UK Health Security Agency

English surveillance programme for antimicrobial utilisation and resistance (ESPAUR)

Report 2021 to 2022

Annexe

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Antibacterial resistance

Data on the antibiotic susceptibility of pathogens causing bacteraemia was obtained from SGSS (Second Generation Surveillance System), a national database maintained by UK Health Security Agency (UKHSA) that contains laboratory data supplied electronically by approximately 98% of hospital microbiology laboratories in England. SGSS comprises 2 modules, a communicable disease reporting (CDR; formerly CoSurv/LabBase2) module and an antimicrobial resistance (AMR; formerly AmSurv) module. The CDR module includes antimicrobial susceptibility test results for bloodstream isolates of the key pathogens being monitored as part of the UK 5-year AMR Strategy, although any test results suppressed from clinical reports by the sending laboratories are not captured when the data is submitted. In contrast, the AMR module contains more comprehensive antibiogram information as it includes results for all antibiotics tested (including results suppressed from clinical reports) for isolates from all clinical sources. For trends included within this report, resistance data is taken from the AMR module.

In previous ESPAUR reports, hospital microbiology laboratories have reported antimicrobial susceptibility test results as ‘susceptible’, ‘intermediate’ or ‘resistant’. These categories were defined as follows:

1. Susceptible: a bacterial strain is said to be susceptible to a given antibiotic when its growth is inhibited in vitro by a concentration of the drug that is associated with a high likelihood of therapeutic success.
2. Intermediate: a bacterial strain is said to be intermediate when the concentration of antibiotic required to inhibit its growth in vitro is associated with an uncertain therapeutic outcome at standard antibiotic doses. It implies that an infection due to the isolate may be appropriately treated in body sites where the antibiotic is physically concentrated or when a high dosage of drug can be used.
3. Resistant: a bacterial strain is said to be resistant to a given antibiotic when the concentration required to inhibit its growth in vitro is associated with a high likelihood of therapeutic failure.

The breakpoint criteria for categorising clinical isolates as susceptible, intermediate or resistant to individual antibiotics have changed over time. As noted in the ESPAUR report 2019, in 2019 the EUCAST definitions were amended to rename the ‘intermediate’ category to ‘susceptible, increased exposure’ (with an adjusted increased dose), as the antibiotic should still work for treatment. The definition changes cannot be retrospectively applied.

As patients may have more than one positive blood culture taken, blood cultures taken from the same patient that yielded growth of the same pathogen during a rolling 14-day period from the initial positive blood culture were regarded as comprising the same episode of infection and were de-duplicated, retaining the worst-case scenario susceptibility result for each antibiotic tested (resistant > intermediate > susceptible).

Antibiotic groupings used in the bloodstream infection (BSI) antimicrobial susceptibility analyses within the report are:

- third-generation cephalosporins comprised cefotaxime, ceftazidime, cefpodoxime and ceftriaxone, unless otherwise indicated
- carbapenems comprised meropenem or imipenem, except where neither were tested, in which cases results for ertapenem were used if available; the exception was for *Pseudomonas* spp. where ertapenem was excluded
- the only aminoglycoside included was gentamicin
- fluoroquinolones are ciprofloxacin, unless otherwise defined
- glycopeptides comprised vancomycin and/or teicoplanin
- colistin included results recorded as polymyxin

Data on the incidence of *Escherichia coli* and *Staphylococcus aureus* bacteraemia was from the national mandatory surveillance schemes while data on the incidence of other pathogens was derived from cases reported to the AMR module of SGSS. As the latter data was provided on a voluntary basis, case ascertainment will have been incomplete.

Data on additional bacterial pathogens causing hospital BSI in England can be found in Chapter 2 data tables.

Incidence trends, age and sex distributions are presented based on SGSS CDR module data, and antibiotic resistance trends are presented based on SGSS AMR module data. This data continue the series previously published in separate annual voluntary surveillance bacteraemia reports (published in the Health Protection Report series) and include *Serratia* spp., *Enterobacter* spp., *Citrobacter* spp., *Morganella* spp., *Providencia* spp., *Proteus* spp., *Strenophomonas* spp., *Pseudomonas* spp. and Polymicrobial BSIs. For these pathogens, trends in incidence, susceptibility testing results to key antibiotics (for the period 2017 to 2021), and in some cases, age and sex breakdowns in BSI in England are available (2021 data only) are presented.

Invasive group A streptococcal disease is notifiable in England and Wales under the Health Protection (Notification) Regulations 2010. Records of invasive group A streptococcal (GAS) based on isolates submitted to the UKHSA Antimicrobial Resistance and Hospital Associated Infections Reference Unit (AMRHAI, Colindale) were merged with SGSS laboratory reports (services have moved from the Respiratory and Vaccine Preventable Bacteria Reference Unit;

RVPBRU). In this report, invasive specimens are defined as isolates from a normally sterile site, and include blood, cerebral-spinal fluid (CSF), bone, joint, brain and pleural fluid specimens.

Limitations and caveats

In England, the mandatory surveillance scheme for *E. coli* bacteraemia does not include susceptibility testing data, which is collected through a parallel voluntary laboratory reporting system. Comparison of the incidence reported between the 2 systems indicated that the ascertainment achieved in the laboratory reporting system was 84% in 2021 (81% in 2020; Annexe Table 2.1) and varied by local geography across the country (ranging between 79% and 96%; Annexe Table 2.2).

Annexe Table 2.1. Ascertainment factor applied to estimate total number of resistant bloodstream infections

Year	Mandatory *E. coli* bacteraemia reports	SGSS AMR *E. coli* bacteraemia reports	% ascertainment	Ascertainment factor
2017	41,333	35,631	86%	1.160
2018	42,557	36,686	86%	1.160
2019	43,715	37,996	87%	1.151
2020	37,823	31,012	82%	1.220
2021	37,889	31,838	84%	1.190

Annexe Table 2.2. Regional ascertainment factor applied to estimate total number of resistant bloodstream infections (2021)

Region	Mandatory *E. coli* bacteraemia reports	SGSS AMR *E. coli* bacteraemia reports	% ascertainment	Ascertainment factor
London	4,731	3,765	80%	1.257
West Midlands	3,958	3,622	92%	1.093
East Midlands	3,309	3,162	96%	1.046
East of England	4,124	3,635	88%	1.135
North East	2,275	1,796	79%	1.267
Yorkshire and Humber	4,212	3,422	81%	1.231
North West	5,243	4,232	81%	1.239
South West	3,884	3,297	85%	1.178
South East	6,115	5,036	82%	1.214

Since April 2017 reporting of bacteraemia caused by *Klebsiella* spp. and *Pseudomonas aeruginosa* is also mandatory. Initial reviews of ascertainment between the mandatory and voluntary surveillance schemes for each pathogen were assessed for 2021 as 83% (*Klebsiella* spp.) and 85%, for *P. aeruginosa*.

Rapid molecular techniques are used to identify the mecA gene (meticillin-resistant *S. aureus* (MRSA) indicator) avoiding the requirement to undertake susceptibility testing for isoxazolylpenicillins (such as oxacillin). This information is not captured in the SGSS data. Figure 2.1 and Figure 2.11 in the report present the mandatory surveillance results for MRSA bacteraemia which represents a more accurate burden of MRSA in England. Whereas Figure 2.12 (resistance differences between MRSA and meticillin-susceptible *S. aureus* (MSSA)) is using SGSS AMR data. The ascertainment of *S. aureus* reports in SGSS AMR compared with the mandatory surveillance indicates 82% cases (79% MRSA and 76% MSSA) are reported. In the absence of European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints, daptomycin Minimum Inhibitory Concentrations (MICs) for enterococci were interpreted using ecological cut-offs (ECOFFs).

Estimating the burden of antibiotic-resistant bloodstream infections

Data used to update the key bug and drug summaries in the ESPAUR report was utilised to generate a preliminary estimated burden of resistant bacteraemia in England. The total number of resistant infections is generated by calculating the proportion of each pathogen that were reported as resistant to one or more specific antibiotics and ensuring that that infection report is not counted in any subsequent antibiotic combinations to avoid double counting. A full list of pathogen and antibiotic combinations, including the reduced number of drug and bug combinations used within the National Action Plan (NAP) AMR burden monitoring, is shown in Annexe Table 2.3.

For each year, the ascertainment level of cases of *E. coli* bacteraemia reported on a voluntary basis to the AMR module of SGSS was estimated by comparison with mandatory surveillance reports (Annexe Table 2.1). This value was then applied to the other pathogens under surveillance to estimate the total number of BSIs for each pathogen each year (except for *S. aureus,* where the mandatory surveillance totals for both MRSA and MSSA were used). The same method with region-specific numbers was used to calculate the regional AMR burden (regional numbers and ascertainment factors are listed in the data tables accompanying the report.

Annexe Table 2.3. Bacteria and antibiotic resistance categories included in the AMR burden analysis within the ESPAUR report; ESPAUR BSI AMR burden combinations and National Action Plan (NAP) estimate combinations

Bacteria	Antibiotic resistance	ESPAUR BSI AMR burden	NAP estimate AMR burden
Escherichia coli	Carbapenem-resistant	✓	✓
	Third-generation cephalosporin-resistant (excluding isolates also resistant to carbapenems)	✓	✓
	Aminoglycoside-resistant (excluding isolates also resistant to carbapenem and/or third-generation cephalosporin)	✓	
	Fluoroquinolone-resistant (excluding isolates also resistant to carbapenem and/or third-generation cephalosporin and/or aminoglycoside)	✓	
Klebsiella pneumoniae	Carbapenem-resistant	✓	✓
	Third-generation cephalosporin-resistant (excluding isolates also resistant to carbapenem)	✓	✓
	Aminoglycoside-resistant (excluding isolates also resistant to carbapenem and/or third-generation cephalosporin)	✓	
	Fluoroquinolone-resistant (excluding isolates also resistant to carbapenem and/or third-generation cephalosporin and/or aminoglycoside)	✓	
Klebsiella oxytoca	Carbapenem-resistant	✓	
	Third-generation cephalosporin-resistant (excluding isolates also resistant to carbapenem)	✓	

Bacteria	Antibiotic resistance	ESPAUR BSI AMR burden	NAP estimate AMR burden
	Aminoglycoside-resistant (excluding isolates also resistant to carbapenem and/or third-generation cephalosporin)	✓	
	Fluoroquinolone-resistant (excluding isolates also resistant to carbapenem and/or third-generation cephalosporin and/or aminoglycoside)	✓	
Acinetobacter spp.	Carbapenem-resistant	✓	✓
	Aminoglycoside- and fluoroquinolone-resistant (excluding isolates also resistant to carbapenem)	✓	✓
Pseudomonas spp.	Carbapenem-resistant	✓	✓
	Resistant to 3 or more antimicrobial groups (excluding isolates also resistant to carbapenem)	✓	✓
Enterococcus spp.	Glycopeptide-resistant	✓	✓
Staphylococcus aureus	Methicillin-resistant	✓	✓
Streptococcus pneumoniae	Penicillin- and macrolide-resistant (excluding isolates only resistant to penicillin)	✓	✓
	Penicillin-resistant (excluding isolates also resistant to macrolides)	✓	✓

Acquired carbapenemase-producing Gram-negative bacteria

Data on confirmed acquired carbapenemase-producing Gram-negative bacteria was obtained from both the Antimicrobial Resistance and Healthcare-Associated Infections (AMRHAI) Reference Unit and from the Antimicrobial Resistance (AMR) module of SGSS (see the Antibacterial resistance methods section for details).

As patients may have more than one positive specimen taken, specimens taken from the same patient that yielded growth of the same pathogen and carbapenem resistance mechanism within a 52-week period from the initial positive specimen were regarded as comprising the same episode of infection and were de-duplicated. Acquired carbapenemase-producing Gram-negative bacteria positive referred isolates and local laboratory isolates were combined for this de-duplication process, with resistance mechanism results from the AMRHAI Reference Unit retained preferentially where patient specimen overlap occurred. A summary of the distribution of the carbapenemase families covered by the AMRHAI Reference Unit (including those outside the ‘big 5’ families) is presented in Annexe Table 2.4, below. The local laboratory data presented only includes results from the 'big 5' carbapenemase families.

UKHSA strongly recommends that all diagnostic laboratories should be able to detect the 4 carbapenemase families in bold (the ‘big 4’). The following table uses these symbols: ¥ = combinations of mechanism and species would not be considered as exceptional results. A = intrinsic to *A. baumannii* and only expressed when associated with an insertion element; B = almost exclusively reported in *Enterobacter* spp. with less than a handful of reports in other genera; C = reported only in *Serratia marcescens*.

Where an 'exceptional' carbapenemase and species combination result (cells without a ¥ symbol in Annexe Table 2.4) has been identified, isolates are requested to be sent to AMRHAI Reference Unit for confirmation.

