Public Health England

Protecting and improving the nation's health

English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR)

Report 2018 – 2019

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communication
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SUSTAINABLE DEVELOPMENT GOALS

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Executive summary

The data in the report, presented by Trust or Clinical Commissioning Group is publicly available on the PHE Fingertips AMR Local Indicators. From April 2016 to March 2019, 15, 236 accessed this website 53,712 times, spending an average of 19 minutes on the site per visit.

There were an estimated 60,788 antibiotic resistant severe infections in 2018; equivalent to 165 new antibiotic resistant infections per day.

For the seven priority bacterial pathogens reported, the rate of bloodstream infection (BSI) in 2018 was 145 per 100,000 of the population (22% increase from 2014). The proportion of these priority pathogens that were resistant to key antibiotics rose for *Escherichia coli* and *Klebsiella pneumonia,* reduced for *Staphylococcus aureus* and remained stable for other priority pathogens. The 30-day all cause fatality was higher for antibiotic resistant compared to antibiotic susceptible BSIs.

In 2018, *E coli* was the commonest cause of BSI in England (76.0 cases per 100,000 population). Children under 1 and adults over 65 years were most at risk. Antibiotic resistance was more frequently detected in hospital onset *E. coli* BSI cases than community onset cases. Rapid increased use of cephalosporin and quinolone antibiotics over the last 3 years was associated with increased resistance detected in *E. coli* BSI.

In 2018, more than 1.5 million microbiologically positive urine samples were reported to PHE; almost 60% were *E. coli.* Nitrofurantoin, despite increased use, was not associated with changes in the proportion of resistance detected. Antibiotic resistance increased with age.

In 2018, more than 4000 bacterial isolates referred to the national reference laboratory had a carbapenemase gene detected; however, despite the increase in detections from bacteria, only 142 BSIs with carbapenemase-producing Gram-negative bacteria were identified. This reflects the important work NHS staff delivered to prevent invasive infections in healthcare settings.

Antibiotic consumption peaked in 2014. From 2014 to 2018 it has reduced by 9% from 20.0 to 18.2 defined daily doses per 1000 inhabitants per day between 2014 and 2018; reductions occurred in general and dental practice and increased in other community and hospital settings.

The number of antibiotic prescriptions dispensed in the community reduced by 16.7% (from 750 to 624 per 1,000 inhabitants per year) between 2014 and 2018. Reductions occurred across all age groups, but particularly in the under 65s.

Dental antibiotic prescriptions dispensed in the community have reduced by more than 25% in the last 5 years.

Antibiotic use in hospitals increased by 2.8% (when using hospital admissions as the denominator) in the last 5 years; the rate of increase has slowed compared to the previous 5 years. Prior to 2014, carbapenems and piperacillin/tazobactam were increasing by approximately 5% per year; this has now stopped and the consumption has now significantly reduced in hospitals. However, there were statistically significant increases in cephalosporin and quinolone antibiotic consumption.

The financial incentives - Commissioning for Quality and Innovation (CQUIN) for NHS Trusts and the Quality Premium (QP) for Clinical Commissioning Groups - had positive impacts on antimicrobial stewardship for sepsis and antibiotic prescribing for urinary tract infections respectively.

Innovation in improving knowledge and behaviour in healthcare workers has continued. Key antimicrobial stewardship (AMS) projects delivered in the last year included the development and piloting of an AMS peer-review tool; developing a bespoke downloadable report from PHE Fingertips data; developing and delivering a survey of healthcare workers knowledge and attitudes on antibiotics and resistance; evaluation of tools to improve infection management in primary care; behavioural analysis projects on AMS and catheter-associated UTI; and national antibacterial prescribing audit in dental hospitals.

Ongoing projects to engage with professionals and the public included the Keep Antibiotics Working and Antibiotic Guardian campaigns. PHE also worked with students to deliver the now annual healthcare student national AMS conference. eBug for children and young adults celebrated its tenth anniversary since its launch with a conference celebrating its global engagement.

Increasing number of BSI over last 5 years

No. bloodstream infections (000's)

21%
increase since 2014

32%
increase since 2014

2014   2015   2016   2017   2018

Burden of the commonest bloodstream infection and resistance to clinically important antibiotics, 2018

Bloodstream infections

Antibiotic-resistant bloodstream infection

Gram-positive

32%

18%

Other Gram-negatives

50% *E.coli*

Gram-positive

13%

Other Gram-negatives

14%

73%

E.coli

Increasing burden of infection and antibiotic-resistant infection 2014-2018

Bloodstream infections

2014   **2018**

21% increase

15,000 more bloodstream infections

Antibiotic-resistant bloodstream infections

2014   **2018**

32% increase

4,100 more antibiotic-resistant bloodstream infections

Timeline of CPE activities and events in England

2000

2003

2005

2007

2008

2009

2011

2013

2014

2015

2016

2017

2018

2019

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*)

Mid-2009: Start of KPC outbreak in Manchester

July 2009: Resistance alert issued: 'CPE in the UK: NDM-β-lactamase: repeated importation from Indian subcontinent'

June 2009: First KPC-producing *K. pneumoniae* identified in Manchester

January 2009: Resistance alert issued: 'CPE in the UK: multi-faceted emergence'

2011: HPA† and ARHAI‡ publish guidance on detection, control and treatment of carbapenem resistant infections

March 2013: UK 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

† HPA, Health Protection Agency (forerunner of PHE)
‡ Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection
* Standards for Microbiological Investigation

Resistance in *E. coli* bacteraemia higher in hospital onset cases versus community-onset

Community onset

13%
Resistant

1.5 times higher

Hospital onset

19%
Resistant

Detections of bacteria carrying carbapenemases have increased from 72 to 4028 over the last 10 years

No. confirmed carbapenemases

4000

3000

2000

1000

0

2009 2010 2011 2012 2013 2014 2015 2016 2017 2018

Year
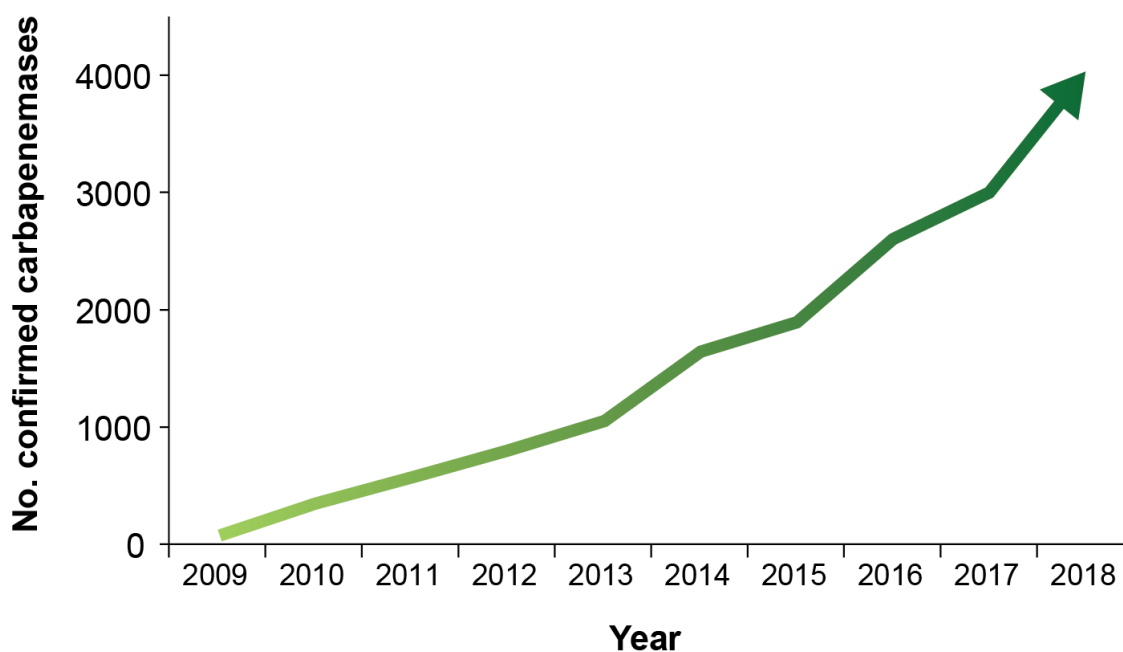
CPE-positive blood cultures are increasing

Number of invasive isolates

(y-axis) No. confirmed carbapenemase producers

(x-axis) Year: 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018
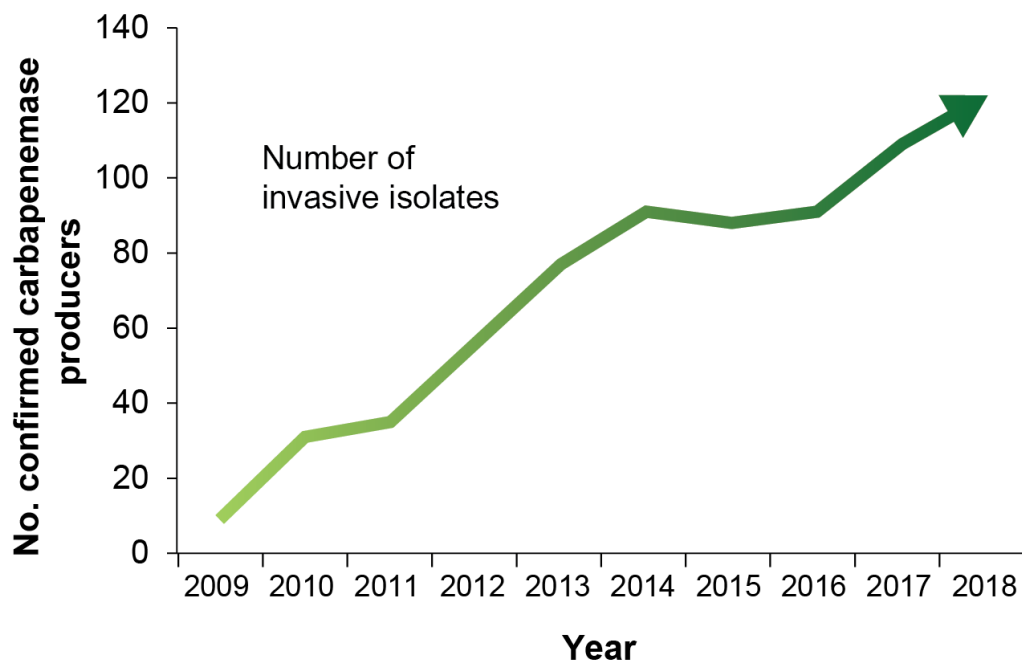
The 30-day all-cause case fatality rate of invasive CPE infections is ...

23.8%
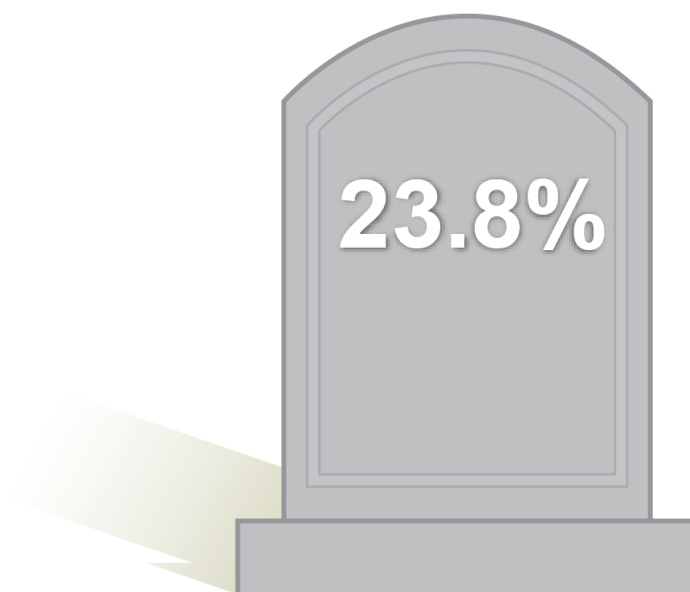
Nearly 50% of diagnostic laboratories have introduced methods to identify CPE locally

Fifty-five (48.7%) of laboratories reported use of methods capable of carbapenemase identification

The most commonly adopted methods were:

commercial PCR (**60.0%**)

immunochromatographic assays (**43.6%**)

(Note, some laboratories used both methods.)

55

The majority (**>90%**) of laboratories could identify isolates harbouring KPC, OXA-48-like or NDM

Fewer laboratories could identify VIM and IMP (**76.4%** and **65.5%**, respectively).

Nearly all (**98.1%**) laboratories recorded these results on their LIMS.
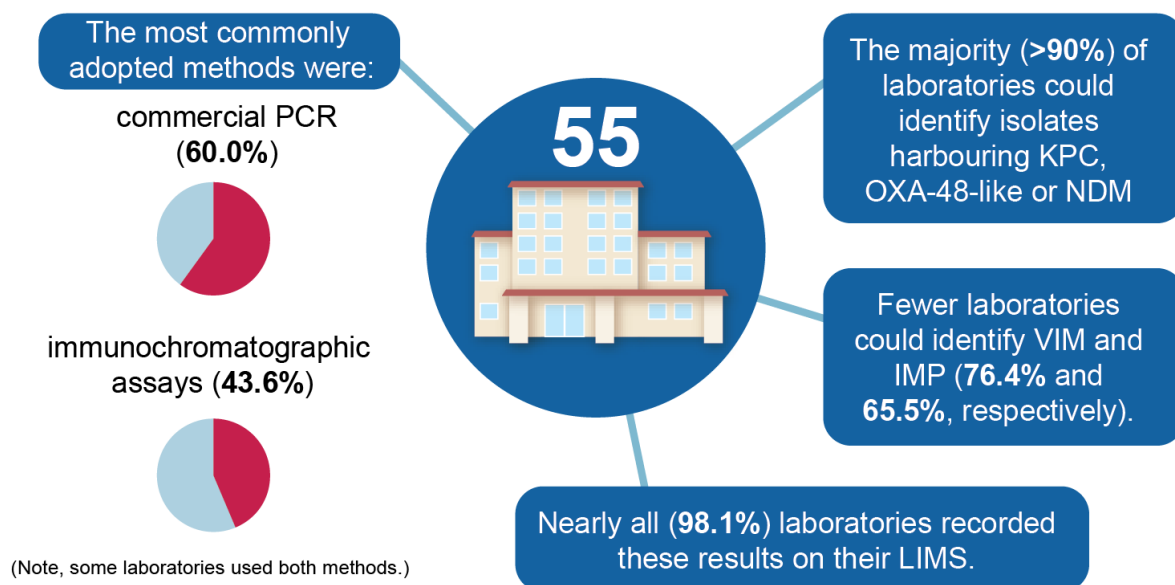
Total consumption of antibiotics continued to decline

2014 **20.0**

2016 **19.2**

2018 **18.2**
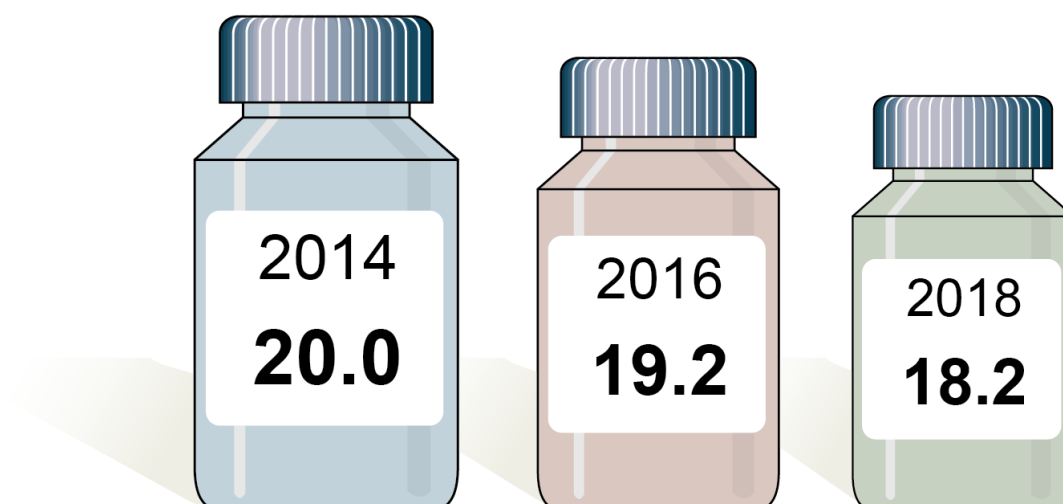
Total antibiotic consumption by prescriber setting as proportion of overall prescribing, England, 2018

72%

General practice

13% Hospital inpatients

8% Hospital outpatients

4% Dental practices

4% Other community settings
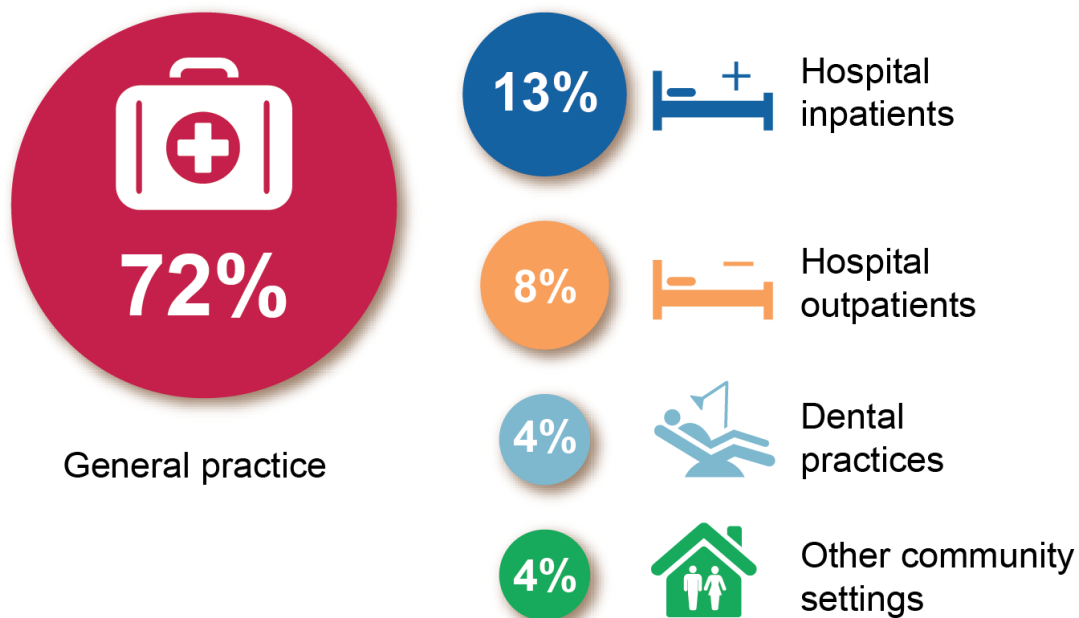
Trimethoprim-to-nitrofurantoin (Primary care)
DDDs per 1,000 inhabitants per day

2016 0.992 **Trimethoprim** **2018** 0.590 → **40.5%** reduction

2016 0.884 **Nitrofurantoin** **2018** 1.124 → **27.1%** increase
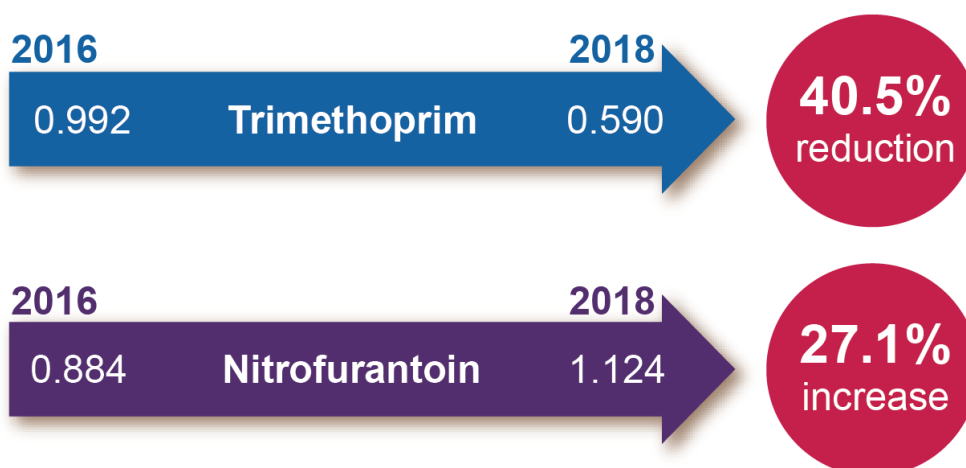
Resistance and usage (secondary care) - 3GC & quinolones

● 3rd, 4th and 5th-generation cephalosprin (consumption)
● 3rd-generation cephalosporin % resistance

● Quinolone (consumption)
● ciprofloxacin % resistance
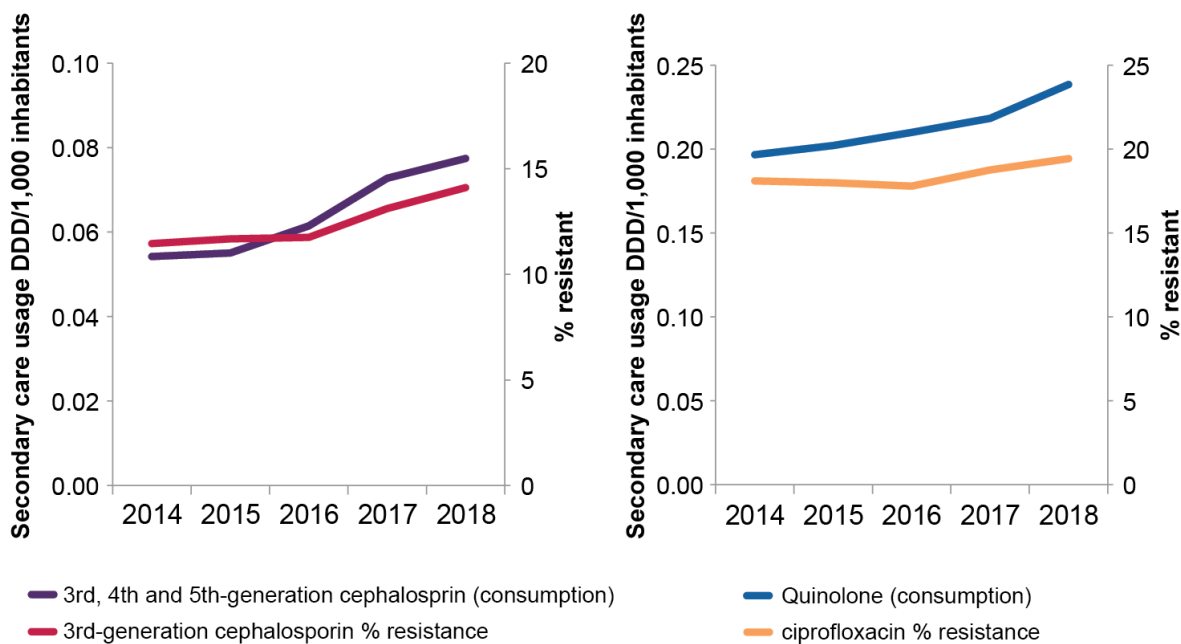
From 2014 to 2018, 42.9% rise in use of 3rd, 4th and 5th-generation cephalosporin (DDDs per 1,000 inhabitants per day), is associated with 23.2% increase in 3rd-generation cephalosporin resistance to *E. coli*

From 2014 to 2018, 21.2% rise in quinolones consumption is associated with 7.4% rise in ciprofloxacin resistance to *E. coli*

Innovative model to incentivise
the development of new antibiotics

Public Health England

NHS England

NICE National Institute for Health and Care Excellence

Reducing the impact of serious infections
CQUIN scheme - 2018/19 performance

29

29 out of 148 Trusts met target to reduce Total Antibiotic use

119

49 out of 148 Trusts met target to increase antibiotics in the Access category

49

99

84 out of 148 Trusts met target to reduce Total Carbapenem use

64

84

Reducing the impact of serious infections CQUIN scheme - 2018/19 performance

69%
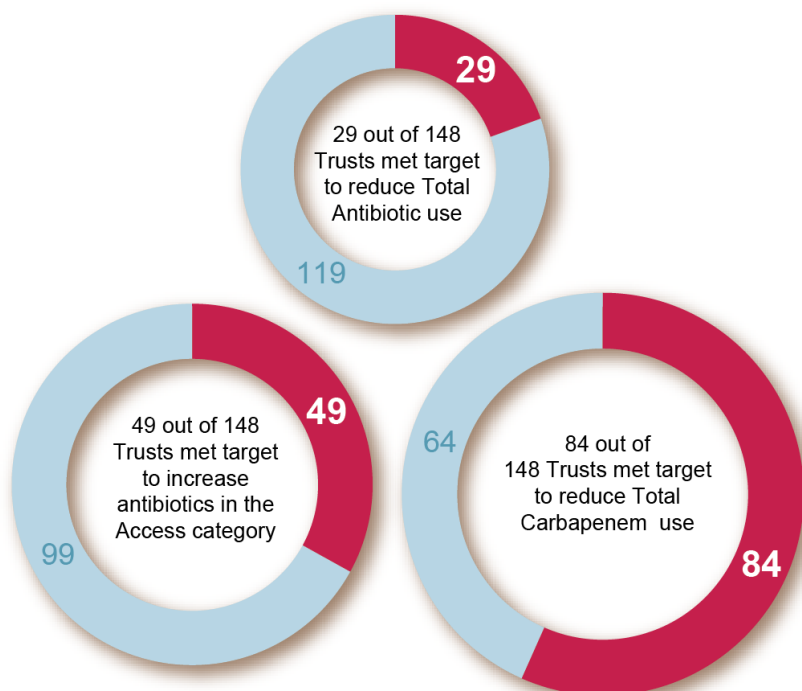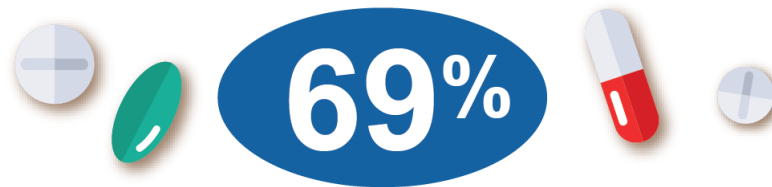
of antibiotics that were prescribed to 26,242 hospital patients with a diagnosis of possible sepsis had a timely and expert review with documented outcome and where appropriate IV to oral switch decision in 2018/19

Reducing inappropriate antibiotic prescribing in primary care 2015-2019
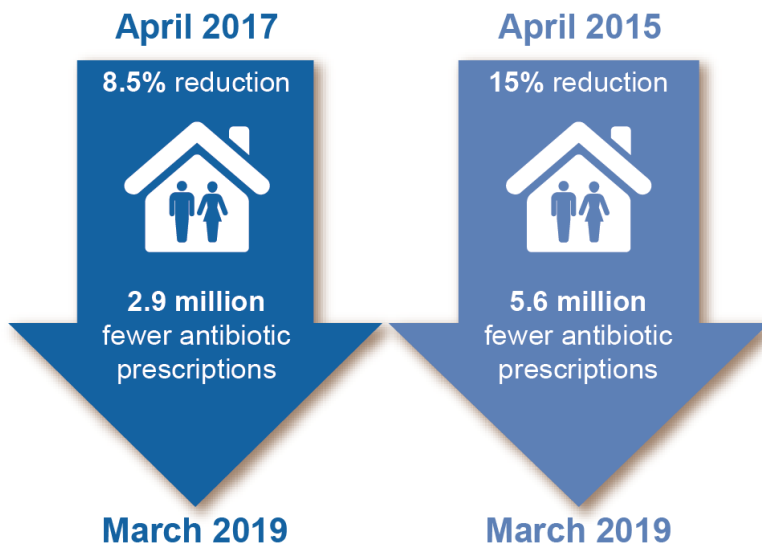
Reducing broad spectrum antibiotic prescribing in primary care 2015-2019
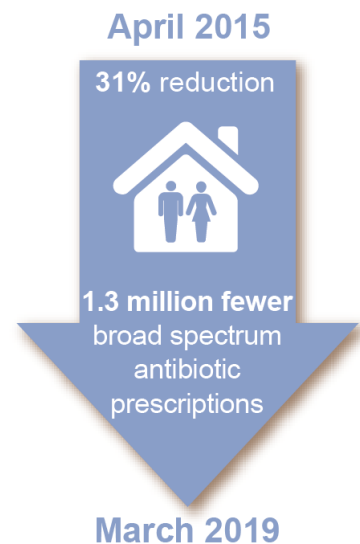
April 2017

8.5% reduction

2.9 million fewer antibiotic prescriptions

March 2019

April 2015

15% reduction

5.6 million fewer antibiotic prescriptions

March 2019

April 2015

31% reduction

1.3 million fewer broad spectrum antibiotic prescriptions

March 2019

**Improving the management of Urinary
Tract Infection in primary care 2017-2019**

40%
reduction in
trimethoprim use

April 2017

March 2019

0.5 million
fewer prescriptions in
people aged 70+ years
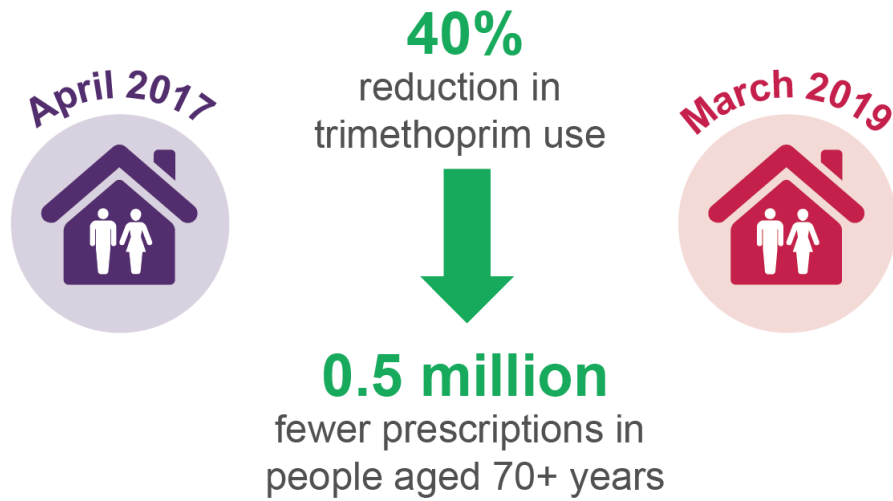
Timeline of *C. auris* detection and activities in England

2013

2015

2016

September 2013: First detection of *Candida auris*

November 2015: First Hospital Outbreak declared

June 2016: National Incident Management Team convened

June 2016: Guidance for the laboratory investigation, management and infection prevention and control for cases of *Candida auris* published

July 2016: *Candida auris* identified in England article published in the HPR

August 2016: *Candida auris* in England: an update published in the HPR

January 2017: Yeasticidal activity of chemical disinfectants and antiseptics against *Candida auris* assessed

2017

November 2016: Third Hospital Outbreak declared

August 2016: Second Hospital Outbreak declared

December 2017: All Hospital Outbreaks declared over

August 2017: *Candida auris*; infection control in community care settings published

August 2017: *Candida auris*; a guide for patients and visitors

August 2017: Updated Guidance for the laboratory investigation, management and infection prevention and control for cases of *Candida auris* published

2018

May 2018: Re-introduction and transmission in second outbreak hospital; contained

April 2018: European Centre of Disease Prevention and Control Rapid Risk Assessment on *Candida auris* in Healthcare Settings updated

March 2018: Intensive care unit *Candida auris* prevalence survey concluded

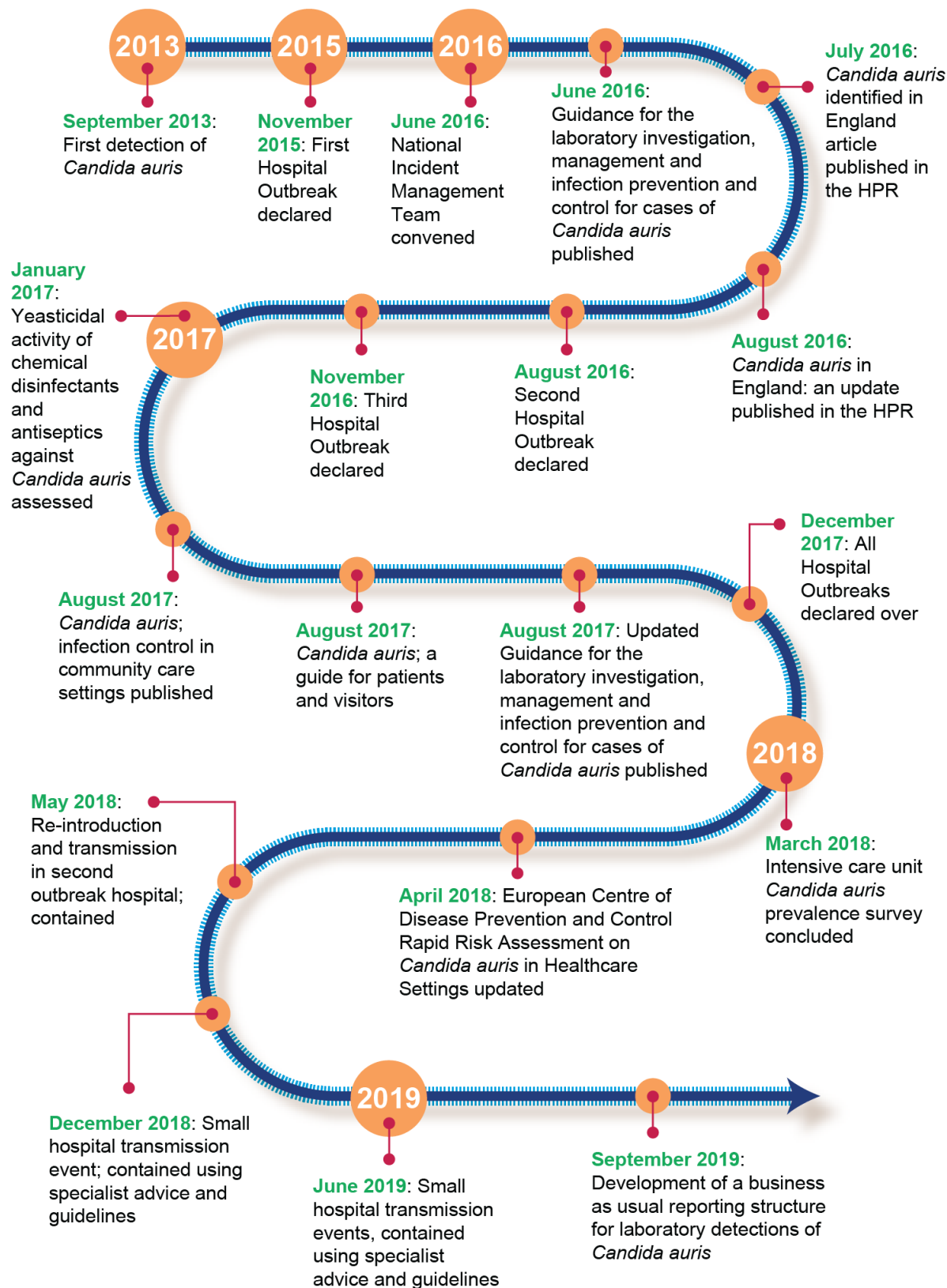**December 2018**: Small hospital transmission event; contained using specialist advice and guidelines

2019

June 2019: Small hospital transmission events, contained using specialist advice and guidelines

September 2019: Development of a business as usual reporting structure for laboratory detections of *Candida auris*

Antimicrobial Stewardship tools developed and tested

Antimicrobial Stewardship Peer Review Tool assessing:

- AMS leadership and management
- antimicrobial prescribing management
- surveillance, resistance and standards
- risk assessments for antimicrobials
- patient and carers
- education and training on the use of antimicrobials

Antimicrobial prescribing and stewardship template report for PHE Fingertips was developed

Antibiotic prescribing

Antimicrobial resistance

HealthCare associated infections

Antimicrobial Stewardship
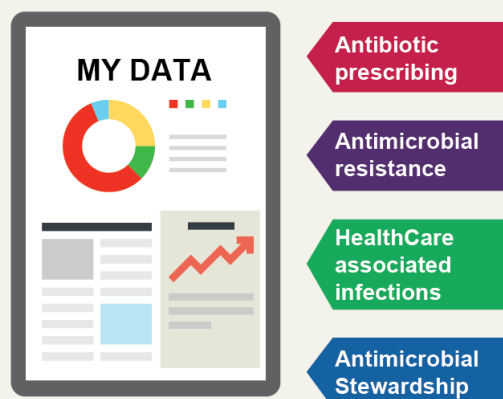
The TARGET Toolkit

www.rcgp.org.uk/targetantibiotics

Over 61,000 views per year

Promoted by 99% of CCGs

Recognised in the UK AMR 5-year national action plan

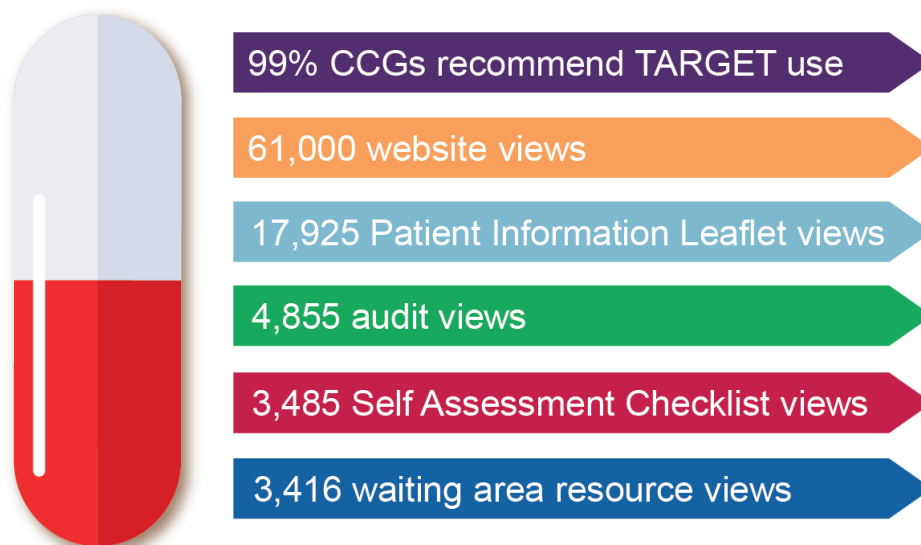New UTI resources have received NICE endorsement

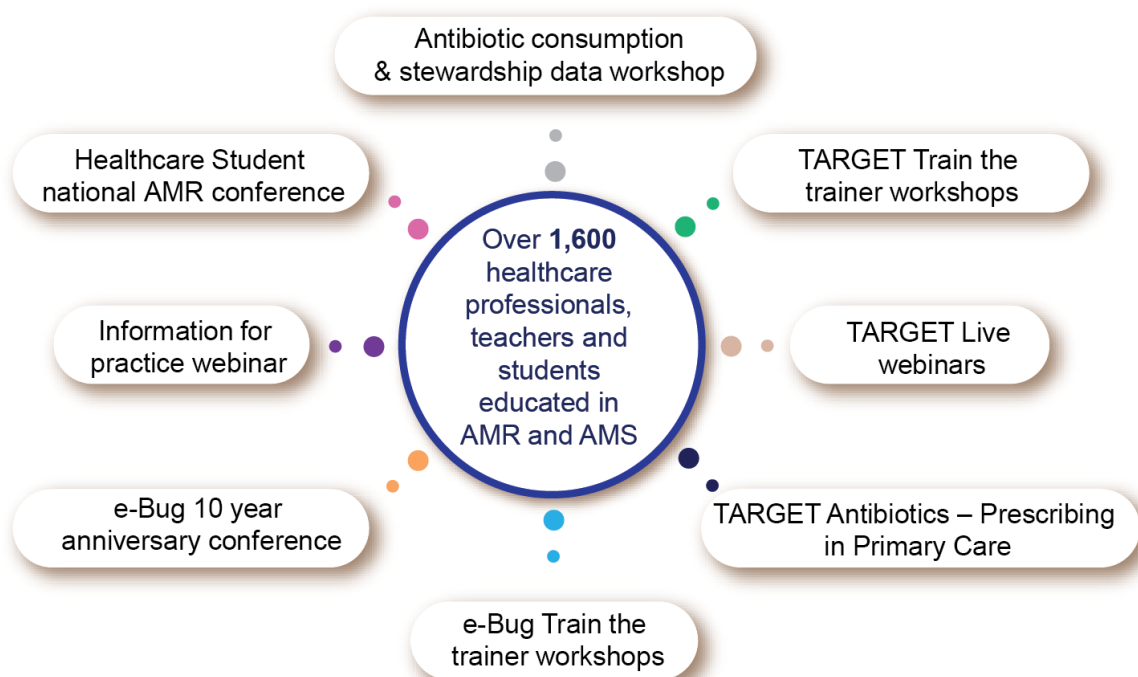Over 12,000 patient information leaflets were downloaded

Almost 2,000 antibiotic prescribing audits were viewed

TARGET toolkit usage

- 99% CCGs recommend TARGET use
- 61,000 website views
- 17,925 Patient Information Leaflet views
- 4,855 audit views
- 3,485 Self Assessment Checklist views
- 3,416 waiting area resource views

Professional education and training overview

Antibiotic consumption & stewardship data workshop

Healthcare Student national AMR conference

TARGET Train the trainer workshops

Information for practice webinar

Over **1,600** healthcare professionals, teachers and students educated in AMR and AMS

TARGET Live webinars

e-Bug 10 year anniversary conference

TARGET Antibiotics – Prescribing in Primary Care

e-Bug Train the trainer workshops

1. Introduction

The English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR) was established in 2013 to support Public Health England (PHE) in the delivery of specific aspects of the UK Antimicrobial Resistance (AMR) Strategy 2013 to 2018.[1] This report, which is the final one focussing on this strategy, also highlights work that has started in support of the objectives in the UK's new five year national action plan for tackling AMR from 2019 to 2024.

The two key aims of ESPAUR are to:

- develop and maintain robust surveillance systems for monitoring and reporting trends in antimicrobial use and resistance in order to measure the impact of surveillance, antimicrobial stewardship (AMS) and other interventions on AMR that affect human health
- develop systems and processes to optimise antimicrobial prescribing across healthcare settings

To meet these aims, we have improved our automated data collection systems which collect AMR data from NHS microbiology laboratory information systems. Ninety-nine percent of laboratories now submit AMR data electronically through our automated surveillance system, with more than 90% of laboratories reporting susceptibility data daily. We have also improved our feedback of this data to our end-users through bespoke reports available online to registered NHS users2 and through our public-facing access on Fingertips Public Health Profiles using the following key profiles - AMR Local Indicators, GP profile and Public Health Outcomes Framework.3 The data on Fingertips can be downloaded and further analysed using a range of available statistical tools. From April 2016 to March 2019, 15,236 users accessed the AMR Local Indicators 53,712 times, spending an average of 19 minutes on the site per visit.

The trends in resistance in the priority drug/bug combinations that were a key component of the 2013-2018 strategy are outlined in Chapter 2. With the improvements in both AMR and antibiotic use data, we can now demonstrate

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[1] UK 5 year AMR Strategy 2013- 2018
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/244058/20130902_UK_5_year_AMR_strategy.pdf
[2] Registration page for AMR reports at PHE https://sgss.phe.org.uk/Security/RegisterTerms
[3] Public Health Profiles – Fingertips https://fingertips.phe.org.uk/

the impact of changes in antibiotic prescribing guidelines on AMR. We have also shown the capacity to rapidly react to and investigate exceptional clinical situations such as the impact of shortages of piperacillin/tazobactam and the subsequent increased use of third-generation cephalosporins and fluoroquinolones on antimicrobial-resistant Gram-negative bloodstream infections; the numbers of which increased by 15% between 2017 and 2018.

This chapter also demonstrates a 4% reduction in trimethoprim resistance in urinary tract infections between 2015 and 2018, associated with a reduction in trimethoprim use.

Chapter 3 presents analysis on the increasing number of carbapenemase-producing Gram-negative bacteria and the work on-going with the NHS to mitigate the impact of this trend in England. This work is arguably having an effect, with less than 150 reported bloodstream infections caused by carbapenemase-producing Gram-negative bacteria (less than 0.5% of all Gram-negative bacteria), which is in marked contrast to the situation reported in a number of other countries.

We have also worked with partners to improve the availability and open-access of antimicrobial prescribing data and optimise antimicrobial prescribing across healthcare settings. The current data, which are reported in Chapter 4, shows the excellent progress to reduce overall and broad-spectrum prescribing in primary care settings. Reducing total antibiotic prescribing has proved more challenging in secondary care, though significant progress in reducing key antibiotics such as piperacillin/tazobactam and carbapenems has occurred.

Over the last four years, we have worked with NHS England and NHS Improvement to develop financial incentives for quality improvement in primary and secondary care and to measure their impact following implementation. The outcomes of the 2017-19 schemes are highlighted in Chapter 5, along with insights into how these schemes could be improved in the future.

An update on the current work on fungal surveillance and stewardship is included in Chapter 6; including an update on the NHS England Improving Value Antifungal Stewardship Project and Candida auris.

In Chapter 7, we report on AMS initiatives, including an assessment of a secondary care peer-review tool for AMS. It also outlines the qualitative research and process evaluations that have been performed on AMS tools for primary care, particularly outlining work to develop urinary tract infection prevention, diagnosis and management tools. Chapter 8 highlights the education, training and public engagement work including the public and

professional campaigns, Keep Antibiotics Working and Antibiotic Guardian respectively.

Finally, the engagement and delivery of the partner organisations who sit on the ESPAUR oversight group is presented in Chapter 9. We would like to use this opportunity to express our enormous gratitude to the individuals who attended meetings and provided relevant input, which significantly helped ESPAUR to continue to develop and improve our outputs.

2. Antimicrobial Resistance

Introduction

This chapter focusses on the trends in resistance for the drug/bug combinations recommended for surveillance by the Advisory Committee on Antimicrobial Prescribing, Resistance and Healthcare-Associated Infections (APRHAI)[4] in support of the 2013-2018 UK 5-year Antimicrobial Resistance (AMR) strategy.[5] It includes the "shadow" list of drug/bug combinations for which APRHAI recommended a watching brief should be kept (Annex Chapter 2). The data presented cover the period from 2014 to 2018, except where shorter timelines are reviewed in more detailed analyses, and when reviewing the 5-year strategy where data are compared to the baseline period of 2013. This report also draws focus on AMR in non-blood clinical isolates and a review of trends in glycopeptide-resistant enterococci (GRE). The data sources and analytical methods used are described in Annex Chapter 2 of this report.

Developments towards ongoing actions highlighted in earlier ESPAUR reports[6] are presented including the development of methodology to assess the burden of excess mortality and highlights from the One Health and international collaborations over the last year.

