillins (without BLI) had the highest use in secondary care, both accounting for around one fifth of prescribing. This was followed by tetracyclines at 14%, with the remaining groups comprising 10% or less of the total. There were statistically significant decreasing trends observed between 2017 and 2021 for the prescribing of penicillins (without BLI) (-14.6%), macrolides, lincosamides and streptogramins (-29.9%), and oral metronidazole (-16.3%). Anti-*Clostridioides difficile* agents showed the opposite pattern, with a statistically significant increasing trend in usage over the same 5-year period (+50%, from 4 to 6 DDDs per 1,000 admissions).

All antibiotic groups decreased in usage in secondary care from 2020 to 2021, except for anti-*C. difficile* agents which increased from 5.4 to 5.9 DDDs per 1,000 admissions (+9.2%). The largest decreases in usage between 2020 and 2021 were observed for 'macrolides, lincosamides and streptogramins' (from 573.7 to 460.2 DDDs per 1,000 admissions; -19.8%) and 'third, fourth and fifth-generations cephalosporins' (from 110.2 to 92.8 DDDs per 1,000 admissions; -15.7%).

Between 2017 and 2020, tetracyclines and penicillins (BLI combinations only) had year-on-year increases in usage, and in 2021, usage dropped for both antibiotic groups compared to 2020 (tetracyclines from 716.9 to 631.5 DDDs per 1,000 admissions, -11.9%; and penicillins (BLI combinations only) from 906.5 to 844.7 DDDs per 1,000 admissions, -6.8%).

Table 3.4 Antibiotic consumption in trusts by antibiotic group, expressed as DDDs per 1,000 admissions, England, 2017 to 2021

Antibiotic Group	2017	2018	2019	2020	2021	Trend	p-value
Penicillins (excluding β-lactamase inhibitors)	1139.5	1135.2	1108.9	1081.4	973.1		0.039+
Penicillins (β-lactamase inhibitor combinations only)	787.4	829.7	829.9	906.5	844.7		0.186
First and second-generation cephalosporins	97.1	96.8	93.6	102.4	96.8		0.689
Third, fourth and fifth-generation cephalosporins	93.6	98.8	95.9	110.2	92.8		0.722
Carbapenems	71.8	65.9	63.7	71.4	63.8		0.491
Tetracyclines	571.8	619.3	703.5	716.9	631.5		0.320
Macrolides, lincosamides and streptogramins	656.0	629.1	572.2	573.7	460.2		0.018+
Sulfonamides and trimethoprim	251.9	245.4	241.9	288.9	271.7		0.224
Quinolone antibacterials	291.5	315.7	294.0	315.8	278.6		0.686
Anti-*Clostridioides difficile* agents^	4.0	4.1	4.4	5.4	5.9		0.011+
Oral metronidazole	122.6	117.3	114.0	115.6	102.7		0.039+
Other antibacterials*	361.5	381.5	387.2	425.1	403.3		0.074

+ Statistically significant p-value for trend from 2017 to 2021
^ Anti-*Clostridioides difficile* agents include: oral vancomycin and fidaxomicin
* Other antibacterials (ATC 3rd level pharmacological subgroup 'J01X') include: glycopeptide antibacterials, polymyxin, steroid antibacterials, imidazole derivatives, nitrofuran derivatives, other antibacterials

AWaRe – Access, Watch and Reserve

In 2017, WHO classified the Essential Medicine List key antibiotics into 3 categories (AWaRe): to improve access (Access), to monitor important antibiotics (Watch) and preserve 'last resort' broad-spectrum antibiotics (Reserve). Adapted WHO AWaRe categories are used in England (29), with several national- and trust-level antibiotic consumption targets based on these (25, 30). As such until the target period has completed (2024), updates in the categorisation have not been implemented.

In 2022, NHS England and Improvement launched the Standard Contract 2022 to 2023 which sets targets for trusts to reduce their use of ‘Watch’ and ‘Reserve’ antibiotics by 4.5% compared to their 2018 baselines (31). Nationally published Fingertips indicators for monitoring the progress at NHS acute trust level are available for AWaRe antibiotics (32).

In 2021, in NHS acute trusts, antibiotics in the 'Access' category were prescribed the most, with 51.3% of DDDs per 1,000 admissions (2,242 DDDs per 1,000 admissions). The second highest category was ‘Watch’ antibiotics at 45.3% (1,982 DDDs per 1,000 admissions). Only 3.1% of antibiotics used in secondary care were 'Reserve' antibiotics (137 DDDs per 1,000 admissions). A small number of antibiotics are not classified in any of the AWaRe categories, with prescriptions of these 'Other' antibiotics making up 0.2% of DDDs per 1,000 admissions. These percentages are in line with data from previous years.

Between 2017 (the NAP baseline year) and 2020, an increase of 4.7% and 15.8% was observed in the 'Watch' and 'Reserve' antibiotic prescriptions in England, respectively (from 2,134 to 2,234 DDDs per 1,000 admissions, and 133 to 154 DDDs per 1,000 admissions, respectively), as well as an increase of 6.1% in ‘Access’ antibiotics (from 2,341 to 2,485 DDDs per 1,000 admissions).

However, when comparing 2017 to 2021, a decrease of 7.1% was observed in 'Watch' antibiotics (2021: 1,982 DDDs per 1,000 admissions), an increase of 3.0% in 'Reserve' antibiotics (2021: 137 DDDs per 1,000 admissions), and a decrease of 4.2% in 'Access' antibiotics (2021: 2,242 DDDs per 1,000 admissions).

The AWaRe consumption rates described above are calculated using hospital admissions as the denominator, which is in-line with the rest of the secondary care section in this report. It’s important to note that the COVID-19 pandemic had a pronounced impact on hospital admissions, which may drive some of the changes observed in AWaRe consumption rates reported above. In 2020, hospital admissions were around 22% lower than in 2019, and, despite increasing in 2021, they were still 12% lower than in 2019. Furthermore, COVID-19 saw changes in the case-mix of hospitalised patients. These factors may have driven some of the changes in AWaRe consumption rates reported above. (To note, the NAP baseline and targets use population as the denominator and represent UK targets. Consumption of 'Access', 'Watch' and 'Reserve' antibiotics calculated as DDDs per 1,000 inhabitants per day (DID), showed a decline across all AWaRe groups between 2019 and 2021, following a slight increase in consumption for all categories between 2017 to 2019).

The use of colistin in secondary care increased year-on-year between 2017 and 2020, from 21.4 to 31.9 DDDs per 1,000 admissions. In 2021, use dropped by 15.1% to 27.1 DDDs per 1,000 admissions compared to 2020. The prescribing rate for colistin is highest among acute specialist trusts (2021: 83.7 DDDs per 1,000 admissions). In 2020 there were pronounced increases in colistin use across all trust types, with the exception of acute multiservice trusts, during the COVID-19 pandemic. These increases were followed by reductions in 2021.

Over the past 5 years, there was a decrease of 10.9% in carbapenem consumption from 71.8 to 63.8 DDDs per 1,000 admissions (Table 3.4). However, there was a sharp increase between 2019 and 2020 (12.1%), likely due to the increased use of meropenem during the COVID-19 pandemic following its inclusion within NICE hospital-acquired pneumonia (HAP) guidelines (33). Carbapenem consumption fell across all trust types between 2020 and 2021, except for acute multiservice which increased by 9.3% from 46.7 to 51.0 DDDs per 1,000 admissions.

In 2017 there was a global shortage of piperacillin with tazobactam. Since then, use has increased from 83.9 to 112.1 DDDs per 1,000 admissions from 2017 to 2021, with most marked increases between 2019 and 2020 (21.5%, from 96.1 to 116.8 DDDs per 1,000 admissions), seen across all trust types within this time period. This is likely because piperacillin with tazobactam was included within both the NICE guideline: antibiotics for pneumonia in adults in hospital (NG139, Sep 2019) and the COVID-19 rapid guideline: antibiotics for pneumonia in adults in hospital (NG173, May 2020). Between 2020 and 2021 total use of piperacillin with tazobactam decreased by 4%, with all trust types showing decreases over this period.

Following the piperacillin with tazobactam shortage in 2017 and the implementation of stewardship schemes which aimed to reduce the use of unnecessary broad-spectrum antibiotics, there was an increase in usage of alternative antibiotic options. Year-on-year increases between 2017 and 2020 in many cephalosporins and quinolones (Table 3.5) were observed. However, in 2021, usage decreased across these antibacterials compared to 2020, except for the recently licenced cephalosporin with β-lactamase inhibitor combination ceftazidime with avibactam. In particular, ceftolozane with tazobactam use decreased by 97.1% (from a low baseline of 0.7 DDDs per 1,000 admissions in 2020 to 0.0 DDDs per 1,000 admissions – almost no usage in 2021), and ceftazidime by 18.1% (15.4 to 12.6 DDDs per 1,000 admissions) (Table 3.5).

Table 3.5 Quinolone antibacterials and cephalosporins consumption in trusts, expressed as DDDs per 1,000 admissions, England, 2017 to 2021

Antibiotic	2017	2018	2019	2020	2021	Trend	p-value
Ciprofloxacin	203.5	213.8	197.3	209.0	189.5		0.356
Levofloxacin	61.4	74.2	75.9	82.0	70.5		0.338
Cefuroxime	42.6	43.4	42.4	44.3	42.2		0.880
Cefotaxime	22.4	23.6	21.9	26.1	22.0		0.792
Ceftazidime	19.4	18.2	17.5	15.4	12.6		0.006+
Ceftriaxone	50.7	55.7	54.8	66.6	56.5		0.069
Ceftazidime with avibactam	-	0.3	0.5	0.8	1.0		<0.000+
Ceftolozane with tazobactam	0.2	0.4	0.5	0.7	0.0		0.875

Note: 2018 is the first full year during which ceftazidime with avibactam was authorised for use in the UK.

Speciality prescribing

Prescribing by specialist groups in secondary care is reported in Table 3.6, below. (See Chapter 3 of the Annexe accompanying this report for specialities grouping by antibiotic class). Intensive care units (ICUs) had the highest antibiotic usage out of the specialist groups, with 70.0 DDDs

per ICU admission during the 2021 to 2022 financial year. AE and non-specific outpatient departments were the next highest, with 19.3 DDDs per speciality admission. From 2017 to 2021, most speciality groups increased their use of antibiotics, with the exception of geriatrics (from 3.8 to 2.4 DDDs per admission, -10.6%) and general medicine (from 2.7 to 2.3 DDDs per admission, 15.0%). Notable increases include orthopaedics, from 2.9 to 4.6 DDDs per admission (+59.5%), and AE and non-specific outpatient departments from 14.9 to 19.3 DDDs per admission (+29.2%). ICU prescribing increased from 63.4 to 70.0 DDDs per admission (+10.5%) (data in the Annexe accompanying this report).

Prescribing increased in all speciality groups in 2021 compared to 2020 (the Annexe accompanying this report). This is unsurprising as many elective procedures were cancelled in 2020 during the early part of the COVID-19 pandemic. Elective procedures have since resumed, although remain under pre pandemic levels. The largest percentage increases in antibiotic pescribing were seen in orthopaedics (from 2.6 to 4.6 DDDs per admission, +76.5%) and specialist surgery (from 1.4 to 2.4 DDDs per admission, +75.6%), and the largest increases were seen in ICU (from 54.8 to 70.0 DDDs per admission, +27.8%) and AE and non-specific outpatient departments (from 12.1 to 19.3 DDDs per admission +58.9%) (data in the Annexe accompanying this report).

ICUs accounted for the highest usage of piperacillin with tazobactam and carbapenems in 2021 (6.7% and 6.6% of total ICU DDDs per ICU admission, respectively) (Table 3.6, below). Paediatrics were the highest users of colistin (2.9% of total paediatrics). These specialist groups remain unchanged from financial year April 2020 to March 2021 as the highest users of these antibiotic classes.

Table 3.6 Percentage of all antibiotic prescribing attributed to piperacillin with tazobactam, carbapenems and colistin in secondary care by speciality, expressed as DDDs per speciality admission, England, 2021 to 2022

Specialist group	DDDs per admission	Piperacillin/ tazobactam	Carbapenems	Colistin
Intensive Care Unit	70.0	6.7%	6.6%	0.2%
AE and non-specific Outpatient Department	19.3	0.9%	0.3%	0.1%
Specialist Medicine	5.0	2.9%	2.0%	2.0%
Other	4.7	2.5%	1.6%	0.0%
Orthopaedics	4.6	2.8%	1.3%	0.0%
General Surgery	4.4	2.9%	0.7%	0.4%
Geriatrics	3.4	4.3%	1.7%	0.0%
Specialist Surgery	2.4	1.7%	1.4%	0.7%
Obstetrics and Gynaecology	2.4	0.8%	0.4%	0.0%
Paediatrics	2.3	1.7%	1.4%	2.9%

Specialist group	DDDs per admission	Piperacillin/ tazobactam	Carbapenems	Colistin
General Medicine	2.3	3.4%	1.4%	0.1%

Antifungal consumption

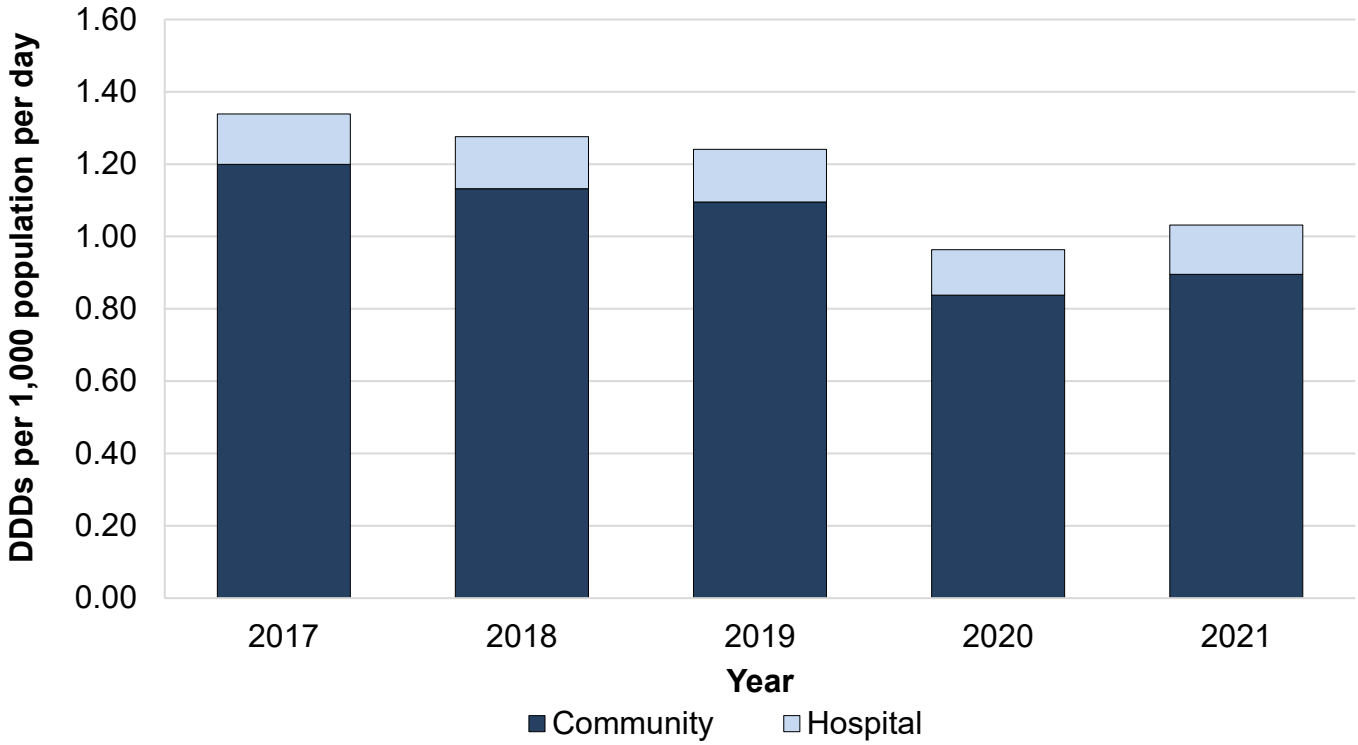
Total antifungal consumption

IQVIA data has been used as the source in this year's report for the antifungal consumption section (see Chapter 3 in the Annexe accompanying this report). This has been aligned with the rest of the chapter, as well as permitting robust analyses on specialties. The previous year's report utilised Rx-info data, and there are slight differences in the consumption levels based on these 2 data sources. Although the trends are similar, IQVIA reports slightly lower DDDs compared with Rx-Info for antifungal consumption. Ketoconazole tablets, which are recorded within the Rx-Info data but not the IQVIA data, are one example where differences have been identified; ketoconazole tablets are mainly used for the treatment of Cushing's syndrome, as opposed to treatment of fungal infections, in England.

Total consumption of systemic antifungals prescribed in the community and NHS hospitals in England decreased by 22.9% from 1.34 DID in 2017 to 1.03 to 2021 in 2021 (Figure 3.5, below). As presented in last year's ESPAUR report, antifungal usage in 2020 exhibited a large decrease as a result of the COVID-19 pandemic. The effect of the pandemic was lesser in 2021 with usage increasing by 7.1% from 2020 to 2021 (Figure 3.5, below).

The decrease between 2017 and 2020 was predominantly driven by reduced use in the community, with only a 2.1% decrease in hospital usage from 0.139 to 0.136 DID. In 2021, 87% of systemic antifungal prescribing took place in the community setting. It is difficult to know if this is a true representation of community use as several antifungal agents can be supplied as over the counter (OTC) medicines, which are not captured in this data set.

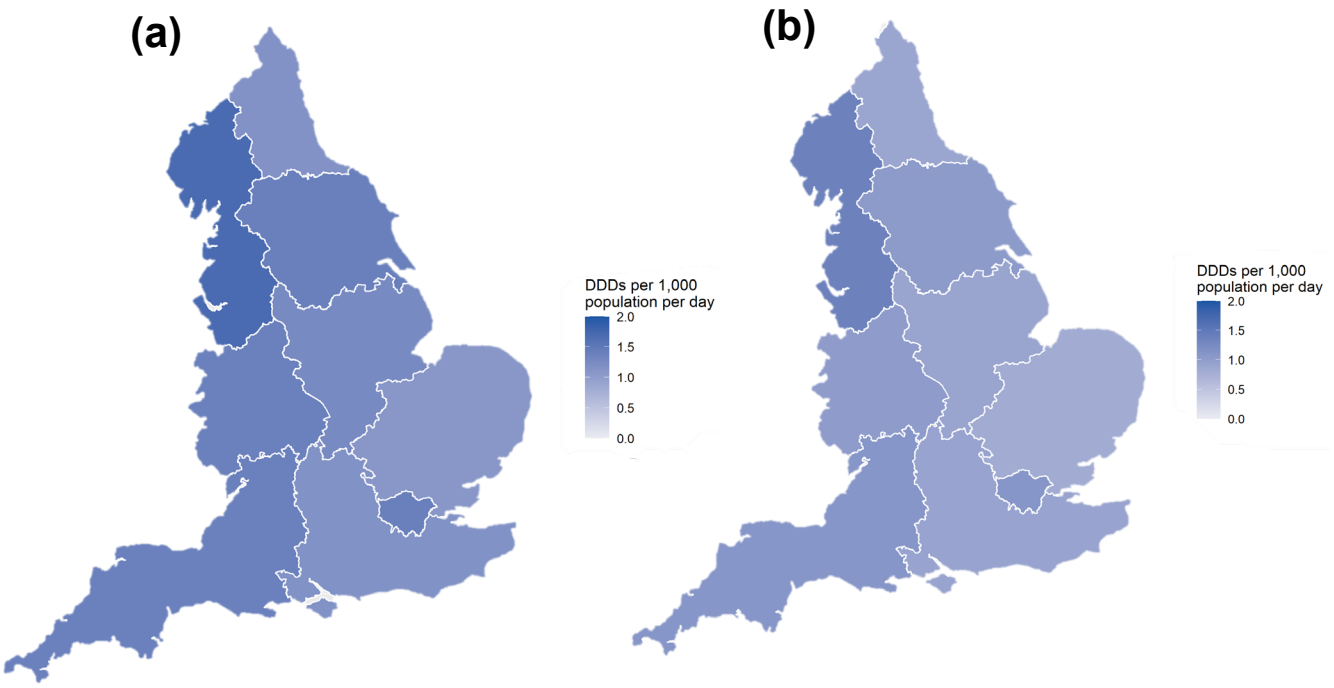
Figure 3.5. Total consumption of systemic antifungals in the community and acute hospitals in England, expressed as DDDs per 1,000 population per day, 2017 to 2021



3.3. Regional variation in antifungal consumption in England

There was marked regional variation in prescribing of antifungals in England (Figure 3.3.1). In 2021, and for the previous 4 years, the North West had the highest prescribing rate (1.37 DID). East of England had the lowest prescribing rate in 2021 (0.81 DID).

Figure 3.3.1. Total consumption (primary and secondary care) of systemic antifungals for UKHSA centres, expressed as DDDs per 1,000 inhabitants per day, (a) 2017, and (b) 2021



Across all regions prescribing decreased between 2017 and 2021, most markedly in the East Midlands, which decreased by 27.5% from 1.26 to 0.91 DID. The decrease in prescribing was most pronounced from 2019 to 2020; percentage decrease from 2017 to 2019 ranged 4.3% to 11.2%, whilst from 2019 to 2020 it ranged from 19.5% to 25.4% in the separate centres. This larger decrease was likely a result of the COVID-19 pandemic, as previously mentioned. All regions then showed increased prescribing from 2020 to 2021, ranging from 3.6% increase in the East Midlands, to 9.7% in the North West.

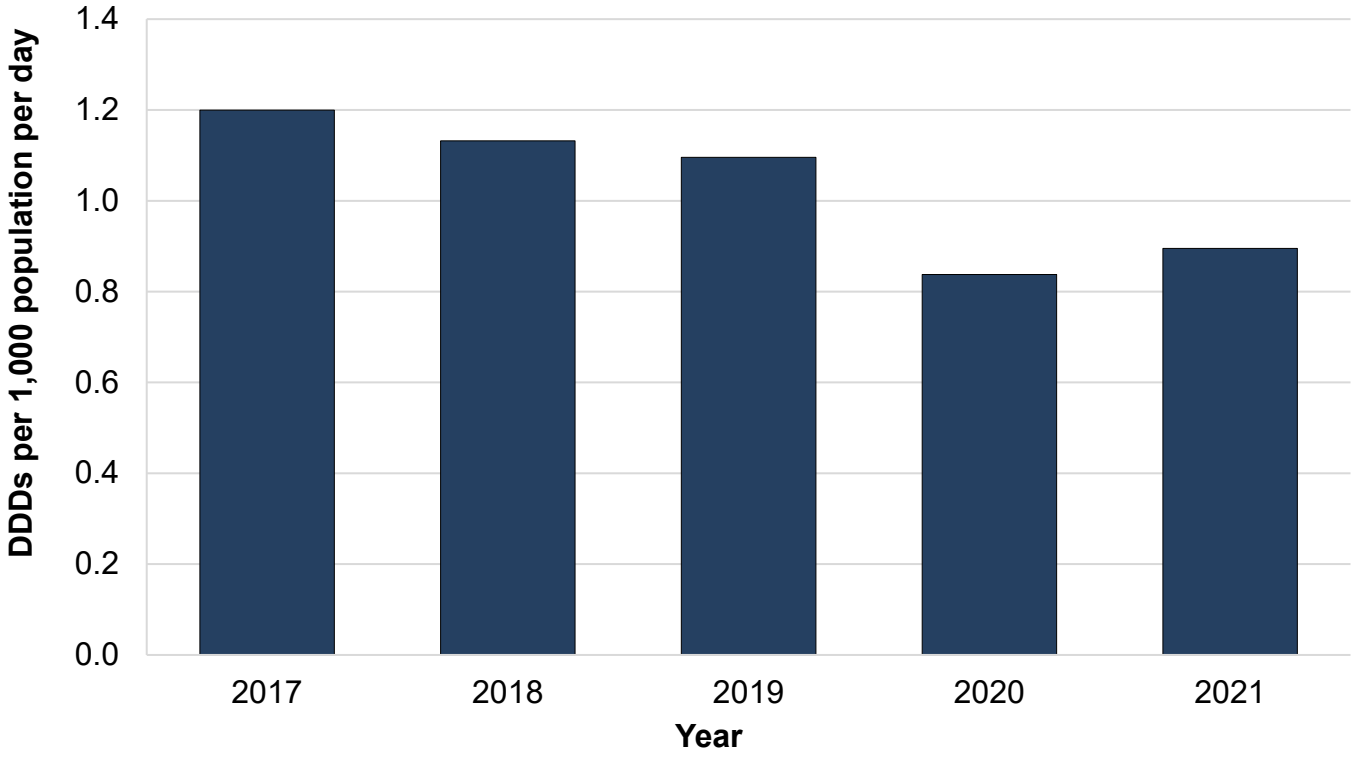
Differences in the resident population characteristics and distribution of specialist care trusts may account for the variations seen between regions.

Antifungal prescribing in primary care

The total prescribing of systemic antifungals in the community decreased by 25.4%, from 1.2 to 0.9 DDDs per 1,000 inhabitants per day (DID), between 2017 and 2021 (Figure 3.6, below).

Figure 3.6 shows that the greatest decrease in total systemic antifungals prescribed in the community was between 2019 and 2020 (23.5%, 1.1 to 0.84 DID), with annual reductions previously at less than 10% (2017 to 2018: 5.6%, 1.2 to 1.13 DID; and 2018 to 2019: 3.2%, 113 to 1.1 DID). There was then an increase of 6.9% from 2020 (0.84 DID) to 2021 (0.9 DID).

Figure 3.6. Total consumption of systemic antifungals in the community in England, expressed as DDDs per 1,000 population per day, 2017 to 2021

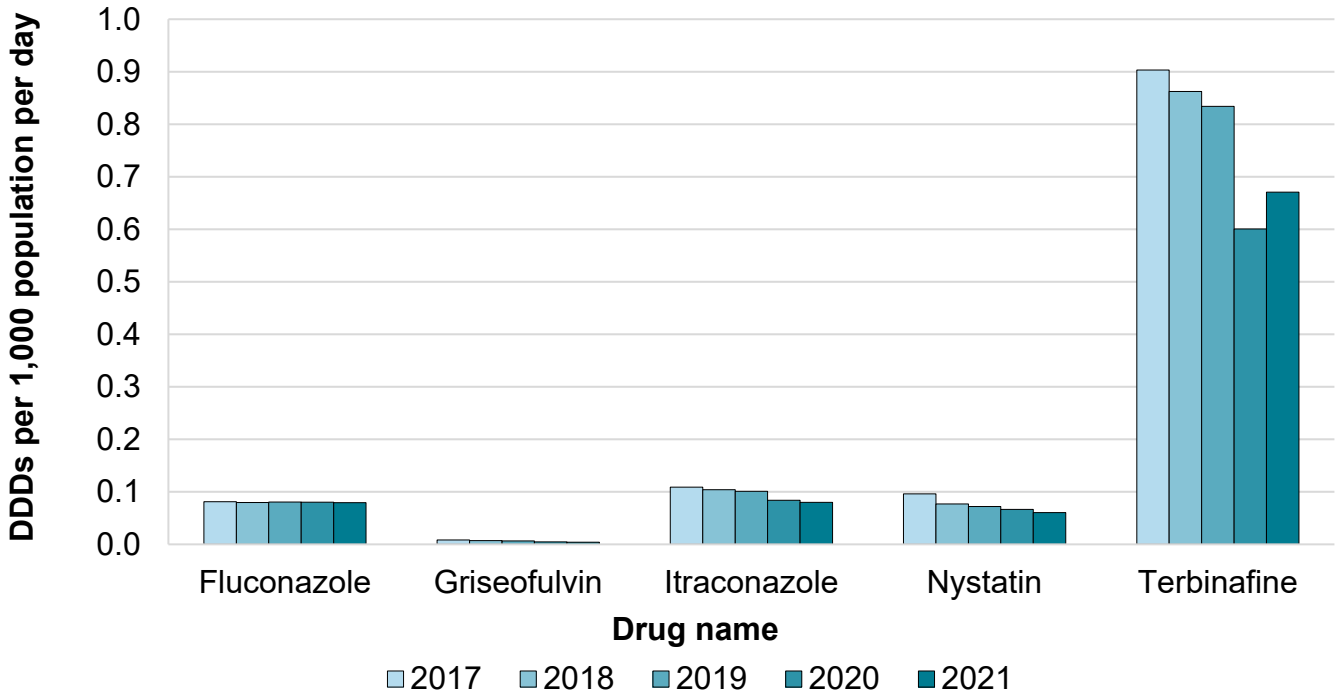


As Figure 3.7 (below) shows, the most frequently prescribed antifungal in the community was terbinafine (0.67 DDDs per 1,000 inhabitants per day in 2021). Terbinafine is an oral agent active against common dermatophyte infections of the skin, hair and nails. Usage of terbinafine decreased by 25.7% from 2017 to 2021, with a large decrease in 2020 related to the COVID-19 pandemic lockdowns where transmission of dermatophyte infections was reduced.

Terbinafine was the only drug to show an increase between 2020 and 2021 (+11.6%, 0.6 to 0.67 DID), with the return to more social interaction in 2021. Fluconazole usage has stayed steady over the last 5 years, remaining at 0.08 DID from 2017 to 2021. Oral fluconazole, most often used for cutaneous and mucosal yeast infections, is available over the counter (OTC) hence numbers presented may not reflect true use. Itraconazole, nystatin and griseofulvin usage have decreased each year since 2017 (between 2017 and 2021, -26.6%, from 0.11 to 0.08 DID; -37.3%, from 0.1 to 0.06 DID; and -51.4%, from 0.008 to 0.004 DID, respectively).

There are a limited number of drugs shown in Figure 3.7, as there are limited types of antifungal prescribed for systemic use in the community setting; more variety can be seen in the hospital setting.

Figure 3.7. Total consumption of systemic antifungals by drug in the community in England, expressed as DDDs per 1,000 population per day, 2017 to 2021



Antifungal prescribing in secondary care

As can be seen in Figure 3.8, total consumption of systemic antifungals in NHS acute trusts in 2021 was 191 DDDs per 1,000 admissions. This represents a 7.1% increase in the rate of prescribing from 2017 (178 DDDs per 1,000 admissions) but a 4.5% decrease from 2020 (200 DDDs per 1,000 admissions). The decrease in prescribing rate from 2020 to 2021 suggests that in 2021 antifungal prescribing and admissions were beginning to return to pre-pandemic levels.

Figure 3.8. Total consumption of systemic antifungals in NHS acute hospital trusts in England, expressed as DDDs per 1,000 admissions, 2017 to 2021

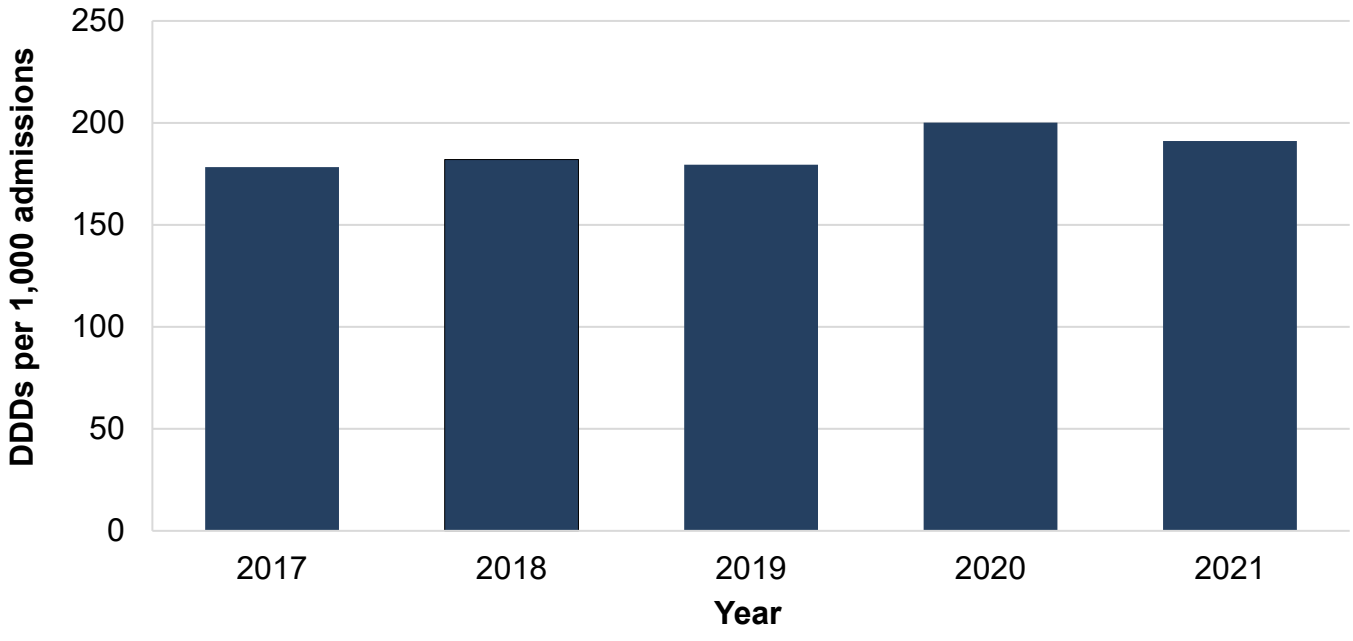


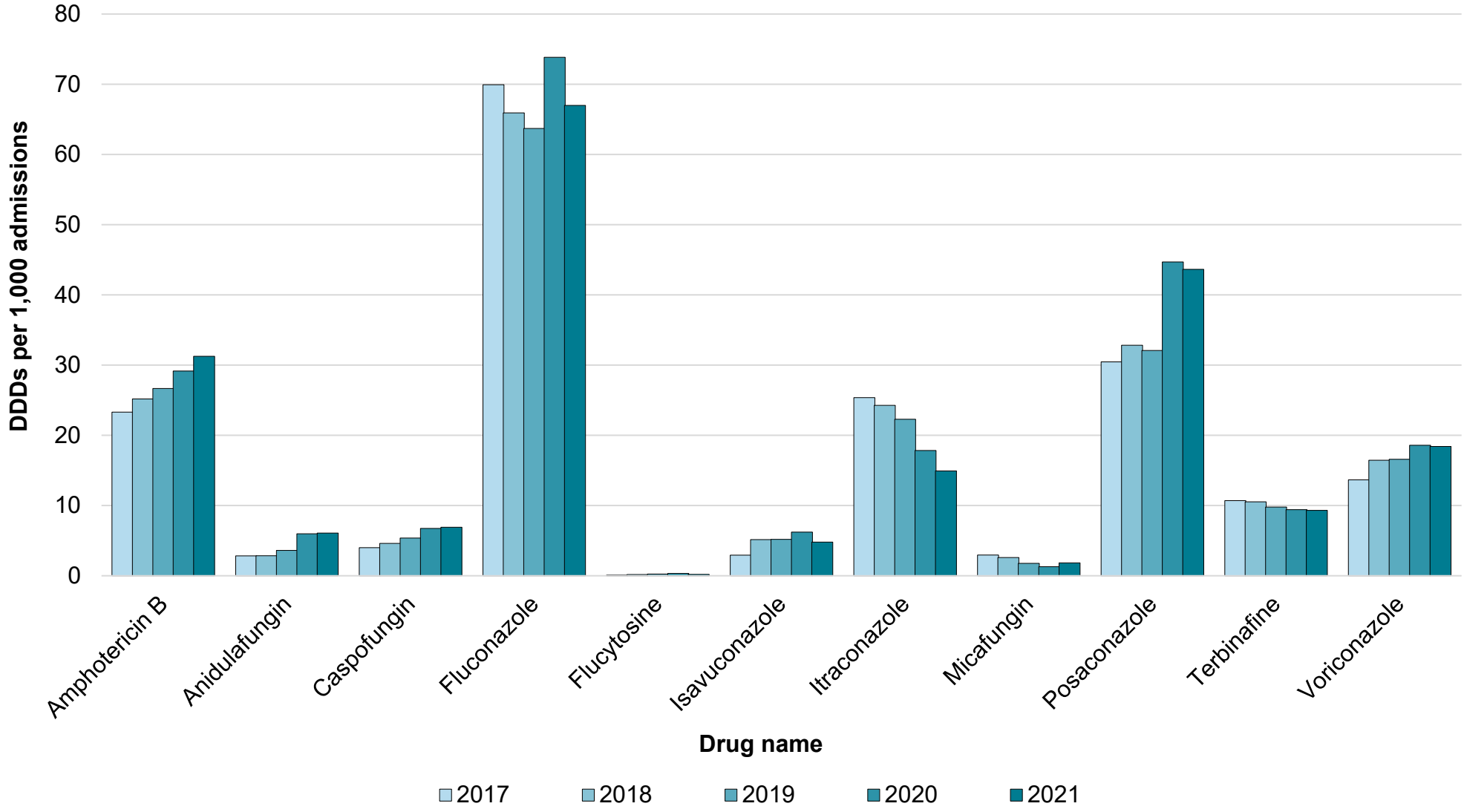
Figure 3.9 (below) shows the prescribing of individual antifungals in secondary care. Fluconazole was the most frequently prescribed antifungal and azole (2021: 67 DDDs per 1,000 admissions). From 2017 to 2019 prescribing had been decreasing, but increased in 2020 and decreased in 2021 (-9.3% compared with 2020). The next highest azole prescribed was posaconazole (2021: 43.6 DDDs per 1,000 admissions). Posaconazole prescribing increased in 2020 and slightly decreased into 2021. Voriconazole usage also increased in 2020 and then stayed similar into 2021, to 18.4 DDDs per 1,000 admissions. In 2021, isavuconazole and itraconazole usage were at 4.8 and 14.9 DDDs per 1,000 admissions, respectively. Itraconazole usage has decreased year-on-year between 2017 and 2021, with a 41.2% reduction overall during this time period.

