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Adaptation of the WHO Essential Medicines List for national antibiotic stewardship policy in England: being AWaRe

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Objectives: Appropriate use of and access to antimicrobials are key priorities of global strategies to combat antimicrobial resistance (AMR). 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). This classification was assessed for antibiotic stewardship and quality improvement in English hospitals.

Methods: Using an expert elicitation exercise, antibiotics used in England but not included in the WHO AWaRe index were added to an appropriate category following a workshop consensus exercise with national experts. The methodology was tested using national antibiotic prescribing data and presented by primary and secondary care.

Results: In 2016, 46/108 antibiotics included within the WHO AWaRe index were routinely used in England and an additional 25 antibiotics also commonly used in England were not included in the WHO AWaRe index. WHO AWaRe-excluded and -included antibiotics were reviewed and reclassified according to the England-adapted AWaRE index with the justification by experts for each addition or alteration. Applying the England-adapted AWaRe index, Access antibiotics accounted for the majority (60.9%) of prescribing, followed by Watch (37.9%) and Reserve (0.8%); 0.4% of antibiotics remained unclassified. There was unexplained 2-fold variation in prescribing between hospitals within each AWaRe category, highlighting the potential for quality improvement.

Conclusions: We have adapted the WHO AWaRe index to create a specific index for England. The AWaRe index provides high-level understanding of antibiotic prescribing. Subsequent to this process the England AWaRe index is now embedded into national antibiotic stewardship policy and incentivized quality improvement schemes.

Introduction

Appropriate use of and access to antimicrobials is a key priority of global strategies to combat antimicrobial resistance (AMR). The WHO recently updated the Essential Medicines List (EML) and proposed a novel metric for antimicrobial use: the AWaRe index.[1] This index classified key antibiotics into three categories: to improve access (Access); to monitor important antibiotics (Watch); and to preserve effectiveness of 'last resort' antibiotics (Reserve).[2]

The Access group consists of first and second choices for the empirical treatment of the most common infection syndromes and antibiotics that should consistently be widely available globally. The Watch group are antibiotic classes considered to have higher toxicity concerns and/or resistance potential. The Reserve group includes new antibiotics and treatment options reserved for complex infections or MDR.

The WHO recently demonstrated the use of the AWaRe index in the analysis and interpretation of global antibiotic consumption data.[3] The AWaRe index was intended for use by WHO member states to estimate the relative use of narrow-spectrum and broad-spectrum antibiotics, to aid evaluation of progress in optimizing antibiotic use and to help in defining goals for future quality

improvement.[4,5] However, country-specific variation in AMR, antibiotic use and treatment guidelines require each country to review this index to ensure it is relevant and optimized for country-specific use.

Antimicrobial prescribing quality measures in England are currently enacted through national incentivized quality improvement goals. A national Quality Premium, an incentivized quality improvement programme for primary care in England, has been in place since the financial year 2015–16, focusing on reducing total and broad-spectrum (cephalosporins, quinolones and amoxicillin/clavulanate) use. There has also been an Antimicrobial Commissioning for Quality and Innovation (CQUIN) scheme in place since 2016/17; these CQUINs have been focused on reducing total, piperacillin/tazobactam and carbapenem consumption in secondary care.[6,7]

Recent antibiotic shortages, particularly of piperacillin/tazobactam in 2017 in England, have not only highlighted the fragility of antibiotic supply chains but also of prescribing quality measures focused on single antibiotics.[8] In this study we assessed the WHO AWaRe index for use as an antimicrobial stewardship quality improvement indicator in England.