As part of its ongoing efforts to tackle the threat to public health posed by AMR, the UK Government published a follow up 5-year[7] and 20-year national action plan (NAP).[8] Building on the previous strategy (2013 to 2018), several surveillance systems and methodologies have been developed with a view to improving data quality and awareness of critical issues regarding AMR. In this chapter we introduce the key elements for AMR surveillance in the future. It highlights the continued impetus to improve, measure and monitor the burden of AMR, introduced in the 2018 ESPAUR

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[4]Advisory Committee on Antimicrobial Prescribing, Resistance and Healthcare Associated Infection Annual report 2015. Available online from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/707165/ARHAI_annual_report_2014_to_2015.pdf

[5] DH, DEFRA. UK Five Year Antimicrobial Resistance Strategy 2013 to 2018. Published Setemeber 2013. Available from https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/244058/20130902_UK_5_year_AMR_strategy.pdf

[6] PHE. English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR) Report 2018. Published October 2018. Available from: https://www.gov.uk/government/publications/english-surveillance-programme-antimicrobial-utilisation-and-resistance-espaur-report

[7] DHSC. Tackling antimicrobial resistance 2019 to 2024: the UK's 5-year national action plan. January 2019. Accessed through: https://www.gov.uk/government/publications/uk-5-year-action-plan-for-antimicrobial-resistance-2019-to-2024

[8] DHSC. Contained and controlled: the UK's 20-year vision for antimicrobial resistance. January 2019. Accessed via: https://www.gov.uk/government/publications/uk-20-year-vision-for-antimicrobial-resistance

Report,[9] to feed in to the NAP target to reduce antimicrobial-resistant infections by 10% by 2024.

Box 2.1 - New susceptibility definitions

In January 2019, the European Committee on Antimicrobial Susceptibility Testing (EUCAST) introduced new definitions for susceptibility test results. The 'Intermediate' susceptibility result has been replaced by a new category designated 'Susceptible, increased exposure' (SIE), meaning that there is a high likelihood of therapeutic success if the dosing regimen is amended to increase exposure to the agent by increasing its concentration at the site of infection.[10]

A small number of English laboratories use the US Clinical & Laboratory Standards Institute (CLSI) breakpoint definitions. These definitions retain the 'Intermediate' (I) susceptibility result for many antibiotics to accommodate technical variation, or the potential to be susceptible if concentrated at certain anatomical sites; however, CLSI have a term, 'Susceptible Dose Dependent (SSD)' for antibiotics where a higher dose or exposure can be used, however this is only available as a result for some pathogen/antimicrobial combinations.[11]

In line with the changes in EUCAST definitions and in contrast to previous ESPAUR Reports,[12,13] the antimicrobial susceptibility test results within the present report are presented as the proportion of isolates that are resistant rather than non-susceptible or intermediate.

Trends in resistance in Gram-negative bloodstream infections

Incidence of bacteraemia for each of the key pathogens highlighted in the 5-year Strategy increased between 2014 and 2018.[14] Of the organisms under review, *Escherichia coli* was the commonest cause of bloodstream infection (BSI) and increased, from 65.7 cases per 100,000 population in 2014 to 76.0 cases per 100,000 population in 2018, an overall increase of 12%. In 2018, the total number of BSIs

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[9] PHE. English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR) Report 2018. Published October 2018. Available from: https://www.gov.uk/government/publications/english-surveillance-programme-antimicrobial-utilisation-and-resistance-espaur-report

[10] **European Committee on Antimicrobial Susceptibility Testing (EUCAST).** New definitions of S, I and R. 2019. http://www.eucast.org/newsiandr/**. Accessed 20 August 2019**

[11] Molitor, E. Susceptibility Categories Should Be Agreed Upon. *J Clin Microbiol* 2019 57(9)

[12] PHE. English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR) Report 2016. Published November 2016. Available from: https://www.gov.uk/government/publications/english-surveillance-programme-antimicrobial-utilisation-and-resistance-espaur-report

[13] PHE. English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR) Report 2017. Published October 2017. Available from: https://www.gov.uk/government/publications/english-surveillance-programme-antimicrobial-utilisation-and-resistance-espaur-report

[14] Advisory Committee on Antimicrobial Prescribing, Resistance and Healthcare Associated Infection Annual report 2015. Available online from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/707165/ARHAI_annual_report_2014_to_2015.pdf

reported as positive for one of the key pathogens was 81,042 (145 per 100,000 population), up from 64,876 (119 per 100,000 population) reported in 2014.
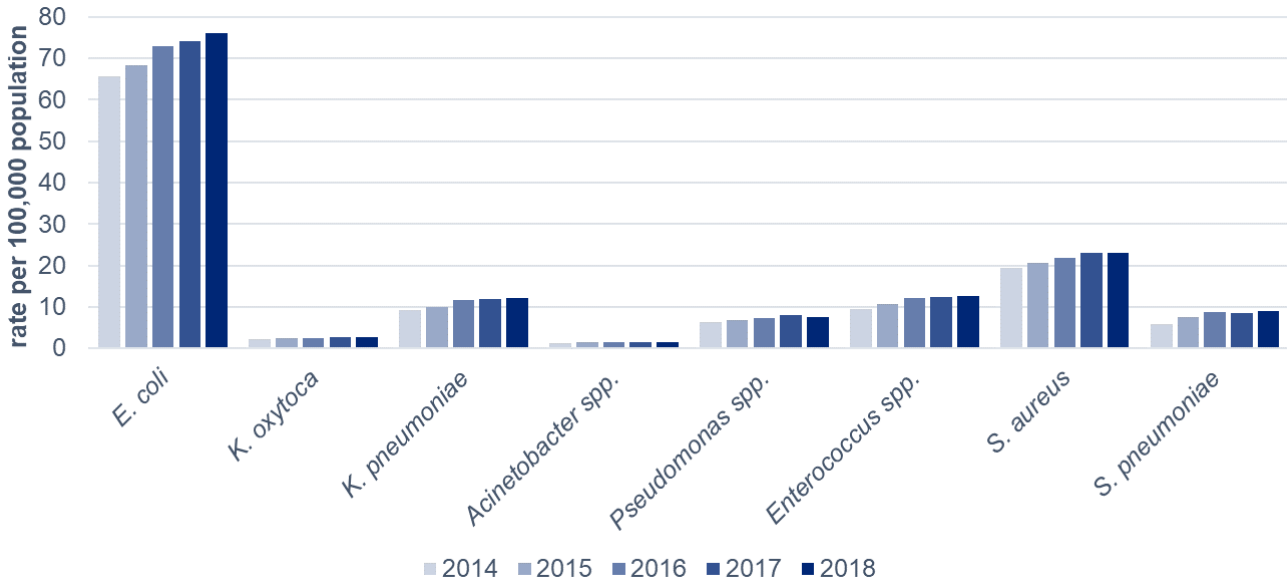
E. coli and *Staphylococcus aureus* incidence are based on mandatory surveillance reports
Figure 2.1. Incidence of bloodstream infection caused by key pathogens*, per 100,000 population; England 2014 and 2018

The age distribution of BSIs reported as positive for one of the key pathogens in 2018 indicated higher rates in infants and in the elderly, with an incidence of 225 per 100,000 in the <1 year age group, and 276 per 100,000 and 694 per 100,000 population in the 65 to 74 years and the 75 year and over age groups respectively.

The five-year trends in resistance to key antibiotics in clinically important Gram-negative and Gram-positive pathogens causing bacteraemia, are shown in Figure 2.2 to Figure 2.4. Detailed trend data, including numbers reported as susceptible or resistant are available on-line in the data tables and PowerPoint presentations published alongside this report.

As shown in Figure 2.2, the proportion of isolates of *E. coli*, *Klebsiella pneumoniae* and *Klebsiella oxytoca* resistant to key antibiotics remained stable or increased slightly between 2014 and 2018. Further investigations looking at the increases in resistance in *E. coli* bacteraemia is shown in Box 2.4.

Box 2.2 - Piperacillin/tazobactam and co-amoxiclav antimicrobial susceptibility testing.
Pseudomonas spp. and *E. coli* non-susceptibility to piperacillin/tazobactam and urinary *E. coli* isolates non-susceptibility to co-amoxiclav appeared to increase significantly between December 2016 and June 2017. However, ongoing work by PHE has questioned the robustness of this finding, as some data, particularly that reported from laboratories using specific automated antibiotic susceptibility testing devices were over-estimating resistance levels, particularly intermediate resistance in the case of piperacillin/tazobactam testing in comparison to alternative methods. Following notification of these findings, and changes in laboratory methods including the automated reporting cards and software updates, the numbers of reports of intermediate resistance to piperacillin/tazobactam fell sharply during 2018. The changes in S, I and R definitions introduced in 2019 by EUCAST, described in Box 2.1, have shifted the focus to whether some can still be used as a therapeutic option, looking at resistance without including intermediate results. Clinicians working with results from laboratories using EUCAST definitions are less likely to feel the impact of mis-classification of resistance, keeping more antibiotics available to use.
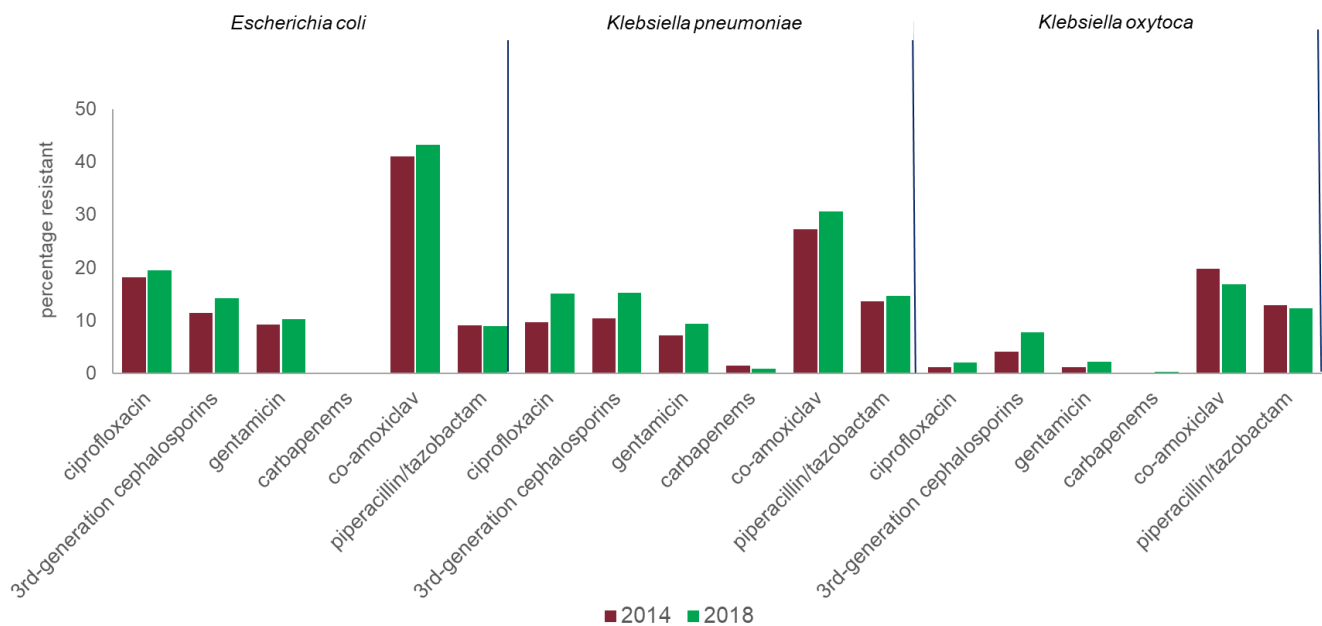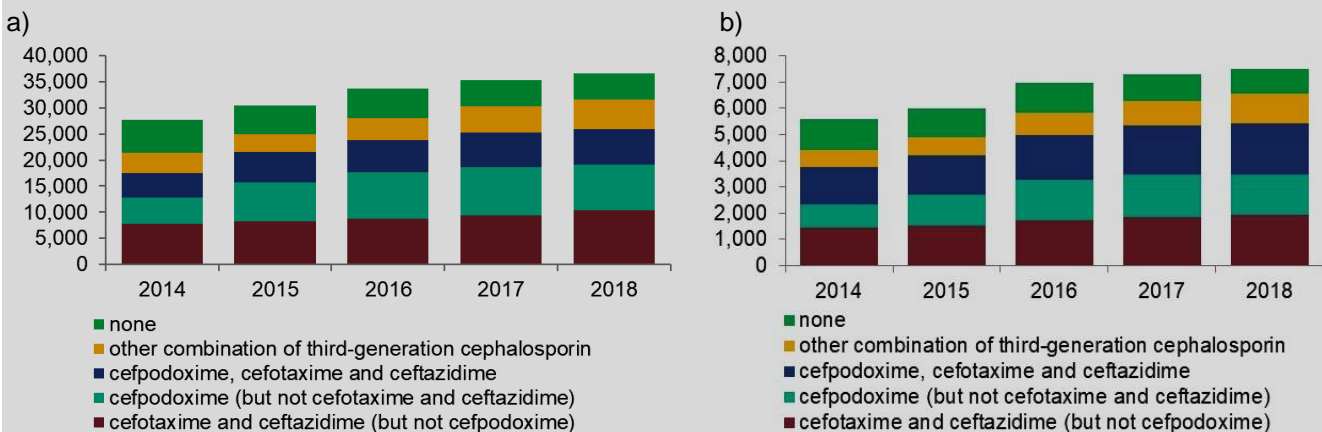

Figure 2.2. Antibiotic resistance in Enterobacterales species BSI to key antibiotics; England 2014 and 2018

Of note are increases in resistance to both ciprofloxacin and third-generation cephalosporins in *K. pneumoniae*, from 10% to 15% between 2014 and 2018. In contrast, the proportion of isolates of *Pseudomonas* spp. resistant to key antibiotics remained stable or decreased slightly over the same period (Figure 2.3). More detailed trend data, including numbers reported as susceptible, intermediate or resistant are available in the appendix (available on-line).

Box 2.3 – Using cephalosporin susceptibility as markers for identifying Extended-Spectrum β-lactamases

Resistance to third-generation cephalosporins in *E. coli* (and other Enterobacterales) is a broad indicator of the presence of extended-spectrum β-lactamases (ESBLs), resulting in bacteria resistant to cephalosporins and associated with increased morbidity and mortality. Accurate and timely detection of ESBL is important to ensure appropriate antimicrobial therapy is given.[15,16] The guidance for laboratories in England indicates that identification of potential ESBL presence, using ceftazidime and cefotaxime and/or cefpodoxime susceptibility tests, in all clinically relevant isolates of *E. coli* or *Klebsiella* spp.should be assessed.[17,18]

Local laboratory testing procedures for ESBL identification differ, which ensures that the level of testing for third-generation cephalosporin antibiotics vary by laboratory. All three recommended third-generation cephalosporin antibiotics, alongside ceftriaxone, are used to assess third-generation cephalosporin resistance within this report. Nineteen percent of *E. coli* and twenty-six percent of *K. pneumoniae* bacteraemia reports were tested for all three recommended third-generation cephalosporins in 2018 (Box figure 2.1) with >80% of sampes reported as tested against at least one third-generation.

a)

b)

- none
- other combination of third-generation cephalosporin
- cefpodoxime, cefotaxime and ceftazidime
- cefpodoxime (but not cefotaxime and ceftazidime)
- cefotaxime and ceftazidime (but not cefpodoxime)

*from cefotaxime, ceftazidime, cefpodoxime and ceftriaxone

Box figure 2.1. The number of third-generation cephalosporin* susceptibility tests reported per episode of a) *E. coli* and b) *K. pneumoniae* bacteraemia

[15] Rottier WC, Ammerlaan HS, Bonten MJ. Effects of confounders and intermediates on the association of bacteraemia caused by extended-spectrum beta-lactamase-producing Enterobacteriaceae and patient outcome: a meta-analysis. *J Antimicrob Chemother* 2012;67:1311-20.

[16] Schwaber MJ, Carmeli Y. Mortality and delay in effective therapy associated with extended-spectrum beta-lactamase production in Enterobacteriaceae bacteraemia: a systematic review and meta-analysis. *J Antimicrob Chemother* 2007;60:913-20.

[17] BSAC. Detection of extended-spectrum β-lactamases (ESBLs) in *E. coli* and *Klebsiella* species. http://bsac.org.uk/wp-content/uploads/2012/02/Ecoliklebsiella.pdf

[18] Public Health England. (2016). Detection of Enterobacteriaceae producing extended spectrum β-Lactamases. UK Standards for Microbiology Investigations. B 59 Issue 4.1. https://www.gov.uk/uk-standards-for-microbiology-investigations-smi-quality-andconsistency-in-clinical-laboratories
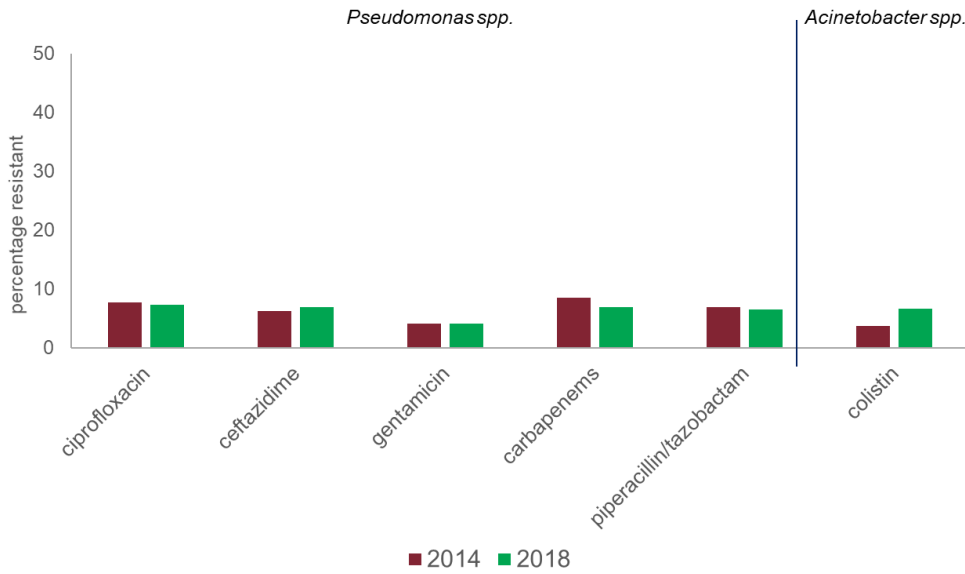
Figure 2.3. Antibiotic resistance in *Pseudomonas* spp. and *Acinetobacter* spp. BSI to key antibiotics; England 2014 and 2018

In response to the need to preserve last resort antibiotics, new combinations of antibiotics and inhibitors, such as ceftazidime/avibactam and ceftaroline/tazobactam, have been made available for use within England. More detail on these antibiotics and their use in England is provided in Chapter 4. Although susceptibility testing for these newer antibiotics is currently selective (resistance to first and second line antibiotics) and uncommon resistance has nonetheless been recorded. In 2018, 505 (1.4%) E. *coli*, 134 (2.0%) *K. pneumoniae* and 101 (2.4%) *Pseudomonas* spp. from blood were tested for ceftazidime/avibactam susceptibility, and 3 (0.6%), 8 (6.0%) and 6 (5.9%) were reported as resistant, respectively. Similarly, for ceftaroline/tazobactam, in 2018, 298 (0.8%), 67 (1.0%) and 117 (2.8%) of *E. coli*, *K. pneumoniae* and *Pseudomonas* spp. bacteraemia respectively were tested for susceptibility, and 19 (6.4%), 17 (25.4%) and 10 (8.5%) were resistant. The data published for *E. coli* bacteraemia via the Fingertips web portal demonstrate that increases in resistance vary geographically (by CCG as well as by NHS Trust).[19] A review of the resistance increases in *E. coli* bacteraemia following hospital admission show that hospital-onset bacteraemia over time have higher increases in percentage resistance compared with those considered community-onset (Box 2.4).

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[19] PHE. Public Health Profiles – AMR local indicators. Available: https://fingertips.phe.org.uk/profile/amr-local-indicators

Box 2.4 – Comparison of levels of resistance in community-onset versus hospital-onset bloodstream infections caused by *E. coli* and relationship with antibiotic prescribing

A total of 36,967 (87% of 42,533 total cases) *E. coli* bacteraemia mandatory surveillance cases reported in 2018 were linked to susceptibility data in SGSS. The proportion of resistant isolates was higher in hospital-onset compared to community-onset cases (Box figure 2.2). The difference was most noticeable for carbapenems where resistance was 76% higher in hospital-onset cases, although it should be noted that the overall proportion of resistant isolates remained very low at 0.5% (29 cases). Resistance to piperacillin/tazobactam, gentamicin, third-generation cephalosporins and ciprofloxacin were also higher in hospital-onset compared to community-onset cases (43%, 34%, 33% and 24% higher respectively).

Between 2012 and 2018 resistance of *E. coli* from BSI to key antibiotics was consistently higher in hospital-onset cases than in community-onset cases. In terms of the trend in resistance there were sharp increases from 2016 in resistance to third-generation cephalosporins, carbapenems, gentamicin and ciprofloxacin, especially in hospital-onset cases. The possibility that resistance in community-onset cases may relate, at least in part, to prior healthcare exposure will be further investigated.

a)   b)
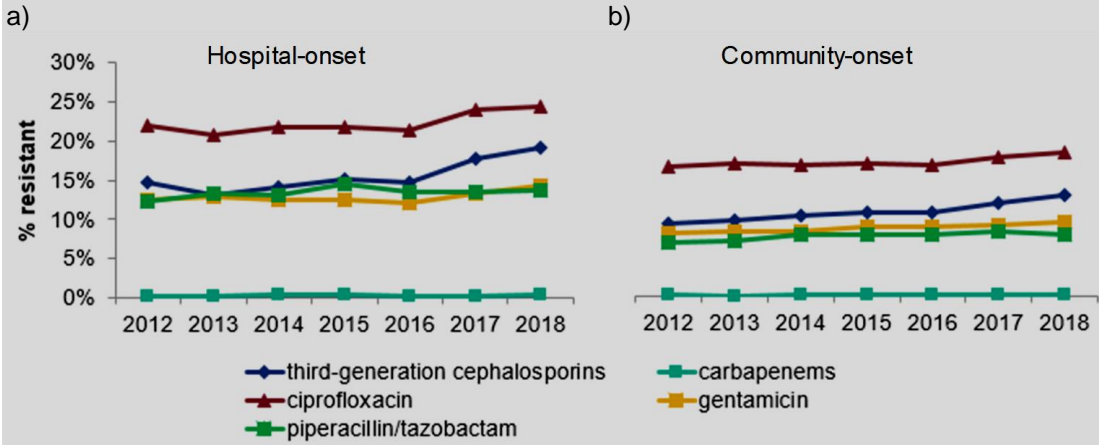
Box figure 2.2. Proportion of *E. coli* bacteraemia resistant to key antibiotics in a) hospital-onset and b) community-onset cases, England 2012- 20

Looking at demographic analysis, using reports of *E. coli* bacteraemia, for both antibiotic groups the increase in resistance was predominantly observed in adults, whereas in children a reduction in resistance was seen over the last five years (Box figure 2.3). The increase in third-generation cephalosporin resistance between 2014 and 2018 was greater in males than females (27% vs. 19%), and the increase in quinolone resistance was similar between males and females between 2014 and 2018, at 8% and 10% respectively.

a)

Third-generation cephalosporin

b)
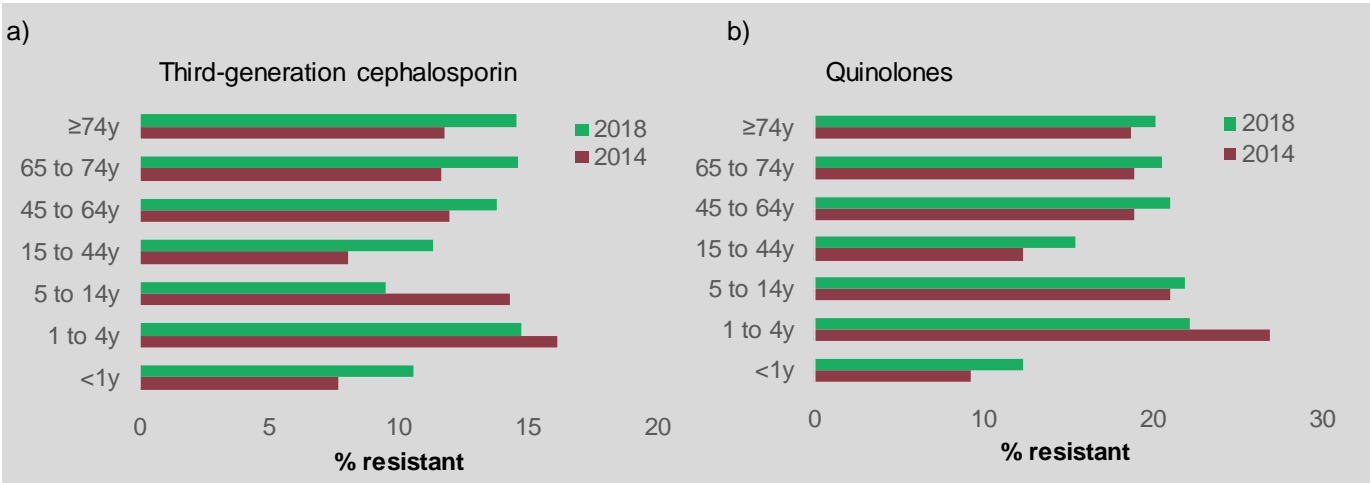
Quinolones

Box figure 2.3. Antibiotic resistance for a) third-generation cephalosporin and b) quinolones in *E. coli* bacteraemia by age group, England 2014-2018

Increases in third-, fourth- and fifth-generation cephalosporin and quinolone prescribing occured between 2016 and 2018, possibly as a result of the shortage of piperacillin/tazobactam (Box figure 2.4; more detail available in Chapter 4).

a)

b)
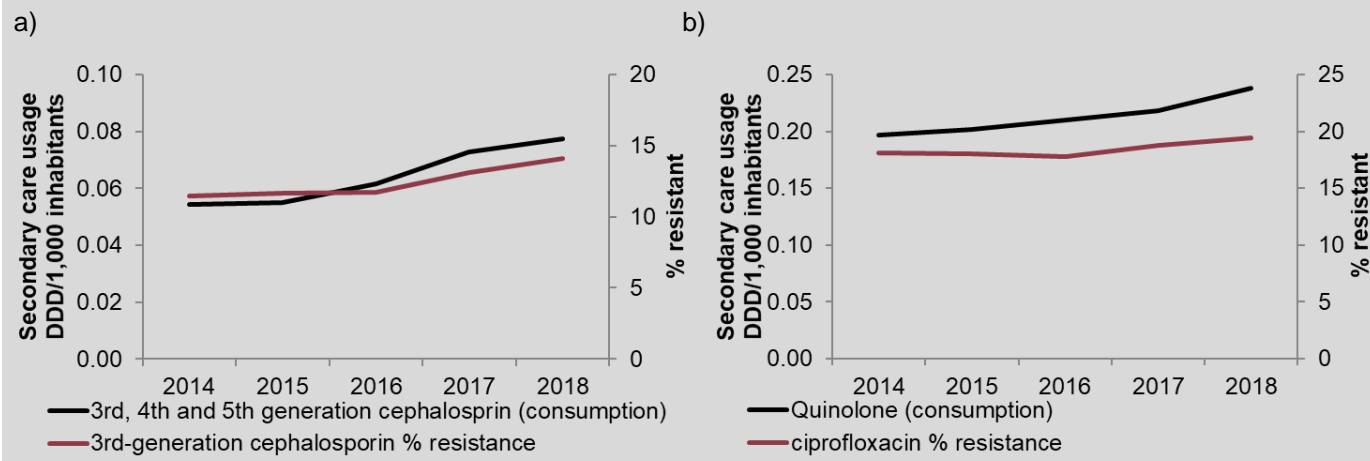
DDD – Defined Daily Doses

Box figure 2.4. Trend in secondary care antibiotic consumption (DDD per 1,000 inhabitants per day) and percentage resistance in *E. coli* bacteraemia for a) third-generation cephalosporin and b) quinolones, England 2014-2018

Trends in resistance in Gram-positive bloodstream infections

Data on susceptibility of *Streptococcus pneumoniae* BSI are shown in Figure 2.4. The proportions of isolates resistant to penicillin, tetracycline and to erythromycin remained stable between 2014 and 2018, at 1%, 6% and 7% respectively. Resistance to the moxifloxacin and/or levofloxacin (fluoroquinolones) was noted at 1% in *S. pneumoniae* BSI in 2018.

The overall proportion of enterococci from bloodstream isolates reported as resistant to glycopeptides decreased marginally between 2014 and 2018, from 16% to 15%. A more detailed look at trends in GRE, including species and infection type, is presented later in this chapter. *Enterococcus* spp. bacteraemia resistance to linezolid was 1% in 2018 and, while only rarely tested, resistance to daptomycin was 4%.
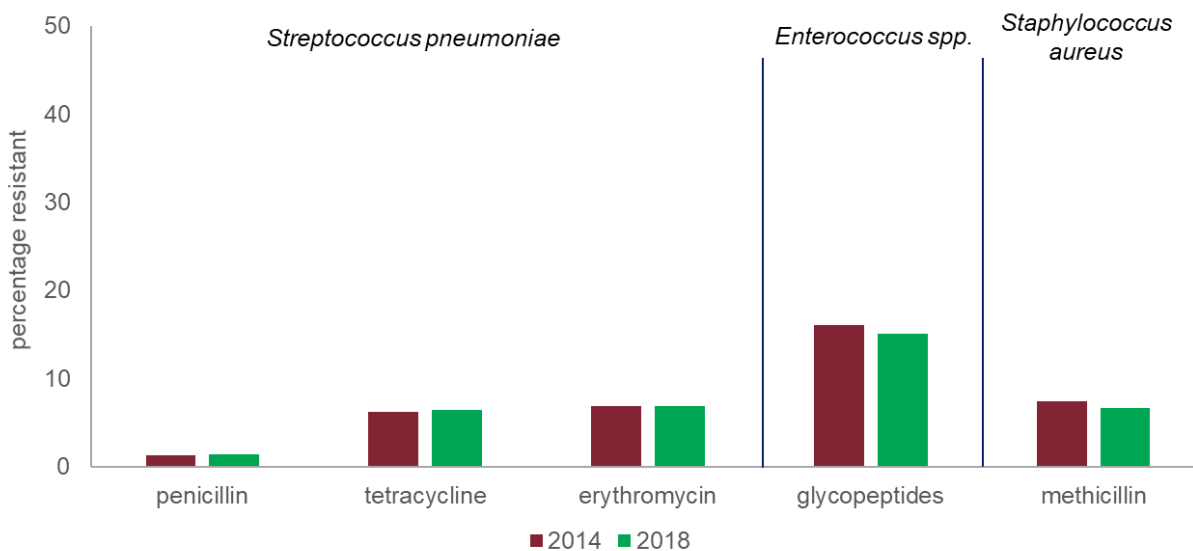
Figure 2.4. Antibiotic resistance in *Enterococcus* spp., *S. pneumoniae* and *S. aureus* BSI to key antibiotics; England 2014 and 2018

Based on reporting to the national mandatory surveillance system, there was little change in the proportion of *Staphylococcus aureus* BSI that were methicillin-resistant *S. aureus* (MRSA) between 2014 (7.5%) and 2018 (6.7%). Resistance to daptomycin and linezolid remained low in *S. aureus* bacteraemia in 2018, with <1% resistance reported for both antibiotics.

Box 2.5 highlights trends in macrolide resistance in Gram-positive bacteria where macrolides are used for treatment, particularly in patients with penicillin allergy.

Box 2.5 – Macrolide resistance in Gram-positive infections

Although a decrease in prescribing of macrolides in hospitals and primary care is reported in Chapter 4, the numbers of BSIs caused by macrolide-resistant Gram-positive bacteria increased over time (Box figure 2.5). Variation in burden was seen by age group, with higher numbers of resistant infections seen in patients over-25 years of age, the levels increasing with increasing age.
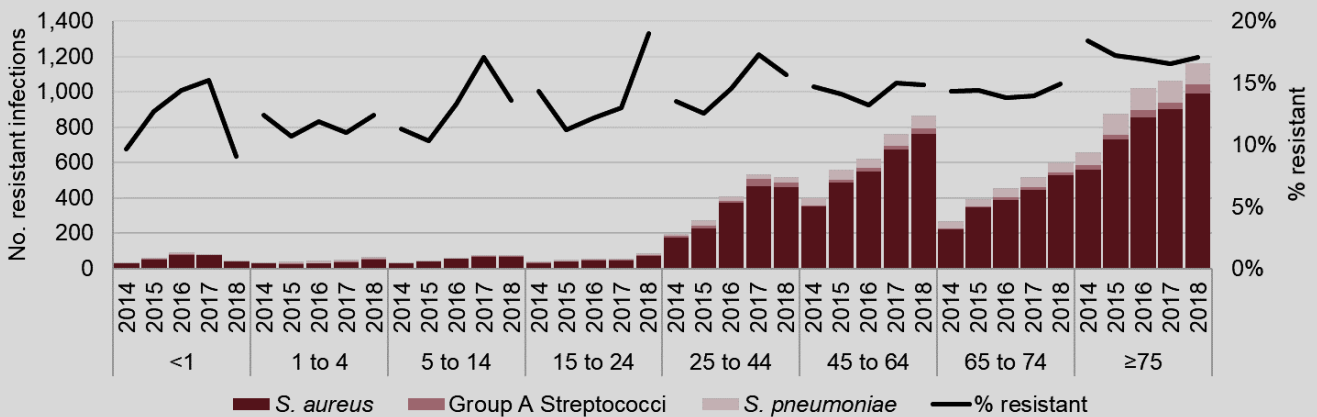
Box figure 2.5. Number and proportion of Gram-positive bacteraemia resistant to macrolides by age group in England, 2014-2018

In group A *Streptococcus* isolated from paediatric throat swabs in 2018, macrolide resistance varied dramatically by age group, ranging from 3.4% resistance in the 1-4-year age group to 18.2% in the young adult age group (Box table 2.1)

Box table 2.1. Erythromycin susceptibility in Group A *Streptococcus* throat swabs in paediatric age groups, England 2018

Age Group	Susceptible	Resistant	Total	% Resistant
<1y	135	7	142	4.9%
1-4y	4,874	169	5,043	3.4%
5-14y	14,238	657	14,895	4.4%
15-24y	3,910	871	4,781	18.2%
≥25y	15,467	1,081	16,548	6.5%
Total	**38,634**	**2,785**	**41,419**	**6.7%**

5 year AMR Strategy 2013 to 2018, key drug/bug combinations review

The UK 5-year AMR strategy[20] highlighted key drug/bug combinations to monitor, which have been the focus of the report so far. The strategy aimed to assess change in antibiotic resistance in 2018 in comparison to values recorded in 2013. The proportion resistant for each combination have been presented in Table 2.1, with a trendline.

Table 2.1: Trends in resistance in key drug/bug combinations in bacteraemia¥, 2013 to 2018, England*

Bacteria	Antibiotics	% Resistant			Trend
		2013	2018	P value	
Escherichia coli	ciprofloxacin	17.6	19.4	<0.001	
	third-generation cephalosporins	10.7	14.1	<0.001	
	gentamicin	9.2	10.2	<0.001	
	carbapenems	0.1	0.1	0.097	
	co-amoxiclav	37.3	43.3	<0.001	
	piperacillin/tazobactam	8.4	8.9	0.066	
Klebsiella pneumoniae	ciprofloxacin	9.7	15.1	<0.001	
	third-generation cephalosporins	10.7	15.2	<0.001	
	gentamicin	8.2	9.4	0.042	
	carbapenems	0.7	0.9	0.316	
	co-amoxiclav	24.0	30.7	<0.001	
	piperacillin/tazobactam	13.2	14.6	0.043	
Klebsiella oxytoca	ciprofloxacin	1.4	2.0	0.326	
	third-generation cephalosporins	5.0	7.8	0.897	
	gentamicin	1.2	2.1	0.099	
	carbapenems	0.4	0.3	0.867	
	piperacillin/tazobactam	11.9	12.2	0.828	
Pseudomonas spp.	ceftazidime	6.1	6.9	0.215	
	carbapenems	7.4	6.9	0.438	
Acinetobacter spp.	colistin	5.2	6.7	0.727	
Streptococcus pneumoniae	penicillin	1.2	1.4	0.453	
	erythromycin	7.2	6.5	0.321	
Enterococcus spp.	glycopeptides	14.6	15.1	0.457	
Staphylococcus aureus	meticillin	9.0	6.7	<0.001	
Neisseria gonorrhoeae	ceftriaxone	0	0	- - -	
	azithromycin‡	0.8	9.7	<0.001	

¥ *N. gonorrhoeae* resistance figures are taken from the GRASP sentinel surveillance system which includes specimens other than blood; *Third-generation cephalosporin = ceftazidime and/or ceftazidime; carbapenems = meropenem and/or imipenem; ‡ In 2018 the azithromycin breakpoint for *N. gonorrhoeae* was removed by EUCAST, values presented for 2018 are based on the previous breakpoint ≥0.5 mg/l

[20] Advisory Committee on Antimicrobial Prescribing, Resistance and Healthcare Associated Infection Annual report 2015. Available online from:
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/707165/ARHAI_annual_report_2014_to_2015.pdf

Burden of antibiotic resistance

While the proportion of isolates showing resistance to key antibiotics has generally remained stable over time with increases being noted for some antibiotics in recent years (Box 2.4). The year-on-year increases in the incidence of bacteraemia shown in Figure 2.1 meant that the burden of resistance, as reflected by the numbers of resistant infections, nonetheless increased over time.

Using the methodology and pathogen/antibiotic combinations described in Annex – Chapter 2, the estimated total numbers of BSIs caused by pathogens resistant to 1 or more key antibiotics increased from 12,972 in 2014 to 17,108 in 2018, a rise of 32% (Figure 2.5).

As shown in Figure 2.5, the burden of antibiotic-resistant BSIs is particularly marked for those caused by Enterobacterales (formerly known as Enterobacteriaceae). The burden of resistant infections remains unchanged for Gram-positive infections.
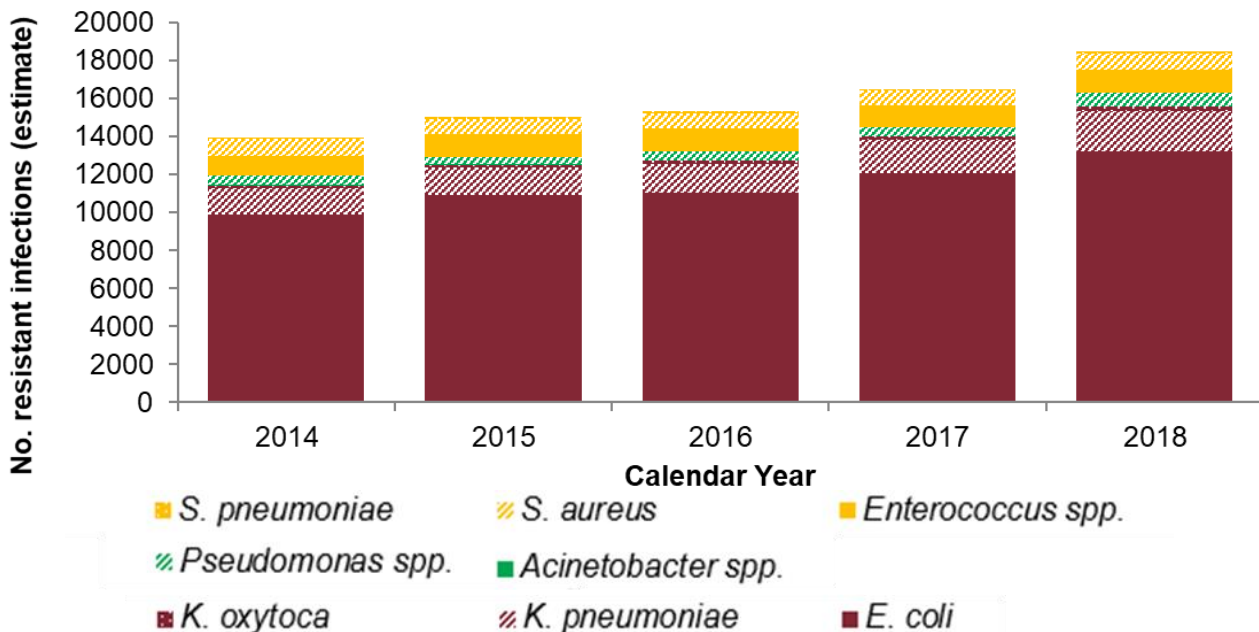
Figure 2.5. Annual estimated burden of antibiotic-resistant BSI; England 2014 -2018

Regional variation in the burden of AMR is noted (Figure 2.6), alongside regional variation in the incidence of related BSIs. The rate of resistant BSIs (as per the list in Annex table 2a.3) was highest in London (42.9 per 100,000 population), whereas the greatest estimated rate of infection per population was recorded in the North East (224 per 100,000 population).

a)   b)

Figure 2.6. Regional variation in rate per 100,000 population of a) the estimated burden of AMR and b) the estimated numbers of BSI in England in 2018

In November 2018, Cassini *et al*. published a methodology for estimating attributable deaths due to antibiotic-resistant bacteria.[21] This method calculated a ratio relating the number of an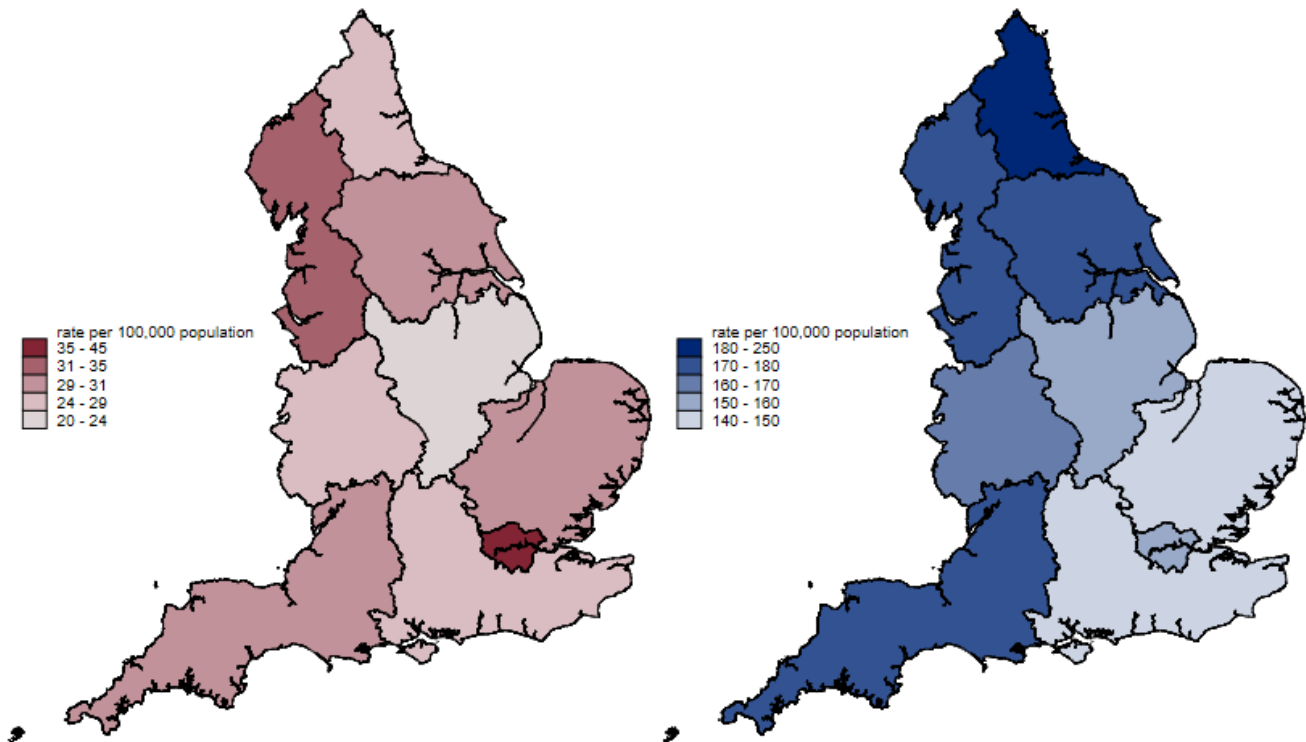tibiotic-resistant BSI to the number of antibiotic-resistant surgical site infections (SSI), antibiotic-resistant urinary tract infections (UTI) and antibiotic-resistant respiratory infections using point prevalence survey data alongside BSI data reported through ECDC surveillance schemes. This ratio, for the UK, is applied to the number of antibiotic-resistant BSI for key antibiotic and pathogen combinations to generate the estimated total on resistant infections. Using this methodology there were an estimated total of 72,805 resistant infections (59,983 in 2017) and 2,985 deaths in England in 2018 (up from an estimated 2,459 deaths in England in 2017) when colistin resistance was included. However, the Gram-negative bacteria where colistin were tested was extremely small and unlikely to be tested by the gold standard methodology (broth microdilution), the estimates without colistin data included are thought to be more accurate. Without colistin, there were an estimated 60,788 resistant infections and 2,492 deaths in 2018, and 55,812 resistant infections and 2,288 deaths in 2017.

The crude 30-day all-cause case fatality in *E. coli* BSI is lower than for patients with *K. pneumoniae* (Table 2.2). In 2018, 14% *E. coli* BSI cases died within 30-days (all

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[21] Cassini *et al*. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. *Lancet Infect Dis* 2019; 19:56-66

causes) compared with 20% for *K. pneumoniae* BSI. This varied by susceptibility test result, with those that have a resistant result recording a higher case fatality within 30-days.

Table 2.2. All-cause 30-day case fatality rate in patients with *E. coli* and *K. pneumoniae* BSI by antibiotic susceptibility, England, 2018

Pathogen/Antibiotic	Resistant	Susceptible
E. coli		
Third-generation cephalosporin*	16%	14%
Carbapenems	5%	14%
Co-amoxiclav	16%	12%
K. pneumoniae		
Third-generation cephalosporin*	23%	19%
Carbapenems	37%	20%
Co-amoxiclav	22%	19%

*carbapenem sensitive

Improvements in estimating the incidence and mortality associated with resistant infections

An improved model for estimating the burden of AMR in BSIs was developed that also incorporates mortality estimates; a summary of the preliminary results is presented in this section. We derived unadjusted 30-day mortality numbers and rates for the listed pathogens in relation to their susceptibility or resistance to key antibiotics, using NHS mortality data linked with bacteraemia cases reported in SGSS between January 2017 and December 2018 inclusive. Mortality attributable to resistance cannot be determined simply from the difference in mortality rate between resistant and susceptible cases due to confounding by factors such as age, sex and underlying comorbidities, which are likely to differ between the susceptible and resistant case populations. Table 2.3 presents excess mortality attributable to resistance after adjustment for the confounders of age, sex and comorbidity. Therefore the presentation of unadjusted mortality estimates (Table 2.4) should be interpreted with caution.

For community-associated cases it is appropriate to use a logistic regression analysis to account for such confounding. The impact of antibiotic-resistant infections on 30-day mortality in community-associated cases (55% of the total), estimated using logistic regression adjusting for sex, age and comorbidity (as measured by the Charlson index),[22] is shown in Table 2.3 The adjusted attributable mortality is in general lower

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[22] Sundararajan V. *et al.* International Methodology Consortium for Coded Health Information (IMECCHI). Cross-national comparative performance of three versions of the ICD-10 Charlson Index. *Med Care* 2007;45:1210-1215.

than unadjusted attributable mortality. The greatest number of deaths during 2017 and 2018 that can be attributed to resistance was in *E. coli* infections with 111 deaths; however, uncertainty in the attributable mortality estimates is high (Table 2.3). For hospital-associated cases patients, varying time at risk before becoming infected and other time-dependent confounders need to be considered, and therefore the use of more advanced models is required. Such work is ongoing.