Amphotericin B is a broad-spectrum agent suitable for most invasive yeast and mould infections. Usage of it has increased every year since 2017, increasing by 34.1% from 23.3 DDDs per 1,000 admissions in 2017 to 31.2 DDDs per 1,000 admissions in 2021.

In 2021, rate of echinocandin antifungals was 6.1, 6.9 and 1.8 DDDs per 1,000 admissions for anidulafungin, caspofungin and micafungin, respectively. Since 2017 both anidulafungin and caspofungin usage have increased (2017 to 2021: +115% and + 72.6%, respectively, although rates are still small). Micafungin usage, however, has decreased by 37.7%, from 3.0 to 1.8 DDDs per 1,000 admissions between 2017 and 2021.

Flucytosine, which is rarely prescribed alone, has the lowest levels of prescribing, at 0.2 DDDs per 1,000 admissions. Flucytosine usage has been increasing since 2017, peaking in 2020, with usage dropping by 42.2% in 2021. Terbinafine usage has also been decreasing since 2017, from 10.7 to 9.3 DDDs per 1,000 admissions in 2021.

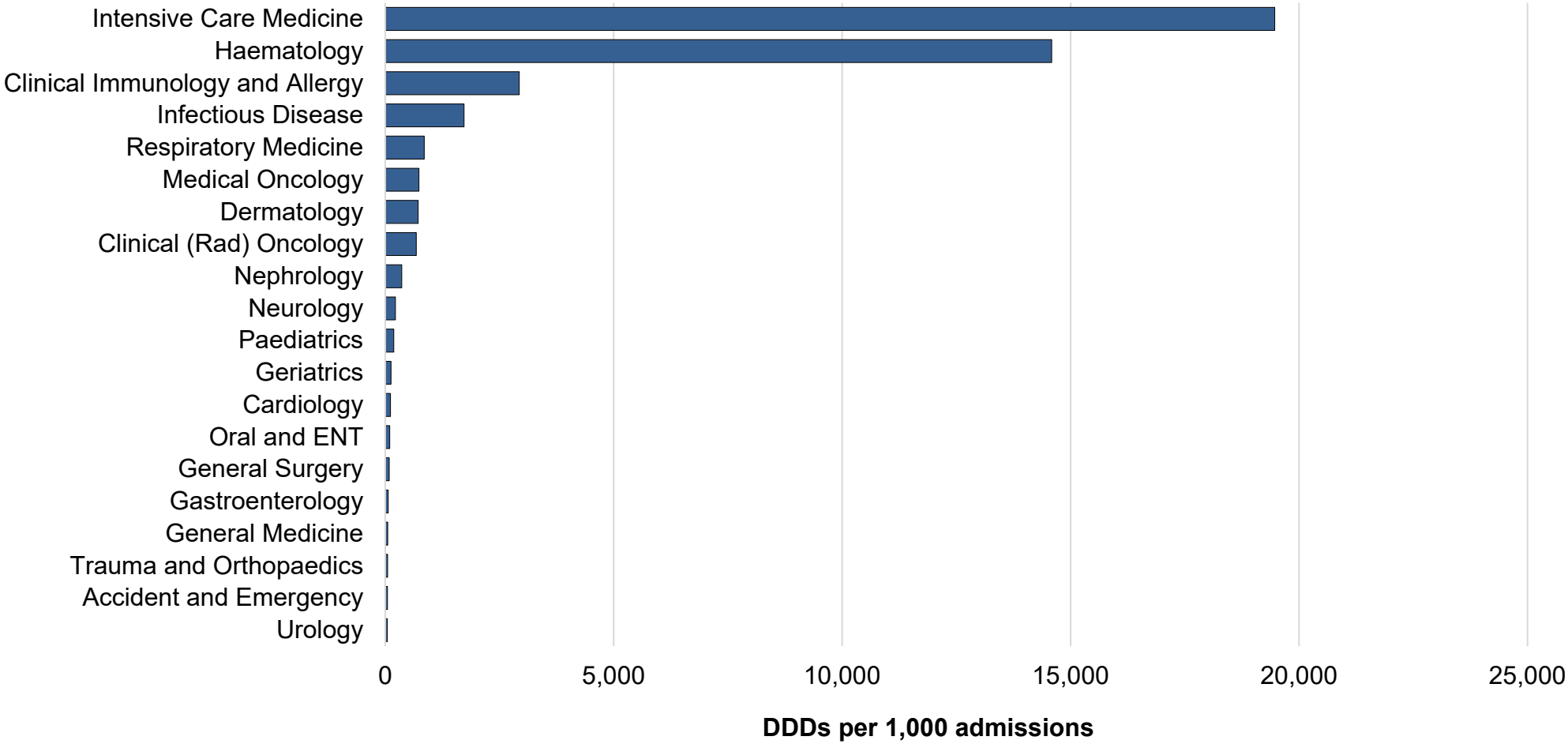
Figure 3.9. Total consumption of antifungals by drug in NHS acute hospital trusts, 2017 to 2021



By specialty

In 2021 the specialty with the highest systemic antifungal prescribing rate was ‘Intensive Care Medicine’ (19,469 DDDs per 1,000 admissions) followed by ‘Haematology’ (14,585 DDDs per 1,000 admissions) (Figure 3.10).

Figure 3.10. Antifungal consumption in NHS acute hospital trusts’ top 20 specialities



Antiviral consumption: hepatitis C virus

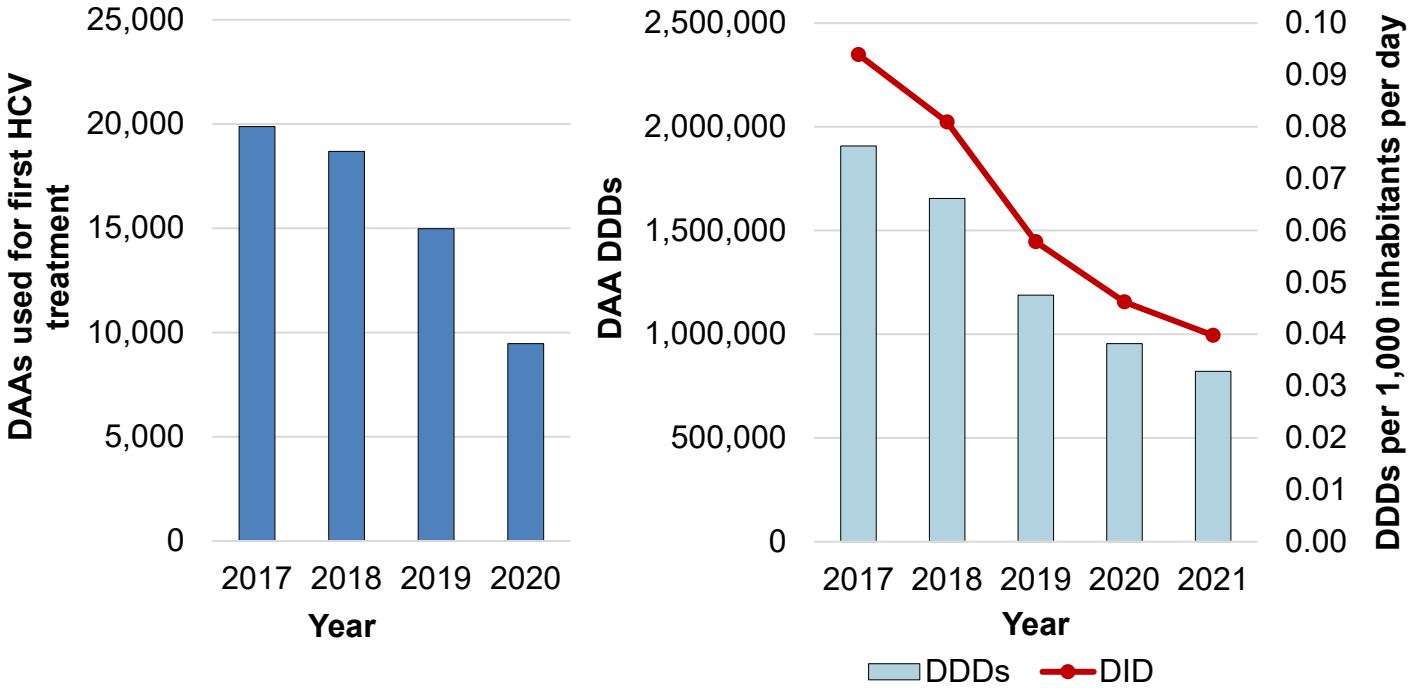
3.4. Antiviral prescribing for the treatment of hepatitis C virus (HCV)

In 2020, England estimates suggest that approximately 81,000 people are living with chronic Hepatitis C virus (HCV; a bloodborne virus that infects and damages the liver) infection (34). The prevalence has decreased from 129,000 people in 2015, reflecting increased access to effective treatments that provide eradiation of the HCV (34). Treatment of HCV with direct-acting antiviral (DAA) drugs has been associated with an approximate 80% reduction in hepatocellular carcinoma, 90% reduction in liver-related mortality and 75% reduction in all-cause mortality (34 to 37).

Where first-line DAA therapy is unsuccessful, re-treatment regimens are available, with high cure rates. However, unsuccessful therapy provides the opportunistic development of mutations in viral genes which encode the protein targeted by the drugs, causing subsequent antiviral drug resistance. Hence monitoring of access to HCV treatment not only forms an important part of the response to the WHO HCV elimination targets, but can inform and be used to monitor use and efficacy of DAAs. Current monitoring focuses on patients accessing treatment based on data captured in the Hepatitis C Patient Registry and Treatment Outcome System (38). The registry reports that most treatment occur within secondary care (approximately 83% in 2017, which has however, decreased over time, to approximately 50% in 2020, with an increase in community drug services and prisons).

The data presented in Figure 3.4.1 (below) a) comes from the registry (extracted July 2022, is subject to change) and provides patient-level information on the drugs recorded for patients first treatment (to note, certain patients may have had more than one drug at first treatment and these have been included within the data), b) presents dispensed Hepatitis C antivirals from IQVIA. The consumption data validates the trends presented from the registry. For the period of 2017 to 2020, there was a declining trend in DAAs treatments reported and DAA DDDs (to 2021), likely related to decreasing prevalence, mentioned above. This declining trend has previously been reported since 2015 (34). The greater reduction noted in 2019 and 2020 are most likely also related to reduced access to care and changes in healthcare delivery during the COVID-19 pandemic (34). IQVIA consumption data suggests this decline is not as steep in 2021.

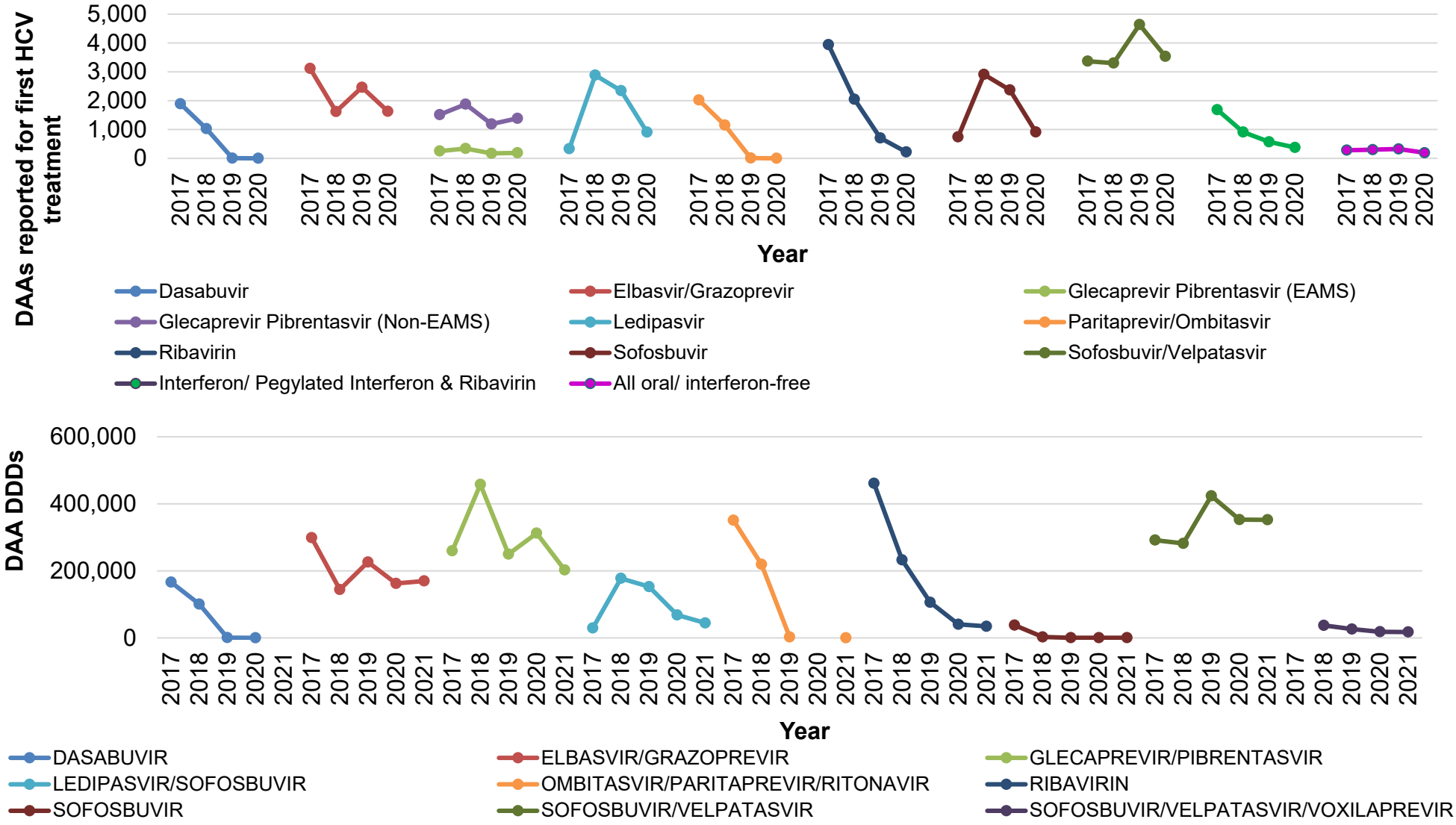
Figure 3.4.1. a) DAAs used as first HCV treatment reported to the hepatitis C Patient Registry and Treatment Outcome System b) DDDs and DDDs per 1,000 inhabitants per day



* DDDs and rate, using IQVIA data, does not include interferon drugs (which have been included as combinations within the registry drugs).

Figure 3.4.2 shows the most commonly reported or dispensed DAAs. Ribavirin (often used in combination with other HCV medications) accounted for the greatest drug reported to the Hepatitis C Patient Registry and Treatment Outcome System and greatest DDDs in 2017, this has vastly decreased year on year, with a reduction of 69% in reports and decline of 62% DDDs between 2019 and 2020. An increase, in reports and DDDs, for sofosbuvir with velpatasvir occurred between 2017 and 2019 (which also accounted for the largest proportion of reports and DDDs in 2019), reduced in 2020 by -24% in reports and -34% DDDs (from 4,637 to 3,534 reports, 423,723 to 35,2819 DDDs, between 2019 and 2020).

Figure 3.4.2. Most often reported or dispensed DAA, by drug a) DAAs reported as first HCV treatment to the Hepatitis C Patient Registry and Treatment Outcome System Patients first treatment DAAs b) DDDs and DDDs per 1,000 inhabitants per day



* DDDs, using IQVIA data, does not include interferon drugs (which have been included as combinations within the registry drugs).

Antimalarial consumption

This section contains consumption data reported for the treatment and prophylaxis against malaria and is new to the ESPAUR report.

Consumption of antimalarials, in primary and secondary care combined, can be seen in Table 3.7. Quinine use was the greatest of all the antimalarials assessed. There was a decreasing trend (-33%) in DID between 2017 and 2021 for quinine use, with no substantial change in decline coinciding with COVID-19. To note, atovaquone is used as one of 2 components (along with proguanil) in the drug Malarone for malarial treatment, but may also, less commonly, be used as standalone drug for treatment of Pneumocystis pneumonia; We are unable to distinguish use of this drug for non-antiparasitic purposes, due to lack of data on prescribing indication.

Table 3.7. Total antimalarial consumption in England, expressed as DDDs per 1,000 inhabitants per day, 2017 to 2021

Antimalarials	2017	2018	2019	2020	2021
Quinine *	0.8307	0.7578	0.6852	0.6093	0.5595
Atovaquone/proguanil **	0.0033	0.0040	0.0046	0.0063	0.0064
Chloroquine ***	0.0018	0.0013	0.0011	0.0011	0.0007
Mefloquine	0.0015	0.0002	0.0001	0.0000	0.0001
Primaquine	0.0008	0.0011	0.0010	0.0010	0.0008
Artemether/lumefantrine	0.0001	0.0002	0.0002	0.0001	0.0002
Piperaquine phosphate/artenimol	0.0000	0.0000	0.0000	0.0000	0.0000

* Quinine includes: quinine bisulfate, quinine dihydrochloride, quinine sulfate
** Atovaquone/proguanil includes: proguanil, proguanil/atovaquone, atovaquone. (Atovaquone alongside use as antimalarial may also be used for treatment of pneumocystis pneumonia).
*** Chloroquine includes: chloroquine and chloroquine phosphate

Discussion

Despite improved infection prevention measures by health care professionals and general population alike and changes in service delivery (fewer face-to-face consultations in primary care and less hospital admissions, particularly during the first year of the COVID-19 pandemic), there were other factors which would have altered prescribing needs and behaviours, such as: social restrictions encouraged through national and regional ‘lock-down’ measures (increased household spread of infections), wearing of masks impacting circulation of pathogens, and changes in the case mix of patients consulting in primary care (reduction in appointments for the very young) as well as those admitted into hospital (with delayed and cancelled elective procedures and increases in more acutely ill patients and admissions to intensive care and high

dependency units). With services beginning to resume, consumption trends are somewhat changing to reflect this in 2021.

Continued declines in total antibiotic consumption have been observed, with a 4.3% decrease between 2017 and 2019, followed by a sharp decline between 2019 and 2020 (10.9%), and a slighter decrease of 0.5% between 2020 and 2021. This decreasing trend highlights the impact that the COVID-19 pandemic has had on antimicrobial consumption in England, in addition to improvements in antimicrobial stewardship and progress towards the NAP targets (25).

Declines seen across all antibiotic groups (apart from oral metronidazole) in 2020 have continued in most antibiotic groups between 2020 and 2021, apart from significant increases noted for penicillins (excluding BLIs), carbapenems, anti-*Clostridioides difficile* agents, and 'other antibacterials' (see chapter 3 in the Annexe accompanying this report for full definitions).

Antibiotic consumption for these classes, however, remained lower than 2019 levels. The incline in carbapenems is likely related to their inclusion within NICE HAP guidelines (NG139, Sep 2019) and COVID-19 rapid guideline: antibiotics for pneumonia in adults in hospital (NG173, May 2020) (33, 39). Increased use in anti-*Clostridioides difficile* agents may be related to noted increases in hospital-onset *Clostridioides difficile* infections, as reported in '*Increased use in anti-Clostridioides difficile* agents'.

By setting, the largest reductions in antibiotic prescribing have consistently been within the GP setting. In 2021, consumption has also decreased in dental practices, following a spike between 2019 and 2020, but has increased in hospital inpatient, outpatient, and other community settings between 2020 and 2021.

Over the past 5 years there had been a general decrease in primary care items per 1,000 inhabitants per day across all age groups. In 2021, compared with 2020, there were increases amongst the younger age groups (greatest increase seen amongst 0 to 4 years old; +51.7%, from 0.34 to 0.52 items per 1,000 inhabitants per day). This was observed following a great reduction in the younger ages (particularly 0 to 4 years) in 2020 and is more in line with 2019 rates. Antibiotic prescribing for the elderly (65 and above) have continued to decrease.

Antifungal consumption did not demonstrate a decrease between 2020 and 2021 as was seen with antibiotic use. While it is not possible to further describe these trends without indication data nor to understand the appropriateness of use, the literature reports antifungal agents have been administered as prophylaxis or combination therapy among COVID-19 patients (40). This may be related to the increasing prevalence of invasive fungal infections (usually acquired by immunocompromised patients in hospitals and in the ICU settings). Chapter 2 also described the increasing incidence of candidaemia over the past two-years, further reinforcing the importance of improved antifungal stewardship and surveillance (41 to 43).

The lack of prescription indication data also makes it difficult to comment on trends in antiparasitic agents. Assuming a large proportion of atovaquone is prescribed as an antimalarial

as part of the atovaquone with proguanil combination, there does not seem to be a major shift in prescribing since 2017. This will be investigated further once data is made available.

UKHSA have worked alongside key stakeholders to bring together relevant information to inform on trends and the impact of external forces on antibiotic prescribing, and progress towards the NAP. Improvements and reductions in antibiotic prescribing have been made, although it is worth noting we are seeing increases in consumption heading towards pre-pandemic levels since healthcare services have started to resume activities. Continued stewardship and surveillance are therefore needed to ensure sustained progress.

Antimicrobial consumption surveillance

Unintended consequences

During the COVID-19 pandemic, prescribing of antibiotics recommended for respiratory tract infections in primary care decreased by nearly 50% in winter 2020 to 2021 compared with the previous winter (92.0 items per 1,000 population in 2019 to 2020 to 48.4 in 2020 to 2021). Specifically, amoxicillin usage saw the largest decrease (-60.1%) (44).

Using this ‘natural experiment’ of reduced primary care prescribing, a retrospective cohort study (utilising linked patient-level prescribing data and microbiological records) has been planned, to assess the association between wide-scale amoxicillin (and co-selection antibiotics) reductions and the incidence of *E. coli* urinary tract and bloodstream infections.

Unified Infections Data Set

The AMR Research Capital funded (by the National Institute for Health Research, AMR call 2018) Unified Infection Data set (UID) has been designed to perform routine and on-demand data linkage from 4 core data sets held by UKHSA. The system aims to improve surveillance, health protection functions, epidemiological analyses and public health intelligence research. The system has now been iteratively tested and piloted, and is in a phase of preliminary use. Various linkage projects are underway utilising the UID, with further details included in the Research chapter (Chapter 8).

COVID-19 therapeutics: Monoclonal antibodies and antiviral therapies

Following global mass vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), fast-paced research continued with examining the use of established and novel direct-acting antivirals (DAAs; which include complex biologicals such as neutralising monoclonal antibodies (nMAb)). These agents have since been deployed in England as treatment for patients who continued to present with severe to critical COVID-19 illness, or for patients with non-severe illness but at high risk of progression into severe illness and hospitalisation (that is, patients of older age, multiple comorbidities, immunocompromised). To retain activity of DAAs for COVID-19 treatment and detect or mitigate possible mutations conferring resistance to them, stewardship of these therapeutics and surveillance is essential. UKHSA, alongside collaborators across the NHS and research communities, developed a programme of public health activities to support the stewardship of DAAs. Genomic, virological, and epidemiologic surveillance within a stewardship framework were established. The new

COVID-19 therapeutics chapter (Chapter 7) in this ESPAUR report highlights and expands on the work carried out.

UK collaboration (4 nations) and participation in international surveillance

Consumption data for England continues to be monitored and collated alongside those of the devolved administrations (Northern Ireland, Scotland, and Wales) to understand the UK-wide picture of total, primary and secondary care consumption and progress made towards the UK AMR 5-year NAP for antimicrobial reduction targets (25). Secondary care antibiotics categorised into the WHO AWaRE index has been embedded within NAP ambitions as well as quality improvement schemes. The AWaRe categorisations were adapted to create a specific index for the UK and are revised over time, discussions with stakeholders including APRHAI have commenced.

Participation in the European Centre for Disease Prevention and Control (ECDC) via the European Surveillance of Antimicrobial Consumption Network (ESAC-Net) ceased following UK's exit from the European Union. The last submission was for 2019 data. England, alongside the UK devolved administrations, have become focal members, submitting and validating data (for England and Scotland, for the years covering 2016 to 2020) to the WHO Global Antimicrobial Resistance and Use Surveillance System (GLASS) antimicrobial consumption module, referred to as GLASS-AMC.

Future actions

Ecological surveillance of national aggregate-level antibiotic consumption was established in 2020 to monitor changes during the COVID-19 pandemic. Trends continue to be monitored on a monthly basis to inform AMS activities at a national level. Future work is planned to combine certain AMU and AMR trends (see Chapter 2 'Antimicrobial resistance').

Future work aims to gain access and utilise patient-level antimicrobial prescribing data to inform on appropriateness of antibiotic prescribing within the GP practice setting.

Work on assessing potential unintended consequences following changes in antibiotic use in England will continue. This will build on previous collaborative work between UKHSA and the Health Protection Research Unit in Healthcare-Associated Infections and Antimicrobial Resistance (HPRU HCAI and AMR) at Imperial College London, as well as projects with the University of Oxford HPRU and London School of Hygiene and Tropical Medicine (LSHTM).

Further assessment into the impacts of COVID-19 on dental consumption is planned. Future research should explore remote management of patients and implications on antibiotic consumption, as well as the attitudes, knowledge and behaviours explaining the increased prescribing within the dental setting observed in 2020.

The assessment into the variations seen in antibiotic consumption across the country will be expanded, looking at associations with deprivation and health inequalities. Literature describes higher prescribing, as well as healthcare seeking behaviour, in more deprived areas (27, 45, 46).

Data for other populations with special considerations (for example, children and young people) with regards to antimicrobial prescribing will be analysed once appropriate data sets are made available.

UKHSA will engage an ESPAUR antifungal sub-group to inform antifungal prescribing and resistance surveillance.

UKHSA plans to use the integrated genomic, microbiological, and epidemiological COVID-19 therapeutics surveillance methods to expand ongoing assessment of other new antimicrobials (47 to 50).

Monitoring trends of new antibiotics and inhibitor combinations is currently completed on an ad hoc basis. While trends in certain older antibiotics, such as ceftazidime with avibactam (launched in England in 2017, used for management of multidrug-resistant Gram-negative bacterial infections) has consistently had low consumption, its usage is slightly increasing (between 2017 and 2021). Other newer antibiotics are still uncommon (for example, cefepime; meropenem and vaborbactam; imipenem, cilastatin and relebactam; and delafloxacin). Ongoing surveillance is important to assess changes in consumption alongside subsequent implications on resistance to these drugs, through changes seen in susceptibility testing (see Chapter 2 ‘Antimicrobial resistance’). This will inform roll-out, guidance and stewardship.

4. Antimicrobial stewardship

Tackling antimicrobial resistance (AMR) requires action on multiple fronts to optimise antimicrobial use and reduce the emergence and transmission of resistance. An important element of this approach is the implementation of antimicrobial stewardship (AMS) interventions. AMS enables healthcare workers to choose the most appropriate drug, dosage and duration of treatment, whilst limiting the microbe's ability to develop or acquire resistance. Optimising prescribing in this way is a key focus of the UK's 5-year National Action Plan on tackling AMR which includes a target to reduce UK antimicrobial use in humans by 15% by 2024.

In this chapter we provide a summary of key national primary and secondary care antimicrobial stewardship interventions led by UKHSA. In addition, and new to the AMS chapter this year, we outline ongoing work to tackle health inequalities associated with antibiotic resistance and prescribing.

Professional and public education and training is a key strand of AMS. Further information, including World Antimicrobial Awareness Week (WAAW) AMS resources such as the Antibiotic awareness toolkit for healthcare professionals in England, is available in the Professional and Public Education and Training (PPET) chapter.

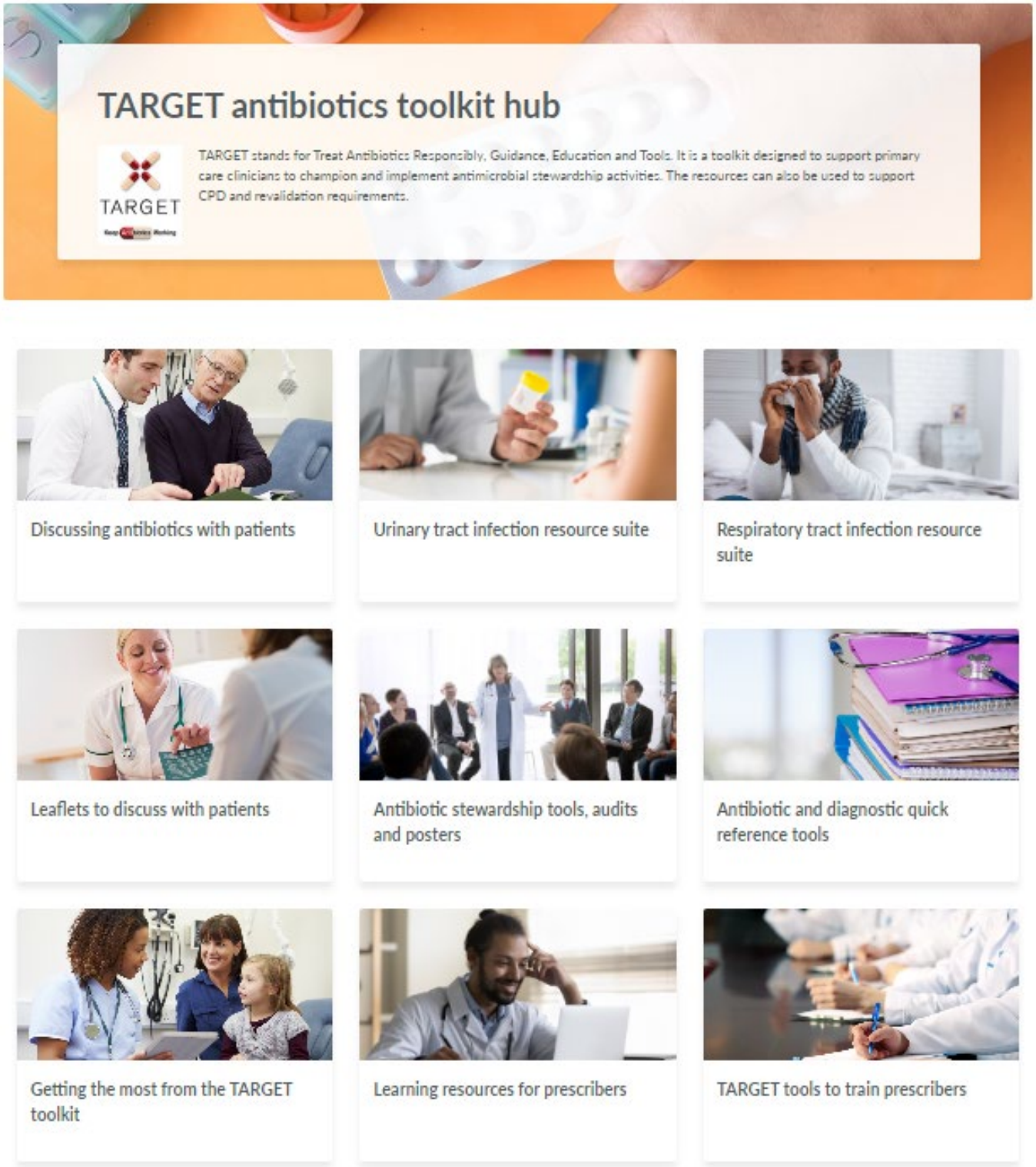
Primary care AMS

TARGET Antibiotics Toolkit – website and resources

The TARGET (Treat Antibiotics Responsibly, Guidance, Education and Tools) antibiotics toolkit is a suite of AMS resources to support primary care clinicians to champion and implement AMS activities. The toolkit, designed and developed by UKHSA, is hosted on the RCGP website.

The TARGET toolkit website (51) underwent a major redesign and went live on 1 November 2021. The redesigned website included a new landing page (Figure 4.1, below), and new sections to provide evidence-based resources to support clinicians to discuss antibiotic use with patients; this included 2 useful evidence-based approaches: 'finding the right words' and 'discussing back-up or delayed antibiotic prescriptions'. This new content was developed in collaboration with the National Institute for Health and Care Research (NIHR) funded STEP-UP group and informed by general practitioners and Clinical Commissioning Groups (CCGs). The TARGET patient-facing leaflets are amongst the most popular resources on the Toolkit and are translated into 26 different languages to help inform patients whose first language is not English. In 2021 the urinary tract infection (UTI), Common Infection and respiratory tract infection (RTI) leaflets were published in an accessible webpage format (HTML) (52). This allowed them to be read on a handheld device and easily shared via SMS text or email.

Figure 4.1. Redesigned landing page and layout of the TARGET antibiotics toolkit, hosted on the RCGP website (51)



Use of healthcare communication services to implement TARGET resources

To implement the HTML versions of the TARGET leaflets in primary care remote consultations, UKHSA collaborated with the company accuRx who develop software that allows GPs to

communicate digitally with patients. AccuRx software integrates with existing GP systems and is used by 98% of GP practices in England. The content and wording of 6 SMS template messages to share TARGET leaflets covering advice on common infections, RTIs and UTIs were created in a workshop with 10 prescribers. The templates went live on the accuRx free text messaging service in July 2021.

In December 2021 a SNOMED code (systematised nomenclature of medicine – clinical terms), a clinical coding system used in healthcare (53), was assigned to leaflets so that coding would be applied automatically, therefore saving time of GPs to manually do this. This allows practices and clinical commissioning groups (CCGs) to audit use of the leaflets and adherence to NICE guidelines around AMS (52), which include provision of self-care and safety netting advice to patients. NHS Hampshire, Southampton, and Isle of Wight CCG found that SNOMED coding of the TARGET patient information leaflet on EMIS increased by 69% between November to December 2021 when the code was added. This highlights the value of assigning codes to templates in accuRx and other systems, to improve the efficiency of coding.

