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Impact of COVID-19 on 'Start Smart, Then Focus' Antimicrobial Stewardship at One NHS Foundation Trust in England Prior to and during the Pandemic

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Abstract: Background: Antimicrobial resistance (AMR), a major global public health threat that has caused 1.2 million deaths, calls for immediate action. Antimicrobial stewardship (AMS) promotes judicious antibiotic use, but the COVID-19 pandemic increased AMR by 15%. Although there are paramount data on the impact of COVID-19 on AMS, empirical data on AMS implementation during the pandemic are lacking. This study aimed to investigate antibiotic prescribing and AMS implementation prior to the pandemic (PP) in 2019 and during the pandemic (DP) in 2020 at one NHS Foundation Trust in England. Method: This cross-sectional study involved adult patients admitted to one NHS Foundation Trust in England, focusing on those prescribed antibiotics for respiratory tract infections (RTIs). This included cases of pneumonia in both years under study and COVID-19 cases in 2020. Data were retrospectively extracted from medical records using a validated data extraction tool, which was developed based on the 'Start Smart, Then Focus' (SSTF) approach of the AMS Toolkit. Results: This study included 640 patients. The largest age group in the study was 66–85 years, comprising 156 individuals (48.8%) PP in 2019 and 148 (46.3%) DP in 2020. CAP was the predominant diagnosis, affecting approximately 126 (39.4%) PP and 136 (42.5%) DP patients. Regarding the timing of antibiotic review post-admission, reviews were typically conducted within 48–72 h, with no significant difference between 2019 and 2020, with an odds ratio of 1.02 (95% CI 0.97 to 1.08, p-Value = 0.461). During the pandemic, there was a significant difference in both AMS interventions, 'Continue Antibiotics' and 'De-escalation', with odds ratios of 3.36 (95% CI 1.30–9.25, p = 0.015) and 2.77 (95% CI 1.37–5.70, p = 0.005), respectively. Conclusion: This study emphasises the need for robust AMS to ensure adherence to guidelines. It acknowledges the impact of comorbidities and advocates for sustained stewardship efforts to combat resistance both during and after the pandemic era.

Keywords: antimicrobial stewardship (AMS); antibiotic prescribing; respiratory tract infections (RTIs); pneumonia; COVID-19 pandemic; antimicrobial resistance (AMR)

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1. Introduction

Antimicrobial resistance (AMR) poses an urgent global threat necessitating immediate action. The rising prevalence of multi-drug-resistant infections worldwide presents immense health consequences, including escalating morbidity, mortality, and economic burden [1]. The 2016 O'Neill review sounded the alarm on an impending 'silent pandemic', projecting over 10 million annual deaths from AMR by 2050, amounting to one death every three seconds [2]. This alarming prediction highlights the critical need for coordinated efforts and innovations to avert this public health crisis. In 2019, the World Health Organisation (WHO) identified AMR as one of the top ten global health threats requiring prompt intervention [3]. That same year, AMR-related deaths had already reached 1.2 million worldwide, emphasising the need for action [1].

Antimicrobial stewardship (AMS), an organisational approach promoting judicious antibiotic use, is pivotal to the UK's 5-year AMR strategy [4]. The UK Health Security Agency (UKHSA) has recognised antimicrobial stewardship's vital role in tackling AMR, providing the 'Start Smart, Then Focus' toolkit to implement stewardship in acute-care settings [5]. This toolkit promotes timely, responsible antibiotic use by initiating effective therapies and then actively reviewing regimens within 24–72 h. The 'Start Smart, Then Focus' principles apply to all antibiotic prescriptions to streamline antimicrobial use. Antimicrobial stewardship encompasses interventions aimed at improving appropriate antibiotic prescribing across all healthcare settings [6,7].