Annexe Table 2.4. Distribution of carbapenemase genes covered by AMRHAI Reference Unit molecular assay (based on AMRHAI data)

Carbapenemase family	Associated with common ‘host’ organism		
	Enterobacterales	***Pseudomonas* spp.**	***Acinetobacter* spp.**
KPC	¥	<10	<10
OXA-48-like	¥	<10	0
NDM	¥	¥	¥
VIM	¥	¥	<10
IMP	¥	¥	¥
IMI/NMC-A	B	0	0
GES	¥	¥	0
FRI	<10	0	0

Carbapenemase family	Associated with common 'host' organism		
	Enterobacterales	*Pseudomonas* spp.	*Acinetobacter* spp.
SME	<10[C]¥	0	0
DIM	0	<10	0
GIM	<10	0	0
SIM	0	<10	0
SPM	0	<10	0
OXA-23-like	0	0	¥
OXA-40-like	0	0	¥
OXA-51-like[A]	0	0	¥
OXA-58-like	0	0	¥

Quarterly mandatory laboratory returns data

National Health Service (NHS) acute trusts are required to complete quarterly mandatory laboratory returns (QMLR) for the 'total number of faecal specimens and rectal swabs taken for carbapenemase-producing Enterobacterales (CPE) screening' to the Healthcare-Associated Infections (HCAI) Data Capture System (DCS).

Reporting of quarterly totals of rectal swabs and faecal specimens taken for CPE screening was added to the mandatory quarterly laboratory returns section of the HCAI DCS in October 2019 but became mandatory in October 2020. (This was notified to all acute trusts through the HCAI DCS information cascade system in October 2020).

Trust-level CPE screening QMLR data was extracted from the HCAI-DCS on 22 April 2022. Acute trust codes were linked to the Estate Returns Information Collection (ERIC) data for 2019 to 2020 to establish acute trust type. A full list of QMLR CPE screening totals for the January to December 2021 period are included by acute trust by region in Annexe Table 2.5, below, and by acute trust in the data tables accompanying the report.

Annexe Table 2.5 QMLR returns for the total number of rectal swabs and faecal screening specimens taken for CPE screening by region*, England, 2021

	Number of trusts				Total screens reported	
Region	Submitted screens*	Submitted zero screens	Did not submit screens	Submitted data for all 4 quarters (%)	Number	%
East of England	10	0	4	10 (71)	15,184	4.9
East Midlands	6	0	2	4 (50)	38,536	12.4

	Number of trusts				Total screens reported	
Region	**Submitted screens***	**Submitted zero screens**	**Did not submit screens**	**Submitted data for all 4 quarters (%)**	**Number**	**%**
London	20	1	2	12 (55)	98,009	31.6
North East	6	0	1	4 (57)	4,609	1.5
North West	22	0	3	17 (68)	55,566	17.9
South East	18	1	0	14 (78)	24,087	7.8
South West	15	0	0	9 (60)	8,353	2.7
West Midlands	13	2	2	11 (73)	54,864	17.7
Yorkshire and Humber	11	0	3	6 (43)	12,211	3.9
Total	**121**	**4**	**17**	**87 (63)**	**310,411**	**100.0**

* For at least one calendar quarter during 2021.

The total number of screens reported for the first mandatory quarter was reported in the last ESPAUR report 2020 to 2021.

Notification data

Following the inclusion of carbapenemase screening in the notification schedule, a mechanism to combine reference laboratory referrals with local laboratory-confirmed carbapenemases was implemented. Data presented in the Antimicrobial resistance chapter in the main ESPAUR report includes analyses on counts of combined clinical infection and routine screening samples reported by laboratories using the recommended molecular or immunochromatographic methods to both SGSS and the AMRHAI Reference Unit. This differs slightly from the weekly case totals included within the causative agents of notified diseases reports which currently only include local laboratory reports.

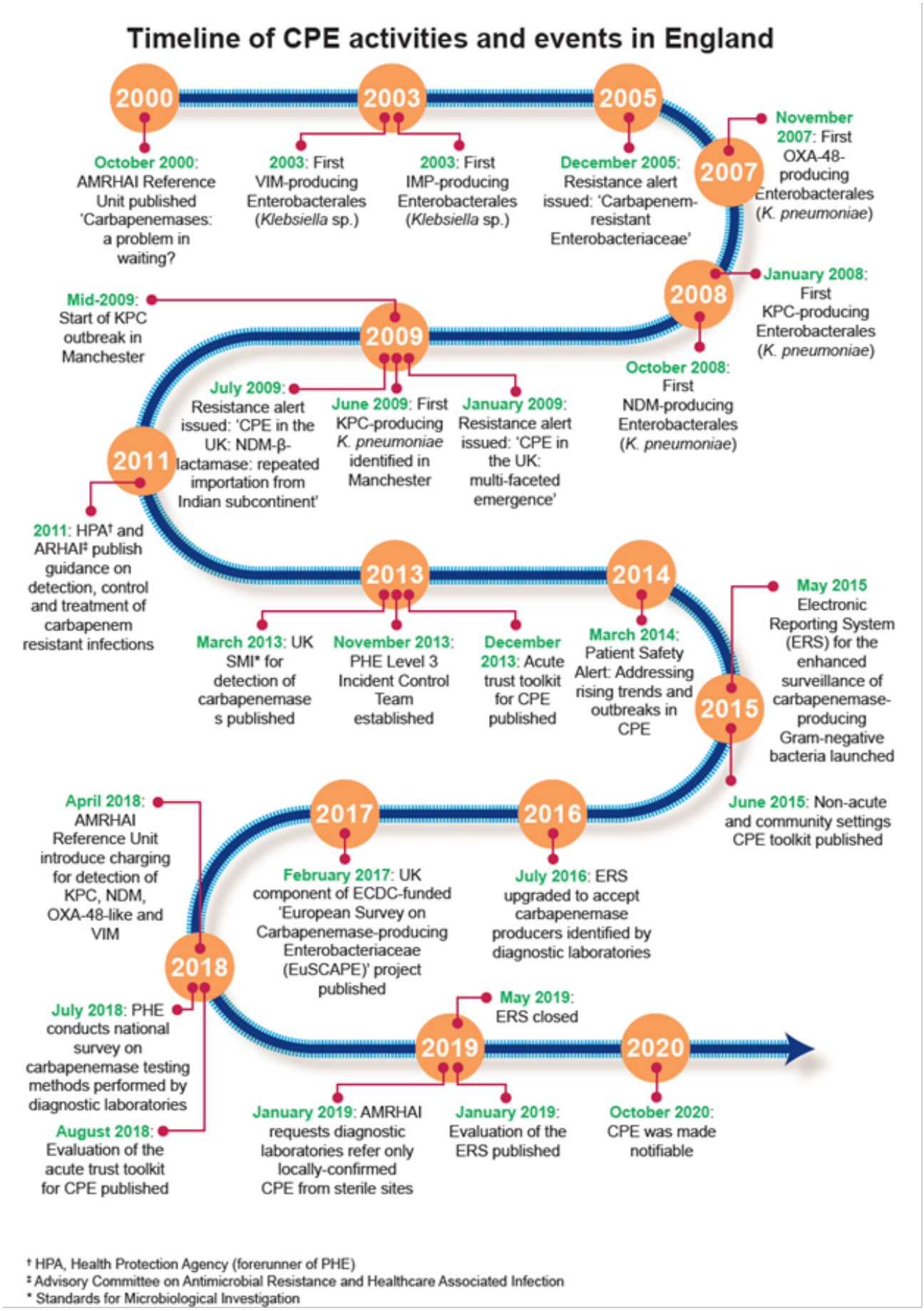
For the purpose of the ESPAUR report and for the notification data, specimen reports of a positive carbapenemase-producing Gram-negative bacteria fall into 3 specimen type categories: ‘invasive’, ‘screening’ and ‘everything else’. A full list of the specimen types and how they are grouped is available in the data tables accompanying this report, but at a high level:

- invasive group specimens include: blood, CSF and bone and joint specimens
- screening group specimens include: faecal, rectal swab, skin swab specimen
- the other specimens include: urine, respiratory, catheter and lowe genital tract specimens

Timeline of CPE activities

The Antimicrobial Resistance and Healthcare Associated Infections (AMRHAI) Reference Unit within UKHSA received and confirmed an increasing number of carbapenemase-producing Gram-negative bacteria year-on-year since 2006. Amongst Enterobacterales sent for referral in 2006, 4 were identified as carbapenemase producers compared to more than 4,000 identified in 2018. In response to the observed increase, UKHSA (then Public Health England (PHE)) established an incident control team in 2013 and implemented a number of initiatives aimed at preventing and controlling the spread of CPE (Annexe Figure 2.1. An accessible text version of the figure is available below it).

Annexe Figure 2.1 Timeline of CPE activities and events in England



Text alternative to Annexe Figure 2.1

The timeline of CPE activities included:

- October 2000: AMRHAI Reference Unit published 'Carbapenemases: a problem in waiting?'
- 2003: First VIM-producing Enterobacterales (*Klebsiella* sp.)
- 2003: First IMP-producing Enterobacterales (*Klebsiella* sp.)
- December 2005: Resistance alert issued: 'Carbapenem-resistant Enterobacteriaceae'
- November 2007: First OXA-48-producing Enterobacterales (*K. pneumoniae*)
- January 2008: First KPC-producing Enterobacterales (*K. pneumoniae*)
- October 2008: First NDM-producing Enterobacterales (*K. pneumoniae*)
- January 2009: Resistance alert issued: 'CPE in the UK: multi-faceted emergence'
- June 2009: First KPC-producing *K. pneumoniae* identified in Manchester
- July 2009: Resistance alert issued: 'CPE in the UK: NDM-β-lactamase: repeated importation from Indian subcontinent'
- mid-2009: Start of KPC outbreak in Manchester
- 2011: The Health Protection Agency (HPA; forerunner to PHE) and the Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection (ARHAI) publish guidance on detection, control and treatment of carbapenem resistant infections
- March 2013: UK Standard for Microbiological Investigation (SMI) for detection of carbapenemases published
- November 2013: PHE Level 3 Incident Control Team established
- December 2013: Acute trust toolkit for CPE published
- March 2014: Patient Safety Alert: Addressing rising trends and outbreaks in CPE
- May 2015 Electronic Reporting System (ERS) for the enhanced surveillance of carbapenemase-producing Gram-negative bacteria launched
- June 2015: Non-acute and community settings CPE toolkit published
- July 2016: ERS upgraded to accept carbapenemase producers identified by diagnostic laboratories
- February 2017: UK component of ECDC-funded 'European Survey on Carbapenemase-producing Enterobacteriaceae (EuSCAPE)' project published
- April 2018: AMRHAI Reference Unit introduce charging for detection of KPC, NDM, OXA-48-like and VIM
- July 2018: PHE conducts national survey on carbapenemase testing methods performed by diagnostic laboratories
- August 2018: Evaluation of the acute trust toolkit for CPE published
- January 2019: AMRHAI requests diagnostic laboratories refer only locally-confirmed CPE from sterile sites
- January 2019: Evaluation of the ERS published
- 1 May 2019: ESR closed
- 1 October 2020: CPE was made notifiable

Critical antibiotic resistance in foodborne bacteria

Surveillance of antibiotic resistance in foodborne bacteria is undertaken by the UKHSA Gastrointestinal Bacterial Reference Unit. Antibiotic resistance data for referred samples in England is derived through whole genome sequencing (WGS), identifying genes that confer resistance. The antimicrobial resistance determinants were predicted using a validated bioinformatics tool 'Genefinder'.

Sexually transmitted infections

Surveillance of antibiotic resistance in *Neisseria gonorrhoeae* is monitored through the Gonococcal Resistance to Antimicrobials Surveillance Programme (GRASP), which comprises a suite of surveillance systems to detect and monitor AMR in *N. gonorrhoeae* and to record potential treatment failures. Trend data is derived from the national sentinel surveillance system, which collects gonococcal isolates from consecutive patients attending a network of 27 participating sexual health services (SHSs) (25 in England, 2 in Wales) and their 21 associated laboratories over a 2 to 3 month period each year. Gonococcal isolates are referred to the UKHSA AMR in Sexually Transmitted Infections (AMRSTI) national reference laboratory for antimicrobial susceptibility testing and the results are linked to patient demographic, clinical and behavioural data for analysis of antimicrobial susceptibility trends in patient sub-groups.

Tuberculosis

Data for AMR in tuberculosis data for 2000 to 2021 was extracted from the Enhanced Tuberculosis Surveillance system (ETS). More detail on the methods and data sources are described in the Tuberculosis in England annual report.

Antifungal resistance

Routine surveillance

Data on the laboratory reports of *Candida* spp. from 2017 to 2021 was obtained from UKHSA's SGSS, as described in the Antibacterial resistance section of Chapter 2. The SGSS CDR module was used to obtain incidence trends of candidaemia and the species distribution of *Candida* spp., the SGSS AMR module data was used for assessing the antifungal susceptibility.

As reported in last years report, several taxonomic revisions to species previously classified in *Candida* have been implemented in the period covered by this report. Two species, formerly *C. kruseii* and *C. lusitaniae*, have been reclassified as *Pichia kudriavzveii* and *Clavispora lusitaniae* respectively in SGSS. As they are now no longer reported in the Candida genus, these 2 species have been excluded from contributing to the totals. This may mean rates of candidaemia and species incidence reported may not reflect what has been reported prior to 2020. A full list of species causing fungaemia (fungal bloodstream infections) identified from SGSS CDR module can be found as part of the monomicrobial and polymicrobial data tables included in the Chapter 3 data tables accompanying this report.