From the initial launch in July 2021 to April 2022, 5,487 leaflets were shared through SMS templates nationally and the UTI leaflet for women under 65 was consistently used the most, making up 46% of all the leaflets sent. Further work will aim to increase awareness and use of the SMS leaflet templates and to investigate if use of the templates reflects trends in remote consultations and prescribing.

TARGET promotional campaigns

TARGET ran 2 joint campaigns with the RCGP to promote the TARGET antibiotics toolkit (51). One focused on promoting the uptake and use of the UTI resources over the period of 8 July to 4 August 2021. The other was to encourage healthcare professionals to access up to date guidance on antibiotic prescribing, understand the implications of antibiotic prescribing or resistance and feel supported to discuss these issues with patients. This campaign was implemented as part of the World Antimicrobial Awareness Week (WAAW) activities in November 2021. The UTI campaign aimed to increase use of the UTI suite of resources at a peak period for UTI consultations and prescribing decisions, and the WAAW campaign promoted the launch of the redesigned website, new resources, HTML leaflets and live webinars (see chapter 6 for information on the webinars).

The main target audience for both campaigns was GPs, with some channels also targeting extended members of the primary care team and Google search advertising extending the reach to patients as well as professionals. Campaign content included:

- promotional emails to over 40,000 RCGP members
- featured content in the RCGP weekly digest, learning bulletin and primary care development newsletters to members and primary care professionals
- paid Facebook campaign to RCGP members
- digital display advertising on the RCGP site

- weekly Twitter posts
- a GP-authored blog post on the RCGP blog

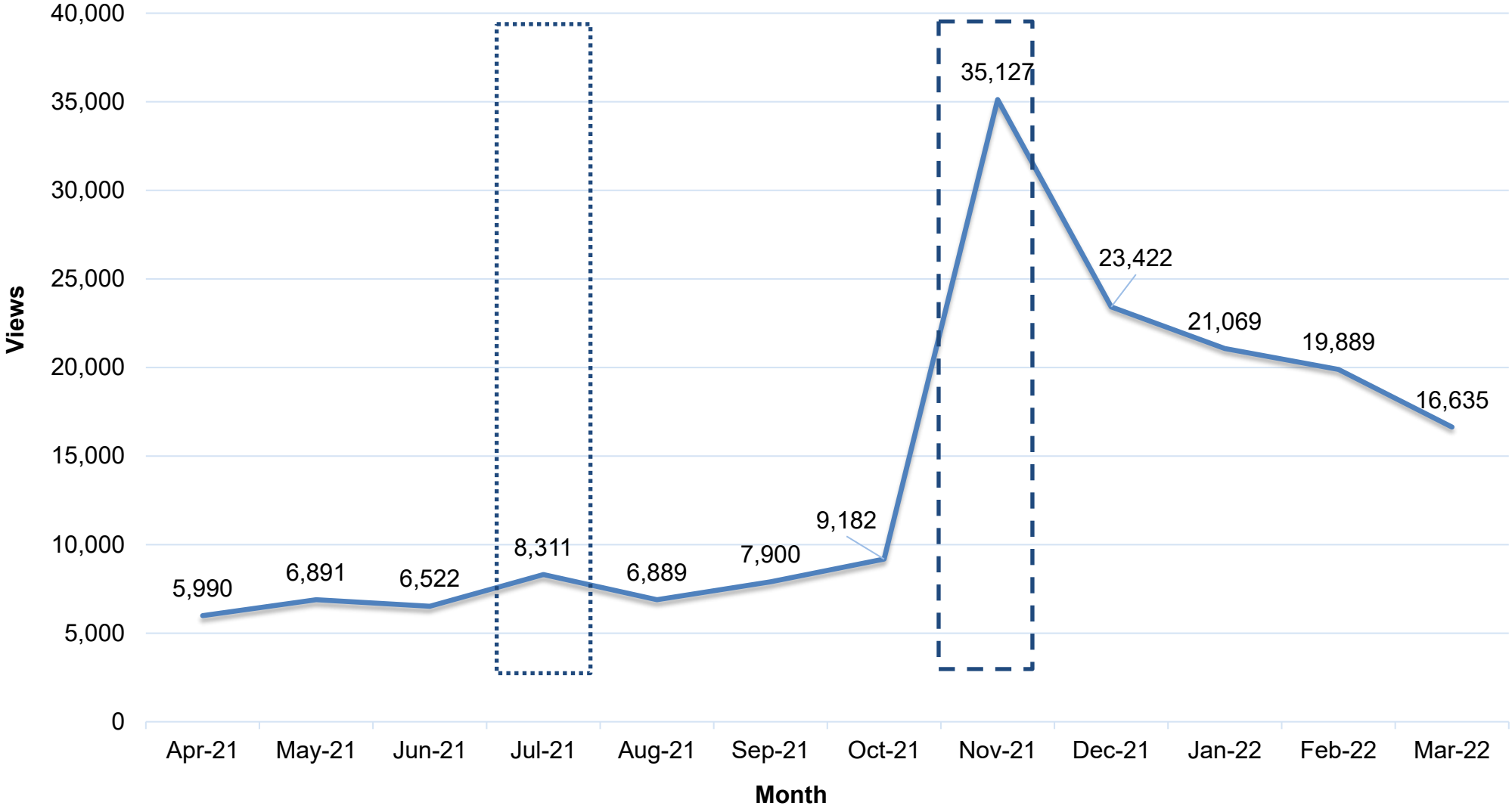
Instagram stories and quiz questions targeting ‘first5’ GPs were developed with a focus on UTIs and management of common infections in primary care. For the campaign over WAAW, direct links to the toolkit were added to the Instagram questions, which drove over half the traffic to the toolkit from all organic social media activity resulting in a 22% increase in views and a 53% increase in engagement. Respondents were asked to select the correct multiple-choice answer relating to delayed prescribing for clinical scenarios including acute sore throat, acute otitis media, and UTI in older adults. The average proportion of correct responses was 65%, a substantial increase on 35% in the July UTI campaign.

The success of the campaigns can be seen through increased visits to the TARGET website (see Figure 4.2). During the 4-week campaign period for WAAW, the TARGET landing page (which was linked to the majority of the marketing) was viewed over 10,000 times. This is double the average views of 4,736 over the 2 preceding 4-week periods in September to October and October to November and the following 4-week period in December to January.

TARGET website visits and resource downloads

Figure 4.2 shows website views of the TARGET Toolkit between April 2021 and March 2022. The total number of views of the website was 167,827 and there was a trend of increasing views over the year. November 2021 had the highest number of views of the year (35,127), almost 4 times that of the previous month (9,182) which coincided with the TARGET promotion campaign, and launch of the redesigned website. From December 2021 to March 2022, the views steadily decreased, but remained higher than before the relaunch of the website. The most viewed page between April 2021 and March 2022 was the ‘Leaflets to discuss with patients’ section, which tends to be the most popular page year on year. A total of 28,887 leaflets were downloaded, and UTI and RTI leaflets make up 34% and 30% of the downloads, respectively.

Figure 4.2 TARGET Toolkit monthly views between April 2021 to March 2022. The data points represent the total monthly visits to the website. Promotional campaigns and the release of the new website layout are indicated by the dotted and dashed lines, which can be seen in July 2021 and November 2021, respectively



Evidence-based and system-wide intervention to review the dose and duration of long-term and repeat antimicrobial prescriptions in primary care

In line with the UK's 5-year National Action Plan (NAP) ambition to "enhance the role of pharmacists in primary care to review the dose and duration of antimicrobial prescriptions (especially long-term or repeat ones) and work with prescribers to review those that are inappropriate through evidence-based, system-wide interventions," UKHSA, in collaboration with partners, has developed evidenced-based 'How to…?' guides.

This project supports the development of initiatives for the management and review of long-term and repeated antibiotic use, encouraging shared decision-making and personalised treatment, considering safety and effectiveness of interventions. No previous AMS interventions were identified that supported clinical pharmacists within primary care teams in their role proposed by the NAP. Thus, the most common clinical conditions with highest use of long-term and repeated antibiotics were identified in order to focus AMS interventions. This was achieved in partnership with individual Primary Care Networks (PCN) and via data retrieval and analysis from the national OpenSAFELY platform, particularly considering pre and during COVID-19 pandemic periods.

Data for an individual sample PCN was analysed to identify the antibiotics with highest frequency of long-term and repeated issues in the preceding 6 months. The antibiotics identified were lymecycline 408mg capsules (n=37, 16%), doxycycline 100mg capsules (n=27, 12%), oxytetracycline 250mg tablets (n=27, 12%), amoxicillin 500mg capsules (n=16, 7%) and trimethoprim 100mg tablets (n=16, 7%). Clinical indications for these antibiotics were inferred to be acne (lymecycline, oxytetracycline), respiratory tract infections including chronic obstructive pulmonary disease (COPD) exacerbation (doxycycline, amoxicillin), urinary tract infections (trimethoprim).

Interim analysis of data via the OpenSAFELY platform highlighted that COPD as a comorbidity, urinary tract infection, COPD exacerbation or lower respiratory tract infection, splenectomy (comorbidity), skin and soft tissue infection, and acne were most commonly linked to repeat prescribing both pre and during the COVID-19 pandemic. There was notable reduction in frequency of COPD exacerbation or lower respiratory tract infection during the pandemic period versus pre-pandemic period. Manuscript on the data analysis is being prepared for peer review submission.

In view of the potential impact and strengthening of AMS, the clinical conditions COPD exacerbation and acne were focused on for initial booklet development. A booklet for urinary tract infection is currently under development by NHS England. These guides, in the form of booklets, aim to support primary care teams in the review of patients with long-term or repeat antibiotics for acne and COPD exacerbations. They are due to be published on the TARGET website.

National implementation of the TARGET Antibiotic Checklist: an antimicrobial stewardship tool in community pharmacies

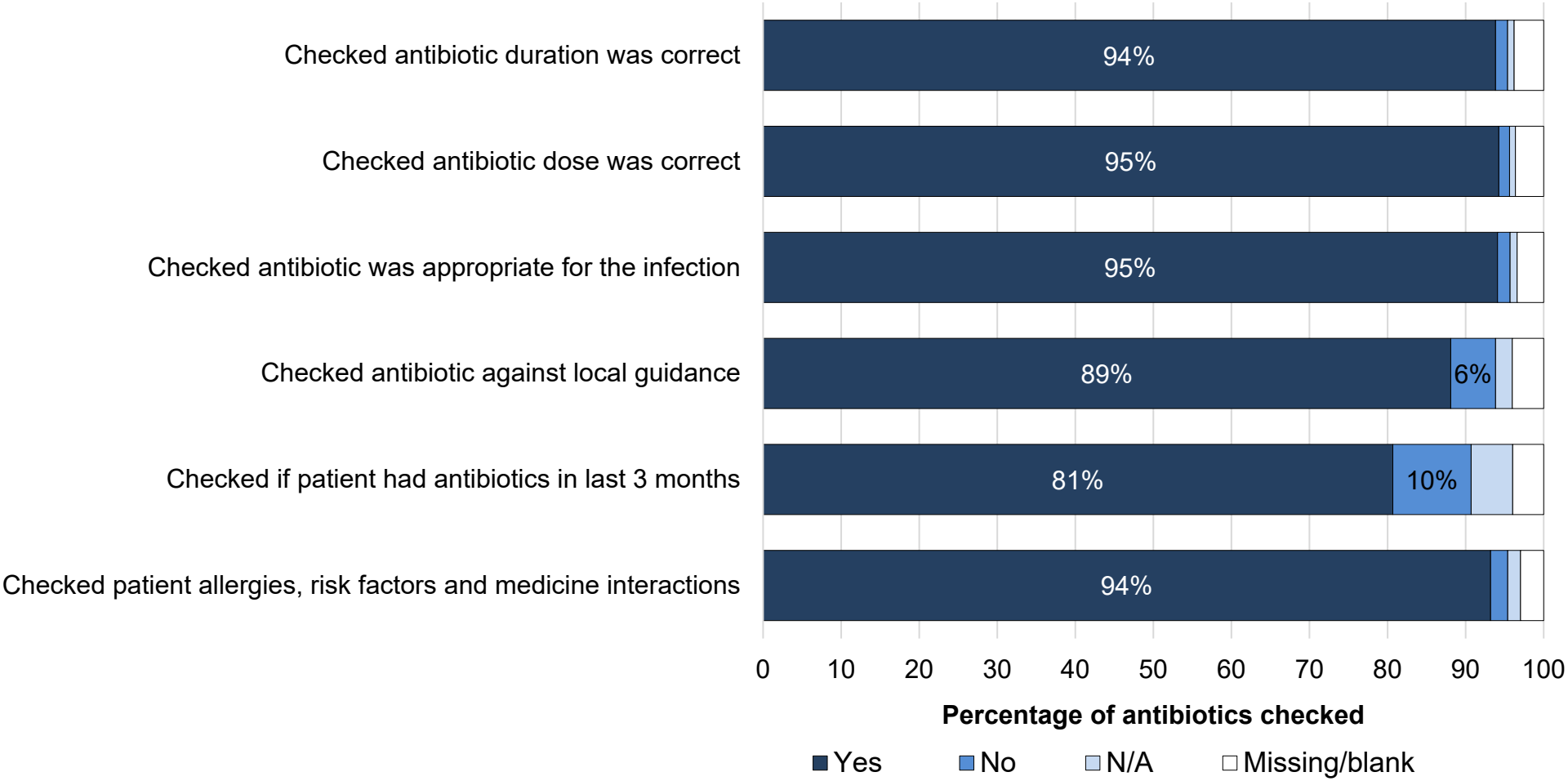
The TARGET Antibiotic Checklist (available via the TARGET Antibiotics Toolkit (51) was co-developed with pharmacy staff and other key stakeholders, to support community pharmacy staff in their role ensuring the safety of patients and educating the public about appropriate antibiotic use and managing common infections. The TARGET Antibiotic Checklist (51) was included as a criterion of the 2021 to 2022 Pharmacy Quality Scheme (see Chapter 5 for information on the PQS). All community pharmacies in England (n=11,232) were eligible to participate in the PQS from September 2021 to April 2022, therefore providing an opportunity to implement and evaluate a community pharmacy AMS intervention on a national scale. Data was submitted from 8,374 community pharmacies (74% of pharmacies in England) who used the TARGET Antibiotic Checklist (51) with 213,105 antibiotic prescriptions dispensed to patients; 86% of the pharmacies entered data for 25 patients and 44% surpassed this.

Antibiotics were mainly collected for a respiratory (47%) or urinary (20%) infection. Generally, patients' reported knowledge on antibiotic use was good. However, areas requiring advice from the pharmacy team included side effects (17%); symptom duration (15%); food consumption (15%) and alcohol (13%) guidance; and missed dose (12%). Pharmacy teams reported using the patient's knowledge assessment to tailor their advice to patients for 80% of the prescriptions and 32% of patients were provided with an infection self-care leaflet.

Figure 4.3, below, shows the percentage of antibiotic appropriateness and safety checks completed by pharmacy teams for antibiotic prescriptions. Pharmacy staff reported checking for patient allergies and the antibiotic duration, dose and appropriateness of antibiotics (94% to 95%). They also reported checking antibiotic prescribing guideline adherence (89%), and if the patient had taken antibiotics in the last 3 months (81%). Pharmacists reported contacting the original prescriber to discuss 2739 (1.3%) prescriptions.

The PQS is an effective lever for implementing and embedding AMS activities at pace in community pharmacy and future PQS activities should continue to build on this. This data collected outside of a research setting gives a realistic snapshot of current community pharmacy AMS. High engagement suggested principles may be embedded and future research should monitor this and the impact on primary care and patients' understanding and behaviour towards antibiotics.

Figure 4.3. Antibiotic safety and appropriateness checks prompted by the TARGET antibiotic checklist reported by community pharmacy staff for 213,105 antibiotic prescriptions, as part of the 2021 to 2022 PQS



Secondary care AMS

Evidence-based antimicrobial intravenous-to-oral switch (IVOS)

The Start Smart – Then Focus antimicrobial stewardship toolkit outlines 5 'antimicrobial prescribing decision' options, the second of which is 'switch antibiotics from intravenous to oral' in line with local policies.

The literature outlines numerous benefits for IVOS; including decreased risk of catheter-related infections, reduced costs and increased patient mobility and comfort (55). In clinically stable patients, studies report that a timely IVOS is safe and of equal efficacy to the full course of intravenous therapy, with no negative impact on patient outcome (56, 57).

Acute hospitals have adopted individualised IVOS policies as there is no standardised IVOS criteria for the UK. The aim of the project was to develop evidenced-based national IVOS criteria by collating from local policies, the literature and expert opinion, using the Delphi method to inform UK-wide antimicrobial IVOS criteria for adults and tool for implementation.

Adult antibiotic IVOS policies were obtained through stratified sampling of UK acute hospitals for collation of IVOS criteria. A literature search was undertaken in OVID Embase and Medline databases (for PROSPERO registration of rapid review see CRD42022320343). Articles without IVOS criteria were excluded, as were those focusing on a specific antimicrobial or infection (for generalisable criteria). IVOS criteria from both local policies and the literature were extracted into Excel spreadsheets.

Forty-five IVOS policies were included and 16 out of 477 papers were identified from the literature search for inclusion. This formed the basis of 42 IVOS criteria entering the 4-Step Delphi consensus-gathering process. IVOS criteria were formatted into 5-point Likert scale questions for Step One, a pilot or first round questionnaire (24 respondents). These were reviewed in Step Two virtual meeting (15 participants) who accepted 37 IVOS criteria to inform Step Three, a second round questionnaire (242 respondents).

Of the Step Three respondents, there were representatives of all 4 UK nations (England n=195, Northern Ireland n=18, Scotland n=18, Wales n=11). The majority were female (n=154; n=7 preferred not to say) and based in NHS acute teaching trusts (n=121). Antimicrobial or infection specialist pharmacists were the highest respondents (n=65) followed by general physicians (n=55).

Most respondents (n=161) considered timely antimicrobial IVOS to have a positive impact on patient outcomes of clinically stable patients. The highest frequency IVOS barrier encountered was lack of time to review patient for IVOS suitability (n=97), followed by lack of senior agreement to IVOS (n=95), no suitable oral option available (n=92) and lack of a decision support tool for IVOS (for example, checklist) (n=64).

Twenty-seven IVOS criteria went forward into Step Four, a pre-workshop survey (48 respondents) and workshop (33 participants) to finalise agreed criteria and develop tool for criteria operationalisation. Step Four outcome was the approval of final 23 IVOS criteria and feedback on a draft IVOS tool. Annexe Figure 4.1 contains a draft version of an antimicrobial IVOS tool designed from Step Four feedback. Final IVOS criteria for use and example tools will be published on 'Final IVOS criteria for use and example tools' and in peer-reviewed publications.

Overall, this project involved 279 participants across the UK nations to agree evidence based, UK-wide IVOS criteria for hospitalised adult patients. This total number accounts for individuals who provided expert advice outside of questionnaires, virtual meeting and workshop, and ensures individuals who participated in more than one step are only included once in total count.

Health inequalities associated with antibiotic-resistant infections and antimicrobial prescribing

The burden of infectious disease is known to disproportionately impact vulnerable groups and this has been reinforced by the COVID-19 pandemic, which has brought health inequalities to the forefront of the global emergency response (58). In the UK, the AMR programme of the UKHSA has committed to tackling and reducing antimicrobial health inequalities nationwide. The AMR health inequalities workstream aims to embed a systematic approach to reducing health inequalities in AMR by:

- improving our understanding of the association between health inequalities and antimicrobial usage and resistance
- developing a health inequalities and AMR engagement strategy within the division including learning from the wider public health community
- producing recommendations for public health action

Most BSI specimens are reported in the ‘Most deprived’ quintile by Index of Multiple Deprivation (IMD). Susceptibility testing for AMR burden combinations is high (above 95%) in all IMD quintiles. Active plans are underway to assess AMR and utilisation data, Group B Streptococcal and *Escherichia coli* BSI, and healthcare outbreaks by IMD and ethnicity.

Work is ongoing to raise awareness of scarlet fever rash on darker skin and assess underdiagnosis in black and Asian children.

Scoping review

A scoping review of the literature was undertaken to investigate the association between elements of health inequalities and the risk of antibiotic-resistant infections and antimicrobial prescribing in high income countries (HICs). Elements of inequalities explored included:

- socio-economic status and deprivation (Employment status, income levels, deprivation categories)
- protected characteristics (age, gender, ethnicity, sexual orientation, disability)
- vulnerable groups (migration status, sex workers, people who inject drugs, the homeless)
- geography (urban or rural dwelling)

Antibiotic-resistant infections

From 137 papers, 10 met the pre-set eligibility criteria. Most of the papers were published from the USA (6), other countries included Australia (1) and the UK (1). The 2 most frequently studied pathogens were *Streptococcus* spp. (5) and *Staphylococcus aureus* (5), followed by Enterococci (2). Six papers focused on ethnicity. Other elements of inequalities included age (3), migration status (1), people who inject drugs (PWID) (1), income (1), deprivation (1) and geography (1).

Two studies in the USA found that black patients, African-Americans and Hispanic patients had higher rates of meticillin-resistant *S. aureus* (MRSA). Immigrants had lower rates of MRSA infection (though not statistically significant) but significantly higher rates of meticillin-susceptible *S. aureus* (MSSA) wound infection, in comparison to US-born citizens. In areas of high deprivation, paediatric cystic fibrosis patients were twice as likely to contract MRSA. Across multiple countries in Europe, income inequality was strongly associated with MRSA infection (r=0.86, 95% CI: 0.83-0.89).

There was a weak association between *Streptococcus pneumoniae* infection resistant to penicillin and macrolides, and income inequality (r=0.34, 95% CI: 0.25-0.43). *Enterococcus faecalis*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* resistance was moderately associated with income inequality (r=0.54, 95% CI: 0.49-0.6; r=0.50, 95% CI: 0.42-0.57; r=0.51, 95% CI: 0.47-0.56, respectively). In the USA, higher rates of penicillin-resistant *S. pneumoniae* were found in Hispanic patients in comparison to non-Hispanic white patients. However, no significant differences were found between groups for other drug-resistant *S. pneumoniae* infections.

Helicobacter pylori clarithromycin resistance was found to be common among Maori, Pacific People and Oriental ethnicities in South Auckland.

Antibiotic prescribing

Fifty-eight of the 402 identified studies met the inclusion criteria, 50 papers (86%) had one or more protected characteristics, 37 (64%) socio-economic characteristics, 21 (36%) geography and 6 (10%) vulnerable groups. Thirty-four (59%) papers discussed antibiotic prescribing, 14 (24%) dispensing and 10 (17%) reported use (data collection for 8 studies was via surveys and 2 via interviews). Thirty-seven studies (64%) were undertaken in the community setting, 13 (22%) in the hospital setting and 8 (14%) had a cross-sector approach. Research of 34 studies (59%) was done in the USA.

Findings included higher rate of fluoroquinolone prescribing in the USA for white patients compared to non-white patients for ear infections, with no difference in whether a generic or brand version was used; rural areas of the USA were less likely to have nitrofurantoin for UTIs appropriately prescribed. In Australia, Chinese migrants who were satisfied with GP services were less prone to self-medicate with antibiotics, and those who reported no barriers to using primary health services were less likely to use non-prescribed treatment. Within the community setting in England, areas of higher deprivation had increased antibiotic prescribing for any infection, where areas classed as 'most deprived' showed increased prescribing rates of broad-spectrum antibiotics.

Summary and next steps

The review highlighted that there is evidence that ethnicity, income inequality and deprivation status can increase the risk of suffering from an antibiotic-resistant infection. Subsets of people from ethnic minorities in the USA and South Auckland have higher rates of antibiotic-resistant *S. aureus*, *S. pneumoniae* and *H. pylori* infection. Income inequality in Europe is strongly associated with MRSA infection and moderately with *E. faecalis*, *K. pneumoniae* and *P. aeruginosa*. Research in this area regarding resistance in *Acinetobacter* spp. and *Enterobacter* spp. is lacking.

In addition, there is evidence to show that factors commonly known to be associated with health inequalities influence antibiotic use in HICs. Trends were identified for age (older age groups had highest antibiotic use), sex (overall, females had highest antibiotic use except for indications including acne, respiratory tract infections and pharyngitis), income (lower income had highest antibiotic use) and deprivation (high deprivation had high antibiotic use). Ethnicity, insurance and geography showed country-specific trends.

The papers are being prepared for peer-review submission. Ongoing research is needed to determine how factors commonly known to be associated with health inequalities and wider social determinants of health interact and affect antimicrobial use. The Core20PLUS approach to tackling health inequalities in England could be adopted, with a focus on infections as a clinical area.

Future actions

TARGET plan to review the UTI quick reference diagnostic tools and develop a simplified diagnostic flowchart for UTI to support AMS in the care home setting. The TARGET website will be updated to improve the visibility of the AMS resources for the community pharmacy setting. Additionally, an online tool, similar to the TARGET Antibiotic Checklist will be developed and evaluated to support pharmacy staff in providing advice to patients who do not attend the pharmacy in person.

TARGET is developing diagnostics picture guides to provide a resource with diverse images to assist with diagnosis to drive improved antibiotic prescribing and a reduction in AMR. The

picture guides on cellulitis, leg ulcers and impetigo will educate healthcare professionals on the different presentations of skin infections for a range of skin tones.

The skin infection resources will be informed by analysis of UK antibiotic prescribing data for skin infections, and an antibiotic prescribing survey of UK GPs, exploring confidence in skin infection management and knowledge of NICE guidance. A comparison between prescribing data and survey findings will help understand the difference between ‘what prescribers do’ and ‘what prescribers say they do’.

The antimicrobial IVOS criteria will be piloted in acute hospital settings. The validation of criteria internationally will be considered to facilitate criteria adoption by other countries.

UKHSA is committed to embedding health inequalities across its work. Future projects include:

- deploying a survey of knowledge, attitudes, and health-seeking behaviours towards antibiotics in different populations
- publishing data analysis on ethnicity and IMD in the ESPAUR report, and embedding into routine reporting
- identifying and improving surveillance reporting gaps required to understand the impact of AMR and AMR-targeted interventions on Core20PLUS populations
- publishing the health inequalities scoping review

5. NHS England: improvement and assurance schemes

Reducing antibiotic prescribing in primary care

The NHS System Oversight Framework provides clarity to Integrated Care Systems (ICSs), trusts and commissioners on how NHS England will monitor performance; sets expectations on working together to maintain and improve the quality of care; and describes how identified support needs to improve standards and outcomes will be co-ordinated and delivered.

The NHS System Oversight Framework for 2021 to 2022 replaced the NHS Oversight Framework for 2019 to 2020, which brought together arrangements for provider and Clinical Commissioning Group (CCG) oversight in a single document.

The NHS System Oversight Framework reflects an approach to oversight that reinforces system-led delivery of integrated care, in line with the vision set out in the NHS Long Term Plan, the White Paper – Integration and innovation: Working together to improve health and social care for all, and aligns with the priorities set out in the 2021 to 2022 Operational Planning Guidance. This framework applies to all ICSs, CCGs, NHS trusts and foundation trusts.

Oversight metrics

A single set of oversight metrics, applicable to ICSs, CCGs and NHS trusts, was developed to flag potential issues and prompt further investigation of support needs with ICSs, place-based systems and/or individual trusts and commissioners.

These metrics align to the 5 national themes of the System Oversight Framework:

- quality of care, access and outcomes
- preventing ill health and reducing inequalities
- people
- finance and use of resources
- leadership and capability

NHS System Oversight Framework 2021 to 2022

The NHS System Oversight Framework 2021 to 2022 includes 2 AMR-related metrics, both applicable to primary care (for CCGs): ‘Antimicrobial resistance: appropriate prescribing of antibiotics and broad-spectrum antibiotics in primary care.’ The metrics and associated targets are set out in Table 5.1. The target for total prescribing of antibiotics is aligned with the UK AMR National Action Plan (2019 to 2024) ambition to reduce community antibiotic prescribing by 25% from a 2013 baseline by 2024.

Table 5.1. NHS System Oversight metrics and targets (March 2024) for antibiotic prescribing

Code	AMR metric description	Target
SO44a	Antimicrobial resistance: total prescribing of antibiotics in primary care. The number of antibiotic (antibacterial) items prescribed in primary care, divided by the item-based Specific Therapeutic group age-sex related prescribing unit (STAR-PU) per annum.	At or less than 0.871 items per STAR-PU
SO44b	Antimicrobial resistance: proportion of broad-spectrum antibiotic prescribing in primary care. The number of broad-spectrum antibiotic (antibacterial) items from co-amoxiclav, cephalosporin class and fluoroquinolone class drugs as a percentage of the total number of antibacterial items prescribed in primary care.	At or less than 10%

NHS system oversight framework performance[1] 2021 to 2022

For the 12 months to 31 March 2022, the number of ICSs meeting the target for total prescribing of antibiotics at or less than 0.871 items per STAR-PU was 21 out of 42 (50%) and the number of ICSs meeting the target for broad-spectrum antibiotic prescribing at or less than 10% was 35 out of 42 (83%). The number of ICSs meeting both targets was 17 out of 42 (40%).

For the 12 months to 31 March 2022, the number of CCGs meeting the target for total prescribing of antibiotics at or less than 0.871 items per STAR-PU was 36 out of 106 (34%) and the number of CCGs meeting the target for broad-spectrum antibiotic prescribing less than 10% was 89 out of 106 (84%). The number of CCGs meeting both targets was 29 out of 106 (27%).

For England as a whole, total antibiotic prescribing for the 12 months to 31 March 2022 exceeded the target of prescribing at or less than 0.871, and was at 0.853 items per STAR-PU which is 27% below the 2013 to 2014 baseline of 1.161 (National Action Plan ambition 25% reduction). The proportion of broad-spectrum antibiotics also exceeded the target at 8.7% (target at or less than 10%).

The proportion of CCGs meeting the national target to reduce the proportion of co-amoxiclav, cephalosporins and quinolones to less than or equal to 10% improved in 2021 to 2022 at 84% in comparison to 44% for 2020 to 2021, but remains below the pre-pandemic performance of CCGs when 90% met or exceeded this target.

Comparison is confounded by changes in the number of general practice consultations coinciding with the COVID-19 pandemic. As of March 2022, general practice (GP) consultations

[1] Data taken from NHS System Oversight Framework Dashboard AMR metrics 44a and 44b, produced by the NHS Business Services Authority.

and antibiotic prescribing patterns for primary care appear to be returning close to pre-pandemic levels. Healthcare delivery within this setting has not fully returned to pre-pandemic ways, with continued use of remote consultations alongside increasing face-to-face (totalling to similar pre-pandemic levels as mentioned). The impact on antibiotic prescribing of an increase in the proportion of GP consultations taking place remotely is uncertain and is being further investigated with improved (patient-level) data access (see Chapter 3).

NHS System Oversight Framework final performance data by ICS and CCG for the antibiotic consumption targets for 2021 to 2022 are collated by NHS Business Services Authority and made available within the NHS England and NHS Improvement AMR Programme Workspace in FutureNHS.

NHS Pharmacy Quality Scheme 2021 to 2022

The Pharmacy Quality Scheme (PQS) forms part of the Community Pharmacy Contractual Framework (CPCF). It supports delivery of the NHS Long Term Plan and rewards community pharmacy contractors that deliver quality criteria in 3 quality dimensions: clinical effectiveness, patient safety and patient experience. NHS England and NHS Improvement, in collaboration with internal and external stakeholders, has developed the PQS for 2021 to 2022. Details of the PQS for 2021 to 2022 have been provided in Part VIIA of the Drug Tariff NHSBSA.

The Antimicrobial Stewardship (AMS) criterion of the 2021 to 2022 Pharmacy Quality Scheme included a roll out of the TARGET Antibiotic Checklist to community pharmacies in England. This built on the previous years' PQS which asked teams to complete the 'AMS for Community Pharmacy' e-Learning, a practice level AMS action plan and to sign up to become an Antibiotic Guardian.

Pharmacy teams were required to submit evidence that they had reviewed their current AMS practice using the TARGET Antibiotic Checklist, to be carried out over 4 weeks with a minimum of 25 patients; or up to 8 weeks if the minimum number of patients was not achieved within 4 weeks. Pharmacy teams were required to input the data from the TARGET Antibiotic Checklist into a secure UKHSA platform and respondents received an automated confirmation via email for each form they had submitted.

The PQS ran from 1 September 2021 to 31 March 2022, and in that time 8,374 community pharmacies submitted evidence to the UKHSA portal from 213,105 antibiotic prescriptions assessed with the TARGET Antibiotic Checklist. See Chapter 4 for background on the TARGET Antibiotic Checklist and a summary of the data submitted as part of the PQS.

Reducing antibiotic consumption by NHS trust providers of acute care

In the financial year 2019 to 2020, the NHS Standard Contract introduced a requirement for all NHS trusts providing acute care to reduce their overall antibiotic consumption by 1% from their own 2018 calendar year baseline value. Consumption was measured as defined daily doses (DDD) per 1,000 hospital admissions and performance was reported in the ESPAUR report for 2019 to 2020. The planned NHS Standard Contract for 2020 to 2021 included a requirement for all NHS trusts providing acute care to reduce antibiotic consumption by 2% from 2018 baseline value, however, this requirement was suspended in March 2020 in response to the COVID-19 pandemic.

NHS standard contract 2021 to 2022

The antibiotic consumption reduction target was reinstated in the NHS Standard Contract for 2021 to 2022 for all NHS trusts providing acute care and the requirement to reduce antibiotic consumption by 2% from each trust's own 2018 calendar year baseline value was retained. An overview of changes to antibiotic consumption targets, scope and performance against targets is provided in Table 5.2.

For 2021 to 2022, 69 out of 138 (50%) of participating NHS trusts met the target to reduce total antibiotic consumption by 2% from 2018 and antibiotic consumption across all participating trusts at financial year end was 4,465 DDD per 1,000 admissions.

Table 5.2. Summary of changes to antibiotic consumption targets and achievement 2019 to 2022

NHS Standard Contract	Target reduction in antibiotic consumption from calendar year 2018 baseline	Number of trusts that met requirement	Antibiotic consumption value at year end
2019 to 2020	1% reduction in total DDD per 1,000 admissions (compare with 2018)	43 out of 145 (30%)	4,612 DDD per 1,000 admissions
2020 to 2021	Suspended due to COVID-19 pandemic	Not available	Not available
2021 to 2022	2% reduction in total DDD per 1,000 admissions (compare with 2018)	69 out of 138 (50%)	4,465 DDD per 1,000 admissions
2022 to 2023	4.5% reduction in DDD per 1,000 admissions for antibiotics from the WHO 'Watch' and 'Reserve' categories (compare with 2018)	Current	Current

NHS Standard Contract final performance data by trust for the antibiotic consumption targets for 2021 to 2022 are available within the NHS England and NHS Improvement AMR Programme Workspace in FutureNHS.

NHS Commissioning for Quality and Innovation (CQUIN) scheme 2021 to 2022

The Commissioning for Quality and Innovation (CQUIN) framework supports improvements in the quality of services and the creation of new, improved patterns of care. The CQUIN framework was suspended in March 2020 in response to the COVID-19 pandemic and therefore the NHS Standard Contract 2021 to 2022 did not include any CQUIN schemes. The planned CQUIN for NHS trusts that provide services for acute care to promote appropriate antibiotic prescribing for urinary tract infection (UTI) in adults aged 16 and over was carried forward to financial year 2022 to 2023.

