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Impact of COVID-19 pandemic on the utilization and quality of antibiotic use in the primary care setting in England, March 2019–March 2023: a segmented interrupted time series analysis of over 53 million individuals

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ABSTRACT

Background: Amid the COVID-19 pandemic, we evaluated the short-term impact of COVID-19 on antibiotic use in primary care in England, focusing on both antibiotic quantity (overuse) and quality (misuse) of use.

Research design and methods: A population-based segmented interrupted analysis was applied on monthly dispensed antibiotics prescriptions using the Prescription Cost Analysis dataset (March/2019–March/2023). The quantity was assessed using number of items dispensed per 1000 inhabitants (NTI) and defined daily doses per 1000 inhabitants per day (DID), while quality was evaluated using WHO's Access Watch Reserve (AWaRe) classification, the proportion of '4C' antibiotics and the percentage of broad- to narrow-spectrum antibiotics.

Results: Findings indicate 8.6 (17.2%) and 0.4 (2.6%) increase in the NTI and DID, respectively, with a statistically significant uptick in trend noted after the second lockdown (β_5) for 'total antibiotics' for NTI only ($\beta_5 = 1.6$; 95% CI:0.17, 3.1). Quality assessment showed an increase in 'Access' antibiotics from 77% in March/2019 to 86% in March/2023; however, COVID-19 had no significant impact on WHO AWaRe classes.

Conclusion: COVID-19's impact on antibiotic use quality and quantity appeared to be minimal, though an increase in utilization post-second lockdown coincided with healthcare system recovery. This suggests a nuanced impact of the pandemic, highlighting the importance of continued antimicrobial stewardship.

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1. Introduction

Antimicrobial resistance (AMR) poses a significant global public health challenge, primarily fueled by the inappropriate use of antibiotics, encompassing both overuse and misuse [1,2], linked to increased mortality, morbidity, and costs [1]. As a result, optimizing antimicrobial use, particularly in ambulatory care where the majority of utilization occurs, becomes a pivotal focus for antimicrobial stewardship programs (ASPs). This involves promoting judicious prescribing of antibiotics from the World Health Organization (WHO) 'Access' list when appropriate and concurrently reducing the prescription of broad- versus narrow-spectrum antibiotics to mitigate AMR [2–4]. The WHO Access Watch Reserve (AWaRe) classification categorizes antibiotics into three groups. Antibiotics in the 'Access' group are essential antibiotics with low-resistance potential, representing the first or best choice in their class for most patients. Those in the 'Watch' group have higher resistance potential and are recommended as first- or second-choice treatments for a limited number of infections. Those in the 'Reserve' groups are seen as 'last-resort' options and should be reserved for multi-drug-resistant infections when all other alternatives have failed [4]. In view of their greater resistance potential, antibiotics in the 'Watch' and 'Reserve' groups should be more carefully monitored, with ASPs instigated where there are concerns [3]. By guiding antibiotic prescription policies, healthcare practices, and ASPs, the AWaRe framework and Book aim to reduce the spread of AMR through promoting the rational use of antibiotics [4–7]. Additionally, there is an emphasis on minimizing patients' exposure to broad spectrum antibiotics (namely "4Cs" – cephalosporins, clindamycin, co-amoxiclav, or fluoroquinolones) as they are associated with increasing risk of *Clostridioides difficile* infections [8]. However, the effectiveness of ASP activities has encountered substantial challenges during the COVID-19 pandemic [9–11]. In the United Kingdom (UK), routine ASP activities witnessed a notable 64% reduction during the pandemic,

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primarily attributed to the implications of social distancing measures and staff reallocation [11].

Concerns regarding the disruption of ASP activities during the pandemic are heightened by the frequent prescription of antibiotics to patients hospitalized with COVID-19 even in the absence of substantial evidence supporting bacterial co-infections or secondary infections [12–14]. The likelihood of prescribing common respiratory antibiotics for COVID-19-related pneumonitis rose, primarily attributed to the shared clinical features between COVID-19 and bacterial pneumonia [14]. This situation was exacerbated by guidelines in several countries recommending antibiotic prescriptions, despite COVID-19 being a viral infection [15].

As mentioned, the primary care setting is recognized as the principal domain for antibiotic dispensing, with approximately 90% or more of antibiotics prescribed in this setting [16,17]. A comparable proportion of antibiotic prescribing is evident in the primary care setting in the UK, standing at 80%, making it an important setting to monitor to ensure that antibiotics are being prescribed appropriately. The impact of COVID-19 on antibiotic utilization in ambulatory care, as opposed to hospitals, has yielded mixed findings [18]. Several Low-Middle Income Countries (LMICs) in Africa, Asia, and Central and Eastern Europe reported increased antibiotic usage during the pandemic, measured mainly as number of defined daily doses per 1000 inhabitants per day [19,20]. High-income countries, however, have shown a different scenario [18].

Australia, the United States (US), and several European countries, including France, Italy, the Netherlands, Portugal, and Spain showed a reduction in antibiotic use during COVID-19 [21–24]. In the UK, the situation mirrors the varied results seen globally. McCloskey et al. (2023) [25] demonstrated an overall downward trend in antibiotic utilization from 2014 to 2022, aligning with governmental and health authority initiatives to curb unnecessary antibiotic prescribing [26]. However, there was an increase during the initial stages of the pandemic before reverting to pre-pandemic levels. This contrasts with Armitage and Nellums (2021), who reported a 15.5% reduction in antibiotic prescriptions in England between April and August 2020 compared to the same period in 2019 [27]. Hussain et al. (2021) also noted a 13.5% reduction in antibiotic use from March to September 2020 compared to 2019, especially for respiratory tract infections [28].

In Scotland, antibiotic prescriptions increased by 44% in March 2020 compared to March 2019, then decreased by 34% in April and May 2020 due to the impact of social distancing and other restrictions implemented to slow the spread of COVID-19 [29]. Given the varied impact of COVID-19 on antibiotic prescribing, including within the UK, and ongoing concerns about rising AMR rates, there is an urgent need to evaluate the pandemic's impact on not only the quantity of antibiotic use but also the quality of antibiotic prescribing in England's primary care settings. This includes evaluating the effects of the pandemic over a prolonged duration to robustly measure any trends. Notably, the latest antibiotic surveillance report from England, examining antibiotic usage, only encompasses data up to 2022 [30]. We believe this is the first study to fully assess antibiotic use patterns in terms of both the quantity and quality of prescribing in primary care in England, which assesses the short-term impact of COVID-19 the pandemic beyond 2022 and over 36 months after the first national lockdown in March 2020. The findings can be used to guide future initiatives if pertinent.