In previous ESPAUR reports, hospital microbiology laboratories antifungal susceptibility test results were grouped into 'reduced-susceptibility'. For the purpose of this report, antifungal susceptibility test results reported as ‘susceptible’, ‘intermediate’ or ‘resistant’, as determined locally, are presented alongside a proportion that are resistant.

The breakpoint criteria for categorising clinical isolates as susceptible, intermediate or resistant to individual antifungals have changed over time, the classification presented is the same as at the time of the specimen and has not subsequently been adjusted.

Antifungal resistance for *Candida* species will focus on 3 key antifungal drugs (amphotericin B, caspofungin and fluconazole). These drugs are focussed on as they represent 3 different classes of antifungal drug and are the most frequently tested for and used.

As patients may have more than one positive blood culture taken, blood cultures taken from the same patient that yielded growth of the same pathogen during a rolling 14-day period from the initial positive blood culture were regarded as comprising the same episode of infection and were de-duplicated.

Reference laboratory surveillance

Perspective from the National Mycology Reference Laboratory

The UKHSA National Mycology Reference Laboratory (MRL) receives referred samples of fungal isolates from NHS trusts, regional mycology reference centres and private microbiology laboratories throughout the UK. In addition, the MRL provides a primary diagnostic service for local laboratories. Samples are received for superficial, subcutaneous, deep-seated and disseminated fungal infections. Patient groups include those with dermatophytosis, chronic obstructive pulmonary disease (COPD) and cystic fibrosis, intensive care unit (ICU) patients and haematology and oncology patients including those who have received solid organ, stem cell and bone marrow transplants. The MRL is the UK coordinating centre for fungal outbreaks.

Since 2019, the MRL has received 31 isolates of *Mucor circinelloides* from clinical samples, *Mucor circinelloides* is a multi-drug-resistant, rapidly invasive mould affecting patients with compromised immunity, uncontrolled diabetes or trauma and associated with high mortality.

Most mucoraceous mould infections spread by invasion of blood vessels into contiguous tissues, it is extremely rare for them to undergo haematogenous dissemination. However, in several cases haematogneous dissemination has been noted. Small infectious propagules, termed oidia, are produced *in vivo*, which can disseminate through the bloodstream, causing infection at remote sites. Production of oidia *in vivo* is rare in the Mucorales and not encountered in most other pathogenic genra. Susceptibility is assessed by application of breakpoints derived for *Aspergillus fumigatus* and isolates of *M. circinelloides* are susceptible to amphotericin B (susceptibility breakpoint 1.0mg/L) but are resistant to the echinocandins and often resistant to the mucoraceous-mould-active azole agents isavuconazole (susceptibility breakpoint 1.0mg/L) and posaconazole (susceptibility breakpoint 0.25mg/L).

The MRL has detected 16 cases of *Alternaria* in humans since 2016. These can present as cutaneous lesions of the limbs, usually in solid organ transplant recipients, and keratitis. *Alternaria species are* often resistant to voriconazole which would be the treatment of choice for most cases of phaeohyphomycosis, so for treatment of subcutaneous cysts caused by *Alternaria,* itraconazole is the preferred option (1). The treatment for keratitis would be topical natamycin.

The UK has also seen the emergence of a terbinafine-resistant dermatophyte within the *Trichophyton mentagrophytes / interdigitale* group, now named as *Trichophyton indotineae*.

Initially report in India, but now spreading to many other countries, it can cause aggressive and recalcitrant groin infections (*tinea cruris*) in particular, although infection can be more widespread. Since 2019, more than 40 terbinafine-resistant clinical isolates of dermatophytes within this group have been identified in the UK, predominantly in the London area, which are either proven or suspected to be *T. indotineae*.

Perspective from the Mycology Reference Centre, Manchester

The NHS Mycology Reference Centre Manchester (MRCM) offers a highly specialised diagnostic service primarily serving Manchester, north of England and Scotland but also receives daily referrals from throughout the UK and beyond. The MRCM also works in partnership with the National Aspergillosis Centre (NAC) and other hospitals to provide laboratory services predominantly for chronic pulmonary aspergillosis patients situated throughout the UK and is an integral component of the Manchester Fungal Infection Network which includes the NAC and the Manchester Fungal Infection Group. Laboratory services are also regularly provided for samples from patients following solid organ transplant, those with fungal asthma, COPD or cystic fibrosis, as well as those on extracorporeal membrane oxygenation (ECMO).

In 2021, 6,518 yeast and mould isolates were processed for standard antifungal susceptibility testing at the MRCM laboratory following the EUCAST standard (4,178 in 2020). In addition, the laboratory tested >150 mould and yeast isolates for Ibrexafungerp susceptibility as part of patient screening for the Phase 3 clinical trial).

MRCM recorded decreased fluconazole susceptibility in *Candida* species, with 86% of *C. albicans* being susceptible in 2020 compared with 84% in 2021, and 97% of *C. parapsilosis* in 2020 vs 95% in 2021. Additionally, more *C. parapsilosis* isolates were reported as intermediate to echinocandins rather than resistant (micafungin 94% intermediate in 2021 versus 80% in 2020). With the recent EUCAST update of 'intermediate' to 'susceptible, increased exposure', this will have an impact on the use and dosing of echinocandins (2).

Reports have emerged that agricultural use of antifungals may be helping to drive antifungal resistance. Mechanisms of resistance in agricultural environments lead to cross-resistance to clinical azoles in isolates from patients, and patient isolates have also been shown to be

resistant to non-azole fungicides only used in farming, suggesting the *A. fumigatus* strains had been in these agricultural environments before infecting the patients (3, 4, 5).

Antifungal susceptibility profiles of *Aspergillus* spp. strains tested at the MRCM during 2021 have stayed similar with previous years. Although, of note the trend of decreasing azole susceptibility continued, with 86% of *A. fumigatus* being susceptible to voriconazole in 2020 compared with 83% in 2021 (6). Similarly in 2020, 98% of *A. fumigatus* isolates were susceptible to amphotericin B but this decreased to 95% in 2021. A spectrum of cryptic species of *A. fumigatus* isolated from patients with chronic and allergic aspergillosis, continues to be recorded (7). In addition, there seems to be more cases of invasive infections caused by non-fumigatus *Aspergillus*, including resistant strains. These appear to be small numbers, but this is being closely monitored.

Antiviral resistance

The methods for resistance data in influenza virus are further described in the weekly national flu reports and flu annual report. The winter season is defined as week 40 (approximately the first week of October in a calendar year) to week 20 the following year (mid-May of a calendar year).

Influenza virus

UKHSA screens Influenza positive samples for mutations in the virus neuraminidase (NA) and the cap-dependent endonuclease (PA) genes, which are known to confer neuraminidase inhibitor or baloxavir resistance, respectively. The samples are primarily obtained for surveillance; however, diagnostic testing is also performed on patient samples with a suspected antiviral-resistant strain.

Influenza virus susceptibility to the neuraminidase inhibitor class of antivirals has been monitored routinely in the UK since 2005 using a combination of phenotypic and genotypic testing. Whole genome sequencing of influenza virus positive clinical samples allows screening of the neuraminidase for known amino acid substitutions that cause resistance to neuraminidase inhibitors. Viruses with novel neuraminidase amino acid substitutions in enzymatic or structurally significant sites are flagged for phenotypic assessment.

Following whole genome sequencing, a subset of viruses are selected for virus isolation, based on sequence features. Isolates are then tested in a neuraminidase enzyme inhibition assay to determine the phenotypic susceptibility to oseltamivir and zanamivir. Results are reported in the weekly national flu reports during the active influenza season and summarised in the flu annual report for each flu season.

The 2021 to 2022 winter season data (presented within this year's annual flu report) will also provide baseline data in support of future antiviral and vaccine surveillance activities.

Human immunodeficiency virus (HIV)

The detection of HIV resistance in drug-naïve people indicates the transmission of drug-resistant variants, an important occurrence which limits first-line regimen options. Tracking drug resistance in the treatment-experienced population provides an insight into the causes of treatment failure. The prevalence of drug resistance mutations in the UK was tracked from 2001 to 2016 in both drug-naïve and treatment-experienced people with HIV by the UK National HIV Drug Resistance Database (DRD), which received results of resistance tests performed as part of routine care from 15 participating virology laboratories. The last available UK HIV DRD data is from 2016 and support from the Medical Research Council ended in 2020.

More recent data is available from the UKHSA's Antiviral Unit (AVU). Within national HIV surveillance programs, samples from individuals with newly-diagnosed HIV-1 are routinely submitted to UKHSA for recency testing as part of the Recent Infection Testing Algorithm (RITA).

Hepatitis C virus (HCV)

Recommended first line combinations in the UK usually contain an NS5A inhibitor with either an NS5B polymerase inhibitor or NS3 protease inhibitor. Two antiviral combinations are available with activity against almost all viral strains common in the UK, sofosbuvir-velpatasvir and glecaprevir-pibrentasvir. The success of direct-acting antiviral (DAA) drug roll-out underpins the UK's commitment to WHO HCV elimination targets.

Testing for HCV drug resistance is not universally recommended prior to initiating DAA therapy, as there is no or minimal impact of resistance on cure rates in DAA-naïve individuals in many scenarios. The European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) have produced guidelines on particular scenarios when resistance testing may be considered or recommended. There is currently no role for phenotypic resistance testing in clinical management, as this is costly, laborious and available only within research contexts.

There is no national database of HCV resistance in the UK. However, the UKHSA AVU provides a HCV genotyping and resistance testing service for the NHS and receives approximately 1,500 samples per year. Prior to 2019, resistance testing was available for HCV subtype 1a only.

Subsequently, testing has been performed with whole genome sequencing, which identifies the viral genotype and subtype, as well as the resistance profile of the NS3, NS5A and NS5B genes, in a single test. The data used in this report only includes subtype 1a NS5A samples from years 2016 to 2021, as prior to 2019 it was the only genotype with available data.

Herpes simplex virus (HSV)

The UKHSA AVU is the only laboratory in the UK offering a phenotypic drug susceptibility testing service for HSV. Through this service, the AVU has generated an archive of hundreds of

phenotypically characterised clinical isolates over the past 12 years. Recently the archive has been sequenced and together with previously published data, this led to the development of a genotype-to-phenotype database called herPHEgen®. The database contains approximately 10% novel resistance-associated mutations and polymorphisms and this number continues to grow. This has proven to be an invaluable tool that has enabled us to offer a much faster antiviral resistance testing service to the NHS.

Hepatitis B virus (HBV)

Current protocols used in the Blood Borne Virus Unit (BBVU), UKHSA Colindale laboratory rely on amplification and sequencing of the HBV polymerase region between domains A to E which cover the identification of described antiviral resistant mutations. Due to HBV genome organisation, analysis of the overlapping envelope region allows for the concurrent assignment of the HBV genotype. Programmes of HBV virus characterisation are broad and run in parallel and will include analysis for antiviral resistance.

Additional data sources

Population data used in the chapter was taken from the Office for National Statistics annual Mid-year population estimates published data for the corresponding geographic region and year. Geographies were assigned to infection episodes based on patient postcode where available, where not available the reporting laboratory postcode was used. The postcodes were then assigned to regions and presented at this level.

A SPINE trace was performed on records of patient episodes to identify those with reported 30-day all-cause mortality. Case fatality rates were calculated at 30 days in line with the 30-day all-cause fatality subsequent to MRSA, MSSA and Gram-negative bacteraemia and *C. difficile*, 2020 to 2021 report protocol.

The index of multiple deprivation (IMD) is a way of summarising how deprived people are within an area, based on a set of factors that includes their levels of income, employment, education and local levels of crime. Episodes were linked to IMD using patient postcode (and GP or laboratory postcode where patient postcode was unavailable) and the IMD decile score was identified by the lower super output area the patient resided in.

The Office for Health Improvements and Dispartities developed a method for assigning ethnic group based on hospital admissions data. As different ethnicities may be recorded in different treatment episodes, the method selected a single ethnic group from a patient's HES records. Episodes were linked to ethnic group using patient NHS number and date of birth.

Statistical analyses

P values were calculated to assess the change in resistance over time, these were generated using an unadjusted binomial regression model for each drug and bug combination. A significant change is defined by a p value less than 0.05 ($p<0.05$).

Trends in incidence and resistance are shown at national, regional and IMD decile level for England. Incidence rates are calculated per 100,000 population per year using the mid-year populations.

Binomial confidence intervals were calculated to 95% for the percentage resistance for the ethnic group analysis.

Analyses were completed using Stata v15 and v17 (StataCorp).