Plans for 2022 to 2023

FutureNHS AMR Programme Workspace

The NHS England and NHS Improvement AMR Programme Workspace was relaunched on the FutureNHS web-based platform in March 2022 to support local, regional and national stakeholders to access guidance, resources (including frequently asked questions) and performance data for national improvement and assurance schemes. The workspace will also be used to host content and resources relevant to AMR, AMS and infection prevention and management and to facilitate networking within the AMR and AMS communities. Access to FutureNHS requires registration but is open to NHS staff with an nhs.net email address.

NHS Oversight Framework 2022 to 2023

The NHS Oversight Framework was relaunched for 2022 to 2023, replacing the NHS System Oversight Framework for 2021 to 2022. The NHS Oversight Framework reflects the significant changes enabled by the Health and Care Act 2022 including the formal establishment of Integrated Care Boards and the merging of NHS Improvement (comprising of Monitor and the NHS Trust Development Authority) into NHS England.

A set of oversight metrics was published to align with the 5 national themes of the NHS Oversight Framework:

- quality of care, access and outcomes
- preventing ill health and reducing inequalities
- people
- finance and use of resources
- leadership and capability

The AMR metrics and targets for antibiotic prescribing set out in Table 5.1 have been retained for the NHS Oversight Framework 2022 to 2023.

NHS Standard Contract 2022 to 2023

The scope of the antibiotic requirement in the NHS Standard Contract 2022 to 2023 has been narrowed to antibiotics in WHO 'Watch' and 'Reserve' categories (adapted for use in England). This change brings the performance measure into alignment with the ambition set out in the UK AMR National Action Plan for 2019 to 2024. In order to maintain trajectory towards the National Action Plan 10% reduction target, the NHS Standard Contract 2022 to 2023 requires each NHS trust that provide acute services to reduce consumption of antibiotics from the 'Watch' and 'Reserve' categories by 4.5% from the 2018 baseline.

The NHS Standard Contract for 2022 to 2023 also includes a requirement for sepsis identification, screening and treatment for 2 cohorts: service users presenting as emergencies; and inpatient service users. The operational standard indicator is set at 90% for the proportion of patients screened for sepsis and the proportion of patients that, if found to have suspected sepsis, receive intravenous antibiotics within one hour of diagnosis.

NHS Commissioning for Quality and Innovation (CQUIN) Framework 2022 to 2023

There are 15 indicators in the 2022 to 2023 CCG/Integrated Care Board (ICB) CQUIN scheme. The NHS England and NHS Improvement AMR Programme is responsible for 2 CQUIN indicators for 2022 to 2023:

- CCG2: 'Appropriate antibiotic prescribing for UTI in adults aged 16 and over'
- CCG3: 'Recording of NEWS2 score, escalation time and response time for unplanned critical care admissions'

Two additional CQUIN indicators for 2022 to 2023 are relevant to infection and antibiotic prescribing:

- CCG5: 'Treatment of community acquired pneumonia in line with British Thoracic Society (BTS) care bundle'
- CCG14: 'Assessment, diagnosis and treatment of lower leg wounds'

For the 2022 to 2023 CQUIN scheme, the CQUIN financial incentive (1.25% as a proportion of the fixed element of payment) will only be earnable on the 5 most important indicators for each contract (from the 9 CQUIN indicators relevant to acute service providers), as agreed by commissioners. Regardless of this local decision on financial incentivisation, all providers in scope for CQUIN, will be required (as mandated by NHS Digital through information standards notices and/or approved collections) to report their performance against all CQUIN indicators to

the relevant national bodies where they deliver the relevant services, irrespective of whether the indicator is included within their CQUIN scheme.

CCG2: Appropriate antibiotic prescribing for UTI in adults aged 16 and over

This indicator requires case compliance against 5 care processes:

- documented diagnosis of specific UTI based on clinical signs and symptoms
- diagnosis excludes use of urine dipstick in people aged 65 and over and in all catheter-associated UTI (CAUTI)
- empirical antibiotic regimen prescribed following NICE or local guidelines
- urine sample sent to microbiology as per NICE requirement
- for diagnosis of CAUTI, documented review of urinary catheter use is made in clinical record

Full scheme payment requires achievement of 60% or greater case compliance, with part payment for 40% to 59% case compliance. Further details of the scheme and FAQs are available via the AMR Programme Workspace on the FutureNHS platform.

CCG3: Recording of NEWS2 score, escalation time and response time for unplanned critical care admissions

This CQUIN indicator requires 60% of all unplanned critical care unit admissions from non-critical care wards of patients aged 18 and over, to have a NEWS2 score, time of escalation (T0) and time of clinical response (T1) recorded.

6. Professional and public education, engagement, and training

Education and engagement of healthcare professionals (HCPs) and the public is crucial to antimicrobial stewardship (AMS) and is highlighted in the UK 20-year vision for tackling antimicrobial resistance (AMR) and the 5-year National Action Plan (NAP) (59, 60). The COVID-19 pandemic significantly disrupted education and training, however, as social restrictions eased in the last year, this chapter highlights the renewed vigour for professional and public education, engagement and training in England from 2021 to 2022. There is currently no mandatory training on AMS for HCPs.

Professional training and engagement focused on renewing key AMS messages across the patient pathway, including primary care and community pharmacy training on educating patients about antibiotic use. The use of online and remote learning established over the COVID-19 pandemic has continued across all sectors. Engagement with the Antibiotic Guardian campaign continued at high levels in 2021, particularly driven by community pharmacy. A redesign and national roll out of the e-Bug resources aimed to support schools and communities to reinvigorate key infection prevention and control (IPC) and AMR messages. Groundwork for national implementation of TARGET training and e-Bug resources aims for consistent education of HCPs and the public in the future.

Healthcare professional education and training

TARGET and BSAC FutureLearn e-Learning course

The TARGET Antibiotics: Prescribing in Primary Care e-learning course, developed in collaboration with the British Society for Antimicrobial Chemotherapy (BSAC), is a free course hosted on FutureLearn. It consists of 6 weekly, one-hour modules aimed at HCPs and covers AMS topics related to management of common infections. The course ran from 5 April 2021 to 5 May 2022. Half of the users (170 of 339) actively participated in the course (table 6.1).

The course was well-received, with 24 (96%) out of 25 respondents stating that the course either met or exceeded their expectations. The number of learners has declined (1,437 learners registered in 2020 to 2021). The course will continue throughout 2022 to 2023 with rolling registration and a review and update planned in 2023.

Table 6.1. TARGET Antibiotics: prescribing in primary care e-Learning course participation

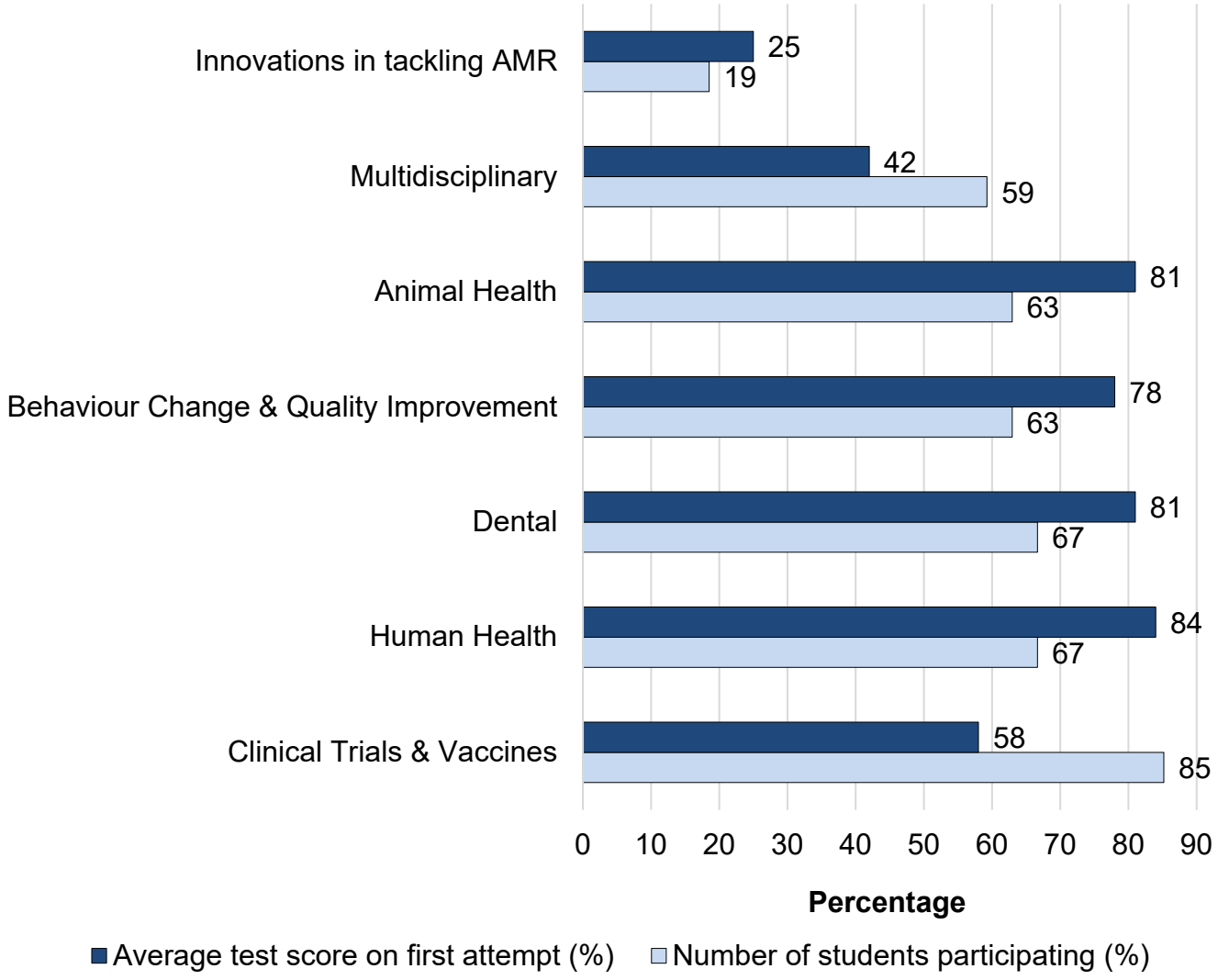
Success measures (5 April 2021 to 5 May 2022)	Number
Registered learners (viewed at least one step of the course)	339
Active learners (marked at least one step as ‘complete’)	170 (50.1%)

Antibiotic Guardian Healthcare Students Conference online modules

The National Healthcare Students' AMR Conference has been held annually since 2017 and recorded sessions were developed as online modules on the Antibiotic Guardian website in 2021. 229 students from 21 Universities (6 international) registered for access to the online platform between November and December 2021.

27 students participated in post-module quizzes (Figure 6.1). See Table 6.1 in the Annexe accompanying this report for information on participants. 'Clinical trials and vaccines' was the most attended module while 'Innovations in tackling AMR' had the lowest participation and average test score. Nine students provided further feedback stating a preference for the flexible online approach of the conference.

Figure 6.1. Percentage of students participating in Healthcare Students' Conference modules and average percentage of correct answers in the post-module quiz

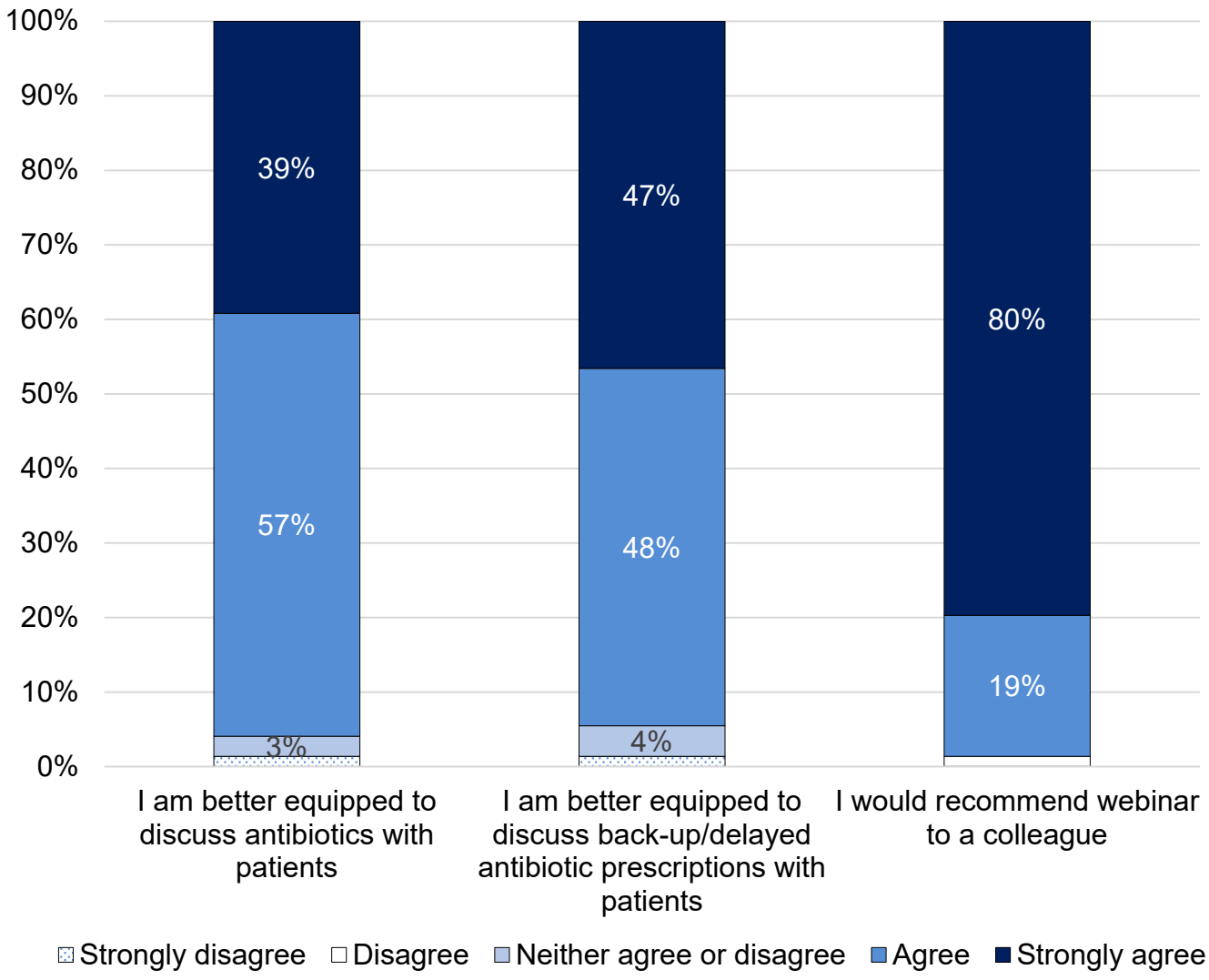


TARGET webinar on discussing antibiotics with patients

TARGET and the RCGP ran a two-part live webinar for primary care prescribers in November 2021, covering communication methods to enhance discussions about antibiotics, and back-up or delayed antibiotic prescriptions with patients. Of 499 registrants, 244 attended the live webinar (48.9%) – the majority were general practitioners (GPs) (49%) or GPs in training (24%). Of 74 attendees who provided feedback, 99% rating the webinar as excellent or good.

At least 95% of attendees reported improvements to their skills in discussing antibiotics with patients and 99% would recommend the webinar to a colleague (Figure 6.2). Attendees expressed a demand for training on AMS topics, and future training should focus on topics highlighted by attendees (see Table 6.2 in the Annexe accompanying this report), including skin infections (currently in development), clinical scenarios and audits. Webinars can be viewed on the TARGET website.

Figure 6.2. Feedback from 74 attendees of the TARGET and RCGP webinar



AMS in Community Pharmacy Shared Learning for the Pharmacy Quality Scheme

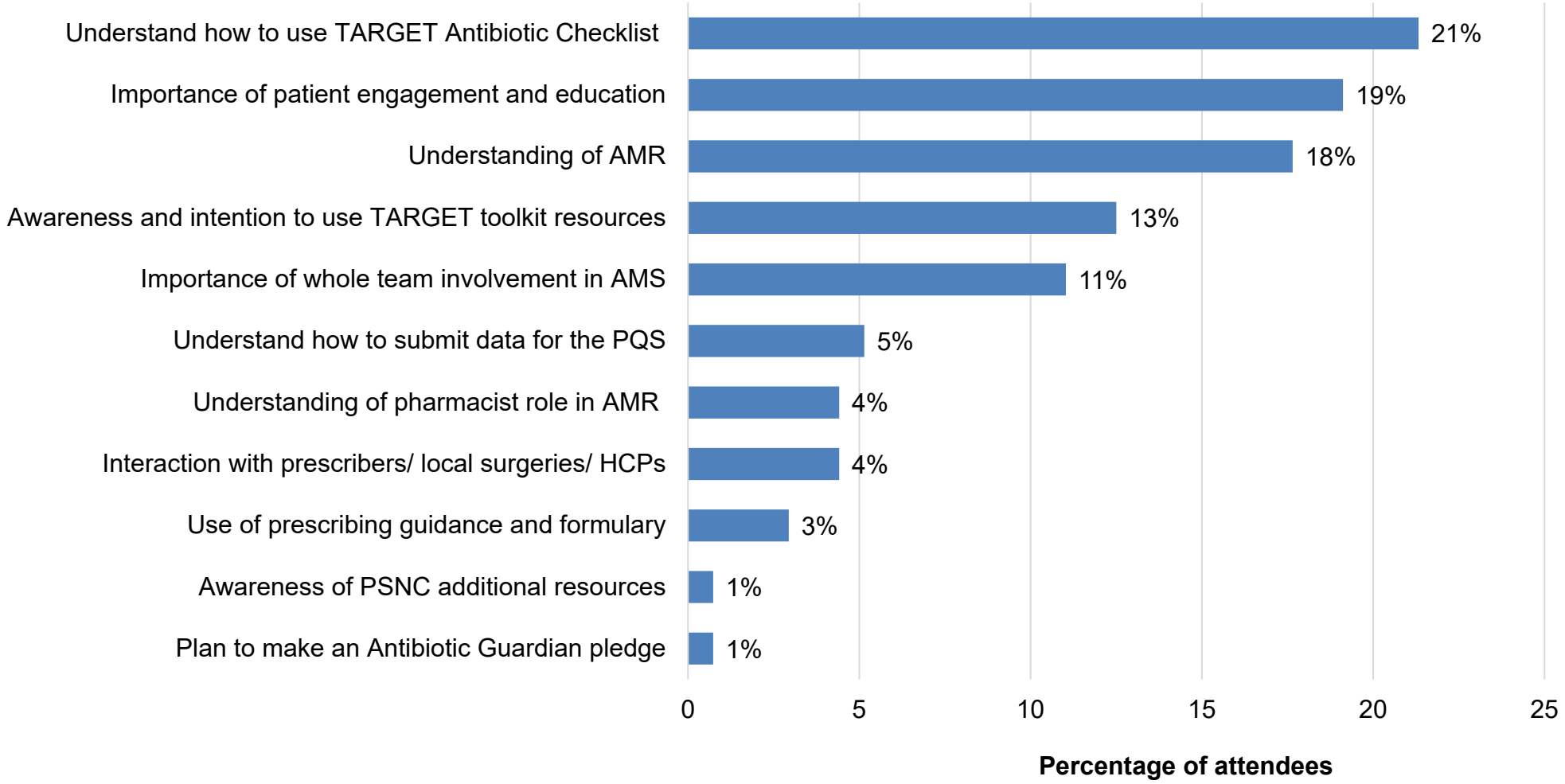
ESPAUR, the Pharmaceutical Services Negotiating Committee (PSNC) and NHS England (NHSE) held a webinar in November 2021 to support community pharmacy teams to meet the AMS criteria of the 2021 to 2022 Pharmacy Quality Scheme (PQS) (see Chapter 5 for more information on PQS).

A panel of 3 pharmacists shared practical experience of the TARGET Antibiotic Checklist, implementing an AMS plan, local antibiotic formulary and patient self-care. A recording is available on the Antibiotic Guardian website.

Feedback on the webinar was provided by 171 attendees, of which 87% rated the webinar 8 out of 10 or higher. Figure 6.3 shows attendees' key learning from the webinar, of which understanding of how to use the TARGET Antibiotic Checklist and importance of educating patients were reported the most. Furthermore 77.2% planned to embed the TARGET Antibiotic Checklist into everyday practice after the PQS.

The webinar format is an effective way to share learning and promote the uptake of the PQS; addition of a panel discussion provided practical advice to pharmacy teams. Evaluation findings also support the growing literature that the TARGET Antibiotic Checklist can support community pharmacy staff in their AMS role (61, 62). See Annexe tables 6.3 and 6.4 for participant demographics.

Figure 6.3. Graph showing the key learning points reported by the 171 attendees of the AMS for Community Pharmacy shared learning webinar



TARGET AMS Train-the-Trainer

TARGET AMS 'Train-the-Trainer' workshops aim to train primary care HCPs on TARGET who would then go on to cascade training in their local area or setting. Although workshops have not been delivered since 2020, 2 existing trainers delivered workshops and received feedback from 12 attendees in their areas in 2021. All attendees stated that the workshop helped them understand the importance of responsible antimicrobial prescribing and 75% reported they understood how to optimise their prescribing. This demonstrates the longevity of the Train-the-Trainer model, and that workshops can continue without involvement from the central TARGET team. TARGET plan to re-establish the workshops with a national implementation planned for 2022 to 2023. See the Future work section for more details.

World Antimicrobial Awareness Week (WAAW) Knowledge Café

A 'Knowledge Café' shared-learning event was held on 22 September 2021, with a panel discussion of HCPs and patient representatives. Attendees were allocated a virtual 'café table' to reflect on plans for 2021, anticipated barriers and available resources, before re-joining the main group to consolidate learning. 196 colleagues registered to attend the knowledge café or access the recording of the session and over 120 colleagues attended the session. A recording of the event is available on the Antibiotic Guardian event webpage.

A post-workshop questionnaire was completed by 34 attendees and 19 indicated which activities mentioned during the Knowledge Café they were likely to include in local WAAW plans. The WAAW digital notes were selected most (37%) and 16% highlighted the AMR boardgame, online quizzes, use of patient stories or case studies and Q&A sessions with healthcare colleagues. See Table 6.5 in the Annexe accompanying this report for all activities.

Public and professional engagement activities

Antibiotic Guardian

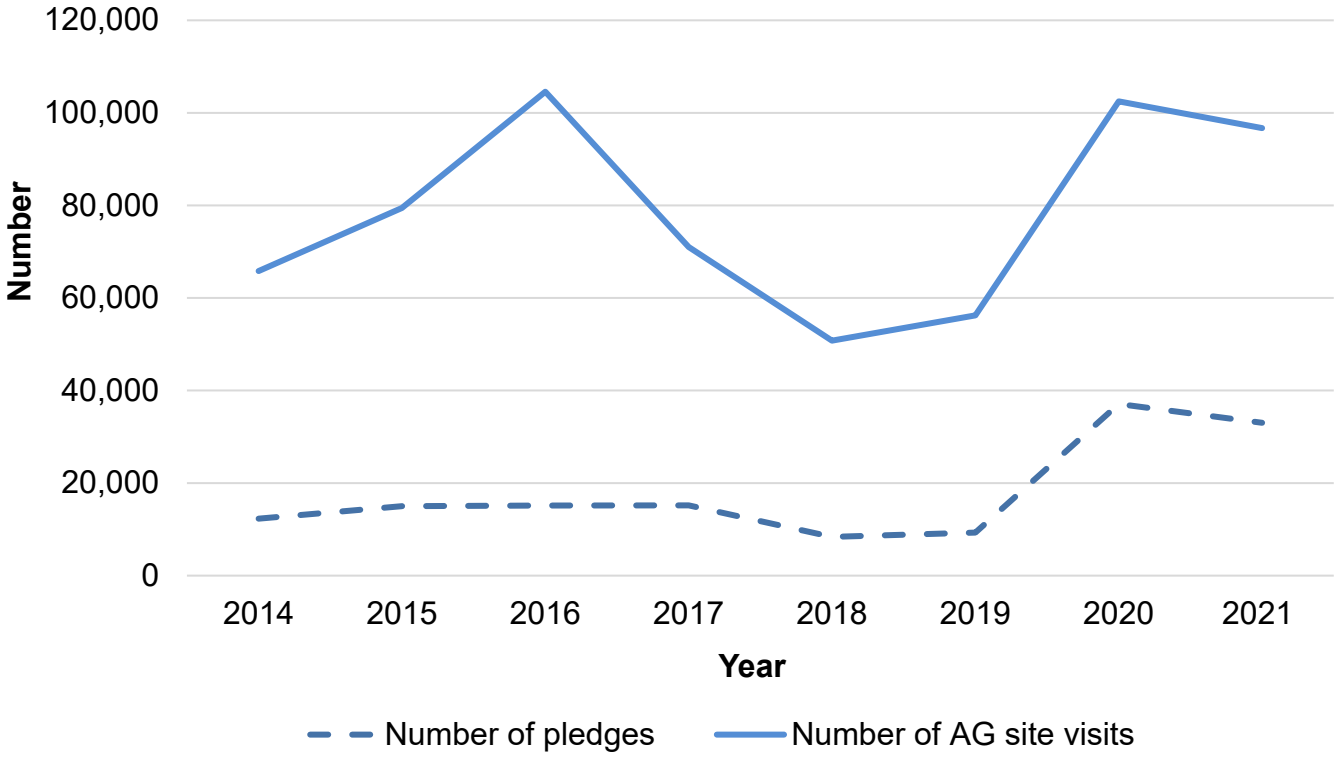
Public Health England (PHE now UKHSA) launched the pledge-based Antibiotic Guardian (AG) campaign in 2014, with the aim of transitioning from raising awareness to increasing engagement. The campaign uses an online pledge-based approach among human and animal health professionals, scientists and educators and the public. From initiation in 2014 to the end of 2021, there have been 144,446 pledges on the main AG webpage (Figure 6.4, below). During 2021, the campaign website was visited 96,697 times, resulting in 33,045 pledges, 842 of which were made during WAAW (18 to 24 November 2021).

The majority of all pledges were made by those identifying as a health or social care professional or leader (94,122 pledges). Of these 68,192 were made by those belonging to 'pharmacy teams', including from primary and secondary care and community pharmacy. Annexe table 6.6 has a breakdown of pharmacy team pledges from 2014 to the end of 2021. Between 2014 and the end of 2021, 36,894 users stated finding out about AG through

community pharmacy. The majority of these (34,165) were healthcare or social care professionals, whilst 625 were members of the public and 231 were students, educators or scientists. This demonstrates the long-lasting impact of initiatives that have promoted AG through community pharmacy, including webinars and training, and the PQS requirement for all patient facing staff to become an Antibiotic Guardian from 2020 to 2021.

Ninety-four organisations registered their AMS activities on the AG website in 2021, 73 were from the UK and 22 were international. Highest numbers were from Hospitals, GP practices, NHS trusts and community pharmacy. See Annexe Table 6.7 for full break down.

Figure 6.4. Graph showing the trend in Antibiotic Guardian pledges (including international pledges) each year, from 2014 to 2021 and annual number of visits to the Antibiotic Guardian main pledge page



Pharmacy workers' knowledge, attitudes and behaviour towards antimicrobial stewardship through the Antibiotic Guardian Campaign

A service evaluation was conducted in collaboration with University of Manchester to explore the impact of the AG campaign upon those working within UK pharmacy teams (primary care, secondary care, community pharmacy, academia). Of the 5,344 pharmacy workers invited to complete the online questionnaire, 783 responses were received (14.6% response rate).

Questions covered demographics, self-reported AMS activities, opportunity to support prudent antibiotic use and motivations for pledging. Capability for AMS was measured with a set of knowledge questions.

There was a statistically significant difference between job roles and capability score (F= 13.776, p<.001). Pharmacists, including Academic and Hospital Pharmacists and Pharmacy Technicians reported higher confidence and capability scores than Dispensers and Pharmacy Assistants. Respondents reported strong knowledge of AMR and high confidence in fulfilling their AG stewardship pledge within daily practices (92.7% of all respondents answered all capability questions, as measured by knowledge, correctly). No statistically significant associations were found between motivations for pledging and subsequent behaviour.
This evaluation supports the value of the AG pledge-based approach to engage and educate pharmacy workers. Future training may need to target specific job roles to account for the difference in AMS capability.

Public perceptions of antibiotics after Antibiotic Guardian pledge

Qualitative research was conducted in collaboration with University of Manchester to explore public attitudes towards antibiotic use following an AG pledge made during the month of WAAW 2020. Ten members of the public participated in semi-structured interviews via teleconference to discuss awareness of the campaign, prescribing and antibiotic use. Table 6.2 summarises themes identified through a thematic and framework analysis of interviews.

Pledging solidified existing beliefs and the perception of contributing to something important, as one participant described: “It gave me that feeling that I was doing something good and being part of something that was big”. Behavioural motivations for appropriate antibiotic behaviours stemmed from personal responsibility, moral obligation and concerns about AMR. Participants were keen to promote responsible perceptions in relation to antibiotics and resistance.

Participants’ longstanding commitment to AMR demonstrates the importance of pre-existing interest for individuals’ decision to pledge to an AMR-focused campaign.

Table 6.2. Themes of public views towards antibiotics following an Antibiotic Guardian pledge. N refers to number of participants who discussed the theme

Theme	Sub-theme	n
Campaign awareness	Incidental internet searching	3
	Pre-existing scientific interest and endeavours	3
	Professional networks	2
	Social media	2
	Can’t remember	2
Motivation to pledge	Uncertainty about the future of antimicrobial resistance	6
	Personal gratification	7
	Personal responsibility and moral obligation	4
Perceptions of prescribing	Widespread overprescribing	9
	Clinician dependent prescribing values	5

Theme	Sub-theme	n
	Age-related prescribing	6
Impact of campaign	Solidified existing beliefs	10
	Increased commitment to minimise AMR	6
	Increased antimicrobial resistance knowledge	3
Impact of COVID-19	COVID-19 irrelevant to pre-existing beliefs	5
	Appreciation for infection prevention	3
	ABR deprioritised	3
Campaign promotion	Promotion to friends and family	5
	Antimicrobial resistance stigma	5
	Wider targeting	4
	Frequency of messaging	9

Antibiotic Guardian Schools Ambassadors Programme

The AG Schools Ambassadors programme, first piloted in 2019, aims to connect HCPs with local schools and community groups, in order to share information about antibiotic use, AMR and infection prevention and control. In 2021, the programme aimed to target the regions with the most deprived lower-layer super output areas (LSOAs) (63) through cascading information through regional AMS pharmacy leads and the regional AMS pharmacy network. A total of 110 colleagues registered in 2021 (79 in 2019) and the targeted engagement activity led to higher engagement in North West, Midlands, North East, and Yorkshire areas than previous years.

Of 25 ambassadors who provided feedback, 88% confirmed that they participated in the programme in 2021; 8 respondents promoted an article for distribution in school newsletters, 6 provided a toolkit (which includes eBug resources) for schools to plan a lesson, 5 provided a lesson in person and one recorded a short video. Of those that participated in the programme, 75% stated that taking part in this programme helped them personally and/or professionally. The AG Schools Ambassadors programme demonstrates the dedication of HCPs to engage with schools around AMR including antibiotic use and infection prevention and control, even during the pandemic, and the utility of regional AMS lead networks in increasing engagement in areas of deprivation. Future work will focus on strengthening this focussed regional approach and designing robust indicators of impact.

World Antimicrobial Awareness Week (WAAW) and European Antimicrobial Awareness Day (EAAD) 2021

WAAW took place between 18 and 24 November 2021 and EAAD on 18 November. Despite ongoing barriers introduced by the COVID-19 pandemic, WAAW and EAAD continued to provide an excellent opportunity to engage with HCPs and the public on tackling AMR. A toolkit for healthcare professionals in England provided guidance to support the NHS, local authorities

and others to lead activities and encourage responsible use of antibiotics. In the context of the COVID-19 pandemic, the focus of the toolkit was on digital activities. The webpage hosting the toolkit was visited 2,019 times between publication in October 2021 to the end of 2021. Key learning from 2020 was to work with local communications teams to streamline messaging around WAAW and a digital guide provided tips on designing effective AMS messages grounded in knowledge mobilisation methodology.

Figure 6.5 shows a selection of digital sticky notes which could be shared on social media and other platforms, including editable versions for colleagues to include their own messages. Digital notes promoted 'interesting' or lesser-known facts aligned with 5 daily themes for each of the weekdays of WAAW (prevention, diagnostics, clinical, AMR and the environment, allergy).

Figure 6.5. Selection of digital notes that were promoted for use during WAAW 2021

For the first time in 2021, custom teleconference backgrounds and screensavers were created for colleagues to use during WAAW and the WHO Go Blue for AMR campaign was promoted and supported. Figure 6.6, below, shows examples of these backgrounds, which included messages aligned with the digital notes for each day and editable versions were created for colleagues to include their own wording or institutional logos. The design of these backgrounds was based around the two-tone pill motif used in both 'Keep Antibiotics Working' and 'Antibiotic Guardian' campaign materials.

Figure 6.6. Teleconference backgrounds designed for use during WAAW 2021

WAAW and EAAD Twitter activity

A Twitter poll was hosted by UK Clinical Pharmacy Association (UKCPA) Pharmacy Infection Network (PIN) and ran for each of the 5 weekdays of WAAW. The questions were designed by the National WAAW planning subgroup to align with the daily themes, the average number of participants per day was 39.

The annual WHO global Twitter storm ran between 3pm and 4pm GMT on 18 November 2021. UKHSA supported the Twitter storm by producing and promoting a custom tweet card for use by colleagues during this hour. Based on an analysis of Twitter activity during WAAW 2021, there were 15,452 tweets relating to WAAW from 6,189 users, and 37,719 retweets from 17,808 users during the week. By 10 February 2022 these tweets had received 41,865 retweets. Overall, 824 (13%) accounts received 80% of all retweets, while 2,669 (43%) received no retweets. Table 6.3 shows that use of the hashtags #KeepAntibioticsWorking and #AntibioticGuardian has declined between 2019 and 2021.

Table 6.3. Social media metrics of the hashtags #KeepAntibioticsWorking and #AntibioticGuardian on Twitter from 2017 to 2021 during the week of WAAW. Tweets are original posts made by users, and retweets are shares of other users' posts

Years	Retweets	Tweets	Total tweets	Total users
2017	6,335	3,369	9,704	4,131
2018	9,717	3,234	12,951	5,498
2019	10,082	2,995	13,077	6,438
2020	4,646	2,023	6,669	3,477
2021	4,454	1,816	6,270	2,582

Public education and engagement with e-Bug

The e-Bug programme, operated by UKHSA, seeks to reach and equip those who work with, or support children and young people (aged 3 to 25 years) in all communities with information and activities to build knowledge around microbes, disease, hygiene, vaccination and AMR. By promoting behaviour change amongst children and young people, UKHSA are supporting the aims of the AMR NAP by ensuring that the extensive work to address AMR is future proofed and supporting young people to be agents of change in their communities.