Methods

The NHS Business Services Authority and IQVIA provided national-level antibiotic prescribing data for primary and secondary care in England (2011–16). Prescribing data for clinical antibiotics only were included in this study; no topical, anti-parasitic or anti-TB formulations were included. Prescribing data were translated into DDDs using the WHO ATC/DDD index. These data contain all dispensed antibiotic data from public (NHS) patients within primary care (estimated at 95% of total antibiotic prescribing in the community with no data included on private patients, based on comparisons with wholesale data) and public and private patients that are cared for in NHS hospitals (estimated at 95% of hospital prescribing, based on similar prescribing in inpatients and outpatients in the private sector for bed base and patients reviewed). Almost 15 000 general practices or primary care sites and 154 acute hospital trusts (management organizations for secondary care), representing more than 370 clinical hospitals or hospital outpatient locations, were included in the dataset with some variation over time as primary care practices and hospital sites opened and closed.

The full list of antibiotics used is available in Table S1 (available as Supplementary data at *JAC* Online). Mid-year population estimates were provided by the Office for National Statistics (ONS). Hospital admission episodes were determined from monthly submissions from NHS hospitals to NHS Digital. Data were analysed using Microsoft Excel and Stata V15.

The AWaRe index was adapted for national use in England by expert elicitation with members of the Department of Health and Social Care (DHSC) Advisory Committee on Antibiotic Prescribing, Resistance and Healthcare-Associated Infection (APRHAI) and oversight group for the English Surveillance Programme for Antimicrobial Use and Resistance (ESPAUR). All antibiotics in current guidelines or which comprised greater than 0.2% of total DDD consumption in England were reviewed and assessed against the framework for decision-making provided in the WHO Report on Surveillance of Antibiotic Consumption.[3] Once reviewed, PHE analysed the data and presented results to the expert group for further discussion using two key metrics: DDDs per 1000 inhabitants per day for comparing antibiotic use in primary and secondary care and DDDs per 1000 admissions for comparisons between hospital organizations. DDDs per 1000 admissions were log-transformed in order to normalize the values and develop funnel plots to determine variation and outliers in hospital prescribing across the England AWaRe index categories. Finally, national quality improvement ambitions for prescribing of antibiotics from each of the three AWaRe groups were developed based on the adapted England AWaRe index and were proposed to the UK government for implementation within the NHS in England.

Results

In 2016, the total antibiotic consumption in England was 21.5 DDDs per 1000 inhabitants per day with 91% of prescribing occurring in primary care. Forty-six antibiotics included within the WHO AWaRe index were routinely used in England. However, a further 25 antibiotics also commonly used in England were not included in the AWaRe index, accounting for 12.4% of total prescribing volume (Figure 1).

Adaptation of the AWaRe list for the UK was achieved using an expert elicitation process for antibiotics that were not in the WHO AWaRe categories. In total the status of 37 antibiotics was determined or changed; the rationale for each of these changes is outlined in Table 1. Changes were made predominantly in relation