AMR resources

This will group together the locations and names of other AMR-relevant publications that UKHSA and others produce to help people know that there is more information available, including:

- quarterly reports on acquired carbapenemase-producing Gram-negative bacteria identified in human samples in England
- notifications of infectious diseases (NOIDs)
- *Escherichia coli* (*E. coli*): guidance, data and analysis
- *Pseudomonas aeruginosa*: guidance, data and analysis
- Klebsiella species: guidance, data and analysis
- *Clostridium difficile*: guidance, data and analysis
- *Staphylococcus aureus*: guidance, data and analysis
- MRSA, MSSA, Gram-negative and CDI quarterly report (official statistics)
- MRSA, MSSA, Gram-negative bacteraemia and CDI; independent sector (annual official statistics)
- pyogenic and non-pyogenic streptococcal bacteraemia annual data from voluntary surveillance
- group A streptococcal infections activity during the 2021 to 2022 season
- Fingertips public health UKHSA data: AMR local indicators
- UK One Health Report: antibiotic use and antibiotic resistance in animals and humans
- EARS-Net (European Antimicrobial Resistance Surveillance Network) data
- Central Asian and European Surveillance of of Antimicrobial Resistance (CAESAR) data
- GLASS (Global Antimicrobial Resistance and Use Surveillance System) AMR routine data surveillance

- podcast: Infection Control Matters on Apple Podcasts
- the European Union Summary Report on Antimicrobial Resistance in zoonotic and indicator bacteria from humans, animals and food in 2019 to 2020
- Tuberculosis in England: national quarterly reports
- National flu and COVID-19 surveillance reports: 2021 to 2022 season

Supplementary analyses

Antifungal resistance

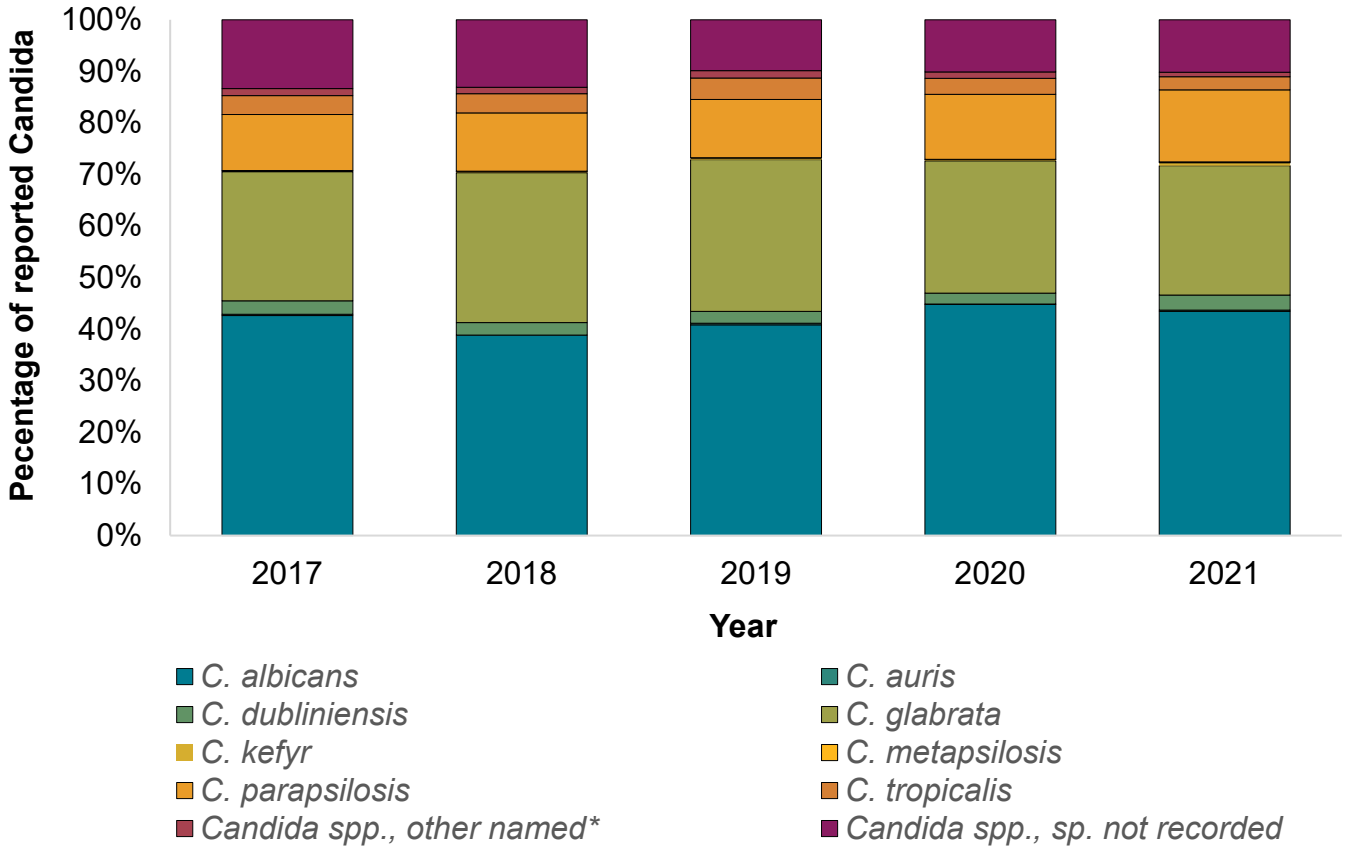
Incidence of candidaemia by region, and species frequency

Regionally, variation in incidence of candidaemia can be seen. The region with the highest rate of candidaemia in 2021 was the East Midlands (4.4 per 100,000 population), closely followed by East of England (4.3 per 100,000 population). The lowest recorded rate continued to be in Yorkshire and Humber (2.2 per 100,000 population), as it has been for the past 5 years. Further regional data for incidence from 2017 to 2021 can be found in the Chapter 2 data tables.

Annexe figure 2.2, below, shows *Candida albicans* was the most frequently isolated *Candida* species across the 5-year period, accounting for 43% of candidaemia in 2021 (909 out of 2,090). In common with many other surveillance studies the second most frequently reported species was *Candida* (*Nakaseomyces*) *glabrata*, which was identified in 25% (525) of candidaemia episodes in 2021.

The frequency of isolating these 2 species has not changed in the last 5 years, with *C. albicans* and *C. glabrata* accounting for 43% (800 out of 1,875) and 25% (469 out of 1,875) of isolated species in 2017, respectively. This is not the case for all species, with *C. parapsilosis* increasing from 11% of isolated species in 2017 to 14% in 2021. The number of isolates also increased from 204 in 2017 to 292 in 2021 (43.1% increase). There were 4 *C. auris* bloodstream infections reported to SGSS in 2021. During 2021, 10% of *Candida* isolates were not identified to species level, a decrease from the 13% not recorded in 2017.

Annexe Figure 2.2. Reports of sterile site isolates of *Candida* by species, 2017 to 2021



Bloodstream isolates from organisms previously classified as *Candida*

Candida kruseii and *Candida lusitaniae* have been reclassified as *Pichia kudriavzveii* and *Clavispora lusitaniae* respectively. Although it has not happened on SGSS yet, *Candida glabrata* is also likely to move to *Nakaseomyces glabrata*. These changes better reflect their true lineage and is significant as *P. kudriavzevii,* in common with other *Pichia species,* is innately resistant to fluconazole. *Nakaseomyces glabrata,* unlike most *Candida* species demonstrates reduced susceptibility to fluconazole and *Clavispora lusitaniae* sometimes demonstrates the rare phenomenon amongst *Candida* species of innate or emergent resistance to amphotericin B. The numbers of bloodstream isolates for these species over the last 5 years can be seen in Annexe Table 2.6.

Annexe Table 2.6. Reports of recently reclassified non-*Candida* species from sterile site isolates, 2017 to 2021

Organism name	2017	2018	2019	2020	2021
Pichia kudriavzevii	35	38	29	19	29
Clavispora lusitaniae	26	18	31	30	42

From 2020 to 2021, both species showed an increase in the number of isolates. However, from 2017 to 2021, there was a 17.1% decrease in the number of *Pichia kudriavzevii* isolates, whilst the number of *Clavispora lusitaniae* specimens isolated increased by 61.5%. The number of isolates for both species remained relatively low.

3. Antimicrobial consumption

All data presented in this chapter in tables can be accessed in the ‘Chapter 3 data tables’ and all figures can be accessed via the downloadable slideset, both available from the ESPAUR report web page.

Antibiotic consumption: data sources

Primary care

Information on prescribing of antibiotics in the community was obtained from the PHE Antibiotic Prescribing Data Warehouse, a project initiated by the ESPAUR Oversight Group. Data is sourced from the NHS Digital database and are extracted each month as a snapshot in time from the GP Payments system.

Age group data for primary care was obtained from ePACT2 from NHS BSA.

Primary care prescribing data includes antibiotic prescribed from general practice and other community settings such as out-of-hours services and walk-in centres. The full list of primary care prescribing settings is provided in the Annexe.

Secondary care

Information on the use of antibiotics in secondary care was obtained from IQVIA (formerly QuintilesIMS, formed from the merger of IMS Health and Quintiles). The database held by IQVIA contains information from 99% of NHS hospital pharmacy systems for drugs dispensed to individual patients and wards.

Data from all NHS acute trusts was included and organisational changes is reflected up to the latest year of data provided in the report. Trusts can amend their prescribing data for up to a period of 2 years, hence data for the last 2 years is provisional and is subject to change.

Dental care

Information on the use of antibiotics prescribed in NHS dental surgeries was obtained from NHS BSA through a data request.

Antifungal consumption: data source

In the previous ESPAUR report (2020 to 2021) information on hospital prescribing from 2016 to 2020 was obtained from Rx-Info, which is used in 100% of NHS acute hospitals.

The data source in this year's report for the antifungal consumption section is now IQVIA, and is consistent 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 is one example where differences have been identified. (Ketoconazole tablets are not used for the treatment of antifungal infections but are used for the treatment of Cushing's syndrome).

Information on prescribing of antifungals in the community continues to be obtained from the PHE Antibiotic Prescribing Data Warehouse, a project initiated by the ESPAUR Oversight Group. Data is sourced from the NHS Digital database and are extracted each month as a snapshot in time from the GP Payments system.

Classification of prescribing data

The classification of antibiotics for this report is based on the Anatomical Therapeutic Chemical / Daily Defined Dose (ATC/DDD) index 2019 managed by the World Health Organization (WHO) Collaborating Centre for Drug Statistics Methodology. Data covered all antibiotics in the ATC group 'J01', (antibiotics for systemic use) and 4 additional oral agents outside the 'J01' group used to treat *Clostridium difficile* infections, fidaxomicin (A07AA12), metronidazole (P01AB01), tinidazole (P01AB02) and vancomycin (A07AA09).

Third level pharmacological sub-grouping within ATC group 'J01'

Penicillins ('β-lactam antibacterials, penicillins') include extended-spectrum penicillins, β-lactamase sensitive and resistant penicillins, and β-lactamase inhibitors either alone or in combination with penicillins.

'Other β-lactam antibacterials' includes cephalosporins, carbapenems, and monobactams. Anti-*Clostridioides difficile* (formerly *Clostridium difficile*) agents include: oral vancomycin (ATC code: A07AA09) and fidaxomicin (ATC code: A07AA12). Oral metronidazole (ATC code: P01AB01) has been separated from this group, as opposed to previous years, following feedback from stakeholders.

'Other antimicrobials' (ATC 3rd level pharmacological subgroup 'J01X') includes glycopeptides, polymyxins, steroid antibacterials, imidazole derivatives, nitrofuran derivatives, and other antimicrobials: fosfomycin, methenamine, linezolid, daptomycin and tedizolid.

The classification of antifungals for this report are also based on the ATC/DDD index 2021 managed by the WHO Collaborating Centre for Drug Statistics Methodology. Data covered all antifungals in the ATC group ‘J02’, (antimycotics for systemic use) and one additional systemic antifungal outside the 'J02' group, terbinafine (D01BA02).

ATC and DDD methodology

The ATC system aims to identify the active therapeutic ingredient of all human medicines and assigns drugs a measure of use known as the DDD, which is the assumed average maintenance dose per day for a drug used for its main indication in adults. It is important to note however that while the DDD is used as a unit of measurement of drug use, it does not necessarily reflect the recommended or prescribed daily doses used in practice as therapeutic doses for individual patients may vary depending on characteristics such as age, weight, ethnic differences, type and severity of disease and pharmacokinetic considerations.

Denominators

Mid-year populations (inhabitants) for each year were extracted from the Office National Statistics (ONS). Hospital admission data for each year was extracted from Hospital Episode Statistics (HES) from NHS Digital. In addition, hospital admissions by speciality was extracted from NHS digital for the financial year 2020 to 2021. Please note that admissions by speciality are published annually by NHS Digital and 2020 to 2021 data was the latest available at the time of reporting.

Trend analysis

National trends in the consumption of antibiotics were assessed using linear regression; the dependent variable was antibiotic consumption in DDD per 1,000 inhabitants per day and the explanatory variable being year. A statistically significant trend ($p<0.05$) is denoted with the inclusion of $^{+}$. STATA 15 was used in all analysis.

Other community settings categories

A table defining how community settings have been mapped to the setting categories used within the report.

Other community settings	Setting category
Other	Other
Walk-in centre	Walk-in centre
Out-of-hours	Out-of-hours
WIC and OOH practice	Out-of-hours

Other community settings	Setting category
Public health service	PH service
Community health service	Community service
Hospital service	Hospital
Optometry service	Other
Urgent and emergency care	Urgent care
Hospice	Hospice
Care home or nursing home	Nursing home
Border Force	No data reported
Young offender institution	Custody
Secure training centre	No data reported
Secure children's home	Custody
Immigration removal centre	Custody
Court	No data reported
Police custody	No data reported
Sexual assault referral centre	No data reported
Other: justice estate	No data reported
Prison	Custody

Trusts definitions

Trusts definitions in the ESPAUR report are based on the Estates Returns Information Collection (ERIC).