The COVID-19 pandemic, triggered by SARS-CoV-2, and starting in China in December 2019, rapidly spread globally [8]. By June 2023, around 644 million people had tested positive for COVID-19, resulting in approximately 6 million deaths [9]. Research suggests increased antimicrobial use during the pandemic may have contributed to rising resistant infections worldwide [10]. In 2021, the US Centres for Disease Control and Prevention (CDC) reported a 15% pandemic-related increase in AMR deaths in 2020, underscoring the need for more research and action [11]. In the UK, bloodstream infections rose 11.7% from 2018 to 2022 [12]. As healthcare returns to pre-pandemic patterns, maintaining focus on AMR as the 'silent pandemic' is critical. While secondary-care antibiotic use rose slightly in 2021, usage per admission declined, suggesting increases reflected expanding hospital activity rather than more prescriptions. However, with relaxed pandemic mitigations in 2022, substantial jumps occurred in pathogen and antibiotic-usage rates [13]. Therefore, providing empirical data on the pandemic's influence on antimicrobial prescribing and stewardship is essential to re-evaluate and update policies and antimicrobial stewardship roadmaps. This will mitigate future emergency impacts on stewardship in acute-care settings and alleviate the AMR threat. This cross-sectional retrospective study was conducted on an English NHS Trust.

This study aims to investigate antibiotic prescribing and AMS implementation prior to the pandemic (PP) in 2019 and during the pandemic (DP) in 2020 at one NHS Foundation Trust in England. The objectives were as follows:

(1) To evaluate AMS implementation between PP and DP periods using the SSTF toolkit;
(2) To determine the prevalence of inappropriately prescribed antibiotics PP and DP;
(3) To identify factors influencing antibiotic prescribing and AMS implementation both PP and DP.

This study contributes to addressing gaps in the literature by providing a comparative analysis of AMS implementation and antibiotic prescribing patterns prior to and during the COVID-19 pandemic. Its findings offer insights into the challenges and changes in antimicrobial stewardship during an unprecedented global health crisis, thus informing future strategies and policy updates in the context of AMR and global health emergencies.

2. Materials and Methods

2.1. Study Design and Setting

This cross-sectional retrospective study was undertaken to estimate the prevalence of inappropriate antibiotic prescribing in adult patients aged 25 years and above who were admitted to one NHS Foundation Trust in England between 1 August 2021 and 28 February 2023. This secondary-care provider serves approximately 400,000 people and consists of about 742 beds. The data extraction tool was prepared based on the SSTF AMS Toolkit from UKHSA [5]. The study was reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement [14].

2.2. Participants

To ensure maximum diversity, a stratified sampling approach was used for selecting medical records (MRs). The study included adult patients aged 25 and older, pregnant women, and immunocompromised patients admitted to the Trust. Admissions from both 2019 and 2020 were included, with a specific focus on patients prescribed antibiotics for respiratory tract infections (RTIs), including pneumonia cases in both years and COVID-19 in 2020. Exclusions were made for patients who spent less than 48–72 h in the accident and emergency (A&E) department, those not prescribed antibiotics, and children. The study protocol was sent to representatives of the Citizens' Senate, a patient care organisation with a good representation of many older people. They reviewed it and provided feedback. This study has been officially registered with the ISRCTN registry. The ISRCTN registry is a primary registry acknowledged by the WHO and the International Committee of Medical Journal Editors (ICMJE), accepting all clinical research studies [15]. Further details on participant eligibility are provided in the study protocol, which is published on the ISRCTN website [15]. Additionally, this study was registered in Octopus, the global primary research record [16].

2.3. Data Sources and Variables

The primary author (RA) extracted data from the electronic medical records of patients within the Trust. These data encompassed age, sex, allergies (which were classified into 'allergy', 'side-effect', or 'no documentation') [17], indications for treatment, comorbidities, C-reactive protein (CRP) levels [18], white blood cell (WBC) count, serum creatinine levels, chest X-ray results, and the duration of antibiotic treatment, categorised as $\leq$3 days (shorter duration) and $\geq$6 days (longer duration). Additionally, the length of hospital stay (LOS) and patient outcomes, whether discharged or deceased, were also included.

Patient selection was based on electronic health record (EHR) entries identified by their respective ICD-10 codes for respiratory tract infections (RTIs). This encompassed a range of conditions, including both specific and indeterminate diagnoses. Specific conditions included community-acquired pneumonia (CAP), chronic obstructive pulmonary disease (COPD), hospital-acquired pneumonia (HAP), and ventilator-associated pneumonia (VAP). Notably, in 2020, the selection also extended to cases of COVID-19 pneumonia. Alongside these, indeterminate diagnoses such as upper respiratory tract infections (URTIs), lower respiratory tract infections (LRTIs), and unspecified pneumonia were also considered. The primary diagnosis of RTIs in these records was pivotal in determining the initial or empirical antibiotic prescribed to the patients.