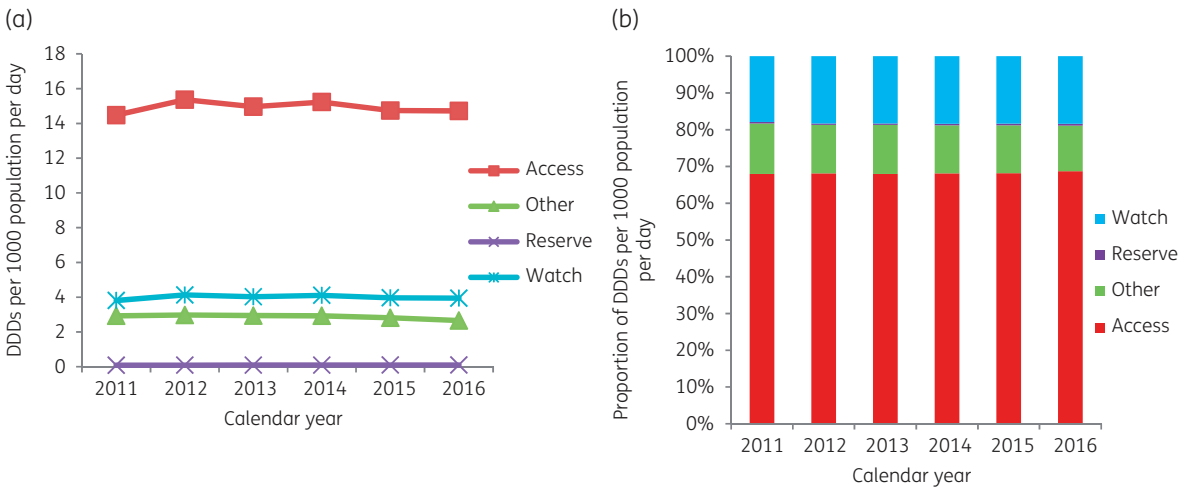

Figure 1. (a) Antibiotic consumption in England (primary and secondary care) as DDDs per 1000 population per day by WHO AWaRe category. (b) Proportion of antibiotic DDDs per 1000 population per day in England (primary and secondary care) by WHO AWaRe category. Other, antibiotics not included in the WHO AWaRe index. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

Table 1. Recategorization of antibiotics within the AWaRe index for use in English national stewardship policy

ATC name	ATC code	AWaRe WHO	AWaRe England	Rationale for movement
Amikacin	J01GB06	Access	Watch	antibiotic used for resistant Gram-negative infections
Amoxicillin and enzyme inhibitor	J01CR02	Access	Watch	to avoid overuse as resistance increasing and associated with increased risk of *C. difficile* infections
Ampicillin combinations	J01CA51	Other	Access	similar category as amoxicillin; rare use
Cefaclor	J01DC04	Other	Watch	associated with increased risk of *C. difficile* infections
Cefadroxil	J01DB05	Other	Watch	associated with increased risk of *C. difficile* infections
Cefalexin	J01DB01	Access	Watch	associated with increased risk of *C. difficile* infections
Cefamandole	J01DC03	Other	Watch	associated with increased risk of *C. difficile* infections
Cefazolin	J01DB04	Access	Watch	associated with increased risk of *C. difficile* infections
Cefoxitin	J01DC01	Other	Watch	associated with increased risk of *C. difficile* infections
Cefprozil	J01DC10	Other	Watch	associated with increased risk of *C. difficile* infections
Cefradine	J01DB09	Other	Watch	associated with increased risk of *C. difficile* infections
Cefuroxime	J01DC02	Other	Watch	associated with increased risk of *C. difficile* infections
Ceftazidime and enzyme inhibitor	J01DD52	Watch	Reserve	novel combination reserved for treatment failures
Chloramphenicol	J01BA01	Access	Watch	second-line antibiotic, use in penicillin allergy
Clindamycin	J01FF01	Access	Watch	associated with increased risk of *C. difficile* infections
Dalbavancin	J01XA04	Watch	Reserve	novel antibiotic reserved for treatment failures and OPAT
Doripenem	J01DH04	Watch	Reserve	reserved to conserve use for resistant Gram-negative infections
Ertapenem	J01DH03	Watch	Reserve	reserved to conserve use for resistant Gram-negative infections
Fosfomycin (oral)	J01XX01	Other	Access	narrow spectrum, recommended for uncomplicated UTI
Fusidic acid	J01XC01	Other	Access	narrow spectrum
Imipenem	J01DH51	Watch	Reserve	reserved to conserve use for resistant Gram-negative infections
Lymecycline	J01AA04	Other	Watch	used for acne, alternative non-antimicrobial drugs available
Meropenem	J01DH02	Watch	Reserve	reserved to conserve use for resistant Gram-negative infections
Minocycline	J01AA08	Other	Watch	used for acne, alternative non-antimicrobial drugs available
Neomycin	J01GB05	Other	Access	not routinely used in England, monitor carefully for change in use
Oxytetracycline	J01AA06	Other	Watch	used for acne, alternative non-antimicrobial drugs available
Piperacillin	J01CA12	Other	Watch	avoid overuse as resistance increasing
Pivmecillinam	J01CA08	Other	Access	narrow spectrum, recommended for uncomplicated UTI
Pristinamycin	J01FG01	Other	Watch	not routinely used in England, monitor carefully for change in use
Quinupristin	J01FG02	Other	Watch	not routinely used in England, monitor carefully for change in use
Telavancin	J01XA03	Watch	Reserve	not routinely used in England, monitor carefully for change in use
Temocillin	J01CA17	Other	Watch	antibiotic used for resistant Gram-negative infections
Tetracycline	J01AA07	Other	Access	narrow spectrum, recommended in treatment guidelines
Ticarcillin	J01CA13	Other	Watch	not routinely used in England, monitor carefully for change in use
Tobramycin	J01GB01	Other	Watch	antibiotic used for resistant Gram-negative infections
Tetracycline combinations	J01AA20	Other	Watch	used for acne, alternative non-antimicrobial drugs available