Table 2.3 Attributable mortality for resistant compared to susceptible community associated BSI

Pathogen	Attributable mortality (resistant compared to susceptible)		
	Unadjusted (rate)	Adjusted [95% CI]	Adjusted rate [95% CI]
Enterobacterales*	250 (2.7%)**	101 [32, 173]	1.1% [0.3%, 1.9%]
Escherichia coli	218 (2.6%)	111 [46, 179]	1.3% [0.5%, 2.1%]
Klebsiella pneumoniae	28 (3.6%)	17 [-5, 40]	2.2% [-0.7%, 5.2%]
Klebsiella oxytoca	5 (6.1%)	5 [-2, 13]	6.5% [-2.6%, 16.9%]
Non-fermenters Gram-negative*	16 (7.7%)**	18 [4, 33]	8.7% [1.9%, 15.9%]
Acinetobacter spp.	6 (7.6%)	4 [-1, 12]	5.3% [-1.3%, 16.0%]
Pseudomonas spp.	10 (7.8%)	13 [3, 26]	9.8% [2.3%, 19.7%]
Gram-positive*	61 (7.2%)**	50 [25, 76]	5.8% [2.9%, 8.9%]
Enterococcus spp.	17 (8.7%)	18 [5,31]	9.0% [2.5%, 15.6%]
Staphylococcus aureus	37 (6.4%)	15 [-3, 36]	2.6% [-0.5%, 6.2%]
Streptococcus pneumoniae	7 (9.2%)	6 [-1, 14]	7.9% [-1.3%, 18.4%]

* For all pathogens, resistance data is aggregated over antibiotics to which the pathogen tested positive, antibiotics along with exceptions are listed in Annex table 2a.3; ** Unadjusted mortality rate for species groupings weighted according to number of resistant cases of species within group.

Table 2.4 BSI and 30-day mortality by pathogen according to resistance to key antibiotics

Pathogen	COMMUNITY ASSOCIATED				HOSPITAL ASSOCIATED			
	No. of cases (as per SGSS)		Mortality (rate)		No. of cases (as per SGSS)		Mortality (rate)	
	Susceptible	Resistant	Susceptible	Resistant	Susceptible	Resistant	Susceptible	Resistant
Enterobacterales*	41,231	9,326	4,884 (11.8%)	1,320 (14.2%)	27,566	9,776	5,495 (19.9%)	1,978 (20.2%)
Escherichia coli	34,444	8,486	3,796 (11.0%)	1,153 (13.6%)	20,652	8,070	3,929 (19.0%)	1,552 (19.2%)
Klebsiella pneumoniae	5,447	763	874 (16.0%)	150 (19.7%)	5,451	1,576	1,278 (23.4%)	387 (24.6%)
Klebsiella oxytoca	1,340	77	214 (16.0%)	17 (22.1%)	1,463	130	288 (19.7%)	39 (30.0%)
Non-fermenters Gram-negative*	3,478	207	655 (18.8%)	51 (24.6%)	5,540	557	1,364 (24.6%)	175 (31.4%)
Acinetobacter spp.	668	75	65 (9.7%)	13 (17.3%)	734	107	99 (13.5%)	21 (19.6%)
Pseudomonas spp.	2,810	132	590 (21.0%)	38 (28.8%)	4,806	450	1,265 (26.3%)	154 (34.2%)
Gram-positive*	22,282	856	3,864 (17.3%)	215 (25.1%)	18,740	2,111	4,613 (24.6%)	657 (31.1%)
Enterococcus spp.	3,795	199	720 (19.0%)	55 (27.6%)	7,300	1,368	1,950 (26.7%)	443 (32.4%)
Staphylococcus aureus	10,762	581	1,925 (17.9%)	141 (24.3%)	9,755	710	2,218 (22.7%)	205 (28.9%)
Streptococcus pneumoniae	7,725	76	1,219 (15.8%)	19 (25.0%)	1,685	33	445 (26.4%)	9 (27.3%)
TOTAL	66,991	10,389	9,403 (14.0%)	1,586 (15.3%)	51,846	12,444	11,472 (22.1%)	2,810 (22.6%)

(*) For all pathogens, resistance data is aggregated over antibiotics to which the pathogen tested positive, antibiotics along with exceptions are listed in Annex table 2a.3

Box 2.6 - New mobile colistin resistance (*mcr*) genes

Colistin is one of a few remaining therapeutic options for the treatment of serious infections caused by multi-resistant Gram-negative bacteria. Most colistin resistance arises from mutations in chromosomal genes that encode enzymes that modify the lipopolysaccharide in the bacterial outer membrane leading to decreased binding of colistin. However, since 2015 several mobile colistin resistance (*mcr*) genes have been identified. In contrast to chromosomally-encoded resistance, *mcr* genes can transfer amongst diverse strains, species and genera due to their association with mobile genetic elements such as plasmids and transposons. In ESPAUR 2017 we reported on the first *mcr* variants to emerge;[23] however, since then additional variants have been described. *mcr-6* (initially reported as a variant of *mcr-2*) was identified in an isolate of *Moraxella* spp. isolated from a pig in Great Britain.[24] Three isolates of *K. pneumoniae* from chickens in China were found to harbour plasmids bearing both *mcr-7* and the ESBL, CTX-M-55.[25] *mcr*-8 was identified in four *K. pneumoniae* isolates from pigs and a chicken also in China; worryingly, three of these isolates were also carbapenem-resistant due to the presence of *bla*NDM.[26] Retrospective screening of the National Center for Biotechnology Information (NCBI) database by the same researchers identified *mcr-8* in a *K. pneumoniae* isolated from an inpatient in Western China; this isolate was also found to produce an NDM carbapenemase. The initial identification of many *mcr* variants in veterinary, rather than clinical, bacterial isolates suggests that veterinary use of colistin is driving their emergence.

To date, there have been no publications reporting large-scale screening for *mcr* variants -6, -7 and -8. However, in a review of AMRHAI's archive of whole-genome sequences of ~3,200 confirmed carbapenemase-producing Enterobacterales (CPE) referred between January 2014 and June 2016 for *mcr* variants -1 to -8 identified only a single isolate of OXA-48-producing *E. coli* positive for *mcr-1* (AMRHAI, unpublished data). Similarly, screening of whole-genome sequences of ~34,000 *Salmonella enterica* referred to PHE between April 2014 and September 2017 identified 52 *mcr*-positive isolates (*mcr-1* = 32, *mcr-3* = 19 and *mcr-5* = 1). The isolates belonged to diverse serotypes and the majority were associated with travel to South East Asia (Gastrointestinal Bacteria Reference Unit, unpublished data). AMRHAI has been routinely screening for *mcr-1* to *mcr-5* in Enterobacterales, *Acinetobacter* spp. and *Pseudomonas* spp. confirmed phenotypically as colistin-resistant since 2016 and all Enterobacterales investigated for carbapenem resistance have been screened for *mcr-1* and *mcr-2* since January 2018. Up until the end of 2018, 13 additional isolates from 10 patients have been identified as harbouring an *mcr* gene; all have been positive for *mcr*-1. Of these, four were also confirmed CPE.

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[23] PHE. ESPAUR Report 2017.
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/656611/ESPAUR_report_2017.pdf

[24] AbuOun M. *et al*. *mcr*-1 and *mcr*-2 (*mcr*-6.1) variant genes identified in *Moraxella* species isolated from pigs in Great Britain from 2014 to 2015. *J Antimicrob Chemother*. 2018; 72: 2745-2749.

[25] Yang Y-Q. *et al.* Novel plasmid-mediated colistin resistance gene mcr-7.1 in *Klebsiella pneumoniae*. *J Antimicrob Chemother*. 2018; 73: 1791-1795.

[26] Wang X. *et al.* Emergence of a novel mobile colistin resistance gene, *mcr*-8, in NDM-producing *Klebsiella pneumoniae* *Emerg Microbes Infect* 2018; 7:122.

Trends in resistance as assessed by the proportions of urine isolates resistant to key antibiotics

The National Institute for Health and Care Excellence (NICE) empirical treatment guidelines for lower/uncomplicated UTIs were updated in collaboration with PHE in October 2018, and recommend nitrofurantoin, trimethoprim, ciprofloxacin, fosfomycin, pivmecillinam and cefalexin as treatment options.[27]

Between 2015 and 2018, 6,146,663 urine samples were reported to PHE's SGSS AMR module, of which 3,503,425 (57%) were UTIs cause by *E. coli.* Sixty percent of *E. coli* positive UTI samples were from community healthcare settings (GPs and community care hospitals), and 40% were from acute settings.

Among all bacterial isolates from UTI samples, decreases in resistance was observed to trimethoprim between 2015 and 2018 (34.9% to 31.0%), and small decreases were observed for fosfomycin (11.6% to 7.9%), and pivmecillinam (12.1% to 9.9%) between 2015 and 2018 (Figure 2.7). These changes most likely relate to the increased emphasis on nitrofurantoin as first-line treatment and the implementation of the Quality Premium in primary care to drive this improvement in antibiotic prescribing (reported further in Chapter 5).

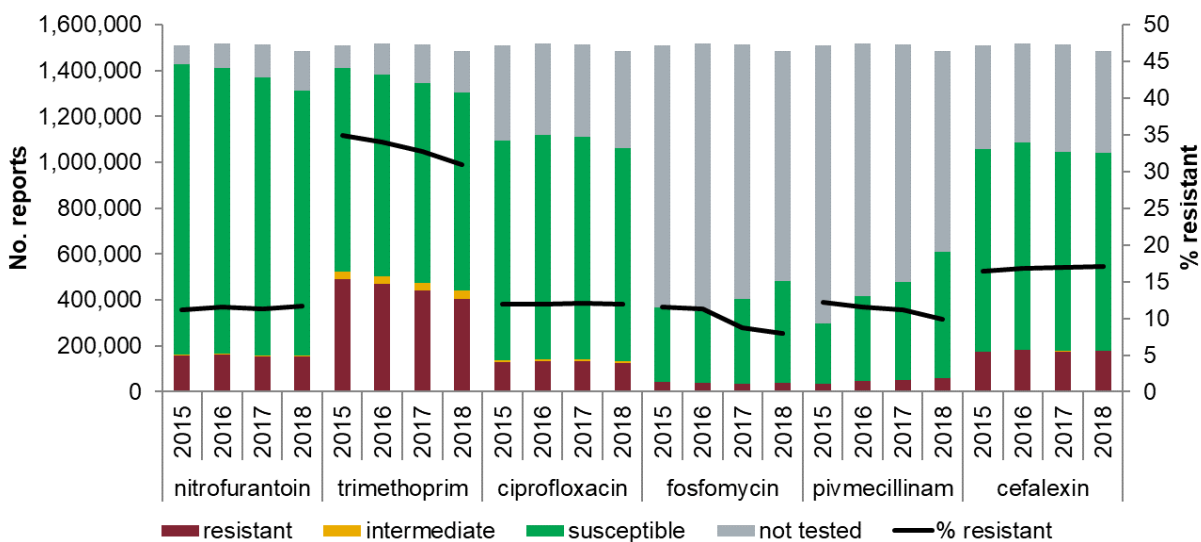**Figure 2.7. Resistance in all bacterial isolates from UTI specimens to key antibiotics; England 2015-2018**

Resistance of *E. coli* from UTI to key antibiotics was highest in older age groups (≥65 years old). For example, in 2018, resistance to nitrofurantoin was 1.0% in the <1 year

[27] NICE, 2018. UTI (lower): antimicrobial prescribing [https://www.nice.org.uk/guidance/ng109/resources/visual-summary-pdf-6544021069]

age group and 4.3% in the ≥65 year age group, while resistance to ciprofloxacin was 6.9% in the <1 year age group and 14.4% in the ≥65 year age group (Figure 2.8).

Among all organisms isolated from UTI samples in 2018, resistance was generally higher in isolates from males compared to females, in all age groups. In both males and females, resistance was higher in the older age groups; for example, in UTI samples from females, resistance to nitrofurantoin was 4.3% in <1 year olds and 13.8% in ≥65 year olds. Similarly, in male UTI samples, resistance to nitrofurantoin was 6.3% in <1 year olds and 22.9% in ≥65 year olds.
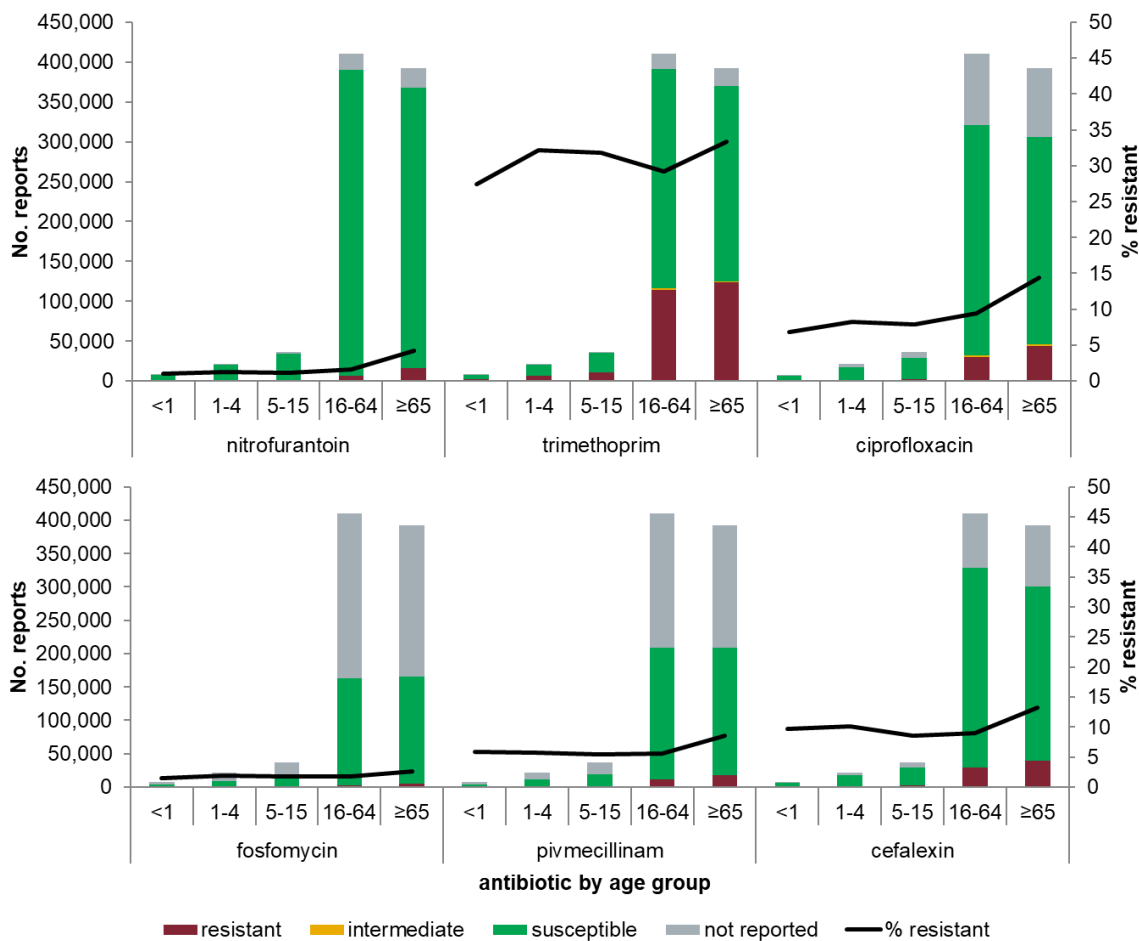
Figure 2.8. Resistance in *E. coli* from UTI specimens to key antibiotics by age group (years); England 2018

A decrease in resistance of *E. coli* to trimethoprim was observed between 2015 to 2018 (35.1% to 31.2%) in England. This decrease was seen in all age groups, with the largest decrease occurring in those aged 65 years or older (38.0% resistance in 2015, compared to 33.4% in 2018) (Figure 2.9).

A decrease in trimethoprim resistance was also observed in community *E. coli* or coliform urine specimens reported on the PHE Fingertips portal at Clinical

Commissioning Group (CCG) level,[28] although these values differ from those presented here due to inclusion data for urines reported as positive for "coliforms" as well as differences in the protocol for data de-duplication.
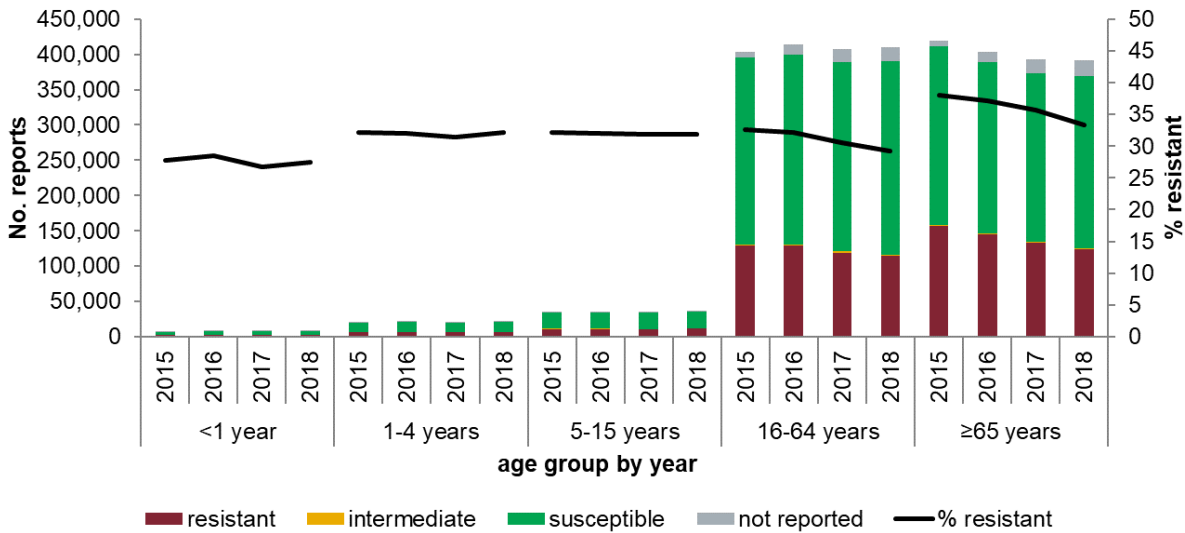

Figure 2.9. Resistance in _E. coli_ from UTI specimens to trimethoprim by age group (years); England 2015-2018

Trends in glycopeptide resistant Enterococci (GRE)

The change over time in resistance of _Enterococcus_ spp. bloodstream isolates to vancomycin or teicoplanin (glycopeptides) is shown in Figure 2.4, with 15% being resistant to a glycopeptide in 2018.

Identification of GRE to species level aids in confirming whether an isolate has intrinsic (_van_C gene; e.g. _Enterococcus casseliflavus_ or _Enterococcus. gallinarum_) or acquired, and potentially transferable resistance (_van_A or _van_B genes; e.g. _Enterococcus faecalis_, _Enterococcus faecium_ or _Enterococcus avium_).

The distribution of _Enterococcus_ spp. causing BSI remained stable between 2014 and 2018, with increases in the number identified as _E. faecalis_ or _E. faecium_ and decreases in the number of isolates only identified to genus level, which is most likely related to more widespread use of MALDI-TOF for identification.[29] _E. faecalis_ was the most common species in 2018 (44%) followed by _E._ faecium (38%) when isolated from

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[28] PHE. Public Health Profiles – AMR local indicators. Available: https://fingertips.phe.org.uk/profile/amr-local-indicators

[29] PHE. Laboratory surveillance of _Enterococcus_ spp. bacteraemia in England, Wales and Northern Ireland: 2017 Health Protection Report. Volume 12. Issue 46. Available:

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/765458/hpr4618_AA_ntrcccs.pdf

blood. Glycopeptide resistance varied between species, accounting for 22% of *E. faecium* but only 2% of *E. faecalis* (Figure 2.10).
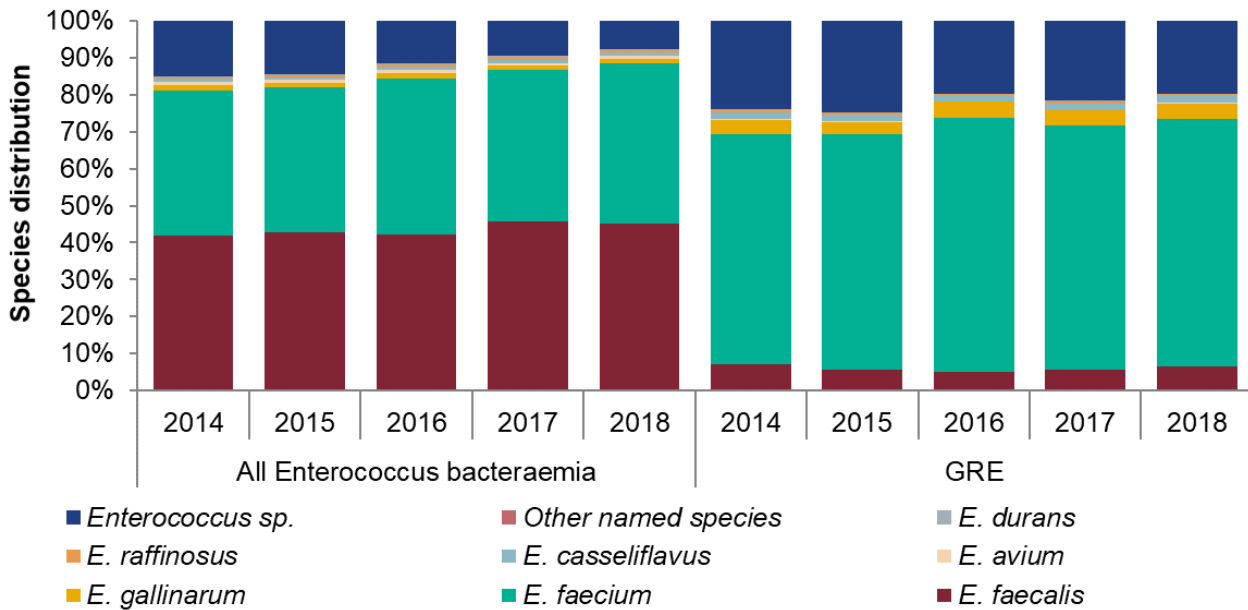
*Other species includes *E. hirae*, *E. cecorum*, *E. gilvis*, *E. columbae*, *E. maldoratus* and *E. italicus*

Figure 2.10. Species distribution in enterococcal bloodstream isolates and glycopeptide-resistant enterococcal bloodstream isolates in England, 2014 to 2018*

The distribution of *Enterococcus* spp. identified from blood varied with patient age, with *E. faecalis* more common in patients aged <1 year compared with the other age groups where *E. faecium* is more common (Figure 2.11).
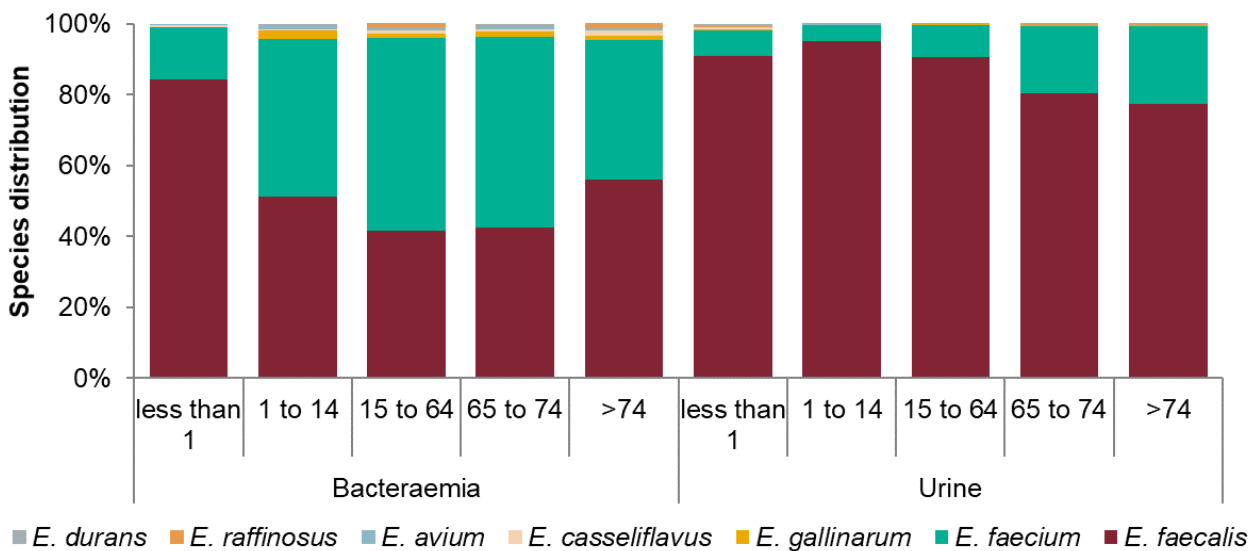

Figure 2.11. Age group distribution for *Enterococcus* spp. identified from bloodstream and urine isolates, England, 2018

Enterococcus spp. is the second most commonly recorded genus, after *Escherichia*, in UTI laboratory reports in England (Research Abstracts Chapter; Wilson, K *et al.*). Similar to BSIs, *E. faecalis* was the commonest species identified (Figure 2.11). The proportion of enterococci from sites other than blood that were glycopeptide-resistant is lower than seen in bacteraemia cases (15%), however it increased year-to-year between 2014 and 2018, from 5% to 7% respectively. Glycopeptide resistance also varies with age, tending to higher resistance in more elderly age groups.

Linezolid resistance remains rare in enterococci, with 1% of *Enterococcus* spp. from blood reported as linezolid resistant in 2018. Of the enterococcal bacteraemia isolates that were tested for both glycopeptide and linezolid resistance in 2018, 0.6% were resistant to both drugs (27/4,794), up from the 0.3% reported in 2017 (13/4,466). In 2014, 77% of linezolid-resistant enterococci from blood were reported as *E. faecium*, reducing to 55% in 2018 following an increase in the number of linezolid-resistant *E. faecalis* being reported over time.

Box 2.7 - Emergence of *poxtA*, a novel mobile oxazolidinone resistance gene
Oxazolidinones such as linezolid and tedizolid are one of few remaining treatment options for GRE, particularly *E. faecium* that is inherently resistant to β-lactams. Most oxazolidinone resistance can be attributed to mutations within chromosomal genes, primarily genes encoding for 23S ribosomal RNA. However, plasmid-mediated resistance determinants *cfr*, *optr*A and, more recently *poxt*A, have been described. These genes are of public health importance as outbreaks involving both strain spread and gene spread may be harder to control. *poxt*A was first described in a linezolid-resistant clinical isolate of MRSA in Italy in 2018 but has also been identified in *E. faecalis* and *E. faecium* of human and animal origin, thus demonstrating the mobile nature of *poxt*A.[30,31] *poxt*A encodes an ATP-binding cassette superfamily protein, which confers resistance to phenicols, oxazolidinones and tetracyclines via ribosomal protection. Retrospective screening of 23 linezolid-resistant enterococci and staphylococci referred to AMRHAI, for which no underlying linezolid resistance mechanism had previously been demonstrated, identified six *poxt*A-positive *E. faecium* (four from 2017, two from 2018). AMRHAI have evaluated an in-house real-time PCR for the detection of the G2576T 23S ribosomal RNA mutation and acquired *cfr*, *optr*A and *poxt*A genes, with the aim of implementing this for routine screening for *poxt*A amongst linezolid-resistant Gram-positives referred to AMRHAI.

Only 0.1% of *Enterococcus* spp. urine isolates were reported as resistant to both glycopeptide and linezolid in 2018 (52/60,662). Similar to the BSI reports, there was an increased number of linezolid- and glycopeptide-resistant *E. faecalis* reported.

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[30] Antonelli A *et al*. Characterization of poxtA, a novel phenicol-oxazolidinone-tetracycline resistance gene from an MRSA of clinical origin. *J Antimicrob Chemother* 2018; 73:1763-1769

[31] Kuroda *et al*. Complete Genome Sequence and Characterization of Linezolid-Resistant *Enterococcus faecalis* Clinical Isolate KUB3006 Carrying a cfr(B)-Transposon on Its Chromosome and *optr*A-Plasmid. *Front Microbiol* 2018; 9:2576.

Box 2.8 - Identification of *optrA* in linezolid-resistant *E. faecalis* isolated from companion animals in the UK

Linezolid resistance is rare in enterococci but has been detected in isolates originating from humans and livestock. A review looking into transmission of linezolid-resistant *E. faecalis* between companion animals at a UK small-animal hospital found four isolates (three cats, one dog) resistant to linezolid and gentamicin, but susceptible to glycopeptides. All four isolates were positive for the plasmid-mediated linezolid resistance gene *optr*A. Plasmid-mediated resistance has greater potential to be a public health threat since standard infection prevention and control measures may not successfully contain transfer of these genes among strains, species and genera.

Standard protocols for management of colonized/infected animals should prevent transmission to veterinary staff, and therapeutic options (ampicillin or glycopeptides) remain should an infection occur. However, transmission of this organism to owners carries the potential for plasmid-mediated spread to other bacteria, particularly in healthcare environments, and is of public health importance. This demonstrates the importance of a One-Health approach to monitoring emergence and dissemination of resistance mechanisms of public health importance.

Surveillance of antimicrobial resistance in *Neisseria gonorrhoeae*

Resistance in *N. gonorrhoeae* is monitored through the Gonococcal Resistance to Antimicrobials Surveillance Programme (GRASP), which comprises a suite of initiatives to detect and monitor resistance and potential treatment failures. Trend data are derived from the national sentinel surveillance system which collects gonococcal isolates from consecutive patients attending a network of 26 participating genitourinary medicine (GUM) clinics (24 in England, 2 in Wales) over a 3-month period each year. The isolates are referred to PHE's 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. In addition, primary diagnostic laboratories may report the results of their routine susceptibility testing to SGSS. PHE's national reference laboratory also undertakes *ad hoc* testing of gonococcal isolates referred from primary diagnostic laboratories for investigation of suspected resistance to ceftriaxone and/or azithromycin. New treatment guidelines for gonorrhoea in the UK were published in January 2019, recommending 1g ceftriaxone monotherapy[32] instead of ceftriaxone (500mg intramuscularly) in combination with azithromycin (1g oral).

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[32] British Association for Sexual Health and HIV (BASHH) guidelines. Available: https://www.bashh.org/guidelines

Between 2017 and 2018, there was a reduction in susceptibility to the current first-line therapy, ceftriaxone, with the percentage of isolates with MICs ≥ 0.03 mg/L rising from 16.6% in 2017 to 24.6% in 2018. Although no isolate with ceftriaxone resistance was observed in the sentinel programme in 2018, three ceftriaxone resistant cases were confirmed by the PHE national reference laboratory on direct referral in 2018.

An increase in resistance among GRASP isolates to azithromycin, ciprofloxacin, penicillin, cefixime and tetracycline was noted between 2017 and 2018. It should be noted that in 2018 the azithromycin breakpoint for *N. gonorrhoeae* was removed by EUCAST, values presented for 2018 are based on the previous breakpoint ≥0.5 mg/l. Also of note in 2018, *N. gonorrhoeae* isolates from men who have sex with men were less susceptible to ceftriaxone, cefixime and azithromycin than those from women and heterosexual men.

Further data on antimicrobial resistance in *N. gonorrhoeae* are reported in the GRASP report available online.[33]

Tuberculosis

In 2018, there were 4,655 notified cases of tuberculosis (TB) in England, equating to 8.3 cases per 100,000 population. Notifications were more frequent in the 15 to 44-year age group (55% 2,456/4,655), and 72% of notifications were in persons born outside of the UK (3,283/4,580).[34]

The proportion of people with initial isoniazid resistance without multidrug-resistant TB (MDR-TB) in 2018 increased to 6.6%, after remaining relatively consistent at an average of 5.4% (range: 4.8-5.9%) over the past 10 years (Figure 2.12). Drug resistance to pyrazinamide increased five-fold from 0.61% (21/3,465) to 3.66% (103/2,814) between 2016 and 2018, with most of these (81.6%) displaying monoresistance. There were fewer people with multi-drug/rifampicin resistant TB (MDR/RR-TB) in 2018 compared with 2017 (44 versus 54). Of these, four had confirmed initial extensively drug-resistant TB. Extensively drug-resistant TB (XDR-TB) is defined as resistance to isoniazid and rifampicin (MDR-TB), plus resistance to at least one injectable agent (capreomycin, kanamycin or amikacin) and at least one fluoroquinolone (ofloxacin, moxifloxacin or ciprofloxacin).

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[33] PHE. Surveillance of antimicrobial resistance in *Neisseria gonorrhoeae* in England and Wales. Key findings from the Gonococcal Resistance to Antimicrobials Surveillance Programme (GRASP). Report 2019. Published October 2019. Available: https://www.gov.uk/government/publications/gonococcal-resistance-to-antimicrobials-surveillance-programme-grasp-report

[34] PHE. Tuberculosis in England; annual report 2019. Published August 2019. Available: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/821334/Tuberculosis_in_England-annual_report_2019.pdf

The number of people in the drug resistant cohort (confirmed or treated as MDR/RR-TB) decreased between 2017 and 2018 (62 versus 47). Of people in the 2016 drug-resistant cohort, 65.2% (45/69) had completed treatment by 24 months, and 10.1% (7/69) remained lost to follow-up by the last recorded outcome.
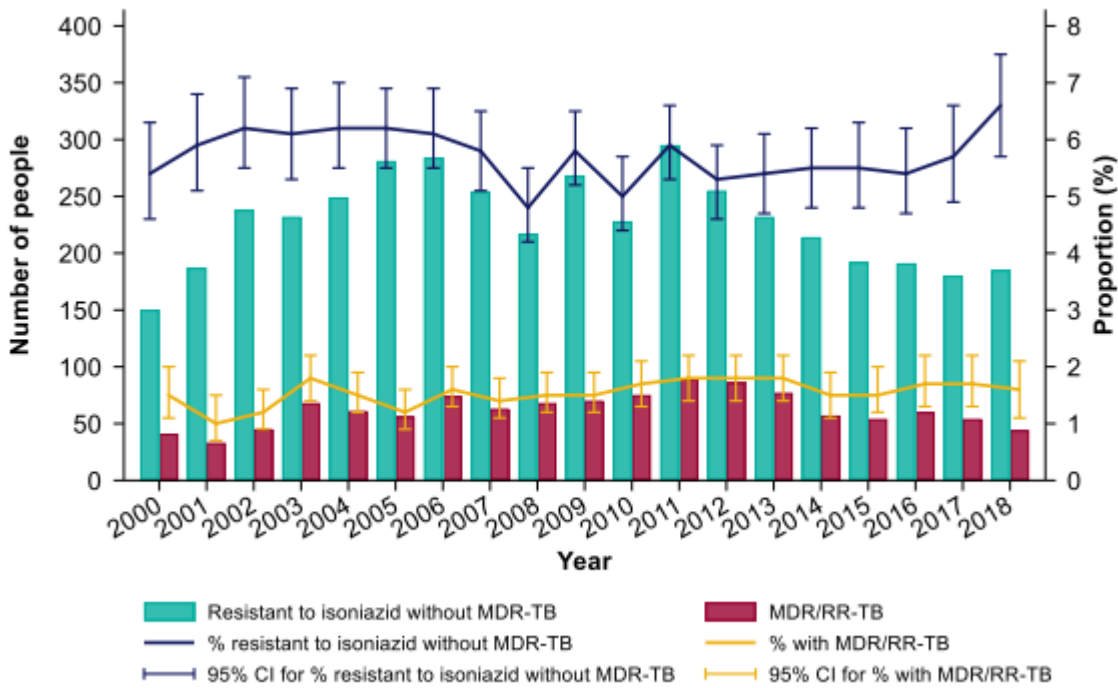
[a]People with culture confirmed TB with a result (drug sensitivity testing or whole genome sequencing) for at least isoniazid and rifampicin

Figure 2.12. Number and proportion[a] of people notified with TB with initial drug resistance, England 2000 to 2018

No one with culture-confirmed TB notified in 2018 was identified to have acquired resistance on repeat testing, compared to 6 people in 2017. Among people with culture-confirmed TB notified between 2000 and 2018 23, 165 (0.2%) were known to have acquired resistance while on treatment in England, of which 30.3% (50) acquired resistance to rifampicin and 35.2% (58) acquired resistance to isoniazid.

Further data on AMR in TB are reported in the Tuberculosis in England annual report available on-line.[35]

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[35] PHE. Tuberculosis in England; annual report 2019. Published August 2019. Available: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/821334/Tuberculosis_in_England-annual_report_2019.pdf

UK participation in international surveillance of AMR

EARS-Net (European Antimicrobial Resistance Surveillance Network)

The European Centre for Disease Prevention and Control (ECDC) EARS-Net surveillance collects data on resistance to key antibiotics in blood culture and cerebrospinal fluid (CSF) isolates for eight organisms (*E. coli*, *K. pneumoniae*, *P. aeruginosa*, *Acinetobacter* spp., *S. pneumoniae*, *S. aureus*, *E. faecalis*, and *E. faecium*).

In June 2019, antimicrobial susceptibility testing data from 71 laboratories in England has been submitted along with data from Northern Ireland, Scotland and Wales, covering the year 2018. The EARS-Net report will be published on European Antibiotics Awareness Day in November 2019, and in the online Surveillance Atlas of Infectious Diseases.[36]

In addition to antimicrobial susceptibility testing data, information is provided on reporting coverage and representativeness, and has been updated in 2019 to include estimates of geographical, hospital and isolate representativeness to the national population.

Currently, not all laboratories in England participate in EARS-Net surveillance, and due to regional antimicrobial susceptibility testing differences the results presented in the EARS-Net data may differ from other sources. To address this, additional laboratories will be recruited to provide a geographically representative sample in EARS-Net surveillance.

GLASS (Global Antimicrobial Resistance Surveillance System)

The second World Health Organization (WHO) GLASS report was published in January 2019, and included data from the UK, covering blood and urine isolates from 2017, and a description of the current status of AMR surveillance nationally.[37] This is a change from the previous report, where no data for the UK were available.[38]

The early implementation phase of GLASS, which covers the years 2015 to 2019, aimed to collect information on resistance among human priority bacterial pathogens from clinical specimens considered a threat globally and to collect information on

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[36] European Centre for Disease Prevention and Control. Data from the ECDC Surveillance Atlas – Antimicrobial Resistance: https://atlas.ecdc.europa.eu/public/index.aspx
[37] Global antimicrobial resistance surveillance system (GLASS) report: early implementation 2017-2018. Geneva: World Health Organization; 2018. Licence: CC BY-NC-SA 3.0 IGO.
[38] Global antimicrobial resistance surveillance system (GLASS) report: early implementation 2016-2017. Geneva: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO.

countries AMR surveillance along with providing guidance to countries on the development of effective AMR surveillance. Following data collection in July 2019, covering 2018 data, the results and lessons learnt from the early implementation phase will be reviewed and next steps for the future development of GLASS will be set.

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

Box 2.9 - International assistance and training

As stated in the UK Government's UK 5-year action plan for AMR, 2019 – 2024[39] containing and controlling AMR requires not only national but also coordinated international action across all stakeholders. PHE has:

- organised and facilitated a 'Visualisation of AMR data' workshop at KwaZulu-Natal University, South Africa in November 2018, as part of eAMR data project funded by the South African MRC/UK MRC.
- successfully applied to the Fleming Fund fellowship fcheme and will be hosting a Nigerian Fellow in 2019 to strengthen surveillance and laboratory capacities in Nigeria.
- working with WHO headquarters and an expert consultation team the WHO collaborating centre (CC) at PHE developed the WHO global interprofessional AMR competency framework for health workers. Following this WHO CC has developed a comprehensive curriculum document for health care workers (HCWs) globally to assist in training specific to AMR. This is in the final editing stages and will be launched shortly.
- the WHO CC at PHE participated in the global summit of WHO and the Asia Europe Foundation in Tokyo, in 2018 on the importance of AMR in universal health coverage (UHC)

Discussion

Data presented show that the burden of AMR continues to rise, driven predominantly by increases in the number of Gram-negative BSIs and latterly by increased resistance to third-generation cephalosporins and quinolones; early data suggest that this is driven by rises in the use of these antibiotics in secondary care and associated with the piperacillin/tazobactam shortage. However, there were reductions in resistance observed in UTI bacterial isolates consequent to the changes in antibiotic prescribing for

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[39] DHSC. Tackling antimicrobial resistance 2019 to 2024: the UK's 5-year national action plan. January 2019. Available: https://www.gov.uk/government/publications/uk-5-year-action-plan-for-antimicrobial-resistance-2019-to-2024

UTI particularly in primary care. Further work to understand these changes and identify relevant areas for intervention will require a multilevel approach.

The assessment of the burden of AMR has shown that there were increases in the estimated resistance for each of the pathogens included in surveillance during 2014 to 2018. The non-fermenter Gram-negatives showing the biggest relative change, driven by recorded resistance to colistin, most likely driven by a low level of colistin susceptibility testing by local laboratories.

The UK 5-year national AMR action plan highlighted the importance of international collaboration in the support of monitoring and training around AMR. The UK is increasingly involved in international collaborative efforts to tackle AMR (Box 2.9) includes a number of examples], as well as being involved in Global and European surveillance programmes. The UK is widely recognised as a world leader in the development of AMR surveillance and this allows us to develop improved estimates of the burden of AMR in our population.

Although new antibiotic/inhibitor therapeutic options are now available in England, surveillance has already shown that resistance to ceftazidime/avibactam and ceftaroline/tazobactam has emerged during the short period of its availability. This highlights the importance of having local and reference laboratory capacity to identify emerging resistance for any new antibiotics (or combinations).

The change in EUCAST guidance for interpreting and recording the S, I and R susceptibility results, described in Box 2.1, is likely to elicit a positive change, by indicating that treatment using the agent is still possible with an appropriate dose will limit the progression to using some of the novel antibiotic combinations or agents of last resort.

The ESPAUR surveillance data are progressively presented in more granular detail including an improved understanding of age-related and hospital-associated AMR patterns. Diverse actions are required to show an impact in different bacteria, location of acquisition of infection and patient populations. Essential to all are reducing inappropriate antibiotic use and prevention of infection.

Box 2.10 - Paediatric AMR – A paediatrician's perspective

AMR is a growing problem in children. While uncommon in the past, children increasingly develop infections that are difficult to treat, including infections for which oral antibiotics no longer work, or infections that require antibiotics with more side-effects. This happens even in infants, when a mother's resistant bacteria may be transmitted to her baby around the time of birth, or if they need prolonged hospitalisation. In older children, antibiotic-resistant bacteria can appear after a single course of antibiotics.

Data presented here show that infants have the highest incidence of BSIs (225 per 100,000 population) in people younger than 65 years. The majority of these are caused by Gram-negative bacteria; an increasing proportion of *E. coli* causing bacteraemia in infants are resistant to third-generation cephalosporins and fluroquinolones, compared to 2014 [Box 2.4]. Likewise, enterococcal bacteraemia is more common in infants (46 per 100,000 population) than older paediatric age groups, with 3% resistance to glycopeptides. Carbapenemase-producing Enterobacterales may exhibit different mechanisms of resistance in children compared to adults (Chapter 3).

Because social interactions are age-specific and children tend to mix more with their peers than adults do, the potential for transmission of some infections varies by age group.[40] This is illustrated by the high proportion of scarlet fever outbreaks originating in schools and nurseries compared to other settings.[41] Good infection prevention and control practices tailored to children and young people will help limit the spread of these infections.

What else can be done to keep antibiotics working? A key action is to stop the unnecessary use of antibiotics. Antibiotics are the most commonly used category of medicine in children; many are prescribed for longer than necessary or are not needed at all. In the community, where 80% of antibiotics are prescribed (Chapter 4) almost a third of antibiotic prescriptions by GPs are for children up to 14 years (Figure 4.4). One of the most common indications for antibiotic prescribing in children is sore throat – despite antibiotics not being recommended in most cases. A national upsurge of scarlet fever in the past few years has heightened awareness about group A streptococcal infections, and clinicians should keep the potential resistance of group A *Streptococcus* to macrolides (3% in 1-4-year-olds but up to 18% in 15-24-years-old; [Box 2.5] in mind. Resistance to penicillin, the recommended first-line treatment, has not been reported. In secondary care, national efforts to create a paediatric antimicrobial stewardship network would support the benchmarking and harmonisation of antimicrobial prescribing for paediatric infections

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[40] Prem K, Cook AR, Jit M. Projecting social contact matrices in 152 countries using contact surveys and demographic data. *PLoS computational biology* 2017; 13(9), p.e1005697.

[41] Lamagni T *et al.* Resurgence of scarlet fever in England, 2014–16: a population-based surveillance study. *Lancet Infect Dis* 2018;1 8:180-187.

Anyone can be an Antibiotic Guardian (Chapter 8). It is important for clinicians to discuss the reasons for prescribing antibiotics with patients and their families, to prescribe them only when needed, and only for the recommended duration; likewise, it is important for the public not to request antibiotics for infections that self-resolve, to discuss the need for antibiotics with their clinician, and to take antibiotics as prescribed.

Children are a vulnerable population and it is essential to protect them from side effects associated with unnecessary antibiotic use. This becomes even more important because children may harbour antibiotic-resistant bacteria for years potentially risking future untreatable infections. All these issues highlight the need for a robust surveillance system for antimicrobial-resistant infections and for the use of antimicrobial agents in children.

Future actions

ESPAUR will continue to:

- emphasise the importance of infection prevention and control with the objective of reducing the numbers of antibiotic-resistant infections
- develop methods to estimate the clinical burden in terms of resistant infections in terms of excess morbidity (resulting in hospitalisation and increased length of hospital stay) and mortality
- link microbiology data in SGSS with patient-level clinical, epidemiological and risk factor data in hospital episode statistics (HES)[42]
- develop a new infrastructure to assess antimicrobial prescribing and resistance at patient level
- participate in the Global Burden of Disease AMR project

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[42] NHS Digital. Hospital Episode Statistics (HES): https://digital.nhs.uk/data-and-information/data-tools-and-services/data-services/hospital-episode-statistics

3. Carbapenemase-producing Enterobacterales

Background

Carbapenems are β-lactam antibiotics that have a broad spectrum of activity against both Gram-positive and Gram-negative bacteria.[43] They are often referred to as "antibiotics of last resort" due to their activity against multiresistant bacteria.[44] Increasing levels of carbapenem resistance amongst Gram-negative bacteria in Europe has occurred in recent years.[45] Carbapenem resistance due to the emergence of acquired (plasmid-encoded) carbapenemases is of particular concern due to their ability to transfer within and between bacterial species and genera.[46,47,48]

Carbapenem resistance encoded by a mobile genetic element was first described in England in 2003. Since then, several prominent mechanisms conferring carbapenem resistance due to the production of a carbapenemase enzyme have been identified in England, such as KPC, NDM, OXA-48-like, VIM and IMP. These mechanisms have been found in many Gram-negative species including *Escherichia coli*, *Klebsiella pneumoniae* and *Enterobacter cloacae*. In some instances, more than one mechanism of resistance has been detected in the same bacterial isolate.

