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Impact of the COVID-19 pandemic on the utilisation and quality of antibiotic use in the Scottish primary care setting: a population-based segmented interrupted time-series analysis

Hayam Al Balushi[a,b*], Amanj Kurdi [a,c,d,e*], Najla Almutairi[a], Kirmanj Ismail Baker[f], Karwan M Amen[g], Hardee Karwi[h], Andrew Seaton [i,j] and Brian Godman [a,e]

[a]Strathclyde Institute of Pharmacy and Biomedical Sciences, Strathclyde University, Glasgow, UK; [b]Directorate General of Pharmaceutical Affairs and Drug Control, Ministry of Health, Oman; [c]Department of Clinical Pharmacy, College of Pharmacy, Hawler Medical University, Kurdistan Regional Governorate, Erbil, Iraq; [d]College of Pharmacy, Al-Kitab University, Kirkuk, Iraq; [e]Department of Public Health Pharmacy and Management, School of Pharmacy, Sefako Makgatho Health Sciences University, Pretoria, South Africa; [f]Department of Surgery, College of Medicine, University of Kirkuk, Kirkuk, Iraq; [g]Department of Nursing, College of Nursing, Hawler Medical University, Erbil, Iraq; [h]Azadi Teaching Hospital, Kirkuk Health Directorate, Ministry of Health, Kirkuk, Iraq; [i]Department of Internal Medicine, Queen Elizabeth University Hospital, Glasgow, UK; [j]School of Medicine, University of Glasgow, Glasgow, UK

ABSTRACT

Background: Inappropriate use of antibiotics is expected to increase during the COVID-19 pandemic, but there are limited data on COVID-19's long-term impact. We assessed the impact of COVID-19 on the quantity and quality of antibiotic use in Scotland.

Research design and methods: A segmented interrupted time series was applied to monthly dispensed antibiotics using prescription cost analysis data from March/2019 to March/2023. Antibiotic use was quantified using the number of items dispensed/1000 inhabitants (TIDs) and defined daily dose/1000 inhabitants/day (DIDs). The quality of antibiotic use was assessed using key quality indicators including the WHO AWaRe classification, proportion of broad-spectrum and ″4C″-antibiotics.

Results: Overall, for all antibiotics, there was a non-significant increase in TIDs and DIDs before the first lockdown (March/2020) (β_1), but a decline in the level immediately after the first (β_2) and second lockdowns (β_4) (November/2020), albeit non-significant. However, a significant increase in the time trend after the second lockdown (β_5) for all antibiotic classes was observed. COVID-19 had no negative impact on AWaRe utilisation, with the proportion of all antibiotics from the Access group increasing from 76% in March/2019 to 90% in March/2023. The proportion of ″4C″ antibiotic reduced significantly after the second lockdown.

Conclusions: Neither the utilisation nor the quality of total antibiotic use appeared to have been significantly affected by COVID-19.

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1. Introduction

In March 2020, the World Health Organization (WHO) recognised the COVID-19 outbreak as a global health pandemic [1], with more than 6.9 million deaths by early September 2023 [2]. The pandemic also has had a profound impact on global health along with appreciable economic consequences [3–5]. The virus overwhelmed many health-care systems, leading to shortages of medicines and supplies [6–8]. While the public health measures introduced at the start of the pandemic (e.g. lockdown measures) were effective in slowing the spread of the virus [9–11], there were many unintended consequences. The closure and limited access to primary care and outpatient clinics has resulted in decreased immunization rates as well as adversely affecting the identification and active management of patients with non-communicable diseases across countries [12–16]. All these effects have impacted the medication-seeking patterns and transmission of infectious diseases, including those with acute respiratory infections, which are commonly managed with anti-bacterial therapy [17–20]. In the USA, social mitigation measures have led to an observed decrease in influenza cases and visits for influenza-like symptoms, which are a key driver of antibiotic prescribing [21,22]. As a result, a persistent fall in commonly prescribed antibiotics, especially for respiratory infections [23,24] was observed. A similar picture was seen in Canada [22,25].

However, a mixed picture has been seen in England at the start of the pandemic where the number of antibiotic prescriptions in general practice fell by 15.5% between 1 April 2020 and 31 August 2020 compared to the corresponding period in 2019 [26]. When factoring in the reduction in the absolute number of GP appointments over this time and estimating the rate of antibiotic prescribing, the absolute number of antibiotic

CONTACT Amanj Kurdi amanj.baker@strath.ac.uk Strathclyde Institute of Pharmacy and Biomedical Science, University of Strathclyde, 161 Cathedral Street, Glasgow G4 0RE
*Joint first authors.
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prescriptions was 6.7% higher than expected, suggesting inappropriate antibiotic prescribing [26]. In their recently published study on the impact of COVID-19 on the subsequent prescribing of antibiotics in primary care in England, Zhong et al. (2023) found that inappropriate antibiotic prescriptions for otitis externa was at a prevalence of 39.3% and those for upper respiratory tract infections (URTIs) at 69.6% [27]. The most frequent antibiotics prescribed inappropriately, which were defined as those antibiotic prescriptions that deviated from recommended guidelines for the recorded infection, were amoxicillin and doxycycline for patients diagnosed with URTIs and amoxicillin and co-amoxiclav for those with otitis externa [27]. Any impact of the pandemic on the frequency of inappropriate prescribing though was temporary; however, there were notable fluctuations between March 2020 and April 2021 [27]. Inappropriate prescribing of antibiotics is a concern as this increases antimicrobial resistance (AMR) [28], which is associated with high morbidity and mortality [29,30]. In addition, AMR appreciably increases the costs of care [31–33]. It is estimated that by 2050 there will be 10 million deaths annually from AMR globally, as a result becoming the next pandemic unless key issues are addressed [34,35].