Supporting UK school leavers to understand how to wash hands, prevent infections and use antimicrobials appropriately

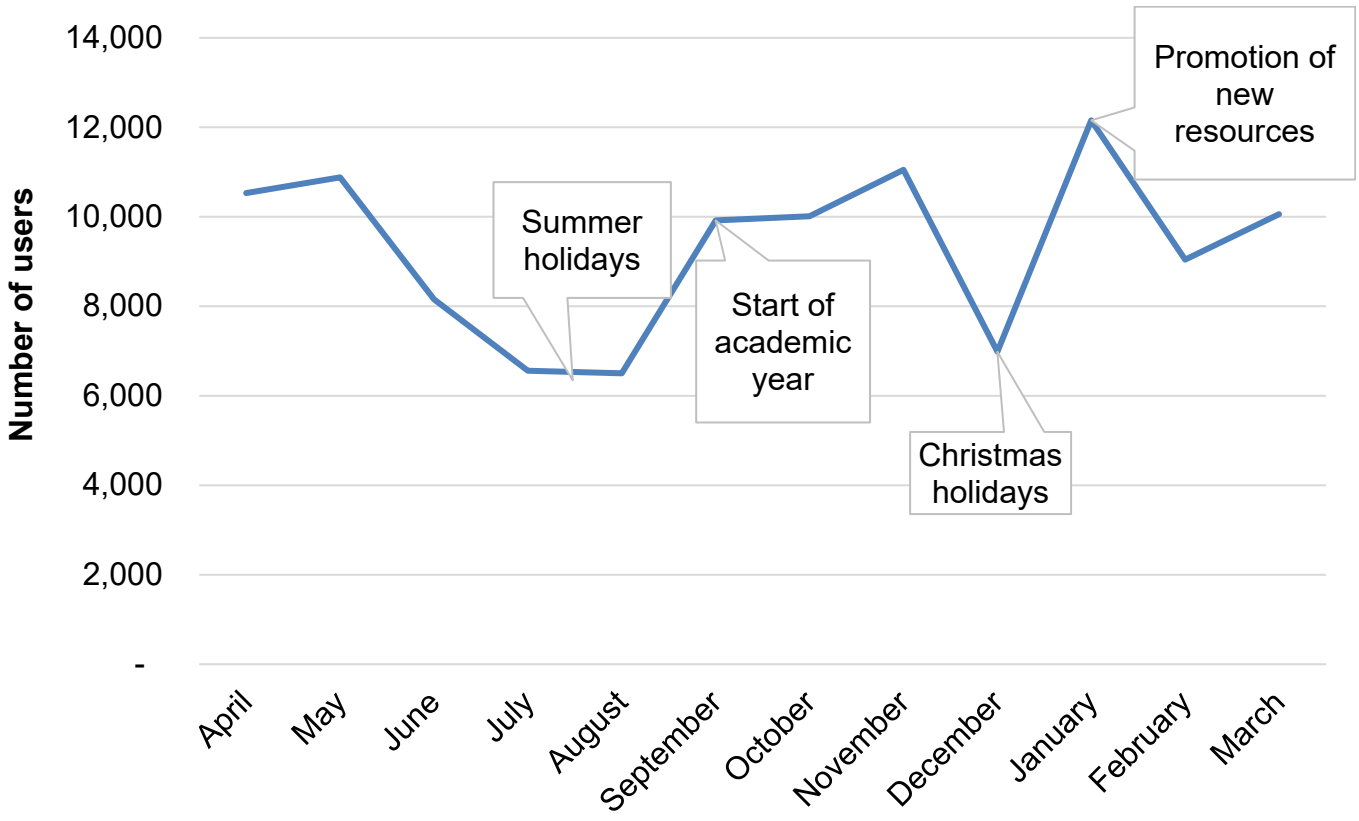
The e-Bug programme completed a full review and update of educational resources aimed at teachers and school nurses. This included expanding the resources to cover the early years foundation stage (ages 3 to 5 years) through to key stage 4 (ages 14 to 16 years), introducing guidance for educators, and mapping lessons to the national curriculum. The materials were developed through an iterative process of feedback and updates, involving 16 teachers and 8 experts from across UKHSA, as well as international partners. All materials have been accredited by the Association for Science Education and e-Bug was included in the updated UKHSA guidance 'Health protection in education and childcare settings'.

Educational packs were disseminated to every maintained school and academy across England (over 20,000 schools), in collaboration with NHSE in January 2022. The packs were accompanied by a letter from Dame Professor Jenny Harries, and complimented by communications through UKHSA, children and young people leads, directors for public health, and the Department for Education.

Initial market research has identified that educators in England have a gap in knowledge on AMR, potentially resulting in unequal learning and opportunities for children and young people. To address this the e-Bug programme aim to explore opportunities to integrate IPC and AMR into the national curriculum.

The resources are available on the e-Bug website in accessible, adaptable formats. Figure 6.7 shows that between April 2021 and March 2022, 105,949 users have accessed the website viewing a total of 520,914 pages. 29,203 new users have accessed the website since the resources were updated in January 2022. The trend in views follow the academic year with peaks during school term time and troughs during holidays.

Figure 6.7. Number of UK users accessing the e-Bug website each month between 1 April 2021 and 31 March 2022. Graph is labelled with school summer holidays (July to August), start of academic year (September), Christmas holidays (December), promotion and roll out of new resources (January)



Ensuring children and young people facing socio-economic, educational and/or health inequalities receive messaging on infection prevention and control

The e-Bug materials have been made suitable for teachers to use with children and young people with special educational needs (SEN) or in alternative provision settings (APS). This has included the development of differentiated material and ensuring all resources are available in an accessible format, to enable educators to adapt the material to their students' requirements. The programme is currently redeveloping the website to meet web content accessibility guidelines (WCAG) level AA standards, ensuring that users with disabilities and/or using assistive technologies are able to access all content without barriers. The website, and resources will be free to access and available in a range of languages.

International messaging on IPC and AMR

The e-Bug programme is working to re-engage partner countries to adopt long term messaging on IPC and AMR with children and young people. The programme offers resources for countries who have a public education component in their National Action Plans or seek to increase public engagement in their health security agenda. The programme has worked closely with

Portugal, Norway and France to translate and adapt the new e-Bug materials for their contexts and advise on resource implementation.

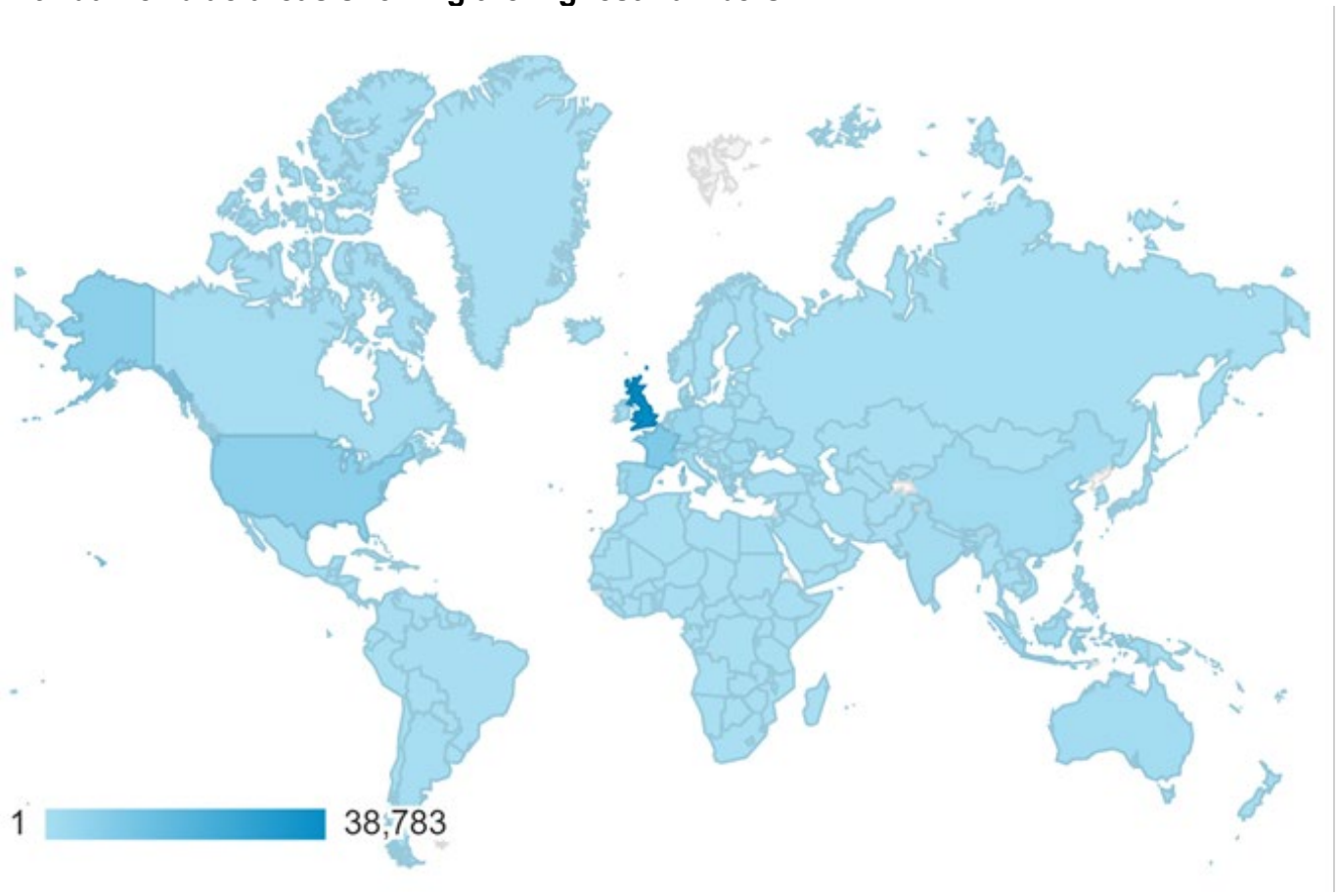
By working in partnership with the European Commission funded SafeConsume programme, e-Bug have developed materials to promote behaviour change around food safety. The materials were implemented across Portugal, Denmark, France, Greece and Hungary, and have now been offered to other countries for translation. Lessons from content development has been published in the Food Control journal (64).

In other countries, the focus has been on building future partnerships, which offer an opportunity for the UK to lead the way in equipping the next generation to respond to AMR and for all countries to share learning. Future aims are to focus on lower and middle-income countries (LMICs). However, in the meantime, individuals from across the world are accessing e-Bug resources through the website with highest number of users from the UK, France and the USA (see Table 6.4 and Figure 6.8).

Table 6.4. Top 10 countries accessing the e-Bug website from April 21 to March 22

Top 10 countries accessing the e-Bug website	Number of users (April 21 to March 22)
UK	37,783
France	9,839
USA	6,959
Spain	3,835
Germany	3,585
Albania	2,466
Indonesia	2,247
Italy	2,224
Romania	2,118
China	2,073

Figure 6.8. Top 10 countries with highest users accessing the e-Bug website between 1 April 2021 and 31 March 2022. The map shows density of visitors to the e-Bug website, with darker blue areas showing the highest numbers.



e-Bug Future Learn Courses

e-Bug offers 2 e-Learning courses aimed at educators and childcare practitioners through FutureLearn. Both courses were developed with BSAC and are accredited by the Royal College of Pathologists. Both courses have had high engagement in 2021 to 2022 (Table 6.5) demonstrating the demand for training and resources for school settings to improve the management of infections in younger children.

1. e-Bug Health Educator training is designed to support educators to teach students about the spread, prevention, and treatment of infections and antibiotic use. A total of 96% of learners reported improvement in their knowledge, and the course exceeded expectations of 71%.

2. The Preventing and Managing Infections in Childcare and Pre-school course is designed to support individuals working in these settings to prevent and manage infections. The course includes information on microbes, the importance of hygiene in a childcare environment, controlling outbreaks and immunity. Most learners agreed that the course improved their knowledge (93%) and met or exceeded their expectations (97%).

Table 6.5. Success measures of the 2 e-Bug FutureLearn courses, 2021 to 2022

Success measures (1 April 2021 to 31 March 2022)	e-Bug health educator	Childcare and pre-school
Total users	730	981
Percentage of active learners (completed at least one module)	56%	70%
Countries	95	93
Star rating and reviews	4.7 stars, 55 reviews	4.8 stars, 137 reviews

Assessing public health-seeking behaviours and attitudes towards antibiotic use

We provide interim finding from 2 independent studies recently conducted to assess public health-seeking behaviour and attitudes towards antibiotic use.

Changes in public health-seeking behaviours and attitudes towards antibiotic use for respiratory tract infections during the first 2 years of the COVID-19 pandemic

COVID-19 exerted significant strain on national healthcare services across England. To explore changes in public health-seeking behaviours for respiratory tract infections (RTIs), and knowledge of, and attitudes towards antibiotics, national surveys were conducted in March 2022 (pandemic year 2), March 2021 (pandemic year 1) with findings compared to a baseline survey from before UK lockdown restrictions in March 2020.

Comparing responses to a telephone survey of 1,663 adults (2022), 1,676 adults (2021) and a face-to-face survey of 2,022 adults (2020) across England. Data is weighted to match the profile of the English population.

The incidence of self-reported RTIs in the 12 months pre survey initially dropped during the first year of the pandemic (71% 2020 versus 50% 2021; $p \leq 0.05$) only to increase back to almost pre pandemic levels in 2022 (50% 2021 versus 67% 2022; $p \leq 0.05$). There was no change in reported GP consultation (25% 2020 versus 23% 2021 versus 27% 2022) during this time. Of those who visited the GP, self-reported expectation for antibiotics increased in 2021 (56% 2021 versus 38% 2020, $p < .05$) and remained in 2022 (49%). However, those reporting receiving antibiotics were similar (52% 2020 versus 54% 2021 versus 48% 2020, not significant). In 2022, 80% of respondents who visited their GP reported being satisfied with their health care outcome.

The incidence of those classed as self-managers, that is, did not consult a health care professional for their most recent RTI, increased (61% 2021 versus 73% 2022; $p \leq 0.05$).

Respondents reported more proactive symptom management, with greater reports of seeking over-the-counter remedies (35% 2020 versus 35% 2021 p<.05 versus 35% 2022, not significant), taking extra rest (24% 2020 versus 43% 2021 p<.05 versus 43% 2022, not significant) and using alternative medicines (21% 2020 versus 38% 2021 p<.05 versus 38% 2022, not significant). Some behaviours observed for the first time in 2021 have continued but at a lower level, such as staying at home (43% 2022 versus 57% 2021) or self-isolating (26% 2022 versus 39% 2021).

During the pandemic 14% (2021) and 16% (2022) of respondents thought that antibiotics work for the symptoms of COVID-19. A total of 28% (2021) and 24% (2022) falsely think that antibiotics can treat the majority of cold and flu symptoms. Although 79% of respondents said they would be pleased if a GP said they themselves did not need antibiotics; this was fewer than 2021 (79% versus 83%: p<0.05). Just over one-fifth (21%) in 2022 would challenge the GP on the need for antibiotics, similar to 2021 (19%).

Control restrictions imposed during the pandemic dramatically impacted health-seeking behaviours across England and enabled greater self-management for RTIs. Although it may be perceived as a positive outcome, it is essential that the public know when to seek help to avoid potential unintended consequences associated with self-management. There is still some work to be done to educate the public as to what conditions can effectively be treated by antibiotics, particularly among those most likely to challenge GPs who do not prescribe antibiotics when the patient expected them to.

Assessing the impact of wider determinants of health on antimicrobial use, understanding, and health-seeking behaviours from an English population survey

The COVID-19 pandemic has had an unprecedented impact globally and has influenced many wider determinants of health of relevance to current and future healthcare seeking behaviours, including the impact on antimicrobial resistance. This study sought to understand and describe the influence of wider determinants of health on public attitudes towards and knowledge of antibiotic activity, resistance, and usage in England.

An online survey was undertaken by Basis Market Research with 2,063 individuals over 18 years of age between 28 April and 9 May 2022. Data is weighted to match the profile of the English population.

Just over 2 in 5 (44%) of all respondents reported taking antibiotics at least once in the previous 12 months. Reported antibiotic usage was higher amongst 18 to 34 year olds (61%; p≤0.01), those from urban populations (48%; p≤0.01), deprivation group IMD 1-2 (55%; p≤0.01), the financially vulnerable (53%; p≤0.01), and those in insecure jobs (62%; p≤0.01). Those registered as disabled were more likely to have used antibiotics in the past 12 months (62%; p≤0.01), which was higher again for those limited a lot by their disability (67%; p≤0.01).

The majority of respondents reported having received antibiotics from a healthcare professional (92%). However, 18 to 34 year olds and those in insecure employment were more likely to obtain antibiotics from elsewhere including use of leftover stock (14% all versus 23%; p≤0.01 and 31%; p≤0.01 respectively), obtaining abroad (11% all versus 15%; p≤0.05 and 29%; p≤0.01 respectively) and use of those originally prescribed for someone else (6% all versus 9% n.s. and 15% respectively; p≤0.05).

Understanding of appropriate antibiotic use was lower in younger adults, those living in urban areas, more deprived, financially vulnerable, and those limited by disability. The younger adults, financially vulnerable, and those in insecure jobs were less confident in a doctor's decision not to prescribe antibiotics (81% for all versus 72%, 77%, and 73% respectively; p≤0.01) and were more likely to want to take antibiotics 'just in case' (36% for all versus 48%; p≤0.01, 41%; p≤0.05, and 52%; p≤0.01 respectively).

Just over 2 in 5 (41%) of all respondents stated that they had received advice about antibiotics in the past 12-months, and for younger, financially vulnerable and those in insecure jobs, this was more likely outside of primary care (36% for all versus 48%, 41%, and 52% respectively; p≤0.05) including from out-of-hours and hospital services, and indirectly from other resources.

Some wider determinants of health assessed in our study had an impact on antimicrobial use, understanding, and health-seeking behaviour suggesting the need for a targeted educational and/or behavioural intervention approach for these groups. Those reporting financially vulnerability and in insecure employment, irrespective of deprivation status or income, represent an additional risk group for antimicrobial use and reduced awareness, despite often having obtained advice on antibiotics. This may be because much of the advice administered during the COVID-19 pandemic was given verbally. Research indicates that patients have a better understanding when given both written and verbal instructions, rather than verbal instructions alone.

Future actions

TARGET Antibiotics Toolkit

TARGET are developing a webinar focussing on the NICE guideline updates for antibiotic prescribing for skin infections and will include behavioural theory throughout to provide prescribers with the capability, opportunity, and motivation to adopt guidance into everyday practice. TARGET will update the Train-the-Trainer materials and relevant online learning platforms, working with NHSE Regional AMS leads to cascade workshops targeting areas with high prescribing.

Antibiotic Guardian and WAAW

Antibiotic Guardian shared learning and awards event will open for entries in 2022, with shortlisted entries announced during WAAW 2022. The Antibiotic Guardian Schools

Ambassadors programme will run for a fourth year and strengthen focus on areas of deprivation, as well as evaluating impact and engagement from ambassadors and schools. WAAW 2022 will focus on consolidating the resources produced in 2020 and 2021. Daily themes for 2022 communications will focus on promoting shorter antibiotic course lengths (where clinically appropriate), antibiotics in the context of the environment and sustainability, promoting quality diagnostics and vaccines in support of tackling AMR, and antibiotic allergies and de-labelling.

e-Bug programme

The updated e-Bug website will be launched in September 2022, with material developed for parents, carers and students. To prepare for the launch of the new website, the programme will be re-establishing formal partnerships and starting the process of translating e-Bug resources into additional languages.

The programme aims to integrate messaging on IPC and AMS into the curriculum and increase focus on other hard to reach groups, such as developing all teaching resources in formats that can be displayed on a screen to eliminate printing costs, developing guidance for parents, carers and community groups, and creating content for children and young people to access outside of the classroom. These materials will be co-created with users from low resource settings to ensure that they are suitable for use in areas of deprivation.

e-Bug is developing a training of trainers (ToTs) programme in coordination with NHSE and local authorities to support educators to deliver messaging on infection prevention control (IPC) and AMS to children and young people, with the aim of reaching all schools by 2024. This approach will be complimented by a series of webinars for educators hosted throughout the school year, and the existing freely available Future Learn courses.

7. COVID-19 therapeutics

In March 2020, WHO declared that COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a Public Health Emergency of International Concern.

Coordinated international efforts identified therapeutic candidates to treat severe illness from COVID-19. In the UK, there are several large-scale clinical trials ongoing that operate in partnership with the NHS, UK academic institutions and public health bodies. This chapter includes surveillance data on 5 directly acting antiviral COVID-19 therapies in use in England between 1 October 2021 and 31 March 2022 as well as antimicrobial stewardship outputs.

These are 3 antivirals: nirmatrelvir plus ritonavir (Paxlovid), remdesivir (Veklury), molnupiravir (Lagevrio); and 2 neutralising monoclonal antibody therapies (nMAbs): sotrovimab (Xevudy) and casirivimab with imdevimab (Ronapreve).

See Chapter 7 methods and caveats in the Annexe accompanying this report for information on the clinical use of the therapies and changes to commissioning guidance and policies. Also see UKHSA's therapeutics technical briefings for genomic, virological and epidemiological surveillance data.

Effective therapeutics are a vital part of our defence against COVID-19, especially for patients at higher risk of severe disease. Yet the development of resistance is a real threat. The UK Health Security Agency's (UKHSA) COVID-19 Therapeutics programme was commissioned by the Department of Health and Social Care (DHSC) with the remit to evaluate the use and role of COVID-19 treatments. Genomic, virological, and epidemiologic surveillance systems assess for early detection of genomic mutations associated with resistance, monitor the supply and access of COVID-19 therapies, and inform stewardship and guidance around their effective use.

This chapter focuses mainly on epidemiological surveillance of the 5 COVID-19 therapeutics. Due to the timing of COVID-19 therapeutic use in England, the chapter spans the financial year 2021 to 2022. The following sections provide summaries from the genomics and resistance workstreams, COVID-19 therapeutic usage and supply data, and finally, how this knowledge has informed effective stewardship.

COVID-19 therapeutics Blueteq treatment requests and Rx-info medicines supply data in England run from 1 October 2021 to 31 March 2022 in this report. Clinicians submit Blueteq forms to request treatment with high-cost medicines, including COVID-19 therapeutics. Not all treatment requests may have resulted in patients receiving treatment with these drugs but the electronic or patient prescribing data was not accessible. Blueteq treatment requests data is at patient-level, while Rx-info's medicines supply data is at an aggregate-level and is NHS trust-based. The Rx-info system and database contains standardised transactional data on the procurement, stock and issuing of medicines by NHS trusts, and therefore provides a broad

picture of COVID-19 therapeutics usage. Data is presented, where possible, by NHS region, sex, age, ethnicity, and index of multiple deprivation.

Methods and research activities can be found in chapter 7 of the Annexe accompanying this report. Data and figures presented in the chapter are available in the chapter 7 data tables and chapter 7 figures slidedeck on the ESPAUR web page.

Resistance

In order to identify treatment-emergent viral mutations, SARS-CoV-2 sequences sampled from >1,400 patients who had undergone treatment (but not cleared infection) by March 2022 were compared to sequences from >5,000 patients taken before treatment. Statistical analyses were broken down by variant and by treatment. Mutations in 11 amino acid residues, which may help the virus evade treatment, were identified. Statistically significant changes in mutation frequencies between pre- and post-treatment samples were observed in the Spike protein in isolates from patients infected with Delta and treated with casirivimab with imdevimab (E406D/Q, G446V, Y453F and L455F/S) and among patients infected with Omicron BA.1 (P337R/S and E340A/D/K/V, K356T and R493Q) or BA.2 (E340K) and treated with sotrovimab. These mutations were further characterised using structural modelling and neutralisation assays in collaboration with academic partners (65). Three of the residues were in non-structural protein (NSP) 12 (E136A/D, V166A/L and V792I) and isolated from patients treated with remdesivir for infections with variants other than Omicron or Delta (mostly Alpha). None of the mutations were present at a prevalence >0.5% in the complete UK genomic data set (that is, not limited to samples from patients receiving therapeutics), nor were they increasing in frequency. The genomic data set was also screened for potential transmission events, defined as identification of at least 2 genetically similar samples, including one from a patient having received a COVID-19 treatment. No such events were detected. Analyses are repeated weekly and published in the therapeutics technical briefings.

Findings from the UKHSA COVID-19 therapeutics surveillance programme have allowed frontline clinicians to select the most effective treatment available for patients found to have a specific variant or mutation. Although the programme has yet to offer an accredited, real-time clinical service, clinicians submitting samples for sequencing can contact the programme for further genomic information.

Treatment requests

NHS England (NHSE) publishes treatment request statistics weekly on the NHS Foundry platform which provides real-time data to COVID Medicines Delivery Units (CMDUs). Data presented here is from the Blueteq system, which records treatment requests, including data from CMDUs and secondary care. (See chapter 7 data tables for description of data, and the Stewardship section, below, for information on development of the Blueteq form).

As of 22 August 2022, for the period of 1 October 2021 to 31 March 2022, a total of 51,962 treatment requests for monoclonal antibodies and antivirals were recorded in the Blueteq system (Table 7.1). Of these, sotrovimab had the highest number of treatment requests in England, making up almost 38% of all English treatment requests. Note that not all these therapeutic agents were available throughout the period. For example, casirivimab with imdevimab requests became limited after the onset of the Omicron variant in winter 2021 to 2022 and nirmatrelvir plus ritonavir has also only been included in the clinical commissioning policy since February 2022. See the timeline infographic for more information.

Table 7.1. Number of treatment requests in Blueteq and percentage of overall requests between October 1 2021 and March 31 2022

Therapeutic	Number of requests	Percent
Sotrovimab	19,749	38.0%
Remdesivir	11,926	23.0%
Molnupiravir	8,120	15.6%
Nirmatrelvir plus ritonavir	6,999	13.5%
Casirivimab with imdevimab	5,168	9.9%
Total	**51,962**	**100.0%**

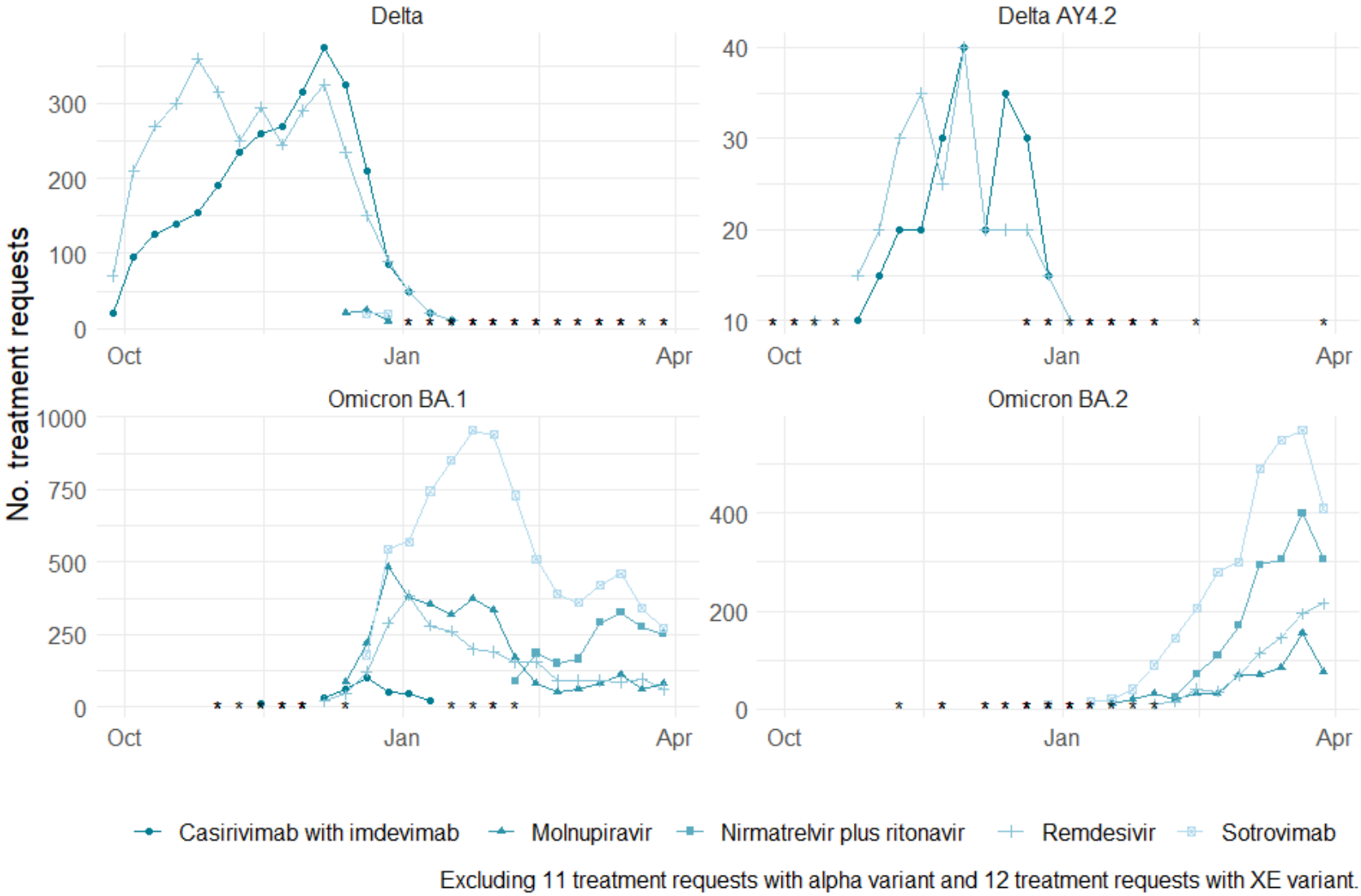
While treatment requests have varied over time throughout the pandemic as new treatments are introduced, these have also changed by variant prevalence as in the case of casirivimab with imdevimab (Figure 7.1). This therapeutic agent was found to have a reduced efficacy against Omicron (66), and thus treatment requests for this therapeutic agent were limited due to its removal from the interim clinical commissioning policy after the onset of the Omicron variant.

This highlights the importance of the interim clinical commissioning policy, as clinicians are not aware of the whole genome sequencing results at the time of treatment other than the circulating dominant variants at the time. This surveillance directly informs national discussions on treatment use against specific variants. For example, while the US Food and Drug Administration (FDA) removed sotrovimab for use against Omicron BA.2 based on laboratory analyses, the programme showed no significant difference in effectiveness between Omicron BA.1 and BA.2 variants, therefore it was never removed from the UK's clinical commissioning policy (67).

With the onset of the Omicron BA.1 and BA.2 variants that had unprecedented case rates, requests for sotrovimab increased drastically. These results also reflect the different rates of hospitalisation associated with the variants. For example, remdesivir, which has been the most commonly used treatment in hospitalised patients, had fewer treatment requests for patients with Delta sublineage AY4.2 compared to those with Delta and Omicron BA.1, which had higher case numbers and hospitalisation rates.

Figure 7.1. Number of treatment requests in Blueteq by therapeutic agent and SARS-CoV-2 variant

Asterisks indicate masked points at time points with only 1 to 7 treatment requests.



Overall request rates over this time period show a large range between regions (Table 7.2 and Figure 7.2). London and the East of England had the highest rates of treatment requests per 100,000 population and per 100,000 COVID-19 cases. The rates relative to COVID-19 cases and the rate relative to the population were approximately twice that observed in the North West. Though not statistically significant, the South East had a higher treatment request rate per 100,000 population but a lower rate per 100,000 COVID-19 cases than the North East and Yorkshire. This highlights the regional variation in COVID-19 reported cases that may impact these treatment request rates.

Table 7.2. Number, percentage and rate (per 100,000 population and per 100,000 COVID-19 cases) of treatment requests in Blueteq by NHS Region between October 1 2021 and March 31 2022

Region	Number of requests	Percentage	Rates per 100,000 population	Rates per 100,000 COVID cases
East of England	7,979	15%	121.6 (100 to 143.2)	590 (542.4 to 637.6)
London	9,901	19%	110 (89.4 to 130.5)	586.9 (539.4 to 634.4)
South West	6,006	12%	106 (85.8 to 126.2)	521.7 (477 to 566.5)
South East	8,222	16%	92 (73.2 to 110.8)	439.5 (398.4 to 480.5)
North East and Yorkshire	7,205	14%	83.4 (65.5 to 101.3)	452.9 (411.1 to 494.6)
Midlands	8,444	16%	79.2 (61.8 to 96.7)	428.1 (387.6 to 468.7)
North West	4,205	8%	59.3 (44.2 to 74.4)	313.7 (279 to 348.4)

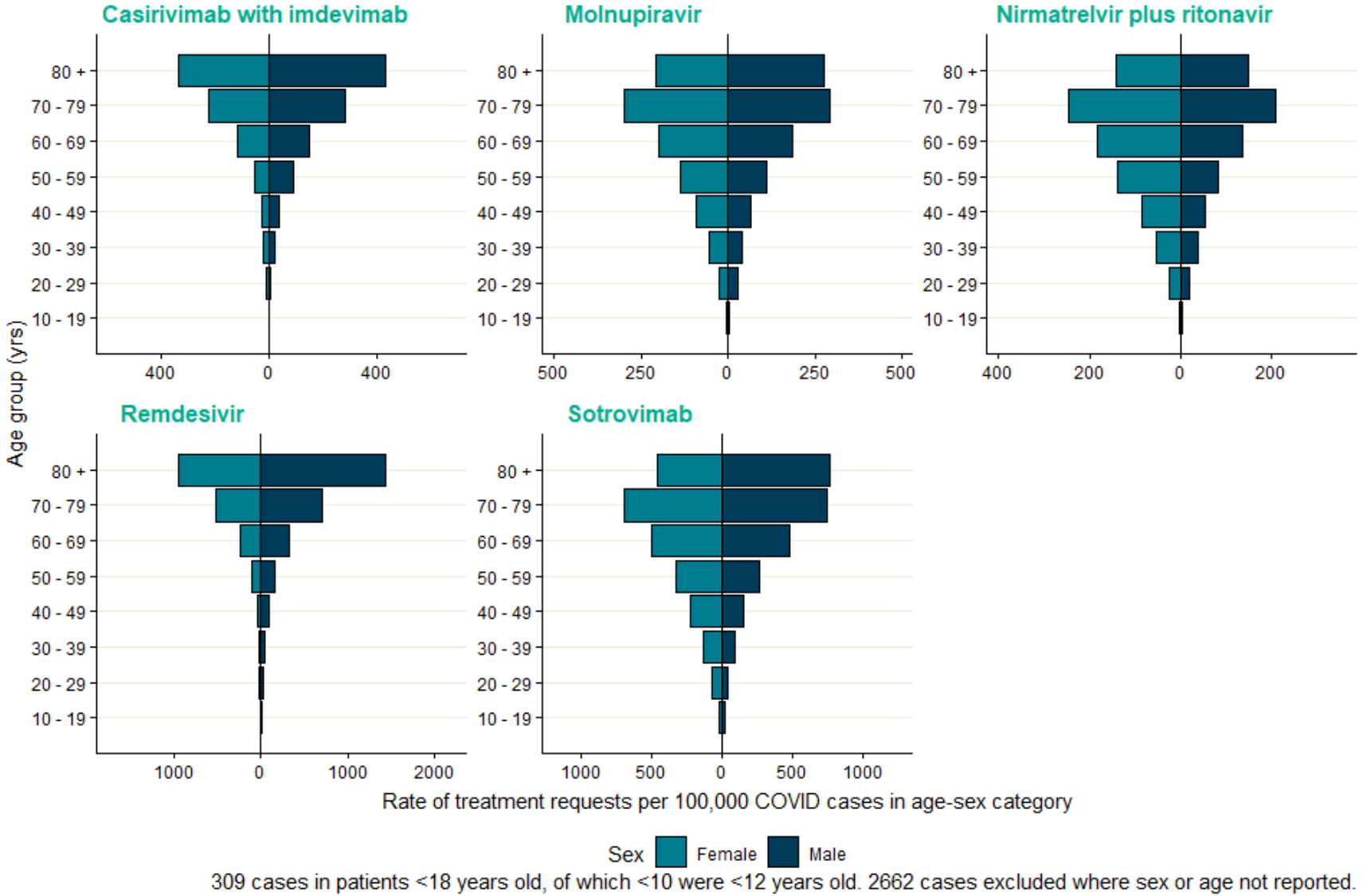
Figure 7.2. Rate of requests in Blueteq (per 100,000 COVID-19 cases) over time and by therapeutic and region

Asterisks indicate masked points at time points with only 1 to 7 treatment requests.