In this NHS Foundation Trust, the initiation of empirical antibiotic treatment is based on an initial, tentative diagnosis at the time of patient admission. The primary author meticulously evaluated the alignment of the chosen empirical antibiotic treatments with the local antibiotic guidelines to ascertain their appropriateness. These local guidelines serve as a gold standard, detailing the criteria for selecting empirical antibiotics, encompassing considerations for the type of infection, patient-specific factors, and local resistance patterns. The assessment process involves a thorough review of the antibiotics prescribed, and examining aspects such as the type of antibiotic, its dosage, route of administration, and prescribed duration. This review extends beyond the initial diagnosis and is dynamically adapted based on the patient's clinical response, results from microbiological testing, and additional diagnostic procedures, like chest X-ray findings. This method ensures that the antibiotic therapy aligns not only with the preliminary diagnosis but also remains responsive to the evolving clinical scenario and diagnostic insights, thus optimising patient care whilst adhering to antimicrobial stewardship practices.

The study's sample size was carefully determined based on Public Health England's estimate that 20% of all antibiotics prescribed in the UK might be inappropriate [19]. Using Minitab statistical software, the sample size was computed, factoring in the overall population size, a 10% margin of error, and a 95% confidence interval. Data were collected from medical records PP and DP. The study involved a systematic sampling of 320 patient records from 2019 PP and an equal number from 2020 DP, totalling 640 records. Data from each year were systematically sampled to ensure representativeness and to provide a robust dataset for analysing antibiotic prescribing trends.

A data extraction tool was employed to obtain the necessary data from patients' medical records. A mind map was created to help organise the data extraction tool in relation to the antibiotic use process and the UKHSA toolkit for AMS [12], as presented in the Supplementary Materials of Figure S1. In order to extract data from patients fitting the inclusion criteria, access to the Trust's electronic system was required. Prior to commencing 'Data Extraction', the primary author completed training modules for all these systems and subsequently gained access to them. The data extraction tool was prepared in order to obtain the necessary information from the patient's medical records. The AMS data extraction tool was prepared, encompassing demographic information, primary diagnosis, SSTF criteria, AMS interventions, investigations, and patient outcomes. The extraction process took approximately 45 min per patient medical record for the primary author to gather the required data. The data extraction for each patient is shown in Table S1 of the Supplementary Materials.

The primary author reviewed the literature and the UKHSA's AMS Toolkit to develop the data extraction tool. The authors discussed, recognised, and agreed to the the elements within the tool. A pilot study was conducted to provide an initial overview of the data and to evaluate the feasibility of the data extraction tool in addressing the research questions. To validate the tool, two independent authors separately extracted data from 1% of the sample (four patient records). An agreement rate of 80% or higher was used as a measure of the tool's validity. Additionally, to assess the tool's reliability, both authors independently extracted data from another 1% of the sample (four records). Inter-rater reliability was determined by comparing the percentage agreement in data extracted independently. Any disagreements were resolved through discussion.

2.4. Statistical Methods

Descriptive analyses were conducted. Data on categorical or binary variables were presented as numbers (n) and proportions (%), while continuous variables with non-normal distributions were summarised using mean and standard deviation (SD). The 'Start Smart' approach data, including age, gender, allergies, indication, comorbidities, and duration, were described using numbers (n) and percentages (%) and further analysed via logistic regression. Similarly, the 'Then Focus' approach data, covering WBCs, CRP, serum creatinine, chest X-rays, day of antibiotic review, and type of AMS intervention, were presented in numbers (n) and percentages (%) and underwent advanced analysis via logistic regression.

In this study, the prevalence of inappropriate antibiotic prescribing was evaluated based on local antimicrobial prescribing guidelines. Inappropriate antibiotic prescribing was assessed by comparing prescriptions to hospital antimicrobial guidelines both PP and DP. The appropriateness of antibiotic prescribing according to local guidelines was assessed for both empirical antibiotic selection ('Start Smart') and the antibiotics prescribed post-review ('Then Focus'). Additionally, AMS implementation was assessed using the AMS Toolkit from UKHSA [12]. The decisions made following this review were utilised to determine the type of AMS intervention and the appropriateness of antibiotic prescribing in relation to the local guidelines [20]. A framework for data analysis was established and is presented in the Supplementary Materials as Figure S2. For more advanced statistical analysis, IBM SPSS Statistics version 22.0, RStudio version 2022, and R version 4.2.2 were employed [21,22].