The Antimicrobial Resistance and Healthcare Associated Infections (AMRHAI) Reference Unit within Public Health England (PHE) has received and confirmed an increasing number of carbapenemase-producing Gram-negative bacteria year-on-year since 2006; amongst Enterobacterales sent for referral in 2006, four were identified as carbapenemase producers compared to more than 4,000 identified in 2018. In response to the observed increase, PHE established an incident control team in 2013 and

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[43] Papp-Wallace, K. M., Endimiani, A., Tracacila, M. A., *et al.* Carbapenems: past, present, and future. *Antimicrob Agents Chemother*. 2011; **55**: 4943-60

[44] Paterson, D. L, Bonomo, R. A. Extended-spectrum beta-lactamases: a clinical update. *Clin Microbiol Rev*. 2005; **18**: 657-86

[45] ECDC. Surveillance of antimicrobial resistance in Europe – Annual report of the European Antimicrobial Resistance Surveillance Network (EARS-Net) 2017. 2018. Available: https://ecdc.europa.eu/sites/portal/files/documents/EARS-Net-report-2017-update-jan-2019.pdf

[46] ECDC. Rapid risk assessment: Carbapenem-resistant Enterobacteriaceae - first update 4 June 2018. Available: https://ecdc.europa.eu/sites/portal/files/documents/RRA-Enterobacteriaceae-Carbapenems-European-Union-countries.pdf

[47] Goren, M. G., Carmeli, Y., Schwarber, M. J. *et al.* Transfer of carbapenem-resistant plasmid from *Klebsiella pneumoniae* ST258 to *Escherichia coli* in patient. *Emerg Infect Dis*. 2010; **16**: 1014-7

[48] Decraene V, Phan HTT, George R. *et al.* A Large, refractory nosocomial outbreak of *Klebsiella pneumoniae* carbapenemase-producing *Escherichia coli* demonstrates carbapenemase gene outbreaks involving sink sites require novel approaches to infection control. *Antimicrob Agents Chemother*. 2018; **62**: e01689-18. https://doi.org/10.1128/AAC.01689-18

implemented a number of initiatives aimed at preventing and controlling the spread of carbapenemase-producing Enterobacterales (CPE) (Figure 3.1).
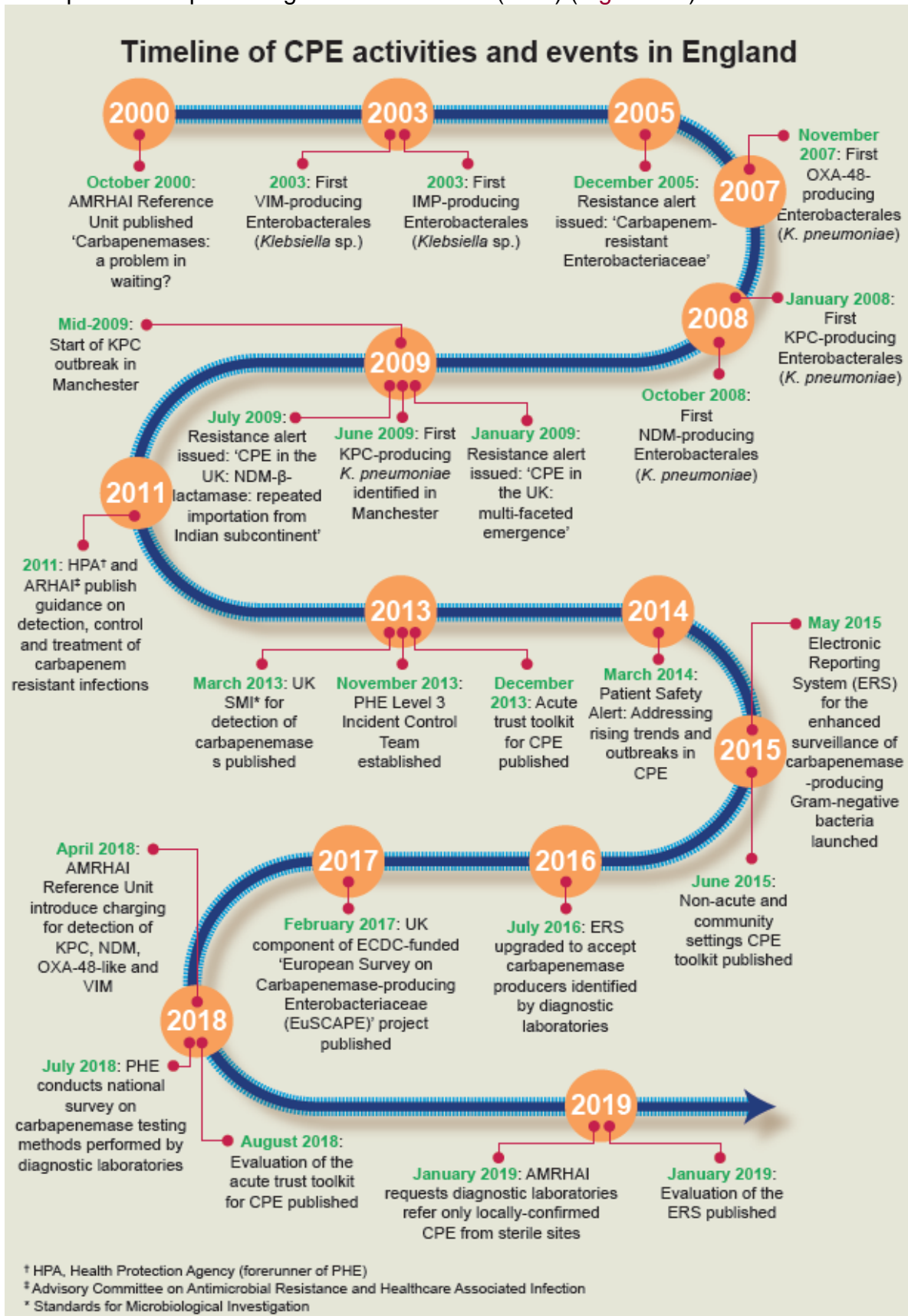
Figure 3.1: Timeline of CPE activities and events

Annual and monthly breakdowns of analyses presented in this chapter can be found in Annex chapter 3.

Reference laboratory

As in previous years the AMRHAI Reference Unit saw an increase in the total number of carbapenemase-producing Enterobacterales referred in 2018, with 4028 isolates confirmed as positive for at least one carbapenemase by either AMRHAI, regional PHE or NHS laboratories (Figure 3.2); most isolates represented colonisations with only 3.0% of confirmed CPE identified from invasive isolates (Figure 3.3). The 'big 5' carbapenemase families (KPC, OXA-48-like, NDM, VIM and IMP), and combinations thereof, continue to account for >99% CPE. The OXA-48-like family continue to predominate, accounting for 52.0% of confirmed CPE in 2018, followed by NDM (26.5%), KPC (11.2%), IMP (3.7%) and VIM (1.7%). CPE were referred from all nine PHE regions, but with foci in London (47.1% of CPE), the North West (21.3%) and the West Midlands (11.8%).

Figure 3.2: Number of confirmed CPEs referred to PHE's AMRHAI Reference Unit, 2009–2018.

Figure 3.3: Number and proportion of blood cultures confirmed as carbapenemase-producing Enterobacterales by PHE's AMRHAI Reference Unit, 2009–2018

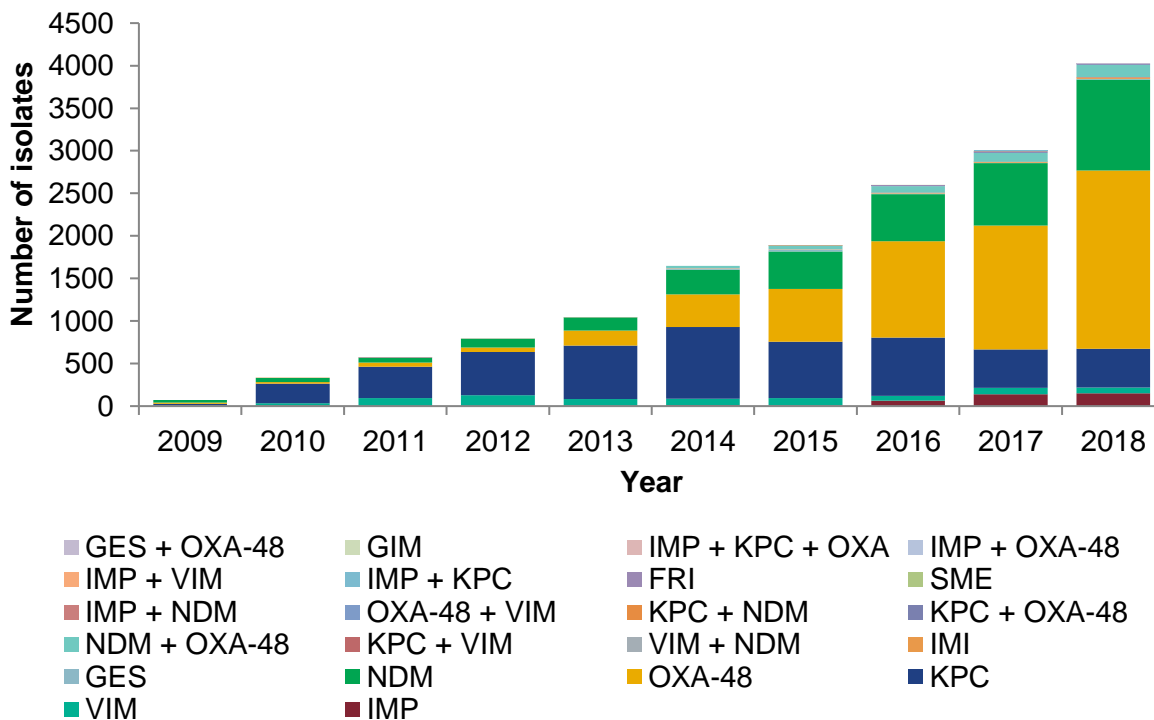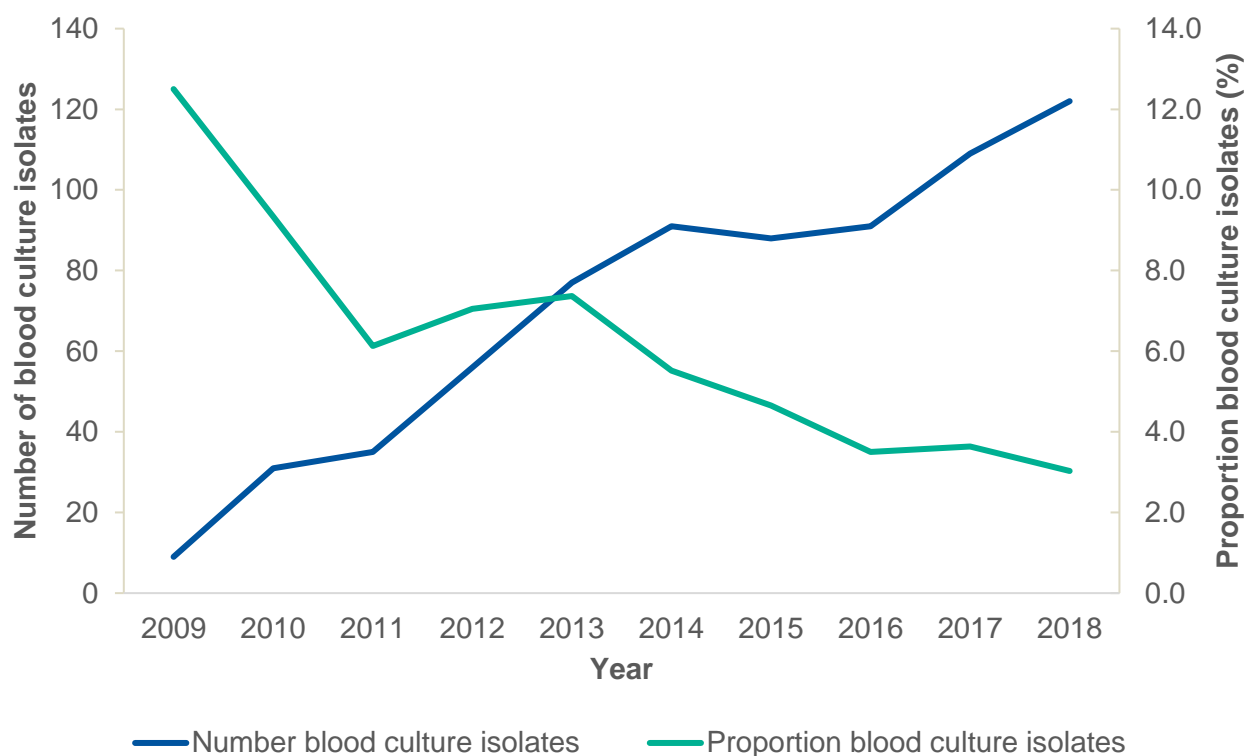In 2018, AMRHAI identified the first GIM (German imipenemase) metallo-carbapenemase producers in the UK. These were identified as *Citrobacter freundii* isolated from environmental screening swabs taken in the West Midlands and there were no associated clinical isolates. GIM carbapenemase was first reported in *Pseudomonas aeruginosa* clinical isolates from Germany in 2002,[49] but has since been reported in *Acinetobacter* spp. and various Enterobacterales. The role of the hospital environment, in particular sink biofilms, in the persistence of a GIM-producing multi-species outbreak has been demonstrated.[50] CPE harbouring combinations of two carbapenemases (most commonly NDM + OXA-48-like) are still relatively uncommon but appear to be increasing in occurrence; they accounted for 2/571 (0.35%) of all confirmed CPE in 2011 rising to 162/4028 (4%) of all confirmed CPE in 2018. However, 2018 saw referral of the first CPE harbouring three plasmid-mediated carbapenemases; an *E. coli* isolated from a sputum specimen in the East of England, with confirmed KPC + OXA-48-like + IMP.

Prior to the implementation of whole genome sequencing by the Gastroinestinal Bacteria Reference Unit (GBRU), three carbapenemase-positive *Salmonella enterica*

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[49] Castanheira, M., Toleman, M. A., Jones, R. N. *et al*. Molecular characterisation of a beta-lactamase gene, bla$_{GIM-1}$, encoding a new subclass of metallo-beta-lactamase. *Antimicrob Agents Chemother.* 2004; **48**:4654-61.

[50] Wendel, A.F., Ressina, S., Kolbe-Busch, S. *et al*. Species diversity of environmental GIM-1-producing bacteria collected during a long-term outbreak. *Appl Environ Microbiol.* 2016; **82**: 3605-10

isolates were identified following screening of cefotaxime-resistant non-typhoidal salmonellae for ertapenem resistance.[51] These were an NDM-1 positive *S. enterica* Senftenberg isolated in 2008 from a patient with unknown travel history, one OXA-48 positive *S. enterica* serovar Typhimurium isolated in 2013 from a patient with history of travel to Africa and one OXA-48 positive *S. enterica* serovar Paratyphi B isolated from a patient with no history of recent travel. GBRU implemented whole genome sequencing for routine surveillance of referred gastrointestinal isolates in 2014 and genotypic AMR surveillance including carbapenem resistance is performed using a standardised in-house bioinformatics pipeline. Among isolates that have been sequenced (54,856 *Salmonella* spp. sequenced between 1st April 2014 and 8th July 2019; 5,529 *Shigella* spp. and 9,934 Shiga toxin-producing *E. coli* sequenced between 1st May 2015 and 8th July 2019), six *Salmonella* spp. isolates (from two patients) were found to have carbapenemase genes, comprising five OXA-48-positive *S. enterica* serovar Kentucky from a patient with a history of travel to Jordan and one OXA-181-positive *S. enterica* serovar Abony from a patient with unknown travel history. All isolates originated from faeces except one serovar Kentucky from urine. No carbapenemase genes were identified among the *Shigella* spp. or *E. coli* gastrointestinal isolates.

Enhanced surveillance of carbapenemase-producing Enterobacterales

In response to increased detection of CPE by the AMRHAI Reference Unit, PHE implemented an Electronic Reporting System (ERS) for the enhanced surveillance of carbapenemase-producing Gram-negative bacteria in May 2015.[52] The system was launched to serve two main purposes: to enable web-based referral of suspected carbapenemase producers to specialist laboratories (national and regional) for confirmatory testing; and for hospitals to provide additional information on patients infected or colonised with confirmed carbapenemase producers. In July 2016, the system was upgraded to allow diagnostic laboratories performing local carbapenemase confirmatory testing to report their results via the ERS. The aims of the enhanced surveillance programme were to monitor changes in the epidemiology of carbapenemase producers in England and collect data to inform measures to control the spread of carbapenemase producers in acute healthcare settings.

Initial uptake of the system was slow but achieved good national coverage within the first year (Figure 3.4). Referrals via the ERS remained stable at approximately 70% until March 2018. However, with increased NHS laboratories performing local CPE tests, referrals via the ERS reduced to below 50% in the first quarter of 2019. The system was

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[51] Day MR, Meunier D, Doumith M. *et al*. Carbapenemase-producing *Salmonella enterica* isolates in the UK, *J Antimicrob Chemother* 2015; 70: 2165–2167.

[52] Freeman R, Ironmonger D, Puleston R. *et al*. Enhanced surveillance of carbapenemase-producing Gram-negative bacteria to support national and international prevention and control efforts. *Clin Microbiol Infect* 2016; 22: 896-7

closed on 30th April 2019 when PHE introduced methodology to report carbapenemases on the SGSS. Between May 2015 and March 2019, 14,410 isolates were referred or reported via the ERS; of these, 12,656 (87.8%) were Enterobacterales and of these 7,116 (56.2%) were confirmed as carbapenemase producers (Figure 3.4).
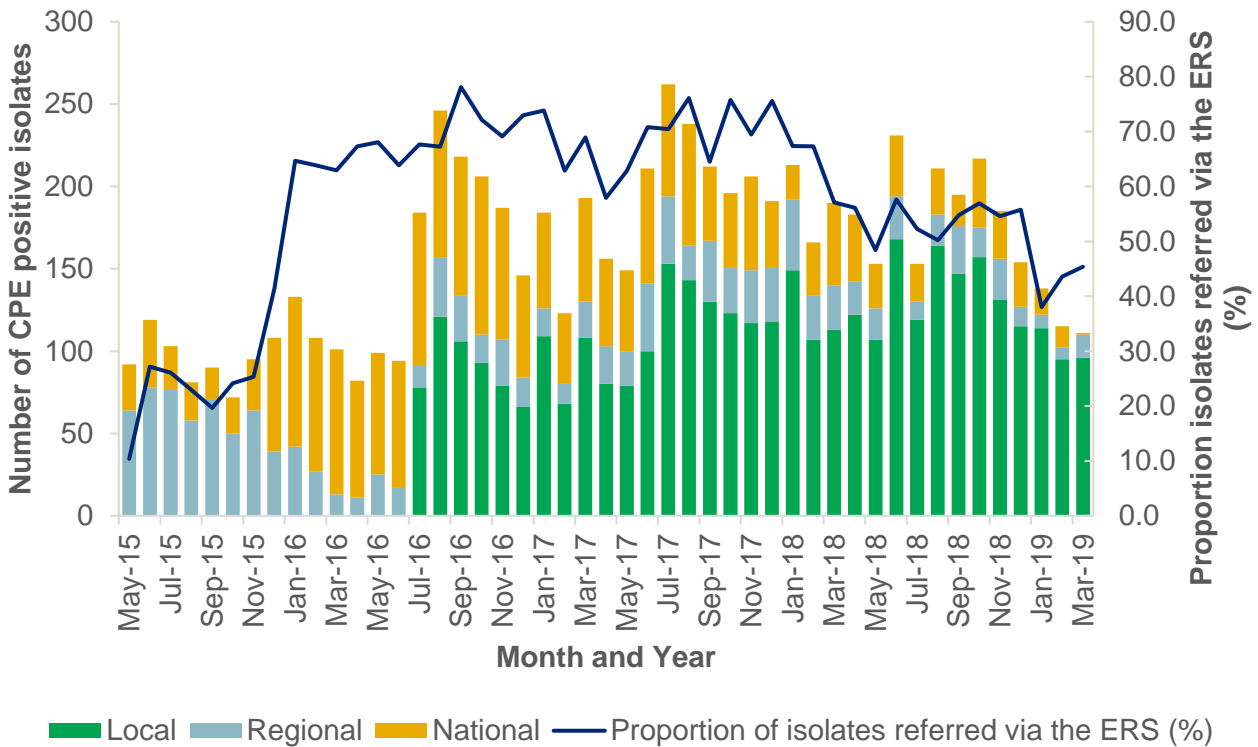
Figure 3.4: Proportion of isolates referred to the AMRHAI Reference Unit via the ERS and number of CPE positive isolates identified at local, regional and national level, May 2015–March 2019

Epidemiological analysis

Following the removal of duplicates (same organism from the same specimen type from the same patient within one year), 6,857 cases of CPE infection or colonisation were reported via the ERS. Just over half were male (3,679; 53.7%) and the median age was 69.4 years (interquartile range 54.6 – 80.1). The majority of patients resided in the UK (6,251; 91.2%).

The majority of specimens were screening samples (5,527; 80.6%) and this has remained consistent (Figure 3.5). Of the 1,318 clinical specimens, the most commonly reported sources were urine (693; 52.6%), blood (159; 12.1%) and sputum (87; 6.6%). Over 33 species were identified as having acquired carbapenemase genes, the most frequently identified being *K. pneumoniae* (2,681; 39.1%), *E. coli* (2,080; 30.3%), *E. cloacae/E. cloacae* complex (966; 14.1%) and *C. freundii* (306; 4.5%). The proportion of

blood culture isolates across the most commonly reported species can be seen in Table 3.1. The most commonly identified resistance mechanisms were OXA-48 (3091; 45.1%), KPC (1813; 26.4%) and NDM (1444; 21.1%).

There were 238 cases identified as invasive infections (based on sterile sites stated in 'Laboratory reporting to Public Health England: A guide for diagnostic laboratories'[53]). Mortality information was obtained by tracing CPE data captured via the ERS against the NHS spine using NHS number, name, date of birth and sex. Sixteen (6.7%) cases could not be traced. For patients with multiple specimens, the most recent specimen was included in the analysis. Two hundred and two patients were included in the analysis and 30-day case fatality rate (CFR) for invasive CPE infections was 23.8% (95% credible interval 18.1–30.0); similar to the 30 day CFR reported for carbapenem resistance BSI reported in Chapter 2.

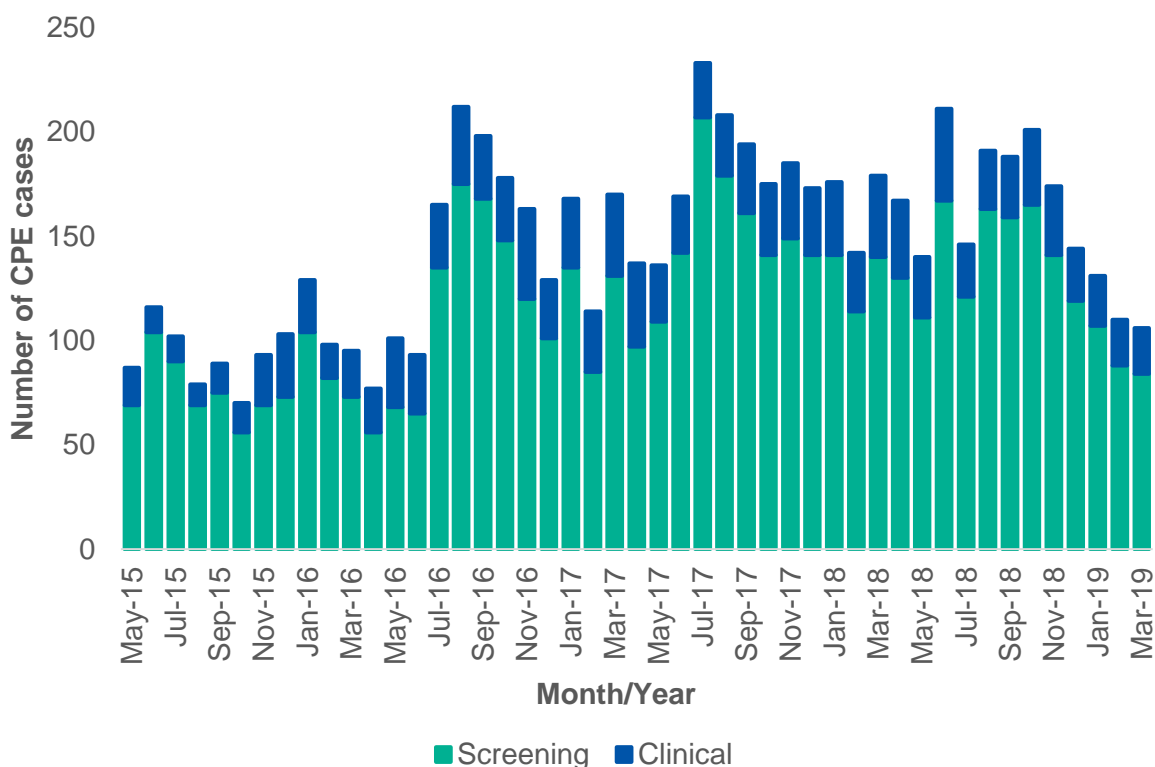**Figure 3.5: Number of CPE confirmed cases confirmed by regional/national laboratories or reported by diagnostic laboratories via the ERS, May 2015–March 2019**

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[53]PHE. Laboratory reporting to Public Health Engalnd: A guide for diagnostic laboratories. Published July 2016. Available: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/739854/PHE_Laboratory_Reporting_Guidelines.pdf

Table 3.1: Number and proportion of CPE-positive blood culture isolates from the total CPE isolates referred on ERS for the four most commonly identified species, May 2015–March 2019

Pathogen	No. cases with blood cultures positive for CPE	Total number of CPE cases reported	Proportion of all cases that were blood cultures (%)
K. pneumoniae	82	2681	3.1
E. coli	30	2080	1.4
E. cloacae (complex)	29	966	3.0
C. freundii	1	306	0.3

The majority of cases were NHS acute trust inpatients (5,988; 87.3%). One hundred and thirty three (90.5%) NHS acute Trusts submitted data on at least one inpatient with CPE. Foreign travel in the 12 months preceding specimen collection was not provided or was reported as "unknown" for the majority (81.0%) of cases, with 604 (8.8%) cases having a documented history of overseas travel in the previous 12 months and 696 (10.2%) reporting no travel. The most frequently reported countries were India (170; 28.1%), Pakistan (74; 12.3%) and Egypt (36; 6.0%). Similarly, the majority of cases did not have information on whether they had received healthcare abroad in the 12 months before the specimen was taken, with 5,708 (83.2%) reported as "unknown" or no data provided. Four hundred and twenty seven (6.2%) cases did report healthcare abroad in the previous 12 months with the most frequently reported countries being India (112; 26.2%), Pakistan (46; 10.8%) and Egypt (29; 6.8%).

Of the 6,011 inpatient cases reported (NHS acute and community trust), admission date was provided for 27.0%. Clinical specialty was also poorly completed, with only 1,150 (19.1%) reports providing this information. Where clinical specialty was provided, general surgery (168; 14.6%), general medicine (152; 13.2&), accident and emergency (97; 8.4%), geriatric medicine (95; 8.3%) and critical care medicine (74; 6.4%) were the most frequently reported. There were 1,768 records with a response indicating whether the patient had been screened on admission, with 909 (51.4%) indicating that an admission screen had been performed and 280 (15.8%) indicating that an admission screen had not been performed (the remaining were reported as "unknown"). Of those that were reported as having had an admission screen, 228 (25.1%) were found to be positive.

Diagnostic laboratory survey and new guidance on CPE methods

Since the launch of the ERS an increasing number of diagnostic laboratories have introduced methods to routinely identify carbapenemases. In 2018, a national survey of diagnostic laboratories in England was carried out to determine methods used for the identification of carbapenemases. The PHE Field Serivce information managers conducted telephone interviews of structured questions with senior laboratory staff and responses were collected and submitted electronically. The survey was open between

11th July – 19th August 2018 and 113/120 (94%) laboratories responded. Eighty (70.8%) laboratories reported using phenotypic methods for the detection of carbapenemase activity; these results were stored on laboratory information management system (LIMS) in 88.3% of laboratories. However, only 29.6% of laboratories reported using EUCAST screening cut-offs for carbapenem susceptibility testing to determine whether to proceed to local or reference laboratory referral for carbapenemase testing.

Fifty-five (48.7%) laboratories reported use of methods capable of carbapenemase identification. The most commonly adopted methods were commercial PCR (60.0%) and immunochromatographic assays (43.6%); note, some laboratories used both methods. The majority (>90%) of these laboratories could identify isolates harbouring KPC, OXA-48-like or NDM; VIM and IMP could be identified by fewer laboratories (76.4% and 65.5%, respectively). Nearly all (98.1%) laboratories performing molecular testing recorded the results on their LIMS.

In response to this survey, the AMRHAI reference unit published a report in May 2019 on the 'Commercial assays for the detection of acquired carbapenemases'.[54] To enable diagnostic laboratories to make an informed choice on the implementation of commercially-available carbapenemase detection methods when considering local business needs, the report strongly recommends the implementation of an assay for the detection of the 'big 4' carbapenemases in frontline diagnostic laboratories. Local testing with rapid turnaround will have maximal impact on individual patient management and help prevent onward transmission.

Outbreaks

The Health and Social Care Act 2008 requires healthcare providers to report outbreaks to PHE, including CPE outbreaks (Criterion 5 and 9 of the Code of Practice on the prevention and control of infections). In addition to the published outbreaks noted below, PHE has advised and supported healthcare providers in the investigation and control on more than 100 outbreaks; however this may still under-represent the true burden of outbreaks.

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[54] Meunier D, Freeman R, Hopkins K. Commercial assays for the detection of acquired carbapenemases. PHE: London, 2019. Available at:
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/804995/Detection_of_carbapenemase_report.pdf

A literature search showed that relatively few CPE outbreaks in England were published between 2013-2018. Reported outbreaks involved KPC, [55,56] NDM[57] and OXA-48-like[58] enzymes. These outbreaks occurred in several different clinical settings, including renal units, liver units and two outbreaks involving multiple ward types.

Reported outbreaks have been controlled through the effective application of infection prevention and control measures, increased screening to identify patients colonised with CPE and ward closures. Due to their complexity, outbreaks of CPE can be large, prolonged and challenging to control. Consequently, the operational efficiency of units and hospitals can be adversely affected. If outbreaks are not controlled swiftly this can lead to an endemic situation which is difficult to eradicate. In addition, such outbreaks can be costly; the cost of prolonged outbreaks can exceed £1m,[59] with the cost of one outbreak in northwest England estimated at £5m.[60,61]

Infection prevention and control

PHE published the 'Acute trust toolkit for the early detection, management and control of carbapenemase-producing Enterobacteriaceae' in December 2013.[62] The toolkit was published in response to the increased incidence of CPE in England and provided practical advice for clinicians and front-line staff aimed at reducing and preventing the spread of CPE within and across healthcare settings.

Subsequent to the publication of the acute trust toolkit, the 'Toolkit for managing carbapenemase-producing Enterobacteriaceae in non-acute and community settings'

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[55] Decraene V, Phan HTT, George R. *et al*. A large, refractory nosocomial outbreak of *Klebsiella pneumoniae* carbapenemase-producing *Escherichia coli* demonstrates carbapenemase gene outbreaks involving sink sites require novel approaches to infection control. *Antimicrob Agents Chemother*. 2018; 62: e01689-18. https://doi.org/10.1128/AAC.01689-18

[56] Martin J, Phan HT, Findlay J. *et al*. Covert dissemination of carbapenemase-producing *Klebsiella pneumoniae* (KPC) in a successfully controlled outbreak: long-and short-read whole-genome sequencing demonstrate multiple genetic modes of transmission. *J Antimicrob Chemother*. 2017; 72: 3025-34

[57] Torok E, Brodrick H, Khokhar F. *et al*. Prospective surveillance and rapid whole-genome sequencing detects two unsuspected outbreaks of carbapenemase-producing *Klebsiella pneumoniae* in a UK teaching hospital. *Open Forum Infect Dis* 2017; 4: S43-S44

[58] Thomas CP, Moore LS, Elamin N. *et al*. Early (2008–2010) hospital outbreak of *Klebsiella pneumoniae* producing OXA-48 carbapenemase in the UK. *Int J Antimicrob Agents* 2013; 42: 531-6

[59] Otter JA, Burgess P, Davies F. *et al*. Counting the cost of an outbreak of carbapenemase-producing Enterobacteriaceae: an economic evaluation from a hospital perspective. *Clin Microbiol Infect* 2017; **23**:188-96.

[60] Dunhill L. Costs of hospital bug outbreak rocket to £5m at major FT. HSJ. Published on-line 26 January 2016. Available: https://www.hsj.co.uk/hsj-local/providers/central-manchester-university-hospitals-nhs-foundation-trust/costs-of-hospital-bug-outbreak-rocket-to-5m-at-major-ft/7001937.article

[61] Manchester trust struggling to contain hospital bug. Nursing Times. Available: https://www.nursingtimes.net/news/hospital/manchester-trust-struggling-to-contain-hospital-bug/7002164.article

[62] PHE. Acute trust toolkit for the early detection, management and control of carbapenemase-producing Enterobacteriaceae. Publishe December 2013. Available: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/329227/Acute_trust_toolkit_for_the_early_detection.pdf

was published in June 2015.[63] This toolkit provided practical advice for health and social care staff working in community and non-acute settings, including community hospitals, mental health trusts, care homes and primary care, amongst other settings.

Antimicrobial prescribing and stewardship principles to consider to contain carbapenemase-producing Enterobacterales (CPE)

During the year, 'Antimicrobial Prescribing and Stewardship: Principles to Consider' was developed through an expert consensus process.

It was recommended that NHS organisations should regularly review their Antimicrobial Stewardship (AMS) Programme in accordance with actions outlined in the Health and Social Care Act 2008, Code of Practice on the prevention and control of infections and related guidance criterion 3,[64] Start Smart then Focus toolkit,[65] TARGET Antibiotics toolkit[66] and recommendations specified in NICE Guidance NG15[67] and NICE/PHE Antimicrobial prescribing guidelines.

A full draft of the new CPE framework will be made available for consultation here in late 2019.

Discussion

Global surveillance has shown an increase in the prevalence of CPE. PHE has had systems in place to identify the emergence of carbapenemases for many years. Since 2013, in response to an observed increase in the identification of CPE in England, PHE intensified its CPE activities, which aimed to improve our understanding of these bacteria and control and prevent their spread within healthcare settings. Based on specimens referred to the AMRHAI reference unit for identification of carbapenemase activity we have seen an overall increase in the number of blood culture isolates

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[63] PHE. Toolkit for managing carbapenemase-producing Enterobacteriaceae in non-acute and community settings. Published June 2015. Available:
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/769414/CPE-Non-AcuteToolkit_CORE.pdf

[64] Department of Health. The Health and Social Care Act 2008: Code of Practice on the prevention and control of infections and related guidance. July 2015 criterion 3. Available:
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/449049/Code_of_practice_280715_acc.pdf

[65] PHE. Start Smart – Then Focus. Antimicrobial Stewardship Toolkit for English Hospitals. Published March 2015. Available:
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/417032/Start_Smart_Then_Focus_FINAL.PDF

[66] TARGET Antibiotics toolkit - https://www.rcgp.org.uk/clinical-and-research/resources/toolkits/target-antibiotic-toolkit.aspx

[67] NICE Guideline NG15. Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use. 2015.
https://www.nice.org.uk/guidance/ng15/resources/antimicrobial-stewardship-systems-and-processes-for-effective-antimicrobial-medicine-use-pdf-1837273110469

identied as CPE positive. The 30 day all-cause CFR associated with invasive CPE infections is similar to the bacteraemia CFR and lower than reported internationally.[68,69]

Between 2013 and 2018 we have continued to see an increase in the number of isolates referred to the AMRHAI reference unit despite the increased uptake of commercially-available methods by diagnostic laboratories. Although it appears that the proportion of CPE blood culture isolates has decreased in this time, this is likely due to an increase in the number of suspected CPE from clinical and non-clinical (for example, colonisation) sites referred to the AMRHAI Reference Unit following various communications to alert laboratories to the increasing prevalence of CPE in healthcare settings. Relying on reference laboratory data for surveillance purposes has its limitations as isolates received by the AMRHAI Reference Unit do not represent the true prevalence of carbapenemases in England.

In April 2018 the AMRHAI Reference Unit introduced a charge for performing screening for four of the most commonly identified carbapenemases (KPC, OXA-48-like, VIM and NDM; the 'big 4') and no longer requests that laboratories send them locally-confirmed carbapenemase producers unless isolated from sterile sites. Consequently, data captured via the ERS reduced significantly, resulting in an artificial decrease in the number of CPE reported via the system. Further to this, an evaluation of the ERS found that although this was the only system in England able to gather intelligence on risk factors associated with CPE, the completeness of enhanced data was poor and prevented the original aims of the system being met.[70] With an increasing proportion of diagnostic laboratories identifying carbapenemases using molecular tests and the enhanced surveillance system unable to meet its objectives, PHE modified its approach to surveillance.

Effective infection prevention and control remains essential and it is crucial that guidelines for CPE remain relevant to the emerging situation. An evaluation of the CPE acute trust toolkit found that although awareness of the toolkit was high among trusts, compliance with the recommendations varied greatly.[71] The authors recommended that future guidance should involve substantial involvement of clinicians working across a variety of settings and should undergo regular review and updating in light of the evolving CPE situation.

[68] Balkan II, Aygun G, Aydin S. *et al.* Bloodstream infections due to OXA-48-like carbapenemase-producing Enterobacteriaceae: treatment and survival. *Int J Infect Dis* 2014; *26*: 51-56.
[69] Ramos-Castaneda JA, Ruano-Ravina A, Barbosa-Lorenzo R. *et al.* Mortality due to KPC carbapenemase-producing *Klebsiella pneumoniae* infections: Systematic review and meta-analysis: Mortality due to KPC *Klebsiella pneumoniae* infections. *J Infect* 2018; *70*: 438-448.
[70] Jermacane D, Coope CM., Ironmonger D. *et al.* An evaluation of the electronic reporting system for the enhanced surveillance of carbapenemase-producing Gram-negative bacteria in England. *J Hosp Infect.* 2019; 102: 17-24
[71] Coope CM, Verlander NQ, Schneider A. *et al.* An evaluation of a toolkit for the early detection, management, and control of carbapenemase-producing Enterobacteriaceae: a survey of acute hospital trusts in England. *J Hosp Infect* 2018; 99: 381-389

When dealing with outbreaks, a multimodal approach is required to achieve control. Early detection of CPE and rapid implementation of enhanced control measures is crucial to prevent further colonisation, carriage and spread. An additional consideration is that once colonised patients are released from hospital there is a risk that these organisms may spread in community settings, such as a long-term care facilities and care homes. Better information and understanding of the nature of outbreaks will help improve the management and increase the effectiveness of control. Furthermore, efforts to learn from outbreaks can be effective in early identification and prevention of future outbreaks.[72]

Future work

New approach to surveillance

To accommodate advances in testing methodologies and referral practices, PHE has modified its surveillance approach to allow more efficient data capture and streamline isolate referral to AMRHAI as follows:

- modifications to PHE's Second Generation Surveillance System (SGSS) have been made to allow diagnostic laboratories to report locally-confirmed CPEs to PHE. This work is ongoing and requires the need to standardise outputs across a range of LIMS used by diagnostic laboratories (16 different systems were identified in the survey.) A pilot for uploading results to SGSS was conducted in the West Midlands at the end of 2018 and the findings are being used to inform system configuration in other laboratories. To ensure timely progression of this work reporting of local CPE results via SGSS has been added to Field Service's weekly audit for monitoring SGSS activities.
- PHE is working to enable electronic requesting via the National Pathology Exchange (NPEx) Lab2Lab messaging system in a phased deployment. Phase 1 (2019/20) will initially deliver in-bound NPEx electronic requesting with electronic reporting continuing to be delivered by the PHE eLab system with the intention of delivering full end to end Lab2Lab messaging in subsequent phases.

This new approach will facilitate linkage to other datasets and will be vital in improving our understanding of the epidemiology of CPE in England, without increasing the data burden on the NHS.

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[72] Gharbi M, Moore LS, Gilchrist M *et al*. Forecasting carbapenem resistance from antimicrobial consumption surveillance: lessons learnt from an OXA-48-producing *Klebsiella pneumoniae* outbreak in a West London renal unit. Int J Antimicrob Agents 2015; 46: 150-156

This capacity development of SGSS to allow locally confirmed carbapenemase producers to be captured for surveillance avoid the requirement of manual reporting to PHE. To ensure its success and allow comprehensive national capture of data on CPE, diagnostic laboratories should establish processes that allow confirmatory testing of suspected acquired carbapenemase producers locally and ensure that these results are captured by their LIMS.

Outbreak monitoring

SGSS collates data on AMR and coverage of this surveillance system across the NHS has improved substantially in recent years. As a consequence, data on carbapenem-resistant isolates are routinely collected, analysed and reported on a quarterly basis back to the NHS. PHE has developed exceedance algorithms to detect excess cases of infections reported through SGSS; with the progress on capture of CPE mechanisms we aim to develop methods to monitor potential clusters and outbreaks across the healthcare system.

New CPE framework for infection prevention and control

PHE has previously published guidance on the prevention and control of CPE in both acute and non-acute settings. A steering committee is delivering ongoing activities related to surveillance, outbreak control, laboratory diagnosis, modelling and research, and providing substantive updates to guidance documents. A full draft of the new CPE framework will be made available for consultation here in late 2019.

CPE objectives in the UK's Tackling Antimicrobial Resistance National Action Plan

PHE is supporting actions outlined in the United Kingdom's 'Tackling Antimicrobial Resistance National Action Plan' to prevent and control the transmission of carbapenem-resistant bacteria, including reducing the number of specific human drug-resistant infections by 10% by 2025; reducing UK antimicrobial use in humans by 15% by 2024; and making carbapenem-resistant Gram-negative infections a notifiable disease in existing laboratory reporting systems. Specifically for CPE, we will:

- support the inclusion of carbapenem-resistant Gram-negative infections on the Health Protection (Notifications) Regulations list of causative agents
- update PHE surveillance systems to ensure that data can be captured through automated technologies from NHS microbiology laboratories to allow effective reporting of carbapenem-resistant Gram-negative invasive infections

Ongoing and future research

A number of CPE research projects are underway at PHE to:

- understand the national picture, including determining testing methods used nationally, analysis of national datasets to estimate the proportion of patients admitted to hospitals with CPE, and more detailed Trust data to understand mortality and risk factors
- estimate the role of sinks in the transmission of CPE, further understand hospital sink microbiomes and estimate survival and persistence of CPE in the hospital environment. Mathmatical modelling methods are being used to estimate patient-to-patient transmission as well as the impact of patient referral networks throughout the NHS on CPE transmission in collaboration with the National Institute of Health Research HCAI & AMR Health Protection Research Units
- evaluate interventions including screening strategies in Trusts, as well as model-based (cost) effectiveness evaluations of screening and control
- improve epidemiological understanding using whole-genome sequencing data

Research abstracts and recent publications are presented in the Research Abstracts section.

Future work will continue to make the best use of surveillance systems and integration of whole genome sequencing (WGS) data, to gain insight for public health action.

4. Antibiotic consumption

Introduction

Optimising the use of antimicrobials to ensure safe and effective patient care is one of the main strategies to tackle AMR, reflected in the UK Governments' ambition to reduce antimicrobial use in humans by 25% by 2024 from the 2014 baseline.[73] Continuous surveillance of antibiotic consumption is therefore essential to determine the level of use and the effectiveness of antimicrobial stewardship (AMS) programmes in different prescriber populations.

Antibiotics are prescribed in several settings in England: general practice (GP), dental practice, hospitals, out-of-hours services and walk-in centres. Data on antibiotic consumption for primary and secondary care between 2014 and 2018 are presented in this chapter; information on methods and research activities can be found in the Annex Chapter 4. Data and figures presented in the chapter are available in the on-line chapter data tables and figures appendix.

Alterations of Defined Daily Doses 2019

The World Health Organisation (WHO) Collaborating Centre for Drug Statistics Methodology assigned and implemented new Defined Daily Doses (DDDs) in the Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD) index 2019 for formulations of some of the most commonly used antibiotics in England (Table 4.1).[74] The new DDDs have been applied to the antibiotic consumption data presented in this report. The impact of the changes on the consumption level is presented in Figure 4.1.

As a result of the DDD changes, the level of total antibiotic consumption in terms of DDDs per 1,000 inhabitants per day (DID) has reduced from 20.3 to 18.2 DID in 2018 (Figure 4.1); this level of reduction was consistent over time. This decrease was predominantly driven by DDD changes for amoxicillin and co-amoxiclav.

In primary care, the largest change, when comparing the new DDDs to the previously used DDDs, was observed in oral amoxicillin (4.2 to 2.8) and co-amoxiclav (0.686 to 0.458). For secondary care, co-amoxiclav had the greatest difference pre- (0.706) and

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[73] Department of Health and Social Care. UK 5-year action plan for antimicrobial resistance 2019 to 2024. 2019. Available online from: https://www.gov.uk/government/publications/uk-5-year-action-plan-for-antimicrobial-resistance-2019-to-2024

[74] WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index 2019. 2018. Available online from: https://www.whocc.no/atc_ddd_index/

post-DDD (0.471) change. Oral amoxicillin had the second largest change (0.344 to 0.229), followed by parenteral amoxicillin (0.096 to 0.032).

Table 4.1 WHO DDD alterations 2019

Antibiotic	Adm Route*	Previous DDD	New DDD	Unit	ATC code
Ampicillin	P	2.0	6.0	g	J01CA01
Amoxicillin	O	1.0	1.5	g	J01CA04
Amoxicillin	P	1.0	3.0	g	J01CA04
Temocillin	P	2.0	4.0	g	J01CA17
Co-amoxiclav	O	1.0	1.5	g	J01CR02
Cefepime	P	2.0	4.0	g	J01DE01
Meropenem	P	2.0	3.0	g	J01DH02
Ciprofloxacin	P	0.5	0.8	g	J01MA02
Colistin	P	3.0	9.0	MU	J01XB01

* Administration Route: O = oral; P = parenteral
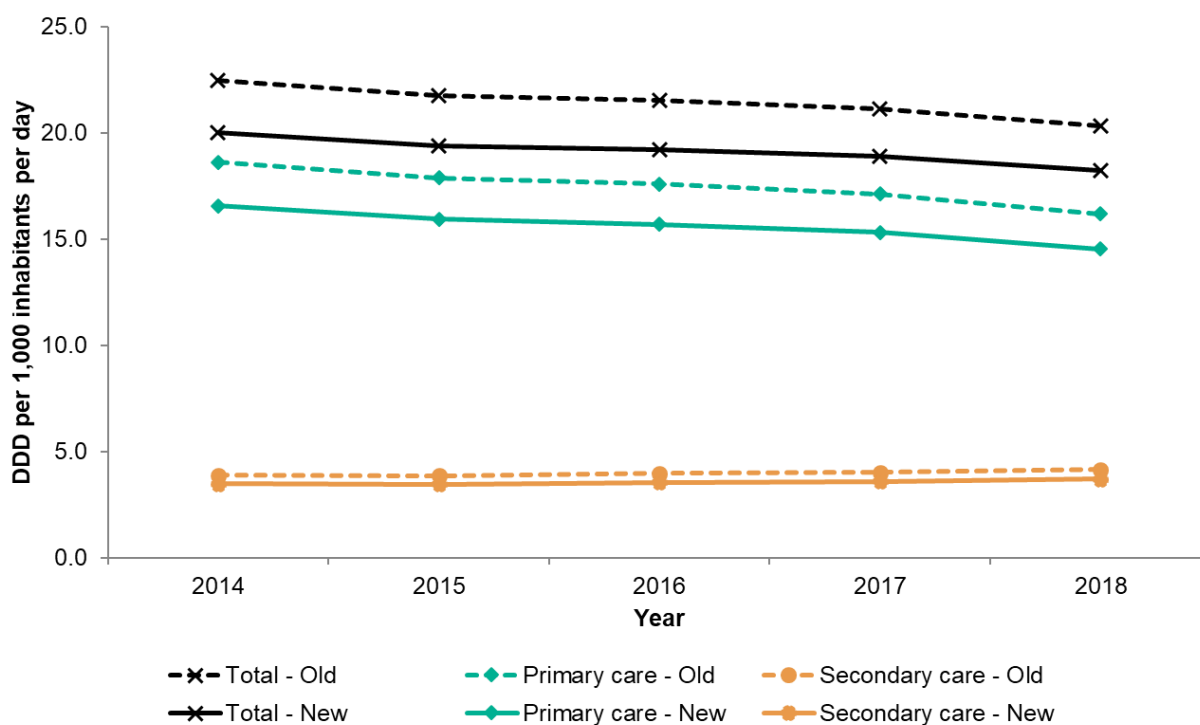
Figure 4.1 Comparison of antibiotic consumption using historic and new DDDs, expressed as DDDs per 1,000 inhabitants per day, England 2014-2018

Total antibiotic consumption

Total antibiotic consumption in England has been decreasing since 2014, the peak of antibiotic consumption over the last 20 years. Antibiotic usage measured in terms of DDDs per 1,000 inhabitants per day has declined by 9.0%, from 20.0 in 2014 to 18.2 in 2018, using the new DDD measurements (Figure 4.1).