The patterns around the prescribing of antibiotics in ambulatory care during the COVID-19 pandemic are inconsistent. An analysis of pharmaceutical sales data in 71 countries showed that the sales of four antibiotics and their groups (cephalosporins, penicillin, macrolides, and tetracyclines) fell sharply during April and May 2020 [22]. There were similar findings in Portugal, with antibiotic utilisation decreasing by >5 defined daily dose/1000 inhabitants/day (DID) since the start of the pandemic [36], with similar reductions in the USA [23,24]. Similar trends were also observed in Scotland [37] as well as other European countries once lockdown and other measures were introduced typically in March 2020 [37,38]. However, most of these studies assessed only antibiotic utilisation patterns (not their quality of use) in the few months after the start of the pandemic, leaving information on antibiotic utilisation patterns 2–3 years after the pandemic start scarce. In contrast, we have seen an appreciable increase in the utilisation of antibiotics during the COVID-19 pandemic particularly in low- and middle-income countries [39–42].

Despite the inconsistent/mixed findings of previous studies about the impact of COVID-19 on the extent of antibiotic use, there is limited evidence on the impact of COVID-19 on the quality of antibiotics used. Consequently, we sought to provide deeper insights into the impact of COVID-19 not only on the utilisation patterns but also on the quality of antibiotics prescribed in Scotland. This is important in Scotland given ongoing activities by the health authorities to improve antibiotic utilisation in recent years [43–45]. The findings can be used to provide future guidance if needed.

2. Methods

2.1. Study design and data sources

This analysis was a retrospective, repeated cross-sectional study of antibiotics dispensed in the primary care setting in Scotland using Prescription Cost Analysis (PCA) data (an aggregated, publicly available dataset) from March 2019 to March 2023 [46]. PCA dataset contain information about all prescribed medicines issued by GPs and dispensed in the community [46,47].

2.2. Study subjects and prescriptions

This study included all systemic antibiotic prescriptions, stratified into 11 antibiotic classes based on the British National Formulary (BNF) classification Chapter 5 (Supplementary File 1) [48]. Preparations for inhalation, suppositories, and topical preparations were excluded. The study did not require ethical approval as we used a publicly available aggregated anonymous dataset.

2.3. Study outcomes

The study outcomes were the quantity and quality of antibiotic utilisation trends. The utilisation trends were measured using two utilisation metrics: the monthly total number of dispensed items/1,000 inhabitants (TID) and the monthly defined daily dose (DDD)/1,000 inhabitants/day (DID). The quality of antibiotics use was assessed using standard quality indicators including, first the WHO AWaRe (as a tool to assess antibiotic stewardship), where antibiotics are classified into three different groups (Access, Watch, Reserve) to emphasize the importance of their appropriate use, with antibiotics in the Access group typically recommended as first-line use where appropriate, with those in the Watch and Reserve groups reserved to reduce AMR [49,50]. The WHO AWaRe list and the modified UK AWaRe list were used as a reference [49,51]. Secondly, the percentage of "4C"-antibiotics (Co-amoxiclav, Clindamycin, Cephalosporins, Quinolones) and thirdly, the percentage of broad-spectrum vs. narrower spectrum antibiotics (Supplementary File 1) due to concerns with the impact on AMR of excessive prescribing of these antibiotics [45]. The broad vs. narrow spectrum utilisation was typically used as a quality indicator before the publication of the AWaRe classification with subsequent percentage utilisation rates [52,53]. Antibiotic utilisation was measured in the 12 months pre-COVID-19 (March 2019–February 2020), 7 months after the first national COVID-19 lockdown in March 2020 (April 2020–October 2020), and 28 months after the second national COVID-19 lockdown in November 2020, equating to a total study duration of 49 months.

The UK Office for National Statistics was used to obtain a mid-year point population size estimate. DDD/1000 inhabitants/day is an internationally well-recognized utilisation metric that seeks to overcome population variation when comparing medicine use across countries [38,54,55]. DDDs are defined by the WHO as the 'assumed average maintenance dose of a drug per day used for the drug's main indication in adults' [56]. The DDD/1000 inhabitants/day was calculated by summing the monthly total dispensed amount (mg) for each antibiotic (by multiplying each quantity by its strength), adjusted by their WHO assigned DDD value, and subsequently, divided by the estimated mid-year population size, multiplied by 1000, and divided by number of days in each month. For combination products, we divided the monthly dispensed quantity by their assigned DDD values based on their number of daily unit doses as per WHO guidance [56].

2.4. Data analysis

Descriptive statistics were used to describe the utilisation trends over time. Changes in utilisation trends during the study period were presented as absolute and relative percentage changes. Linear regression was used to perform a trend analysis over time to obtain the average monthly changes in utilisation. A segmented linear regression analysis of the interrupted time series was performed to assess the impact of the first and second national lockdown [57]. The regression coefficients, which were fitted to the original scale of the study outcome measures, obtained from the analysis were presented, together with their 95% confidence intervals. The baseline level (β_1), the level change immediately after the first COVID-19 lockdown (β_2), the time trend after the first lockdown (β_3), the level change immediately after the second lockdown (β_4), and the time trend after the second lockdown (β_5) were assessed and presented.

3. Results

3.1. Utilisation trends

Overall, there were a total of 2,785 dispensed items/1,000 inhabitants over the entire study period, which equates to approximately three antibiotic items per individual, with penicillin being the most frequently prescribed antibiotic (46.9%, $n = 1308.4$), followed by tetracycline (15.2%, $n = 425.7$). Over the study period, there was a 23.8% increase in the slope ($n = 13.9$) of the number of dispensed items/1000 inhabitants for total antibiotics between March 2019 and March 2023, with a statistically significant increase in the monthly average trend of 0.23 dispensed items/1000 inhabitants (95% CI: 0.055, 0.402) (Table 1 and Figure 1).

For the individual antibiotic classes, we observed an increase in the slope for all antibiotic classes, except for aminoglycosides (−29.8%, $n = 0.0019$) and quinolones (−19.1%, $n = 0.261$) which showed a reduction in their average monthly utilisation (Table 1 and Figure 1). The highest increase was observed for penicillin (34.1%, $n = 9.48$) with an average monthly increase of 0.169 dispensed items/1000 inhabitants (95% CI: 0.052, 0.285) (Table 1).

Analysis of the DID utilisation showed similar results to TID, showing a non-significant increase (13.4%, $n = 2.47$ DID) for total antibiotics and a significant increase for penicillin (27.4%, $n = 1.6$ DID) with a significant average monthly increase of 0.026 DID (Table 2).