Any antibiotics categorized as both Access and Watch within the WHO AWaRe index were automatically classified as Watch antibiotics for UK stewardship purposes. The rationale for all other reclassifications is presented in this table. OPAT, outpatient parenteral antimicrobial therapy.

to: (i) antibiotics recommended in national guidance; (ii) policies to reduce the risk of *Clostridioides* (*Clostridium*) *difficile* infection; (iii) the presence of emerging or established AMR; or (iv) preserving the use of certain antibiotics for MDR infections. In addition, given a national antibiotic stewardship policy priority to reduce use of piperacillin/tazobactam and carbapenems, these were moved from Access to Watch and Reserve categories, respectively.

Using the modified England AWaRe index, Access antibiotics accounted for the majority (60.9%) of prescribing across all English healthcare sectors in 2016, compared with 68.7% using the WHO AWaRe index, followed by Watch (37.9% versus 18.4%), Reserve (0.8% versus 0.4%) and Other (0.4% versus 12.4%) (Table 2 and Figure 1b). However, these results primarily reflect antibiotics dispensed in community or primary healthcare settings, where more than 80% of prescribing occurs. Furthermore, the proportion of antibiotics within the Access category increased year on year from 2011 to 2016 from 60.2% to 63.3% of total prescribing (5% increase). Conversely, antibiotics prescribed from the Watch and Reserve categories declined by 8% (from 39.2% to 36.0% of total

Table 2. Proportion of DDDs per 1000 population prescribed within AWaRe England categories across healthcare sectors over time

	Year	All England (%)	Primary care (%)	Secondary care (%)
Access	2011	58.77	60.17	51.63
	2012	59.24	60.82	50.80
	2013	59.05	60.76	50.38
	2014	59.39	61.17	50.46
	2015	59.81	61.90	49.72
	2016	60.88	63.29	49.72
Watch	2011	40.24	39.18	45.65
	2012	39.82	38.58	46.39
	2013	39.95	38.65	46.56
	2014	39.58	38.25	46.26
	2015	39.05	37.45	46.79
	2016	37.94	36.01	46.86
Reserve	2011	0.70	0.33	2.61
	2012	0.70	0.32	2.73
	2013	0.76	0.32	2.97
	2014	0.78	0.30	3.21
	2015	0.83	0.29	3.43
	2016	0.83	0.28	3.33
Other	2011	0.29	0.33	0.12
	2012	0.25	0.28	0.09
	2013	0.24	0.27	0.09
	2014	0.25	0.29	0.07
	2015	0.31	0.36	0.06
	2016	0.36	0.42	0.08

prescribing) and 13% (from 0.33% to 0.28% of total prescribing), respectively. This coincided with a policy focus and corresponding response in the primary and community healthcare sector on reducing broad-spectrum antibiotics.

In the acute hospital sector, unsurprisingly, more Watch and Reserve antibiotics were used; in 2016, Access antibiotics accounted for the majority (49.7%), followed by Watch (46.9%), Reserve (3.3%) and Other (0.1%) (Table 2). In addition, between 2011 and 2016 hospital prescribing within the Access category decreased by 4%, the Watch category increased by 3% and the Reserve category increased by 28% though still remained <3% of total prescribing.