Over this period, significant rises in consumption of third, fourth and fifth-generation cephalosporins and 'other antibacterials' (Annex Chapter 4 for full definitions), particularly nitrofurantoin, occurred. Carbapenems and quinolones consumption not change significantly. Declining levels of consumption were observed for all other antibiotic groups (Table 4.2).

In 2018, the most commonly used antibiotic groups were penicillins (38.4%), tetracyclines (25.2%) and macrolides (15.8%).

The majority of antibiotics were prescribed in the GP setting (72.4%; 13.2 DID), followed by hospital inpatients (12.7%; 2.3 DID), hospital outpatients (7.5%; 1.4 DID), other community settings (3.9%; 0.710 DID) and dental practice (3.5%; 0.640 DID). Prescribing in the GP setting has continuously decreased over the past 5 years. In contrast, antibiotic prescribing for hospital inpatients has increased (Figure 4.2) but the absolute increase in consumption has been small in secondary care compared to the decrease observed in primary care (0.219 DDDs per 1,000 inhabitants per day increase in hospitals vs. -2.0 DDDs per 1,000 inhabitants per day in primary care).

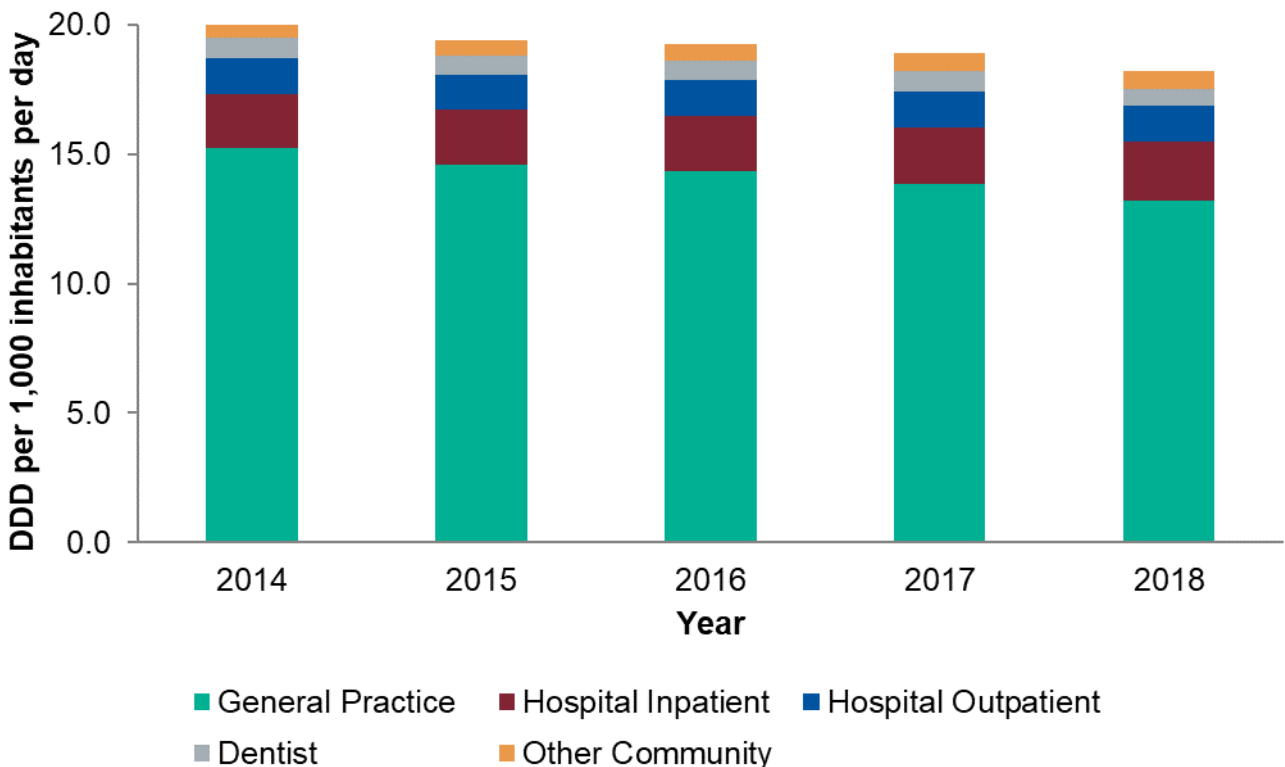**Figure 4.2 Total antibiotic consumption by setting, expressed as DDDs per 1,000 inhabitants per day, England, 2014-2018**

Table 4.2 Total antibiotic consumption by antibiotic groups, expressed as DDDs per 1,000 inhabitants per day, 2014-2018

Antibiotic Group	2014	2015	2016	2017	2018	Trend	p-value
Penicillins (excluding inhibitors)	6.437	6.212	6.292	6.160	5.885		0.038[+]
Penicillins (inhibitor combinations only)	1.276	1.208	1.145	1.103	1.116		0.020[+]
First and second-generation cephalosporins	0.347	0.301	0.268	0.258	0.243		0.010[+]
Third, fourth and fifth-generation cephalosporins	0.057	0.057	0.063	0.074	0.079		0.009[+]
Carbapenems	0.058	0.058	0.056	0.056	0.052		0.060
Tetracyclines	4.930	4.828	4.735	4.685	4.596		0.001[+]
Macrolides, lincosamides and streptogramins	3.362	3.229	3.204	3.119	2.871		0.014[+]
Sulfonamides and trimethoprim	1.438	1.357	1.267	1.056	0.849		0.004[+]
Quinolone antibacterials	0.536	0.519	0.515	0.522	0.547		0.619
Anti-*Clostridioides difficile* agents^	0.004	0.004	0.004	0.004	0.004		0.354
Oral metronidazole	0.377	0.356	0.333	0.329	0.305		0.002[+]
Other antibacterials*	1.094	1.156	1.227	1.398	1.549		0.004[+]

+ Statistically significant p-value for trend from 2014 to 2018
^ Anti-*Clostridioides difficile* agents: oral vancomycin and fidaxomicin
* Other antibacterials (ATC 3rd level pharmacological subgroup 'J01X') include: glycopeptide antibacterials, polymyxin, steroid antibacterials, imidazole derivatives, nitrofuran derivatives, other antibacterials (full list in chapter annex)

Penicillins

Consumption of penicillins, the most commonly prescribed group of antibiotics, decreased by 9.2% over the last 5-years, from 7.7 to 7.0 DDDs per 1,000 inhabitants per day. The main decreases from 2014 to 2018 were observed in dental prescribing (-18.4%) and in the GP setting (-14.2%), whereas it has been steadily increasing in the other community (32.3%) and in hospital inpatients (7.9%). This may be driven by reduced inappropriate prescribing for coughs and sore throats in primary care and reduced use of antibiotics with alternative dental management in dental practices.

Amoxicillin (-16.7%) and co-amoxiclav (-9.9%) prescribing continued to decrease in 2018, compared to 2014. The use of pivmecillinam increased steadily from 0.020 to

0.071 DDDs per 1,000 inhabitants per day, most likely to be related to changes in the PHE and NICE guidance for urinary tract infection (UTI) prescribing.[75]

Piperacillin/tazobactam usage decreased by 31.7% over the 5-year period, with a sharp reduction in 2017 (from 0.105 DID in 2016 to 0.065 DID in 2017) due to the shortage of international supply[76] and a subsequent 6.4% increase from 2017 to 2018.

Cephalosporins

Total cephalosporin consumption decreased by 20.2% from 0.403 to 0.322 DDDs per 1,000 inhabitants per day between 2014 and 2018, which was largely driven by decreasing use of first-generation cephalosporins (cefalexin and cefradine). However, use of the third-generation cephalosporins, ceftazidime and ceftriaxone, increased significantly over the 5-year period, with the largest increase observed in 2017, probably reflecting the use of alternative antibiotics following the shortage of piperacillin/tazobactam. Ceftazidime/avibactam, a new cephalosporin with a novel β-lactamase inhibitor, was used at low volumes in secondary care.

Tetracyclines

Tetracyclines remained predominantly prescribed in the GP setting (87.6% in 2018). The overall consumption of tetracyclines reduced slightly between 2014 and 2018 (-6.8%). The use of minocycline (-55.5%), oxytetracycline (-40.9%) and tetracycline (-41.3%) decreased over this period, but an increase was observed for doxycycline use (8.2%). This may reflect reduced use for conditions such as acne and alternatives to penicillins for the treatment of cough, sinusitis and acute exacerbations of chronic respiratory diseases.[77]

Quinolones

After a 3.9% decline in quinolone use between 2014 and 2016, consumption increased 4.8% from 2016 to 2018. GP prescribing of quinolones declined consistently throughout 2014 to 2017, with a slight increase in 2018. In contrast, hospital inpatient prescribing increased by 36.5% in the last 5 years, with larger increases observed from 2016 to 2018, driven by the piperacillin/tazobactam shortage. Ciprofloxacin accounted for 75.6% of quinolone use in 2018 and the trend has remained broadly stable at 0.414 DDDs per

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[75] NICE; Urinary tract infection (lower): antimicrobial prescribing. 2018. available on-line from https://www.nice.org.uk/guidance/ng109

[76] BSAC; DH advises on Piperacillin-Tazobactam infection supply problems 2017. available on-line from http://www.bsac.org.uk/dh-advises-on-piperacillin-taxobactam-injection-supply-problems/

[77] NICE; Antimicrobial prescribing guidelines. 2019. available on-line from https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/antimicrobial-prescribing-guidelines

1,000 inhabitants per day. However, levofloxacin use consistently increased from 2014 to 2018 (96.9%; 0.037 to 0.074 DDDs per 1,000 inhabitants per day).

Box 4.1 Importance of monitoring the use of new antibiotics – ceftazidime/avibactam (see abstract in Research Annex)

Ceftazidime/avibactam (CAZ-AVI), a novel cephalosporin/β-lactamase inhibitor combination, was licensed in 2015 to treat complicated and hospital-acquired infections caused by multi-drug resistant Gram-negative bacteria, including those producing extended-spectrum β-lactamases (ESBLs) and carbapenem-resistant Enterobacterales (CRE).

The PHE Antimicrobial Resistance and Healthcare Associated Infections (AMRHAI) reference unit has included CAZ-AVI on the panel of antibiotics tested against Gram-negative bacteria since its approval in the USA in 2015. CAZ-AVI was launched in the UK in March 2017. In June 2018, the European Centre for Disease Prevention and Control published a risk assessment which concluded that emergence of CAZ-AVI-resistant CRE poses a public health threat due to the likelihood of exchange of resistance determinants between bacterial species. Transmission within healthcare settings and potential adverse outcomes for patients,[78] and routine and reference laboratory testing have highlighted the presence of CAZ-AVI resistance in England. Of 5,640 isolates tested at the national reference laboratory, 12.6% were CAZ-AVI-resistant; of these, 87.3% were resistant due to production of metallo-β-lactamases against which CAZ-AVI lacks activity. However, CAZ-AVI resistance was also observed in twelve *Klebsiella pneumoniae* isolates producing both KPC and OXA-48, one *Citrobacter freundii* and one *Escherichia coli* both producing OXA-48-like.

Use of CAZ-AVI in the clinical setting is still low in England but has steadily increased since its launch in the UK in March 2017 (from 1,449 DDDs between March-December 2017 to 5,303 DDDs in 2018) in secondary care. This emphasises the importance of vigilance by clinicians and microbiologists working in clinical specialities where CAZ-AVI is used, in order to detect newly emerging resistance and prevent further spread within healthcare settings.

PHE is currently strengthening its surveillance on the use of new antibiotics and working with clinical laboratories to strengthen local detection of carbapenemase genes from clinical isolates.

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[78] European Centre for Disease Prevention and Control; Rapid risk assessment: Emergence of resistance to ceftazidime-avibactam in carbapenem-resistant Enterobacteriaceae. 2018. available on-line from https://ecdc.europa.eu/en/publications-data/rapid-risk-assessment-emergence-resistance-ceftazidime-avibactam-carbapenem

Macrolides

From 2014 to 2018 total macrolide consumption declined from 3.4 to 2.9 DDDs per 1,000 inhabitants per day (-14.6%), largely due to a decrease in erythromycin usage (-48.3%). In contrast, azithromycin consumption continued to increase in 2018, possibly related to the NICE evidence review for treatment of bronchiectasis.[79]

Sulfonamides and trimethoprim

Use of sulfonamides and trimethoprim decreased significantly (-41.0%) over the 5-year period since 2014 (1.438 DDDs per 1,000 inhabitants per day), particularly from 2016 to 2018 (1.267 and 0.849 DDDs per 1,000 inhabitants per day respectively). This decrease was mainly driven by declining use in the GP setting (-45.6%), although all settings have shown a decreasing trend during the 5 years. The decrease was mainly due to the decline in trimethoprim use, in line with the updated UTI guidance[80] and the Quality Premium in primary care.

Box 4.2 Quality Premium, UTI and *E. coli* bloodstream infection (see abstract in Research Annex)

A project investigating the impact of the trimethoprim-to-nitrofurantoin 2017/18 Quality Premium on the incidence of *E. coli* bloodstream infection (BSI) in England using interrupted time-series analysis is underway. The reduction in trimethoprim-to-nitrofurantoin prescribing was associated with an 11% decrease in *E. coli* BSIs in England between April 2017 and March 2018. Further work will explore differential impact across the country and the impact on antibiotic resistance detected in *E. coli* BSIs.

Nitrofurantoin and trimethoprim

Nitrofurantoin consumption continued to increase in all settings, from 0.866 in 2014 to 1.219 DDDs per 1,000 inhabitants per day in 2018 (40.8%), particularly in the GP setting (36.5%). This increase in nitrofurantoin consumption, in contrast to a decrease in trimethoprim usage, is most likely due to nitrofurantoin being recommended as the first-line treatment of lower uncomplicated UTIs in adults since 2014, the inclusion of a target for reduction in the trimethoprim-to-nitrofurantoin prescribing ratio in the Quality Premium 2017/18, and the reduction target of trimethoprim over the age of 70 in the Quality Premium 2018/19.

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[79] NICE; Non-cystic fibrosis bronchiectasis: long-term azithromycin. 2014. available on-line from https://www.nice.org.uk/advice/esuom38/chapter/Key-points-from-the-evidence
[80] NICE; Antimicrobial prescribing guidelines. 2019. available on-line from https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/antimicrobial-prescribing-guidelines

Aminoglycosides

There was an 8.4% rise in aminoglycoside usage between 2014 and 2018, from 0.119 to 0.129 DDDs per 1,000 inhabitants per day, due to increases in both in- and out-patient hospital settings. Aminoglycosides prescribing in the GP setting reduced by 60.6% in the last 5 years, which may relate to the specialised commissioning guidelines for inhaled aminoglycoside prescriptions for bronchiectasis.[81]

Parenteral glycopeptides and daptomycin

Parenteral glycopeptides (vancomycin and teicoplanin) and daptomycin consumption have all increased from 2014 to 2018, with teicoplanin use as the main reason for the overall rising trend (25.3%).

The use of parenteral glycopeptides and daptomycin occurred almost exclusively in hospitals (99.5%), with the level of prescribing in both hospital settings increasing over the 5-year period; inpatients (22.4%) and outpatients (5.8%).

Colistin

Consumption of colistin, a last-resort antibiotic used to treat multidrug-resistant infections, has risen slightly in the last 5 years (14.6%), although the level of consumption has remained low; 0.039 DDDs per 1,000 inhabitants per day in 2018.

From 2014 to 2018, colistin prescription in community settings has continued to decline, mainly due to the decline seen in the GP setting (-21.1%; absolute change of -0.005 DDDs per 1,000 inhabitants per day). On the other hand, usage in hospital settings has increased, particularly in hospital outpatients, numbers of which have nearly tripled (0.006 to 0.017 DDDs per 1,000 inhabitants per day) and may again relate to specialised commissioning of bronchiectasis.[82]

Oral Metronidazole

Oral metronidazole consumption declined by 19.1%, from 0.377 DID in 2014 to 0.305 DID in 2018. This was mainly driven by declining use in the GP (from 0.137 to 0.100 DID) and dental (from 0.131 to 0.109 DID) settings.

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[81] NHS England; Clinical Commissioning Policy: Inhaled Therapy for Adults and Children with Cystic Fibrosis. 2014. available on-line from https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2015/01/a01-policy-inhld-thrpy-cf.pdf
[82] NHS England; Clinical Commissioning Policy: Inhaled Therapy for Adults and Children with Cystic Fibrosis. 2014. available on-line from https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2015/01/a01-policy-inhld-thrpy-cf.pdf

Prescribing in primary care (in items)

Antibiotic prescribing in primary care settings measured in terms of antibiotic items has fallen from 2.052 to 1.710 items per 1,000 inhabitants per day (749.4 to 624.5 items per 1,000 inhabitants per year), a drop of 16.7% from 2014 to 2018 (Figure 4.3). On average, in primary care there were 8.5 DDDs per item, per 1,000 inhabitants per day, in 2018, which was 5.3% higher than 8.1 in 2014. Meaning less antibiotics have been prescribed on average and the higher number of DDDs is likely related to the higher dose or duration (for example, longer course or continuous prophylaxis) of antibiotics.

General Practice accounts for 85.8% of primary care prescribing. Reductions have occurred in the GP setting (-17.3%) and dental prescribing (-26.8%) from 2014 to 2018. Other community prescribing on the other hand has increased (15.6%), mainly due to prescribing in the other and urgent care categories described below.
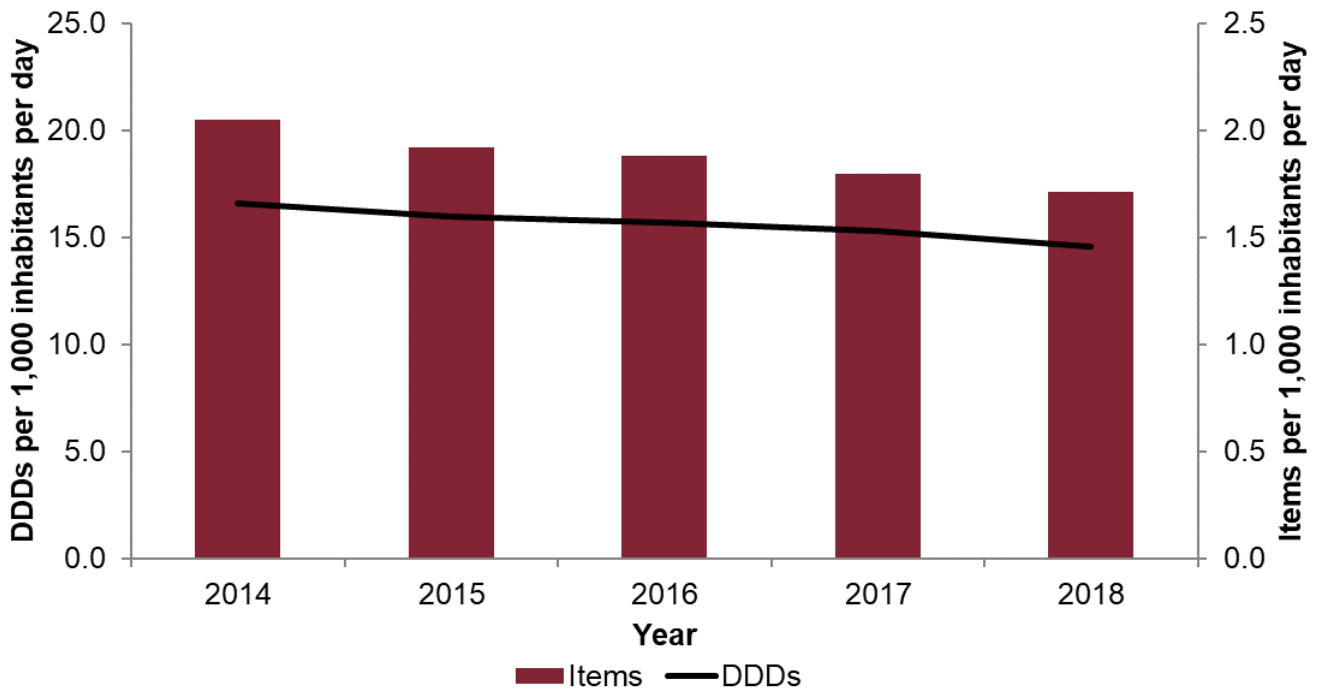
Figure 4.3 Total antibiotic consumption in primary care, expressed as DDDs and Items per 1,000 inhabitants per day, England, 2014-2018

General practice

In the GP setting, penicillins remained the most commonly prescribed group (48.4%), driving the overall reduction of antibiotic items prescribed in this setting (-17.3%) between 2014 and 2018. The second and third most commonly prescribed antibiotic items were tetracyclines (14.0%) and macrolides (11.9%).

All other key antibiotic groups have also shown reductions in the numbers of items prescribed. Fewer items were prescribed in all age groups, as seen in Figure 4.4. Reduction in erythromycin use was also observed in all age groups, with the younger (5-14 years) and older age groups (over 75 years) being statistically significant.

The exception to the decrease was the other antibacterials group (Annex Chapter 4 for full definition), for which prescribing increased by 75.8% from 2014 to 2018. This was due to nitrofurantoin prescribing increasing from 0.102 to 0.181 items per 1,000 inhabitants per day, probably reflecting the impact of the Quality Premium described above.
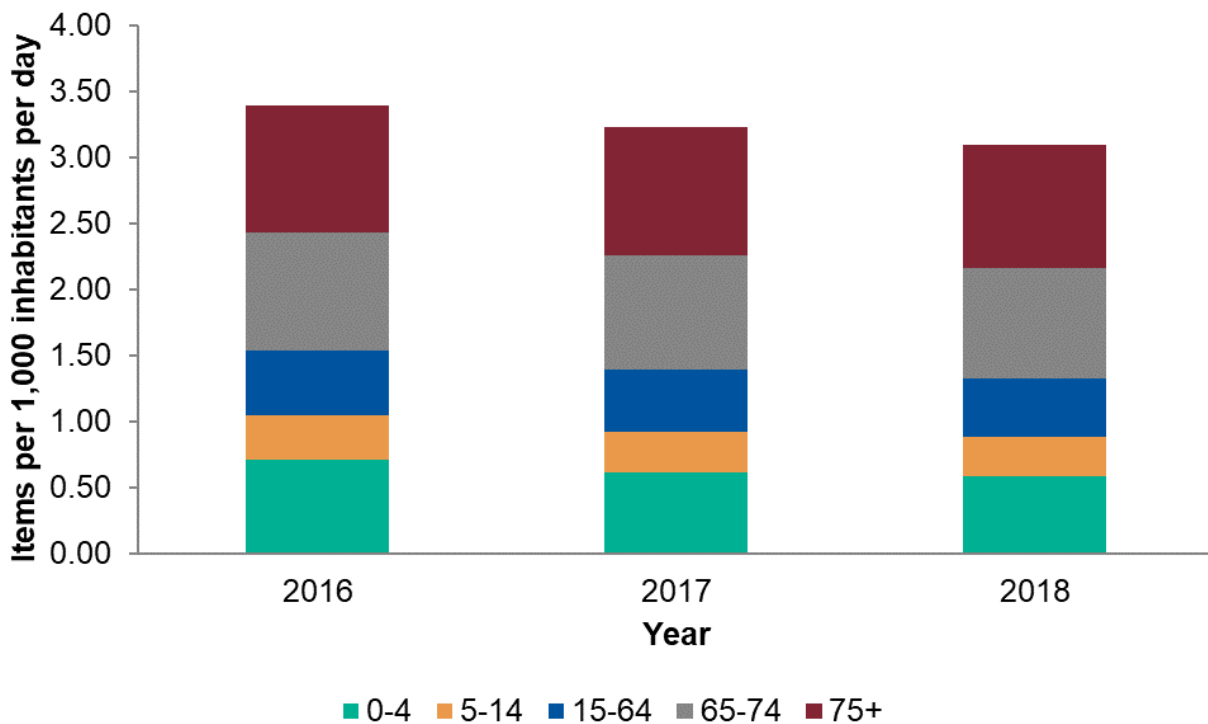
Figure 4.4 Total consumption in items in general practices by age group, expressed as items per 1,000 inhabitants per day, England, 2016-2018

Other community

Other community primary care prescribing, including a number of community services (full list in Annex Chapter 4), increased by 15.6% since 2014 to 0.106 items per 1,000 inhabitants per day in 2018.

Out-of-hours services accounted for the half of all antibiotic items prescribed in the other community settings (53.6%) and has remained largely stable. Other and urgent care settings have both seen a rise in the number of antibiotic items prescribed over the 5-year period at 208.9% and 88.5%, suggesting increased use of these services by the population.

Although the other settings have seen a large increase, the numbers of antibiotic items prescribed remained low at 0.016 items per 1,000 inhabitants per day in 2018. Increases seen in urgent care prescribing may possibly be a data artefact due to misclassification of walk-in centres when data were reported to the NHS Business Services Authority (BSA), since the 2013 NHS re-organisation.[83]

Dental

Dental prescribing for NHS practices reduced further in 2018 (-26.8% from 2014). Amoxicillin items (66.0% of total antibiotic items prescribed in the dental setting) reduced from 0.121 to 0.090 items per 1,000 inhabitants per day (-25.6%) in the last 5 years, driving the decrease in dental prescribing (Table 4.3).

Table 4.3 Dental antibiotic consumption for the most commonly used antibiotics, expressed as DDDs and items per 1,000 inhabitants per day, 2014-2018

Antibiotic		2014	2015	2016	2017	2018
Amoxicillin	Items	0.121	0.112	0.104	0.096	0.090
	DDDs	0.586	0.567	0.541	0.578	0.480
Co-amoxiclav	Items	0.001	0.001	0.001	0.001	0.001
	DDDs	0.003	0.003	0.003	0.003	0.002
Clarithromycin	Items	0.000	0.000	0.000	0.000	0.000
	DDDs	0.002	0.003	0.003	0.004	0.004
Clindamycin	Items	0.001	0.001	0.001	0.001	0.001
	DDDs	0.003	0.003	0.003	0.006	0.002
Erythromycin	Items	0.008	0.007	0.006	0.005	0.004
	DDDs	0.053	0.048	0.045	0.072	0.036
Metronidazole	Items	0.053	0.049	0.045	0.042	0.039
	DDDs	0.131	0.124	0.118	0.123	0.109

Prescribing in secondary care (by admissions)

Despite increasing hospital AMS activity, antibiotic use in secondary care measured using hospital admissions as the denominator rather than the total population increased by 2.8% (from 4,589 to 4,717 DDDs per 1,000 admissions); in simple terms that for every patient a hospital admits the hospital overall antibiotic use is equivalent to about 5 days of antibiotics. Hospital inpatient prescribing increased by 6.1% while hospital outpatient decreased by 2.3% from 2014 to 2018.

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[83] Department of Health and Social Care; Health and Social Care Act 2012: post-legislative assessment. 2014. available on-line from https://www.gov.uk/government/publications/health-and-social-care-act-2012-post-legislative-assessment

One of the likely reasons for on-going increases in hospital prescribing is changes in hospital antibiotic guidelines, which have moved from recommending single broad-spectrum antibiotics (e.g. piperacillin/tazobactam) to combinations of narrow-spectrum antibiotics. For example, replacing a single broad-spectrum antibiotic with amoxicillin, metronidazole and gentamicin would change the DDDs from 1 to 3 for the same indication. This is generally regarded as more prudent prescribing but cannot be measured at present because patient-level data are not available.

Antibiotic consumption differs in different trust types (definitions in chapter annex); with increasing trends in specialist, multiservice, medium and large Trusts during the same period. Small and teaching Trusts have remained broadly stable with some fluctuations.

The proportions of trusts prescribing by antibiotic groups in 2018 has remained largely similar to 2017, besides tetracyclines use (623.0 DDDs per 1,000 admissions) which have risen to a similar level to macrolides usage in 2018. Significant increases in prescribing were shown in third, fourth and fifth-generation cephalosporins and quinolones in the last 5-years, which is described in the piperacillin/tazobactam section below (Table 4.4).

Prescribing of key antibiotics that are reserved for multi-drug resistant bacteria, namely colistin, piperacillin/tazobactam and carbapenems account for a small proportion of total prescribing (3.8%) in secondary care. Figures for the key antibiotics can be found in the on-line appendix.

Piperacillin/tazobactam usage has remained low following the international shortage in 2017, with a small increase of usage in 2018 (88.6 DDDs per 1,000 admissions) compared to 2017 (84.4 DDDs per 1,000 admissions). This trend was observed in all Trust types (Figure 4.5).

Table 4.4 Antibiotic consumption in Trusts by antibiotic group, expressed as DDDs per 1,000 admissions, England, 2014-2018

Antibiotic Group	2014	2015	2016	2017	2018	Trend	p-value
Penicillins (excluding inhibitors)	1168.8	1133.7	1156.5	1147.7	1138.9		0.374
Penicillins (inhibitor combinations only)	795.1	794.8	816.3	793.1	833.5		0.220
First and second-generation cephalosporins	103.0	96.6	91.4	97.8	97.3		0.516
Third, fourth and fifth-generation cephalosporins	71.6	72.0	79.8	94.2	99.4		0.009[+]
Carbapenems	75.5	75.6	72.6	72.3	66.3		0.034[+]
Tetracyclines	538.4	523.0	548.2	575.9	623.0		0.041[+]
Macrolides, lincosamides and streptogramins	680.1	673.7	678.8	662.8	634.1		0.066
Sulfonamides and trimethoprim	304.1	287.2	275.3	253.7	245.2		0.001[+]
Quinolone antibacterials	259.9	264.5	272.5	282.3	304.5		0.011[+]
Anti-*Clostridioides difficile* agents^	3.8	4.2	3.8	4.0	4.1		0.512
Oral metronidazole	138.3	130.1	122.7	120.6	116.6		0.006[+]
Other antibacterials*	302.1	320.3	332.3	364.2	383.5		0.001[+]

+ Statistically significant p-value for trend from 2014 to 2018
^ Anti-*Clostridioides difficile* agents include: oral vancomycin and fidaxomicin
* Other antibacterials (ATC 3rd level pharmacological subgroup 'J01X') include: glycopeptide antibacterials, polymyxin, steroid antibacterials, imidazole derivatives, nitrofuran derivatives, other antibacterials (full list in chapter annex)

Carbapenems consumption in secondary care has decreased in the last 5 years, with 66.3 DDDs per 1,000 admissions consumed in 2018. Meropenem use decreased by 10.9% in 2018, compared to 2017. The usage of carbapenems in most Trust types has decreased, although use in specialist trusts significantly increased by 0.5% compared to 2017.

The reductions of important broad-spectrum antibiotics consumption, piperacillin/tazobactam and carbapenems, was associated and likely drove an increase in fluoroquinolone and cephalosporin usage in hospitals. Both fluoroquinolones and all four cephalosporin classes were recommended as alternative antibiotics during the piperacillin/tazobactam shortage in 2017 and their use has increased as shown in Table 4.5.

The two new cephalosporins with β-lactamase inhibitors (ceftolozane/tazobactam and ceftazidime/avibactam) were used in small numbers in the secondary care.
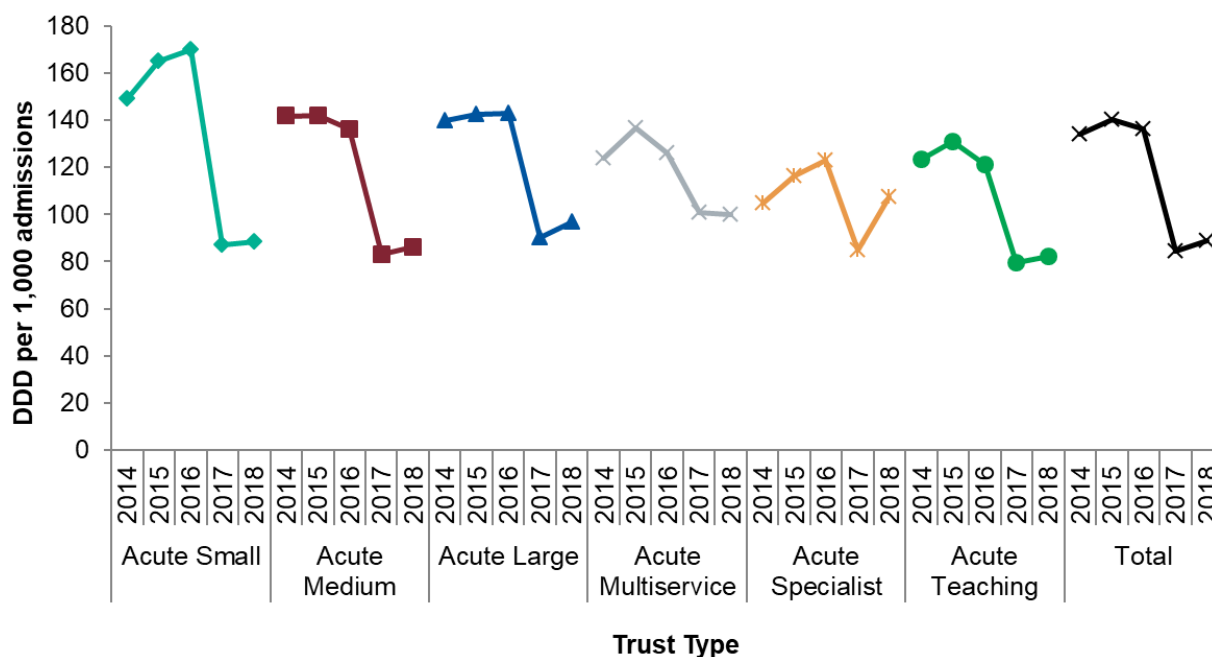
Figure 4.5 Piperacillin/tazobactam consumption in Trusts by Trust type, expressed as DDDs per 1,000 admissions, England, 2014-2018

Box 4.3 Piperacillin/tazobactam shortage (see abstract in Research Annex)
During the global shortage of piperacillin/tazobactam from April 2017 an increase in *Pseudomonas aeruginosa* BSIs was observed from April to December 2017. Investigation of the relationship using negative binominal regression showed that lower levels of piperacillin/tazobactam consumption were significantly associated with a higher incidence of *P. aeruginosa* BSIs (incidence rate ratio=0.987, p-value=0.015). Work is underway to determine whether there is an optimal level of piperacillin/tazobactam usage related to *P. aeruginosa* BSIs.

Table 4.5 Fluoroquinolone antibacterials and cephalosporins consumption in Trusts, expressed as DDDs per 1,000 admissions, England, 2014-2018

Antibiotic	2014	2015	2016	2017	2018
Ciprofloxacin	193.2	192.3	195.7	193.7	202.1
Levofloxacin	34.8	40.2	46.4	61.8	74.5
Cefuroxime	37.4	35.7	35.6	42.9	43.6
Cefotaxime	22.6	20.2	21.7	22.6	23.7
Ceftazidime	13.2	12.9	14.6	19.6	18.3
Ceftriaxone	34.6	37.9	42.6	51.0	56.0
Ceftazidime/avibactam	-	-	-	0.1	0.3
Ceftolozane/tazobactam	-	-	0.1	0.2	0.4

- not authorised for use in the UK

Colistin consumption in secondary care continued to increase (from 11.0 to 24.0 DDDs per 1,000 admissions between 2014 and 2018), although the usage remains low (0.5% of total hospital prescribing). The increase in colistin use was seen for both the inhaled

(214.2%) and parenteral (58.3%) administration route. The increased use of the inhaled route is relative to the parenteral route, as the DDD for the parenteral form has changed in the ATC/DDD index 2019.

A broadly similar trend in colistin consumption was observed in all trust types during the last 5 years, although use in specialist trusts increased from 51.5 to 185.5 DDDs per 1,000 admissions between 2014 and 2018, while multi-service (-21.5%) and small (-7.6%) trusts continued to see decrease in use.

Speciality prescribing

Secondary care antimicrobial consumption was analysed and is reported by specialty grouping in this chapter. Specialities within each group are defined in (Annex Chapter 4)

In terms of speciality, antibiotic consumption was highest within intensive care units (ICUs) comprising 61.8 DDDs per ICU admission in 2018. All specialities observed an increasing trend of prescribing from 2014 to 2018, with the exception of specialist medicine.

In 2018, the highest piperacillin/tazobactam and carbapenems prescribing in hospitals occurred in ICUs (5.4% and 4.9% of total DDDs per admissions respectively), whereas the highest colistin prescribing was in paediatrics (2.6%) (Table 4.6).

Table 4.6 Proportion of all antibiotic prescribing attributed to piperacillin/tazobactam, carbapenems and colistin in secondary care by speciality, expressed as DDDs per admissions, England, 2018

Specialist Group	DDDs per admission	Piperacillin/ tazobactam	Carbapenems	Colistin
Intensive Care Unit	61.8	5.4%	4.9%	0.2%
AE/Non-specific Out-Patient Department	15.3	0.7%	0.4%	0.1%
Geriatrics	3.7	2.9%	1.5%	0.0%
General Medicine	3.4	2.6%	1.8%	1.1%
General Surgery	3.5	1.9%	1.0%	0.1%
Specialist Medicine	3.8	2.0%	1.9%	0.1%
Other	4.2	1.9%	1.4%	0.1%
Orthopaedics	2.9	1.4%	1.2%	0.0%
Obstetrics and Gynaecology	2.5	0.6%	0.3%	0.0%
Paediatrics	2.1	1.3%	1.3%	2.6%
Specialist Surgery	2.1	1.3%	1.4%	0.3%

Antibiotic consumption surveillance

Prescribing data warehouse

PHE's prescribing data warehouse was launched in January 2017 to integrate the primary care data collated by NHS BSA and secondary care data provided by IQVIA, as well as NHS Trusts as part of the Commissioning for Quality and Innovation (CQUIN) payments framework.[84]

It was announced in February 2019 that PHE will also receive antibiotic consumption data from all NHS Acute Trusts from Rx-Info, to fulfil the NHS Standard Contract requirement for trusts to submit antibiotic consumption data to PHE.[85]

UK

In order to monitor the antimicrobial reduction targets set in the UK AMR 5-year National Action Plan,[86] the UK will continue to collate antimicrobial usage data from each devolved administration (DA) (Northern Ireland, Scotland, and Wales), to provide a UK-wide picture.

One Health

In the UK One Health Report[87] on antibiotic use in animals and humans and antibiotic resistance, the UK results for the EU harmonised indicators was presented. The indicators were recommended by the European Centre for Disease Prevention and Control (ECDC), European Food Safety Authority (EFSA) and European Medicines Agency (EMA) for monitoring antibiotic consumption in the EU member states.

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[84] NHS Improvement; Reducing the impact of serious infections CQUIN 2018/19. 2018. available on-line from https://improvement.nhs.uk/resources/reducing-impact-serious-infections-antimicrobial-resistance-sepsis-cquin-2018-19/

[85] NHS Improvement; Antimicrobial resistance: Total antibiotic consumption moves to the NHS Standard contract for 2019/20. 2019. available on-line from https://improvement.nhs.uk/documents/4934/FINAL_20190228_NHS_Standard_Contract_FAQs_1920_v6.pdf

[86] Department of Health and Social Care. UK 5-year action plan for antimicrobial resistance 2019 to 2024. 2019. Available on-line from: https://www.gov.uk/government/publications/uk-5-year-action-plan-for-antimicrobial-resistance-2019-to-2024

[87] Veterinary Medicines Directorate; UK One Health Report - Joint report on antibiotic use and antibiotic resistance, 2013–2017. 2019. available on-line from https://www.gov.uk/government/publications/uk-one-health-report-antibiotic-use-and-antibiotic-resistance-in-animals-and-humans

European collaboration

The UK submits antibiotic consumption data to ECDC via the European Surveillance of Antimicrobial Consumption Network (ESAC-Net).[88] PHE submits the national data for England and the devolved administrations submit their national data individually. Data for 2018 were submitted in June 2019.

The ESAC-Net interactive database is currently not available due to the adjustment of historic antibiotic consumption data to take account of the new 2019 DDDs. In the published report[89] for 2017, which used the ATC/DDD index of the publication year, the UK ranked 13th lowest for community antibiotic consumption (out of 25 countries submitting data) and the fourth highest for hospital antibiotic consumption (out of 22 countries). While it is useful to compare the consumption data and trends within countries, the reliability of comparisons across countries is less robust and limited by the variation in antibiotics used and the in-country ability to collect prescribing data.

Discussion

Prescribing

Total antibiotic consumption in England fell again in 2018, with a 3.5% reduction compared to the previous year; the overall reduction over the 5-years from 2014 to 2018 was 9.0% (from 20.0 to 18.2 DDDs per 1,000 inhabitants per day). The implementation of the new DDD index 2019 resulted in a further apparent reduction of antibiotic consumption as measured in DDDs, especially for amoxicillin and co-amoxiclav, although this effect was consistent over time.

The overall increase in antibiotic consumption in secondary care was small in absolute numbers (0.219 DDDs per 1,000 inhabitants per day), compared to the decreases observed in primary care (-2.0 DDDs per 1,000 inhabitants per day) over the past 5-years.

Most antibiotics are prescribed in the GP setting (72.4% in 2018). The use of antibiotics in general practice decline over the last 5-years irrespective of whether consumption was measured as DDDs (-13.3%) or items (-16.7%); the relative difference between DDDs and items reflects that higher doses and/ or longer durations of antibiotic use within each prescription. In contrast, other community prescribing increased by 27.4%

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[88] European Centre for Disease Prevention and Control. Antimicrobial consumption database (ESAC-Net). 2018. Available on-line from: https://ecdc.europa.eu/en/antimicrobial-consumption/surveillance-and-disease-data/database

[89] European Centre for Disease Prevention and Control. Annual reports and protocols on antimicrobial consumption. 2019. Available on-line from: https://www.ecdc.europa.eu/en/antimicrobial-consumption/surveillance-and-disease-data/report-protocol

over the same period; however, this setting contributes to only a small proportion of overall prescribing (3.9% in 2018). Dental prescribing which accounts for 3.5% of community antibiotic consumption also decreased use substantially (-19.2%); however dental antibiotic use only includes NHS prescriptions and the use in private dental practice cannot be measured.[90]

For secondary care, hospital prescribing continued its increasing trend in 2018 (6.3%) compared to 2014, when measured in DDDs per 1,000 inhabitants per day. However this rate of increase is lower than it was from 2010 to 2014, when it increased by 11%. The increase was slightly less, at 2.8%, when measured using hospital admissions as the denominator (measure as hospital activity prescribing); again this is lower than 2010 to 2014 when antibiotic consumption, using the same denominator increased by 6%. The driver of the increases in secondary care consumption was largely due to increased prescribing in hospital inpatients (6.1% from 2014 to 2018).

Prescribing, resistance and unintended consequences

Several ESPAUR projects have shown the impact of changes in prescribing on important outcomes such as BSI rates (*abstracts in annex*). These have highlighted the importance of monitoring possible unintended clinical outcomes related to interventions impacting on antibiotic prescribing patterns such as quality improvement initiatives,[91] behavioural change campaigns, revised guidelines or even drug shortages.

The consumption of piperacillin/tazobactam increased slowly in 2018, after use dropped significantly in 2017 following the global shortage and the NHS quality improvement measures aimed at reducing its use. Prescribers switched to fluoroquinolones and increasingly to third- and fourth-generation cephalosporins as alternatives, which has been associated with a rise in cephalosporin resistance rates (see AMR Chapter).

This not only raises the question of how to manage antibiotic shortages but also clearly warrants close monitoring of cephalosporin use, given the potential impact on MRSA[92] and *C. difficile*[93] infection rates, and also antibiotic resistance which could pose a threat to new β-lactam antibiotics such as ceftazidime/avibactam. The latter has already shown an impact on the burden of antimicrobial-resistant BSIs, with recent increases

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[90] ESPAUR. ESPAUR 2010 to 2014: report 2015. 2015. Available on-line from:
https://www.gov.uk/government/publications/english-surveillance-programme-antimicrobial-utilisation-and-resistance-espaur-report

[91] Balinskaite *et al*. An Assessment of potential unintended consequences following a national antimicrobial stewardship program in England: An interrupted time series analysis. *Clin Infect Dis* 2019; 69: 233-242.

[92] Public Health England; *Staphylococcus aureus*: guidance, data and analysis. 2017. available on-line from
https://www.gov.uk/government/collections/staphylococcus-aureus-guidance-data-and-analysis

[93] Public Health England; *Clostridium difficile*: guidance, data and analysis. 2018. available on-line from
https://www.gov.uk/government/collections/clostridium-difficile-guidance-data-and-analysis

having been mainly driven by cephalosporin-resistant *E. coli* infections (see AMR Chapter).

Prescribing appropriate antibiotics

The association between antibiotic use and development of resistance again stresses the importance of appropriate use; prescribing of the correct antibiotic and for the shortest possible duration to avoid driving resistance. Total antibiotic consumption could be easily reduced if antibiotic courses were routinely prescribed and dispensed (correct antibiotic pack size) for common infection consistent with NICE guidance.[94]

Colistin consumption continued to increase in hospitals, despite better alternative antibiotics such as ceftazidime/avibactam being available. This highlights the importance of improvement in the detection of carbapenemases and other resistance mechanisms to provide the information needed for a prescriber to switch more rapidly from empirical to more tailored prescribing.

Transparent and easily accessible data about antibiotic use are paramount for prescribers to support safer and more appropriate use. PHE's Fingertips[95] dashboard provides validated antibiotic use indicators at different geographical and organisational levels, which support development of local action plans, allow comparison with other indicators such as co-morbidities, smoking prevalence, deprivation and meet the metrics of the AMR NAP. Other sources of similar data are also available (NHS England's Antibiotic Quality Premium Monitoring Dashboard, OpenPrecribing, PresQIPP) and are used by different individuals with different needs such as monitoring of incentives and other non-antimicrobial prescribing use, costs and trends.