In terms of the impact of the COVID-19 lockdown measures on the utilisation pattern of antibiotics, there was a non-significant positive change in the baseline slope for both metrics (TID and DID) ($\beta_1 = 0.669$ [95% CI: −0.34, 1.678] and 0.131 [95% CI: −0.0796, 0.34], respectively) (Tables 3 and 4). However, there was a reduction in the level immediately after the first lockdown (β_2), the slope after the first lockdown (β_3) and the level immediately after the second lockdown (β_4), albeit non-significant (Table 3). This was followed by a significant increase in the number of antibiotics dispensed in the period after the second lockdown for total antibiotics ($\beta_5 = 2.103$; 95% CI: 0.222, 3.985) and specifically for penicillin ($\beta_5 = 1.387$, 95% CI: 0.125, 2.65), tetracycline ($\beta_5 = 0.563$, 95% CI: 0.240, 0.886), and macrolides ($\beta_5 = 0.246$, 95% CI: 0.050, 0.441) (Figure 1 and Table 3). Similarly, the DID slope after the second lockdown increased significantly for total antibiotics ($\beta_5 = 0.491$, 95% CI: 0.102, 0.880), penicillin ($\beta_5 = 0.261$, 95% CI: 0.049, 0.473), tetracycline ($\beta_5 = 0.143$, 95% CI: 0.043, 0.244), and macrolides ($\beta_5 = 0.092$, 95% CI: 0.0003, 0.184) (Table 4 and Figure 2).

Table 1. Absolute, relative, and average monthly changes for the number of items dispensed/1000 inhabitants between March 2019 and March 2023.

Variables	Absolute change	Relative change	Average monthly change (95% CI)
Penicillin	**9.484**	**34.1**	**0.169 (0.052,0.285)**
Cephalosporins and other beta-lactams	**0.139**	**13.7**	**0.002 (0.001,0.003)**
Tetracyclines	**2.541**	**29.4**	**0.038 (0.008,0.069)**
Aminoglycosides	**−0.0019**	**−29.7**	**−0.000036 (−.000057,10.000015)**
Macrolides	0.218	4.2	0.003776 (−0.014,0.022)
Clindamycin and lincomycin	0.029	26.5	0.000041 (−0.00013,0.00021)
Some other antibacterials**	**0.176**	**62.3**	**0.003034 (0.002,0.003)**
Sulfonamides and trimethoprim	0.338	4.7	−0.000255 (−0.009,0.008)
Metronidazole, tinidazole and ornidazole	**0.355484**	**14.346298**	**0.004372 (0.001,0.007)**
Quinolones	**−0.261389**	**−19.125154**	**−0.004774 (−0.006, −0.003)**
Other antibiotic for UTI	**0.872741**	**19.896196**	**0.012736 (0.007,0.018)**
Total Antibiotics	**13.892375**	**23.799191**	**0.228938 (0.055,0.402)**

***Includes: Chloramphenicol, Colistimethate, Colomycin, Fosfomycin, Fucidic acid, Linezolid, Rifaximin, Vancomycin, based on the British National Formulary.

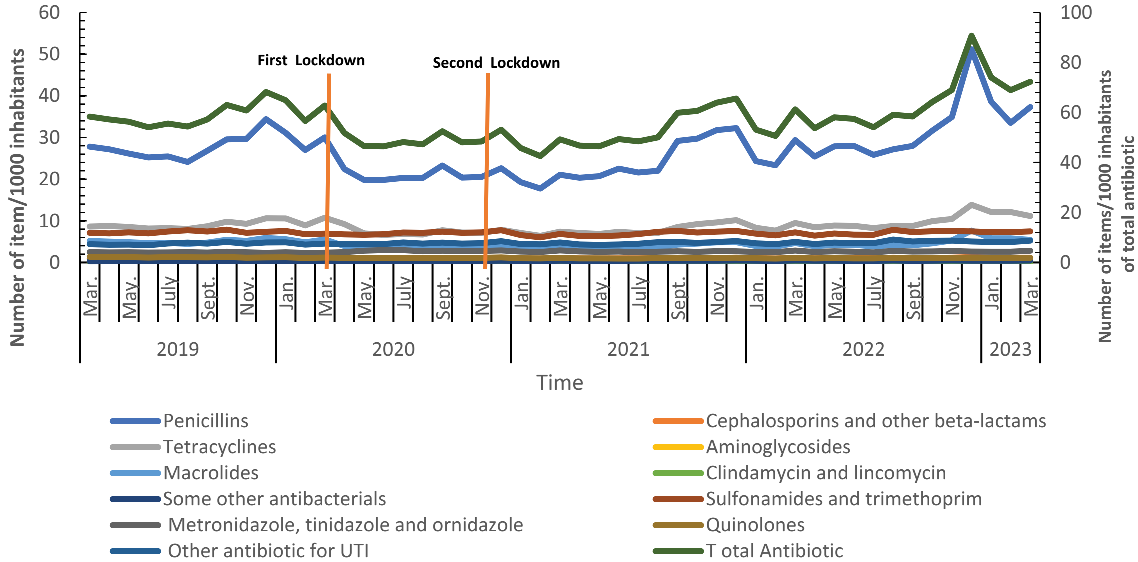

Figure 1. Total number of items dispensed/1000 inhabitants of systemic antibiotics in Scotland from March 2019 to March 2023.

Table 2. Absolute, relative, and average monthly changes for defined daily dose/1000 inhabitants/day between March 2019 and March 2023.