Age-sex pyramids demonstrate that males and females did not differ significantly in the rate of treatment requests per 100,000 COVID cases per age-sex category (Figure 7.3). As would be expected, treatment requests for all therapeutic agents followed an inverted pyramid structure consistent with the age-sex structure of the patient population highly vulnerable to COVID-19.

Though the clinical commissioning policy states that only those over age 18 years are eligible for treatment, and in some cases those over age 12 years, there were fewer than 10 treatment requests captured for patients who were less than 12 years of age in the Blueteq data. All of these patients were hospitalised, and the majority of these treatment requests came from the same NHS trust. Of these requests, most were for remdesivir in children under 3 years, and the remaining requests were for casirivimab with imdevimab. While fewer than 10 requests for patients under 12 years were captured in the data, there are likely to be more prescriptions off-licence for COVID-19 therapeutics in this age group (<12 years). Because of this limitation of the data, we do not include treatment requests for children under 10 years old in the figure presented below.

Figure 7.3. Rate of requests in Blueteq (per 100,000 COVID-19 cases) by therapeutic, age group and sex



309 cases in patients <18 years old, of which <10 were <12 years old. 2662 cases excluded where sex or age not reported.

The breakdown in therapeutic agent requests by ethnicity, despite small numbers in some ethnic groups, indicates a divergence between the White, Indian, and Mixed ethnic groups compared to the Black, Pakistani and Other Asian groups (Table 7.3). While the distribution of treatments was comparable between the White, Indian and Mixed ethnic groups, a larger percentage of treatment requests for the Black, Pakistani and other Asian groups were for remdesivir (over 30% compared to 18% to 20% for these other ethnic groups).

Sotrovimab, the most requested agent overall throughout this period, made up less than 30% of requests in the Black ethnic group compared to the White, Indian and mixed ethnic groups, where it made up between 40% and 47% of requests. While percentage of treatment requests by setting differ between ethnic groups, the relevance is unclear without full details on the population eligible for treatment, and without details on the pathway to access (being offered and accepting treatment). The distribution of ethnic groups at each of these stages may differ but this data is not currently available to UKHSA.

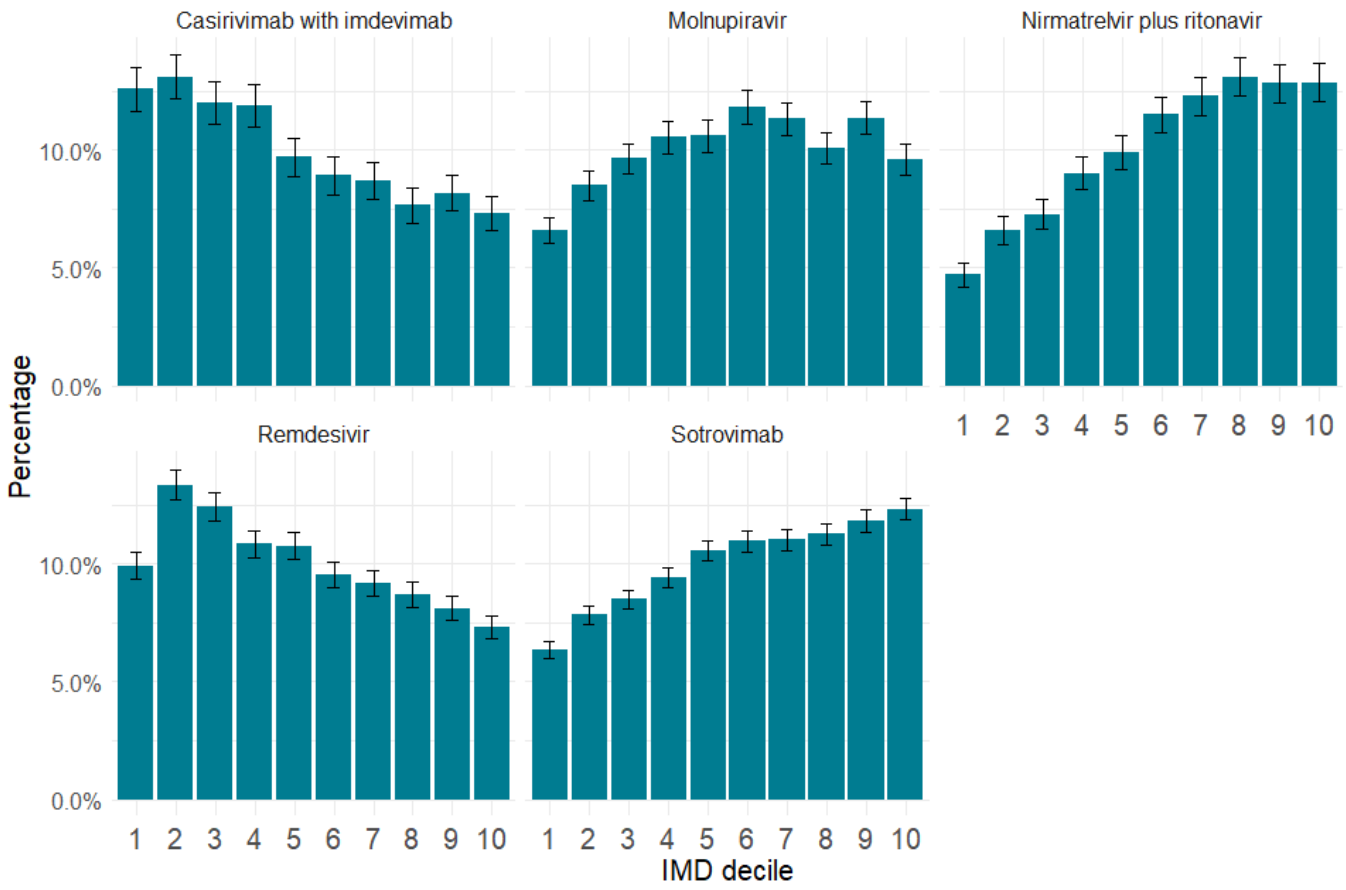
Table 7.3. Distribution of Blueteq treatment requests by ethnic groups (presented as number of treatment requests, not rates by ethnic group population)

Ethnicity	Casirivimab with imdevimab	Molnupiravir	Nirmatrelvir plus ritonavir	Remdesivir	Sotrovimab	Total
Black, African, Caribbean, Black British	349 16.3% (14.7% to 17.8%)	304 14.2% (12.7% to 15.6%)	159 7.4% (6.3% to 8.5%)	783 36.5% (35.4% to 37.6%)	551 25.7% (24.6% to 26.8%)	2,146 (100%)
Indian (Asian or Asian British)	85 7.5% (5.9% to 9%)	200 17.5% (15.3% to 19.8%)	108 9.5% (7.8% to 11.2%)	254 22.3% (20.6% to 24%)	493 43.2% (41.5% to 44.9%)	1,140 (100%)
Mixed or Multiple ethnic groups	59 10.1% (7.7% to 12.6%)	95 16.3% (13.3% to 19.3%)	80 13.7% (10.9% to 16.5%)	129 22.2% (19.4% to 25%)	219 37.6% (34.8% to 40.4%)	582 (100%)
Pakistani (Asian or Asian British)	90 15.4% (12.5% to 18.3%)	72 12.3% (9.7% to 15%)	30 5.1% (3.3% to 6.9%)	194 33.2% (31.4% to 35%)	198 33.9% (32.1% to 35.7%)	584 (100%)
White	3,670 9% (8.7% to 9.3%)	6,639 16.2% (15.9% to 16.6%)	5,854 14.3% (14% to 14.7%)	8,329 20.4% (20% to 20.7%)	16,381 40.1% (39.7% to 40.4%)	40,873 (100%)
Other Asian and Asian British	153 14.7% (12.6% to 16.9%)	128 12.3% (10.3% to 14.3%)	66 6.3% (4.9% to 7.8%)	364 35% (33.5% to 36.5%)	329 31.6% (30.2% to 33.1%)	1,040 (100%)
Other	98 14.2% (11.6% to 16.8%)	69 10% (7.8% to 12.2%)	50 7.2% (5.3% to 9.2%)	277 40.1% (38.2% to 42.1%)	196 28.4% (26.5% to 30.3%)	690 (100%)

Ethnicity	Casirivimab with imdevimab	Molnupiravir	Nirmatrelvir plus ritonavir	Remdesivir	Sotrovimab	Total
Unknown	664 13.5% (12.6% to 14.5%)	613 12.5% (11.6% to 13.4%)	652 13.3% (12.3% to 14.2%)	1,596 32.5% (31.6% to 33.5%)	1,382 28.2% (27.2% to 29.1%)	4,907 (100%)

A similar trend emerges in the breakdown of therapeutic agent and setting by Index of Multiple Deprivation (IMD) (Figure 7.4). Treatments commonly used in the community such as nirmatrelvir plus ritonavir and sotrovimab had a higher percentage of requests from those in the least deprived IMDs, whereas treatments commonly administered in hospitals such as remdesivir and casirivimab with imdevimab showed the reverse pattern. This is emphasised in the split by treatment location (community versus hospitalised). Findings from the OpenSAFELY collaborative also suggest disparities (68).

Figure 7.4. Distribution of Blueteq treatment requests by Index Multiple Deprivation (IMD) decile (most (1) to least (10) deprived). Percentage data is based on absolute number of treatment requests not rates

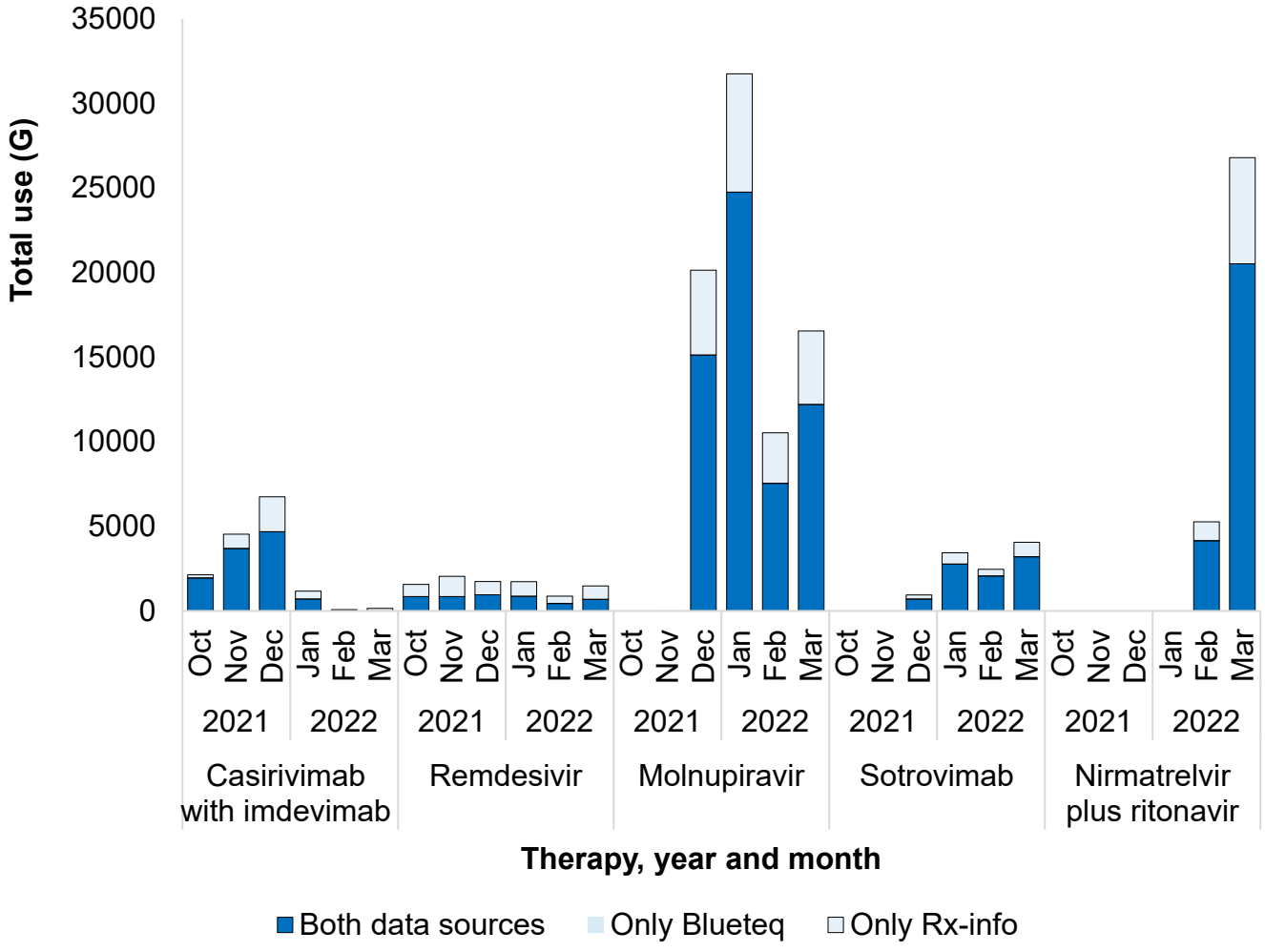


Medicines supply data

This section compares COVID-19 therapeutics medicines supply data sourced from Rx-info with treatment requests (Blueteq) data. The Rx-info system and database contains standardised transactional data on the supply of medicines by trusts, including dispensing, procurement and stock issuing to wards. See the Introduction and the methods section in Chapter 7 of the Annexe accompanying this report for further descriptions of this data. See the downloadable slidedeck of Chapter 7 figures for comparisons by therapy and region.

Figure 7.5 shows that for all 5 therapies there was an excess of quantity, in grams, recorded in Rx-info's medicines supply data compared to quantity, in grams, of treatment expected based on treatment requests captured in the Blueteq system for all months where the therapy was in use (light blue bars). See the methods section in Chapter 7 of the Annexe accompanying this report for dosing schedules for each therapy. Possible reasons for the discrepancy between Rx-info and Blueteq usage data are presented in the Discussion, below. Remdesivir generally has the highest percentage of excess grams recorded in Rx-info's data compared to Blueteq (ranging from 45 to 59% across the months it was in use), whereas sotrovimab (16 to 26%) and nirmatrelvir plus ritonavir (21 to 23%) had the lowest range of excess Rx-info grams across the months they were in use.

Figure 7.5. Comparison of Blueteq treatment requests and Rx-info medicines supply data (in grams) by COVID-19 therapeutic and month. Grams are estimated based on grams per treatment course



The following section explores how the knowledge gleaned from the epidemiological surveillance workstreams, described above, helps to inform effective stewardship of COVID-19 therapeutics.

Stewardship

To support the rollout and stewardship of the COVID Therapeutics, a task and finish Antimicrobial Stewardship working group led by UKSHA in collaboration with the NHSE Antimicrobial Prescribing and Medicines Optimisation (APMO) Workstream was initiated in November 2021. Outputs delivered included:

- development of a minimum data set for Blueteq forms for COVID-19 therapeutics
- monitoring feedback from NHS antimicrobial stewardship community and highlighting challenges with interpretation and/or implementation of clinical policy and concerns about stewardship of COVID-19 therapeutic agents; as well as led on education and training for infection teams leading on COVID-19 therapeutics.
- proposing research questions focused on stewardship to inform epidemiological analysis and evidence synthesis
- webinar for COVID-19 therapeutics (for antimicrobial stewardship teams)
- translation of patient information leaflets into 29 languages and accessible formats

Minimum data set for Blueteq forms

The Stewardship workstream developed a minimum data set for Blueteq forms which was accepted and implemented by NHS England (NHSE). For more information on the Blueteq form see the methods section in Chapter 7 of the Annexe accompanying this report.

The Blueteq digital system is licensed by the NHS to prospectively capture individual patient information, including eligibility criteria, to support the clinical and financial governance of new therapeutic agents.

The AMS research questions proposed included:

1. Is the efficacy of COVID-19 therapies affected by SARS-CoV-2 variant, age, comorbidities, ethnicity, antibody or vaccination status?
2. Is the risk of resistance emerging affected by age, comorbidities, ethnicity, antibody or vaccination status?
3. Are there any disparities in the proportion of patients started on antivirals or nMABs by age, sex, socioeconomic and ethnicity status? If so, reasons why – at the point of decision, patient consent.

Antimicrobial Stewardship Webinar for COVID-19 Therapeutics (for AMS teams)

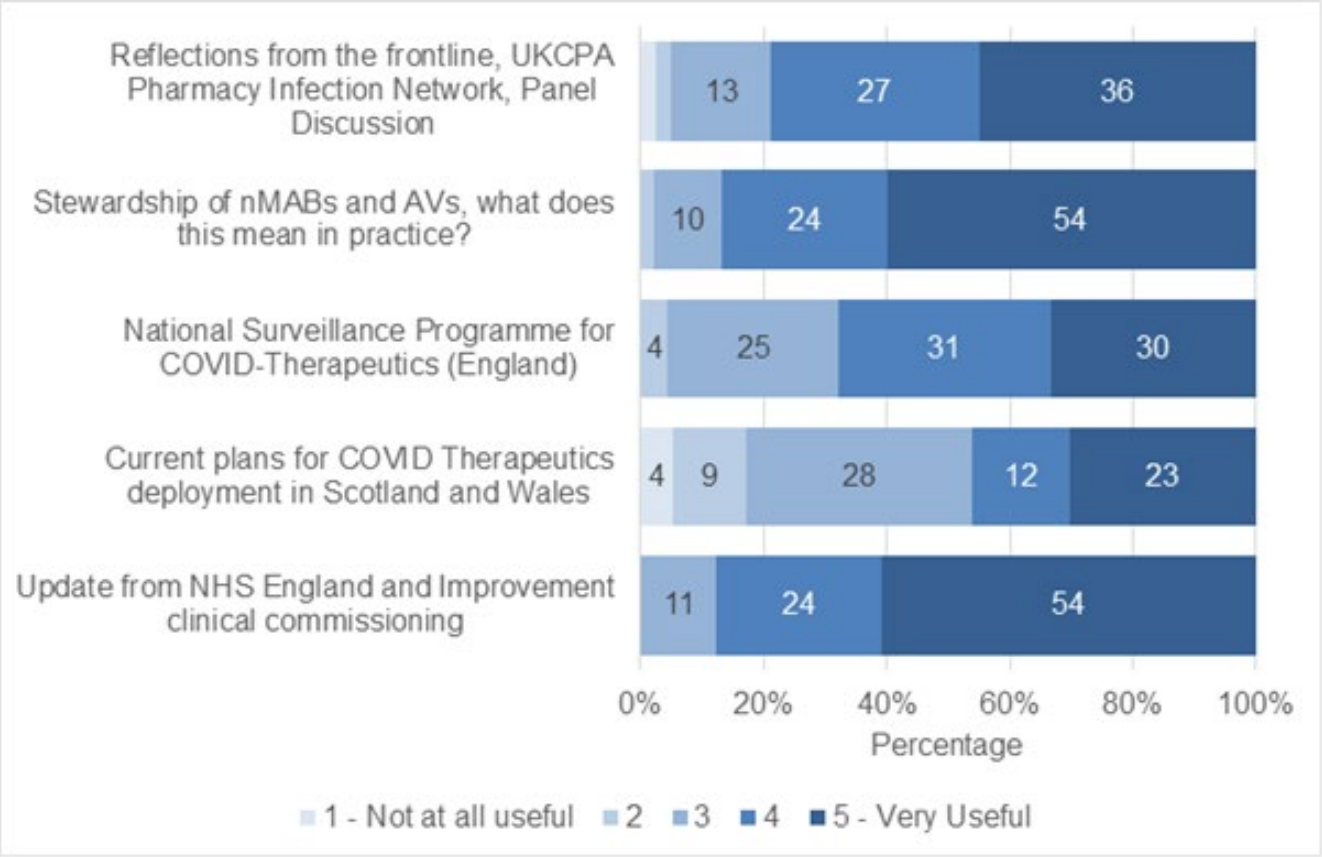
UKHSA and NHS England and Improvement held a virtual, multidisciplinary webinar in December 2021 to provide clinical policy updates and support on COVID-19 therapeutics, particularly for the secondary care setting. There was also a panel discussion coordinated by

UK Clinical Pharmacy Association/Pharmacy Infection Network (UKCPA-PIN) with 5 pharmacists who shared reflections and experience from trusts located across England.

The webinar received 341 registrations and there were 178 live attendees. The majority (89%) were pharmacists, 80% of attendees worked in England.

Of the 97 who completed feedback forms (54% response rate among attendees), 42% requested similar webinars to be run monthly. Attendees rated the usefulness of the topics covered in the session highly (Figure 7.6). This highlights that healthcare professionals welcome regular updates and communication on evolving healthcare topics such as COVID-19 therapeutics. It also further demonstrates the benefit of using virtual webinars as a tool for rapid updates, education and communication for healthcare professionals across wide geographical areas. See the Chapter 7 data table for full data.

Figure 7.6. Usefulness of topics covered in the COVID-19 therapeutics webinar, rated by attendees. Attendees rated each topic from 1 (not at all useful) to 5 (very useful)



Translation of patient information leaflets

Patient information leaflets for molnupiravir and nirmatrelvir plus ritonavir initially only available in English were translated into 29 languages and accessible versions (Braille, large print, British sign language and audio) by UKHSA Healthcare Associated Infections, Fungal, Antimicrobial Resistance, Antimicrobial Usage and Sepsis and Immunisation and Vaccine Preventable Diseases Divisions.

All versions are also available via:

- Nirmaterlvir plus ritonavir (Paxlovid)
- Molnupiravir

Cascade of surveillance data

Information from COVID-19 therapeutic agent surveillance indicating relatively low uptake of antivirals in one region of England was shared by the NHS England regional antimicrobial stewardship lead with regional medical, nursing and pharmacy teams. A recommendation was issued to COVID-19 Medicines Delivery Units in the region to emphasise to clinical teams and patients the information published in the NICE living COVID-19 guideline as evidence of patient benefit from antiviral treatment.

Discussion

UKHSA's COVID-19 therapeutics programme has supported the deployment of COVID-19 therapies in England by undertaking genomic, virological, and epidemiological surveillance, through both national surveillance systems and academic collaboration. Effective therapies are particularly important for protecting the health of patients at greater risk of developing severe COVID-19. Between 1 October and 31 March 2022, over 51,000 patients in England received treatment requests for neutralising monoclonal antibodies and antivirals against SARS-CoV-2. The programme has routinely identified new mutations and variants that may have reduced susceptibility to therapeutics in clinical use and made these findings publicly available through the therapeutics technical briefings.

Therapeutic treatment requests largely follow the trends that would be expected within the context of the setting they are administered in. For instance, remdesivir which is commonly used in the hospital setting had more treatment requests over the Delta wave than the Delta sublineage AY4.2 wave, as the Delta variant had higher hospitalisation rates than sublineage AY4.2. Another example is the large number of treatment requests for sotrovimab over this period, as this was the first-line option for community settings which replaced casirivimab with imdevimab in December 2021 with the emergence of Omicron.

One key finding on the usage of COVID-19 therapies is the discrepancy between the treatment requests (Blueteq) and the medicines supply data (Rx-info). Whereas Blueteq captures patient-level applications for renumeration of high-cost medicines, Rx-info captures stock movements within hospital pharmacies and potentially provides a more comprehensive picture of usage.

Separate analysis (not shown here) comparing Rx-info usage data with secondary care dispensing data (sourced from IQVIA) for key antibiotics found that most data in Rx-info is accounted for by patient dispensing, and less than 14% (depending on the antibiotic) was likely due to other stock movements. A similar trend is expected for COVID-19 therapeutics. Total usage levels for each COVID-19 therapy within Rx-info are higher than Blueteq, and the

differences are larger than the likely difference between dispensing versus other stock movements alone (see the downloadable slidedeck for chapter 7 for further breakdowns by therapy and region).

Collaboration with NHSE is ongoing to explore and understand the discrepancies. There are multiple potential explanations, including that Rx-info data has some clinical trial dispensing events which are not recorded on the Blueteq system. Secondly, a lack of capacity within the clinician workforce during the pandemic may also have prevented manual submission of Blueteq data for every patient. Thirdly, it is possible some information was entered incorrectly. Finally, there is also the potential risk that therapeutic agents may have been prescribed outside of the marketing authorisation (for example, to a small number of severely unwell children) and this was not reported in Blueteq. The Blueteq system provided a valuable mechanism for recording eligibility criteria for patients treated with new therapeutic agents and for confirming adherence to clinical policy, contributing to the clinical and financial governance of these critically important new medicines, in addition to supporting antimicrobial stewardship. Corroborating dispensing data with Blueteq data may represent an important opportunity for stewardship of future new treatments for infection.

Analysis of treatment requests from Blueteq showed variation in requests by NHS region, age, sex, ethnicity and IMD by therapeutic agent. Without data on individuals who were eligible, offered and accepted each treatment, this is considered an exploratory analysis and may not directly reflect inequities in access to treatment. Further work in this area would complement and inform the work that NHSE conduct, through the NHS Foundry platform and beyond, to rapidly deploy antiviral and nMAb agents and manage operational delivery and performance.

The programme has provided an evidence base for important changes to clinical commissioning policies for COVID-19 therapeutics, as described above for sotrovimab and Omicron BA.1 versus BA.2. On an individual basis, it has supported clinicians in tailoring treatment to specific variants and mutations, according to the principles of antimicrobial stewardship.

The experience and relationships developed during the rapid scale-up of a new surveillance programme on COVID-19 new therapeutic usage will be used in the future for other new anti-infectives, strengthening the antimicrobial usage surveillance programmes already in use, and assessing the effectiveness and equity in access to new agents.

Other planned work will explore the incidence of secondary infections in the population of patients who have been prescribed COVID-19 therapeutics compared to those who are untreated, and between therapies. Considering the actions of some directly acting antiviral agents on the immune system, it is unknown whether COVID-19 therapies impact susceptibility to secondary infections. However, since patients are more commonly prescribed COVID-19 therapies in the community, and fewer are in hospital where secondary infections have higher incidence, the sample sizes may be small.

Finally, surveillance of future therapies that are added to the clinical commissioning policy will be included in this surveillance and stewardship programme.

Future actions

Future activities include:

- investigate patient outcomes in various demographic strata following treatment with COVID-19 therapies
- collaborate with NHSE to explore and understand the discrepancies between Blueteq and Rx-info usage data
- explore the incidence of secondary infections in the population of patients who have been prescribed COVID-19 therapeutics compared to those that are untreated and between therapies
- conduct surveillance of any future new antimicrobial agents
- undertake epidemiological surveillance to assess for early signals of treatment resistance or failure with new variants or mutations detected from genomic horizon scanning surveillance analyses
- development of a process for reporting predicted resistance profiles from genomic data to clinicians, once accreditation is in place

8. Research

Introduction

A wide range of new and ongoing research projects have been undertaken in the field of healthcare-associated infections (HCAI) and antimicrobial resistance (AMR) in the last year.

The projects underway cover many research and development priorities, including improvements in surveillance and data collection to enhance the insights drawn from them, increased understanding of the mechanisms of disease transmission, the burden and risk factors for carriage, infection and serious clinical outcomes. Work has been directed to the development of novel diagnostics and treatments as well as studies to contribute to evidence on existing control strategies, including infection prevention and control (IPC), antimicrobial stewardship (AMS), diagnostics, antimicrobials and novel alternatives, such as vaccination and host-directed therapies.

The work covers many of the major themes of the National Action Plan (NAP) for AMR (69). This is highlighted in Figure 8.1 which illustrates the wide distribution of almost 60 publications from UKHSA across almost all of the NAP's major themes. A complete list of these AMR-related publications from April 2021 to March 2022 is provided in the Annexe accompanying this report.

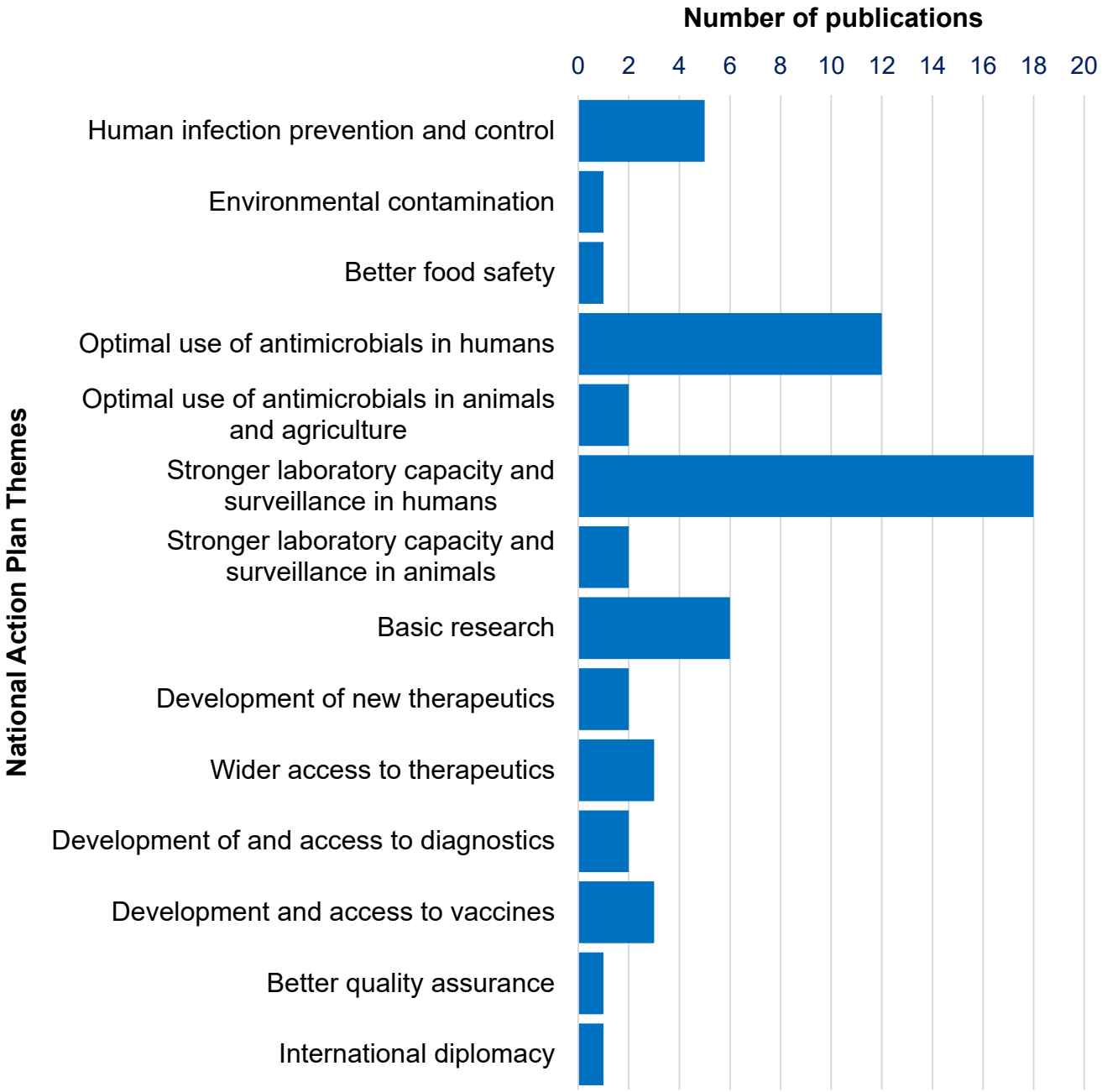
This chapter gives examples of AMR and HCAI research projects undertaken with UKHSA from April 2021 to March 2022. Again, the projects showcased highlight research across many of the NAP's major themes, including:

- 'Stronger laboratory capacity and surveillance in AMR'
- 'Human infection prevention and control'
- 'Optimal use of antimicrobials'

Further projects cover the themes of 'Basic research', the 'Development of new therapeutics' and 'Development and access to novel diagnostics'.

Key research is presented from the 2 National Institute for Health Research (NIHR) Health Protection Research Units (HPRUs) in the topic area of HCAI and AMR, led by Imperial College London and Oxford University in partnership with UKHSA. In unity with the goals of the HPRUs, the chapter highlights the embedding of knowledge mobilisation and evaluation of impact to harness knowledge sharing.

Figure 8.1. AMR publications from April 2021 to March 2022, by National Action Plan theme



Stronger laboratory capacity and surveillance of AMR

Emerging trends in national surveillance

Receiving isolates from hospitals all over the country, the AMRHAI Reference Unit is in a fortunate position to be able to note emerging national trends among isolates received. A recent example concerns New Delhi metallo-β-lactamase (NDM)-producing *Escherichia coli*.

It has become clear that most NDM-positive isolates of *E. coli* received by AMRHAI from hospitals in England now carry the bla_{NDM-5} allele in multi-replicon IncF plasmids (70). In about a third of cases, they also carry the 16S rRNA methylase gene rmtB. These 2 elements alone provide resistance to most β-lactams, including the carbapenems, and all clinically relevant aminoglycosides, including the new antibiotic plazomicin. Isolates co-harbouring bla_{NDM-5} and rmtB noted to date have belonged to 11 different sequence types (STs) and have been received from 15 hospital groups from 7 different regions, showing that this is not a clonal problem, although STs 167 and 405 and single locus variants of these types do predominate. All the plasmids studied shared a highly conserved region that included other resistance genes (bla_{TEM-1B} (conferring resistance to β-lactams), sul1 (conferring resistance to sulfamethoxazole), aadA2 (conferring resistance to aminoglycosides streptomycin and spectinomycin), dfrA12 (coding for trimethoprim resistance) and ble (coding for bleomycin resistance). This conserved region has also been found in similar plasmids in isolates of *E. coli* and *Klebsiella pneumoniae* from other countries and continents showing that this is a widespread problem. Although tested isolates have been resistant to most antibiotics, including, in some cases, the ceftazidime/avibactam plus aztreonam combination, some options remain, notably colistin, fosfomycin and tigecycline.

Clearly, it is important to be aware of the emergence of these plasmids among NDM-positive *E. coli* and of the most likely potential therapeutic options.

The Unified Infection Dataset

Surveillance, incident response and research projects in the HCAI, Fungal, AMR, AMU & Sepsis Division at UKHSA have begun to benefit from the development of UKHSA's 'Unified Infection Dataset' (UID). The UID is a data linkage tool that can be used to build queries extracting and linking national microbiology data with NHS hospital admission, A&E attendance, Office for National Statistics (ONS) mortality, and COVID-19 case data. Linkage to primary care prescribing data will be implemented later this year. The UID has been used to automate production of data outputs for surveillance of bacterial and fungal infection co-occurring with SARS-CoV-2 infection and to monitor cases of COVID-19 acquired in healthcare settings, and it has also been used in support of incidents involving *Staphylococcus capitis* in hospitalised infants (see also Chapter 2, 2.5) and acute paediatric hepatitis of unknown aetiology.

Current projects in which the UID is providing linked data for UKHSA scientists include investigations of patient outcomes associated with Panton-Valentine Leukocidin (PVL) *Staphylococcus aureus*, while future projects include investigations of childhood bacterial infections in babies born by caesarean section and development of a dashboard to provide aggregate antimicrobial susceptibility test result data for England.

E. coli bloodstream infections during the COVID-19 pandemic

The incidence of *E. coli* bacteraemia increased each year from the start of the mandatory surveillance in 2011 to the beginning of the COVID-19 pandemic in 2020. A reduction was observed at the start of the pandemic for all reported cases and community-onset cases,

whereas the incidence rate of hospital-onset cases remained largely stable, except for a sharp decrease seen in April to June 2021 (71).

To quantify the effect of COVID-19 on *E. coli* bacteraemia, the difference between the observed and expected (using the underlying trend prior to COVID-19) cases has been calculated. The analysis will explore whether the gap in cases could be explained by the following: (i) competing risk from COVID-19, (ii) undiagnosed *E. coli* bacteraemia, and (iii) reduced healthcare interactions.