New antibiotics

Monitoring the usage of new antibiotics and detecting emerging resistance to these drugs is a crucial component of antimicrobial usage surveillance to inform AMS activities and preserve treatment effectiveness. The UK Government's commitment to pilot pull incentives (paying pharmaceutical companies for their antibiotic drugs based on how valuable their medicines are to the NHS rather than on the quantity used), will also require high quality surveillance data to assess drug candidates for the pilot and evaluate the work.

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[94] NICE; Antimicrobial prescribing guidelines. 2019. available on-line from https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/antimicrobial-prescribing-guidelines
[95] Public Health England; AMR local indicators. 2019. available on-line from https://fingertips.phe.org.uk/profile/amr-local-indicators/data

Box 4.4 Planning for new antibiotics (see abstract in Research Annex)
The high costs and scientific complexity of discovering new molecules that defy existing resistance mechanism and the impact of antimicrobial stewardship (new antibiotics are often reserved as last-resort or rare use treatments) has been implicated in market failure for antimicrobial development. Despite these challenges, several promising drug candidates (for example cefiderocol, plazomicin, murepavadin) are currently in the clinical phases of development and are preparing to seek approval by the European Medicines Agency. In July 2019, the UK Government announced the launch of an innovative model to incentivise the development of new antibiotics, testing alternative funding models for new antimicrobials.[96] This aims to more incentivise investment for pharmaceutical companies for new antimicrobials. PHE is collaborating with NICE and NHS England on this project.

Future actions

ESPAUR will continue to:

- measure the level of antimicrobial consumption and corresponding resistance rates, especially for new antibiotics and emerging resistance
- assess the impact of changes in the usage of antimicrobials from AMS programmes, antibiotics shortage or change in guidelines, and monitor possible consequences of policy changes
- collaborate with DAs in the UK and veterinary colleagues to inform human antibiotics usage as a whole to compare to the 5 year targets as set out in the National Action Plan and using the One Health surveillance approach
- influence the prescribing appropriate antibiotics, such as shorter duration of treatment and aligning package sizes and development of antimicrobial stewardship interventions
- support the incentivised model project for the development of new antibiotics

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[96] Department of Health and Social Care. Development of new antibiotics encouraged with new pharmaceutical payment system. 2019. Available on-line from: https://www.gov.uk/government/news/development-of-new-antibiotics-encouraged-with-new-pharmaceutical-payment-system

5. Use of NHS England levers to improve antimicrobial stewardship and reduce risk of antimicrobial resistant infections 2017 – 2019

This chapter reports the impact of the NHS England quality improvement schemes to drive changes in antibiotic prescribing practice in 2017/18 and 2018/19. This includes the Commissioning for Quality and Innovation (CQUIN) scheme for NHS Trusts, the Clinical Commissioning Group (CCG) Quality Premium (QP) and the CCG Improvement Assessment Framework.

CQUIN scheme: Reducing the impact of serious infections (antimicrobial resistance and sepsis)

In contrast to most CQUIN schemes which run for one year, this scheme[97] was run over two consecutive years (2017/18 - 2018/19) with the aim of providing greater certainty and stability regarding CQUIN goals, thereby giving health communities more time to focus on implementation. It intended to deliver clinical quality improvements and drive transformational change, and the CQUIN scheme linked together sepsis and antimicrobial stewardship improvement. The scheme was open to all providers of NHS acute care. Trust data were reported quarterly to PHE and published on the PHE Fingertips portal.[98] Guidance and details of the indicator specifications were published by NHS England[99] with resources to support the scheme published by NHS Improvement.[100] This chapter focusses on the antimicrobial stewardship and consumption aspects. Further details on the methodologies used in this chapter are available in Annex Chapter 5

CQUIN 2c: Antibiotic review in patients with sepsis

This scheme aimed to improve the 72 hour clinical review of antibiotics prescribed in patients with sepsis who were still inpatients at 72 hours. CQUIN performance was measured by audit of a minimum of 30 antibiotic prescriptions each quarter and defined

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[97] NHS England CQUIN 2017/19. Available on-line: https://www.england.nhs.uk/nhs-standard-contract/cquin/cquin-17-19/
[98] Public Health England; AMR local indicators. 2019. available on-line from https://fingertips.phe.org.uk/profile/amr-local-indicators/data
[99]NHS England CQUIN 2019/20. Available on-line: https://www.england.nhs.uk/nhs-standard-contract/cquin/cquin-19-20/
[100] NHS Improvement. Reducing the impact of serious infections CQUIN 2018/19. Available on-line: https://improvement.nhs.uk/resources/reducing-impact-serious-infections-antimicrobial-resistance-sepsis-cquin-2018-19/.

as the proportion of antibiotic prescriptions that had a review within 72 hours and achieved the targets outlined in Table 5.1.

Table 5.1: Reducing the impact of serious infections 2017-19 CQUIN scheme 2c indicator: antibiotic review. Specification for Year 1 and Year 2 of the scheme.

2017/18	2018/19
Essential criteria:	Essential criteria:
1. Appropriate clinical review by either an senior infection doctor, infection pharmacist, or senior member of the clinical team within 72 hours.	1. Appropriate clinical review by either: an senior infection doctor, infection pharmacist, or senior member of the clinical team.
Other specifications:	

2. The proportions of antibiotic outcomes submitted and assessed by the following parameters:
  •started on sepsis antibiotic treatment pathway and alive and still an in-patient at time of review
  •if no blood cultures were sent or blood cultures negative at 24-72 hours, a clinical review documenting why antibiotics need to be continued by describing the clinical syndrome, antibiotic choice based on syndrome, local intravenous to oral switch guidelines, and duration defined
  •if blood cultures were sent and positive by 24- 72 hours, clinical review should document these results, ensure the narrowest spectrum antibiotic treatment is prescribed following local intravenous to oral switch guidelines and duration defined
	2. Documented outcome of review recorded as one of 7 options:
	  • stop
	  • intravenous to oral switch with a documented review date or duration of the oral antibiotic
	  • outpatient parenteral antibiotic therapy
	  • continue with new review date or duration
	  • change antibiotic with escalation to broader spectrum antibiotic with a documented review date or duration
	  • change antibiotic with de-escalation to a narrower spectrum antibiotic with a documented review date or duration
	  • change antibiotic (for example to narrower/broader spectrum) based on blood culture results with a documented review date or duration

3. The documented outcome of this review was to be recorded under categories including: stop, intravenous to oral switch, outpatient parenteral antibiotic therapy, continue, change antibiotic.	3. Where appropriate an intravenous to oral switch decision. If the decision was for the patient to remain on intravenous antibiotics, a documented rationale for not switching clearly documented.
To achieve the CQUIN scheme it was essential only to report the number of antibiotic prescriptions reviewed within 72 hours.	To achieve the CQUIN scheme all 3 criteria had to be reported individually and all 3 criteria met within the antibiotic prescription review.

The milestones for achievement of this indicator according to CQUIN specification were 25% of prescripters for quarter 1 submissions, 50% for quarter 2, 75% for quarter 3 and 90% for quarter 4. This allowed progressive quality improvement but also made achieving the target challenging in quarter 4. Following high achievement in year 1 the CQUIN 2c indicator was made more stringent in year 2 in order to drive improvements in antimicrobial stewardship. Exceptions to the minimum number of prescriptions were made for trusts which did not routinely have sufficient number of patients with sepsis.

More than 50,000 antibiotic prescriptions for patients with suspected sepsis were audited and reported in this 2-year CQUIN 2c indicator. The results are outlined in Table 5.2. One hundred and thirty-seven NHS trusts participated submitting performance data for at least one quarter and 100 trusts submitted data for all eight quarters. Year 2 required more rigourous review and reporting of antibiotic prescription review outcomes; resulting in lower performance in year 2 than year 1. The variation in performance between quarters is shown in Figure 5.1. There was regional variation in the number of trusts participating and the outcome of the reviews; NHS regional performance is reported in Annex Chapter 5.

Table 5.2: Reducing the impact of serious infections 2017-19 CQUIN scheme 2c indicator: antibiotic review. Trust performance and CQUIN scheme achievement.

|	2017/18				2018/19			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Acute Trust number								
Eligible to participate	154	154	154	154	148	148	148	148
Submitted data	118	122	116	117	124	125	127	125
Proportion submitting data	77%	79%	75%	76%	84%	84%	86%	84%
Antibiotic prescriptions reviewed								
Total number	5800	6602	6274	6804	6506	6725	6635	6376
Number meeting Criteria 1	5295	6191	5742	6155	5411	5660	5602	5952
Number meeting all Criteria	(Not applicable)				2896	4913	5172	5077
Proportion meeting Criteria 1	91%	94%	92%	90%	83%	84%	84%	93%
Proportion meeting all Criteria	(Not applicable)				45%	73%	78%	80%
Acute Trust achievement								
Proportion achieved antibiotic review Criteria 1	100%	98%	95%	86%	99%	97%	90%	79%
Proportion achieved full CQUIN target (calculated from Appendix)	(Not applicable)				72%	87%	69%	51%
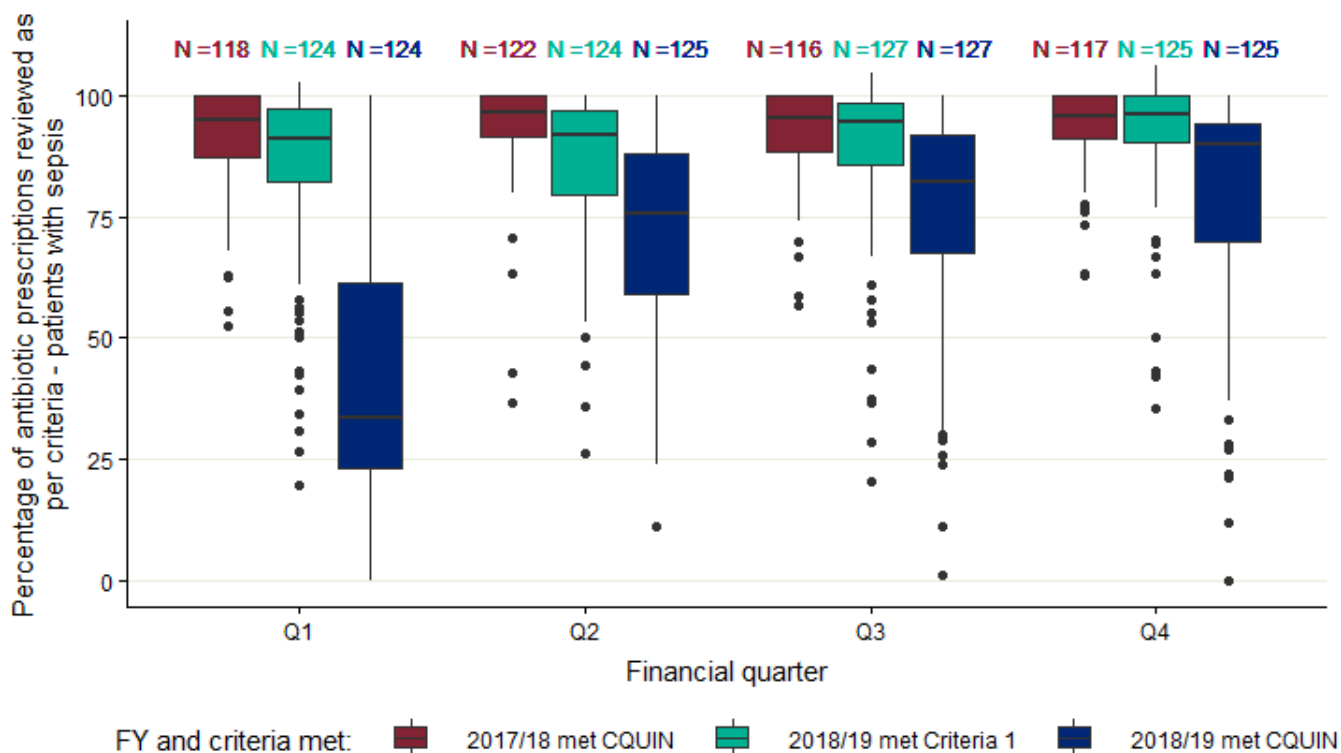
Figure 5.1 Reducing the impact of serious infections 2017/19 CQUIN scheme 2c indicator: antibiotic review. Boxplot showing the percentage of antibiotic prescriptions reviewed by the CQUIN criteria component 1 (appropriate clinical review) and met the CQUIN.

CQUIN 2d: Reduction in antibiotic usage per 1,000 admissions and proportion of antibiotic usage (for both inpatients and out-patients) within the Access AWaRe category

The 2017-19 AMR CQUIN scheme aimed to reduce the use of systemic antibiotics. Individual trust targets for both years of the scheme were set for three indicators with annual data based on January 2016 to Decemeber 2016 baseline performance (Table 5.3). CQUIN scheme performance was reported using antibiotic Defined Daily Dose (DDD) values per 1,000 admissions. For contractual reasons WHO ATC/DDD Index values in place prior to 2019 were used and these are the values reported in this chapter.

In the second year of the 2017-19 AMR CQUIN scheme targets were revised to further reduce antibiotic consumption and following a global shortage of piperacillin/tazobactam in the first year of the scheme, the piperacillin/tazobactam component was removed and replaced with a target to increase the proportion of antibiotic usage within the Access group of the AWaRe categories.[101]

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[101] Budd E., *et al.* Adaptation of the WHO Essential Medicines List for national antibiotic stewardship policy in England: being AWaRe, *J Antimicrob Chemother*. 2019 74:3384-3389.

Table 5.3. Reducing the impact of serious infections CQUIN scheme 2017-19: 2d Indicators in use by year of scheme.

	2017/18 (Year 1) target	2018/19 (Year 2) target
Total antibiotic usage as measured by DDD per 1,000 admissions	• 1% reduction for those trusts with 2016 consumption indicators below 2013/14 median value • 2% reduction for those trusts with 2016 consumption indicators above 2013/14 median value	• trusts that met their 2017/18 target are required to achieve a reduction of 1% against their 2017/18 target (or not increase if already achieved) • trusts that did not meet their 2017/18 target are required to achieve a reduction of 2% against their 2017/18 target
Total usage of carbapenems as measured by DDD per 1,000 admissions		• trusts that met their 2017/18 target are required to achieve a reduction of 2% against their 2017/18 target (or not increase if already achieved) • trusts that did not meet their 2017/18 target are required to achieve a reduction of 3% against their 2017/18 target
Total usage of piperacillin/tazobactam as measured by DDD per 1,000 admissions		NA
Increase in the proportion of antibiotics within the Access group	NA	• access group ≥55% of total antibiotic consumption (as DDD/1,000adm) OR • increase by 3 percentage points from baseline 2016 calendar year

Trust performance in both years was measured as complete financial year data and CQUIN achievement was categorised as 'met' or 'not met' for each indicator with individual trust targets, depending on their baseline data and achievement in 2017/18. Indicators were not linked, allowing trusts to participate in 1, 2 or all 3 indicators.

The scheme was available to all providers of NHS acute care (151 in Year 1 and 148 in Year 2) with the requirement that they submitted baseline year data for targets to be set. trust performance was reported quarterly to PHE and published on the PHE Fingertips

portal.[102] Resources to support the scheme were published by NHS Improvement[103] and provide more detail of scheme content including individual trust targets. Participation in NHS CQUIN schemes is part of the NHS Standard Contract, but some NHS trusts did not participate in some or all of the 2 Year CQUIN scheme components. This is reflected in this report which has omitted trusts with incomplete CQUIN 2d scheme data submitted for part of either year of the scheme. Complete details of individual trust participation is shown in Annex Chapter 5.

CQUIN scheme performance was reported throughout the 2 year period using the World Health Organisation (WHO) ATC/DDD Index values in place during Q1 2017 to Q3 2018. Tuberculosis, anti-parasitic, topical antibiotics and antibiotic formulations for which the DDDs were not assigned by WHO were excluded.

Total antibiotic usage as measured by Defined Daily Dose (DDD) per 1,000 admissions 2017/18 to 2018/19.

During the two years 130 and 117 trusts participated in Year 1 and 2 of the scheme respectively to reduce total antibiotic usage as shown in Table 5.4. For those trusts who participated in the 2017-19 CQUIN scheme, total antibiotic use increased in Year 1 by 2.5% and was reduced by 1.17% from the 2016 baseline, to 4,703.6 DDD/1,000 admissions by end of the scheme.

In the second year of the CQUIN scheme, trust mergers reduced the number of trusts eligible to participate. From the trusts participating there was a marginal increase in the overall proportion meeting their CQUIN target to reduce total antibiotic use from 24.6% (32/130) to 24.8% (29/117) during the two years of the CQUIN scheme. The proportion of trusts with lower reduction targets meeting their targets increased from 21.1% (12/57) to 70.4% (19/27) during the two years while the proportion of those with higher targets decreased from 27.3% (20/73) to 11.1% (10/90). Data are reported in Table 5.4.

A total of 117 trusts participated in both years of the scheme; only 19 trusts (16.2%) met their CQUIN target in both years. These data are reported in Annex Chapter 5.

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[102] Public Health England; AMR local indicators. 2019. available on-line from https://fingertips.phe.org.uk/profile/amr-local-indicators/data
[103] NHS Improvement. Reducing the impact of serious infections CQUIN 2018/19 at:
https://improvement.nhs.uk/resources/reducing-impact-serious-infections-antimicrobial-resistance-sepsis-cquin-2018-19/

Total carbapenem usage as measured by Defined Daily Dose (DDD) per 1,000 admissions 2017-19

Trust participation reduced during the scheme from 84.8% (128/151) in the first year to 78.4% (116/148) in the second year; more challenging targets in year 2 may have driven poorer participation. A total of 117 NHS trusts participated in both years of the scheme, with 62 (53%) meeting their target reductions in both years; data are available in Annex Chapter 5.

In the first year of the scheme 57.8% (74/128) of participating trusts met their CQUIN target to reduce total carbapenem use and this increased to 72.4% (84/116) in the second year of the scheme. The proportion of trusts with higher target reductions and achieved their targets fell from 67.2% to 46.8% from year 1 to year 2 while the lower target group achievement increased from 49.3% to 91.0%. Trusts with lower carbapenem baseline use were less likely to meet the CQUIN reduction targets, potentially due to less opportunity to further improve usage. Data are reported in Table 5.3.

For those trusts who participated in the 2017/19 CQUIN scheme, total carbapenem use reduced by 11.0% from the 2016 baseline, to 88.6 DDD/1,000 admissions by end of the scheme.

Total piperacillin/tazobactam usage as measured by Defined Daily Dose (DDD) / 1,000 admissions 2017/18

Almost 85% (128 of 151) eligible NHS trusts participated in the 2017/18 CQUIN scheme to reduce piperacillin/tazobactam use. Global supply chain shortages during the year contributed to the reduction in usage and high achievement levels of 124/128 (96.8%) trusts meeting their targets to reduce piperacillin/tazobactam use. Given the large reductions in this year, this was not included in Year 2 targets.

Increase in the proportion of antibiotics within the Access group 2018/19

Out of 148 eligible trusts, 123 participated in the 2018/19 CQUIN scheme to increase the proportion of antibiotic usage within the Access group of the England adapted AWaRe[104] categories from the January to December 2016 baseline to ≥55% of total antibiotic consumption from the Access category of antibiotics or increase the proportion of Access antibiotics by 3% from the 2016 baseline. Although baseline 2016 data was

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[104] Budd E., *et al*. Adaptation of the WHO Essential Medicines List for national antibiotic stewardship policy in England: being AWaRe, *J Antimicrob Chemother*. 2019 74:3384-3389.

necessary for participation in the other CQUIN indicators trusts; 8 trusts without a 2016 baseline figure took part with only 2017/18 data in for this indicator as a baseline was not necessary to participate in the ≥55% of total antibiotic consumption target.

Out of 123 participating trusts 39.8 (49.8%) met at least one CQUIN target with 36 of 115 (29.3%) trusts with baseline values achiving a 3% increase in access group prescribing and 32 (26.0%) trusts reporting ≥55% of total antibiotic consumption from the Access category of antibiotics. From the participating trusts, 13 trusts (10.6%) met both targets.

Box 5.1 Adaptation of the WHO Essential Medicines List for national antibiotic stewardship policy in England: being AWaRe[105]
The WHO recently classified key antibiotics into three categories (AWaRe) to improve access (Access), monitor important antibiotics (Watch) and preserve effectiveness of 'last resort' antibiotics (Reserve). Using an expert elicitation exercise, antibiotics used in England but not included included in the WHO AWaRe index were added to an appropriate category following a workshop consensus exercise with national experts. In addition, certain antibiotics, according to our national antimicrobial stewardship goals were moved from Access to Watch categories, with justification by experts for each change. In 2016, 46/108 antibiotics included within the WHO AWaRe index were routinely used in England and an additional 25 antibiotics commonly used in England were not included in the WHO AWaRe index and required classification.
There was unexplained 2-fold variation in prescribing between hospitals within each AWaRe category, highlighting the potential for quality improvement.

The CQUIN scheme delivered a 0.8% increase in the proportion of antibiotic usage in the Access group from 47.1% in 2016 (the baseline) to 47.9% during 2018/19. Trusts achieving the increase from baseline target had the higher increase in their access group prescribing proportion with 5.4% increase from their overall baseline while trusts which met the ≥55% of total antibiotic consumption Access group prescribing target had an overall 2.8% increase from their baseline.

The 74 trusts who did not meet their CQUIN target reported a median trust value of 44.2%. Of these, 21 trusts did increase the proportion of antibiotics in the Access category during 2018/19, although by less than 3% from their 2016 baseline. In total 58 trusts (22.8%) reduced their Access category prescribing proportion, but 11 of these continued to report performance ≥55%, and therefore met their CQUIN target. Data are reported in Table 5.4.

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[105] Budd E., et al. Adaptation of the WHO Essential Medicines List for national antibiotic stewardship policy in England: being AWaRe, J Antimicrob Chemother. 2019 74:3384-3389.

Table 5.4 Reducing the impact of serious infections CQUIN scheme 2017-19. Trust participation and the impact of the CQUIN scheme on antibiotic prescribing.

	Total antibiotic usage as measured by DDD per 1,000 admissions		Total usage of carbapenems as measured by DDD per 1,000 admissions		Total usage of piperacillin/tazobactam as measured by DDD per 1,000 admissions	Increase in the proportion of antibiotics within the Access group
	2016 to 2017/18	2017/18 to 2018/2019	2016 to 2017/18	2017/18 to 2018/2019	2016 to 2017/18	2016 to 2018/19
Acute Trust number						
Eligible to participate	151	148	151	148	151	148
Participated	130	117	128	116	128	123 (115 with baseline)
Having higher reduction targets	75	96	64	53	80	NA
Participation from all eligible Trusts	86.1%	79.1%	84.8%	78.4%	84.8%	79.1% (77.7% with baseline)
Participation from Trusts given higher targets	97.3%	93.8%	95.3%	88.7%	97.6%	NA
Antibiotic prescription change:						
Starting level in all participating Trusts	4,759.2 DDD/1,000 admissions	4,804.0 DDD/1,000 admissions	99.5 DDD/1,000 admissions	98.5 DDD/1,000 admissions	141.6 DDD/1,000 admissions	47.1%
Overall change in all participating Trusts	increased by 44.8 DDD/1,000 admissions	reduced by 100.5 DDD/1,000 admissions	reduced by 0.3 DDD/1,000 admissions	reduced by 9.9 DDD/1,000 admissions	reduced by 64.9 DDD/1,000 admissions	increased to 47.9%
Overall proportion change in all participating Trusts	2.5% increase	2.1% reduction	0.3% reduction	10.1% reduction	45.8% reduction	0.8% increase
Proportion change in usage from participating Trusts with higher targets (achieving ≥55% Access group prescribing for Access target)	9.5% increase	1.8% reduction	6.2% reduction	16.2% reduction	48.5% reduction	2.8% increase
Proportion change in usage from participating Trusts with lower targets (achieving 3% increase in access group prescribing for Access target)	5.6% increase	2.4% reduction	12.7% increase	4.2% reduction	37.8% reduction	5.4% increase
Proportion change in usage from participating Trusts achieving targets	8.5% reduction	9.7% reduction	17.5% reduction	15.8% reduction	47.5% reduction	3.8% increase
Proportion change in usage from all participating Trusts not achieving targets	4.5% increase	0.7% increase	31.2% increase	2.6% increase	18.5% reduction	1.3% reduction
Acute Trust achievement						
Proportion of participating Trusts that achieved target	24.6%	24.8%	57.8%	72.4%	96.8%	39.8%
Proportion of participating Trusts that achieved target from Trusts with higher targets (achieved ≥55% access group prescribing for Access target)	27.4%	11.1%	67.2%	46.8%	97.5%	26.0%
Proportion of participating Trusts that achieved target from Trusts with lower targets (achieved 3% increase in access group prescribing for Access target)	21.1%	70.4%	49.3%	91.0%	95.8%	29.3%

Reducing Gram-negative Bloodstream Infections (GNBSIs) and inappropriate antibiotic prescribing in at-risk groups Quality Premium 2017-19; and CCG performance against the CCG Improvement Assessment Framework, 2017-19

The NHS England QP scheme rewards CCGs for improvements in the quality of the services they commission. The scheme also incentivises CCGs to improve patient health outcomes, reduce inequalities in health outcomes and improve access to services. During 2015-17, this scheme focused on the reduction of inappropriate antibiotic use, in particular broad-spectrum antibiotics in primary care. Since April 2017, these AMR antibiotic prescribing indicators were integrated into the CCG Improvement Assessment Framework[106] (CCG IAF) and CCG performance is reported monthly within the NHS Antibiotic Quality Premium Monitoring dashboard.[107]

During 2017-19 the QP scheme focus was to reduce Gram-negative bloodstream infections (GNBSI) across the whole health economy, in particular reducing the risk of those infections associated with UTI, by improving the management of UTI in primary care. This required a reduction in the empirical first choice use of trimethoprim for lower UTI, and a reduction in the use of trimethoprim in people aged 70 years or above, aligning to PHE antimicrobial prescribing guidelines.

Reducing Gram-negative blood stream infections across the whole health economy

In 2017/18 CCGs were required to reduce the number of *E. coli* bacteraemias by 10% from a January to December 2016 baseline. The 10% reduction target remained in 2018/19, with the target extended to include 15% and 20% 'stretch' (further reduction) targets to reduce GNBSI.

In 2017/18, 28/207 CCGs met or exceeded the 10% reduction target. In 2018/19 this reduced to 18/195 CCGs, with 6 of the 18 CCGs meeting or exceeding the 20% target, and 4 the 30% target by March 2019.

In 2018/19 the NHS Improvement Infection Prevention Control team led an initiative to reduce urinary catheter-associated UTI, and associated risk of GNBSI; and published resources to support this activity.[108]

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[106] NHS England CCG IAF. Available on-line at: https://www.england.nhs.uk/commissioning/regulation/ccg-assess/

[107] NHS England. Antibiotic quality premium monitoring dashboard. Available on-line at: https://www.england.nhs.uk/ccg-out-tool/anti-dash/

[108] NHS Improvement Resources. Available on-line at: https://improvement.nhs.uk/resources/urinary-catheter-tools/

Reducing first choice use of trimethoprim to treat lower UTI in primary care

In 2017/18, CCGs were required to deliver a 10% (or greater) reduction in the trimethoprim: nitrofurantoin prescribing ratio relative to baseline data for the period June 2015-May 2016) to improve the empirical management of lower UTI according to national prescribing guidelines.[109]

Two hundred and five out of 207 CCGs (99%) met or exceeded the target, delivering a 33% reduction in the prescribing ratio (equating to 1,181,088 fewer trimethoprim prescription items) during the 12 month period. Although this indicator was removed from the scheme in April 2018, further reduction in trimethoprim use has continued in 2018/19. This trend is reported in Figure 5.2.

Reducing trimethoprim prescribing in people aged 70+ years at greater risk of trimethoprim-resistant UTI

The QP scheme aimed to improve the management of UTI in people aged 70 years or above who are at greater risk of infections that are non-susceptible to trimethoprim, increasing the risk of empirical treatment failure and associated bloodstream infections.

CCGs were required to deliver a reduction of ≥10%, in the number of trimethoprim items prescribed to patients aged 70 years or above during 2017/18 (relative to the baseline level of prescribing in June 2015-May 2016), increasing to a 30% (or greater) reduction in 2018/19.

One hundred and sixty nine out of 195 CCGs (87%) met or exceeded targets to reduce use of trimethoprim to treat UTI in people aged 70 years or above by 30% from baseline over the 24 month period 2017-2019. This resulted in a 40% reduction in trimethoprim items prescribed to people aged 70 years or above; from 1.25 million items per year at April 2017, to 755,000 items per year at March 2019. Nitrofurantoin use to treat UTI in people aged 70 years or above increased according to national prescribing guidelines following the reduction in trimethoprim use (Figure 5.2).

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[109] PHE. Managing Common Infections: Guidance for primary care. Available on-line at:
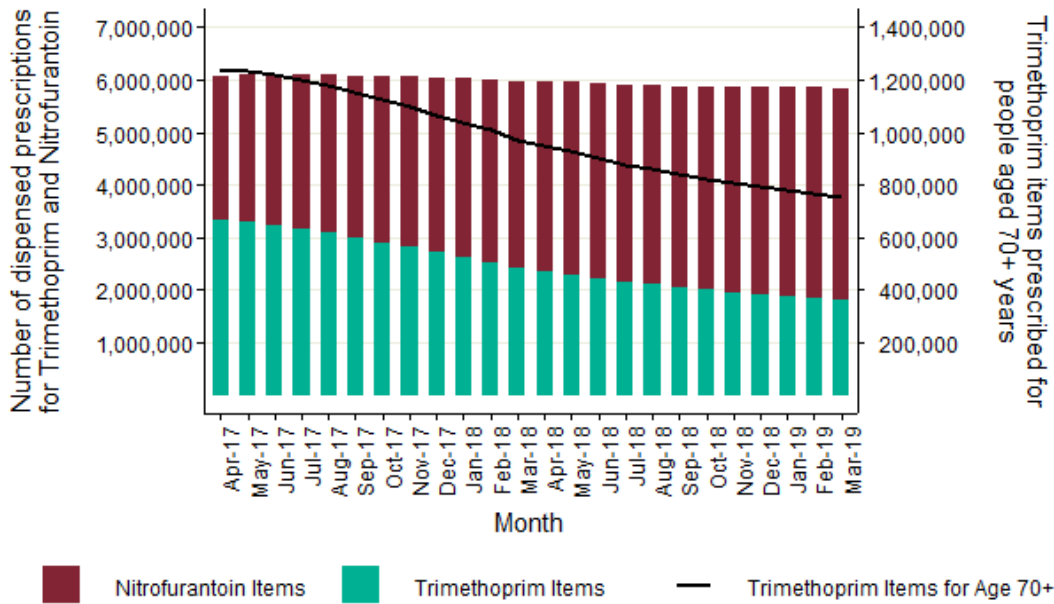https://www.gov.uk/government/publications/managing-common-infections-guidance-for-primary-care

Figure 5.2: Impact of the 2017-18 Quality Premium scheme: reducing empirical use of trimethoprim to treat UTI in primary care

Sustained reduction of inappropriate antibiotic prescribing in primary care England

The 2017-19 QP scheme and the CCG Improvement Assessment Framework required CCGs to continue to reduce inappropriate antibiotic prescribing to at or below national fixed targets as follows:

- antibacterial items measured as Specific Therapeutic group Age-sex Related Prescribing Units (STAR-PU), which take into account variation in the size and nature of the population served by each practice, to be 'at or below 1.161' during 2017/18 and 2018/19, with an additional lower target 'at or below 0.965' introduced in 2018/19 to support the government ambition to reduce inappropriate antibiotic prescribing by 50% from 2013/14 baseline by 2020
- the number of co-amoxiclav, cephalosporins and quinolone items (broad-spectrum antibiotics) as a proportion of all antibacterial items to be 'at or below 10%'

Reduction in total antibiotic prescribing

In 2017/18, 175/207 CCGs (84%) met or exceeded the antibacterial items/STAR-PU target of 'at or below 1.161'. This delivered a 3.1% reduction of 1,063,983 antibiotic prescription items from 34,319,184 (latest 12 months to March 2017) to 33,255,201 items (latest 12 months to March 2018). The median CCG performance was 1.043 at March 2018.

In 2018/19, 186 /195 CCGs (95%) met or exceeded the antibacterial items/STAR-PU target of 'at or below 1.161', with 92 CCGs (47%) meeting the lower CCG IAF target of

'at or below 0.965'. The England antibacterial items/STAR-PU value at March 2019 was 0.953, meeting the government ambition to reduce inappropriate antibiotic prescribing by 50% by 2020 a year early. Data is shown in Figure 5.3.
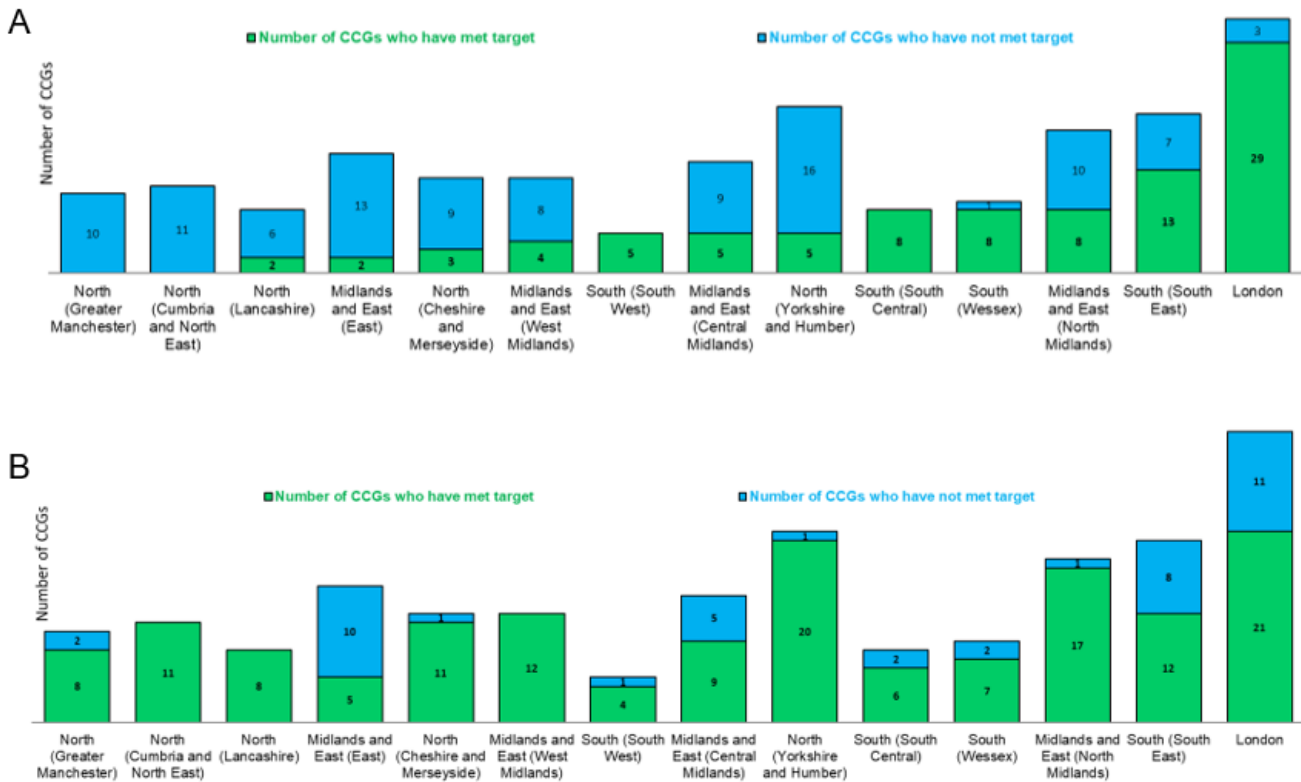
Figure 5.3: CCG performance against 2018-19 CCG Improvement Assessment Framework scheme targets, reported by NHS Area.[110] A) Antibacterial items per STAR PU at or below 0.965. B) Proportion of co-amoxiclav, cephalosporins and quinolones at or below 10% of total antibiotic use.

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[110] Figure taken from NHS Dashboard published at https://www.england.nhs.uk/ccg-out-tool/anti-dash/. Original publication colours have been preserved.

Reduction in broad-spectrum antibiotic prescribing

In 2017/18, 156/207 CCGs (75%) met the target of reducing the proportion of broad-spectrum antibiotics 'at or below 10%', and this was sustained during 2018/19 with 151/195 CCGs (77%) 'at or below 10%'. The median CCG performance was 8.9% at March 2019. The number of CCGs who meeting the CCG IAF targets at March 2019 are shown in Figure 5.4 by NHS Area, demonstrating geographical variation in performance. Complete data for each CCG is reported by NHS England.[111]

During the 2017-19 QP scheme the number of antibiotic items prescribed and dispensed in primary care in England reduced by 2.9 million (8.5%) from 34,319,184 to 31,398,507 items a year. The reduction in antibiotic items was largest in children aged 0-9 years (15% reduction equating to 500,000 items) with the percentage item reduction greatest in people 'age unknown' (21% reduction of 0.37 million items); this reflects the move to the use of digital prescriptions which record patient age. However urgent care providers continue to use paper prescriptions where age identification is less easy to capture; some of the 'age unknown' item reduction may therefore reflect reduced antibiotic prescribing in urgent and out-of-hours care.

Percentage change in number of prescribed dispensed antibiotic prescription items in primary care Endland (all CCGs) following implementation of the NHS Quality Premium scheme April 2017 to March 2019
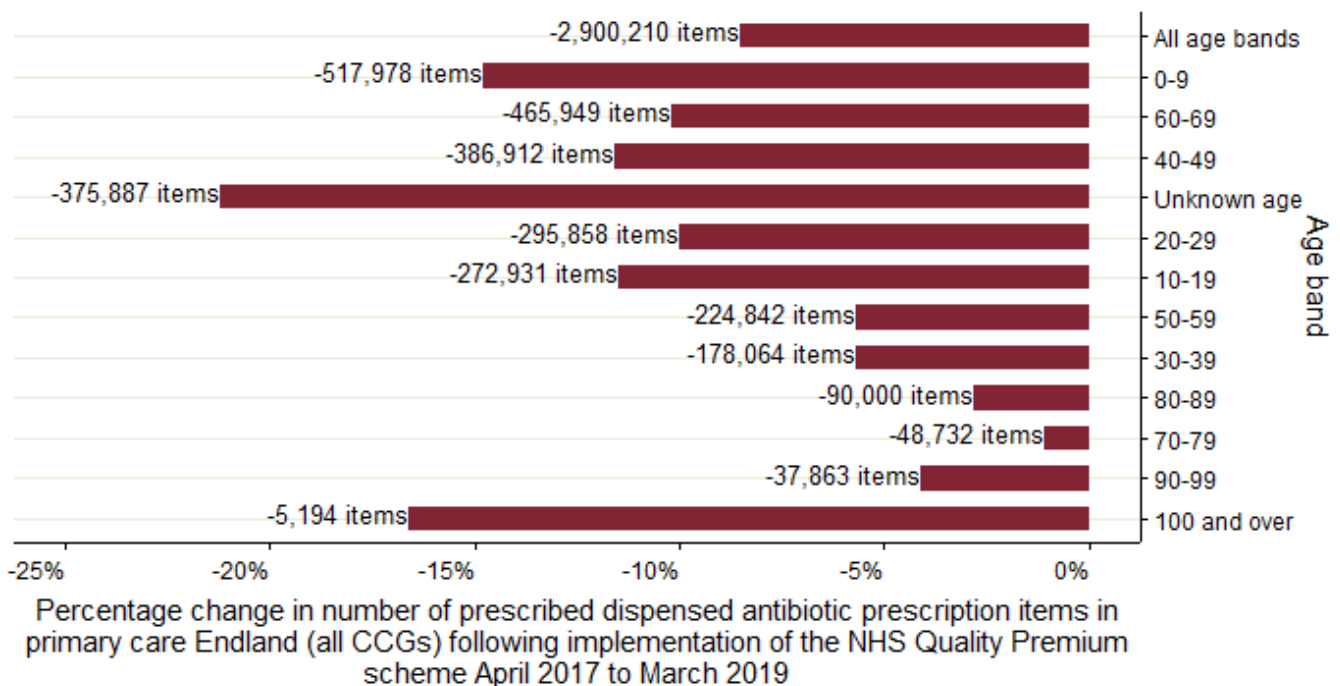
Figure 5.4: Change in the number of antibiotic prescribed and dispensed items by age in primary care in England (all CCGs) following implementation of the NHS Quality Premium scheme April 2017–March 2019.

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[111] NHS England. Antibiotic quality premium monitoring dashboard. Available on-line at: https://www.england.nhs.uk/ccg-out-tool/anti-dash/

The greatest reduction in number of antibiotic prescription items was reported for trimethoprim (46% reduction equating to 1.6 million fewer items), and the greatest increase reported was for nitrofurantoin (47% increase equating to 1.3 million items) which reflects the 2017-19 QP improvement focus to change empirical choice of antibiotic to treat lower UTI. There was a 20% reduction of 0.7 million combined clarithromycin and erythromycin items, and a 17% reduction of 1.5 million amoxicillin items. There was less than 1% reduction in phenoxymethylpenicillin items, with increased prescribing in children aged 0-9 years reflecting the likely increased use related to the higher incidence of scarlet fever infections in this time period.[112]

Use of national improvement schemes for NHS primary care have delivered a 15% reduction of 5.6 million antibiotic prescription items in the 4 year period since they were introduced in April 2015, with all CCGs reducing antibiotic prescribing. This included a 31% reduction of 1.3 million broad-spectrum antibiotics.

Table 5.5 Impact of the 2018-19 CCG Improvement Assessment Framework.

Patient age: 10 year age bands	Number of prescribed dispensed antibiotic prescription items 2016/2017	Number of prescribed dispensed antibiotic prescription items 2017/2018	Number of prescribed dispensed antibiotic prescription items 2018/2019	Change in the number of prescribed dispensed antibiotic prescription items 2017/18 compared to 2018/19	Percentage change in number of prescribed dispensed antibiotic prescription items 2017/18 compared to 2018/19
All age bands	34,299,712	33,257,001	31,399,502	-2,900,210	-8.50%
0-9	3,494,481	3,255,765	2,976,503	-517,978	-14.80%
10-19	2,377,280	2,263,533	2,104,349	-272,931	-11.50%
20-29	2,965,935	2,814,449	2,670,077	-295,858	-10.00%
30-39	3,100,731	3,031,517	2,922,667	-178,064	-5.70%
40-49	3,326,858	3,158,893	2,939,946	-386,912	-11.60%
50-59	3,964,917	3,889,640	3,740,075	-224,842	-5.70%
60-69	4,570,854	4,347,330	4,104,905	-465,949	-10.20%
70-79	4,568,268	4,641,471	4,519,536	-48,732	-1.10%
80-89	3,195,488	3,200,671	3,105,488	-90,000	-2.80%
90-99	934,327	940,511	896,464	-37,863	-4.10%
100+	31,280	29,890	26,086	-5,194	-16.60%
Unknown age	1,769,293	1,683,331	1,393,406	-375,887	-21.20%

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[112] Lamagni T *et al*. Resurgence of scarlet fever in England, 2014–16: a population-based surveillance study. *Lancet Infect Dis* 2018;1 8:180-187.

Box 5.2 Age-related decline in antibiotic prescribing for uncomplicated respiratory tract infections in primary care in England following the introduction of a national financial incentive (the Quality Premium) for health commissioners to reduce use of antibiotics in the community: an interrupted time series analysis[113]

Imperial College London and PHE assessed the impact of the 2015/16 NHS England QP on antibiotic prescribing by GPs for respiratory tract infections (RTIs). The study used an interrupted time series analysis using monthly patient-level consultation (for those diagnosed with a RTI) and prescribing data obtained from the Clinical Practice Research Datalink (CPRD) between April 2011 and March 2017. It assessed the rate of antibiotic prescribing in patients with a recorded diagnosis of uncomplicated RTI, before and after the implementation of the QP.

The results showed that prescribing rates decreased over the 6 year study period. Coincident with the QP start date of April 2015, the rate of antibiotic prescribing decreased by 3% (equating to 14.65 prescriptions per 1000 RTI consultations) and was was sustained over 2 years; children showed the greatest relative reduction (6%).

Discussion

This chapter reports the impact of the NHS England quality improvement schemes to drive changes in antibiotic prescribing practice in 2017/18 and 2018/19 in both acute and primary care NHS settings.

The CQUIN performance was a mixed picture. Overall only 75% of trusts participated in both years. However, more than 51,000 antibiotic prescriptions used to treat patients with suspicion of sepsis were reviewed.

Following high achievement in all quarters in Year 1 of the scheme the criteria for CQUIN achievement were changed to drive further improvements especially in determining the outcome of the antibiotic review. As a result of this achievement dropped considerably in the second year. The proportion of prescriptions meeting Criteria 1 which was shared during the two years was slightly lower in Q1 of Year 2 but increased to similar levels to the Year 1 values in Q4. The proportion of prescriptions meeting the CQUIN targets in Year 2 were almost half of those meeting Criteria 1 in Q1; this proportion increased steadily during the course of the year. However at the end of

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[113] Adapted from S. Bou-Antoun *et al*. Age-related decline in antibiotic prescribing for uncomplicated respiratory tract infections in primary care in England following the introduction of a national financial incentive (the Quality Premium) for health commissioners to reduce use of antibiotics in the community: an interrupted time series analysis, *J Antimicrob Chemother* https://doi.org/10.1093/jac/dky237

the 2 year scheme only 51% of trusts met the most challenging target to review 90% of antibiotic prescriptions as per the CQUIN scheme requirement.

For the total antibiotic consumption measurements (2d), scheme delivered a 1.2% overall reduction in total prescribing from the 2016 baseline in participating trusts. Trust participation did not differ related to the higher or lower targets; suggesting participation at least was not deterred by the higher target. Second year targets were based on the previous years targets rather than their actual antibiotic usage in the previous year. This meant that trusts not meeting the Year 1 targets had very challenging total antibiotic use targets in Year 2. However the trusts with lower targets, reduced more than the high target group. This suggests that targets which are easier to achive may drive improvements as the believe in the organisations ability to achieve the target may result in more effort.

The CQUIN scheme delivered a 11.0% reduction in carbapenem use from the 2016 baseline in participating trusts. A much larger proportion of trusts achieved their carbapenem use targets compared to the total antibiotic use. Unlike total antibiotic use, in the first year there was a higher reduction in overall carbapenem usage in the higher target group of trusts compared to the lower group where usage increased overall and it further reduced in year two achieving higher overall reduction compared to the trusts in the lower target group. This may have reflected a higher capacity for trusts in the high target groups to reduce their Carbapenem usage compared to the lower target groups whose lower initial carbapenem usage may have made further reductions much harder in this group of trusts.

In Year 1 of the scheme global shortages of piperacillin/tazobactam reduced the need and impact of the third 2017/19 CQUIN indicator. The AMR CQUIN scheme targets were revised and the piperacillin/tazobactam component was replaced with a new target to increase the proportion of antibiotic usage within the Access group of the AWaRe categories.

Overall the 123 participating trusts increased their Access group prescribing by 0.8% to 47.9% with the highest overall increase in proportion coming from the trust group achieving the 3% increase from baseline target compared to those who met the 55% Access group target.