Variables	Absolute change	Relative change	Average monthly change (95% CI)
Penicillin	**1.609**	**27.4**	**0.02633650 (0.005,0.046)**
Cephalosporins and other beta-lactams	0.014	9.7	−0.00043851 (−0.00106,0.00019)
Tetracyclines	0.209	3.4	−0.00317291 (−0.0127,0.0063)
Aminoglycosides	−0.0009	−30.1	−0.00001003 (−0.0000243,0.0000042)
Macrolides	−0.173	−6.5	−0.00651309 (−0.01410,0.00108)
Clindamycin and lincomycin	0.007	19.1	−0.00003323 (−0.000088,0.000022)
**Some other antibacterials	0.029	52.7	0.00043586 (0.0003,0.0005)
Sulfonamides and trimethoprim	**0.326**	**17.8**	**0.00532739 (0.0022,0.0084)**
Metronidazole, tinidazole and ornidazole	**0.053**	**16.4**	**0.00068661 (0.00021,0.00116)**
Quinolones	−0.082	−18.6	−0.00164364 (−0.00214, −0.00114)
Other antibiotic for UTI	0.482	50.9	0.00989434 (0.00789,0.01189)
Total Antibiotics	2.474	13.4	0.03086930 (−0.007,0.068)

***Includes: Chloramphenicol, Colistimethate, Colomycin, Fosfomycin, Fucidic acid, Linezolid, Rifaximin, Vancomycin, based on the British National Formulary.

3.2. Quality indicators for antibiotic use

3.2.1. WHO AWaRe classification

During the study period, the Access group of antibiotics were the most frequently prescribed class ranging from 76% of the total utilisation in March 2019 to 90% in March 2023, with a corresponding reduction in the prescribing of antibiotics in the Watch and Reserve groups (Table 5, Figure 3). Overall, there was a slight decrease in the proportion of antibiotics in the Reserve and Watch groups by 21.4% ($n = -0.012$) and 20.5% ($n = -4.59$), respectively. However, the analysis indicated that the average monthly change in the proportion of Access group antibiotics increased by 9.9% ($n = 7.74$) over the study time period (Table 5). Before the first lockdown, there was a significant increase in the baseline trend for the Access group of antibiotics ($\beta_1 = 0.229$, 95% CI: 0.001,0.456) accompanied by a significant decrease for antibiotics in the Watch group ($\beta 1 = -0.171$, 95% CI: −0.277, −0.066) (Table 6). Furthermore, there was a non-significant change in both the level (β_2) and slope (β_3) after the first lockdown (Table 6). However, immediately after the second lockdown (β_4), the proportion of antibiotics in the Watch group increased significantly ($\beta_4 = 0.989$, 95% CI: 0.043, 1.935), followed by a non-significant change in the period after the second lockdown (Table 6 and Figure 3).

3.2.2. 4C antibiotic utilisation

During the study period, there were 366.3 TID of "4C" antibiotic, with co-amoxiclav being the most frequently prescribed

Table 3. Segmented regression analysis of the monthly number of total items of antibiotics dispensed monthly regression coefficient (95% confidence intervals) (between March 2019 and March 2023).

Variables	β1	β2	β3	β4	β5
Penicillin	0.425 (−0.251,1.102)	−4.866 (−12.558,2.825)	−1.158 (−2,579,0.263)	−1.800 (−7.871,4.271)	1.387 (0.125,2.650)
Cephalosporins and other beta-lactams	0.001 (−0.008,0.011),	−0.012 (−0.125,0.100)	−0.006 (0.027,0.014)	0.0002 (−0.088,0.089)	0.011 (−0.007,0.029)
Tetracyclines	0.157 (−0.016,0.330)	−0.355 (−2.322,11.611)	**−0.549** **(−0.912,-0.185)**	−0.134 (−1.687,1.418)	0.563 (0.240,0.886)
Aminoglycosides	0.00007 (−0.00008,0.00022)	0.00118 (−0.00049,0.00285)	−0.00011 (−0.00042,0.00019)	−0.00073 (−0.00205,0.00059)	−0.00002 (−0.00029,0.00026)
Macrolides	0.048 (−0.056,0.153)	−0.756 (−1.945,0.432)	−0.212 (−0.432,0.007)	−0.162 (−1.101,0.776)	0.246 (0.050,0.441)
Clindamycin and lincomycin	0.00015 (−0.001,0.001)	0.01167 (−0.001,0.025)	−0.00088 (−0.003,0.001)	**−0.016** **(−0.027,-0.006)**	0.00137 (−0.00087,0.00360)
Some other antibacterials**	**0.00593** **(0.002,0.009)**	−0.00784 (−0.048,0.032)	−0.00076 (−0.008,0.006)	0.01497 (−0.016,0.046)	−0.003 (−0.010,0.002)
Sulfonamides and trimethoprim	0.01413 (−0.053,0.081)	−0.74516 (−1.513,0.023)	0.06474 (−0.077,0.206)	−0.554 (−1.160,0.052)	−0.056 (−0.182,0.069)
Metronidazole, tinidazole and ornidazole	−0.006 (−0.029,0.0158)	0.136 (−0.118,0.391)	**0.052** **(0.005,0.099)**	**−0.241** **(−0.443, −0.040)**	−0.046 (−0.088, −0.004)
Quinolones	**−0.013** **(−0.023, −0.002)**	−0.040 (−0.159,0.077)	0.00097 (−0.020,0.022)	0.00012 (−0.093,0.093)	0.012 (−0.006,0.032)
Other antibiotic for UTI	0.03615 (−0.007,0.079)	−0.329 (−0.823,0.0164)	−0.001 (−0.093,0.089)	−0.212 (−0.602,0.177)	−0.012 (−0.093,0.068)
Total Antibiotic	0.669 (−0.340,1.678)	−6,963 (−18.42,4.500)	−1.812 (−3.930,0.306)	−3.108 (−12.15,5.94),	2.103 (0.222,3.985)

Results are presented as regression coefficients (95% CI); (β_1) represents baseline trend; (β_2) the level change immediately after the first COVID lockdown; (β_3) the time trend after the first lockdown; (β_4) the level change immediately after the second lockdown, and (β_5) the time trend after the second lockdown. **Includes: Chloramphenicol, Colistimethate, Colomycin, Fosfomycin, Fucidic acid, Linezolid, Rifaximin, Vancomycin, based on the British National Formulary.

Table 4. Segmented regression analysis of the monthly number of defined daily dose of antibiotics dispensed monthly Regression coefficient (95% confidence intervals) (between March 2019 and March 2023).