3. Results

3.1. Clinical and Demographic Characteristics

A retrospective analysis was performed on 640 patients' medical records from the Trust. The demographics of these patients are presented in Table 1. The comprehensive analysis of various variables did not reveal any statistically significant differences between the years 2019 and 2020. Patients admitted for RTIs during these years ranged in age from 25 to 99 years. A slight variation was observed in gender distribution: in 2019, females accounted for 49.4% (158) of the cases, increasing slightly to 49.7% (159) in 2020. The length of hospital stays (LOS) averaged around 13.7% in 2019 and decreased to 12.3% in 2020. The

LOS ranged from a minimum of one day to a maximum of 119 days in 2019. Regarding patient outcomes, the data indicated that the mortality rate (the proportion of deceased patients) remained steady at approximately 15% during the two-year study period, as shown in Table 1.

Table 1. Characteristics and demographics of patients admitted prior to the COVID-19 pandemic (*n* = 320) and during the pandemic (*n* = 320) (in 2019 and 2020).

Patient Characteristics		Prior to the Pandemic—2019 *n* (%)	During the Pandemic—2020 *n* (%)	*p*-Value
Age (Range = 25–99)	Mean (SD)	74.3 (16.0)	76.2 (15.5)	0.127
Gender	Female (%)	158 (49.4)	159 (49.7)	
	Male (%)	162 (50.6)	161 (50.3)	
Patient Outcome	Deceased (%)	48 (15.0)	50 (15.4)	0.886
	Discharged (%)	272 (85.0)	270 (84.4)	
LOS * (Range = 1–119)	Mean (SD)	13.7 (13.7)	13.1 (12.3)	0.525

* Length of hospital stay (LOS); CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus; HAP, hospital-acquired pneumonia; LRTI, lower respiratory tract infection; URTI, upper respiratory tract infection; VAP, ventilator-associated pneumonia.

Comparing the *p*-Value of the patient demographics and outcomes between PP (2019) and DP (2020) showed no significant changes. Mean age differed slightly (PP: 74.3, DP: 76.2; $p = 0.127$), with no significant difference between gender distribution (female $p = 0.886$, male $p = 0.525$) or shift in outcomes (deceased ($p = 0.886$) and discharged ($p = 0.525$)). LOS remained consistent (PP: 13.7 days, DP: 13.1 days; $p = 0.525$), demonstrating consistency in the characteristics of patients and the impact of their conditions on hospitalisation (Table 1).

3.2. Antibiotic Prescription 'Start Smart' Approach

The term 'Start Smart' denotes the initial stage of antibiotic administration or empirical therapy [12]. The difference between the appropriateness of antibiotic prescriptions prior to and during the COVID-19 pandemic seems statistically insignificant. Age and gender do not appear to impact antibiotic prescribing patterns significantly. However, the age group of 66–85 years represented the largest segment of the study population, with 156 individuals (48.8%) PP in 2019 and 148 (46.3%) DP in 2020. For antibiotic allergy classification, only the 'side effects' category showed a significant difference between 2019 and 2020, with an odds ratio (OR) of 7.23 (95% CI 1.54 to 53.37, *p*-Value = 0.023).

Additionally, several factors influenced this initial antibiotic prescribing or empirical therapy ('Start Smart'), including the initial diagnosis 'indication'. For example, CAP was the predominant diagnosis in approximately 126 (39.4%) individuals PP and 136 (42.5%) DP. Uncertain diagnoses, including URTIs, LRTIs, and pneumonia, impact the selection of appropriate antibiotics at admission. These unclear or non-specific diagnoses accounted for 28.8% of admissions PP and 22.8% DP. Regarding COPD, a statistically significant difference was observed between PP and DP, with an odds ratio (OR) of 0.42 (0.19–0.90, $p = 0.029$). Additionally, the analysis revealed a statistically significant difference in the incidence of COVID-19 pneumonia between 2019 and 2020, with an odds ratio (OR) of 20.24 (95% CI 5.82–128.19, *p*-Value < 0.001). Concerning adherence to the empirical antibiotic treatment guidelines, it was observed that guidelines for empirical therapy were followed by 50% of the RTI study population in 2019 and 51% DP in 2020.