CCGs have delivered excellent improvement in primary care, continuing to reduce inappropriate antibiotic use in patients of all ages, while increasing appropriate empirical antibiotic use patients with lower UTI. These improvements have been delivered in all CCGs, although variation in volume of antibiotic use continues. While there is no Quality Premium scheme in use in 2019/21, CCG performance continues to be assessed against 2 AMR metrics within the NHS National Oversight Framework and CCG

performance continues to be reported for both the 2019/20 QP indicators and the National Oversight Framework.[114]

Improving the management of UTI continues to be a priority, and new primary care antibiotic prescribing metrics for UTI have been developed within the NHS RightCare[115] programme and the NHS Business Authority ePACT2[116] Antimicrobial Stewardship Dashboard to support continued improvement in primary care.

Future schemes

In 2019/20 the 2017/19 CQUIN 2c antibiotic review in patients with sepsis indicator was discontinued and two new indicators were introduced to drive antibiotic prescribing improvement as part of the 2019/20 CCG1 CQUIN; a. to improve the diagnosis and management of lower UTIs in older people, and b. to impprove surgical prophylaxis in elective colorectal surgery. Scheme details have been published on NHS England website[117] and performance will be reported on Fingertips on a quarterly basis. Improvement from both schemes will support delivery towards the UK National Action Plan 2019-2024 ambitions to reduce antimicrobial use in humans by 15% by 2024, and halve healthcare associated Gram-negative bloodstream infections.

In 2019/20 the 2017/19 CQUIN 2d prescribing indicators have been discontinued as a CQUIN metric and have been moved to be part of the NHS Standard Contract . As a requirement of the NHS Standard Contract all trusts are now required to reduce total antibiotic consumption by 1% DDDs/1,000 admissions from a 2018 baseline and performance will be reported on Fingertips with 2019 WHO DDD values.

Work with academic colleagues is underway to determine other factors that may influence QP and CQUIN performance.

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[114] NHS England Antibiotic Dashboard. Available on-line at: https://www.england.nhs.uk/ccg-out-tool/anti-dash/
[115] NHS England. NHS Rightcare. Available on-line at: https://www.england.nhs.uk/rightcare/
[116] NHS Business Services Authority. ePACT2. Available on-line at: https://www.nhsbsa.nhs.uk/epact2
[117] NHS England. 2019/20 CQUIN. Available on-line at: https://www.england.nhs.uk/nhs-standard-contract/cquin/cquin-19-20/

6. Antifungal resistance, prescribing and stewardship

Introduction

Increasing reports of invasive fungal disease and the emergence of more intrinsically resistant species of pathogenic fungi, such as *Candida auris,*[118] warranted establishment of the ESPAUR antifungal consumption and resistance surveillance subgroup in 2015.[119] Since then this group of national experts has supported the publication of national antifungal resistance and usage data in annual ESPAUR Reports[120,121] and explored the state of antifungal diagnostics in collaboration with the UK Clinical Mycology Network (UKCMN) and British Society for Medical Mycology (BSMM) by conducting and publishing a national laboratory capacity survey[122] achieving the group's key terms of reference.

NHS England Improving Value Antifungal Stewardship Project

The subgroup's activities were scaled down in 2019. However, focus continues on input into the NHS Improvement's Antifungal Stewardship Project Group. ESPAUR subgroup members have contributed to the group's Antifungal Stewardship audit tool and Diagnostic Gap Analysis Audit Survey. PHE's Fingertips webplatform will be used to publish antifungal usage indicators to support the NHS 2019/20 Prescribed Specialised Services Commissioning for Quality and Innovation (CQUIN) scheme (Anti-Fungal Stewardship - Reduce inappropriate use of anti-fungal agents and prevent the development of resistance to antifungals through the development of anti-fungal stewardship teams).[123]

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[118] Jeffery-Smith A. *et al*. 2018. *Candida auris*: A Review of the Literature. Clin Microbiol Rev. 31:e00029-17

[119] PHE. English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR) Report 2016. Published November 2016. Available from: https://www.gov.uk/government/publications/english-surveillance-programme-antimicrobial-utilisation-and-resistance-espaur-report

[120] PHE. English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR) Report 2017. Published October 2017. Available from: https://www.gov.uk/government/publications/english-surveillance-programme-antimicrobial-utilisation-and-resistance-espaur-report

[121] PHE. English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR) Report 2018. Published October 2018. Available from: https://www.gov.uk/government/publications/english-surveillance-programme-antimicrobial-utilisation-and-resistance-espaur-report

[122] Schelenz *et al*. National mycology laboratory diagnostic capacity for invasive fungal diseases in 2017: Evidence of sub-optimal practice. *J Infect.* 2019 79:167-173

[123] NHSE. PSS1 Medicines Optimisation and Stewardship PSS CQUIN Indicator. Updated July 2019. Available from: https://www.england.nhs.uk/publication/pss1-meds-optimisation-pss-cquin-indicator/

Update on *Candida auris* in England

For the 18 months from January 2018 through to the end of June 2019, England has identified a total of 51 of cases of *C. auris* symptomatic infection (10) and asymptomatic colonisations (41), much lower than the 133 detections reported during 2016, the majority of which were associated with three large hospital outbreaks. There continue to be global reports of prolonged nosocomial outbreaks, and each year new countries report cases of infection for the first time.

Sporadic cases continue to occur in English hospitals, with seven new trusts reporting cases in the calendar year up until end of May 2019. These primarily involved patients repatriated from hospitals overseas (including India, Qatar, Kuwait, Oman, Pakistan, and Kenya). As in 2018, a small number of hospitals that have had previous cases have reported sporadic new cases. Three new hospitals have had inter-patient transmission events reported (all fewer than five cases), and as noted in the previous ESPAUR report there was also transmission in one hospital that had previously seen a large outbreak (thought to be associated with a new introduction).[124] All transmission chains were curtailed due to early outbreak recognition, patient isolation, additional screening and enhanced infection prevention and control measures.

In total, there have been approximately 270 reported cases in England; 25% were associated with a clinical infection, including 35 candidaemias (Figure 6.1). To date, there were no reported deaths attributable to *C. auris* infection in England.

PHE's *C. auris* incident management team, the PHE Porton environmental testing unit, affected hospitals and associated academic and scientific institutions continue to add to the international literature through individual and collaborative research projects. This year, international conference presentations were delivered on the potential for *C. auris* to become airborne during high turbulence activities such as bed making and on the results of the national point prevalence study (where none of 953 patients screened across eight geographically dispersed ICUs were positive; Research Abstracts Chapter; Sharp, A *et al*). Data were also published on the capacity of different routine diagnostic laboratory methods to detect *C. auris*, and on clade-specific differences in *C. auris* isolate behaviour.[125,126]

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[124] PHE. English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR) Report 2018. Published October 2018. Available from: https://www.gov.uk/government/publications/english-surveillance-programme-antimicrobial-utilisation-and-resistance-espaur-report

[125] Sharp A. *et al*. Assessing routine diagnostic methods for detecting *Candida auris* in England. *J infect* 2018; 5: 448-454.

[126] Borman A. *et al*. Comaparative pathogenicity of United Kingdom isolates if the emerging pathogen *Candida auris* and other key pathogenic *Candida* species. *mSphere* 2016; 4(1)

C. auris continues to be an ongoing international threat. Guidance documents will be updated in 2019, and ongoing specialist advice is given to hospitals on how to manage new introductions. Surveillance activities are being integrated into the routine activities of the HCAI/AMR Division of the PHE National Infection Service.
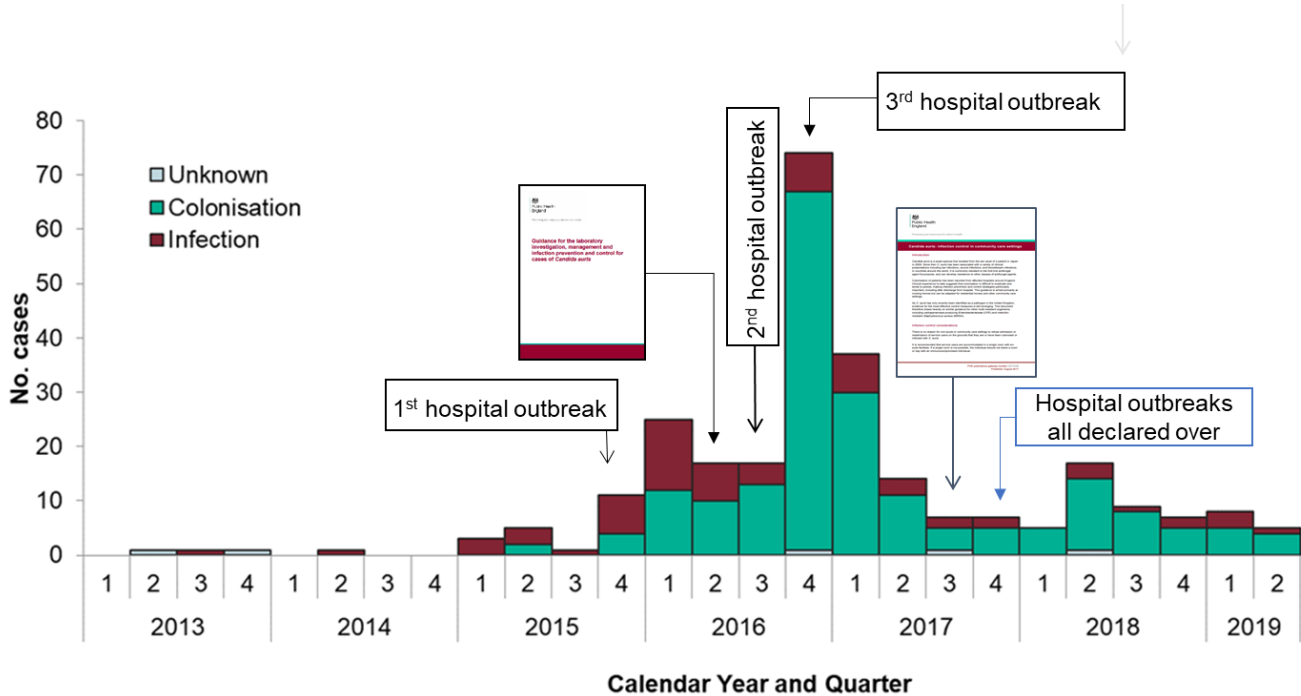

Figure 6.1. Timeline of *Candida auris* incident, England, 2013 to June 2019

UK participation in international surveillance of fungal disease

The European Centre for Disease Prevention and Control (ECDC) undertook a repeat survey on *C. auris* incidence in Europe in June 2019. The UK responded providing an overview of the numbers involved in recent outbreaks/clusters and an update on laboratory capabilities and preparedness. Following on from the 2017 survey,[127] this latest survey continues to develop the European picture of *C. auris,* helping publicise where the risks may be and best practice.

Future actions

- PHE will develop an automated surveillance alert system to allow investigation of any NHS laboratory detected cases of *C. auris*, reports will then be investigated by national and regional teams in real-time.
- PHE will publish NHS England Antifungal CQUIN data on PHE Fingertips AMR local indicators

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[127] Kohlenberg A, *et al*. *Candida auris*: Epidemiological situation, laboratory capacity and preparedness in European Union and European economic area countries, 2013 to 2017. *Eurosurveillance* 2018; Mar;23(13).

7. Antimicrobial stewardship

Introduction

Optimising prescribing, through the development and implementation of antimicrobial stewardship (AMS) programmes and toolkits was one of the seven key areas for action in the UK 5-year Antimicrobial Resistance (AMR) Strategy 2013 to 2018. This chapter outlines the results from key projects during 2018/19 including:

- development and pilot of an AMS Peer review tool
- development of antimicrobial prescribing and stewardship template report for PHE Fingertips
- development of a survey of healthcare workers knowledge and attitudes about antibiotics and antibiotic resistance across Europe
- TARGET (Treat Antibiotics Responsibly, Guidance, Education, Tools) toolkit process evaluation
- behavioural analysis projects on AMS and catheter-associated urinary tract infections (CAUTI)
- national antibacterial prescribing audit in UK dental hospitals

Antimicrobial stewardship peer review tool

A coordinated and comprehensive AMS programme is critical in reducing the emergence of antimicrobial resistance (AMR).[128] The Health Foundation describes peer review as the professional assessment, against standards, of the organisation on healthcare processes and quality of work, with the objective of facilitating its improvement.[129] In 2018, an AMS peer review tool was developed and piloted through a consensus process. It was developed as a voluntary tool to be used by acute hospitals to review and improve AMS. The tool will support hospitals to systematically review their systems and processes to optimise antimicrobial use and improve patient outcomes within their organisation; intended for use with a host site and an external peer reviewer to allow an unbiased review of current AMS practices as well as systems and processes.

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[128] Akpan M, Ahmad R, Shebl N, Ashiru-Oredope D. A review of quality measures for assessing the impact of antimicrobial stewardship programs in hospitals. *Antibiotics* 2016; 5(1):5.

[129] McCormick B. Pathway peer review to improve quality. The Health Foundation, November 2012

The AMS peer-review tool was originally developed and piloted by East of England Antimicrobial Pharmacists Group in 2016 across 8 NHS acute trusts. The average length of time to perform a peer review was 5 hours (2 hours to review key documents before the site visit and 3 hours to carry out the site visit which included attending an AMS committee meeting). The tool and the findings of the pilot were first presented to ESPAUR oversight group in January 2017 and a revised version in July 2018. Feedback from the oversight group members was to simplify the tool by reducing the number of indicators before piloting nationally.

The peer review tool included consolidated recommendations from a number of national AMS guidance and toolkits[130,131,132,133] into one easy to use document. The assessment of an organisation's stewardship programme includes the following domains:

- AMS leadership and management
- antimicrobial prescribing management
- surveillance, resistance and standards
- risk assessments for antimicrobials
- patient and carers
- education and training on the use of antimicrobials

The tool was further updated in January 2019 and validated using the checklist outlined by Pulcini *et al.*[134] in their publication on developing a global checklist for hospital AMS programmes. Table 6.1 summarises the number of indicators from each stage of the toolkit development and update stage.

[130] Public Health England. Start Smart - Then Focus: antimicrobial stewardship toolkit for English Hospitals 2015. Available: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/417032/Start_Smart_Then_Focus_FINAL.PDF

[131] NICE guidance Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use, 2015. https://www.nice.org.uk/guidance/ng15/resources/antimicrobial-stewardship-systems-and-processes-for-effective-antimicrobial-medicine-use-pdf-1837273110469

[132] Antimicrobial Self-Assessment Toolkit (ASAT) for acute hospitals (2012) https://www.imperial.ac.uk/medicine/hpru-amr/applications-and-tools/antimicrobial-self-assessment-toolkit/

[133] Health and Social Care Act 2008: Code of Practice on the prevention and control of infections. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/449049/Code_of_practice_280715_acc.pdf

[134] Pulcini C, *et al.* Developing core elements and checklist items for global hospital antimicrobial stewardship programmes: a consensus approach. *Clin Microbiol Infect* 2019; 25: 20-25.

Table 6.1: number of indicators at each stage of the toolkit development

Section	Area	Original Tool	Stage 1	Stage 2
1	AMS management team/ASC	15	10	6
2	AM Prescribing management	48	20	18
3	Surveillance, resistance and standards	12	7	1
4	Risk assessment for antimicrobials	7	7	5
5	Patients and carers	5	5	4
6	Education and training on the use of antimicrobials	6	4	3
-	Antimicrobial pharmacist	8	6	Moved*
	Total number of indicators	101	59	37

*Moved to the AMS management team/ASCFive NHS Trusts participated in piloting the updated tool comprising two non-teaching Trusts and three teaching Trusts (see annex).

Following peer review, participants were sent a link to an online survey to provide feedback on the AMS peer review tool content and process. Although the numbers of indicators were significantly reduced in the updated tool (37 compared to 101), the time taken for peer review remained an average of 5 hours (1.6 hours to review the document before the site visit and 3.4 hours for the site visit). Feedback from the national pilot highlighted that the reviewer-requested documents were 'mostly relevant' and suggested the tool would be beneficial in 'promoting shared learning across the hospital stewardship programmes' on a voluntary basis. Two weeks was generally viewed as an appropriate lead time for documented evidence of trust AMS programme to be submitted to the reviewer and for the review to be repeated every three years. One of the challenges listed was arranging a convenient date for the peer review on-site visit.

The full results are being prepared for publication.

Antimicrobial prescribing and stewardship template report for PHE Fingertips

The "AMR local indicators" on PHE Fingertips provide a wide range of data on AMR, AMS, healthcare-associated infections (HCAI) and IPC that are publicly available to allow organisations to benchmark themselves against the national picture and other comparable healthcare providers.[135] Feedback on the site emphasised the importance of the indicators but highlighted the challenge of downloading and creating a shareable report. Therefore, a template report providing a narrative on antimicrobial prescribing and stewardship for a specific area or organisations was developed. This report was designed to support non-analysts including clinicians and managers with an easily

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[135] Johnson AP, *et al*. Improving feedback of surveillance data on antimicrobial consumption, resistance and stewardship in England: putting the data at your Fingertips. *J Antimicrob Chemother* 2016; 72: 953-956.

accessible resource, that can be shared or presented to commissioners, IPC teams or AMS committees.

Currently the report is undergoing a consensus review to assess relevance of each indicator to be included. Key data and indicator proposed for the report include:

- NHS England initiatives including rates of *E. coli* bacteraemia and *Clostridium difficile* infection
- antibiotic consumption
- AMS indicators

The final agreed format will be hosted on the Fingertips platform and will automatically update in line with newly released information. A sample report is available in the Annex Chapter 7.

Survey of Healthcare workers knowledge and attitudes on antibiotics and antibiotic resistance

Following a public tender, the European Centre for Disease Prevention and Control (ECDC) procured PHE to lead a Europe-wide survey of healthcare workers' knowledge and attitudes about antibiotics and AMR. Previous European studies[136,137,138] had focussed on assessing the knowledge and attitudes of the public and health students. The overall objectives of the study for ECDC were:

- to gain a better understanding of healthcare workers' knowledge and perceptions to provide a base to support future needs in terms of policy and education changes
- to evaluate the of communication campaigns on AMR on healthcare workers knowledge and behaviour

Initially a rapid literature review was conducted identifying similar studies conducted in European countries in the previous five years to collate a bank of questions for assessing healthcare workers' knowledge and attitudes about antibiotics and AMR. The questions were divided into four themes based on the COM-B (Capability, Opportunity, Motivation and Behaviour) model.[139] The model recognises that behaviour is part of an interacting system involving all its components.

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[136] Eurobarometer 478: Antimicrobial Resistance (in the EU) 2018, European Commission. Available on-line: https://ec.europa.eu/commfrontoffice/publicopinion/index.cfm/ResultDoc/download/DocumentKy/84386
[137] Dyar O, Hills H, Seitz LT, Perry A, Ashiru-Oredope D. Assessing the knowledge, attitudes and behaviors of human and animal health students towards antibiotic use and resistance: a pilot cross-sectional study in the UK. *Antibiotics* 2018; 7(1):10.
[138] Dyar OJ, *et al*. European medical students: a first multicentre study of knowledge, attitudes and perceptions of antibiotic prescribing and antibiotic resistance. *J Antimicrob Chemother* 2013; 69: 842-846.
[139] The behaviour change wheel. Available on-line at: http://www.behaviourchangewheel.com/about-wheel

A quota sampling approach was used to determine the survey sample size with the aim of generating a representative sample from different professional groups and countries. The overall sample size for EU/EEA as well as the sample size per country was calculated using the European Union healthcare personnel statistics. A sample size of 0.002% for each healthcare profession was sampled except for nursing (0.001%) to determine suggested target numbers per profession per country.

The draft survey questions were developed through a modified-Delphi consensus process in collaboration with ECDC and representatives from the EU Member States, Norway and Iceland as well as several professional organisations which made up the project advisory group (PAG). The PAG consisted of 81 individuals representing 55 organisations and countries across Europe. The survey tool included questions assessing capability, opportunities, motivation of all core health professions: doctors (physicians and surgeons), nurses and midwives, pharmacists, dentists and health professional groups such as pharmacy technicians, physiotherapists and biomedical scientists. Infection specialists were not excluded from completing the survey but the survey focused on non-specialists. Following two rounds where members of the PAG were tasked with assessing relevance of each questions and commenting, the questionnaire was piloted across Europe by 224 healthcare professionals and workers from 24 countries with additional comments received on the content, interpretation of questions and time-scale for completion.

The European online survey was available between 28 January and 4 March 2019. Dissemination of the survey was supported by PAG members by sharing with healthcare workers in each country and promoted via social media. Participation was voluntary.

The initial findings from the survey were presented at European Congress of Clinical Microbiology & Infectious Diseases (ECCMID) 2019. The abstract is included in the annex. The report will be published by ECDC to coincide with European Antibiotics Awareness Week in November 2019.

TARGET Toolkit: Process evaluation

Ninety nine percent of CCGs report promoting TARGET to their general practices.[140] In 2018/19, a process evaluation of the TARGET toolkit website was undertaken to assess website use and the resources accessed. Google Analytics was used to collect assess participant interaction with the TARGET website.

TARGET was the most accessed page on the RCGP website by primary care clinicians with over 61,000 views during 2018/19, consistent with previous years. Monthly website views (Figure 7.1) demonstrate website traffic throughout the year; peaks in use can be seen following promotional activities, specifically WAAW/EAAD, or the release of new resources, including:

- May 2018: Publication of a TARGET newsletter
- June 2018: Delivery of a Train the Trainer workshop
- August 2018: Release of UTI Resource Suite and the Train the Trainers pages
- September 2018: Publication of a TARGET newsletter and TARGET exhibit at the Infection Prevention Conference in Glasgow
- October 2018: TARGET presentation at Nursing in Practice conference Publication of the joint PHE/NICE AMR prescribing guidance
- November 2018: EAAD / WAAW
- January 2019: Promotion and release of the TARGET Future Learn On-line course
- February 2019: Release of two TARGET webinars

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[140] Allison R, Lecky D, Beech E, *et al*. Local implementation of AMS initiatives: a mixed-methods study. *Br J Gen Pract* 2018; 68(suppl 1),

Monthly total TARGET website visits
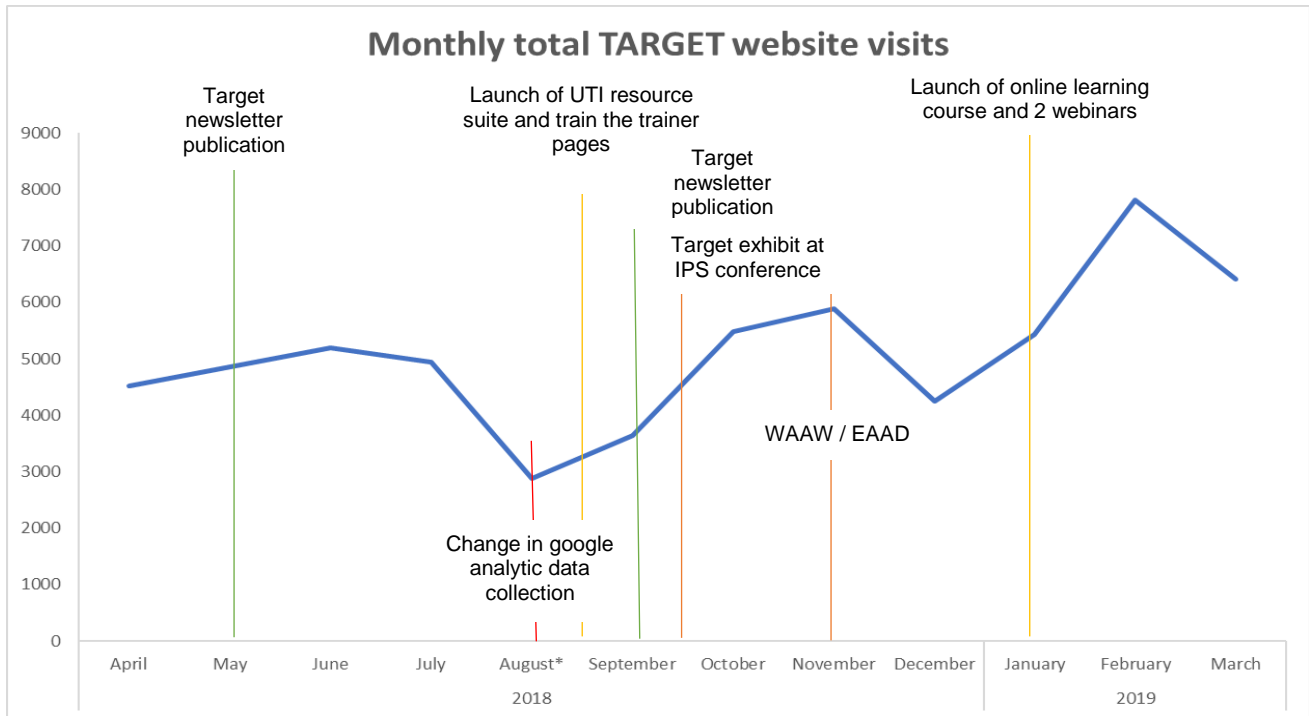
*The figures from 2018/19 may underrepresent the actual figures as the RCGP changed their way of recording website visits in August 2018

Figure 7.1: Monthly TARGET website views (April 2018 - March 2019) highlighting promotional activities

The average time each user spends on the TARGET website was 16:23 minutes and although website views dropped between June and August 2018 (Figure 7.1), user time on the site for the same period increased from 10 to over 20 minutes (Figure 7.2) and has remained at a consistent.
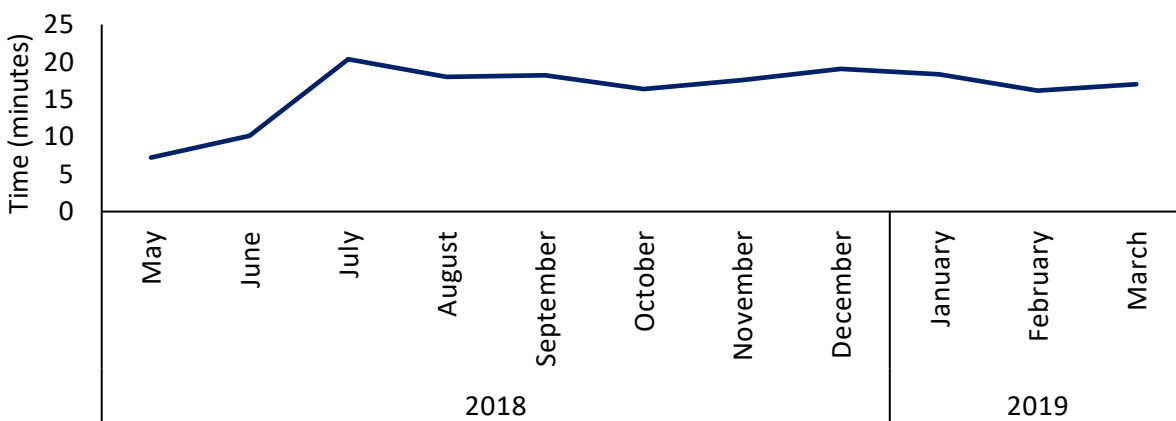

Figure 7.2: Average time in minutes spent on the TARGET website

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The most popular section on the TARGET website was the 'Leaflets to share with patients' section (Figure 7.3) followed by the UTI Resource Suite (released in August 2018). The TARGET Self-Assessment Checklist (SAC)[141] was the third most frequently accessed resource receiving almost 4,000 clicks; the SAC is a short questionnaire for use by GP practices and CCGs to assess their antibiotic prescribing against others in their region and nationally and was updated in line with the new UK 2019 – 2024 5-year action plan in February 2019.

** Launched August 2018
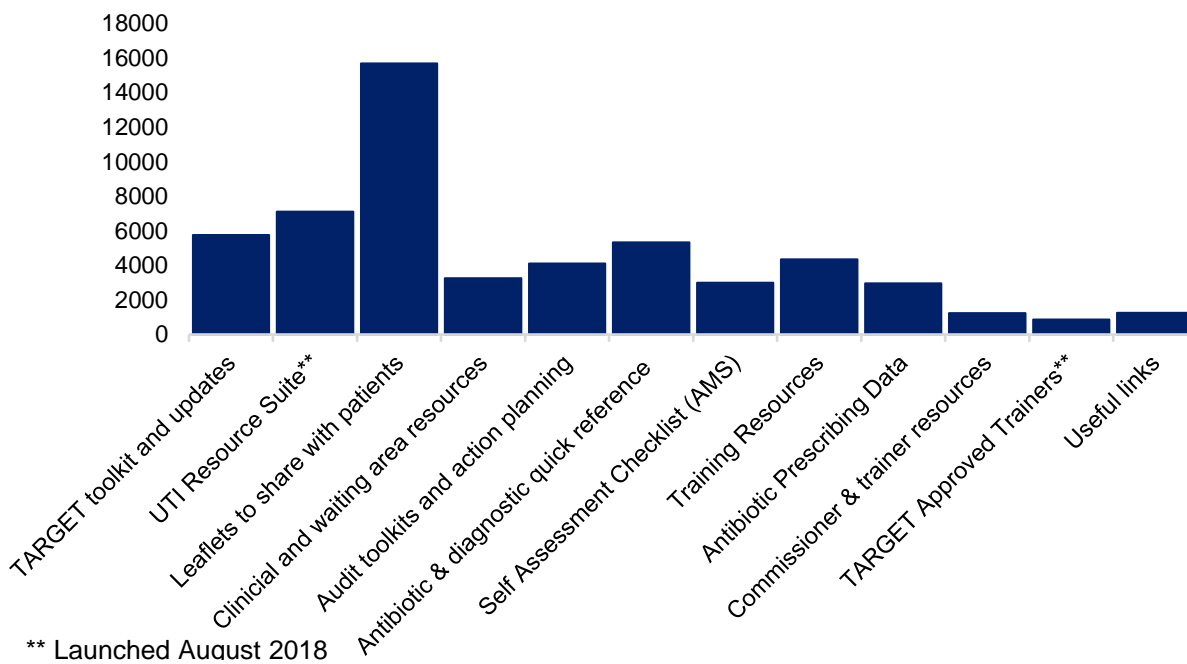
Figure 7.3: Total number of slider clicks on the TARGET website, May 2018 to March 2019

Of the leaflets to share with patients, the TARGET Treating your infection (TYI)-UTI leaflet is the most popular, followed by the TARGET TYI-Respiratory tract infection leaflet (Figure 7.4). The TARGET specific leaflets are more popular than the non-TARGET specific leaflets.

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[141] TARGET Antibiotics toolkit. Avaliable on-line: https://www.rcgp.org.uk/clinical-and-research/resources/toolkits/target-antibiotic-toolkit.aspx

Figure 7.4: User clicks on each link on the leaflets to share with patients available on the TARGET website, April 2018 – March 201

The TARGET resources are constantly being updated to ensure compliance with the latest research and guidance, with all updates and developments being freely available on the TARGET website.[142]

TARGET UTI resource development

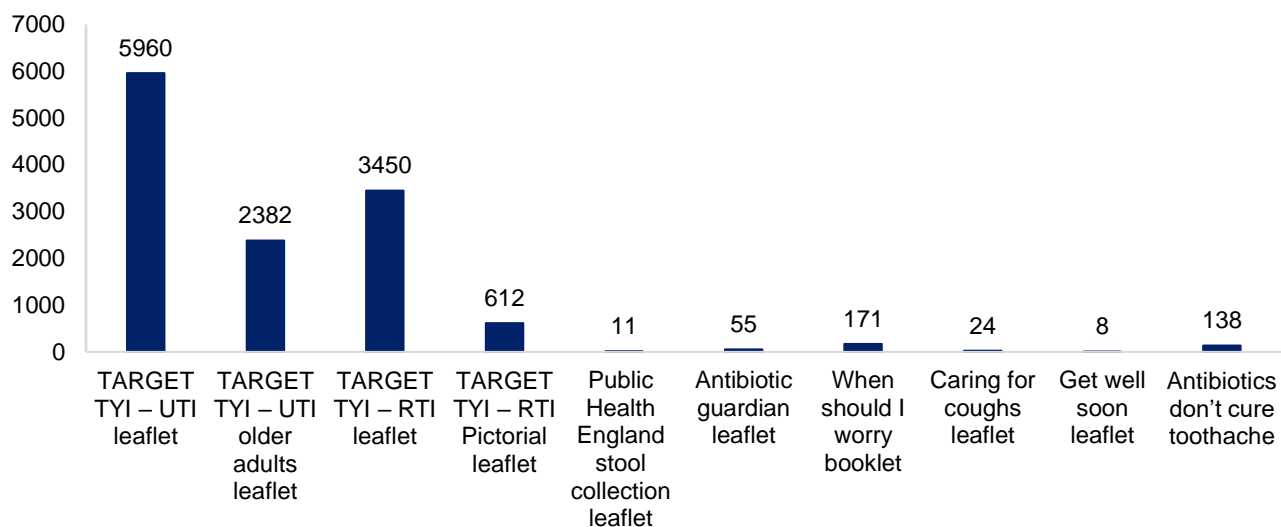To help facilitate the UK 5-year national action plan of halving healthcare-associated Gram-negative bloodstream infection (GNBSI), PHE, via the TARGET programme and other stakeholders has developed a suite of resources aimed at optimising antibiotic prescribing for UTIs. This has included:

UTI Workshop

With input from a consultant microbiologist, a TARGET workshop centred on UTIs in the over 65 year age group was developed and piloted in Gloucestershire. The workshop contained the latest national and local prescribing data, two clinical scenarios, interactive audience participation slides, action planning and introduction to the TARGET suite of resources. Participants reacted extremely well to how their local data were presented; as such future work will involve developing an enhanced feedback data package for general practice use and assessing its acceptability and feasibility with GP

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[142] TARGET Antibiotics toolkit. Avaliable on-line: https://www.rcgp.org.uk/clinical-and-research/resources/toolkits/target-antibiotic-toolkit.aspx

staff. The TARGET UTI Workshop will be published on the TARGET website by November 2019.

UTI Self-assessment checklist

A self-assessment checklist, focussing on the diagnosis and management of UTIs, has also been developed and piloted by GPs.[143]

UTI audits

With GP input, the uncomplicated UTI audit has been adapted using the diagnostic flow chart for patients over the age of 65 and for patients with catheters. The over 65s UTI audit was piloted by four GPs as part of a feasibility study in Gloucestershire and will be published in June 2019. Further work is underway focusing on a UTI audit for patients with catheters.

UTI Diagnostic quick reference tool

The PHE UTI diagnostic quick reference tools have been improved following extensive literature review and research which included multiple stakeholder workshops and qualitative research that assessed General Practice and care home staff views about UTI management and antibiotic use in general. The updated UTI diagnostic quick reference tool was published, including new flowcharts for women under the age of 65 years, children and older adults in November 2018 (see Chapter 7 Annex).

These quick reference tools align with NICE/PHE guideline on AMS and UTIs and received NICE endorsement. The flowcharts include summary tables, a referenced rationale section and a table that provides information on sending urine culture and interpretation.

The flowcharts also are linked to the TYI-UTI leaflets (see Chapter 7 Annex) for women under 65 years and older adults. These have been endorsed by NICE for use with the newly published guidance.

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[143] TARGET Antibiotics toolkit. Avaliable on-line: https://www.rcgp.org.uk/clinical-and-research/resources/toolkits/target-antibiotic-toolkit.aspx

Behavioural insights projects on AMS and CAUTI

Social norms feedback letters to General Practice

A Randomised Controlled Trial in 2015 showed that a letter from England's Chief Medical Officer (CMO) to high-prescribing GPs (in the top 20% nationally), giving feedback about their prescribing relative to the norm, decreased their antibiotic prescribing. The CMO sent further feedback letters in succeeding years. The effectiveness of the repeated feedback was analysed using a Regression Discontinuity Design. In April 2017, GPs in every practice in the intervention group (n = 1,439) were sent a letter from the CMO stating that the practice was prescribing antibiotics at a higher rate than 80% of practices. Practices in the control group received no communication (n = 5,986). The outcome measure was the average rate of antibiotic items dispensed, controlling for STAR-PU (specific therapeutic age-sex-related prescribing unit), from April 2017 to September 2017. The GP practices who received the letter reduced their prescribing rates by 3.69% ([95% CI -3.71, -3.68]; p <.001), representing an estimated 124,952 fewer antibiotic items dispensed.

Exploring the implementation of interventions to reduce antibiotic use and catheter associated urinary tract infections (ENACT)

The University of Oxford and University College London Centre for Behaviour Change were commissioned to consider how best to optimise the suite of national (i) AMS interventions in primary care and (ii) CAUTI interventions aimed at healthcare professionals in primary and community care, secondary care and care homes. These two parallel projects used behavioural science tools and techniques to analyse the barriers and facilitators to AMS and CAUTI-related healthcare professional behaviours in relation to the content of national interventions. Following stakeholder consultation, new and optimised intervention components were proposed. Abstracts on these projects are provided in Annex Chapter 7.

National antibacterial audit in UK dental hospitals

This year the dental subgroup of ESPAUR collaborated with the Association of Clinical Oral Microbiologists (ACOM) and Association of Dental Hospitals (ADH) on a national audit of antibacterial use in UK Dental Hospitals. The audit included sixteen dental hospitals across the UK who participated in a four-week audit during the month of February 2018. Data were uploaded to an electronic server during March and April 2018 and findings were reported in September 2018. The findings were discussed with UK Dental Directors in October 2018 and a plan of interventions was agreed at the end of 2018.

Six hundred and forty two therapeutic and 350 prophylactic antibiotic prescriptions were issued during the month. Pain was reported as the sole influencing factor for antibacterial prescribing in 11.8% of cases. Samples for microbiological testing were taken in only 3.3% of all audited oral infections, with 23% of audited cases not scheduled for any follow up review. Surgical extraction with bone removal was reported as the main procedure to receive antibacterial prophylaxis (33.7%) followed by dental extraction without bone removal (20.6%), prophylactic antibacterial cover was given for periodontal surgery in 7.4% of all the cases. Most prophylactic antibacterial courses were for more than one day postoperatively.

The results of the audit suggested that clinical prescribing could be improved by recognising that:

- pain without other justifiable factors such as signs of spread of infection, should not trigger antibacterial prescription
- the importance of microbiological analysis needs to be highlighted before starting empirical antimicrobial treatment
- follow up regimens need to be addressed when prescribing antimicrobials
- the use of antibacterial prophylaxis in dental extraction with and without bone removal is unjustified in healthy immunocompetent individuals
- timing and duration of prophylaxis, when justified, need to be confined to one dose preoperatively or with additional postoperative doses of no longer than 24 hours
- further monitoring of periodontal surgical prophylaxis should be undertaken

As a result of the audit, the following AMS interventions for the UK Dental Hospitals were progressed:

- dental hospitals were encouraged to evaluate their local guidance against the national guidance and align them where applicable.
- to facilitate discussion and training, all dental hospitals received a resource pack including:
- audit data collection sheets
- summary of the national audit
- national action plan
- individualised feedback
- presentation of results
- signposting to the secondary care scenario educational pack

Future work

The following actions will be progressed for the various AMS projects during 2019/20:

- the learning from the development of the AMS Peer Review Tool as a quality improvement tool will be submitted for peer review. The tool will be made available as a supplementary file and therefore available for hospitals or networks that choose to use the tool to foster shared learning
- the PHE Fingertips template currently focuses on the NHS England initiatives, aggregated at Trust type and sub-region level. Future work includes updating the prescribing and resistance indicators, which will involve a Delphi consensus method on the most appropriate indicators to guide local AMS strategy
- future work on the TARGET UTI toolkit will include a feasibility study to evaluate the TARGET UTI resources, the development of a UTI audit for patients over 65 and catheterised patients, service evaluation of TARGET UTI resources exploring the views of pharmacy staff on giving advice to service users who present with UTI symptoms, as well as the feasibility and acceptability of using the two TARGET UTI leaflets within community pharmacies
- development of an enhanced feedback data package using UTI data for general practice and assess the acceptability and feasibility of this package with GP staff. The work will provide an understanding of what information/data would motivate prescribers to optimise antibiotic use
- the TARGET quick reference tools for Abnormal Vaginal Discharge, Chlamydia, and Fungal Skin and Nail infections will be updated
- continue to test/evaluate interventions using behavioural science-informed feedback to senior management on antibiotic prescribing in primary and secondary care and advise on individual AMS and CAUTI national interventions on improvement based on ENACT
- the National Antibacterial Audit in UK Dental Hospitals will require follow up work including a dental clinician knowledge and attitudes survey, a repeat of the antibacterial audit in February 2020 and seeking collaborative opportunities to support sustainable AMR surveillance programme for oral pathogens
- creation of a national paediatric antimicrobial stewardship network to benchmark antimicrobial prescribing with the aim to harmonise practice in primary and secondary care

8. Professional education and training and public engagement

Introduction

This chapter outlines interventions delivered for professional education and training and public engagement during 2018/19 and includes:

- Antimicrobial stewardship (AMS) workshops
- e-learning
- Healthcare student national AMS conference
- Keep Antibiotics Working national campaign
- World Antibiotic Awareness Week (WAAW) (12-18 November 2018) and European Antibiotic Awareness Day (EAAD)(18 November 2018)
- Twitter activity analysis for the World and European Antibiotic Awareness campaigns
- Antibiotic Guardian (AG) campaign
- e-Bug activities

Professional education and training: e-learning

Information for Practice Webinar - AMR Local Indicators on PHE Fingertips

In January 2019, PHE ran a webinar on the Fingertips AMR Local Indicators. This online webinar intended to raise awareness and action on antibiotic prescribing, AMR, healthcare-associated infections, infection prevention and control, and AMS. The specific objectives for this webinar were to:

- highlight updated contents of the AMR Local Indicators profile
- navigate through the six Fingertips AMR domains
- set up a "Your Data" account to create bespoke indicator and area lists
- export AMR data and reports for analysis.

Of 371 registered participants, 240 joined the live webinar; 54% of registered delegates were pharmacists and/or from Secondary care – Acute NHS Trusts; and 68% had a role leading AMS or infection prevention and control. London, the North West and South East of England were the most represented regions.

Eighty percent of attendees had accessed the resource within the past year, most commonly the antibiotic prescribing (53%), AMR (47%), and HCAI (40%) domains. One

hundred and fifty five people said that they have shared results from PHE Fingertips with other colleagues in the last six months, most commonly by email (51%) or by report (30%). Those who had not previously shared results reported difficulties in nativating the website or understanding the data.

Webinar survey

A post survey webinar, completed by 42 of the 240 delegates who watched the webinar, showed that most delegates agreed that each the objectives were met (Figure 8.1); 88% (37/42) found the content relevant, and 81% (34/42) would recommend it to a colleague.

Figure 8.1 Respondents who agreed the objectives of the webinar have been met (n=42).
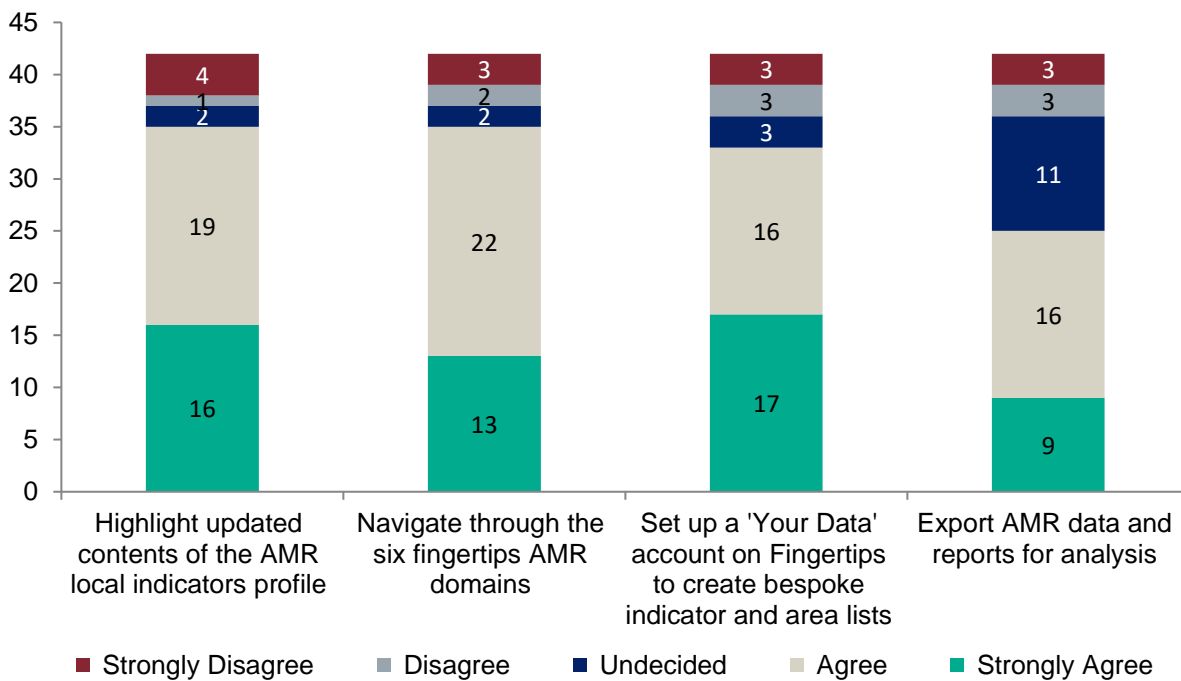
TARGET live webinars

TARGET[144] (Treat Antibiotics Responsibly, Guidance Education Tools) ran four live interactive webinars aimed at healthcare professionals who are familiar with the TARGET toolkit. The webinars (approximately 40 participants each) covered an overview of the TARGET toolkit and ideas for implementation in primary care and the development and review of guidance for the management of urinary tract infections (UTI) for older adults.

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[144] Treat Antibiotics Responsibly, Guidance Education Tools are available at: www.rcgp.org.uk/targetantibiotics

Online course: TARGET Antibiotics – Prescribing in Primary Care

The TARGET Antibiotics – Prescribing in Primary Care e-learning course, developed in collaboration with the British Society for Antimicrobial Chemotherapy (BSAC), is a free course hosted on the Future Learn platform. The course, based on the TARGET webinars,[145] contains six weekly one-hour modules aimed at primary care healthcare professionals involved in the treatment of common infections.

The first course ran in January 2019. A total of 1,637 individuals from 92 countries expressed an interest in the course, and 1,015 (56.3%) took part across all modules. The majority were from the UK, however the next largest group of active learners were in Nigeria, the USA and India. Most users were between 18 – 35 years old. Figure 8.2 gives details of the breakdown of users per week as the course commenced.

End of course survey results

A survey of 114 participants showed that 109 (96%) thought the course either met or exceeded their expectations; 111 (97%) stated that they gained new knowledge or skills on completion of the course; 96 (84%) stated that they would apply their learning in practice and 87 (76%) stated that they would share their learning with colleagues.

Overall, participants were satisfied with the learning and liked the mixture of video, images and quiz to consolidate learning; signposting to relevant resources; and demonstrations. Negative comments focussed on the lack of a free certificate at the end of the course, broken hyperlinks and that the content was UK-based. The course will be re-run in September 2019 and February 2020; registration will open on 6th January for the February cohort at https://www.futurelearn.com/courses/target-antibiotics.

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[145] The webinars are available on-line at http://www.target-webinars.com/

Figure 8.2. TARGET Antibiotics – Prescribing in Primary Care course outline and attendees.

1 **Introduction to AMR in Primary Care**
Explore data sources to understand their practice antibiotic usage.