Variables	β1	β2	β3	β4	β5
Penicillin	0.0703 (−0.043,0.184)	−0.825 (−2.119,0.467)	−0.216 (−0.455,0.022)	−0.301 (−1.322,0.72)	0.261 (0.049,0.473)
Cephalosporins and other beta-lactams	9.119 (−0.005,0.005)	−0.00029 (−0.060,0.060)	−0.00146 (−0.012,0.009)	0.0244 (−0.023,0.072)	1.951 (−0.009,0.009)
Tetracyclines	0.015 (−0.038,0.069)	−0.311 (−0.924,0.301)	−0.124 (−0.237, −0.011)	0.067 (−0.416,0.550)	0.143 (0.043,0.244)
Aminoglycosides	8.132 (−2.1840,0.0001)	0.00024 (−0.0009,0.0014)	−2.314 (−0.0002,0.0001)	−0.0009 (−0.0018,2.270)	−7.732 (−0.0002,0.0001),
Macrolides	0.016 (−0.032,0.066)	−0.299 (−0.860,0.262)	−0.089 (−0.193,0.014)	0.003 (−0.439,0.446)	0.092 (0.0003,0.1846)
Clindamycin and lincomycin	0.0002 (−0.00016,0.00066)	2.995 (−0.004,0.004)	−0.00058 (−0.0014,0.0002)	−0.0028 (−0.0065,0.0008)	0.00047 (−0.0002,0.0012), 0.220
Some other antibacterials**	0.00021 (−0.0008,0.0013)	0.00106 (−0.011,0.013)	4.052 (−0.0022,0.0023)	−0.00011 (−0.010,0.009)	0.00025 (−0.0018,0.0023)
Sulfonamides and trimethoprim	0.0109 (−0.0144,0.0363)	−0.187 (−0.475,0.100)	0.023 (−0.029,0.076)	−0.219 (−0.446,0.008)	−0.023 (−0.070,0.023)
Metronidazole, tinidazole and ornidazole	−0.00064 (−0.0037,0.0024)	0.029 (−0.005,0.065)	0.005 (−0.0008,0.0123)	−0.029 (−0.057, −0.001)	−0.005 (−0.0110,0.0005)
Quinolones	−0.0049 (−0.008,0.001)	−0.0010 (−0.037,0.035)	−0.0010 (−0.0078,0.0056)	0.0176 (−0.011,0.046)	0.0057 (−0.0002,0.0117)
Other antibiotic for UTI	0.023 (0.007,0.038)	−0.051 (−0.228,0.124)	−0.024 (−0.056,0.008)	−0.043 (−0.183,0.095)	0.015 (−0.013,0.044)
Total Antibiotic	0.131 (−0.076,0.340)	−1.645 (−4.017,0.725)	−0.429 (−0.867,0.009)	−0.484 (−2.356,1.386)	0.491 (0.102,0.880)

Results are presented as regression coefficients (95% CI); (β_1) represents baseline trend; (β_2) the level change immediately after the first COVID lockdown; (β_3) the time trend after the first lockdown; (β_4) the level change immediately after the second lockdown; and (β_5) the time trend after the second lockdown. **Includes: Chloramphenicol, Colistimethate, Colomycin, Fosfomycin, Fucidic acid, Linezolid, Rifaximin, Vancomycin, based on the British National Formulary.

(46%, $n = 168.6$ TID), followed by fluoroquinolones (26.2%, $n = 96.2$ TID), and cephalosporins (24.7%, $n = 90.5$ TID). Overall, there was a slight significant decrease in the slope of ″4C″ antibiotics dispensed for the total as well as clindamycin with a relative change of 2.245% ($n = 0.165$), 8.485% ($n = 0.015$), respectively (Table 5 and Figure 4).

Before the first lockdown, there was a non-significant increase in the baseline trend for total ″4C″ ($\beta_1 = 0.066$, 95% CI: 0.133, 0.0005) (Table 6). Furthermore, there was a significant increase in the level immediately after the first lockdown for the total ″4C″ ($\beta_2 = 0.847$, 95% CI: 0.084,1.611), with a non-significant decline in both the slope after the first

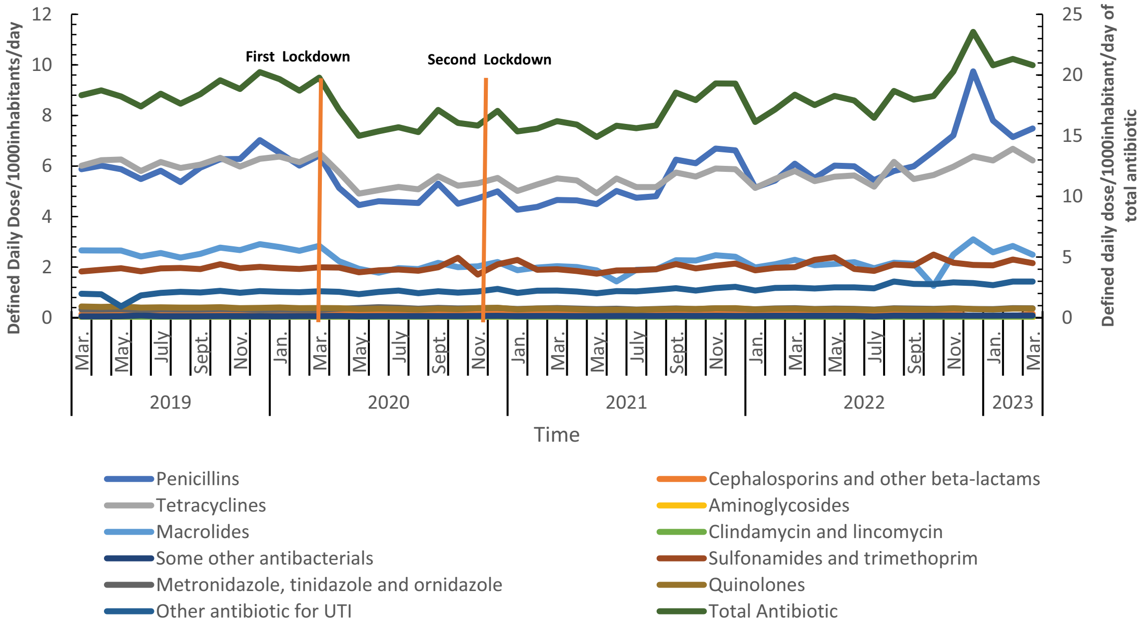

Figure 2. Total number of defined daily dose per 1000 inhabitants per day of systemic antibiotics in Scotland from March 2019 to March 2023.