There was a high degree of variation in prescribing between hospitals within each AWaRe category. In particular, specialist hospitals, predominantly cardiothoracic, haematology/oncology and paediatric monospecialities, were high outliers in the use of Reserve antibiotics and tended to use fewer Access antibiotics. In addition, there remains variation in total prescribing per 1000 admissions across the country, highlighting potential for quality improvement nationally (Figure 2); these funnel plots demonstrate the large variation in antibiotic use across hospital organizations, by England AWaRe category and hospital organization type. These data suggested that there was an opportunity to reduce unwarranted variation in antimicrobial prescribing in secondary care; monitoring of the proportion of antibiotic use in each AWaRe category was therefore recommended to form part of future quality improvement incentive schemes.

Discussion

The AWaRe index supports high-level understanding of antibiotic prescribing, essentially providing a summary of broad- and narrow-spectrum prescribing as a proxy measure for antibiotic prescribing quality. The WHO has acknowledged that the EML AWaRe index will require local adaptation and further revision over time.[2] The WHO published their first global assessment of antimicrobial use in 2018, recognizing the limitations in the data that were available.[3] However, within this publication, the antibiotics that were not included in the original index varied in consumption across countries from 1% to 40%, limiting direct comparisons of results.

We have adapted the AWaRe index for antibiotic stewardship purposes in England using national- and hospital-level data to include antibiotics pertinent to use in English healthcare settings. Although the greatest volume of antibiotics is prescribed in community healthcare settings in England,[8] this sector prescribed a higher proportion of Access antibiotics and a lower proportion of Watch and Reserve antibiotics than the acute secondary care setting. The national Quality Premium for primary care has focused on a reduction in total prescribing and also prescribing of cephalosporins, quinolones and amoxicillin/clavulanate, all of which are in the Watch England AWaRe category. National prescribing data suggest that a relatively high and increasing proportion of narrow-spectrum antibiotics are prescribed in primary care. The variation in the use of Access antibiotics between primary and secondary care most likely relates to different patient acuity, complexity and the prevalence of MDR bacteria in these care settings.

NHS acute hospitals prescribed a lower proportion of Access antibiotics and higher proportions of Watch and Reserve antibiotics than the primary care setting. In addition, a recent study has shown an association between NHS acute hospitals with stronger 'process' elements within their antimicrobial stewardship programmes and a lower proportion of antibiotic prescribing from within the Reserve category.[9] Therefore, application of the AWaRe index in national stewardship initiatives has been focused on the acute secondary care setting.

In April 2018, NHS England introduced a new quality improvement indicator for NHS acute hospitals to achieve in 2018–19. These organizations have been asked to increase the proportion of antibiotic usage within the Access group of the AWaRe (England) index such that the Access group comprises ≥55% of total antibiotic consumption (expressed as DDDs per 1000 admissions) or an absolute increase of three percentage points from 2016 baseline levels.[7] This variation in targets related to their baseline allows them to deliver a quality improvement based on their own baseline rather than comparing them with their peers, as patient-level antibiotic consumption and thus appropriate adjustment is not yet available for national monitoring. Furthermore, in January 2019 the UK government announced a new 5 year national action plan for AMR (2019–24), which included a target for a 10% reduction in the use of Reserve and Watch antibiotics in hospitals from a 2017 baseline.[10]

A disadvantage of any such measure is that they do not take into consideration the age and sex mix of populations of patients served by hospitals, and other factors such as deprivation and complexity of care, that can drive hospital antibiotic prescribing. Nonetheless as each hospital is required to improve from its own baseline levels this is consistent with improving the quality