Human infection prevention and control

Reducing Gram-negative bloodstream infections (GNBSIs)

The ambitions within the AMR National Action Plan (69) outline a reduction in healthcare associated Gram-negative bloodstream infections (GNBSIs) by 2024. With the aim of quantifying the most effective strategies and interventions for reducing GNBSIs, work is ongoing to investigate patient pathways that lead to GNBSIs, with a focus on urinary tract infection (UTI) (catheter and non-catheter related) pathways, considering hospital, community and long-term care facility (LTCF) acquired infections.

An individual based mathematical model of patients and their pathways to GNBSIs has been developed to investigate and quantify the potential benefits of different intervention strategies in reducing incidence of GNBSI and AMR as well as a cost-effectiveness analysis of these strategies.

Model-based evaluation of Carbapenemase Producing Enterobacteriaceae (CPE) transmission and control

An approach (72) involving network analysis to reconstruct patient pathways, using routinely collected electronic health records, has proved very powerful in identifying previously unrecognised contacts between patients who were IMP CPE-positive on screening, implying potential bacterial transmission events. This analysis, combined with detailed plasmid phylogenetic analysis highlighted an interspecies, plasmid-mediated outbreak of blaIMP-CPE, which remained unidentified during standard microbiology and infection control investigations. This analysis shows very clearly that analysing outbreaks at the plasmid level provides greater insight compared to standard analyses, revealing that resistance may be more widespread than suspected and thus allowing more targeted interventions to stop the transmission of resistance within hospital networks.

A plasmid within host conjugation model grounded on population genetics theory (73) helped disentangle horizontal transmission in a range of bacterial hosts from vertical transmission in an *E. coli* ST399 lineage in a hospital outbreak of plasmid-mediated carbapenem resistance. This is the first time that the conjugation rate of a plasmid has been estimated from phylogenetic analysis.

Ongoing work developing models of plasmid evolutionary dynamics, aims to provide greater insight for the identification and control of plasmid-mediated outbreaks, and thus management of CPE.

Intervention and healthcare environment models

A dedicated research facility has been built at UKHSA Porton Down, to support studies assessing the effectiveness of novel infection prevention and control (IPC) procedures and the role of the built environment on AMR transmission. This unique facility, designed to simulate a hospital ward and built in line with NHS building specifications and requirements has a number of flexible spaces to be used to ask applied questions about disease transmission and IPC. These include, single and multiple-bedded rooms, a negative-pressure isolation suite and ancillary spaces (for example, clean and dirty utility rooms, kitchen and office). Rooms are fitted with sinks, showers, toilets and waste disposal as appropriate.

This new capability will facilitate applied microbiology research and will allow transmission dynamics of antimicrobial resistant bacteria and other emerging pathogens to be investigated and a range of infection prevention strategies to be evaluated. In doing so, it will help ‘design out’ healthcare-associated infections and generate evidence to inform strategies and investment to deliver better IPC. It will also provide an environment in which researchers can develop and utilise a range of skills and expertise relevant to transmission within the indoor environment (for example, ventilation and aerobiology, the microbiology of water and water systems, impact of surface modification; novel disinfection strategies).

Optimal use of antimicrobials

STEP-UP: Improve the uptake and Sustainability of Effective interventions to promote Prudent antibiotic Use in Primary care

Recent work has highlighted that while there is evidence that antimicrobial stewardship strategies, including communication skills training, point-of-care C-reactive protein testing (POC-CRPT) and delayed prescriptions (DPs), can help optimise antibiotic prescribing in primary care, uptake of these strategies is limited and inconsistent. STEP-UP brings together a multi-disciplinary team with expertise in health psychology, health economics, primary care, statistics, and clinical epidemiology from across the 2 NIHR Antimicrobial Resistance HPRUs at Oxford and Imperial, and with the University of Southampton. It aims to understand how we can encourage greater use of interventions in general practice in England to reduce unnecessary antibiotic use and the threat of antibiotic resistance.

Researchers explored views of professionals from high-prescribing practices about uptake and implementation of DPs and POC-CRPT to reduce antibiotic use and found they were not viewed as sufficiently useful ‘clinical tools’ but rather as ‘social tools’ (for example, to aid in educating patients) (74).

In a further study, a systematic, user-focussed process of developing a behavioural intervention was used to devise a multicomponent intervention to facilitate practice-wide implementation of evidence-based strategies (75).

Current research augments these qualitative studies with quantitative modelling work aiming to better understand the relationship between antibiotic use across geographies in England, with antibiotic resistance (across resistance types). Better understanding of the relationship between use and resistance can be fed into health economic models to support cost-effectiveness evaluation of stewardship strategies.

AntiMicrobial Stewardship: training and education to deliver behaviour CHange (AMS: TEACH)

AMS interventions to support the appropriate use of antibiotics for healthcare professionals are essential for preserving antibiotics and reducing the risk of AMR. These interventions can be designed and delivered in various ways. However, it is unclear which elements and mode of delivery are the most effective to change healthcare professional practice or cost-effective. This project aims to identify what works for antimicrobial stewardship in hospital-based care across the UK. The key aims are as follows:

1. To carry out a systematic review to synthesise the components of published AMS education and training interventions and assess their (cost-) effectiveness.
2. To interview AMS educators about barriers or enablers to intervention delivery and review training materials to identify and specify the content and mode of delivery.
3. To triangulate research findings and co-produce evidence-based recommendations for improving AMS education and training.

Findings so far highlight variability across hospitals in AMS training provision, with implementation barriers including lack of time and resources, competing interests within the hospital and lack of organisational support. Educators perceive it as part of their role to develop AMS education and training and continuously develop their training and skills to be able to deliver such interventions. Next steps are to triangulate these key findings with the ongoing systematic review, to produce theory and evidence-based recommendations to optimise and enhance the design, delivery and implementation of AMS education and training in secondary care and to inform key policies to support the UK AMR strategy. Links to outputs to date are available.

Basic research

Panton-Valentine leucocidin (PVL) toxin and poor clinical outcomes amongst hospitalised patients with Staphylococcus aureus infection

Staphylococcus aureus is a leading cause of hospital and community-acquired (CA) infections, with the potential for considerable morbidity and mortality. The contribution of Panton-Valentine

leucocidin (PVL) toxin to the pathogenicity of *S. aureus* remains unclear, though it has been associated with certain clinical phenotypes, notably recurrent skin or soft tissue infection and necrotising pneumonia. An association between PVL genes and invasive disease has been reported, suggesting it is an epidemiological marker of severe infection, however, evidence for the pathogenic role of PVL and its effect on clinical outcomes to support current testing and control measures are lacking.

Three national data sets in England were linked to include data on *S. aureus* isolates sent for PVL testing, patient level data on co-morbidities and hospitalisation dates, and all-cause mortality between August 2018 and August 2021. This national retrospective cohort study demonstrates that PVL toxin detection was not associated with 30-day mortality or hospital length of stay in 3 key clinical outcomes of morbidity and mortality in 2,189 hospitalised patients with CA *S. aureus* bacteraemia sent for typing, and weak evidence that PVL was associated with lower odds of readmission within 90 days. Among 2,040 hospitalised patients with CA *S. aureus* skin infection, PVL detection was associated with a lower risk of readmission to hospital within 90 days (adjusted odds ratio, aOR 0.77, 95% confidence interval, CI 0.62-0.97, p=0.027) and shorter duration of hospital stay (1 day (IQR 0-3) versus 3 days (IQR 1-11) in PVL-positive and PVL-negative infections, respectively (p<0.001)). No association was found between PVL toxin and either 90-day readmission or length of hospital stay for 225 patients with respiratory *S. aureus* isolates sent for PVL typing.

These results support findings of other studies and the hypothesis that PVL toxin is not a determinant of severity of *S. aureus* infection, or poorer clinical outcomes, in patients with samples sent for PVL typing. PVL testing at the national reference laboratory is on a voluntary basis based on guidance of clinical suspicion. This might not be equally applied across the country, so the study population may not be representative of the target population of patients with S. aureus infection nationally and may be biased towards more severe or unusual cases. Despite the association between PVL detection and lower risk of readmission to hospital within 90 days and shorter duration of hospital stay in patients who were hospitalised with CA *S. aureus* skin infection, PVL is unlikely to have a true protective effect and the observed effect may relate to clinicians having a lower threshold for admission for patients who are found to be PVL-positive.

These findings have implications for practice and policy, calling into question the benefit of routine screening and decolonisation of suspected PVL *S. aureus*. UKHSA currently recommends PVL testing in the assessment of CA *S. aureus* disease, and in assessment of whether decolonisation of case and contacts is needed. However, this cohort is comprised of isolates voluntarily referred to the UKHSA Staphylococcus and Streptococcus Reference Section (SSRS) so these findings may not be generalisable to community-acquired *S. aureus* infection nationally. Further research is needed to understand if PVL has a specific role in virulence associated with *S. aureus* infection, and to identify any particular host factors associated with unfavourable prognosis, in order to direct clinical and public health policy, guidance, and response.

Estimation of unit costs of resistant infections

Antibiotic resistance (ABR) has been high on the international policy agenda for many years, and whilst there have been advances in our understanding of the potential impact of ABR on public health, healthcare systems and economies, finding specific cost estimates to use in economic evaluations often requires research capacity. Whether it's completely updating previously published systematic reviews or attempting to extract and adapt data from those already out there, it is often a time-consuming exercise representing a potential roadblock in efficient resource allocations tackling ABR.

Therefore, utilising existing evidence, open-access software and a tailored, pragmatic approach to conducting global meta-analyses, an 'easy-to-use' resource of bug-drug-syndrome-country specific ABR costs has been created (due for publication in 2022).

Global Research on AntiMicrobial resistance (GRAM) project

The Global Research on AntiMicrobial resistance (GRAM) Partnership developed a methodological approach (76) to estimate the burden of AMR as part of the Global Burden of Disease, Injuries, and Risk Factors Study (GBD). A capstone report (76) (Antimicrobial Resistance Collaborators, 2022) published in The Lancet in January 2022 estimated that AMR itself caused 1.27 million deaths, and that resistant infections played a role in 4.95 million deaths, globally in 2019. These numbers confirm that the magnitude of bacterial AMR is as large as other major diseases such as HIV, malaria and tuberculosis. Some of the highest rates of AMR burden are located in Low and Middle Income countries (LMIC), concurring with large health disparities to treat infections, limited access to antibiotics, and scarce resources to act upon the AMR threat.

AMR burden estimates can be disaggregated and downloaded from an interactive visualisation tool. Further analysis on specific bacteria and regions of the World is ongoing. This strategic Partnership is formed by the University of Oxford, the Institute of Health Metrics and Evaluation and a network of collaborators including the UKHSA. It is funded by the UK DHSC's Fleming Fund, the Wellcome Trust, and the Bill and Melinda Gates Foundation.

Development of new therapeutics

Open Innovation for AMR

The NAP (69) and 20-year vision documents, published by the DHSC in 2019, highlighted the need to drive innovation to develop new therapeutics using novel approaches from a wider scientific community. Infrastructure funding from the DHSC, (NIHR200658) allowed us to develop new capabilities to evaluate non-traditional antimicrobial agents, such as host-defence peptides, bacteriophage, antibodies, biofilm disruption, immune modulators and other biologics against clinically-relevant, multidrug resistant pathogens. The Open Innovation programme builds on previous work at UKHSA (previously PHE), working in partnership with academia and

industry, in the UK and internationally. This work has developed a detailed screening cascade for antimicrobial evaluation, resulting in a number of publications and patent filings and supporting the ongoing evaluation of potential therapies. Aligned with this activity, an EU Marie Skłodowska-Curie Actions (MSCA) project (STIMULUS) has started to develop single and mixed species biofilm models for evaluation of both novel therapeutic approaches and innovative wound dressings for monitoring infection.
Innovative approaches, using bacterial impedance cytometry (77), are also being developed for rapid assessment of antibiotic susceptibility to support evaluation of antimicrobial agents and as a possible basis for new susceptibility tests to support evidence-based prescribing (NIHR Invention for Innovation; NIHR200968).

The development of interventions for tuberculosis

The Tuberculosis (TB) Programme at UKHSA-Porton has developed an integrated combination of rare in vitro and in vivo capabilities and expertise. This spans fundamental biology, antigen and drug discovery, medium throughput assays using a modernised robotics or flow cytometry suite, and the formulation and preclinical evaluation of treatments in animals. New treatments and vaccines for TB are discovered and evaluated through global collaborations with stakeholders in other Public Sector bodies, academic institutions, the European Union, the National Institute of Health USA, and industry; collaborative projects are resourced through a variety of different funding sources.

A portfolio of refined in vivo models established at UKHSA-Porton to evaluate the efficacy of new therapeutics also provide data on safety, host immune responses, and potential immune biomarkers and correlates. In 2021, models were also applied to test the efficacy of new molecules and vaccines at preventing primary disease, or relapse.

The Drug Discovery Group within the Tuberculosis Programme was awarded funds, in 2020, by the GlaxoSmithKline (GSK) Open Lab Foundation, to discover and characterise candidate drugs that will boost the activity of pyrazinamide (PZA), which is a key component of chemotherapy for TB and is set to continue to be included in new drug combinations. Boosting of PZA efficacy will be used to reduce the emergence of resistance, shorten treatment times, and lead to a reduction in the quantity of PZA consumed by patients, thereby reducing the toxic effects. In vitro assessments are often avoided because of the challenges associated with the standardisation of the acidic environment required for PZA to be active. This has meant a lack of effective in vitro tools for assessing or enhancing PZA activity.

The Drug Discovery Group has developed, a defined, and standardised, high throughput screen, to evaluate libraries of compounds against Mycobacterium tuberculosis. The next stage of the project is to tech-transfer the assay to GSK Tres Cantos, screen large libraries, and identify candidate drugs for further development in a follow-on UKHSA-GSK partnership. The assay method will be published late in 2022 in a fourth edition of the book ‘Antibiotic Resistance Protocols’. There is exploration into the application of this methodology to the screening of compound libraries against other AMR pathogens including, non-tuberculosis mycobacteria, *N.*

gonorrhoeae, and viral threats such as coronaviruses and the Coalition for Epidemic Preparedness Innovations (CEPI) priority pathogens.

Development of and access to diagnostics

Cost analysis of rapid susceptibility testing for hospital urinary tract infections (UTIs)

Diagnostic tests for urinary tract infections (UTIs) can be used to determine if treatment with one out of a range of antibiotics is more likely to be effective at clearing the infection. Results from rapid antibiotic susceptibility tests can be delivered to a clinician within about 1 to 2 hours, instead of the current 24 to 72 hours, thus enabling appropriate treatment sooner. Rapid diagnostic tests therefore have the potential to reduce resistance development and are a key tool in the AMR NAP (69), with the aim that they can be utilised to both strengthen and measure the stewardship goals of the NAP.

Work is being undertaken to show whether a novel rapid antibiotic susceptibility test has the potential to positively impact patient outcomes if applied to UTIs in secondary care. A cost-effectiveness analysis will be performed to assess both the health and economic outcomes associated with the technology.

Health protection research units (HPRUs)

The National Institute for Health Research (NIHR) has funded 14 health protection research units (HPRUs) to run from April 2020 to March 2025 to address public health threats. The HPRUs are partnerships between universities and UKHSA, forming multi-disciplinary centres of excellence across topic areas, with a focus on collaboration, training and knowledge sharing. Two HPRUs were funded in the topic area of HCAI and AMR, led by Imperial College London and Oxford University, both in partnership with UKHSA.

The HPRU with Imperial College London consists of 4 themes:

1. Priority pathogens

Exploring how and why microbes become resistant, why we see this more in some species or groups than others, how to detect which infections are drug resistant and why some patient groups are more at risk than others.

2. Precision prescribing

Working to optimise antimicrobial prescribing, preserving their effectiveness and minimising AMR by tailoring prescribing to the individual and the infection.

3. Practice, design and engineering

Exploring ways of reducing HCAI/AMR through the use of intelligent design. Considering redesigning ways in which information is captured or presented to improve practice and behaviour, physical environments and patient pathways to reduce risk.

4. Population health and policy:

Linking large health data sets available locally and nationally. Developing methods and tools for understanding risk at a population level and where to target action. Evaluating the impact of policies and interventions, including any unintended consequences.

The HPRU with Oxford University consists of 4 complementary themes:

1. Populations

Exploiting large-scale linked electronic health records (EHR) data from multiple sources to optimally automate routine surveillance and identify ‘at-risk’ populations.

2. Interventions

Combining multi-disciplinary approaches to complex interventions, including behaviour change, mathematical modelling and whole genome sequencing (WGS), to develop, improve, pilot and test approaches AMS and management of AMR and HCAI, targeting interventions to those most at-risk.

3. Contexts

Working to increase our understanding of the contexts within which AMR and HCAI proliferate, identifying those that are the most important drivers for AMR and HCAI, and how we can manage and/or reduce their influence.

4. Sequencing

Delivering public health WGS services to industry standards incorporating the newest components to enable UKHSA to expand and renew its services.

Spotlight on key research from the HCAI and AMR HPRU with Imperial College: practice, design and engineering

The lack of access to safe and effective antibiotics, including essential antibiotics on the Access and Reserve WHO category is being increasingly compromised by shortages (78). One of the unintended consequences of these shortages is using sub-optimal therapeutic options and substandard quality antibiotics, leading to treatment failure and emergence of antimicrobial resistance.

In the published review by the NIHR-funded HPRU in HCAI and AMR in collaboration with Global Antibiotic Research and Development Partnership (GARDP), a new global strategy for identifying strategies to forecast, manage, and address essential antibiotic shortages was developed. This strategy includes identifying the gaps in manufacture and supply chain of antibiotics. It is working for more equitable and fair licencing and manufacturing rights in low-

resource settings to enable sustainable access routes for the most common antibiotics at risk of shortages, due to problems with procuring active pharmaceutical ingredients, or inadequate licensing agreements.

Currently, there is a gap in gathering sufficient data on the extent of antibiotic drug shortages and their consequences, particularly the impact on available therapeutic options. In addition to greater collaboration between public-private sector and governments, this work highlighted the need to move to developing regional and global partnerships for forecasting and advocacy to address the underlying issues that drive antibiotic supply and access.

In collaboration with global expert stakeholders and the Wellcome Trust, a research roadmap for optimising antibiotic use in human populations has been developed (79). This roadmap recognises that antibiotic use remains a social process, influenced by sociocultural and economic drivers. Interventions to reduce demand and use of not recommended antibiotics will not succeed if we do not consider the contextual factors which are influencing behaviours and attitudes. Research into this aspect of antibiotic prescribing is lacking from different contexts.

Unless we can achieve sustained optimisation of use of existing agents, no number of new drugs will solve the problem of AMR. To this end, there needs to be a greater understanding of the contextual drivers for antibiotic use. Utilising qualitative approaches alongside the epidemiological and quantitative streams of research tackling AMR will enable:

- data collection on the feasibility and effectiveness in applying the AWaRe system in low- and middle-income countries as well as their relevance in high income countries
- identification of knowledge gaps on implementing WHO guidelines on AMR stewardship by collecting data on the perception of clinicians and caregivers on the WHO Essential Medicines List (EML) book for specific populations such as paediatric or neonatal in LIMCs
- better understanding of the context specific drivers for change in different settings to inform hypotheses and research design

Spotlight on key research from the HCAI and AMR HPRU with Oxford University: Interventions and Contexts

Stopping antibiotics when feeling better: a qualitative study with clinicians, and patients with urinary tract infections, in general practice in England

Stopping antibiotics when patients feel better, even if before the recommended course is completed, may reduce unnecessary exposure to antibiotics and AMR without affecting recovery. This qualitative study aimed to re-examine the advice to complete antibiotic courses and explore clinicians and patients views on the hypothetical advice to stop antibiotics when better. The focus was on antibiotics for urinary tract infections (UTI) but comparisons with other infections were also explored.

A total of 11 primary care clinicians (7 general practitioners) and 19 patients with recent experience of UTI symptoms (14 with recurrent or chronic UTI) were interviewed. Data was analysed thematically.

Participants found the advice to stop antibiotics when better unfamiliar and contradictory to the well-known advice to always complete antibiotic courses and wanted to know reasons for the new advice. They were also concerned that the advice might be ambiguous, leaving patients unsure when exactly to stop antibiotics. Most were concerned that stopping antibiotics when better might lead to recurrence or complications of UTI and contribute to AMR. Patients with recurrent or chronic UTI were particularly worried about negative impact of stopping antibiotics earlier.

However, participants were also interested in the evidence on risks or benefits of stopping antibiotics earlier. Clinicians in particular would be receptive to the new advice if it was supported by evidence and guidelines. Most clinicians and patients viewed the new advice as potentially more appropriate and impactful with longer antibiotic courses (than 3-day courses for UTIs or for other infections). Some clinicians reported already advising patients that they may stop antibiotics when better when prescribing longer antibiotic courses, and some patients reported keeping antibiotics at home with the advice to stop taking them when symptoms resolve for episodes of recurrent UTI. Participants thought that the advice to stop antibiotics when better could be a part of shared decision-making and would need to be given in a way tailored to individual patients.

Emerging data suggests that patients are more concerned about, and averse to, stopping antibiotics when better, particularly in UTI care, whereas clinicians might be more amenable to it. Clinicians and patients may accept the new approach or advice if:

- it was supported by evidence showing that it is safe and beneficial (including impacts on complications and AMR)
- reasons for the change from the familiar message to complete antibiotic courses were explained and publicised
- the advice was personalised to the patient

The mobilome associated with Gram-negative bloodstream infections: a large-scale observational hybrid sequencing based study (80)

Plasmids carry genes conferring AMR and other clinically important traits; their ability to move within and between species may provide the machinery for rapid dissemination of such genes.

Despite this, existing studies using complete plasmid assemblies, which are essential for reliable inference, have been small and/or limited to those carrying particularly AMR genes (ARGs). This study sequenced 1,880 complete plasmids from 738 isolates from Enterobacterales bloodstream infections (BSI) in 2009 (194 isolates) and 2018 (368 isolates) in Oxfordshire, UK, plus a stratified selection from intervening years (176 isolates).

In Enterobacterales BSIs, work has shown that plasmids are largely, but not entirely, constrained to a single host species, although there is substantial overlap of plasmid gene-repertoire between species. Most ARGs are carried by a relatively small number of plasmid groups with biological features that are predictable. Plasmids carrying ARGs - including major carbapenemase-associated plasmids seen globally - are highly genetically related to some plasmids that are not currently carrying these genes in Oxfordshire, suggesting that specific plasmid 'backbones' may represent an acquisition risk for clinically relevant ARGs. In this study isolates generally carried all their ARGs on a single plasmid, reinforcing the importance of antimicrobial stewardship for all classes of antibiotics. These findings suggest that future surveillance should, in addition to tracking plasmids currently associated with clinically important genes, focus on identifying monitoring and reducing selection pressures for the dissemination of high-risk plasmid groups with the potential to rapidly acquire and disseminate these genes.

Knowledge mobilisation

Knowledge Mobilisation (KM) is a broadly defined concept, often considered diffuse and conceptual in nature. A simple definition of KM, however, in the context of public health policy and research, is "the process of optimising the use of research generated knowledge".

Connecting research-based activities and outputs with those involved in influencing decisions or charged with making decisions about public policy and professional practice is complex but is easier when problems are defined and tackled collaboratively. Knowledge mobilisation (the process) is focused on action as an output, which leads to the benefit of society.

The UKHSA has been collaborating with the NIHR-funded HPRUs in HCAI and AMR at the University of Oxford and Imperial College London to integrate KM into their programmes of work, develop KM capacity and to improve the evidence base for the use of KM in future. This work aims to ensure that knowledge from the HPRUs and UKHSA projects is mobilised to policymakers and wider audiences effectively, in order to achieve common impact goals. This work spans all 3 organisations and was initiated in 2021.

Activity thus far has involved the production of a knowledge mobilisation strategy in April 2021, the scoping of KM supporting resources and curation of a KM toolkit. A 'KM Champions' community of practice has been developed for colleagues across the 3 organisations and 2 interactive workshops on KM principles and resources have been held.

Knowledge mobilisation toolkit

The UKHSA knowledge mobilisation (KM) team worked in 2021 to collate resources to support KM activity: the KM Toolkit includes information for those at different levels of understanding and interest in KM, with resources split into 4 sections:

1. Understanding KM: A range of videos, web pages, paper collections and e-learning courses to provide a grounding in KM.

2. Performing KM: Resources designed to support open team discussions and the production of a KM plan, including stakeholder mapping, communications planning and a KM engagement framework designed by the UKHSA team.
3. Evaluating KM: Resources designed to support teams in evaluating their KM capacity, celebrate good practice and plan for improvement. This includes a KM self-assessment tool, an impact evaluation framework and information on monitoring and evaluating policy engagement.
4. Reporting KM: Documents to be included as required to support HPRU KM reporting.

Knowledge mobilisation champions' community of practice

In 2021, a HCAI and AMR KM community of practice was set up as a learning network of people who share a skill and who improve and learn from each other as they interact on a regular basis and currently includes 31 members from UKHSA, 35 members from the University of Oxford and 19 members from Imperial College London.

Workshops

In 2021, 2 workshops were held across UKHSA and the 2 HCAI and AMR HPRUs. These were designed to strengthen connections within and between HPRUs and UKHSA and to share learning around KM. The first was used to launch the KM toolkit and included a focused session on the 'Knowledge to Action' (K2A) framework. The second took a focus on KM evaluation and included a session on the KM 'Maturity Model'.

Knowledge Mobilisation and World Antimicrobial Awareness Week

Ahead of World Antimicrobial Awareness Week (WAAW) which ran from 18 to 24 November 2021, KM principles were integrated into national planning activity. A 'Knowledge Café' was held on 22 September 2021 and was attended by over 120 colleagues. The knowledge café format seeks to help surface a group's collective knowledge, learn from each other, share ideas and insights, and is patterned after the 'world café' methodology.

The Knowledge Café comprised a panel discussion from members of the National WAAW and European Antimicrobial Awareness Day (EAAD) Planning Group, including members from across the healthcare and public health systems, as well as public and patient perspective. The panel discussion was followed by the Knowledge Café portion, in which attendees were allocated a virtual 'café table' in which they took part in facilitated discussions to reflect on 2020 WAAW activity, plans for 2021, anticipated barriers and resources that may be used. Attendees then re-joined the overarching group to consolidate learning.

Ahead of WAAW, a quick guide for working with local comms colleagues to design WAAW communications was developed, including prompts based in the 'Knowledge to action' (K2A) resource from the UKHSA KM Toolkit.

9. Stakeholder engagement

The ESPAUR Oversight Group is comprised of over 20 stakeholder organisations including the devolved administrations, professional and educational bodies, healthcare providers and regulators. Stakeholders have continued to contribute to tackling antimicrobial resistance (AMR) and promote good antimicrobial stewardship (AMS) whilst also supporting the COVID-19 response.

British Dental Association (BDA)

The British Dental Association (BDA) continues to work nationally and internationally to address the role of dentistry in AMR. Within the UK, the BDA has been campaigning on the importance of investing in oral disease prevention and tackling the backlogs of dental care exacerbated by the pandemic, to support a reduction in unnecessary antibiotic prescribing. A further focus has been the need for appropriately funded urgent treatment time, which would remove the current contractual incentive for inappropriate prescribing of dental antibiotics in England.

Internationally, the BDA plays a key role in the AMS work of the Council of European Dentists and World Dental Federation (FDI). Led by Dr Wendy Thompson, a member of the BDA's Health and Science Committee, the antibiotics working group of the FDI Science Committee has contributed extensively to the development of WHO's antibiotics handbook, in particular the chapter on dental infections. The FDI working group also developed an international pledge on AMR, which has been signed by over 70 national dental associations globally. In 2022, the recently-launched FDI Global Antibiotics Research in Dentistry network will be hosting a symposium, 'Two pandemics: COVID and AMR' at the International Association for Dental Research.

The BDA also raised the need for national action plans on AMR to include dentistry at the 2021 World Medical Association conference, hosted by the British Medical Association.

British Infection Association (BIA)

The British Infection Association is the professional body representing NHS Infection Specialists and trainees in Microbiology, Virology and Infectious Diseases. The Association also has a growing Associate Membership made up of allied healthcare professionals working broadly in the field of infection medicine. It publishes the prestigious Journal of Infection and Clinical Infection in Practice (CLIP) a new open-access journal focused the advancement of knowledge and discussion of clinical infection in practice.

During 2021 to 2022 the Best Practice Standards for the delivery of NHS Infection Services developed by the Association in liaison with the Royal College of Physicians and the Royal College of Pathologists have been published in CLIP. The Association has followed this up with

a nationwide survey of NHS hospital infection expertise and services the results of which are in press with CLIP.

The Association has developed a new series of Infection Quick Reference Guides to support front-line clinicians select and interpret diagnostic tests to support appropriate antibiotic prescribing in secondary care. The first 4 guides on sepsis, pneumonia, cellulitis and gastrointestinal infection are now complete and will be published alongside the relevant UK Standards for Microbiological Investigation (SMIs) and through the Association itself.

British National Formulary (BNF)

The BNF continues to update content in line with NICE's management of common infections guidance and any relevant national guidance on the use of antimicrobials. These updates are highlighted to BNF users by the inclusion in the BNF changes record which is published monthly. The BNF also continues to host the NICE/PHE (now UKHSA) summary of antimicrobial prescribing guidance – managing common infections on the BNF website whilst a long-term solution for the governance and hosting is established.

British Society for Antimicrobial Chemotherapy (BSAC)

With members in 40 nations, and over 100,000 learners in more than 200 countries, the BSAC represents a global network of medics and scientists dedicated to ensuring the availability of effective antimicrobial treatments for current and future generations. As a learned society and charity, its mission is to work alongside others to provide high-quality open access support to those who need it most. This support takes many forms: free membership, workshops, conferences, public and political engagement, a range of educational resources (including online courses), professional fora, grants, and research publications via our Journal of Antimicrobial Chemotherapy, and the online open access education and research journal JAC-Antimicrobial Resistance.

The period 2021 to 2022 saw BSAC:

- launch its pioneering UK Antimicrobial Registry scheme – with the aim of improving patient outcomes by collecting real-world data on a range of antimicrobial agents (starting with the 2 new antibiotics selected for the UK's de-linkage pilot scheme)
- unveil its Global AMS Accreditation Scheme – a quality improvement programme that helps healthcare practitioners to assess, develop, and improve infection prevention and control (IPC), epidemiology, and stewardship services, for the management of infections
- start work on its Global AMS Partnership Hub
- commission a series of Vanguard articles to help mark the Society's 50th anniversary

- continue to support its national susceptibility testing programme, supporting harmonisation of methodologies with EUCAST
- work with NHSE&I to support plans for the national rollout of the Outpatient Parenteral Antimicrobial Therapy (OPAT) programme
- add a range of educational courses to its Infection Learning Hub
- support the publication of evidence-based guidelines and good practice recommendations
- provide the secretariat for the All-Party Parliamentary Group on Antibiotics
- stage meetings with UK government representatives and senior policymakers
- inspire public engagement through The Mould that Changed the World
- forge partnerships with community-focused projects in low and middle income countries through its global health initiative Stop Superbugs
- continue to respond to COVID-19 by reinventing its grants programme, establishing an info hub, and commissioning articles from scientists and healthcare professionals
- renovate its Birmingham headquarters

Care Quality Commission (CQC)

The CQC makes sure health and social care services provide people with safe, effective, compassionate, high-quality care and encourages care services to improve. We regulate against the Health and Social Care Act 2008.

The CQC has been working towards its new responsibilities for Integrated Care System (ICS) assurance in the Health and Care Act 2022. The legislation gives CQC a new duty to review each local ICS, and specifies that CQC reviews must look at leadership, the integration of services and the quality and safety of services. The CQC has been engaging with external stakeholders, including NHS England & NHS Improvement AMR Regional Leads, to consider what this would look like in practice.

The CQC has published an updated 'GP Mythbuster' on identifying and responding to sepsis in primary care and an Insight report from the CQC focused well-led inspections reviewing IPC Board assurance in NHS TIPC in care homes and acute trusts was also reviewed in CQC's 'State of Care Report 2021'.

College of General Dentistry (CGDent)

During 2021, the Faculty of General Dental Practice UK (FGDP), which published 'Antimicrobial Prescribing in Dentistry: Good Practice Guidelines', transferred into the College of General Dentistry (CGDent), which now publishes the guidelines.

These are available to view at CGDent standards and guidance.

In its role to maintain standards for the general dental profession, CGDent delivered online continuing professional development events about dental antibiotic prescribing, resistance and stewardship; these were free to view online for all dental professionals, with on-demand access to the recordings also available to the College's members.

During October and November, it led a collaboration of 11 organisations to support WHO's Antimicrobial Awareness Week (WAAW) with a joint communication to UK oral health professionals, and published 2 related blogs, which it disseminated to its 3,000 members and subscribers and published in the Primary Dental Journal (PDJ). In addition, the September 2021 edition of the PDJ, dedicated to the theme of 'Urgent Dental Care and COVID-19', included a number of articles about the pandemic's impact on dental antibiotic prescribing around the world.

ESPAUR dental subgroup

The ESPAUR dental subgroup was reconvened in 2021 after a break during the pandemic. The dental subgroup is composed of dental stakeholders who represent dental care commissioners and providers, regulatory organisations, professional and educational bodies. In 2022 the dental subgroup is focussing on actions to update and refresh the dental AMS toolkit as well as other actions to support the increase in appropriate prescribing in dentistry.

As well as individual stakeholder actions around AMS, some stakeholders within the group came together to support 2021 WHO's WAAW to remind patients that 'antibiotics do not cure toothache' and encouraging dental teams to only prescribe antibiotics as an adjunct to definitive clinical management of the cause when indicated according to national guidelines.

NHS England (NHSE)

The COVID-19 pandemic continued to impact the AMR Programme across 2021 to 2022, particularly in terms of infection trends, prescribing patterns, the impact of remote GP consultations and the cohorts of patients presenting to primary and secondary care. Good progress was made in a number of areas, including:

1. All regions now have identified AMS, Scientific and IPC leads with responsibility for AMR.
2. The initial iteration of the AMR Dashboard has been launched. This enables a range of key data on emergency admissions due to bacterial infection and/or sepsis to be viewed at ICS, CCG, trust, regional and national levels, broken down by individual criteria including age, length of hospital stay, inequalities, readmissions, urinary tract infection (UTI), cellulitis and pneumonia.
3. An AMR Clinical Leadership Group has been introduced.
4. A UTI workstream covers the pathway from prevention to diagnosis and treatment. As part of this, ICSs have been invited to bid for funding to participate in evaluated

pilots, testing out the most effective interventions to improve hydration uptake in older people.

5. Approval was obtained to 2 new Commissioning for Quality and Innovation (CQUIN) improvement goals, one focusing upon appropriate prescribing for UTIs and the other upon the reliable recording of acute deterioration, with the aim of improving appropriate treatment.
6. The Chief Scientific Officer's team have worked with National Institute for Health Research Innovation Observatory for a series of horizon scans to identify the most promising new technologies that support timely, accurate identification of conditions for which antimicrobials may be appropriate.
7. Chapters 1 and 2 of the National IPC Manual have been published.
8. Joint evaluation work with NICE to test a new value-based subscription-style payment model for antimicrobials has progressed, with 2 new drugs supported in draft NICE guidelines.
9. A Children's Dashboard was developed in collaboration with NHS Business Services Authority and published on the ePACT2 platform in September 2021, highlighting variation in prescribing of antibiotics to children aged 0-14 years, facilitating peer comparison and identification of opportunities for improvement through AMS.
10. The RightCare UTI data packs have been incorporated into the Model Health System dashboards with innovative new data visualisations including acute hospital admissions for UTI by deprivation quintile and percentage gradient of inequality for UTI admissions.
11. A national exemplar template was developed in collaboration with NHS Specialist Pharmacy Services for antimicrobial Patient Group Directions (PGDs). A risk assessment framework was developed for infection management services incorporating the supply of antibiotics under the legal authority of a PGD. This framework is available from the AMR Programme Workspace on the FutureNHS platform.