Table 5. Absolute, relative, and average monthly changes for the proportion of total items dispensed/1000 inhabitants between March 2019 and March 2023.

Variables	Absolute change	Relative change	Average monthly change (95% CI)
Access	7.740	9.917	0.121 (0.089,0.1529)
Reserve	−0.012	−21.41	−0.00006 (−0.00095,0.00082)
Watch	−4.598	−20.56	−0.089 (−0.107, −0.070)
Co-amoxiclav	0.580	18.77	0.0034 (−0.001,0.008)
Cephalosporinses	−0.043	−2.52	−0.0016 (−0.005,0.002)
Fluoroquinolones	−0.0718	−30.67	−0.014 (−0.017, −0.010)
Clindamycin	**0.015**	**8.48**	**−0.00064 (−0.00126,-0.00003)**
Grand Total "4C"	**−0.165**	**−2.24**	**−0.0128 (−0.0252,-0.00055)**
Broad spectrum	−2.851	−3.769	−0.042 (−0.085,0.0002)

*P-value obtained from linear regression.

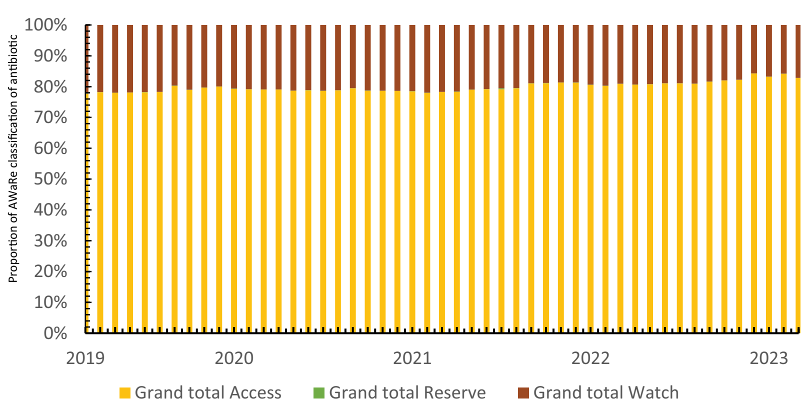

Figure 3. Proportion of Access, Watch and Reserve (AwaRe) classification of systemic antibiotic used in Scotland from March 2019 to March 2023.

Table 6. Segmented regression analysis of the monthly proportion of total items dispensed/1000 inhabitants for quality indicators of antibiotics, regression coefficient (95% confidence intervals) (between March 2019 and March 2023).

Variables	β_1	β_2	β_3	β_4	β_5
Access	**0.229 (0.001,0.453)**	−0.950 (−3.53,1.63)	0.243 – (−0.720,0.233)	1.270 – (−3.307,0.766)	0.247 (−0.176,0.670)
Reserve	0.002 (−0.004,0.010)	−0.00018 (−0.083,0.083)	−0.0031 (−0.018,0.012)	0.0176 (−0.048,0.083)	−0.0012 (−0.014,0.012)
Watch	**−0.171 (−0.277, −0.066)**	0.909 (−0.289,2.108)	0.171 (−0.050,0.392)	**0.989 (0.043,1.935)**	−0.175 (−0.372,0.020)
Co-amoxiclav	−0.004 (−0.032,0.024)	**0.414 (0.081,0.747)**	0.020 (−0.040,0.082)	0.048 (−0.213,0.311)	−0.031 (−0.085,0.023)
Cephalosporinses	−0.015 (−0.033,0.001)	**0.200 (0.002,0.397)**	**0.044 (0.007,0.080)**	0.083 (−0.072,0.239)	−0.047 (−0.079, −0.014)
Fluoroquinolones	**−0.043 (−0.064, −0.023)**	0.182 (−0.046,0.411)	**0.063 (0.020,0.105)**	0.054 (−0.126,0.234)	−0.046 (−0.083, −0.008)
Clindamycin	−0.0018 (−0.005,0.001)	**0.050 (0.010,0.090)**	0.005 (−0.002,0.012)	−0.025 (−0.057,0.005)	−0.005 (−0.012,0.001)
Grand Total ″4C″ antibiotic	0.066 (−0.133,0.0005),	**0.847 (0.084,1.611)**	0.133 (−0.007,0.274)	0.160 (−0.441,0.763)	−0.130 (−0.255, −0.005)
Broad spectrum	0.285 (−0.047,0.619)	−1.23 (−5.024,2.551)	−0.669 (−1.369,0.030)	0.028 (−2.961,3.018)	0.422 (−0.199,1.043)

Results are presented as regression coefficients (95%C), and p-values; (β_1) represents baseline trend; (β_2) the level change immediately after the first COVID lockdown; (β_3) the time trend after the first lockdown; (β_4) the level change immediately after the second lockdown and (β_5) the time trend after the second lockdown.