2. Methodology

2.1. Study design and data sources

This was a repeated cross-sectional study of monthly trends in the quantity and quality of antibiotics use in primary care settings in England using the Prescription Cost Analysis (PCA) dataset [31] (a publicly available, aggregated dataset) from March 2019 to March 2023. Primary care is responsible for the predominant share of antibiotic prescriptions in the United Kingdom accounting for approximately 80.0% of all antibiotics prescribed in England during 2020 [30].

2.2. Study cohort/subjects

This study covered all systemic antimicrobial prescriptions, classified based on the British National Formulary (BNF) [32]. The BNF classifies antibiotics into 11 categories, namely the penicillins, cephalosporins and other beta-lactams, tetracyclines, aminoglycosides, macrolides, clindamycin, 'other antibacterials,' sulfonamides and trimethoprim, metronidazole, quinolones, and urinary-tract infection antibiotics (Supplementary File 1).

2.3. Study outcomes

The primary study outcomes were the quantity and quality of antibiotic use. Quantity of antibiotic use was measured using two well established and validated metrics, namely the monthly number of items dispensed/1000 inhabitants (NTI) and the monthly defined daily doses (DDDs)/1000 inhabitants/day (DID) [33].

In terms of NTI, the monthly total number of items dispensed was obtained for each antibiotic class during the study period, which was then divided by the estimated mid-year population size (obtained from the UK Office of National Statistics [34]) and subsequently multiplied by 1000 to account for the annual variation in the population size over the years.

The DDD is as 'an average maintenance dose of the drug when used on its main indication in adults' [33] and considered as a standard international drug utilization metric [33]. However, we are aware that DDDs for antibiotics can underestimate usage in children. To calculate the DID, firstly, we calculated the total monthly amount (mg) dispensed for each antimicrobial by multiplying the total monthly quantity dispensed by the strength of each antimicrobial. Subsequently, the amount was divided by the defined WHO DDD value [33]. These values were subsequently divided by the estimated mid-year point population size, multiplied by 1000 and divided by number of days in the month [35,36].

For the quality of antibiotics use, three quality indicators were used. Firstly, we used the WHO AWaRe and UK AWaRe modified list [3]. Based on this list, antibiotics were classified into the respective 'Access,' 'Watch' and 'Reserve' groups [4–7], with a minimum target of 60% for 'Access' antibiotics versus total antibiotics [37]. The second measure was the proportion of broad-spectrum antibiotics as a proportion of the total antibiotics based on the BNF classification [32], using a conservative approach to defining broad-spectrum antibiotics, considering as such those explicitly labeled as broad-spectrum in the BNF or those effective against a range of bacteria, including gram-positive, gram-negative, and/or anaerobic bacteria (Supplementary File 2). Finally, the proportion of '4C's' antibiotics (cephalosporins, co-amoxiclav, quinolone, and clindamycin) [8] were used in terms of the NTI. The latter two metrics were used to enable comparisons with older studies before the emerging use of the recent WHO AWaRe as a commonly used quality indicator.

2.4. Data analysis

In this study, the utilization trends were described using descriptive statistics. Absolute and relative percentage changes were used to present the changes in the utilization trends over the study period. For assessing the average monthly change in use over time, a trend analysis using linear regression was used. Subsequently, a segmented regression analysis of interrupted time series [38] was conducted to assess the impact of COVID-19. The results in terms of regression coefficients along with their 95% confidence intervals (CI) and p-values were presented. Five regression coefficients were presented and included β_1 (the baseline trend covering the period from March 2019 to February 2020 representing the change in the study outcomes that occurs with each month before the intervention), β_2 (the level change immediately after the first lockdown in March 2020), β_3 (the time trend change after the first lockdown), β_4 (the level change immediately after the second lockdown in November 2020) and β_5 (the time trend change after the second lockdown). It is worth noting that the first COVID-19 lockdown (announced on 23 March 2020 and officially lifted on 4 July 2020) and second COVID-19 lockdown (announced on 5 November 2020 and lifted on 2 December 2020) in England were not identical in their restrictions. The second lockdown was less restrictive reflecting adaptations to the evolving understanding of the virus, its spread, and the impact of measures previously implemented [39]. The data analysis was conducted using STATA, 13 (United States, California).

3. Results

3.1. Utilization trends

3.1.1. Monthly number of items dispensed/1,000 inhabitants and DDD/1000 inhabitants/day

Over the study period, there were 2,331 NTI of antibiotics, with penicillin being the most frequently prescribed antibiotic (1150 items/1000 inhabitants, 49%), followed by tetracycline antibiotics (315 items/1000 inhabitants, 14%). Generally, there was an increase of 8.60 (17.2%) in the trend of the NTI for all antibiotics, with a statistically significant monthly average change of 0.20 (95% CI: 0.05, 0.34) (Table 1 and Figure 1(a)). When analyzing the trends for individual antibiotics, a declining trend was identified for several antibiotic classes. These included the aminoglycosides (0.002, −23.21%), clindamycin (0.004, −5.7%), quinolones (0.13, −13.7%), sulphonamides/trimethoprim (0.11, −7.5%), and the metronidazole group (0.06, −2.8%). The remaining antibiotic classes showed an increasing trend, i.e. the penicillins (5.60, 21.4%), cephalosporins (0.3, 36.8%), and the tetracyclines (2.0, 30.7%) (Table 1 and Figure 1(a)). In terms of the average monthly changes, compared to the other antibiotic classes, penicillins showed the highest increase with 0.14 items dispensed/1000 inhabitants (95% CI: 0.036, 0.24) (Table 1).

Similarly, for DID, there was an increase of 0.4 (2.6%) in the trend of total antibiotics; however, with a non-statistically significant monthly average change of 0.024 (95% CI: −0.001, 0.05). Penicillins showed an increase of 1.09 (21.4%) with a significant monthly average change of 0.024 (95% CI: 0.005, 0.42), and cephalosporins had a 0.06 (36.80%) increase. On the other hand, negative trends were observed for other antibiotic classes including sulfonamide and trimethoprim (0.04, −7.49%) and the aminoglycosides (0.01, −23.21%); however, acknowledge their low utilization levels (Table 1 and Figure 1b).

The segmented regression analysis revealed that preceding the initial lockdown, there was a non-significant upturn in the baseline trend of NTI for all antibiotics ($\beta_1 = 0.2$; 95% CI: −0.05, 0.34). Simultaneously, there was a non-significant reduction in the level immediately after the first ($\beta_2 = -7.1$; 95% CI: −17.5, 3.5) and second ($\beta_4 = -1.5$; 95% CI: −0.98, 6.820) lockdowns; however, a significant increase in the time trend after the second lockdown ($\beta_5 = 1.6$; 95% CI: 0.17, 3.1) (Table 2). The formal pattern extended to the penicillins, tetracyclines, and antibiotics for 'urinary tract infections.' A noteworthy reduction in the baseline trend was observed for clindamycin ($\beta_1 = -0.003$; 95% CI: −0.001, −0.0004). Additionally, a significant decrease was noted in the level of metronidazole being dispensed post the second lockdown ($\beta_4 = -0.18$; 95% CI: −0.33, −0.04), accompanied by a negative trend post the second lockdown ($\beta_5 = -0.042$; 95% CI: −0.073, −0.011) (Table 2).