Trust	Definition
Acute small, medium or large	Sites that provides a range of inpatient medical care and other related services for surgery, acute medical conditions or injuries (usually for short-term illnesses or conditions). Treatment Centres providing inpatient facilities are classed as General Acute Hospitals.
Acute Teaching	Sites that are a hospital that provides clinical education and training to future and current health professionals. Teaching hospitals work closely with medical students throughout their period of matriculation, and especially during their clerkship (internship) years.

Trust	Definition
Acute Specialist	Sites that undertake a single specialist function, inclusive of Oncology, Orthopaedics, Dental Hospital, Maternity Hospital, Children's Hospital, and Cardio or Thoracic. This category excludes specialist hospitals in the Mental Health or Learning Disabilities sector.
Acute Multiservice	Sites where 2 or more functions are provided by the same provider. Such functions would include any combination of single speciality, acute services, community services, mental health services and learning disabilities services.

Department speciality

Department speciality to department group look-up table.

Department speciality	Department group
Mixed outpatient clinics	AE / Non-specific out-patient department
Aseptic unit	AE / Non-specific out-patient department
A&E	AE / Non-specific out-patient department
Psychogeriatric	Geriatrics
Geriatrics	Geriatrics
Intensive care	Intensive care unit
Dermatology	General medicine
Respiratory, chest or asthma clinic	General medicine
Cardiology	General medicine
Gastroenterology	General medicine
Coronary care	General medicine
Rheumatology	General medicine
Thoracic or chest medicine	General medicine
General medicine	General medicine
Endocrinology	General medicine
Obstetrics and gynaecology	Obstetrics and gynaecology
Fertility and genetics	Obstetrics and gynaecology
Orthopaedics	Orthopaedics
Pain clinic	Other
Radiology	Other

Department speciality	Department group
Physiotherapy	Other
Physically disabled	Other
Rehabilitation or long stay unit	Other
Pathology lab	Other
Mental handicap	Other
Occupational health	Other
Learning disabilities	Other
Child adolescent psychiatry	Other
Other wards or units	Other
Psychiatry and mental illness	Other
Psychiatric day Hospital	Other
Paediatric ICU	Paediatrics
Neonatal unit	Paediatrics
Paediatric or paediatric surgery	Paediatrics
Acute internal medicine	Specialist medicine
Medical oncology	Specialist medicine
Clinical oncology (Radiotherapy)	Specialist medicine
AIDS unit	Specialist medicine
Infectious disease or Isolation	Specialist medicine
Renal medicine	Specialist medicine
Liver unit	Specialist medicine
Neurology	Specialist medicine
G.U.M	Specialist medicine
Haematology	Specialist medicine
GUM medicine	Specialist medicine
Liver (failure) unit	Specialist medicine
Transplantation unit	Specialist surgery
ENT	Specialist surgery
Cardio-thoracic surgery	Specialist surgery
Plastic surgery	Specialist surgery
Oral surgery	Specialist surgery
Vascular surgery	Specialist surgery

Department speciality	Department group
Ophthalmology	Specialist surgery
Urology	Specialist surgery
Neurosurgery	Specialist surgery
General surgery	General surgery
Breast treatment and care	General surgery
Day case theatres	General surgery
Theatre and anaesthetics	General surgery

Antimicrobial consumption: supplementary analyses

Total antibiotic consumption by antibiotic group

Penicillins

Penicillins accounted for 36.7% of total antibiotics prescribed in England in 2021. Between 2017 to 2021, the penicillin most commonly used has remained amoxicillin though its consumption has fallen from 3.30 DID to 2.40 DID. This is followed by flucloxacillin with 1.85 DID in 2017 to 1.64 DID in 2021. Consumption of penicillin slightly increased (+2%) between 2020 and 2021.

Whereas consumption of pivmecillinam has increased significantly over the past 5 years (+64.3%). Pivmecillinam is used to treat lower urinary tract infections in England as per National Institute for Health and Care Excellence (NICE) guidelines. Since the supply shortage in 2017, piperacillin/tazobactam has continued to steadily increase from 0.07 DID to 0.08 DID in 2021 (+22.1%), with an increase of 8.8% between 2020 and 2021.

Cephalosporins

Total cephalosporin consumption declined by 2.6% between 2017 to 2021 from 0.32 DID to 0.31 DID; greatest decline being in cefaclor and cefuroxime (-56.6%). Only 2 classes of cephalosporin saw increased use between 2017 to 2021; cefalexin and ceftriaxone; +2.7% and +36.1% respectively.

First and second generation cephalosporin antibiotic consumption decreased by 4.1% over the f5 years, however third, fourth and fifth generation cephalosporins consumption increased slightly by 3.6%. The increase reflects the consumption rate in hospital inpatient settings which rose from 0.05 in 2017 to 0.06 in 2021 DID.

Tetracyclines

The majority of tetracycline consumption takes place within general practices (87%), with usage decreasing between 2017 and 2021. Doxycycline (56%) and Lymecycline (35.6%) remain the most commonly used tetracyclines. Prescribing of doxycycline increased slightly (3.5%) over the past 5-year period while Lymecycline reduced by (9.1%). Consumption also of minocycline

(-54.8%), oxytetracycline (-47.3%), tetracycline (-30.7%), Demeclocycline (-14.4%) and tigecycline (-2.0%) reduced.

Quinolones

There was a reduction in the consumption of quinolones between 2017 to 2021 (-16.7%) from 0.53 to 0.44 DID. In 2021, ciprofloxacin was the main quinolone prescribed (73.2%), followed by levofloxacin (14.6%). Ciprofloxacin decreased by (-22.2%) from 0.42 to 0.32 DID whereas levofloxacin and ofloxacin consumption increased slightly (5.5% and 10.7%, respectively) between 2017 to 2021. Moxifloxacin, nalidixic acid and norfloxacin prescriptions have all declined over the same 5 year period.

Macrolides

Macrolides are often used as an alternative in patients who have allergies to penicillin (8). Consumption of macrolides showed a decline of (-28.7%) from 3.08 to 2.20 DID between 2017 to 2021. Clarithromycin is the most consumed macrolide, though its use has decreased by 32.8% between 2017 to 2021. Azithromycin increased by 2.9% over the past 5 years. This was the only observed increase in the macrolide class. Erythromycin saw the greatest decline over the same 5 year period (-44.2%).

Sulphonamides, nitrofurantoin, and trimethoprim

Consumption of sulphonamides and trimethoprim showed a decline over the past 5 years across all settings (-30.5%). This decrease is driven by the decline observed in general practice and in the other community setting (-36.5% and -50.9%, respectively). The general practice setting accounts for most (86.0%) sulphonamide and trimethoprim consumption followed by hospital inpatients (6%). There was an increase of 4.7% in prescribing within hospital inpatient settings between 2017 to 2019 and 8.1% between 2020 and 2021, from 0.085 to 0.092 DID.

The trend in overall consumption of nitrofurantoin continued to increase with a rise of 40.8% between 2017 and 2021, increasing to 1.219 DID in 2021. This growth in consumption for nitrofurantoin was observed across all settings. The increase in nitrofurantoin consumption is likely related to initial changes in 2014 to PHE primary care guidelines recommending nitrofurantoin as first-line treatment for lower urinary tract infections in adults. This shift away from the prescription of trimethoprim to nitrofurantoin was further encouraged with the implementation of the 2017 to 2019 Quality Premium.

Aminoglycosides

Aminoglycosides are not commonly prescribed in the primary care setting and as such the consumption for this class of antibiotic has steadily decreased across all settings between 2017 to 2021, with the largest decrease in the general practice setting (-43.2%). Usage in the hospital inpatient setting also fell (-20.0%) between 2017 and 2021, however, between 2020 and 2021 there was an increase of 2.2%.

Parenteral glycopeptides and daptomycin

The use of parenteral glycopeptides (vancomycin and teicoplanin) and daptomycin occurred almost solely in the hospital (99.7% in 2021) with the majority of prescribing occurring in the hospital inpatient setting, with a modest 1.7% decline in this setting between 2017 and 2021. Between 2020 and 2021 there was an increase of 7.4%.

Aminoglycosides decreased by 18.4% between 2019 and 2021, from 0.12 to 0.10 DID. The most commonly prescribed class of parenteral glycopeptides is tecoplanin (71.0%) with usage decreasing by 8.4% since 2017. Daptomycin showed the highest increase in usage over 2017 to 2021 with an increase of 9.7%.

Colistin

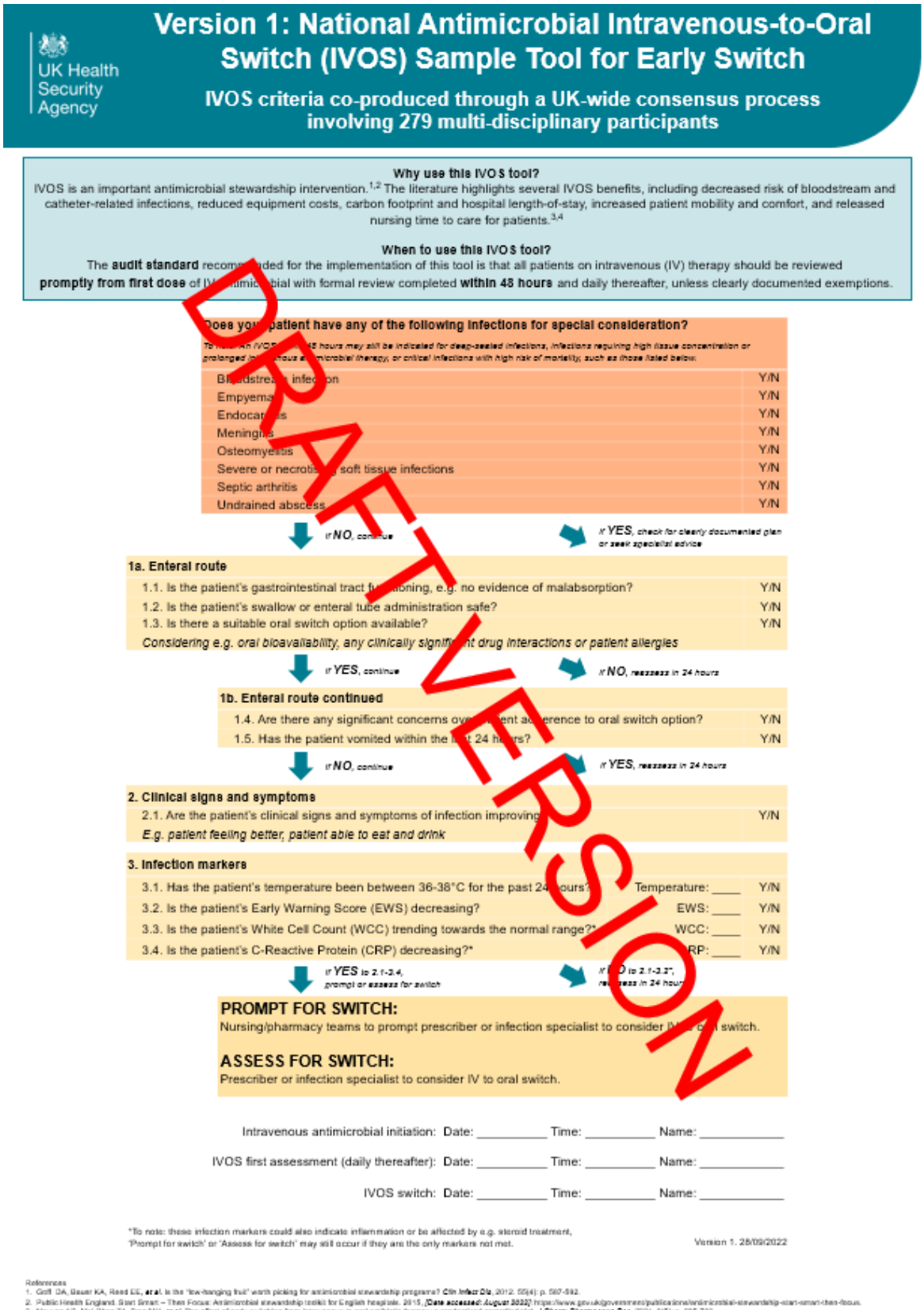
Total consumption for colistin has remained low and largely stable over the past 5 years, due to this class of antibiotic being a last resort used frequently to treat multidrug-resistant infections. In the most recent period between 2020 and 2021 usage of colistin has fallen slightly (-4.2%) to 0.038 down from 0.04 DID. It is possible that this is driven by the reduction in prescribing in the general practice setting, a decrease of 18.8%. Usage of colistin has decreased across all settings with the exception of hospital outpatient which has seen an increase of 20.9% over the past 5 years.

Oral metronidazole

Oral metronidazole accounts for just 1.8% of total consumption of antibiotics. There has also been a reduction in usage over the past 5 years (11.6%) with a decrease across most settings. The use of oral metronidazole increased solely in the dental setting from 0.11 DID to 0.12 DID between 2017 and 2021.

4. Antimicrobial stewardship

Annexe Figure 4.1. Draft version 1 of the Antimicrobial Intravenous-to-Oral Switch (IVOS) criteria tool



Text alternative to Annexe Figure 4.1

Version 1 of the national Antimicrobial Intravenous-to-Oral Switch (IVOS) sample tool for early switch, with IVOS criteria co-produced through a UK-wide consensus process involving 279 multi-disciplinary participants.