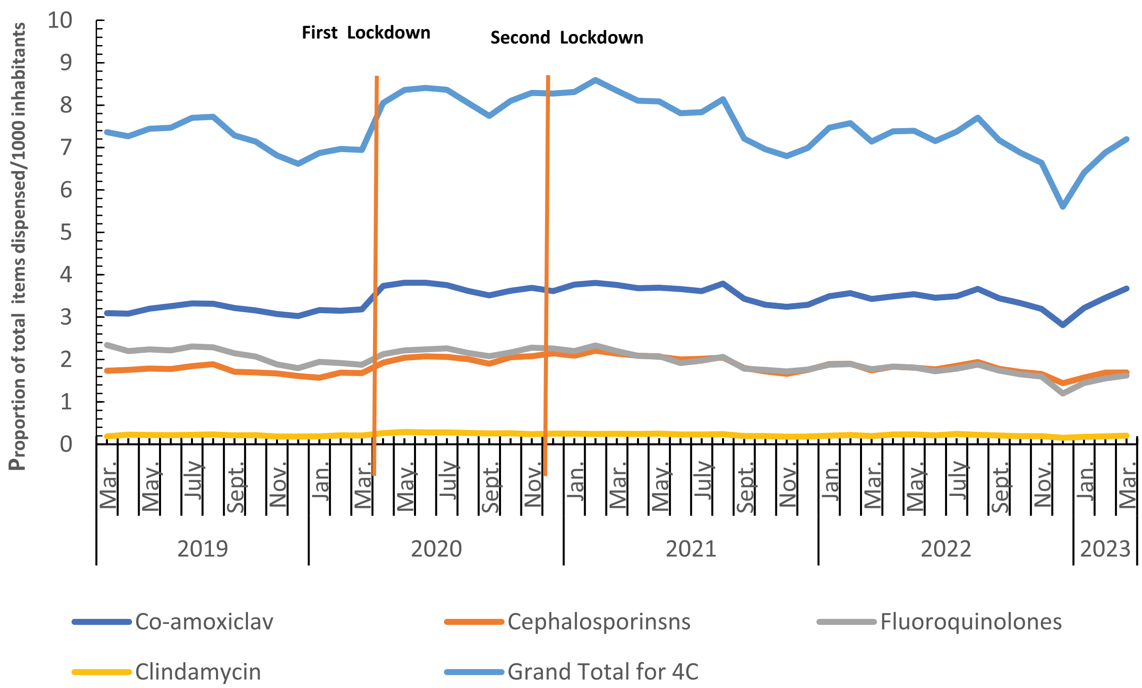

Figure 4. Proportion of ″4C″ systemic antibiotic utilisation in Scotland from March 2019 to March 2023.

lockdown (β_3) and immediately after the second lockdown (β_4) (Table 6). However, there was a significant decline in the proportion after the second lockdown for the total ″4C″ antibiotics (β_5 = −0.130, 95% CI:-0.255, -0.005), for cephalosporins (β_5 = −0.047, 95% CI: -0.079, -0.014) and fluoroquinolones (β_5= −0.046, 95% CI: −0.083, −0.008) (Table 6 and Figure 4).

3.2.3. Broad spectrum utilisation

During the study period, the broad-spectrum antibiotics were the most frequently prescribed (>70%). Overall, there was a slight decline in the proportion of broad-spectrum antibiotics with a relative reduction of 3.76% ($n = -2.85$) (Table 5, and Figure 5). Before the first lockdown, there was a non-significant increase in the baseline trend of broad-spectrum antibiotics dispensed (β_1 = 0.669, 95% CI:-0.047, 0.619) (Table 6). Furthermore, there was a non-significant decline in the level immediately after the first lockdown (β_2) and after the first lockdown (β_3). Moreover, there was no significant increase in proportion either immediately after the second lockdown (β_4) or after the second lockdown (β_4 = 0.028, 95% CI: −2.961, 3.018) (β_5 = 0.422, 95% CI: −0.199, 1.043), respectively (Table 6 and Figure 5).

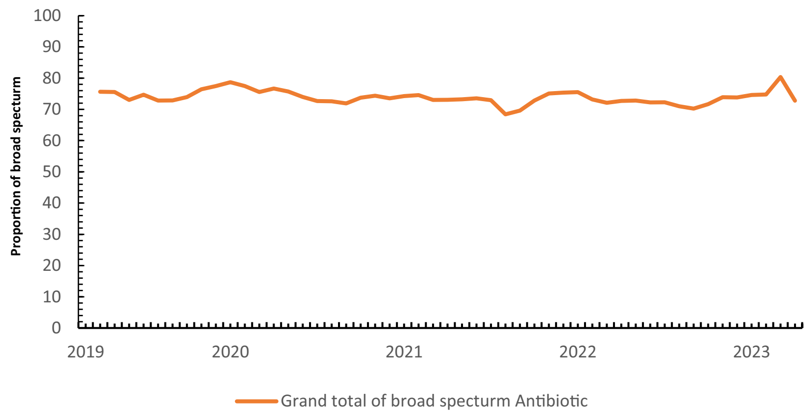

Figure 5. Proportion of broad-spectrum systemic antibiotic utilisation in Scotland from March 2019 to March 2023.

4. Discussion

4.1. Key findings

We believe this is the first comprehensive population-based study in Scotland using a repeated cross-sectional study design to assess not only the utilisation patterns but also the quality of antibiotic use (both of which are key drivers for AMR) over 49 months (March 2019–March 2023) in the primary care setting, including an assessment of the impact of COVID-19 lockdown measures. The observed non-significant increase in the number of DIDs compared with the significant increase in the number of dispensed items for total antibiotics likely indicates using lower dose strength or shorter antibiotic courses (most likely); however, this needs more research using patient-level data. This might be due to prescribers' concerns about diagnosis uncertainty as most primary care consultations were remote during the pandemic. Moreover, the observed decline, but non-significant impact of COVID-19 on antibiotic utilisation immediately following the first lockdown (β_2), after the first lockdown (β_3), and immediately after the second lockdown (β_4), could be explained by low transmission levels of the most common URTIs and limited access to GP services; consequently, less antibiotics prescribed. However, this needs further research before we can say anything with certainty. Subsequently, there was a significant increase in total antibiotics prescribed after the second lockdown with the utilisation pattern returning to the pre-pandemic level. The greatest increase was seen in December 2019–March 2020. We believe that this could potentially be explained by the cross-over of symptoms between community acquired pneumonia and COVID-19, diagnostic uncertainty, and also lack of effective treatments for COVID-19 at that time. Alongside this, perhaps due to patients' panic because of concerns about the outbreak, national lockdown measures, and seasonal changes. A similar trend has been seen in other therapeutic areas such as opioids [58]. Furthermore, the observed non-significant impact of COVID-19 could be also explained by the lack of patient-level factors (such as indication) in the PCA dataset that have been reported to otherwise influence prescribing patterns. The isolation measures implemented in Scotland and across countries helped to reduce the transmission of infections [9,11]. Similar to our findings, published studies in Canada, Portugal, and the USA showed that the consumption of antibacterials declined sharply during the early months of the COVID-19 outbreak [24,25,36]. However, the impact after the second lockdown on increasing antibiotic utilisation for both outcomes could be due to the high transmission chances occasioned by people returning to socializing. Furthermore, the big spike in antibiotic use between November 2022 and March 2023 was likely due to the appreciable Group A Streptococcus (GAS) outbreak in Scotland. This would, at least partially, have impacted on the observed significant increase in antibiotic use during the second lockdown period from the segmented regression analysis even though not related to COVID-19.