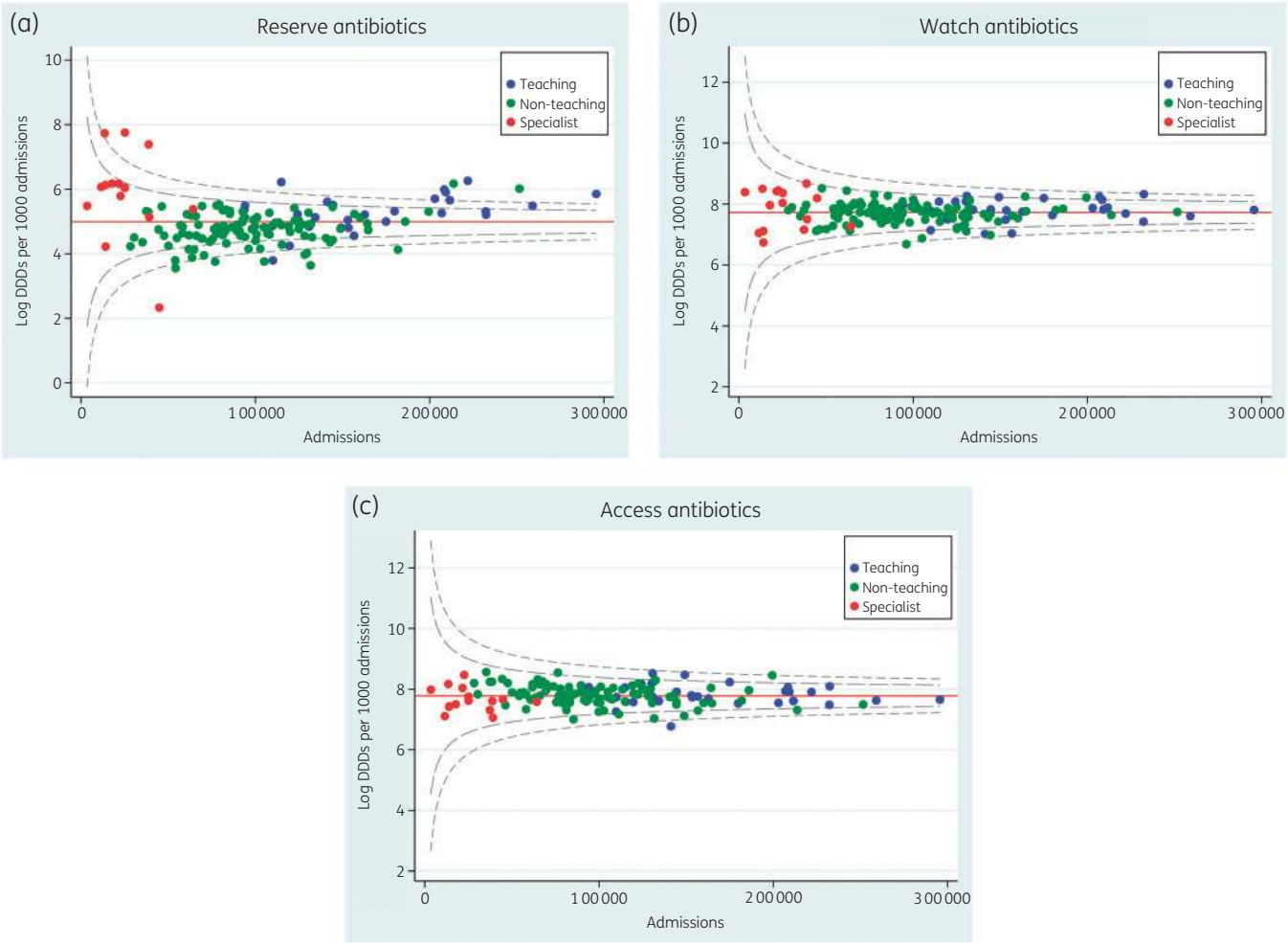

Figure 2. NHS acute hospital-level variation in total prescribing and by hospital type and AWaRe (England) index category in 2016. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

of antibiotic prescribing in each hospital. Further consideration is required to adapt the AWaRe index for use in specialist healthcare settings, including an improved understanding of case-mix. However, until routine electronic prescribing of antibiotics is available nationally, there is limited work that can be performed in this area.