The sample tool includes:

- an initial box answering the questions: ‘Why use this IVOS tool?’ and ‘When to use this IVOS tool?’
- a subsequent box listing 8 types of infection for special consideration prior to IVOS. The infections include bloodstream infection, empyema, endocarditis, meningitis, osteomyelitis, severe or necrotising soft tissue infections, septic arthritis, undrained abscess. If none of these infections are present, an arrow points user down to the next box. If one of these infections is present, an arrow points to a sentence stating ‘check for clearly documented plan or seek specialist advice’
- subsequent boxes regarding the patient’s enteral route, clinical signs and symptoms and infection markers lead the user through a series of IVOS criteria questions that either mean they can continue through the tool or abandon assessment and reassess patient for IVOS in 24 hours
- a final box that, if all IVOS criteria suitably met, leads to a ‘prompt for switch’ if user is part of the nursing or pharmacy teams or an ‘assess for switch’ if user is a prescriber or infection specialist
- finally, at the end of the tool, there is space for inputting information (date, time, name of user) regarding intravenous antimicrobial initiation, IVOS first assessment and IVOS switch
- references that informed the questions ‘Why use this IVOS tool?’ and ‘When to use this IVOS tool?’ are included at the end of the tool

6. Professional and public education and training

Antibiotic Guardian Healthcare Students Conference online learning modules

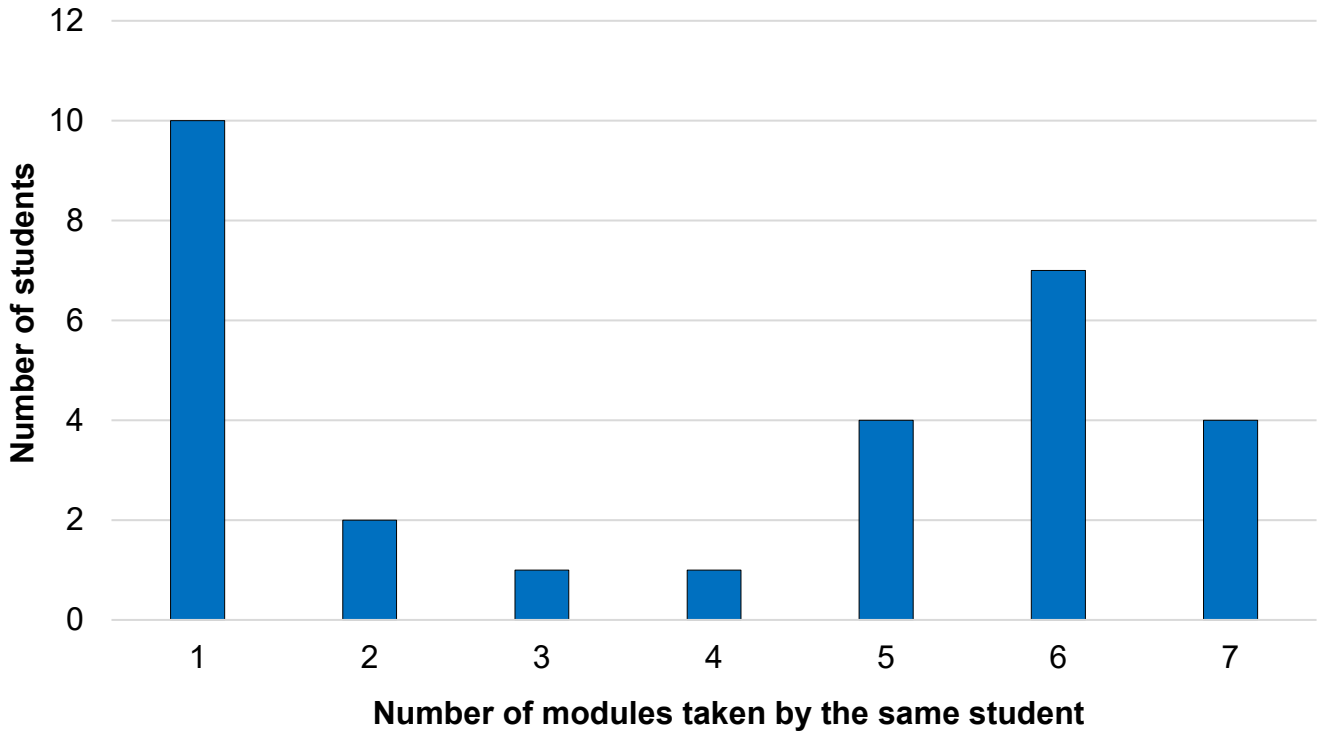
Annexe Table 6.1. A summary of the year of study and degree-type self-reported by participants of the National Healthcare Students' AMR Conference Online Modules 2021

Year of study	Number of respondents
1	5
2	3
3	5
4	10
5	2
Overseas Pharmacists' Assessment Programme (OSPAP)	2

Degree type	
Medicine	15
Pharmacy	9
Biomedical Sciences	1
Biology	1
Dentistry	1

Annexe Figure 6.1, below, shows the number of modules attended. Of students completing the post-module quizzes, 29 students took part in at least one module in 2021, with 24% taking part in 6 and 14% taking part in all 7 modules.

Annexe Figure 6.1. Number of modules attended by participants of the National Healthcare Students' AMR Conference online modules 2021



TARGET webinar on discussing antibiotics with patients

Annexe Table 6.2. Feedback from TARGET webinar attendees on topics that they would like future webinars to focus on (n=74)

Topic	%
Skin infections	32
Clinical scenario training webinars	26
Use of audits	15
AMS and behavioural science	12
Overview of TARGET Toolkit	9
Creating and delivering an AMS action plan	4
Contribution of GP prescriptions to the total wold antibiotic burden	1

Antimicrobial Stewardship (AMS) in Community Pharmacy Shared Learning for the Pharmacy Quality Scheme

Those who completed the evaluation stated they plan to use resources, activities or events mentioned during the webinar in their own action plan, including:

- use of action plan template, the antibiotic counselling sheet and patient leaflets
- accessing the local antibiotic formulary
- use of the TARGET website and toolkit
- use of individual guides for conditions such as UTI and RTI
- liaising with local surgeries
- discussions with colleagues and the whole team about how to approach completion of the antibiotic checklist with patients
- pledge to become an Antibiotic Guardian
- enter data onto Pharmoutcomes.org daily

A total of 87% had already pledged to become an Antibiotic Guardian and 10.5% planned to. Eighty per cent agreed that using the Antibiotic Checklist had improved their confidence in querying antibiotic prescriptions with prescribers.

See tables for demographic data of webinar attendees.

Annexe Table 6.3. Regional breakdown of attendees to the AMS for community pharmacy webinar

If in the UK, which region did you access the webinar from?	Number	Percentage
South East	33	19.3%
London	28	16.4%
North West	24	14.0%
West Midlands	22	12.9%
North East	19	11.1%
Yorkshire and Humber	16	9.4%
East Midlands	14	8.2%
South West	14	8.2%
Northern Ireland	1	0.6%

Annexe Table 6.4. Professional role of attendees to the AMS for community pharmacy webinar

Role	Number	Percentage
Pharmacist	135	78.9%
Pharmacy assistant	10	5.8%
Pharmacy technician or despenser	18	10.5%
Trainee pharmacist	2	1.2%
Trainee pharmacy technician	4	2.3%
blank	2	1.2%

WAAW Knowledge Café event

Annexe Table 6.5. A summary of resources, activities or events that colleagues indicated that they would be likely to include in local WAAW campaigns through the post-Knowledge Café feedback survey

Activity or resource	Number of colleagues that indicated they were likely to engage with activity for WAAW 2021	
	Number	Percentage
Digital notes	7	37
AMR board game	3	16
Question and answer session or 'ask the expert'	3	16
Online quizzes	3	16
Patient stories or case studies	3	16
Social media campaign	3	16
Teleconference background	2	11
eBug or resources for use in schools	2	11
Daily themed messages	2	11
Recording an organisational video	2	11
Antibiotic Guardian Pledge	2	11
Stakeholder engagement	1	5
Internal or external news	1	5
Senior leader engagement	1	5

Antibiotic Guardian

Pledges made on other country pages included 432 from Africa, 98 from South Africa, 5 from Australia, 37 from the Netherlands, 37 from France and 4 from Germany. See Table 6.6 for breakdown of pledges from pharmacy teams from 2014 to 2021.

Annexe Table 6.6. A summary of Antibiotic Guardian pledges made on the main pledge page by pharmacy teams each year, from 2014 to 2021, with breakdown of the sub-category of pledger. These sub-categories were not available in 2014 and the 'Community pharmacist' sub-category was introduced in 2018

Year	Pharmacy teams pledges	Pharmacy team pledge sub-category					
		Academic pharmacist	Community pharmacist	Pharmacy assistant	Pharmacy technician	Primary care pharmacist	Secondary care pharmacist
2014	1,300	N/A	N/A	N/A	N/A	N/A	N/A
2015	1,338	30	0	85	270	398	551
2016	2,111	75	0	145	409	654	756
2017	3,021	81	0	357	544	861	901
2018	1,627	30	245	163	317	350	496
2019	2,410	42	807	242	403	299	574
2020	28,701	125	10,145	13,214	3,166	1,359	394
2021	27,684	47	8,856	13,900	2,885	1,223	392

Annexe Table 6.7. Summary of the organisational AMS pledge activity in 2021, broken down by the type of organisation, from across UK, Hungary, India, North Korea, South Korea, Malaysia, Malta, Mauritius, Myanmar, Nigeria, Poland, San Marino, Solomon Islands, Sri Lanka, Taiwan and Tanzania

Organisation type	Number of registrations in 2021
Hospital	15
GP practice	11
Other	11
Community pharmacy	10
NHS trust or Health and Social Care	10
Regional NHS organisation (for example, CCG, local commissioning group)	8
National NHS organisation	6
Professional body or organisation	6
NHS primary care	5
Animal health professional body	2
Charity	2
Local government	2
National government	2
Private healthcare	2
University	1
Non-departmental public body	1

7. COVID-19 novel therapeutics

All data presented in this chapter in tables can be accessed in the ‘Chapter 7 data tables’, all figures can be accessed via the downloadable slideset, both available from the report landing page.

UKHSA’s surveillance programme to support novel COVID-19 therapeutics includes genomic, virological and epidemiologic surveillance. The data presented within the chapter and Annexe reflects the epidemiological surveillance workstream.

Data sources

Surveillance of the clinical use and supply of COVID-19 novel therapeutic agents utilises treatment request data from Blueteq, and medicines supply data from Rx-info. See below for descriptions of this data.

For information on Blueteq see the Therapeutics Surveillance Protocol. Rx-info is a company that develops software for NHS hospital trust pharmacies and finance departments, and they compile medicines supply data from 100% of NHS acute hospitals.

Patient-level Blueteq treatment request usage data

The Blueteq form was created as an output by the stewardship team within UKHSA’s therapeutics programme. The Blueteq form collects patient-level data using the following fields:

- NHS number
- patient initials
- date of birth
- drug name
- form ID
- interim clinical commissioning policy drug is used within
- estimated treatment start date
- treating NHS trust

For more information on Blueteq see the Therapeutics Surveillance Protocol.

Blueteq data is downloaded each Monday from a secure website. The most recent date of extraction for this report was 22 August 2022, and data was restricted to the period between 1 October 2021 and 31 March 2022.

Information on the usage of COVID-19 specific novel therapeutic agents in clinical use in England was obtained from Blueteq. The Blueteq system manages high-cost drugs for NHS England and as such contains clinical requests made for neutralising monoclonal antibodies

(nMAB) and antiviral therapies used for the treatment of patients with COVID-19. Not all treatment requests may have resulted in patients receiving treatment with these drugs but the electronic or patient prescribing data were not accessible.

Requests for patient neutralising monoclonal antibodies (nMAB) and antiviral therapies of interest are recorded in the Blueteq system, with data extracts received by UKHSA on a weekly basis (with all cumulative treatment requests up to midnight of the previous Sunday included).

Patient treatment data was cleaned for non-approved entries, invalid NHS numbers or duplicate entries. This was then linked to demographic, vaccination (the National Immunisation Management Service [NIMS] data set), hospital stay (Emergency Care Dataset and Secondary Uses Service, SUS, hospital data – the spell during which the patient received therapy), mortality, and viral genomic and mutations data, to provide patient-level epidemiological data on the use of these novel therapeutic agents and the patients treated in England. Mortality data was a combination of the following data sets:

- deaths occurring in hospitals among individuals tested positive for COVID-19, notified to NHS England by NHS trusts
- deaths notified to local Health Protection Teams in the course of outbreak management
- death reports from NHS electronic hospital records which can be linked to a positive SARS-CoV-2 test
- Office for National Statistics (ONS) death registrations which can be linked to a positive SARS-CoV-2 test

Data linkage was completed using deterministic linkage on NHS number.

Rx-info's medicines supply data

Rx-info is a company that develops software for NHS hospital trust pharmacies and finance departments, and they compile medicines supply data from 100% of NHS acute hospital trusts.