Similarly, regarding the DID, there was a non-significant decline in the baseline trend of the total antibiotics dispensed ($\beta_1 = -0.07$; 95% CI: −0.29, 0.15) as well as in their levels after the first and second lockdowns (Table 2). However, there was a non-significant increase in the trend after the second lockdown ($\beta_{5=}$ 0.32; 95% CI: −0.09, 0.72) for all antibiotics (Table 2).

3.2. Quality indicators of antibiotic use

3.2.1. WHO AWaRe classification

The proportion of prescribed antibiotics in the 'Access' group showed the highest increase during the study period (8.15%, 10.5%), from ~ 77% in March 2019 to ~ 86% in March 2023, with a statistically significant increase in the monthly average change of 0.06% (95% CI: 0.02, 0.09) (Table 1), while antibiotics in the 'Watch' and 'Reserve' groups decreased by 0.3% (1.34%) and 0.002% (2.7%), respectively (Table 1 and Figure 2(a)). In terms of the impact of COVID-19, there was a statistically significant increase in the level of 'Watch' and 'Reserve' antibiotics immediately after the first lockdown ($\beta_2 = 2.07$; 95% CI:

Table 1. Absolute, relative, and average monthly changes for the number of items dispensed/1000 inhabitants, Defined Daily Doses/1000 inhabitants/day, and quality indicators during the study period from March 2019 to March 2023.

	Absolute change	Relative change	Average monthly change (95%CI)	P-value**
Number of items dispensed/1000 inhabitants				
Aminoglycosides	−0.002	−23.21	−0.0001 (0.0001, −0.00004)	<.0001
Cephalosporins and other 'non-penicillin' beta-lactams	0.30	36.8	0.005, (0.003, 0.006)	<.0001
Clindamycin	−0.004	−5.70	−0.0003(−0.0005, −0.0001)	0.005
Macrolides	0.24	−0.46	0.007 (−0.011, 0.03)	0.431
Metronidazole	−0.06	−2.80	−0.004 (−0.007, −0.002)	0.002
Penicillin	5.60	21.40	0.14 (0.036, 0.24)	0.008
Quinolones	−0.13	−13.70	−0.002 (−0.003, −0.001)	<.0001
Sulfonamides and trimethoprim	−0.11	−7.50	0.004 (−0.003, 0.011)	0.311
Tetracyclines	1.95	30.70	0.041 (0.015, 0.07)	0.002
Urinary tract infections*	0.54	9.11	0.007 (0.0003, 0.0131)	0.041
'Others antibacterials'*	0.21	69.90	0.005 (0.004, 0.005)	<.0001
Total antibiotics	8.60	17.21	0.20 (0.05, 0.34)	0.0089
Number of Defined Daily Doses/1000 inhabitants/day				
Aminoglycosides	−0.001	−23.21	−0.0001 (−0.0001, −0.00001)	0.0017
Cephalosporins and other 'non-penicillin' beta-lactams	0.06	36.80	0.001 (0.0004, 0.001)	0.0001
Clindamycin	−0.002	−5.70	−0.0001 (−0.0002, −0.00001)	0.016
Macrolides	−0.01	−0.50	−0.006 (−0.014, 0.003)	0.187
Metronidazole	0.001	0.21	−0.001 (−0.001, 0.0002)	0.136
Penicillin	1.09	21.40	0.024 (0.005, 0.042)	0.0145
Quinolones	−0.04	−13.74	−0.001 (−0.001, −0.0003)	0.0002
Sulfonamides and trimethoprim	−0.04	−7.49	−0.003 (−0.005, −0.001)	0.0144
Tetracyclines	0.05	1.26	0.006 (−0.001, 0.014)	0.098
Urinary tract infections*	−0.79	−34.85	−0.003 (−0.001, 0.006)	0.116
'Others antibacterials'*	0.08	69.90	0.001 (0.0002, 0.003)	0.081
Total antibiotics	0.40	2.60	0.024 (−0.009, 0.05)	0.4
Quality indicators				
AWaRe				
Access	8.15	10.5	0.06 (0.02, 0.09)	0.007
Watch	−0.30	−1.34	−0.07 (−0.09, −0.05)	<.001
Reserve	−0.002	−2.70	−0.001 (−0.001, −0.0003)	<.001
'4C' Antibiotics				
Co-Amoxiclav	−0.22	−5.70	−0.009 (−0.02, −0.001)	0.015
Cephalosporin	−0.01	−4.40	0.001 (−0.006, 0.01)	0.807
Clindamycin	−0.08	−27.10	−0.002 (−0.003, 0.001)	0.003
Quinolones	−0.60	−33.50	−0.01 (−0.013, −0.01)	<0.001
Total 4C	−0.99	−11.7	−0.02 (−0.04, −0.003)	0.023
Broad spectrum antibiotics	5.90	8.21	0.013 (0.03, 0.06)	0.529

(Note) *based on the British National Formulary Classification, Chapter 5;** P-values were obtained from the trend linear regression analysis.

0.404, 3.74, and $\beta_2 = 0.03$; 95% CI: 0.009, 0.045, respectively) but a non-significant trend thereafter (Table 2).

3.2.2. '4C' antibiotics utilization

During the study period, 418 NTI of '4C' antibiotics were dispensed, with co-amoxiclav being the most frequently dispensed at 47%. The proportion of NTI for total '4C' decreased by 0.99% (11.7%), with clindamycin (0.08%, −27.10%) and the quinolones (0.6%, −33.5%) showing the highest significant decline (Table 1 and Figure 2(c)). The proportion of total '4C' antibiotics showed a significant increase at baseline ($\beta_1 = 0.95$; 95% CI: 0.77, 1.13) but a decline in its level after the first lockdown (β_3 = -0.89; 95% CI:-1.62, −0.15), which was likely driven by the significant declining time trend for co-amoxiclav showed after the first lockdown (β_3 = -0.47; 95% CI:-0.81, −0.12 (Table 2).

3.2.3. Broad-spectrum utilization

Overall, although the trend of the proportion of broad-spectrum antibiotics increased by 5.9 (8.2%), the average monthly change was non-significant (0.013; 95% CI: 0.03, 0.06) (Table 1 and Figure 2(b)). Similarly, the segmented analysis results indicated statistically non-significant changes across all segments (Table 2).