In comparing comorbidities prior to and during the pandemic, significant differences were observed in several conditions. Heart failure demonstrated a notable increase with an odds ratio (OR) of 2.06 (95% CI 1.23–3.52, $p = 0.007$). Hypercholesterolemia also showed a significant difference with an OR of 1.90 (95% CI 1.14 to 3.20, *p*-Value = 0.014). In contrast, kidney diseases exhibited a lower OR of 0.52 (95% CI 0.32 to 0.84, p-Value = 0.008). Similarly, liver diseases revealed an increased OR of 3.55 (95% CI 1.41–9.82, p-Value = 0.010), while asthma had a reduced OR of 0.50 (95% CI 0.25 to 0.95, p-Value = 0.038). Regarding the duration of antibiotic therapy, there were no significant differences in the duration, whether shorter (≤3 days) or longer (≥6 days), between PP and DP (Table 2).

Table 2. Adjusted ORs of factors affecting 'Start Smart' initial antibiotic prescribing prior to the COVID-19 pandemic (n = 320) and during the pandemic (n = 320) (in 2019 and 2020).

		Prior to Pandemic—2019 *n* (%)	During the Pandemic—2020 *n* (%)	Adjusted OR (95% CI)
Age	25–45	22 (6.9)	22 (6.9)	-
	46–65	52 (16.3)	46 (14.4)	1.13 (0.49–2.68, p = 0.775)
	66–85	156 (48.8)	148 (46.3)	1.35 (0.62–3.04, p = 0.455)
	>85	90 (28.0)	104 (32.4)	1.75 (0.77–4.08, p = 0.186)
Gender	Female	158 (49.4)	161 (50.3)	-
	Male	162 (50.6)	159 (49.7)	0.98 (0.67–1.42, p = 0.910)
Allergy	Allergy	18 (5.6)	17 (5.3)	-
	No Allergy	254 (79.4)	258 (80.6)	1.00 (0.46–2.20, p = 1.000)
	Not Documented	46 (14.4)	29 (9.1)	0.58 (0.23–1.45, p = 0.243)
	Side Effects	2 (0.6)	16 (5.0)	7.23 (1.54–53.37, p = 0.023) *
Indication	CAP	126 (39.4)	136 (42.5)	-
	COPD	30 (9.4)	14 (4.4)	0.42 (0.19–0.90, p = 0.029) *
	HAP	67 (20.9)	52 (16.2)	0.74 (0.46–1.20, p = 0.221)
	VAP	5 (1.5)	1 (0.3)	0.20 (0.01–1.38, p = 0.156)
	URTI	6 (1.9)	8 (2.5)	1.61 (0.46–5.85, p = 0.455)
	LRTI	30 (9.4)	23 (7.2)	0.77 (0.39–1.51, p = 0.452)
	Pneumonia	56 (17.5)	42 (13.1)	0.92 (0.53–1.60, p = 0.769)
	COVID-19 Pneumonia	-	44 (13.8)	20.24 (5.82–128.19, p < 0.001) ***
Comorbidities	Hypertension	143 (44.7)	148 (46.2)	1.17 (0.80–1.72, p = 0.414)
	Hypotension	13 (4.0)	14 (4.4)	1.20 (0.49–2.91, p = 0.689)
	Atrial Fibrillation	61 (19.0)	64 (20.0)	1.02 (0.64–1.63, p = 0.922)
	Heart Failure	32 (10.0)	63 (19.6)	2.06 (1.23–3.52, p = 0.007) **
	Hypercholesteremia	40 (12.5)	58 (18.1)	1.90 (1.14–3.20, p = 0.014) *
	Diabetes Mellitus	65 (20.3)	54 (16.9)	0.76 (0.47–1.22, p = 0.256)
	Hypothyroidism	24 (7.5)	20 (6.2)	0.81 (0.40–1.63, p = 0.555)
	Kidney Diseases	75 (23.4)	46 (14.4)	0.52 (0.32–0.84, p = 0.008) **
	Liver Diseases	8 (2.5)	19 (5.9)	3.55 (1.41–9.82, p = 0.010) *
	Malignancy	50 (15.6)	43 (13.4)	0.95 (0.57–1.57, p = 0.850)
	Osteoarthritis	31 (9.7)	40 (12.5)	1.06 (0.58–1.93, p = 0.843)
	Asthma	35 (10.9)	21 (6.5)	0.50 (0.25–0.95, p = 0.038) *
	COPD	42 (13.1)	40 (12.5)	1.38 (0.76–2.49, p = 0.289)
	Dementia	25 (7.8)	23 (7.2)	0.81 (0.41–1.59, p = 0.538)
	Epilepsy	10 (3.1)	13 (4.1)	1.32 (0.49–3.65, p = 0.580)
	Depression	12 (3.7)	20 (6.2)	1.81 (0.77–4.39, p = 0.178)