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 picture of the total usage of COVID-19 therapeutics in England. The drug-level data captures the amount of medicines dispensed daily (Virtual Medicinal Product [VMP] quantity in daily dispensed grams) and the uptake of these key therapies by NHS acute trusts and regionally. Rx-info data were extracted on 12 June 2022.

The prescription types includes therapies suppled for: day cases, discharge or TTA, homecare, homecare – FP10HNC, inpatient, inpatient – services, mix of in-and outpatient, outpatient, outpatient – FP10HNC, primary care – GP, and unknown. This data usually do not include: breakages or damages, disposal, expired stock, general sales, internal stock transfers, stock adjustments, GP prescriptions, or private patients.

Medicines supply data can be updated within Rx-info, hence this data is provisional and subject to change.

Data analysis

Population data used in the chapter was taken from the Office for National Statistics annual mid-year population estimates published data for the corresponding population.

Comparisons of treated patient (using Blueteq treatment requests) and dispensed therapies (Rx-info medicine supply data) were completed by calculating the total grams of nMABs and antivirals that have an approved Blueteq request form against the grams from Rx-info. The differences in grams between the 2 sources was calculated to highlight discrepancies in total medicines supply (Rx-info) and treatment requests (Blueteq). This analysis was completed for England, and also by NHS region (data found in the data annexe), taking into account stock provided to centres.

Treatment requests were assessed by total count and per 100,000 population by NHS region. Treatment requests by setting were estimated by NHS region and age group. Rates of treatment requests by group (region, age group, ethnicity) were estimated by dividing the number of requests by the COVID-19 case numbers in that group over the specified time period. The total count over time was assessed by variant as well.

STATA 15 was used in all medicines supply data analysis. R was used in all other analyses.

Initiated clinical use of therapies and changes in policies

For the latest clinical guidance and commissioning criteria for COVID-19 therapies, see the Central Alert System (CAS).

Casirivimab with imdevimab (Ronapreve®) was in clinical use from 17 September 2021 in hospitalised patients, and was subsequently removed on 24 February 2022. Sotrovimab and molnupiravir were deployed from the 16 December 2021 in ambulatory settings, for specific patient groups.

nMABs and antivirals are currently recommended as directed by the National Health Service England (NHSE) clinical commissioning policies for non-hospitalised patients and hospitalised patients.

1. A number of these therapeutic agents have been used for COVID-19 during this time period: Remdesivir (Veklury) has been available to patients aged 12 years and over who are hospitalised due to COVID-19 since May 2020. More recently remdesivir has been available

to patients with hospital onset COVID-19 infection and to non-hospitalised individuals at highest risk with COVID-19 infection.

2. Casirivimab with imdevimab (Ronapreve) has been in clinical use for inpatients aged 12 years and over since 17 September 2021 and was briefly available as a treatment for non-hospitalised patients, but currently remains in very limited use for individuals admitted due to COVID-19 with confirmed Delta infection only at the time of writing
3. Sotrovimab (Xevudy) has been in use since mid-December 2021 in both the non-hospitalised at highest risk and the hospital-onset COVID-19 cohorts, for patients aged 12 years and over, and is also being studied in admitted patients within the RECOVERY trial.
4. Molnupiravir (Lagevrio) has been in clinical use in non-hospitalised patients at highest risk since mid-December 2021 for those aged 18 years and over, and in those with hospital onset COVID-19 since early-February 2022; molnupiravir is also being studied for its effectiveness as a community treatment, through the PANORAMIC trial, in individuals over 50 years and all age groups with at least one risk factor for hospitalisation.
5. Nirmatrelvir plus ritonavir (Paxlovid) is now available to both non-hospitalised patients at highest risk, for patients aged 18 years and over, and those with hospital-onset COVID-19 infection.

Table 1. Clinical commissioning policy dates and evidence

Therapy	Date added to clinical commissioning policy	CAS alert (or link to government announcement if no CAS alert)	Evidence
Casirivimab with imdevimab (Ronapreve)	17 September 2021 (removed 24 February 2022)	CAS-ViewAlert (mhra.gov.uk) (removal: 2022 CAS-ViewAlert	Weinrich and others 2021. 'REGEN-COV antibody combination and outcomes in outpatients with COVID-19' O'Brien and others, 2021. 'Subcutaneous REGEN-COV antibody combination to prevent COVID-19' RECOVERY collaborative group: 'Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial'
Molnupiravir	4 November 2021	First oral antiviral for COVID-19, Lagevrio (molnupiravir), approved by MHRA	Bernal and others, 2021. 'Molnupiravir for oral treatment of COVID-19 in nonhospitalized patients'
Nirmatrelvir plus ritonavir (Paxlovid)	10 February 2022	CAS-ViewAlert	Hammond and others, 2022. 'Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with COVID-19'
Remdesivir	26 May 2020	CAS-ViewAlert	Gottlieb and others, 2021. 'Early Remdesivir to prevent progression to severe COVID-19 in outpatients'
Sotrovimab	2 December 2021	MHRA approves Xevudy (sotrovimab), a COVID-19 treatment found to cut hospitalisation and death by 79%	Gupta and others, 2021a. 'Early treatment for COVID-19 with SARS-CoV-2 neutralizing antibody Sotrovimab | NEJM' Gupta and others, 2021b (pre-print). 'Effect of the neutralizing SARS-CoV-2 antibody Sotrovimab in preventing progression of COVID-19: a randomized clinical trial'

Dosing schedules

For information to interpret patient coverage, the therapies are prescribed using the following dosing schedules:

- Casirivimab with imdevimab can be given in one of 2 doses, depending on whether the patient was hopsitalised with COVID-19, or contracted hospital-onset COVID-19:
    - patients hospitalised for COVID-19 = 2.4g
    - patients with hospital-onset COVID-19 = 1.2g
- a course of remdesivir is given as 0.4g (200mg remdesivir on day one, then 100mg on days 2 and 3)
- a course of molnupiravir is given as 8g (4 x 200mg molnupiravir twice daily for 5 days)
- a course of sotrovimab is given as a single dose of 0.5g
- a course of nirmatrelvir plus ritonavir is given as 4g (300mg nirmatrelvir + 100mg ritonavir twice daily for 5 days)

Resistance

A key component in the programme's ability to identify and monitor emerging resistance mutations and variants has been the close integration of genomic surveillance, structural modelling, virological laboratory assessment, and epidemiological surveillance. Genomic identification of variants and mutations of potential concern for therapeutics has been based on screening in UKHSA's genomic data and international databases for rapid growth or mutations in regions assumed to be relevant for susceptibility to therapeutics.

These candidate mutations have then undergone initial assessment where the impact of the mutation was modelled using known structures of therapeutic agents bound to their viral targets. This has been followed by experimental assessment of resistance using pseudovirus assays. Both the structural modelling and the experimental assessment has been carried out in close collaboration with academic partners. In parallel with the genomics-first approach, the programme has integrated epidemiological, treatment, and genomic data in order to identify associations between mutations and particular treatments.

Methods

Analysis of pre and post treatment sequences

SARS-CoV-2 sequences were translated to amino acids and analyses were carried out for each variant (Delta, Omicron BA.1 and BA.2), protein (spike, NSP5, NSP7, NSP8, NSP9, NSP10, NSP12 and NSP14), treatment (casirivimab with imdevimab, sotrovimab, molnupiravir, nirmatrelvir plus ritonavir (paxlovid) and remdesivir) combination. These proteins were selected

because they are theorised using structural models to interact with treatments currently, or recently, in use.

Pre-treatment sequences are those obtained from patients with a sequenced sample within one week prior to treatment initiation (including the day of treatment initiation). The analysis was repeated with a range of cut-offs for defining post-treatment sequences, including post-treatment sequences only if they were sampled at least one, 5,10, or 14 days after treatment.

For each combination, we split the dataset into pre-and post-treatment sequences. At each site in the alignment, the amino acid frequency is calculated in pre- versus post-treatment sequences, as well as the probability (p) of this distribution being non-random. In this way, sites that display unexpected variability with significant frequencies can be identified, and the specific amino acid changes highlighted.

Frequency of potential resistance mutation in the UK genomic dataset

The UKHSA genomic data set is scanned to calculate the frequency of each mutation identified.

Transmission of potential resistance mutations

For sequences with identified potential resistance mutations, we scan the UKHSA genomic dataset for potential transmission partners using CIVET to determine whether mutations might have been transmitted. For each sequence with a mutation, sequences that were genetically close (<2 single nucleotide polymorphisms [SNP]) were identified. Those sequences were verified to come from a different patient than the source sequence. The target sequences were examined for presence or absence of the mutations in the source sequence. There was no evidence of transmission of mutations.

One limitation of this methodology is that it can only identify a potential transmission of a mutation if both the source and recipient have been sequenced. As the sequencing coverage in the UK is reduced, observing such a pair becomes increasingly unlikely, but surveillance scanning of all mutations in UK genomic sequences is performed weekly. Mutation scanning would detect any mutation that is increasing in frequency and may be being transmitted in the wider community (see the Therapeutics Technical briefings)

Antimicrobial stewardship webinar for COVID-19 therapeutics

Those who completed the evaluation reported key learnings including:

- better understanding of treatment criteria, drug therapies and indications
- clarity on the patient pathways and eligibility criteria
- better knowledge of stewardship principles and surveillance

- how to access SPS resources
- better understanding of hospital onset
- considerations of COVID variants
- using nMABs and antivirals in practice and the targeting of certain groups such as low weight adults
- greater understanding of the ambulatory non-hospitalised pathway
- the role of Blueteq data
- updates on clinical commissioning policies and guidelines
- knowing that there is a coordination with CMDU and the national system to the antivirals and the patient groups identified
- hearing about shared challenges and how they have been addressed by other trusts

See tables below for demographic data of webinar attendees and how often attendees would like the webinar to be repeated.

Table 2. Professional role of attendees to the COVID-19 therapeutics webinar

Profession	Number	Percentage
Pharmacists	86	89%
Doctor - GP	1	1%
Doctor - secondary care	7	7%
National government	2	2%
Other	1	

Tables 3 and 4. Regional breakdowns of attendees to the COVID-19 therapeutics webinar

Country you work in	Number	Percentage
England	78	80%
Scotland	11	11%
Northern Ireland	5	5%
Wales	2	2%
Jersey	1	1%

For England (n=78), which region do you work in?	Number	Percentage
East of England	6	6%
London	19	20%
Midlands	7	7%
National	3	3%
North East and Yorkshire	13	13%
North West	9	9%

For England (n=78), which region do you work in?	Number	Percentage
South East	10	10%
Not based in England	19	20%

Table 5. Attendees' responses to how often they would like additional COVID-19 therapeutics webinars to be held

How often would you like us to run additional COVID therapeutics webinars?	Number	Percentage
Monthly	41	42%
Ad hoc	26	27%
Quarterly	12	12%
When there are significant changes	10	10%
Monthly, plus ad hoc as needed based on developments	1	1%
Not sure	4	4%

Methods and caveats

The workstream developed a proposed minimum dataset for Blueteq, combining request from Workstream 5 and AMS requirements:

1. Patient identifier (full name); due to multiple false NHS numbers at present.
2. Community onset versus hospital onset covid (tick box).
3. Name of antiviral.
4. Start date.
5. SARS-CoV-2 antibody result (positive, negative or unknown) and date.
6. Which clinical eligibility criteria met (tick box):
    a. Which of the highest group does patient belong to (tick boxes)?
7. Why was antiviral given instead of nMAB? Three options:
    a. hypersensitivity to the active substance or any of the excipients
    b. unsuitable for nMAB (please state reason)
    c. other – free text
8. Confirm that a dose of oral anti-viral molnupirivir at a dose of 800mg (4 x 200mg capsules) taken orally 12 hourly has been prescribed – yes or no.
9. The prescription has been limited to 5 days – yes or no.
10. If of childbearing potential, has the patient have they been advised to use effective contraception for the duration of treatment and for 4 days after the last dose of molnupiravir – yes or no.

Patient-level data from Blueteq are of treatment requests and do not necessarily relate to treatment provided. If a patient no longer needed the treatment or removed their consent then the data request may remain even though it was not dispensed. Additionally, Blueteq data is not deduplicated by patient, so multiple treatment requests for the same patient may represent separate treatment episodes, combination therapy, or change in therapy due to poor response or side effects.

Blueteq form completion may be delayed, as such there may be Blueteq forms submitted after 31 March 2022 for requests which occurred before 31 March 2022. However since the Blueteq data were extracted 22 August, any impact of this is likely very small. Blueteq form completion is primarily for reimbursement, therefore a form may not be completed if a patient is treated off-license, that is, if they fall outside the remit of the clinical commissioning policy.

Rx-info data is at a trust level and at an aggregate-level, even though data is dispensed via COVID-19 Medicine Dispensing Units (CMDU). This data cannot be stratified further than NHS trust (that is, no age or sex breakdowns and not at CMDU level).

Rx-info data includes RECOVERY trial dispensing, which will not be included in the Blueteq forms, meaning that some of the mismatch between Blueteq and Rx-info may be due to trial medicine dispensing.

Linkage to other datasets based on NHS number may result in incomplete records due to incomplete or mis-recorded NHS numbers. Further efforts are underway to improve the linkage. Additionally, COVID-19 case data used to calculate rates may not be used in future iterations as testing policies and behaviours change.