4. Discussion

4.1. Key findings

Overall, there was a statistically significant increase in the overall trend for antibiotic use in terms of NTI for total antibiotics, driven mainly by the statistically significant increase in penicillins and cephalosporins, compared to the non-significant increase in DIDs (Table 1 and 2), potentially suggests a trend toward prescribing antibiotics at lower doses or for a shorter duration (most likely). This pattern might be attributable to prescribers' apprehensions regarding diagnostic uncertainties, especially given that many primary care consultations had been conducted remotely during the pandemic period. However, this hypothesis warrants further investigation, necessitating analysis of patient-level data. This observation, however, is consistent with the results presented in the English Surveillance Program for Antimicrobial Utilization and Resistance (ESPAUR) report [30], which documented a marginal rise in antibiotic consumption (measured as the number of items per 1000 inhabitants per day, 1.68 in 2021 compared to 1.66 in 2019) even though DID levels in 2022 remained below those recorded in 2019. The noted rise in NTI underscores the ongoing necessity to focus on reducing inappropriate antibiotic use including antibiotic overuse, especially

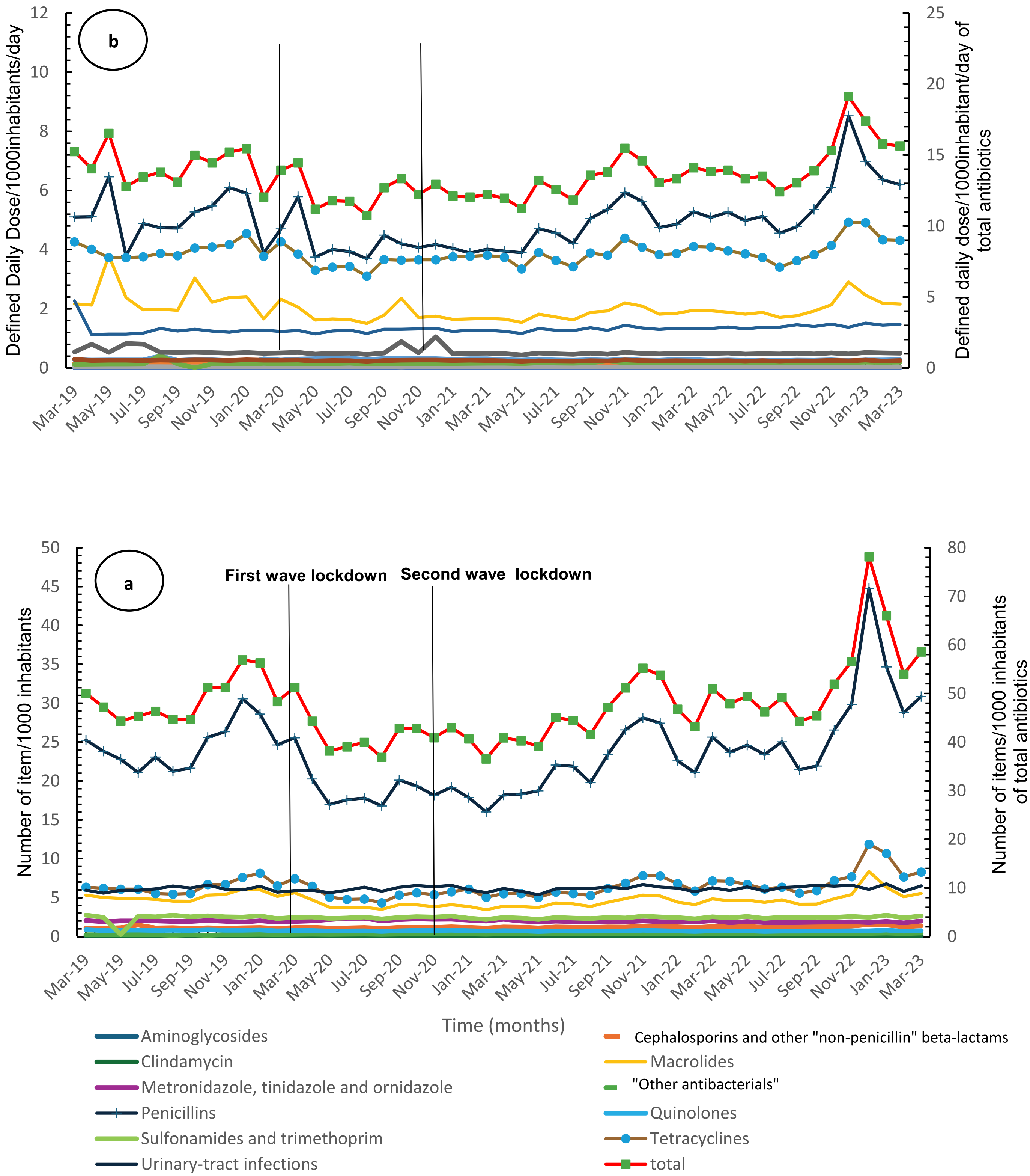

Figure 1. Utilization pattern of systemic antibiotics in the primary care setting in England between March 2019 and March 2023 measured as a) total number of items dispensed per 1000 inhabitants and b) Defined Daily Dose per 1000 inhabitants per day.

the over-use of respiratory antibiotics for viral infections which contributes significantly to the development of antibiotic resistance. This misuse not only renders these critical drugs less effective against bacterial infections but also imposes unnecessary side effects on patients [40].

From the segmented time series analysis, for both NTI and DID, there was a reduction in the levels and trends immediately after the first lockdown (β_2, and β_3) for all antibiotics, albeit not statistically significant; followed by a significant increase in the time trend post the second lockdown (β_5)

Table 2. Segmented regression analysis of the monthly number of antibiotics items dispensed/1000 inhabitants, Defined Daily Doses/1000 inhabitants/day and quality indicators during the period from March 2019 to March 2023.