Overall, there are concerns with appreciable inappropriate prescribing of antibiotics for patients with actual or suspected COVID-19, driving up adverse reactions and AMR [39,59–63]. This is despite a very low prevalence of secondary infections or bacterial co-infections among COVID-19 infected patients, including among hospitalized patients [64–67]. The increasing use of antibiotics across settings in patients with actual or suspected COVID-19 is driven by many factors. These include overlapping clinical features with bacterial pneumonia, insufficient diagnostic tools to differentiate between bacterial and viral infections, and initial clinical uncertainty about the disease [63]. Hence, it is crucial to examine the impact of COVID-19 on the use of antibiotics within countries, especially ambulatory care where the majority of antibiotics are prescribed, and take steps toward improving the appropriateness of antibiotic prescribing where there are concerns [68,69].

In terms of the quality of antibiotic use, there appeared to be no negative impact of COVID-19 as demonstrated by increased prescribing of the Access group of antibiotics, reduction in ″4C″ use, and a non-significant change in the utilisation of broad-spectrum antibiotics. First, looking at ″4C″ antibiotics, the study results indicated that co-amoxiclav was the most prescribed antibiotic (46.64%) within the ″4C″ group. This could be due to GP consultations being remote and diagnosis uncertainty. Consequently, this might have prompted GPs to prescribe co-amoxiclav rather than for instance amoxicillin, due to its features including broad spectrum, efficacy, safety, and tolerability profile. As a result, at least partially explain the observed statistically significant increases in the level of its prescribing immediately after the first lockdown, specifically from April to August 2020. However, these were very small changes (mostly equivalent to around 1%) and hence are unlikely to be clinically significant, which is encouraging. After the second lockdown, there was a statistically significant decline in the utilisation of "4C" antibiotics overall (β_5= −0.130, 95% CI: −0.255, −0.005); however, this is unlikely to be clinically significant either.

In terms of WHO AWaRe indicator, our study found a consistent pattern of the good quality utilisation of antibiotics over time. Prescribing of the Access group increased from 76% to 90%. Moreover, average broad-spectrum use was reduced over the study periods with the highest utilisation found immediately after the second lockdown as the health-care system started to recover. However, these were statistically non-significant.

Finally, we believe that the utilisation and quality of antibiotic use in Scotland appear not to have been negatively impacted by COVID-19. This could be due to the effective antimicrobial stewardship programs promoted and implemented by the Scottish Antimicrobial Prescribing Group (SAPG) [70]. SAPG has made substantial efforts nationally to promote antibiotic reviews, shorten the duration of antibiotic prescribing where pertinent, or stop antibiotic if COVID-19 was confirmed [70–73]. In addition, produce specific prescribing guidance for both primary and secondary care. Alongside this, there was also a Scottish Government letter to all prescribers from the Chief Medical Officer, the Chief Pharmacy Officer, and the Chief Nursing Officer to promote prudent antibiotic prescribing during the pandemic. Our study provides deeper and long-term insight into the trends found in the previous quantitative studies of respiratory antibiotic use in Scotland, where the total number fell after the first lockdown in both studies. However, this was non-significant [37].

4.2. Strengths and limitations

We believe our study has many aspects that add value contributing to the current evidence on the impact of COVID-19, when compared to other studies. First, it assessed both the quality and quantity of antibiotic use over a long time period (49 months). This duration was beneficial as it gave adequate time to investigate if COVID-19 and its associated lockdown measures had affected antibiotic prescribing practices on short- and long-term period. Secondly, our study looked at all the 11 classes of antibiotics and used multiple standards and validated metrics to assess both antibiotic quality and quantity. Moreover, the study dataset covers the entire Scottish population.

However, we acknowledge that the study has limitations. Due to the lack of patient-level information, it was impossible to establish the diagnosis, duration, indications, and other prescribing details including assessing the trend across age groups or by sex. Consequently, we could not specify if antibiotics were prescribed for COVID-19 patients, prophylaxis, or treatment purposes. Ideally, to separate the effect of COVID-19 from other confounders, the trends are supposed to be compared to a control group (an area not affected by the pandemic). This was not possible in this case as COVID-19 impacted the entire country and affected all health-care systems and all therapeutic areas. Consequently, other events/interventions might have happened during this time period which might have confounded the observed impact of COVID-19 such as the GAS outbreak in Scotland during November 2022 and March 2023. Despite these limitations, we believe our findings are robust providing future direction to all key stakeholder groups in Scotland going forward.

5. Conclusion

The utilisation and quality of antibiotic use does not appear to have been significantly affected by lockdown measures introduced in Scotland to slow the spread of COVID-19. However, antibiotic utilisation seems to increase after the second lockdown period where the healthcare system started to recover. Patient-level data is needed to determine more accurate estimates of any changes in antibiotic prescribing (especially across different age groups) and to continue promoting the AMS programs. The combined quality indicators can continue to be used to assess future antibiotic prescribing in Scotland to help reduce AMR.

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Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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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.

Author contributions

Study concept and design: all authors; data collection and management: H Albalushi, A Kudri; data analysis and interpretation: H Albaulshi, A Kudri, N Almutiri, K Bakir, H Karwi, K Amen, A Seaton, B Godman; manuscript writing and drafting: H Albalushi, A Kudri, A Seaton, B Godman; manuscript reviewing and revising as well as providing constructive criticism and final approval: all authors.

ORCID

Amanj Kurdi http://orcid.org/0000-0001-5036-1988
Andrew Seaton http://orcid.org/0000-0002-2509-0597
Brian Godman http://orcid.org/0000-0001-6539-6972

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