Education and Training NHSE - antimicrobial prescribing and medicines optimisation

A workforce survey has been developed to capture the current AMS workforce capacity and level of training and experience in the role across England in acute trusts, community health care trusts and CCGs. The results will be collated and used for workforce planning to fulfil the ambition stated in the current National Action Plan.

The antimicrobial prescribing and medicines optimisation (APMO) team has been working with the national IPC team to embed antimicrobial resistance and stewardship training in the IPC capability framework for generalist health and social care staff. This framework, once approved, will be used to inform mandatory IPC training. The next workstream will be embedding these topics in the capability framework for IPC specialists and working towards a nationally recognised qualification. These deliverables are overseen by the national IPC Education, Workforce and Leadership Steering group, including APMO team members.
The APMO team is collaborating with established research studies, such as AMS TEACH, promoting the study to increase recruitment. The APMO team has also been working with

Health Education England to develop an education framework for pharmacy undergraduates on AMS and resistance for the forthcoming integrated education and training (IET) programme, and the Centre of Pharmacy Postgraduate Education to scope current availability of generalist and specialist support for pharmacists on AMS/AMR post qualification.

NHS England and NHS Improvement Regional AMS Leads

The first NHSE regional AMS lead was appointed in the South West region in 2020 and regional AMS leads were recruited to the remaining 6 regions of England during 2021, reporting to regional chief pharmacists and the national pharmacy and prescribing clinical lead for AMR in the NHSE AMR Programme. Regional AMS leads are responsible for facilitating and co-ordinating activities in each region to support the local delivery of the ambitions of the UK AMR 5-year National Action Plan, including promoting NHSE improvement and assurance schemes.

The NHSE regional AMS leads have established or taken a leadership role in existing regional AMS committees, in many cases sub-committees of the Regional Medicines Optimisation Committee (RMOC), to promote collaboration and sharing of best practice. The regional AMS leads have also joined or contributed to the establishment of multi-professional regional AMR committees in collaboration with regional medical directors and chief pharmacists, regional IPC leads and regional healthcare scientist diagnostics leads. AMR Senior Responsible Officers (SROs) have been appointed in the majority of Integrated Care Systems and the regional AMS leads have been working with SROs on the design and implementation of governance systems and processes to ensure effective antimicrobial stewardship, and the drafting of system plans to address AMR, including workforce plans. The regional AMS leads have also assumed national portfolio roles, leading on key strategic initiatives to facilitate and incentivise quality improvement in antimicrobial prescribing and medicines optimisation.

NHS RightCare UTI Model Health System

RightCare UTI data supports local health systems to identify opportunities for further improvement in the safe and effective management of UTI in primary care, particularly in older people. Details of the RightCare UTI products have previously been reported in the ESPAUR 2020 report. During 2021 RightCare UTI published a new system-level dashboard in the NHS Model Health System. The dashboard contains metrics including inpatient admission and readmission rates; antibiotic prescribing population rates and drug-bug resistance data; population counts for urinary catheters use; and Gram-negative bacteraemia rates – all age-sex standardised and presented with sex breakdowns where possible. Deprivation metrics for inpatient admissions and primary care prescribing of lower UTI antibiotics have also been included.

Dashboard functionality allows NHS systems to identify trends over time as well as variation between peers. Future work to link data sets at a patient level will commence in September 2022. NHS England Regional Antimicrobial Stewardship Leads are supporting ICS use of RightCare UTI data.

Antimicrobial Stewardship Dashboard – Children

NHS England has collaborated with the NHS Business Services Authority to publish the ePACT2 Antimicrobial Stewardship – Children's Dashboard supports a population health approach to improvement at system level and allows NHS organisations to:

- see the variation in antibiotic prescribing for children aged 0 to 14 years
- compare antibiotic prescribing rates over time and between organisations
- understand how many children are prescribed one or more antibiotics
- identify and prioritise opportunities for antimicrobial stewardship improvement
- monitor and report antimicrobial stewardship improvement

NHS England Regional Antimicrobial Stewardship Leads are supporting ICS use of the dashboard which reports monthly and received 64,000 visits in the 6 months following publication in September 2021.

National Institute for Health and Care Excellence (NICE)

Strong progress has been made on the project to develop and test innovative models for the evaluation and purchase of antimicrobials, which NICE is co-leading with NHS England and NHS Improvement. Key objectives are to demonstrate the feasibility of an approach to evaluation that recognises the full public health value of antimicrobials together with payment models that support good stewardship. The model tests paying companies for antimicrobials based on an evaluation of the overall benefit to the NHS, as opposed to the volumes used.

Such models, if widely adopted internationally, have the potential to provide the 'market pull' incentive to stimulate increased investment in the development of new antimicrobials.

The project launched in July 2019 and following engagement with companies and other stakeholders, the project team developed contract documents and an evaluation framework. A competitive tender was launched in June 2020 where the NHS offered 2 contracts to pharmaceutical companies through which we are testing the new approach. The 2 selected antimicrobial products, cefiderocol and ceftazidime with avibactam were announced in December 2020. These products were subject to evaluation by NICE to estimate their value to the NHS using adapted methods for antimicrobials. The draft guidance for both products was published in April 2022 following meetings of the special NICE committee convened for this project held in January and February 2022. The guidance estimates the lifetime value of the products to the NHS in QALYs, and the minimum QALY numbers per year to help inform the payments in subscription-style contracts. Payments are expected to commence early July 2022.

There has been a high level of international interest in the project and the project team is working with the DHSC Global and Public Health Group to collaborate with international partners in promoting similar models.

NICE continues to work with UKHSA (formerly PHE) to develop antimicrobial prescribing guidelines (APGs) for managing common infections. The guidelines offer evidence-based guidance for primary and secondary care and provide recommendations for appropriate antimicrobial use in the context of tackling AMR. A NICE Committee produces these guidelines which are jointly badged by both NICE and UKHSA. In 2021 to 2022 there was one APG published on CDI as well as an update to the otitis media (acute) APG.

The format of APG content comprises a visual summary of the recommendations, the guideline, the associated evidence review and a summary document that includes content from all APGs alongside UKHSA's guidance for primary care. Some guidelines also include decision aids to inform shared decision making, such as 'Cystitis: taking an antibiotic'. NICE will continue to engage both at a national and regional level with key external stakeholders including UKHSA, NHS England/Improvement, Health Education England and the CQC to support the wider implementation of the APGs.

To support the appropriate use and stewardship of new antimicrobials at the point of launch, NICE is also developing evidence summaries for antimicrobial prescribing. Topics published in 2021 to 2022 were on nebulised liposomal amikacin, delafloxacin for community-acquired pneumonia, oritavancin for acute bacterial skin and skin structure infections and also on eravacycline for complicated intra-abdominal infections in adults.

In January 2017, NICE published a guideline AMS: changing risk-related behaviours in the general population (NG63) aiming to change people's behaviour to reduce AMR. It also includes measures to prevent and control infection. This guidance is complementary to the NICE guideline on AMS: systems and processes for effective antimicrobial medicine use (NG15) which provides recommendations about how to correctly use antimicrobial medicines and the hazards associated with their overuse and misuse.

NICE work on COVID-19

Since March 2020, NICE has produced 24 COVID-19 rapid guidelines. These include guidelines on managing COVID-19, guidelines on service delivery during the pandemic and guidance on conditions which require the use of drugs that affect the immune response.

In March 2021, 7 of these original individual guidelines were integrated into one guideline: managing COVID-19 (NG191). The NICE COVID-19 team also developed guidance on the management of the long-term effects of COVID-19 and is responsible for maintaining and updating the NHSE&I specialty guides relating to COVID-19. NICE has continued to review and update the NICE COVID guidance using a 'living guidelines' approach.

The following workstreams in the COVID-19 team link into AMS activities:

Living guideline approach to the COVID-19 rapid guidelines

The suite of COVID-19 rapid guidelines is under continuous review for emerging evidence that may warrant a change to recommendations. Emerging evidence is reviewed, the likely impact on extant recommendations is assessed by the COVID-19 expert panel. Any changes to recommendations are published typically within a 4-week timescale of the evidence becoming available.

Managing COVID-19

As part of creating the integrated guideline on managing COVID-19, guidance was updated on the use of antibiotics within the COVID-19 rapid guidelines managing suspected or confirmed pneumonia in adults in the community and antibiotics for pneumonia in adults in hospital. The panel decided that it was appropriate to refer to the existing NICE antimicrobial guidelines for the management of hospital and community acquired pneumonia (NG138 and NG139) Where secondary bacterial pneumonia was likely, then the antibiotic choices in the existing NICE APGs apply, therefore providing clear and consistent guidance on choice of antibiotics and aiming to improve AMS.

Therapeutics process and links with rapid C-19 initiative

NICE evidence reviews are used to help inform NHSE&I's commissioning policy on COVID-19. This allows the development of guidance that links with the priorities of managing COVID-19 in a rapid way. Recommending only those effective therapeutic interventions for the management of COVID-19 serves to reduce the inappropriate use of antibiotics where benefits are unlikely to be seen. Published recommendations include those on the inappropriate use of azithromycin, doxycycline, and ivermectin in the treatment of COVID-19. In contrast, positive recommendations have also been made on use of antivirals (nirmatrelvir and ritonavir, remdesivir and molnupiravir), corticosteroids, neutralising monoclonal antibodies, tocilizumab, sarilumab and baricitinib in the treatment of COVID-19.

NICE also develops national guidance on new medical devices and diagnostics. The Medical Technologies Evaluation Programme published in 2021 to 2022 final positive guidance in 2 topics that are relevant to AMS:

- ClearGuard HD, an antimicrobial barrier cap for use with central venous catheters in haemodialysis
- Plus Sutures, a range of synthetic, absorbable sutures that are either impregnated with or coated with triclosan, a purified medical grade antimicrobial

Guidance on faecal microbiota transplant in people who have recurrent or refractory CDI is also in development.

The Diagnostics Assessment Programme also represents NICE on the UK AMR Diagnostics Collaborative which brings together key partners across the NHS, industry and academia to deliver the UK's diagnostic ambitions for AMR.

Public Health Agency (Northern Ireland)

The Public Health Agency (PHA) in Northern Ireland continues to support efforts to decrease meticillin-resistant *Staphylococcus aureus* (MRSA) bloodstream infections, CDI, Gram-negative blood stream infections and promote appropriate use of antimicrobials. The Regional HCAI and AMS Improvement Board for Northern Ireland (chaired by PHA) was paused due to pandemic pressures, however, many of the actions have continued, and the HCAI/AMR surveillance team in PHA have continued with routine surveillance and monthly 'Target Monitoring' reports on HCAIs (*S. aureus*, CDI, Gram-negative bloodstream infections) and antimicrobial consumption (AMC) have continued. From February 2020, much of the HCAI/AMR team surveillance team's work has been focused on monitoring and reporting on healthcare-associated SARS-CoV-2 infections. In 2022, we aim to complete work on development of a 'Target Monitoring' dashboard for secondary care. We are also undertaking work to elucidate the effect of the pandemic on antimicrobial usage, and AMR.

PHA, along with colleagues in primary and secondary care, ran a campaign during WAAW 2021 to highlight the importance of AMR to both professionals and the public, and actions that can be taken to ensure antimicrobials remain effective. This included a pledge video, social media campaign, press release and other activities within primary and secondary care including targeted messages and competitions to increase engagement with AMS resources.

Public Health Wales (PHW)

The HCAI, AMR and Prescribing Programme (HARP), PHW, provide professional support to the NHS in Wales to reduce the burden of HCAIs and AMR across Wales. This is delivered through feedback of surveillance data for antimicrobial usage, resistance and HCAI to the NHS and Welsh Government (WG) as well as providing technical expertise in microbiology, AMS and IPC. The HARP team supports and advises the Wales AMR and HCAI Steering Group, chaired by the Deputy CMO Wales as well as the AMR and HCAI Delivery Boards set up to deliver the UK AMR strategy in Wales.

A number of reports are published annually by the HARP team, including antimicrobial prescribing in primary and secondary care, resistance in both primary and secondary care, and the annual Welsh antimicrobial point prevalence study. Due to the national COVID-19 response in PHW, this year we have published fewer reports, and for the second year running focussed the annual antimicrobial point prevalence study on respiratory patients in secondary care. For HCAI surveillance, the HARP team provide a monthly dashboard of HCAI. Wales data is also provided to the UK AMR delivery board and WHO GLASS.

PHW provides a comprehensive, integrated microbiology service for Wales including a network of diagnostic laboratories, reference laboratories and an active genomics programme. The genomics programme has been particularly active this year in the tracing of COVID-19 variants.

Wales has a dedicated AMR Reference Laboratory (Specialist Antimicrobial Chemotherapy Unit), which provides molecular confirmation of AMR, including carbapenemase-producing Gram-negative bacteria. The unit analyse and report targeted surveillance on the mechanisms of resistance to third-generation cephalosporins in Gram-negatives, and drivers of carbapenem use. Each year the Welsh HBs participate in the European Antibiotic Awareness Day (EAAD)/WAAW, supported by materials and communications from PHW and WG.

The focus of the campaign for 2021 was the introduction of the 'Antibiotic Checklist' to all the Community Pharmacies in Wales. Community pharmacies across Wales were provided with a resource pack including the Antibiotic Checklist as well as other self-care leaflets and posters. These resources were also supplied digitally as well as a digital copy of the 'Community Pharmacy Antibiotic Counselling Sheet'. The Antibiotic Counselling Sheet was developed by the Wales Primary Care Antimicrobial Pharmacists Group in collaboration with PHE's TARGET toolkit.

To facilitate use of the Checklist an E-Learning module was developed in collaboration with Health Education and Improvement Wales and the Education sub-group of the All Wales Antibiotic Pharmacist Group based on the E-Learning module developed by PHE (now UKHSA) and HEE. To ensure consistent messaging for patients, GP practices and Hospital Pharmacies with face-to-face patient engagement were provided with similar packs. An Antimicrobial Stewardship messaging social media campaign was also run which was shared with the public via the PHW account.

PHW were instrumental to the update and publication of the All Wales Medicines Strategy Group (AWMSG) Primary Care Antimicrobial Guidelines and associated national audit pack as well as the development and publication of new guidelines for the management of C. difficile and recurrent UTI in adult women.

More information, including all our published reports, can be found on the HACI and AMR programme webpage.

Royal College of Nursing (RCN)

The RCN continued to deliver its Education programme on IPC and AMS using competencies developed with the University of Cardiff.

Additionally, the RCN continues to support AMS programmes impacting on nursing practice. The RCN is currently involved in a number of stewardship activities including a survey of Higher Education Institutes on pre-registration education, asepsis and aseptic technique and Glove Awareness week delivered 2 to 6 May 2022.

The RCN continues to actively support self-care week annually and promotes this via the Public Health Forum and IPC network.

Royal Pharmaceutical Society (RPS)

The Royal Pharmaceutical Society's vision is to become the world leader in the safe and effective use of medicine and we remain committed to the global strategy for AMR through the UK National Action Plan and 20-year vision.

Our mission is to put pharmacy at the forefront of healthcare. From April 2021 to March 2022 our AMR activity has included:

Advisory group activity

The RPS Antimicrobial Expert Advisory Group (AmEAG) meets regularly and advises on AMR, infection prevention and management, AMS and any other issues that affect the pharmacy profession and the public. It provides a central point for requests for advice, expertise, sharing best practice and input and comment from government and other organisations.

Pharmacy resources

We continue developing a range of resources covering topics linked to current practice including podcasts, blogs and webinars:

- interview with Sir Richard Sykes who was appointed chair of the UK government's Vaccine Taskforce in June 2021, providing an insight into the UK COVID-19 vaccine programme
- interview with Professor Dame Sally Davies about AMR and what pharmacy can do to counter this growing threat
- blog by Sharon Pfleger as part of our declaration of Climate and Ecological Emergency, about the threat of the development of AMR and why looking at the hospital's wastewater output was so important to NHS Highland in managing AMR and wastewater in hospitals
- webinar series to support pharmacy consultations including topics such as common ear, nose and eye conditions

Contribution to WAAW/EAAD

As part 2021 WAAW/EAAD, we delivered a digital showcase of the Quality Improvement projects completed by trainees as part of our AMS training programme. This enabled the dissemination of their findings and highlighted the importance of AMS in the wider landscape.

We have published, in MDPI-Pharmacy, the outcomes of this national, cross-sector AMS Training Initiative for pharmacists in England.

Scottish One Health Antimicrobial Use and Antimicrobial Resistance (SONAAR)

In recognition of the importance of the ‘One Health’ ethos to the sustainable control of AMR, the SONAAR programme within ARHAI Scotland monitors trends in antimicrobial use and resistance.

The SONAAR annual report contains information on use of antibiotics in humans in primary care and acute hospitals along with small animal veterinary practices, and the levels of antibiotic resistance found in a range of important human and animal infections. More recently the report has included information on AMR in the environment.

This data is used by organisations such as the Scottish Antimicrobial Prescribing Group (SAPG) to inform antimicrobial prescribing policy and develop initiatives for AMS; the Scottish Microbiology and Virology Network (SMVN) to support the development of testing strategies for NHS diagnostic laboratories in Scotland; and a range of animal stakeholder groups to support development and delivery of a co-ordinated quality-driven approach to veterinary prescribing practice, education and surveillance data. The SONAAR 2021 report will be published in November 2022 and will be available online.

Specialist Pharmacy Service (SPS)

The NHS Specialist Pharmacy Service (SPS) has supported the NICE Guidance on CDI: antimicrobial prescribing by preparing 2 articles on choosing appropriate oral options for vancomycin and for fidaxomicin.

SPS has been in consultation with NHSE on the proposed national PGD template programme as part of their Medicines Governance Do Once programme. At the request of NHSE this has been paused. Work has, however, begun on a PGD template for a single dose administration of benzylpenicillin by registered midwives to individuals in labour where there has been an identified risk of early-onset Group B Streptococcal (GBS) infection developing in the neonate.

This is in line with the Royal College of Obstetrics and Gynaecology Group B Streptococcal Disease guidance and development is being overseen by the NHSE Preventative Medicines in Pregnancy work programme.

SPS has published a suite of resources on drugs in pregnancy and this includes 2 articles on antimicrobials: ‘UTI: treatment during pregnancy’ and ‘Thrush or vaginal candida: treatment during pregnancy’.

It was decided that SPS should no longer host the AMR networks in England on its website. These have now moved to NHS Futures.

Veterinary Medicines Directorate (VMD) and Department for Environment, Food and Rural Affairs (DEFRA)

The latest Veterinary AMR and Sales Surveillance (VARSS) Report, which reports data from 2020 shows that since 2014 there has been a 52% decrease in antibiotic sales for food-producing animals in the UK and a drop of 79% since 2015 in sales of those antibiotics most critically important for human health. This reduction in veterinary antibiotic sales has been achieved through government working collaboratively with vets and farmers, most notably through sector antibiotic stewardship groups and the Targets Task Force chaired by the Responsible Use of Medicines in Agriculture (RUMA) Alliance. The UK farming industry remain committed to responsible antibiotic use, disease prevention and improving farm husbandry, as demonstrated by the publication of ambitious targets in the RUMA Targets Task Force 2 (TTF2) report for further reducing and refining antibiotic usage to 2024. The VMD is working closely with key stakeholders and taking a broad range of approaches to address the challenge of AMR, including by supporting the Farm Vet Champions initiative. This project, led by RCVS Knowledge, encourages vets in farm animal practice to enrol as Farm Vet Champions, and provides them with training and support to set personal and practice level targets (using the SMART Goals Tool) to embed good antimicrobial stewardship in practices and on farms.

The 2020 VARSS report also included data from the Harmonised Monitoring programme which samples healthy animals at slaughter, showing that the UK has achieved some of the lowest levels and biggest reductions, in resistance across Europe. For the first time we reported on early results of our enhanced clinical AMR surveillance programme for veterinary bacterial pathogens, which puts the UK at the forefront of veterinary clinical surveillance for AMR internationally. This included results from use of gold-standard minimum inhibitory concentration (MIC) testing to assess the susceptibility of important veterinary respiratory pathogens to antibiotics. This enhancement of the clinical surveillance programme will support responsible use of antibiotics and increase the ability of clinical surveillance to detect emerging resistance issues in the UK.

Integrated One Health surveillance of AMR is a key ambition of the UK AMR National Action Plan. The VMD is facilitating cross-government working across public and animal health, food safety and the environment through the Defra AMR Coordination (DARC) group's One Health Integrated Surveillance sub-group, which is developing a strategy for achieving integrated AMR surveillance in the UK. Concurrently, VMD is a partner organisation in the FSA-led, cross-governmental PATH-SAFE programme, which aims to utilise innovative approaches to develop a model national genomic surveillance network to improve the detection and tracking of foodborne pathogens and AMR throughout agri-food systems. The VMD is also leading the latest One Health Report on AMR in animals, people, food and the environment, to be published later this year which will underline the importance of an integrated approach to AMR surveillance and control.

References

1. Budd E. ‘Advisory committee on antimicrobial prescribing, resistance and healthcare associated infection annual report 2015’ in ‘Sixth annual report’ 2015
2. DHSC. ‘Tackling antimicrobial resistance 2019 to 2024: the UK’s 5-year national action plan.’ January 2019
3. DHSC (2019). ‘Contained and controlled: the UK’s 20-year vision for antimicrobial resistance’
4. PHE (2020). ‘English surveillance programme for antimicrobial utilisation and resistance (ESPAUR) report 2019 to 2020’
5. UKHSA (2021). ‘English surveillance programme for antimicrobial utilisation and resistance (ESPAUR): report 2020 to 2021’
6. Cassini A and others. ‘Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis.’ Lancet Infectious Diseases 2019: volume 19, pages 56 to 66
7. Moore IF, Hughes DW and Wright GD. ‘Tigecycline is modified by the flavin-dependent monooxygenase TetX.’ Biochemistry 2005: volume 44, pages 11,829 to 11,835
8. He T and others. ‘Emergence of plasmid-mediated high-level tigecycline resistance genes in animals and humans.’ Nature Microbiology 2019: volume 4, pages 1,450 to 1,456
9. Zhang R-m and others. ‘Source tracking and global distribution of the tigecycline non-susceptible tet (X).’ Microbiology Spectrum 2021: volume 9
10. Martelli F and others. ‘Detection of the transferable tigecycline resistance gene tet (X4) in *Escherichia coli* from pigs in the United Kingdom.’ Journal of Antimicrobial Chemotherapy 2022: volume 77, pages 846 to 848
11. O'Neill, J. ‘Review on antimicrobial resistance antimicrobial resistance: tackling a crisis for the health and wealth of nations.’ 2014
12. PHE (2019). ‘English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR) report 2018 to 2019’
13. PHE Health Protection Report (2020). ‘New statutory duty on reporting results of antimicrobials susceptibility testing’
14. Bonnin, R.A., and others. ‘A single *Proteus mirabilis* lineage from human and animal sources: a hidden reservoir of OXA-23 or OXA-58 carbapenemases in Enterobacterales.’ Scientific Reports 2020: volume 10, page 9,160
15. Wirth T and others. ‘Niche specialization and spread of *Staphylococcus capitis* involved in neonatal sepsis.’ Nature Microbiology 2020: volume 5, pages 735 to 745
16. Sassi M and others. ‘Emergence of optrA-mediated linezolid resistance in enterococci from France 2006 to 2016.’ Journal of Antimicrobial Chemotherapy 2019: volume 74, pages 1,469 to 1,472
17. UKHSA. ‘Surveillance of antimicrobials resistance in *Neisseria gonorrhoeae*, 2016’
18. Shenoy ES and others. ‘Evaluation and management of penicillin allergy’. Journal of the American Medical Association 2019: volume 321, page 188

19. Wu JH and others. ‘Potential negative effects of antimicrobial allergy labelling on patient care: a systematic review’. Canadian Journal of Hospital Pharmacy 2018: volume 71, issue 1, pages 29 to 35
20. Joint Task Force on Practice Parameters, and others. ‘Drug allergy: an updated practice parameter’ in: ‘Annals Of Allergy, Asthma and Immunology: official publication of the American College of Allergy, Asthma and Immunology 2010: pages 259 to 273
21. Unemo M and others. ‘WHO global antimicrobial resistance surveillance for *Neisseria gonorrhoeae* 2017 to 2018: a retrospective observational study.’ Lancet Microbe 2021: volume 2 issue 11, pages e627 to e636
22. Yadav A and others. ‘*Candida auris* on apples: diversity and clinical significance.’ mBio 2022: 13
23. Kang SE and others. ‘Evidence for the agricultural origin of resistance to multiple antimicrobials in *Aspergillus fumigatus*, a fungal pathogen of humans.’ G3 Genes | Genomes | Genetics 2022: 12
24. Rhodes J and others. ‘Population genomics confirms acquisition of drug-resistant *Aspergillus fumigatus* infection by humans from the environment.’ Nature Microbiology 2022: volume 7, pages 663 to 674
25. DHSC (2019). ‘UK 5-year action plan for antimicrobial resistance 2019 to 2024’
26. NHS England (2018). ‘Quality premium guidance 2017 to 2019’
27. Thomson K and others. ‘An examination of trends in antibiotic prescribing in primary care and the association with area-level deprivation in England.’ BMC Public Health 2020: volume 20, issue 1, page 1,148
28. Dolk FCK and others. ’Antibiotics in primary care in England: which antibiotics are prescribed and for which conditions?’ Journal of Antimicrobial Chemotherapy 2018: volume 73, supplement 2, pages ii2 to ii10
29. Budd E and others. ‘Adaptation of the WHO essential medicines list for national antibiotic stewardship policy in England: being AWaRe.’ Journal of Antimicrobial Chemotherapy 2019: volume 74, issue 11, pages 3,384 to 3,389
30. NHS England (2016). ‘Commissioning for Quality and Innovation (CQUIN) Guidance for 2017 to 19’
31. NHS England (2021). ‘NHS Standard contract 2022 to 2023’
32. UKHSA. ‘AMR local indicators’
33. NICE. ‘Pneumonia (hospital-acquired): antimicrobial prescribing NG139’
34. Harris H and others (2022). ‘Hepatitis C in England, 2022: working to eliminate hepatitis C as a public health problem’
35. Bang CS and Song IH. ‘Impact of antiviral therapy on hepatocellular carcinoma and mortality in patients with chronic hepatitis C: systematic review and meta-analysis.’ BMC Gastroenterology 2017: volume 17, issue 1, page 46
36. Backus LI and others. ‘Impact of sustained virologic response with direct-acting antiviral treatment on mortality in patients with advanced liver disease.’ Hepatology 2019: volume 69, issue 2, pages 487 to 497
37. Backus LI and others. ‘Direct-acting antiviral sustained virologic response: impact on mortality in patients without advanced liver disease.’ Hepatology 2018: volume 68, issue 3, pages 827 to 838

38. Harris H and others (2018). 'Hepatitis C treatment monitoring' in: 'England: content, completeness and preliminary findings from the hepatitis C patient registry and treatment outcome system'
39. NICE. 'COVID-19 rapid guideline: antibiotics for pneumonia in adults in hospital NG173'
40. Hatzl S and others. 'Antifungal prophylaxis for prevention of COVID-19-associated pulmonary aspergillosis in critically ill patients: an observational study.' Critical Care 2021: volume 25, issue 1, page 335
41. White PL and others. 'COVID-19 and fungal infection: the need for a strategic approach.' Lancet Microbe 2020: volume 1, issue 5, page e196
42. Peghin M and others. 'Improving management and antimicrobial stewardship for bacterial and fungal infections in hospitalized patients with COVID-19.' Therapeutic Advances in Infectious Disease 2022: volume 9, page 20499361221095732
43. Gupta AK and others. 'The increasing problem of treatment-resistant fungal infections: a call for antifungal stewardship programs.' Intenrational Journal of Dermatology 2021: volume 60, issue 12, pages e474 to e479
44. Andrews A and others. 'Respiratory antibacterial prescribing in primary care and the COVID-19 pandemic in England, winter season 2020 to 2021.' Journal of Antimicrobial Chemotherapy 2022: volume 77, issue 3, pages 799 to 802
45. Adekanmbi V and others. 'Antibiotic use and deprivation: an analysis of Welsh primary care antibiotic prescribing data by socioeconomic status.' Journal of Antimicrobial Chemotherapy 2020: volume 75, issue 8, pages 2,363 to 2,371
46. Curtis HJ and others. 'Time trends and geographical variation in prescribing of antibiotics in England 1998 to 2017.' Journal of Antimicrobial Chemotherapy 2019: volume 74, issue 1, pages 242 to 250
47. Hoenigl M and others. 'Invasive candidiasis: investigational drugs in the clinical development pipeline and mechanisms of action.' Expert Opinion on Investigational Drugs 2022: volume 31, issue 8, pages 795 to 812
48. Hoenigl M and others. 'The antifungal pipeline: Fosmanogepix, Ibrexafungerp, Olorofim, Opelconazole and Rezafungin.' Drugs 2021: volume 81, issue 15, pages 1,703 to 1,729
49. Al-Tawfiq JA and others. 'Antibiotics in the pipeline: a literature review 2017 to 2020.' Infection 2022: volume 50, issue 3, pages 553 to 564
50. Butler MS and others. 'Analysis of the clinical pipeline of treatments for drug-resistant bacterial infections: despite progress, more action is needed.' Antimicrobial Agents and Chemotherapy 2022: volume 66, issue 3, page e0199121
51. RCGP (2022). 'TARGET antibiotics toolkit hub' (accessed 15 August 2022)
52. RCGP (2022). 'TARGET antibiotics toolkit hub - Leaflets to discuss with patients' (accessed 15 August 2022)
53. NHS Digital (2022). 'SNOMED CT'
54. NICE. NICE guideline (NG15). 'Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use.' 2015
55. Nguyen AD, M-PT, Tran MH, Pham HT. 'The effect of early switching from intravenous to oral antibiotic therapy: a randomized controlled trial.' Journal of Pharmacy and Pharmacognosy Research 2021: volume 9, issue 5, pages 695 to 703

56. McCarthy K and Avent M. ‘Oral or intravenous antibiotics?’ Australian Prescriber 2020: volume 43, issue 2, pages 45 to 48
57. Wongkamhla T and others. ‘Infectious disease team review using antibiotic switch and discharge criteria shortens the duration of intravenous antibiotic: a single-center cluster-randomized controlled trial in Thailand.’ Open Forum Infectious Disease 2020: volume 7, issue 12, page ofaa539
58. Semenza JC and Giesecke J. ‘Intervening to reduce inequalities in infections in Europe.’ American Journal of Public Health 2008; volume 98, issue 5, pages 787 to 792
59. DHSC (2019). ‘UK 20-year vision for antimicrobial resistance’
60. DHSC (2019). ‘UK 5-year action plan for antimicrobial resistance 2019 to 2024’
61. Allison R and others. ‘Feasibility of a community pharmacy antimicrobial stewardship intervention (PAMSI): an innovative approach to improve patients’ understanding of their antibiotics.’ JAC-Antimicrobial Resistance 2020: volume 2, issue 4, page dlaa089
62. Hayes CV and others. ‘Mixed-method evaluation of a community pharmacy antimicrobial stewardship intervention (PAMSI).’ Healthcare 2022: volume 10, issue 7
63. Ministry of Housing. ‘English indices of deprivation 2019’
64. Hann M and others. ‘Evidence-based health interventions for the educational sector: application and lessons learned from developing European food hygiene and safety teaching resources.’ Food Control 2023: volume 143, page 109,219
65. Ragonnet-Cronin M and others. ‘Genome-first detection of emerging resistance to novel therapeutic agents for SARS-CoV-2.’ bioRxiv 2022: page 2022.07.14.500063
66. Tada T and others. ‘Increased resistance of SARS-CoV-2 Omicron variant to neutralization by vaccine-elicited and therapeutic antibodies.’ eBioMedicine 2022: 78
67. Agency, UHS. (2020) ‘SARS-CoV-2 therapeutics technical briefing 3.’
68. Green A and others. ‘Trends, variation and clinical characteristics of recipients of antivirals and neutralising monoclonal antibodies for non-hospitalised COVID-19: a descriptive cohort study of 23.4 million people.’ In: OpenSAFELY. medRxiv, 2022: page 2022.03.07.22272026
69. HM Government (January 2019). ‘Tackling antimicrobial resistance 2019 to 2024: the UK's 5-year national action plan’
70. Turton JF and others. ‘Wide distribution of *Escherichia coli*-carrying IncF plasmids containing blaNDM-5 and rmtB resistance genes from hospitalized patients in England.’ Journal of Medical Microbiology 2022: volume 71, issue 8, page 001569
71. UKHSA (2022). ‘Quarterly epidemiology commentary: mandatory Gram-negative bacteraemia, MRSA, MSSA and *C. difficile* infections data (up to October to December 2021)’
72. Boonyasiri A and others (2021). ‘Integrated patient network and genomic plasmid analysis reveal a regional, multi-species outbreak of carbapenemase-producing Enterobacterales carrying both blaIMP and mcr-9 genes’
73. Ledda A and others (2022). ‘Hospital outbreak of carbapenem-resistant Enterobacterales associated with a blaOXA-48 plasmid carried mostly by *Escherichia coli* ST399.’ Microbial Genomics volume 8, issue 4, page 000675

74. Borek AJ and others. ‘Implementing interventions to reduce antibiotic use: a qualitative study in high-prescribing practices.’ BMC Primary Care 2021: volume 22, issue 1, pages 1 to 11
75. Borek AJ and others. ‘Development of an intervention to support the implementation of evidence-based strategies for optimising antibiotic prescribing in general practice.’ Implementation Science Communications 2021: volume 2, issue 1, pages 1 to 16
76. Murray CJ and others. ‘Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis.’ The Lancet 2022: volume 399, issue 10,325, pages 629 to 655
77. Spencer DC and others. ‘A fast impedance-based antimicrobial susceptibility test.’ Nature Communications 2020: volume 11, issue 1, pages 1 to 11
78. Shafiq N and others. ‘Shortage of essential antimicrobials: a major challenge to global health security.’ BMJ Global Health 2021: volume 6, issue 11, page e006961
79. Charani E and others. ‘Optimising antimicrobial use in humans: review of current evidence and an interdisciplinary consensus on key priorities for research.’ The Lancet Regional Health 2021: volume 7, page 100,161
80. Lipworth S and others (2020). ‘The mobilome associated with Gram-negative bloodstream infections: a large-scale observational hybrid sequencing based study’

Acknowledgements

An asterix (*) denotes the chapter leads.

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Further acknowledgements

With very many thanks to the ESPAUR Oversight Group for their help in reviewing this report. The authors would also like to extend sincere thanks to Jon White for creating the infographics and Simon Port for formatting and proof-reading the report and related documents.

The authors would like to express their utmost thanks to Professor Alan Johnson, who although retired in March 2019 has helped edit this report and all the previous ESPAUR reports.

This report has been led by Diane Ashiru-Oredope and project managed by Ella Casale, with huge thanks to the support of the ESPAUR Oversight Group Secretariat, Carry Triggs-Hodge.

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Contributors from the Blood Borne Viruses, Blood Safety, Hepatitis, STI and HIV Division at UKHSA, specifically Annastella Costella, Laura Coughlan, Monica Desai, Ruth Simmons.

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About the UK Health Security Agency

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UKHSA is an executive agency, sponsored by the Department of Health and Social Care.

Published: November 2022
Publishing reference: GOV-12239