Antibiotic category	Baseline trend (β_1)	Level change immediately after first lockdown (β_2)	Time trend after first lockdown (β_3)	Level change immediately after second lockdown (β_4)	Time trend after second lockdown (β_5)
Number of items dispensed/1000 inhabitants					
Aminoglycosides	−0.0001 (−0.0002, 0.003) 0.165	0.003 (−0.002, 0.008) 0.21	0.0008 (0.0001, 0.002) 0.08	0.0002 (−0.004, 0.004), 0.92	−0.0001 (−0.0002, 0.001), 0.99
Cephalosporins and other 'non-penicillin' beta-lactams	0.005 (0.003, 0.01) 0.32	0.04 (−0.12, 0.20) 0.64	0.009 (−0.021, 0.04) 0.56	−0.007 (−0.13, 0.12) 0.91	0.006 (−0.02, 0.04) 0.64
Clindamycin	−0.0003 (−0.001, 0.0001) 0.012	0.02 (−0.0004, 0.03) 0.055	0.0023 (−0.000, 0.005) 0.12	−0.01 (−0.023, 0.002) 0.1	−0.0001 (−0.003, 0.002) 0.59
Macrolides	0.0071 (−0.011, 0.025) 0.23	−0.6 (−1.9, 0.70) 0.35	−0.25 (−0.48, −0.01) 0.04	−0.012 (−1.016, 0.99) 0.98	0.25 (0.042, 0.46) 0.01
Metronidazole, tinidazole and ornidazole	−0.004 (−0.007, 0.001) 0.348	0.09 (−0.01, 0.28) 0.33	0.04 (0.005, 0.08) 0.026	−0.18 (−0.33, −0.04) 0.017	−0.042 (−0.073, −0.011) 0.009
Penicillin	0.14 (0.037, 0.30) 0.155	−5.3 (−12.2, 1.64) 0.13	−0.1 (−2.25, 0.31) 0.13	−1.1 (−6.54, 4.38) 0.69	1.1 (−0.09, 2.2) 0.06
Quinolones	−0.002 (−0.003, −0.001) 0.341	−0.032 (−0.112, 0.05) 0.43	0.0003 (−0.015, 0.02) 0.97	−0.001 (−0.07, 0.06) 0.96	0.0027 (−0.011, 0.02) 0.69
Sulfonamides and trimethoprim	0.0035 (−0.003, 0.01) 0.154	−0.19 (−0.86, 0.50) 0.59	−0.04 (−0.16, 0.08) 0.51	−0.08 (−0.61, 0.45) 0.76	0.004 (−0.11, 0.11) 0.94
Tetracyclines	0.04 (0.02, 0.07) 0.158	−0.53 (−2.56, 1.51) 0.6	−0.37 (−0.75, 0.005) 0.05	0.25 (−1.36, 1.86) 0.75	0.4 (0.032, 0.70) 0.03
Urinary tract infections*	0.0067 (0.0003, 0.01) 0.336	−0.6 (−1.17, 0.03) 0.06	0.1 (−0.05, 0.20) 0.25	−0.35 (−0.82, 0.13) 0.14	−0.08 (−0.18, 0.02) 0.12
'Others antibacterials'*	0.01 (0.004, 0.005) 0.142	0.014 (−0.035, 0.07) 0.56	−0.003 (−0.012, 0.01) 0.47	−0.001 (−0.04, 0.04) 0.96	0.001 (−0.008, 0.01) 0.9
Total antibiotics	0.2 (0.05, 0.34) 0.143	−7.1 (−17.5, 3.5) 0.18	−1.5 (−3.45, 0.43) 0.12	−1.5 (−.98, 6.8) 0.72	1.6 (0.17, 3.1) 0.004
Number of Defined Daily Doses/1000 inhabitants/day					
Aminoglycosides	0.0002 (0.0001, 0.0003) 0.00735	−0.001 (−0.003, 0.001) 0.4	−0.001 (−0.0004, 0.001) 0.98	0.0001 (−0.002, 0.002) 0.93	−0.0001 (−0.001, 0.0003) 0.97
Cephalosporins and other 'non-penicillin' beta-lactams	−0.0001 (−0.002, 0.002) 0.973	0.007 (−0.02, 0.03) 0.57	−0.001 (−0.01, 0.004) 0.69	0.001 (−0.02, 0.02) 0.99	0.002 (−0.002, 0.01) 0.32
Clindamycin	−0.001 (−0.001,0.0001) 0.162	0.008 (0.002, 0.013) 0.008	−0.0012 (−0.002, −0.002) 0.02	0.006 (0.0012, 0.001) 0.014	0.002 (0.001, 0.002) 0.001
Macrolides	−0.04 (−0.10, 0.023) 0.221	−0.19 (−0.90, 0.50) 0.58	0.02 (−0.11, 0.15) 0.76	−0.23 (−0.77, .31) 0.39	0.04 (−0.07, 0.15) 0.47
Metronidazole, tinidazole and ornidazole	−0.003(−0.01, 0.002) 0.198	0.04 (−0.03, 0.10) 0.23	0.01 (−0.004, 0.02) 0.19	−0.02 (−0.07, 0.020) 0.3	−0.01 (−0.02, 0.01) 0.28
Penicillin	0.003 (−0.012, 0.13) 0.962	−0.30 (−1.70, 1.13) 0.7	−0.13 (−0.40, 0.13) 0.33	−0.20 (−1.29, 0.90) 0.72	0.22 (−0.013, 0.44) 0.06

(*Continued*)

Table 2. (Continued).