The proportion of total antibiotic prescribing from the Access category of the AWaRe index (as modified for England) is published as an indicator for each hospital on the PHE open access data portal Fingertips;[11] thereby allowing NHS hospitals to track progress towards their CQUIN quality improvement goals and enabling comparisons and shared learning with their selected peers (http://fingertips.phe.org.uk/profile/amr-local-indicators). In England, multimodal activities are recommended to improve antimicrobial stewardship activities including development of national and local guidelines, antimicrobial restriction, selective reporting of antimicrobial susceptibility results, prescriber education, audit and feedback.[12]

We recommend that countries should review the AWaRe categorizations in their country, potentially using similar methodology, and consider which antibiotics from each category should be moved into the relevant category based on resistance profiles and antibiotic use. Quality improvement methodology can then be applied to organizations to improve antimicrobial stewardship and, in particular, preserve antibiotics in the Watch and Reserve categories.

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Primary care prescribing data are reported monthly as open access data from the NHS Business Services Authority.

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Transparency declarations

None to declare.

Supplementary data

Table S1 is available as Supplementary data at *JAC* Online.

References

1 WHO. *WHO Model List of Essential Medicines, 20th List (March 2017)*. 2017. https://www.who.int/medicines/publications/essentialmedicines/20th_EML2017.pdf?ua=1.

2 Sharland M, Pulcini C, Harbarth S *et al*. Classifying antibiotics in the WHO Essential Medicines List for optimal use—be AWaRe. *Lancet Infect Dis* 2018; **18**: 18–20.

3 WHO. *WHO Report on Surveillance of Antibiotic Consumption*. 2018. https://www.who.int/medicines/areas/rational_use/oms-amr-amc-report-2016-2018/en/.

4 McGettigan P, Roderick P, Kadam A *et al*. Access, Watch, and Reserve antibiotics in India: challenges for WHO stewardship. *Lancet Glob Health* 2017; **5**: e1075–6.

5 Hsia Y, Sharland M, Jackson C *et al*. Consumption of oral antibiotic formulations for young children according to the WHO Access, Watch, Reserve (AWaRe) antibiotic groups: an analysis of sales data from 70 middle-income and high-income countries. *Lancet Infect Dis* 2019; **19**: 67–75.

6 NHS England. *Commissioning for Quality and Innovation (CQUIN) Guidance for 2016/17*. https://www.england.nhs.uk/nhs-standard-contract/cquin/cquin-16-17/.

7 NHS England. *Technical Guidance for Refreshing NHS Plans 2018/19 Annex A: Commissioning for Quality and Innovation (CQUIN) Indicator Specification 2017-2019*. https://www.england.nhs.uk/publication/commissioning-for-quality-and-innovation-cquin-guidance-for-2017-2019/.

8 PHE. *English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR) Report* 2018. https://www.gov.uk/government/publications/english-surveillance-programme-antimicrobial-utilisation-and-resistance-espaur-report.

9 Scobie A, Budd E, Harris RJ *et al*. Antimicrobial stewardship: an evaluation of structure and process and their association with antimicrobial prescribing in NHS hospitals in England. *J Antimicrob Chemother* 2019; **74**: 1143–52.

10 HM Government. *Tackling Antimicrobial Resistance 2019-2024: The UK's Five-Year National Action Plan*. 2019. https://www.gov.uk/government/publications/uk-5-year-action-plan-for-antimicrobial-resistance-2019-to-2024.

11 Johnson AP, Muller-Pebody B, Budd E *et al*. Improving feedback of surveillance data on antimicrobial consumption, resistance and stewardship in England: putting the data at your Fingertips. *J Antimicrob Chemother* 2017; **72**: 953–6.

12 NICE. *Antimicrobial Stewardship: Systems and Processes for Effective Antimicrobial Medicine Use*. 2015. https://www.nice.org.uk/guidance/ng15.