Learners 991; Active learners* 723; Social learners** 44

Prescribing in UTIs **2**
Improve prescribing practice for patients with suspected UTIs.

Learners 450; Active learners* 402; Social learners** 38

3 **Assessing the Need for Antibiotics**
Discuss ways to manage patient expectations for antibiotic prescriptions.

Learners 340; Active learners* 316; Social learners** 42

Managing Patient Expectations and Back up/Delayed Prescribing **4**
Identify ways in which back up prescribing can assist their practice.

Learners 285; Active learners* 264; Social learners** 32

5 **Antibiotics for Children**
Evaluate approaches to the prescribing of antibiotics for children.

Learners 252; Active learners* 228; Social learners** 20

Common Practice Approach **6**
Show value of a team approach towards, and assess importance of, AMS.

Learners 240; Active learners* 222; Social learners** 19

*Completed more than 3 steps of the module
**Number of learners who interacted with each other throughout the module

Professional education and training: AMS workshops

TARGET Train the Trainer Workshop in Norfolk

The TARGET Train the Trainer workshop aims to provide primary care staff with knowledge, confidence and skills to facilitate a TARGET AMS workshop for other colleagues in their own locality. Approved TARGET trainer status was granted to trainers who attended the workshop, completed a Self-Assessment Checklist, delivered the workshop in their practice and carried out two delivery audits. In Febraury 2019, an event was conducted in West Norfolk CCG in collaboration with the CCG and PHE East of England team. The training included 25 clinicians (2 student GPs, 7 nurse prescribers, 13 GPs, and 3 practice nurses). Feedback indicated that content was generally good or very good and that people found the discussion with colleagues and the information on the new resources very useful. Out-of-hours practice feedback

indicated that workshops need to include more information on how to diagnose infection without access to lab results; "we don't have access to send MSUs, most patients are treated on the day based on symptoms".

Antibiotic consumption & stewardship data training workshop in collaboration with NHS England and NHS Improvement

In response to gaps in understanding AMS and prescribing metrics highlighted by the Kent & Medway Pilot Leadership review, NHS Improvement and PHE ran the first Antibiotic Consumption and Stewardship Data Training Workshop for the Kent and Medway and Sussex and East Surrey areas in February 2019. The overall learning outcome was to develop skills in gathering, analysing and interpreting antibiotic prescribing data. Delegates were introduced to the following data platforms in the workshop:

- Model Hospital
- PHE Fingertips
- Rx-Info and Define and Refine
- PrescQIPP
- ePACT2

Seventeen delegates participated in the training from a range of specialities including: health protection specialists, pharmacists, medicine/prescribing advisors, and pharmacy technicians. Eight of the 17 delegates completed the pre and post training questionnairs.They reported a better understanding on what data could be accessed from the platforms and that the objectives of the workshop were met.

Professional education and training: conferences

Healthcare students national AMR conference

The UK's second multidisciplinary conference for students on AMR: AMR Conference: Advocating a Behaviour Change was held on 17th November 2018. The Conference promoted collaboration amongst all health-related fields through a One Health approach, providing students and young professionals an opportunity to participate in AMR-related talks and workshops. Over 200 students attended the conference. The presentations from the conference are available online.[146]

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[146] Antibiotic Guardian website is available on-line at: http://antibioticguardian.com/Meetings/students-amr-conference-2018/.

One hundred and fifty pre-conference and 124 post-conference questionnaires from 36 universities were completed. Pharmacy, Medicine and Veterinary medicine were the top three courses represented in both the pre- and post- conference surveys.

Students considered AMR to be a more important challenge than climate change, obesity, food security and gender inequality and agreed or strongly agreed that AMR was important globally (pre: 98.66, n=149; post: 97.52%, n=121); nationally (pre: 96.65%, n=149; post: 97.52, n=121); for individuals (pre: 94.64, n=149; post: 97.52, n=121).

Following the conference, students agreed that they would like more education on the appropriate use of antimicrobials; felt like a strong knowledge of antimicrobials is important in their care; and that knowledge of antimicrobials will impact their future role (Figure 8.3).
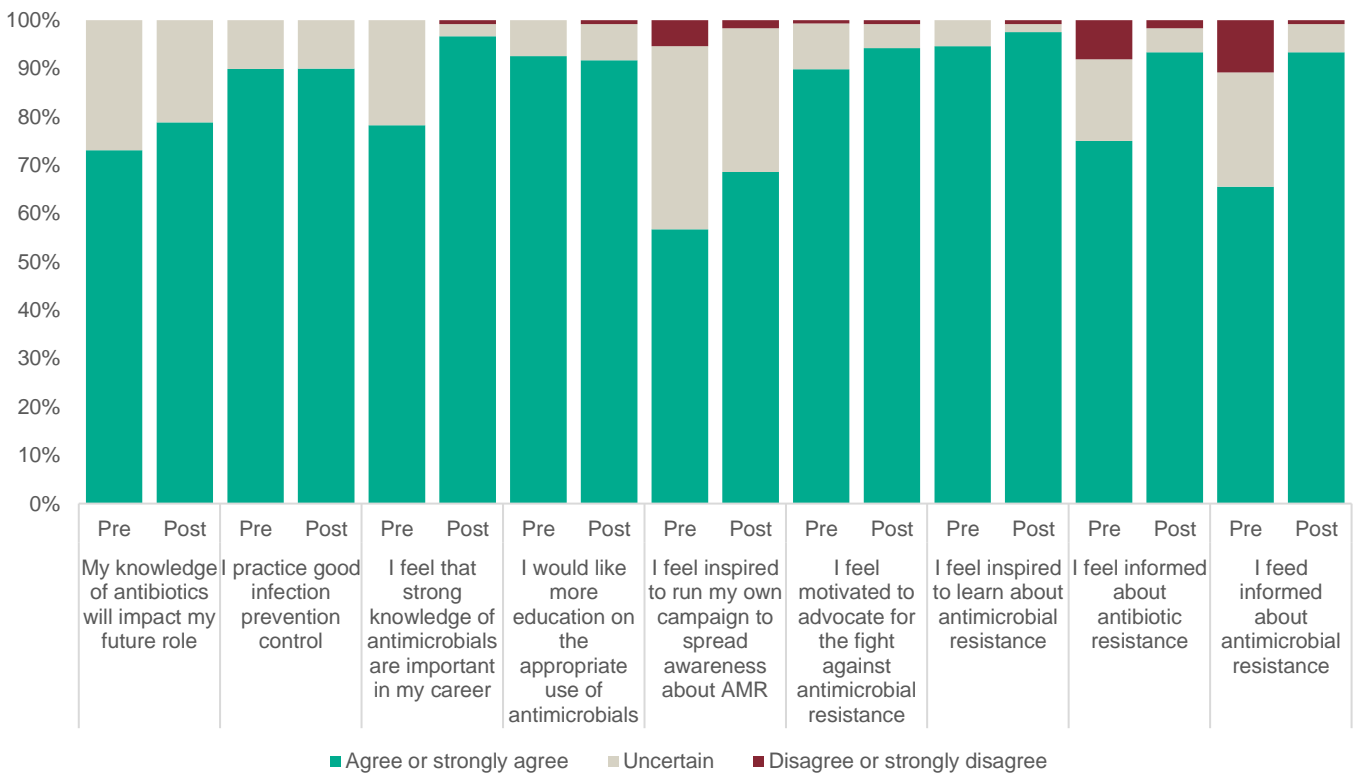

Figure 8.3. Pre and Post-conference responses to motivational and opportunity statements

In the pre-conference survey:

- most students knew that antibiotics kill commensal and pathogenic bacteria (89%), and that overuse of antibiotics makes them less effective (94%)
- the majority of students correctly identified that bacteria can become resistant to antibiotics (98%); however, 61% stated that "humans or animals" can become resistant to antibiotics
- seventy nine percent of respondents said that taking antibiotics often has side effects; 14% did not know the answer to this
- forty-six percent of veterinary medicine students knew that a pig treated with antibiotics cannot be slaughtered for meat production the next day
- there was an increase in the percentage of students who knew that poor infection prevention and control practices cause spread of AMR in the post-conference survey (pre: 85%, post: 96%, p=0.076)
- most students (pre: 76%, post: 79% p=0.45) knew that the best way to clean hands to stop the spread of bacteria is by washing thoroughly with soap and water, followed by using a hand sanitising gel/foam
- more than half of the responding students correctly identified that treating infections for a longer period to prevent resistance was not an effective method to stop the emergence or spread of AMR (Table 8.1)
- the proportion of participants selecting each option was similar pre- and post-conference (p=0.138) except the option 'avoiding the use of antibotics for the treatment of colds and flu'
- future conferences should ensure these key messages are promoted

Table 8.1 Participant responses to which of these methods are NOT effective ways to stop the emergence or spread of antimicrobial resistant organisms.

	Pre-conference (n=144)	Post-conference (n=117)
Treating infections for a longer period to prevent resistance	56%	57%
Take up the offer of the flu vaccine	28%	32%
Avoiding the use of antibiotics for treatment of colds and flu	10%	3%
Good hand hygiene	5%	3%
Isolation of patients colonised with resistant organisms such as MRSA	1%	5%

Health Education England (HEE)

Intervention development

HEE has worked with PHE to develop an animation to support Out of Hospital management of UTIs in elderly patients,[147] which supports TARGET UTI leaflet and UTI diagnostics tool, and complements the other short films in collaboration with the PHE Primary Care Unit and TARGET Toolkit.

Innovation Fund

In 2018-19 HEE invited AMR bids through an 'Innovation Fund' that aimed to encourage and support initiatives that will contribute to workforce development through education and training, particularly around behaviour change with evidence of outcomes.

3 contracts were awarded for delivery for 18/19:

1. The Royal Pharmaceutical Society (RPS) to support key pharmacists within NHS Trusts/Sustainability and Transformation Partnerships (STPs) to develop the skills and behaviours to become effective antimicrobial clinicians, leaders and mentors in the form of a pilot training programme in London and South East.

2. The BSAC and the Antibiotic Review Kit (ARK)[148] team to translate research materials into clinical practice-ready training materials that will be made freely available.

3. The PHE Primary Care and Interventions Unit to develop and deliver training for primary care pharmacists on AMS.

Resources developed through the HEE Innovation Fund will be linked from the e-learning for healthcare[149] AMR and infections webpage. In support of the new UK five-year action plan for AMR, HEE will continue to explore training needs for pharmacists working in community settings to review the dose, duration and appropriateness of antimicrobial prescriptions and will also commission projects to fulfil specific education and training gaps in AMR for the whole workforce.

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[147] Animation on Out of Hospital management of UTIs in elderly patients. Available on-line: https://www.youtube.com/watch?v=lX3bfhMSdcU

[148] Antibiotic Review Kit tools for implementation. Available on-line: http://bsac-vle.com/ark-the-antibiotic-review-kit/

[149] e-learning for healthcare is available at: https://www.e-lfh.org.uk/programmes/antimicrobial-resistance-and-infections/

Keep Antibiotics Working campaign 2018

The ground-breaking 'Keep Antibiotics Working' campaign has become an annual behaviour change initiative to alert the general public to the issue of AMR, with the aim of reducing patient pressure on GPs to prescribe.

The campaign has run nationally for two consecutive years (October 2017 and 2018), following a successful pilot in the North West. Targeted advertising on TV, radio, outdoor, press, digital platforms, social media, alongside PR and extensive partner support from health care professionals, the NHS and local authorities, continues to change the narrative on AMR from not only the future risk to humanity, but also the immediate risk to the individual.

The successful campaign PR launch in October 2018 achieved over 250 pieces of news coverage and appeared on a number of national and regional news programmes. Support on social media saw 650 mentions and key influencers including Dr Zoe Williams, Dr Dawn Harper and Dr Ellie Cannon tweeted support.

PHE continued to work in close partnership with the NHS, and engaged all GP practices in England. During the campaign period, over 270,000 posters and leaflets were distributed to a range of partners including local authorities, health care centres and Housing Associations. In addition, over 19,000 specially designed self-care prescription pads were sent to healthcare professionals, providing a tangible evidence-based intervention to satisfy patient concerns and help alleviate pressure on clinicians to prescribe.

Public awareness is high, with 83% of our audience agreeing that "Taking antibiotics when you don't need them, puts you and your family at risk of antibiotic resistant infections".

Attitudinal shifts continue to be seen among the general public with 78% of the audience reporting that they were unlikely to ask for antibiotics if they'd been told they were not needed.

In 2019, the campaign will continue to improve public awareness of AMR to help reduce patient expectation for antibiotics and support GPs in their conversations with patients. Resources to support 'Keep Antibiotics Working' are available to all GP practices and community pharmacies in England, with additional free resources for a variety of settings that can be ordered or downloaded from the PHE Campaign Resource Centre.

Engagement activities

Summary of activities from World Antibiotic Awareness Week (WAAW) and European Antibiotic Awareness Day (EAAD), 2018

WAAW, led by the World Health Organisation, and EAAD, led by the European Centre for Disease Prevention and Control, promote the international coordination of antibiotic awareness campaigns; PHE coordinates activities for England. Initiatives taken forward for the 2018 campaign were:

1. **Antibiotic Guardian (AG)**
Embedded the new AG resources and branding, developed in 2017. New resources included:

- toolkits for healthcare professionals and students
- AG badges
- junior and family AG resources
- crossword puzzles and quizzes for healthcare professionals and the public
- key antibiotic awareness messages
- Start Smart Then Focus leaflets and secondary prescribers' checklists

During WAAW 2018, www.antibioticguardian.com was visited 9,884 times and 2,736 pledges were received. Table 8.2 shows the number of visits the antibiotic awareness resources webpage[150] has had over the last five years.

Table 8.2: Antibiotic awareness resources webpage - Number of visits, 2014-2018

Year	Number of visits
2014	16,347
2015	25,933
2016	21,832
2017	20,761
2018	13,456

Organisations who pledged to champion/plan key promotional activites within their local area and to members of their organisation during WAAW 2018, or plan other AMR activites/actions, were invited to register these activities on the Antibiotic Guardian website. A total of 139 organisations had registered; 126 were from the UK and 13 from outside the UK (Bangladesh, Dominican Republic, Ghana, India, Nigeria, Saudi Arabia, South Africa and the United States of America). Since organisation registration

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[150] EAAD resources available at: https://www.gov.uk/government/collections/european-antibiotic-awareness-day-resources

commenced in 2017, 398 organsiations have registered on the website, the majority of which are GP practices, although other primary care sectors, secondary care sectors, NHS organisations and public health bodies, private healthcare, community pharmacies, charities, universities and verterninary health are also represented.

Seventy eight percent of organisations pledged to display and share AG materials throughout the winter cold and flu season and 76% pledged to display and share Keep Antibiotic Working campaign materials. As well as using provided resources, organisations also developed local activities to promote antibiotic awareness at conferences, school engagement events, university lectures as well as in health care settings.

2. **AMR Z-card**

e-Bug in collaboration with the Nursing, Maternity and Early Years Directorate and AG launched an AMR-Z card. The aim of the AMR-Z card was to provide young people with a pocket-sized resource about hygiene, infection prevention, self-care and antibiotics.

3. **Kaleidoscopic Antibiotics** - further details in the public engagement section

4. **Youth Badge** - further details in the public engagement section

5. **TARGET leaflets** were sent out to all community pharmacists as part of the 'Help us help you' campaign

6. The second **National Student AMR Conference** was held on 17th November 2018

7. Letters were sent from the Chief Professional Officers to NHS, CCG and Local Authority professionals and management.

Twitter activity analysis for the World and European Antibiotic Awareness campaigns

Social media (Twitter) data was collected from the World and European antibiotic awareness campaigns in November 2018 with the purpose of summarising the activity across the week, and identify the difference in activity by hashtag. A previous summary from 2016[151] showed that there was a difference in tweeting and re-tweeting between global and European hashtags. An alternative approach was taken for the 2017

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[151] Mapping Antibiotic Awareness Week 2016 Twitter activity. Available on-line at:
https://scotpublichealthdotcom.files.wordpress.com/2019/02/waaw-2016-paper-to-upload-2019.docx.pdf

analysis, looking at tweeting by day and hour to identify the diversity of tweeting across the world;[152] this work was presented at the 2018 ECCMID conference.[153]

Data were extracted using a number of tools, as described in a tweet thread.[154] The track was launched in time to capture tweeting from the different global time zones. The official hashtags for the campaigns were #KeepAntibioticsWorking (Europe) and #WAAW2018 (World), with mention of #AntibioticResistance on same website. Search term included hashtags (e.g. #AntibioticAwarenessWeek) and phrases (e.g. "antibiotic awareness week").

Results

There were 14,400 tweets by 5,899 accounts, with 60,222 retweets for the period 12-18 November 2018 (extended to include global tweeting). A list of top tweets is provided in a Wakelet summary.[155]

Excluding replies, there were 13,605 original tweets. Overall, 6,084 (44.7%) tweets received no retweets, and 2,132 (15.7%) tweets received a single retweet. Tweets with a hashtag were more likely to be retweeted. Most of the hashtags (#KeepAntibioticsWorking, #StopSuperBugs, #AntibioticGuardian, #WAAW2018) had a positive impact on retweeting, with the exception of #AntibioticResistance, #Antibiotics and #WorldAntibioticAwarenessWeek (no impact), and #AntibioticAwarenessWeek (negative impact).

Influencers (tweeters, mentioned accounts and retweeters) are mapped in Table 8.3 and Figure 8.4; "just retweeted" and "just tweeted" were the two largest categories, representing 85% of accounts (Figure 8.4). Looking at the central zone (accounts that tweeted, were mentioned and retweeted), helps understand the role of organisations and individuals in generating and disseminating content (Table 8.3).

While #AntibioticResistance was the most used hashtag, it appears to have had no impact on retweeting. As in previous years, there was considerable "hashtag drift", where tweeters started using other hashtags (e.g. #WAAW or #WAAW18 rather than #WAAW2018). These hashtags had different levels of adoption and engagement.

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[152] Toe dipping or immersion? A social network analysis of World Antibiotic Awareness Week 2017: A poster for ECCMID 2018. Available on-line at: https://scotpublichealth.com/eccmid2018/

[153] Mackenzie G, et al. What's in a hashtag? a social network analysis of World Antibiotic Awareness Week 2017. Poster presentation at ECCMID 2018. Abstract available on-line at: https://www.escmid.org/escmid_publications/escmid_elibrary/material/?mid=63251

[154] Tweet Analysis from @gmacscotland. Available on-line at: https://twitter.com/gmacscotland/status/1061759697211011073

[155] Wakelet at: https://wakelet.com/wake/94da7f0b-491b-4630-94cf-f71a95afeafe

There was considerable diversity in tweeting for the world and European antibiotic awareness campaigns during November 2018. To study the full impact of a campaign it is worth looking beyond the official hashtags. Future campaigns should include hashtags in the images.
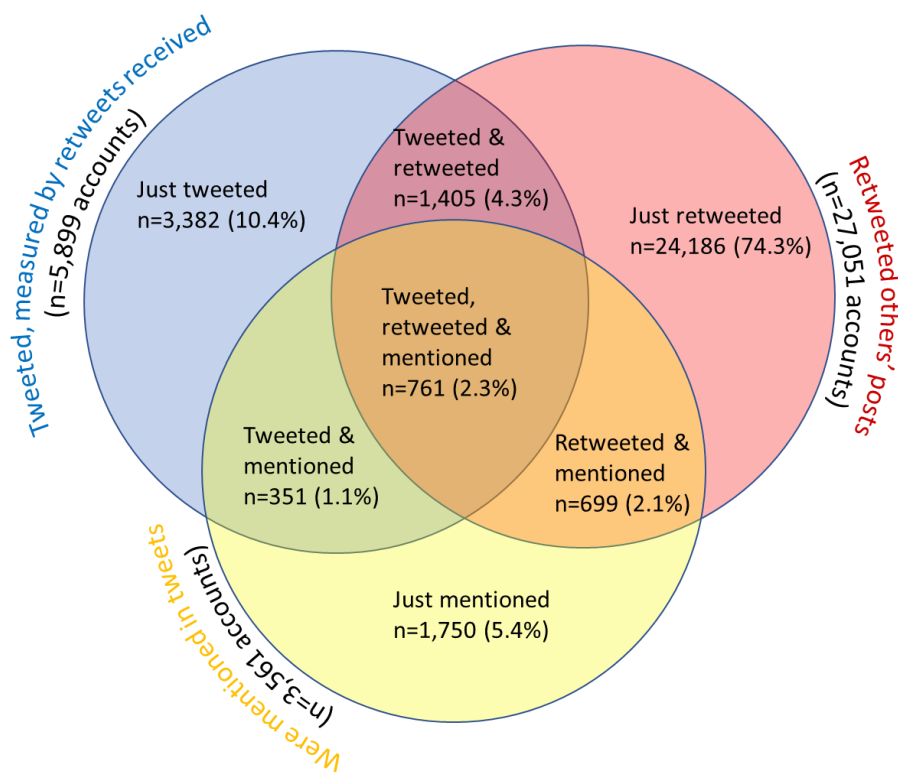

Figure 8.4. WAAW 2018 - Influencers (tweeters, mentioned accounts and retweeters)

Table 8.3: Influencers (tweeters, mentioned accounts and retweeters) during World Antibiotic Awareness Week

Twitter account	Retweets received for tweets	Twitter account	Mentions	Twitter account	Retweets made
WHO	6932	WHO	698	wameyokw	232
EU_Health	1087	CDCgov	186	MicrobLog_me_uk	221
ONU_es	971	uhbipc	182	DrDianeAshiru	163
EAAD_EU	949	EAAD_EU	172	tumaini_tz	151
KKMPutrajaya	862	ECDC_EU	137	KezHolden	121
WHOWPRO	812	DrDianeAshiru	82	uhbipc	111
sanidadgob	756	FAO	73	Frankerr1F	101
CDCgov	729	EU_Health	66	bhogal_pathogen	97
UN	532	Wellcome_AMR	64	codd_jane	91
OIEAntimalHealth	431	reactgroup	61	drmarkgarvey	88

Keep Antibiotics Working campaign

The ground-breaking 'Keep Antibiotics Working' campaign has become an annual behaviour change initiative to alert the general public to the issue of AMR, with the aim of reducing patient pressure on GPs to prescribe.

The campaign has run nationally for two consecutive years (October 2017 and 2018). Targeted advertising on TV, radio, outdoor, press, digital platforms, social media, alongside PR and extensive partner support from health care professionals, the NHS and local authorities, continues to change the narrative on antibiotic resistance from not only the future risk to humanity, but also the immediate risk to the individual.

The successful campaign PR launch in October 2018 achieved over 250 pieces of news coverage and appeared on a number of national and regional news programmes. Support on social media saw 650 mentions and key influencers including TV Doctors Dr Zoe Williams (Good Morning Britain), Dr Dawn Harper (Embarrassing bodies and Good Moring Britain) and Dr Ellie Cannon (This Morning) tweeted support.

PHE continued to work in close partnership with the NHS, and engaged all GP practices in England. During the campaign period, over 270,000 posters and leaflets were distributed to a range of partners including local authorities, health care centres and Housing Associations. In addition, over 19,000 specially designed self-care prescription pads were sent to health care professionals, providing a tangible evidence-based intervention to satisfy patient concerns and help alleviate pressure to prescribe on clinicians.

 Public awareness is high, with 83% of our audience agreeing that "Taking antibiotics when you don't need them, puts you and your family at risk of antibiotic resistant infections".

Attitudinal shifts continue to be seen among the general public with 78% of the audience reporting that they were unlikely to ask for antibiotics if they'd been told they were not needed.

Antibiotic Guardian campaign 2018/19

PHE launched the pledge-based AG campaign in 2014, with the aim of transitioning from raising awareness to increasing engagement. The campaign uses an online pledge-based approach among human and animal health professionals, scientists and

educators and the public.[156] An impact evaluation carried out after the first year of the campaign highlighted that those who chose pledges on the website and became AGs had increased knowledge and behaviour change (self-reported), as well as increased commitment to tackling AMR.

From initiation in 2014 up to the end of 2018, the campaign website has been visited 361,960 times. This translated into 66,000 pledges from 129 countries. AGs are therefore present in 50% of countries worldwide. The number of pledges each year has been 12,315 in 2014, 15,002 in 2015, 15,140 in 2016 and 15,170 in 2017 and 8,373 in 2018. Translations of the AG programme are now available in Dutch, French, German, Russian, Turkish, and Welsh supporting the AMR recommendation related to a worldwide awareness campaign. The campaign has also been launched in South Africa, where 1,018 pledges were made.

In March 2019, a review of the first 57,000 Antibiotic Guardians to understand their demographic, knowledge and the impact analysis was published in the journal Antibiotics.[157]

e-Bug activities 2018/19

e-Bug is an international health education resource that teaches children, young people and communities about hygiene, the spread of infections, antibiotic use, and AMR. Established in 2006 following an EU-wide needs assessment the resources were launched in 2009. Ten years later, the e-Bug resources are included in the 2019 UK Five Year AMR Strategy as a case study of good practice, and endorsed by the National Institute for Health and Care Excellence (NICE) in guidance on 'AMS: changing risk-related behaviours in the general population'[158] that recommends that schools use e-Bug to educate on hygiene, infections and antibiotics.

e-Bug further supports Department of Health and Social Care (DHSC) to deliver the UK global AMR-related commitments. e-Bug resources have been translated into 24 languages and partners in over 30 countries work with schools and governments to implement the resources and improve understanding of AMR globally. e-Bug contributes to the Global Health Strategy by continuing to build excellent relationships with partners worldwide and working in close collaboration with the European Centre for Disease prevention and Control (ECDC).

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[156] Ashiru-Oredope D, Hopkins S. AMR: moving from professional engagement to public action. *J Antimicrob Chemother* 2015; 70: 2927-2930

[157] S Newitt, O Oloyede, R Puleston, S Hopkins, D Ashiru-Oredope. . Demographic, Knowledge and Impact Analysis of 57,627 Antibiotic Guardians Who Have Pledged to Contribute to Tackling Antimicrobial Resistance. *Antibiotics* 2019, *8*(1), 21 https://www.mdpi.com/2079-6382/8/1/21

[158] NICE. AMS: changing risk-related behaviours in the general population. Available at: https://www.nice.org.uk/guidance/ng63

10 year anniversary

To celebrate a decade of e-Bug teaching, and to share practice with international partners and stakeholders, PHE, supported by the Microbiology Society, held a two-day event in January 2019. Presentations and workshops showcased current and emerging trends and technologies in infection prevention and AMR education and ranging from online educational games to engagement of children via Scouts and Girl Guiding. The event was attended by 90 individuals representing over 20 countries, including the Philippines, UK, USA, and Saudi Arabia. 96% of attendees said the meeting was very good or good and impact measurements are reported below.

Website, games and digital media

From 1st April 2018 through 31st March 2019, the e-Bug interactive educational website received almost 1 million visits, the highest figure to record, and was most commonly accessed from the UK (22%); France (11%); Spain (8%); United States (6%); and Greece (3.6%). The student games are still one of the most popular areas of the website (Table 8.4).

Table 8.4. Most e-Bug website page visits

Resource	Apr 17 - Mar 18	Nov 17 (WAAW)	Apr 18 – Mar 19	Nov 18 (WAAW)
All pages (including downloads)	949,772	92,703	988,861	121,530
Student games	144,785	13,342	137,439	15,798
Antibiotic animation video	168,985	15,313	163,802	14,767
Junior teacher homepage England	11,877	1,437	13,308	1,536
Beat the Bugs homepage	2,327	335	2,490	314

A mixed methods evaluation of two of the e-Bug games with 473 children aged 7-16 years found that knowledge increased significantly about antibiotic use, appropriate sneezing behaviours, and vaccinations following playing the e-Bug games.[159]

In collaboration with Fun Kids Children's radio, e-Bug developed a six-episode multi-media series called "Kaleidoscopic Antibiotics" to help children explore and learn the what, how and why around antibiotics and vaccines and their importance to everyday life, exploring antibiotic use, resistance and self-care. Learning with Professor Hallux and Nurse Nanobot, this animation series was launched during WAAW 2018 and hosted on the e-Bug website, FunKids website[160] and YouTube.

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[159] Eley CV, *et al*. Young people's knowledge of antibiotics and vaccinations and Increasing this knowledge through gaming: Mixed-methods study using e-Bug. *JMIR Serious Games* 2019;7(1): e10915.
[160] FunKids website is at: https://www.funkidslive.com/learn/hallux/antibiotics/

Table 8.5. e-Bug and FunKids Learn animation series figures

Features	Dates	Figures
Live audio broadcasts	5th November 2018	380,000 listeners
Audio podcasts	5th Nov 2018 – 28th Feb 2019	4,260 downloads
Animated videos	5th Nov 2018 – 28th Feb 2019	476 views
Online page views	5th Nov 2018 – 28th Feb 2019	11,975 page views

Train the trainer

The e-BugTrain the Trainer model aims to disseminate e-Bug training with local authorities for widespread use of e-Bug in schools and communities. Between 1st April 2018 – 31st March 2019 e-Bug has delivered training to approximately 300 individuals across the UK; 449 individuals this year have received the e-Bug training globally.

Safeconsume EU project

SafeConsume[161] is an EU-funded, transdisciplinary project aiming to improve consumers food hygiene behaviour. e-Bug led a UK and EU needs assessment to explore in depth the needs of young people (11-18 years) and educators to gain a better understanding of their attitudes and beliefs towards food hygiene, food safety and foodborne illness. Findings will inform the development of educational materials to tackle the gaps in knowledge and skills and create safer behaviour with regards to food safety, mitigating the long-term risks of foodborne illness and subsequent antibiotic use. The main barrier to teaching food hygiene and food safety in schools is the need for these topics to be embedded into the national curriculum.

Community resources

The Beat the Bugs community resource was successfully piloted and evaluated.[162] The course was found to be a useful intervention for communities, providing individuals with the knowledge and confidence to manage their own infection and change behaviour around hygiene, self-care and antibiotics.

Based on this success, e-Bug collaborated with Girl Guiding Gloucestershire in 2018 to pilot a Beat the Bugs Challenge Youth Badge for WAAW 2018. Over 60 rainbows, Brownies and Guides participated in an activity day, learning about infections and antibiotics, including the correct way to wash their hands and seeing how far a sneeze can travel. By the end of the event, most of the girls were able to comment on why soap and water was the most effective way to wash hands and that antibiotics were only effective against bacterial infections. The success of this event and the growing interest

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[161] SafeConsume website is at: www.safeconsume.eu

[162] Eley CV, *et al.* A mixed methods pilot of Beat the Bugs : a community education course on hygiene, self-care and antibiotics. *J Infect Prevent* 2018; 19: 278–286.

from other Girlguiding and Scouting organisations across the UK has led to PHE leading on a joint e-Bug and AG national resource pack and Youth badge discussed in future actions.

Future activities and events for professional education and training and public engagement

Professional education and training

- Continue to provide opportunities for antimicrobial pharmacists to develop use of data skills, quality improvement as well as designing interventions usng behaviour change strategies
- host the third health students AMR conference
- continue to increase engagement of healthcare professionals in tackling AMR during WAAW, EAAD and through the Antibiotic Guardian campaign
- continue to provide learning opportunities through webinars
- a series of TARGET workshops will continue to be rolled out across England, these will include:
    - o optomising antibiotic prescribing workshops
    - o orain the trainer workshops
    - o UTIs in the over 65 year olds care home workshops
  - TARGET will also develop a workshop aimed at training the new cohort of practice pharmacists

Public engagement

In 2019, the 'Keep Antibiotics Working' campaign will continue to improve public awareness of AMR to help reduce patient expectation for receiving antibiotics and support GPs in their conversations with patients. This year sees the campaign selected as part of the mandated health campaigns for all GP practices and community pharmacies in England. As such, they will receive tailored resources to support the campaign and there will be additional free resources for community settings, that can be ordered or downloaded from the PHE Campaign Resource Centre.

The next phase of the e-Bug digital strategy review will involve experimenting with several solutions to develop prototypes for a new e-Bug digital service that firstly meets the UK needs and also the Global needs. In addition, the e-Bug team will continue to collaborate with stakeholders to evaluate, disseminate and pilot the Train the Trainer model, in addition to developing new resources relevant to the prevention of infections and food hygiene.

9. Stakeholder engagement

Association of Clinical Oral Microbiologists (ACOM)

Antimicrobial stewardship (AMS) forms a substantial part of the role of Clinical Oral Microbiologists (COMs). Additionally, COMs play key roles in the provision of the following services: diagnostic clinical microbiology; the management of orofacial and maxillofacial infection; and infection prevention, control and decontamination. ACOM has led on many dental AMS projects including those highlighted below:

1. Representing dentistry on the Public Health England (PHE) panel that publishes the Standards for Microbiology investigations (SMI).[163] Standardisation of procedures for the processing, interpretation and reporting of oral microbiology samples ensures the usefulness of the laboratory reports for both individual patient management and surveillance.

2. Leading the UK-wide national audit in Dental Hospitals to identify the patterns of antibacterial prescribing and to inform the development of secondary dental care national AMS programmes.

3. Developing and disseminating resources to facilitate local discussion and training after the first cycle of the national antibacterial prescribing audit in Dental Hospitals. The resource pack included the following:
   A. audit data collection sheets
   B. summary of the national audit
   C. national action plan
   D. individualised hospital feedback
   E. presentation of results
      Invitation to engage with the AMS Clinical Scenario educational pack produced through a collaboration between ACOM and the British Association of Oral Surgeons and the Faculty of General Dental Practice (FGDP)

4. Proposal of a national plan for the development of optimal surveillance of orofacial infection and antimicrobial resistance (AMR). A business case for Clinical Oral Microbiology Regional Centres has been developed and circulated to stakeholders for consideration.

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[163] PHE. Standards for microbiology investigations (UK SMI). Available on-line:
https://www.gov.uk/government/collections/standards-for-microbiology-investigations-smi

British Dental Association

The British Dental Association (BDA) continues to play a central role in national and international efforts to address AMR in dentistry. As the sole dental organisation represented on the Department of Health and Social Care (DHSC) Human Health AMR Stakeholder Group, the BDA was able to collaborate with One Health partners and contribute to the development of the new UK five-year strategy and underpinning 20-year vision.

Supporting dentists to reduce unnecessary prescribing of antibiotics remains a major focus of the BDA's activity. This was highlighted to Parliamentarians at an evidence session co-hosted by the All Party Parliamentary Groups for Dentistry and Oral Health, Pharmacy and Antibiotics in April 2019. The BDA presented a case for funded urgent dental treatment time, to remove a key pressure on dentists to prescribe inappropriately. In conjunction with the FGDP, the BDA also released an updated version of the self-audit tool for dental antimicrobial prescribing, which is available via the BDA website.

The BDA has continued to campaign and influence national policy on the prevention of dental disease and the reduction of waiting lists for child dental general anaesthetics, which are recognised as important measures to drive down antibiotic prescribing in dentistry.

Internationally, the BDA works collaboratively through the Council of European Dentists and the Science Committee of the International Dental Federation (FDI). After participating in a "Call to Action on Antimicrobial Resistance" event in Accra in November 2018, the BDA became a signatory to the Ghana Declaration, which highlights global and national action to address AMR, with a focus on regional co-ordination as a means to accelerate those efforts.

British Society for Antimicrobial Chemotherapy (BSAC)

BSAC is British by name and global by action, supporting healthcare communities internationally through a range of activities that include:

1. The UK Resistance Surveillance Programme, which is the longest running sentinel surveillance scheme (covering respiratory infections and bacteraemia) in Europe and offering a biobank of over 60,000 bacterial isolates to the research community.

2. Hosting a national susceptibility testing centre at Cardiff and actively supporting harmonisation of testing methodologies using the European Committee on Antimicrobial Susceptibility testing (EUCAST) method.

3. Virtual learning platform offering open access education across the globe including:
   A. Massive Open Online Course on AMS, accessed by almost 50,000 learners from 131 countries, with translations in Mandarin, Russian, Spanish and Brazilian Portuguese with a bespoke course for Africa published and a bespoke course for India under consideration.
   B. E-Learning courses on Point Prevalence Surveys, Gram-negative bacterial infections, TARGET prescribing for GPs, outpatient parenteral antibiotic therapy with courses on facilitating uptake of rapid diagnostics, IV to Oral Switch and vaccines under development.
   C. e-Book – Antimicrobial Stewardship: From Principles to Practice

4. Public education through high profile activities such as educating school age children through a high school musical called *The Mould that Changed the World* [mouldthatchangedtheworld.com]

5. Publication of evidence-based guidance and guidelines.

6. Collaborative working with UK and international organisations, working strategically and politically by acting as Secretariat to the All-Party Parliamentary Group on Antibiotics, continuing to work on the Antibiotic Guardian Campaign which the Society originally co-developed and underwrote, and maintaining active membership of the Learned Society Partnership on AMR.

7. Development and launch of *JAC-Antimicrobial Resistance*, an open access peer reviewed journal for educational resources and original research on AMR and stewardship.

In summary BSAC is committed to supporting ESPAUR and implementation of the UK and international strategies on AMR.

Care Quality Commission

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

This year the CQC have updated the antimicrobial prescribing indicators for GP inspections. These are aligned with NHS priorities and are publicly available for all practices on the evidence table part of their reports published on our website Find a family doctor / GP | Care Quality Commission. Inspectors and the specialist advisors who accompany them are trained to probe these questions on inspection.

The CQC has published a report, bringing together findings from its regulatory activity in relation to incidents involving medicines in regulated health and adult social care services, **Medicines optimisation in health and adult social care - Sharing learning from risks and good practice** (Medicines in health and social care | Care Quality Commission). This report highlighted different experiences with medicines, including AMS, across all sectors with the aim of improving practice.

The National Institute for Health and Care Excellence (NICE)

NICE continues to work with PHE to develop antimicrobial prescribing guidelines (APGs) for managing common infections. The guidelines offer evidence-based guidance for primary and secondary care and provide recommendations for appropriate antimicrobial use in the context of tackling AMR. A NICE Committee is producing these guidelines which are jointly badged by both NICE and PHE. In 2018/19 there were eight APGs published on cough (acute), acute exacerbation of chronic obstructive pulmonary disease (COPD), catheter-associated urinary tract infection (UTI), lower UTI, recurrent UTI, prostatitis, acute pyelonephritis and bronchiectasis, with more topics in development. The format of APG content comprises a visual summary of the recommendations, the guideline, the associated evidence review and a summary document that includes content from all APGs alongside PHE's guidance for primary care. Some guidelines also include decision aids to inform shared decision making, such as cystitis – taking an antibiotic. NICE will continue to engage both at a national and regional level with key external stakeholders including PHE, NHS England/Improvement, Health Education England and the CQC to support the wider implementation of the APGs.

To support the appropriate use and stewardship of new antimicrobials at the point of launch, NICE is also developing evidence summaries for antimicrobial prescribing. The first such advice advice, focussing on Ceftazidime-avibactam (Zavicefta), was published in November 2017.

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

NICE collaborated with DHSC colleagues on a research project exploring the concept of undertaking Technology Appraisals of new antimicrobials offering high potential to address unmet need. This project explored the value of enhanced Technology Appraisal of new antimicrobials to inform novel reimbursement model that would delink volume of

prescribing from payment to the pharmaceutical company. The research report, delivered by the DHSC Economic Evaluation Policy Research Unit (EEPRU) at the University of York, was published in October 2018. Drawing on this work NICE, NHS England and DHSC are starting a 'develop and test' project using an enhanced health Technology Assessment of two antimicrobials to inform delinked payment negotiations. Candidate products need to have achieved MA and UK launch in past 2-3 yrs, or a confident expectation of MA by end of 2020.

NICE also produce Medtech Innovation Briefings (MIBs) on new medical devices and diagnostics. These briefings help to avoid the need for organisations to produce similar information locally, saving staff time and resources. MIBs can be quickly developed (in around 15 weeks) on most technologies, and provide factual information for organisations to consider. Other NICE outputs (such as NICE guidelines, diagnostics guidance, or Technology Appraisals) are reserved for technologies that have the potential to deliver substantial benefits, have a high potential to address an unmet need, or where an evaluation of the clinical and cost effectiveness of the technology is beneficial to the NHS. This could be for antimocrobials that have a new mode of action that is less susceptible to development of resistance or for innovative technologies that optimise antibiotic prescribing, for example. Guidance is often supported by adoption tools to encourage the uptake of technologies that are recommended by NICE. NICE's Diagnostics Assessment Programme produces guidance on the use of innovative diagnostic technologies, including those that are relevant to the AMR strategy. Guidance has been published on: Procalcitonin testing for diagnosing and monitoring sepsis; Tests for rapidly identifying bloodstream bacteria and fungi; and Integrated multiplex PCR tests for identifying gastrointestinal pathogens in people with suspected gastroenteritis. Diagnostics guidance is also being developed on 'rapid tests for Group A Streptococcal infections in people with a sore throat'.

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

HealthTech Connect has been developed by NICE with funding from NHS England. It is an online system that aims to improve the identification and development of medical devices, diagnostics and digital health technologies (including those that are relevant to the AMR strategy) that offer benefits to patients and the UK health and care system. Companies add information about their health technology to the system. The information can be accessed by approved accessor organisations that support the development of health technologies, or that have a responsibility for issuing national guidance, advice and policies about health technologies. This may mean that high potential technologies can be expedited through the system faster. More information about HealthTech Connect can be found here.

The NICE Key Therapeutic Topics work includes Antimicrobial Stewardship as a topic. Prescribing data from the comparators developed by NHS Digital are also included to allow organisations to benchmark and assess the degree of variation in key areas of antimicrobial prescribing.

Northern Ireland (NI) section of the stakeholder chapter of the ESPAUR report

The Public Health Agency (Northern Ireland) is continuing to support efforts to reduce MRSA bloodstream infections, Clostridium difficile infections, Gram-negative bacteraemias and antibiotic consumption through the work of the Regional Healthcare-associated Infections and Antimicrobial Stewardship Improvement Board and the Health Protection department. Highlights during 2018 include: public engagement activities which included a social and mass media campaign and engagement with primary and post-primary schools; work on changing prescribing behaviour in primary care using the TARGET resources and a letter from the Chief Medical Officer in NI, and in secondary care through participation in the Antibiotic Review Kit (ARK[164]) study; successful delivery of HCAI & AMR symposium[165] and; the development of a new Trust-facing surveillance system enabling real-time analysis of Gram-negative bacteraemias and monthly updates to ward-level antibiotic consumption data in secondary care. For further details of these and other initiatives and the epidemiology of AMR and AMU in Northern Ireland please refer to our 2018 annual report available on-line.

Public Health Wales (PHW)

The Healthcare Associated Infection, Antimicrobial Resistance and Prescribing Programme (HARP) team, Public Health Wales, provides professional support to the NHS in Wales to reduce the burden of healthcare-associated infections (HCAIs) and AMR across Wales. This is delivered through feedback of surveillance data for antimicrobial usage, resistance and HCAI to the NHS and Welsh Government as well as providing technical expertise in microbiology, AMS and infection prevention and control. The HARP team supports and advises the Wales AMR & HCAI Steering Group, chaired by the Chief Medical Officer for Wales as well as the AMR and HCAI Delivery Boards set up to deliver the UK AMR strategy in Wales.

A number of reports are published by the HARP team, including annual antimicrobial prescribing in primary care, secondary care, resistance in both primary and secondary care, and the annual welsh antimicrobial point prevalence study. For HCAI surveillance,

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[164] Antibiotic Review Kit (ARK). Available on-line: http://www.arkstudy.ox.ac.uk/
[165] Public Health Agency. Healthcare associated infections/ antimicrobial resistance. Information available: https://www.publichealth.hscni.net/directorate-public-health/health-protection/healthcare-associated-infections-antimicrobial-resistanc

the HARP team provide a monthly dashboard of HCAI, as well as a quarterly dashboard of surgical site infections. Wales data is also provided to ECDC.

PHW provides a comprehensive, integrated microbiology service for Wales including a network of diagnostic laboratories, reference laboratories and an active genomics programme. Wales has a dedicated AMR reference laboratory (Specialist Antimicrobial Chemotherapy Unit), which provides molecular confirmation of AMR including carbapenemase producing Gram-negative bacteria. The Unit analyse and report targeted surveillance data on the mechanisms of resistance to third-generation cephalosporins in Gram-negatives and drivers of carbapenem use, every 5 years. Each year the Welsh Health Boards participate in the European Antibiotic Awareness Day, supported by materials and communications from PHW and Welsh Government. More information, including all our published reports, are available on-line.

Royal Pharmaceutical Society

The Royal Pharmaceutical Society (RPS) is committed to continue supporting the UK National Action Plan and 20-year vision, and the global strategy for AMR. The RPS's Chief Executive, President, Executive Team and Expert Groups support this vital work by highlighting the important contribution that pharmacy and pharmaceutical sciences can make to AMR.

The RPS continues to support its members with services and resources to support them in their practice. During 2018, in collaboration with the UK Clinician Pharmacy Association, we delivered interactive workshops in London and Edinburgh, focused on building pharmacists and technicians' confidence in AMS. We also developed a new AMR training programme to support the development of post-foundation pharmacists working in primary and secondary care across London and South East England. Our Science and Research Board and Antimicrobial Expert Advisory Group continue working closely together to provide comments and input across a wide range of work streams relating to antimicrobial utilisation and resistance. We frequently respond to consultations on AMS and management of infections, contribute to national and global AMR campaigns and submit evidence to national initiatives, such as the 2018 Health and Social Care Committee report on AMR.

In February 2019, we hosted our Science and Research Summit, with the Chief Medical Officer Dame Sally Davies opening the day to present the new UK AMR Strategy, and a dedicated session with invited expert speakers covering issues from basic developmental work through stewardship and innovative community engagement.

The RPS continues to work alongside other national groups to support engagement and confidence in optimising the use of antimicrobials. We supported pharmacists applying for the Commonwealth Partnerships for Antimicrobial Stewardship Fleming

Fund grants and continued to encourage all pharmacists to become Antibiotic Guardians.

Scottish One Health Antimicrobial Use and Antimicrobial Resistance' (SONAAR)

Following many years of reporting solely on human antimicrobial use (AMU) and AMR, data relating to resistance among organisms from animals are now published by Health Protection Scotland. This move recognised the importance of the 'One Health' ethos to the sustainable control of AMR. In November 2018, the second 'Scottish One Health Antimicrobial Use and Antimicrobial Resistance' (SONAAR) Report was published. This report describes AMU in humans in Scotland and AMR in a broad range of human and animal infections. These data are used by organisations such as the Scottish Antimicrobial Prescribing Group (SAPG) to inform antimicrobial prescribing policy and develop initiatives for antimicrobial stewardship and the Scottish Microbiology and Virology Network (SMVN) to support the development of testing strategies for NHS diagnostic laboratories in Scotland. The SONNAR 2019 report will be published in November 2019 and will be available on-line.

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Chapter 1: Introduction
Susan Hopkins, Alan Johnson

Chapter 2: Antibiotic Resistance
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Chapter 3: Carbapenemase Producing Enterobacterales
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Chapter 4: Antibiotic Consumption
Amelia Au-Yeung, Berit Muller-Pebody, Susan Hopkins

Chapter 5: NHS Improvement Initiatives
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Chapter 6: Antifungal resistance, prescribing and stewardship
Rebecca Guy, Berit Muller-Pebody, Colin Brown, Elizabeth Johnson, Andy Borman, Susan Hopkins

Chapter 7: Antimicrobial Stewardship
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Chaper 9: Stakeholders
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