Antibiotic category	Baseline trend (β$_1$)	Level change immediately after first lockdown (β$_2$)	Time trend after first lockdown (β$_3$)	Level change immediately after second lockdown (β$_4$)	Time trend after second lockdown (β$_5$)
Quinolones	− 0.0004 (−0.003, 0.002) 0.728	−0.004 (−0.03, 0.02) 0.78	−0.002 (−0.01, 0.003) 0.52	0.01 (−0.02, 0.03) 0.52	0.002 (−0.003, 0.01) 0.78
Sulfonamides and trimethoprim	−0.012 (−0.04, −0.001) 0.041	−0.08 (−0.30, 0.14) 0.46	0.05 (0.011, 0.09) 0.01	−0.09 (−0.26, 0.08) 0.27	−0.03 (−0.07, 0.001) 0.06
Tetracyclines	0.02 (−0.03, 0.07) 0.49	−0.18 (−0.8, 0.41) 0.53	−0.10 (−0.20, 0.02) 0.11	0.21 (−0.25, 0.68) 0.36	0.10 (−0.002, 0.20) 0.05
Urinary tract infections*	−0.03 (−0.06, −0.003) 0.03	0.04 (−0.25, 0.34) 0.74	0.04 (−0.02, 0.10) 0.16	−0.04 (−0.30, 0.20) 0.7	−0.002 (−0.05, 0.05) 0.93
'Others antibacterials'*	0.0004 (−0.01, 0.01) 0.927	−0.02 (−0.12, 0.10) 0.72	−0.004 (−0.02, 0.02) 0.68	0.003 (−0.08, 0.08) 0.94	0.0004 (−0.02, 0.17) 0.96
Total antibiotics	−0.07 (−0.29, 0.15) 0.529	−0.06 (−3.10, 1.90) 0.61	−0.10 (−0.60, 0.40) 0.656	−0.40 (−2.31, 1.60) 0.713	0.32 (−0.09, 0.72) 0.124
Quality indicators					
AWaRe					
Access	0.04 (−0.26, 0.35) 0.78	−1.88 (−5.35, 1.60) 0.28	0.02 (−0.62, 0.66) 0.95	−0.35 (−3.09, 2.40) 0.8	0.08 (−0.50, 0.65) 0.79
Watch	−0.19 (−0.33, −0.04) 0.01	2.07 (0.40, 3.74) 0.02	0.11 (−0.20, 0.42) 0.46	0.70 (−0.61, 2.02) 0.28	−0.08 (−0.35, 0.19) 0.56
Reserve	−0.001 (−0.002, 0.0003) 0.10	0.03 (0.009, 0.045) 0.004	0.0009 (−0.0024, 0.004) 0.57	0.003 (−0.011, 0.018) 0.62	−0.001 (−0.004, 0.002) 0.45
'4C' Antibiotics					
Co-Amoxiclav	−0.06 (−0.10, −0.02) 0.03	−1.01 (−2.98, 0.96) 0.3	−0.47 (−0.81, −0.12) 0.009	0.12 (−1.50, 1.74) 0.89	−0.02 (−0.36, 0.32) 0.89
Cephalosporin	−0.05 (−0.08, −0.01) 0.02	−0.73 (−1.97, 0.52) 0.25	−0.22 (−0.44, −0.003) 0.047	0.05 (−0.98, 1.07) 0.92	−0.07 (−0.28, 0.14) 0.5
Clindamycin	−0.01 (−0.14, −0.002) 0.02	−0.08 (−0.25, 0.10) 0.39	−0.03 (−0.06, 0.002) 0.06	−0.03 (−0.17, 0.12) 0.72	−0.01 (−0.04, 0.02) 0.44
Quinolones	−0.03 (−0.05, −0.01) 0.003	−0.63 (−1.48, 0.22) 0.14	−0.17 (−0.32, −0.02) 0.026	0.006 (−0.69, 0.71) 0.98	−0.05 (−0.19, 0.10) 0.53
Total 4C	0.95 (0.77, 1.13) <0.001	−2.44 (−6.65, 1.77) 0.25	−0.89 (−1.62, −0.15) 0.019	0.15 (−3.32, 3.61) 0.93	−0.15 (−0.87, 0.57) 0.68
Broad spectrum antibiotics	0.15 (−0.20, 0.50) 0.39	−0.70 (−4.64, 3.25) 0.72	−0.22 (−0.95, 0.51) 0.55	1.95 (−1.17, 5.06) 0.21	0.01 (−0.64, 0.66) 0.97

(Note) *Based on the British National Formulary Classification, Chapter 5; Data are presented as regression coefficients (95% CI), p-value.

but only for NTI, with DID showing non-significant increase. We believe these reductions during the period of the first lockdown might reflect the impact of social distance measures and behavioral changes, including better hygiene, on decreasing the transmission of infectious diseases including viral infections such as Influenza and RSV, which are traditionally often treated with antibiotics albeit inappropriately [28,41]. This reduction during the early phase of the pandemic is similar to those observed in a number of other countries especially higher income countries as demonstrated by a comparative analysis spanning 26 European nations [41]. In their study, Ventura-Gabarró et al. (2022) noted a decline in antibiotic usage within the community sector among the studied 26 European countries, with the exception of Bulgaria, during 2020 compared with pre-pandemic levels of 2019. However, in contrast to our finding of a statistically non-significant rise in DID during the long-term period following the second lockdown, there was a conspicuous resurgence in antibiotic utilization across all the 26 European nations in 2021 and 2022 [41]. Notably, the consumption rate in 2022 in 13 of the studied countries exceeded pre-pandemic levels [41].

Looking at the antibiotic classes, respiratory tract infections (RTIs) treated with penicillins accounted for 40% of antibiotics infection prescriptions in primary care in England (26). The prescribing of penicillins in our study showed an increase in the overall trend but a non-significant negative trend after the first and second lockdowns. This is potentially due to the impact of the public health measures and lockdown activities introduced in England; however, we cannot say this with certainty. Moreover, the notable surge in antibiotic consumption (mainly driven by penicillins) observed between November 2022 and March 2023 could likely be attributed to the substantial outbreak of invasive Group A Streptococcus (GAS) in England, especially when the threshold for antibiotic prescribing was lowered given the associated public health concerns from a GAS outbreak alongside antibiotic shortages [30,42]. This GAS outbreak may have contributed, at least in part, to the observed statistically significant increase in antibiotic usage (for NTI) during the second lockdown phase ($\beta_{5,}$ Table 2). Consequently, potentially confounding the observed impact of COVID-19 pandemic because it is important to note that this increase, although coinciding with the COVID-19 pandemic, was not directly related to the COVID-19 virus itself. We are aware that numerous studies have highlighted significant concerns regarding inappropriate antibiotic prescribing for patients with actual or suspected COVID-19 (COVID-19 RTI) [14,20,43]. This concern persists despite a very low prevalence of secondary infections or bacterial co-infections among COVID-19-infected patients [12,13]. The increased use of antibiotics in patients with actual or suspected COVID-19 can be attributed to several factors, including overlapping clinical features with bacterial pneumonia, inadequate diagnostic tools to differentiate between bacterial and viral infections and initial clinical uncertainty about the disease [64]. However, it is important to note that our study did not specifically assess antibiotic use among COVID-19 RTI patients but rather examined antibiotic use in the general population during the COVID-19 pandemic. Therefore, our findings are not directly comparable to studies focusing on antibiotic use for COVID-19 RTI, necessitating cautious comparison and interpretation.

We believe that the significant increase in tetracycline use could reflect the advice of the National Institute for Health and Care Excellence (NICE) during COVID-19 which recommended the use of doxycycline for the management of community-acquired pneumonia with an unknown cause [25]. Generally, for most of antibiotics, their prescribing increased after the end of second lockdown, probably due to the return-to-normal phase. However, this needs further research, especially with using detailed patient-level information including indications, age, other co-morbidities and the type of consultation, i.e. telephone or face-to-face (with greater diagnostic uncertainty with telephone appointments), as all these factors might have influenced antibiotics utilization during COVID-19 [27].