Table 2. *Cont.*

		Prior to Pandemic—2019 *n* (%)	During the Pandemic—2020 *n* (%)	Adjusted OR (95% CI)
Duration	≤3 Days (Shorter)	168 (52.5)	164 (51.3)	-
	≥6 Days (longer)	152 (47.5)	156 (48.7)	1.16 (0.82–1.66, $p = 0.400$)

HPN, hypertension; CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus; HAP, hospital-acquired pneumonia; LRTI, lower respiratory tract infection; URTI, upper respiratory tract infection; VAP, ventilator-associated pneumonia. Notes: *** $p < 0.001$; ** $0.001 \leq p < 0.01$; * $0.01 \leq p < 0.05$.

3.3. Antibiotic Prescription: 'Then Focus' Approach

Table 3 provides an overview of factors impacting 'Then Focus' antibiotic prescribing or pathogen-directed therapy in patients with RTIs prior to and during the COVID-19 pandemic. No significant differences were observed in laboratory tests for white blood cells (WBCs), C-reactive protein (CRP), or serum creatinine. The incidence of positive chest X-ray results indicating pneumonia was higher in 2020 compared to 2019, showing a statistically significant difference with an odds ratio of 1.75 (95% CI 1.04 to 2.97, *p*-Value = 0.037).

Table 3. Adjusted ORs of factors affecting the 'Then Focus' criteria for antibiotic prescribing prior to the COVID-19 pandemic ($n = 320$) and during the pandemic ($n = 320$) (in 2019 and 2020).

		Prior to Pandemic—2019 *n* (%)	During the Pandemic—2020 *n* (%)	Adjusted OR (95% CI)
WBCs		12 (3.8)	11 (3.4)	
CRP		82 (25.6)	78 (24.4)	1.00 (1.00–1.00, $p = 0.595$)
Serum Creatinine		126 (39.4)	123 (38.4)	1.00 (1.00–1.00, $p = 0.860$)
Chest X-rays	Pneumonia %	39 (12.2)	54 (16.9)	1.75 (1.04–2.97, $p = 0.037$) *
	No Pneumonia %	82 (25.6)	65 (20.3)	-
	Not taken %	199 (62.2)	201 (62.8)	1.26 (0.86–1.85, $p = 0.231$)
Day of Antibiotic Review	Mean (SD)	4.2 (2.8)	4.4 (2.9)	1.02 (0.97–1.08, $p = 0.461$)
Type of AMS Intervention	Change Antibiotics (Substitution)	25 (7.8)	20 (6.3)	-
	Continue Antibiotics	14 (4.4)	19 (5.9)	3.36 (1.30–9.25, $p = 0.015$) *
	De-escalation	37 (11.6)	81 (25.3)	2.77 (1.37–5.70, $p = 0.005$) **
	Escalation	65 (20.3)	76 (23.8)	1.50 (0.76–2.99, $p = 0.248$)
	IV-to-Oral Switch	70 (21.9)	58 (18.1)	0.97 (0.48–1.96, $p = 0.928$)
	Stop Antibiotics	94 (29.4)	59 (18.4)	0.86 (0.44–1.71, $p = 0.659$)
	No Intervention	15 (4.6)	7 (2.2)	-

WBCs, white blood cells; CRP, C-reactive protein; AMS, antimicrobial stewardship. Notes: ** $0.001 \leq p < 0.01$; * $0.01 \leq p < 0.05$.