8. Research

List of publications

A list of peer-reviewed publications from April 2021 to March 2022:

1. Berrocal-Almanza LC, Harris RJ, Collin SM, Muzyamba MC, Conroy OD, Mirza A, O'Connell AM, Altass L, Anderson SR, Thomas HL and Campbell C. 'Effectiveness of nationwide programmatic testing and treatment for latent tuberculosis infection in migrants in England: a retrospective, population-based cohort study.' The Lancet Public Health 2022: volume 7, issue 4, pages e305 to e315
2. Acolatse JEE, Portal EA, Boostrom I, Akafity G, Dakroah MP, Chalker VJ, Sands K and Spiller OB. 'Environmental surveillance of ESBL and carbapenemase-producing Gram-negative bacteria in a Ghanaian Tertiary Hospital.' Antimicrobial Resistance and Infection Control 2022: volume 11, issue 1, pages 1 to 15
3. Khan UB, Jauneikaite E, Andrews R, Chalker VJ and Spiller OB. 'Identifying large-scale recombination and capsular switching events in *Streptococcus agalactiae* strains causing disease in adults in the UK between 2014 and 2015.' Microbial Genomics 2022: volume 8, issue 3
4. Allen H, Merrick R, Ivanov Z, Pitt R, Mohammed H, Sinka K, Hughes G, Fifer H and Cole MJ. 'Is there an association between previous infection with *Neisseria gonorrhoeae* and gonococcal AMR? A cross-sectional analysis of national and sentinel surveillance data in England, 2015 to 2019.' Sexually Transmitted Infections 2022
5. Buchanan J, Roope LSJ, Morrell L and others. 'Preferences for medical consultations from online providers: evidence from a discrete choice experiment in the United Kingdom.' Applied Health Economics and Health Policy 2022: volume 19, pages 521 to 535
6. Budgell EP, Davies TJ, Donker T, Hopkins S, Wyllie DH, Peto TE, Gill MJ, Llewelyn MJ and Walker AS. 'Impact of antibiotic use on patient-level risk of death in 36 million hospital admissions in England.' Journal of Infection 2022: volume 84, issue 3, pages 311 to 320
7. Baede VO, David MZ, Andrasevic AT, Blanc DS, Borg M, Brennan G, Catry B, Chabaud A, Empel J, Enger H and Hallin M. 'MRSA surveillance programmes worldwide: moving towards a harmonised international approach.' International Journal of Antimicrobial Agents 2022: volume 59, issue 3, page 106,538
8. Lopez-Diaz M, Ellaby N Turton J, Woodford N, Tomas M and Ellington MJ. 'NDM-1 carbapenemase resistance gene vehicles emergent on distinct plasmid backbones from the IncL/M family.' Journal of Antimicrobial Chemotherapy 2022: volume 77, issue 3, pages 620 to 624
9. Taylor E, Jauneikaite E, Sriskandan S, Woodford N and Hopkins KL. 'Detection and characterisation of 16S rRNA methyltransferase-producing *Pseudomonas aeruginosa* from the UK and Republic of Ireland from 2003 to 2015.' International Journal of Antimicrobial Agents 2022: volume 59, issue 3, page 106,550

10. Aliabadi S, Jauneikaite E, Müller-Pebody B, Hope R, Vihta KD, Horner C and Costelloe CE. ‘Exploring temporal trends and risk factors for resistance in *Escherichia coli*-causing bacteraemia in England between 2013 and 2018: an ecological study.’ Journal of Antimicrobial Chemotherapy 2022: volume 77, issue 3, pages 782 to 792
11. Fifer H, Schaefer U, Pitt R, Allen H, Day M, Woodford N and Cole MJ. ‘Use of genomics to investigate *Neisseria gonorrhoeae* antimicrobial susceptibility testing discrepancies.’ Journal of Antimicrobial Chemotherapy 2022: volume 77, issue 3, pages 849 to 850
12. Martelli F, AbuOun M, Cawthraw S, Storey N, Turner O, Ellington M, Nair S, Painset A, Teale C and Anjum MF. ‘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, issue 3, pages 846 to 848
13. Andrews A, Bou-Antoun S, Guy R, Brown CS, Hopkins S and Gerver S. ‘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
14. Murray CJ, Ikuta KS, Sharara F, Swetschinski L, Aguilar GR, Gray A, Han C, Bisignano C, Rao P, Wool E and Johnson SC. ‘Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis.’ The Lancet 2022: volume 399, issue 10,325, pages 629 to 655
15. Larsen J, Raisen CL, Ba X, Sadgrove NJ, Padilla-González GF, Simmonds MS, Loncaric I, Kerschner H, Apfalter P, Hartl R and Deplano A. ‘Emergence of methicillin resistance predates the clinical use of antibiotics.’ Nature 2022: volume 602, issue 7,895, pages 135 to 141
16. Gerver SM, Nsonwu O, Thelwall S, Brown CS and Hope R. ‘Trends in rates of incidence, fatality and antimicrobial resistance among isolates of *Pseudomonas* spp. causing bloodstream infections in England between 2009 and 2018: results from a national voluntary surveillance scheme.’ Journal of Hospital Infection 2022: volume 120, pages 73 to 80
17. Emes D, Naylor N, Waage J and Knight G. ‘Quantifying the relationship between antibiotic use in food-producing animals and antibiotic resistance in humans.’ Antibiotics 2022: volume 11, issue 1, page 66
18. Sloot R, Nsonwu O, Chudasama D, Rooney G, Pearson C, Choi H, Mason E, Springer A, Gerver S, Brown C and Hope R. ‘Rising rates of hospital-onset *Klebsiella* spp. and *Pseudomonas aeruginosa* bacteraemia in NHS acute trusts in England: a review of national surveillance data, August 2020 to February 2021.’ Journal of Hospital Infection 2021
19. Mabayoje DA, Kenna DTD, Dance DAB, NicFhogartaigh C. ‘Melioidosis manifesting as chronic femoral osteomyelitis in patient from Ghana.’ Emerging Infectous Disseases 2022 January: volume 28, issue 1, pages 201 to 204
20. Borek AJ, Pouwels KB, van Hecke O, Robotham JV, Butler CC and Tonkin-Crine S. ‘Role of locum GPs in antibiotic prescribing and stewardship: a mixed-methods study.’ British Journal of General Practice 2022: volume 72, issue 715, pages e118 to e127
21. Lamagni T, Wloch C, Broughton K, Collin SM, Chalker V, Coelho J, Ladhani SN, Brown CS, Shetty N and Johnson AP. ‘Assessing the added value of group B Streptococcus

maternal immunisation in preventing maternal infection and fetal harm: population surveillance study.' BJOG: An International Journal of Obstetrics and Gynaecology 2022: volume 129, issue 2, pages 233 to 240

22. McHugh MP, Parcell BJ, Pettigrew KA, Toner G, Khatamzas E, El Sakka N, Karcher AM, Walker J, Weir R, Meunier D and Hopkins KL. 'Presence of optrA-mediated linezolid resistance in multiple lineages and plasmids of *Enterococcus faecalis* revealed by long read sequencing.' Microbiology 2022: volume 168, issue 2
23. Coia JE, Wilson JA, Bak A, Marsden GL, Shimonovich M, Loveday HP, Humphreys H, Wigglesworth N, Demirjian A, Brooks J and Butcher L. 'Corrigendum to Joint Healthcare Infection Society (HIS) and Infection Prevention Society (IPS) guidelines for the prevention and control of meticillin-resistant *Staphylococcus aureus* (MRSA) in healthcare facilities.' Journal of Hospital Infection 2022: volume 118, S1 to S39
24. Horner C, Mushtaq S, Allen M, Hope R, Gerver S, Longshaw C, Reynolds R, Woodford N and Livermore DM. 'Replacement of *Enterococcus faecalis* by *Enterococcus faecium* as the predominant enterococcus in UK bacteraemias.' JAC-Antimicrobial Resistance 2021: volume 3, issue 4, p.dlab185
25. Fifer H, Merrick R, Pitt R, Yung M, Allen H, Day M, Sinka K, Woodford N, Mohammed H, Brown CS and Hughes G. 'Frequency and correlates of *Mycoplasma genitalium* antimicrobial resistance mutations and their association with treatment outcomes: findings from a national sentinel surveillance pilot in England.' Sexually Transmitted Diseases 2021: volume 48, issue 12, pages 951 to 954
26. Beale MA, Marks M, Cole MJ, Lee MK, Pitt R, Ruis C, Balla E, Crucitti T, Ewens M, Fernández-Naval C. and Grankvist A.' Global phylogeny of *Treponema pallidum* lineages reveals recent expansion and spread of contemporary syphilis.' Nature Microbiology 2021: volume 6, issue 12, pages 1,549 to 1,560
27. Gagliotti C, Högberg LD, Billström H, Eckmanns T, Giske CG, Heuer OE, Jarlier V, Kahlmeter G, Wong DLF, Monen J and Murchan S. '*Staphylococcus aureus* bloodstream infections: diverging trends of meticillin-resistant and meticillin-susceptible isolates, EU/EEA, 2005 to 2018.' Eurosurveillance 2021: volume 26, issue 46, page 2,002,094
28. Bhattacharya A, Collin SM, Stimson J, Thelwall S, Nsonwu O, Gerver S, Robotham J, Wilcox M, Hopkins S and Hope R. 'Healthcare-associated COVID-19 in England: a national data linkage study.' Journal of Infection 2021: volume 83, issue 5, pages 565 to 572
29. Bielicki JA, Stöhr W, Barratt S and others. 'Effect of amoxicillin dose and treatment duration on the need for antibiotic re-treatment in children with community-acquired pneumonia: the CAP-IT randomized clinical trial.' Journal of the American Medical Association 2021: volume 326, issue 17, pages 1,713 to 1,724
30. Langton Hewer SC, Smyth AR, Brown M, Jones AP, Hickey H, Kenna D, Ashby D, Thompson A, Sutton L, Clayton D, Arch B, Tanajewski L, Berdunov V, Williamson PR. 'Intravenous or oral antibiotic treatment in adults and children with cystic fibrosis and *Pseudomonas aeruginosa* infection: the TORPEDO-CF RCT.' Health Technology Assessment 2021 Nov: volume 25, issue 65, pages 1 to 128
31. Muller-Pebody B, Sinnathamby MA, Warburton F, Rooney G, Andrews N, Whitaker H, Henderson KL, Tsang C, Hopkins S and Pebody RG. 'Impact of the childhood influenza

vaccine programme on antibiotic prescribing rates in primary care in England.' Vaccine, 2021: volume 39, issue 45, pages 6,622 to 6,627

32. Collin SM and Farra A. 'Antimicrobial resistance, infection prevention and control, and conflict in the Middle East.' International Journal of Infectious Diseases.' 2021: volume 111, pages 326 to 327
33. Hayes CV, Mahon B, Sides E, Allison R, Lecky DM and McNulty CA. 'Empowering patients to self-manage common infections: qualitative study informing the development of an evidence-based patient information leaflet.' Antibiotics 2021: volume 10, issue 9, pages 1,113
34. Aranega-Bou P, Ellaby N, Ellington MJ and Moore G. 'Migration of *Escherichia coli* and *Klebsiella pneumoniae* Carbapenemase (KPC)-producing *Enterobacter cloacae* through wastewater pipework and establishment in hospital sink waste traps in a laboratory model system.' Microorganisms 2021: volume 9, issue 9, page 1,868
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9. Stakeholder engagement

The ESPAUR Oversight Group is made up of a consortium of stakeholders. The following organisations are represented on the Oversight Group:

- Department of Health and Social Care (DHSC), including Dental Public Health, Office for Health Improvement and Disparities (OHID)
- DHSC Expert Advisory Committee on Antimicrobial Prescribing, Resistance and Healthcare Associated Infection (APRHAI)
- British National Formulary (BNF)
- British Society for Antimicrobial Chemotherapy (BSAC)
- Care Quality Commission (CQC)
- College of General Dentistry
- Health and Social Care Information Centre
- Independent or private sector healthcare
- IQVIA
- National Pharmaceutical Advisers Group
- National Institute of Health and Care Excellence (NICE)
- NHS England (NHSE)
- Patient representation
- Primary Care Pharmacy Association (PCPA)
- Royal College of Nursing (RCN)
- Royal College of Pathologists
- Royal College of Physicians (RCP)
- Royal College of General Practitioners (RCGP)
- Royal College of Surgeons (RCS)
- Royal College of Paediatrics and Child Health (RCPCH)
- Royal Pharmaceutical Society (RPS)
- Rx-Info Ltd
- Speicalist Pharmacy Service (SPS)
- UK Clinical Pharmacy Association: Pharmacy Infection Network (UKCPA PIN)
- Veterinary Medicines Directorate – DEFRA
- Antimicrobial Resistance and Healthcare Associated Infectio (ARHAI) Scotland, NHS National Services Scotland
- Public Health Scotland
- Public Health Wales
- Public Health Agency Northern Ireland (Health and Social Care Northern Ireland - HSCNI)
- UKHSA (represented by individuals with appropriate expertise from HCAI, antimicrobial utilisation (AMU), AMR, Fungal and Sepsis Division, Behavioural Insights, Regions, Field Service and Communications teams)

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