Findings from the three quality indicators used revealed no negative impact of COVID-19 on the quality of antibiotic use. This is aligned with the findings of Zhong et al. (2023) [44], who reported no major or significant changes in quality of antibiotic use in terms of repeat and inappropriate antibiotic prescribing patterns during the COVID-19 pandemic up to December 2021. Despite a notable rise in the levels of 'Watch' and 'Reserve' antibiotics immediately following the initial lockdown, this surge was not sustained and likely lacked clinical significance. This is evident by the observed continued reduction thereafter resulting in an overall reduction in the use of 'Watch' and 'Reserve' antibiotics, coupled with a concomitant overall increase in 'Access' antibiotics from ~ 77% in March 2019 to ~ 86% in March 2023, a trend that is encouraging. The transient surge in the utilization of 'Watch' and 'Reserve' antibiotics immediately post the first lockdown might be related to prescribers' diagnostic uncertainty [45], likely driven by the shift from face-to-face to remote consultations. Comparable findings were documented by Zhang et al. (2023) [46], revealing a 37% increase in the prescription of broad-spectrum antibiotics (OR = 1.37; 95% CI: 1.36, 1.38) as an immediate consequence of the pandemic. The significant decline in the use of '4C' antibiotics, particularly the significant reduction in the trend of co-amoxiclav post the initial lockdown (April to October 2020), further suggests the lack of any adverse impact of the COVID-19 pandemic on the quality of antibiotic use in England. The pronounced reduction in co-amoxiclav prescriptions within the community we believe could be attributed to the reduced prevalence of upper RTIs, likely stemming from reduced infection transmission resultant from the implementation of COVID-19 preventive measures such as the adoption of face masks and adherence to social distancing rules [28,41]. This aligns with the findings of Hussain et al. (2021), who observed a 6.5% reduction in co-amoxiclav usage in England during the period from March to September 2020 in comparison to the corresponding time-frame in 2018 [28]. However, we cannot say this with certainty in the absence of patient level data.

Similar to the ESPAUR Report findings [30] and the findings by Zhong et al. (2023) [44], our study findings indicate that the utilization and quality of antibiotic use in England appear not to have been adversely impacted by COVID-19. From the first glance, this might contradict the significant impact of COVID-19 on ASPs in primary care in England whereby there was a reported 64% decline in routine ASPs activities during the pandemic with an initial shift in focus from traditional antimicrobial stewardship

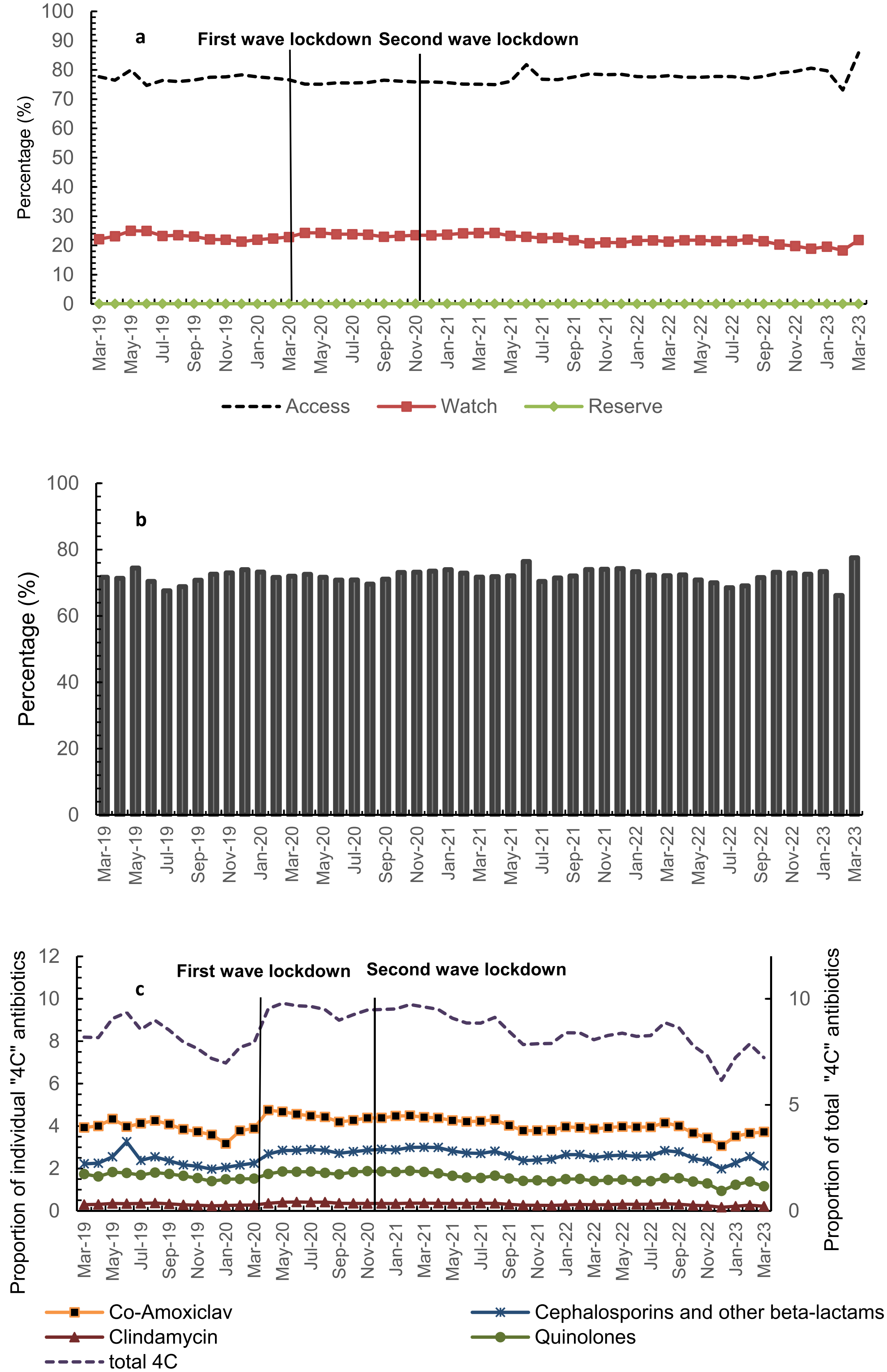

Figure 2. Quality of systemic antibiotics dispensed in the primary care setting in England between March 2019 and March 2023 measured by a) Proportion of the WHO Access Watch Reserve (AWaRe) classification, b) broad-spectrum antibiotics as a proportion of total antibiotics and c) '4C' antibiotics as a proportion of total systemic antibiotics.

activities to the management of COVID-19 cases [11]. However, despite these challenges, the period also saw innovative approaches in ASPs including the use of telemedicine and remote consultations which became integral to ASPs. ASPs were typically adapted by providing decision support tools and guidance for assessing patients remotely, allowing for continued monitoring and guidance on antibiotic prescribing [11,47]. The observed potential lack of any significant impact of COVID-19 in our study possibly suggests that these adaptations have been crucial in maintaining the effectiveness of ASPs during the periods of lockdown. Further ASPs activities included providing primary care clinicians with updated guidance on managing respiratory infections, differentiating between viral and bacterial causes, and the appropriate use of antibiotics. This was crucial as the symptoms of COVID-19 overlap with bacterial infections, risking increased antibiotic prescribing. The National Institute for Health and Care Excellence has also made substantial efforts nationally to promote antibiotic reviews, shorten the duration of antibiotic prescribing where pertinent, or stop antibiotic if COVID-19 was confirmed [48–51]. This was in addition to the guidance provided through the Treat Antibiotics Responsibly, Guidance, Education and Tools (TARGET) toolkit [52], further helping to improve antibiotic prescribing at this critical time. In general, in the UK nations, specific goals for ASPs in primary care are set at national level and delivered by medicines management teams comprising pharmacists and pharmacy technicians. These teams work within GP practices to support optimal use of all medicines and contribute both clinical support and data analysis.