In terms of the timing for antibiotic review post-admission, it was noted that reviews were typically conducted within 48–72 h of admission. There was no significant difference in the timing of these reviews between 2019 and 2020, with an odds ratio of 1.02 (95% CI 0.97 to 1.08, *p*-Value = 0.461).

Regarding AMS interventions, significant changes were observed in only two interventions. The 'Continue Antibiotics' AMS intervention showed a significant difference during the pandemic, with an odds ratio of 3.36 (95% CI 1.30–9.25, $p = 0.015$). Additionally, there was a notable significant increase in the 'De-escalation' AMS intervention, evidenced by a statistically significant odds ratio of 2.77 (95% CI 1.37–5.70, p = 0.005) (Table 3).

In terms of adherence to local antibiotic treatment guidelines in the 'Then Focus' approach, it was found that antibiotic choices made post-review adhered to these guidelines in 64% of the RTI study population PP in 2019. This rate of adherence or appropriateness dropped to 36% DP in 2020.

3.4. Antimicrobial Stewardship Implementation

The bar chart below presents a comparison of antimicrobial stewardship interventions in the years prior to and during the COVID-19 pandemic, specifically 2019 and 2020. From the bar chart, we can see that the percentage of cases with 'No intervention' decreased slightly during the pandemic, from 5% to 2%. There was a noticeable decline in the practice of 'Stop Antibiotics', from 29% PP to 18% DP. The 'IV-to-Oral Switch' also saw a small decrease from 22% to 18%. On the other hand, the 'Escalations' intervention increased from 20% to 24%. Notably, the rate of 'De-escalation' nearly doubled, rising from 12% to 25%, and the practice of 'Continuing antibiotics' went up from 4% to 6%. The frequency of 'Changing antibiotics, or substitution', showed a minor decrease from 7% to 6% (Figure 1).

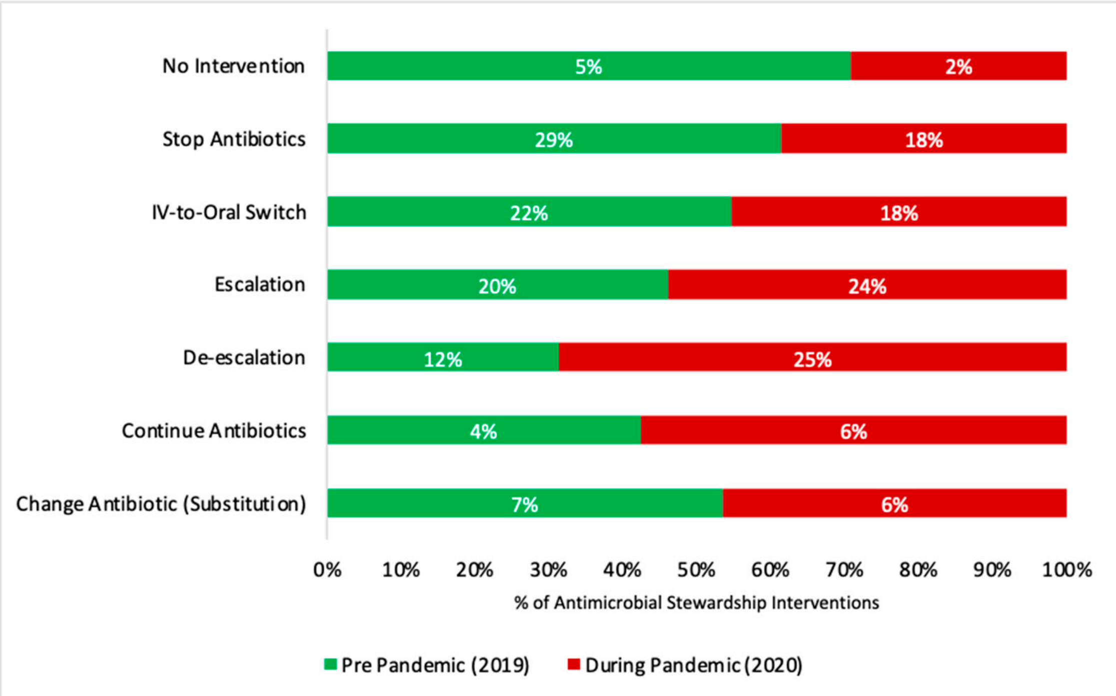

Figure 1. Antimicrobial stewardship interventions prior to and during the COVID-19 pandemic (pandemic (n = 320) and during the pandemic (n = 320) (in 2019 and 2020).