4.2. Strengths and limitations

We believe that our research contributes significantly to the existing body of knowledge regarding the short-term effects of COVID-19 on antibiotic use 36 months after the start of the pandemic. As a result, offering a unique comparative advantage over other studies in several respects. Primarily, it encompassed an extensive evaluation of both the quality and quantity of antibiotic use over a prolonged period of time (49 months). This extended timeframe proved instrumental in facilitating a comprehensive analysis of the short-term influence of COVID-19 and its associated lockdown measures on antibiotic prescribing patterns. Additionally, our study included a thorough examination of all 11 antibiotic classes, and applied multiple established and validated metrics to rigorously assess the quality and quantity of antibiotic use (including analysis by the WHO AWaRe classification which is becoming a key quality metric/tool [4,5,7], promoting the rational use of antibiotics, recommended by the WHO and features as a national target in many countries), through applying an interrupted time series analysis, which is considered the strongest quasi-experimental design to evaluate the effect of an intervention (in this case, COVID-19 lockdowns) [38]. Furthermore, the dataset utilized in our study covers the entire population of England, adding a considerable breadth to our analysis.

Nevertheless, our study is not without limitations. The absence of patient-level data precluded the possibility of determining specific diagnoses, duration of treatment, indications, and other detailed prescribing information, including demographic trends such as age and sex. This limitation also meant that we were unable to definitively ascertain whether antibiotics were prescribed specifically for COVID-19 patients, for prophylaxis, or for treatment of other conditions. It is crucial to note that our study did not specifically examine antibiotic use among COVID-19 patients. This constitutes a potential limitation, as the trends observed in the general population may not directly apply to COVID-19-specific cases. Consequently, comparisons with studies focusing on antibiotic use for COVID-19 should be made with caution. Additionally, it's important to highlight that while the quality indicators used in this study, such as the AWaRe classification, serve as a valuable and relevant means to assess the quality of antimicrobial prescribing promoting rational use of antibiotics [4,5], they are only one set of measures of prescribing quality. The most precise measure of prescribing quality would be the appropriateness of prescribing based on for instance guidance in the AWaRe Book. Unfortunately, assessing this aspect was not feasible due to lack of granular patient-level data such as prescribing indications. Consequently, the conclusions drawn about the quality of prescribing should be interpreted with caution.

Moreover, due to our conservative approach of defining board spectrum antibiotic, our results around broad spectrum antibiotics should also be interpreted with caution when compared to other studies, which might have applied a stricter definition of broad-spectrum antibiotics through restricting this term to only include antibiotics such as co-amoxiclav, cephalosporins, and quinolones, as seen in the most recent ESPAUR report [30]. Ideally, a comparison with a control group unaffected by the pandemic would have been preferable to isolate the impact of COVID-19 from other confounding factors. However, given the pervasive nature of the COVID-19 pandemic across England, such a comparison was not feasible as the pandemic affected the entire country and all therapeutic areas. This situation leaves possibilities for potential confounding factors that may have influenced our findings in relation to the impact of COVID-19 such as the GAS outbreak in England between November 2022 and March 2023. Despite these challenges, we believe that our findings are robust and provide a valuable direction for all key stakeholders in England moving forward.

Finally, regarding the observed increase in NTI, the following points should be carefully noted. First, our data suggest that while there was an increase in the NTI following the second lockdown, this does not necessarily indicate an adverse effect on antibiotic utilization. The increase in NTI could reflect an appropriate response to the evolving healthcare needs during the pandemic particularly during the period after the second lockdown when there was increased chances for transmission of infections due to re-socializing as part of the return-to-normal phase and the substantial outbreak of invasive Group A Streptococcus (GAS) in England [30,42], which resulted in a notable surge in antibiotic consumption between November 2022 and March 2023 (i.e. the observed NTI increase is confounded by other factors and not necessarily directly related to COVID-19 per se). Secondly, the increase in NTI was statistically significant, and its clinical significance should be interpreted with caution due to its relatively small magnitude. Thirdly, the defined daily doses (DID) metric, which is the standard measure for drug consumption and utilization, showed a statistically non-significant increase which indicates no actual increase in antibiotic consumption, suggesting a lack of adverse effect from COVID-19 on antibiotic use. Importantly, the quality of antibiotic prescribing, as measured by the three quality indicators, did not show significant adverse changes. Consequently, based on the above, no apparent adverse effect of COVID-19 on antibiotic utilization and quality could possibly be inferred.

5. Conclusion

Overall, the short-term impact of COVID-19 on the quantity and quality of antibiotic use in England appears to be minimal or non-significant. Nevertheless, there was an observable trend of increased antibiotic utilization following the conclusion of the second lockdown phase, coinciding with the gradual recovery of the healthcare system. To obtain more precise estimates of any changes in antibiotic prescribing, particularly across diverse age demographics, and to further support antimicrobial stewardship programs, there is a critical need for patient-level data. Additionally, the application of combined quality indicators should be sustained for the evaluation of future antibiotic prescribing patterns in England, as a strategy to effectively combat AMR.

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Declaration of interest

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Author contribution statement

We can confirm that all the authors had substantially contributed to the conception and design of this study and interpreting the relevant literature as well as had been involved in writing the manuscript and/or revised it for intellectual content. Further contributions include data collection and management: N. Al Mutairi, A. Kudri; data analysis and interpretation: N. Al Mutairi, A. Kudri, K. Bakir, O. Darweesh, H. Karwi, K. Amen, A. Seaton, B. Godman, J. Sneddon; and final approval: all authors.

Ethics statement

Ethical approval and informed consent for participation were not required for this study in accordance with the national legislation and the institutional requirements because it used publicly available data that did not include any personal identification information.

Data availability statement

The data that support the findings of this study are openly available at [https://www.nhsbsa.nhs.uk/prescription-data/dispensing-data/prescription-cost-analysis-pca-data], reference number [31].

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