4. Discussion

This retrospective analysis evaluated the admissions of patients with RTIs both PP and DP. It also highlighted the implementation of AMS as a crucial part of the UK's five-year AMR strategy in order to enhance patient care and combat AMR [13]. It aimed to improve antibiotic prescribing, using an SSTF approach for antimicrobial stewardship [6]. As previously stated, while the toolkit proved invaluable for analysing AMS in this study, it necessitated additional revisions to encompass other variables that influence the prescription of antibiotics, precisely the initial course upon admission, known as 'Start Smart', and subsequent course(s) after hospitalisation, referred to as 'Then Focus.' By incorporating these updates, we aim to ensure the long-term viability of implementing AMS, particularly in emergencies, while concurrently reducing AMR.

Highlighting potential reasons for antibiotic stewardship is crucial. Recent data published by the European Centre for Disease Prevention and Control (ECDC) up to 2022 provide valuable insights, emphasising the need to understand and address factors contributing to antimicrobial resistance effectively [23]. When employing AWaRe 2022 as the standard for assessing antibiotic prescriptions during the COVID-19 pandemic, it becomes apparent that understanding antibiotic usage patterns in the face of the AMR threat is essential. The increase in the utilisation of 'Watch'-category antibiotics during the pandemic highlights the immediate need for robust AMS measures [24].

Antibiotics were prescribed to this study population either empirically at admission or after a 48–72 h period post-admission. CAP patients had the highest percentage of antibiotic prescriptions, with around 40% PP in 2019 and 43% DP in 2020. This aligns with a study in Denmark, where penicillin with beta-lactamase inhibitor was commonly prescribed for CAP. Only 31.3% (126 patients) of CAP cases were treated according to regional guidelines. Most patients received IV antibiotics within 4 h, and about three quarters switched to oral antibiotics by day 5 [19]. In a 2023 study conducted in England, high rates of antibiotic prescribing were observed alongside low rates of confirmed respiratory infections through cultures. Nearly one third of patients received multiple antibiotic courses, highlighting the impact of COVID-19 on antimicrobial stewardship [25].

Interestingly, another separate 2019 UK study discovered that antibiotic prescribing often deviated from guidelines, particularly for URTIs [21]. Our study has shown that when medical records contain indeterminate diagnoses, it becomes challenging to select appropriate antibiotics upon admission. For instance, a diagnosis might state 'pneumonia' without specifying whether it is community-acquired or hospital-acquired. This lack of detail also applies to URITs and LRTIs, where the exact type of infection is often not defined. This vagueness in diagnosis can substantially impact the appropriate selection of antibiotics upon admission.

In this study, the elderly demographic emerged as the most represented group, with individuals aged 66−85 years constituting the majority. This age bracket comprised 156 participants (48.8%) PP in 2019 and 148 (46.3%) DP in 2020, highlighting the need for safe AMS interventions in this age group. This finding is consistent with a 2023 study from the Netherlands, which demonstrated that a multifaceted antibiotic stewardship intervention effectively and safely reduced antibiotic prescribing in older adults. Successful implementation in various older-adult care settings necessitates active involvement from all healthcare professionals and adaptation to local circumstances [26].

In this study, adherence to local guidelines indicated that approximately 50% of patients received appropriate empirical antibiotics upon admission, with no significant difference between the PP and DP periods. However, there was a notable increase in non-adherence to these guidelines during the pandemic in 2020, with inappropriate antibiotic prescribing rising from 36% PP to 64% DP. This emphasises the necessity of sustaining AMS during pandemics or emergencies. This trend is similar to international research. In Sweden, which is renowned for one of the lowest rates of antibiotic prescriptions in Europe, a study across six sites revealed that 60% of inpatients (4119 out of 6812) were prescribed antimicrobials. By day five, 12.5% of these treatments had been escalated, whilst 21.5% were either narrowed or discontinued, influenced by initial culture collections and radiology results [27]. An English study assessing the risks and appropriateness of antibiotic prescribing in primary care during the COVID-19 pandemic analysed electronic health records from over 9 million patients.

Of the 29.2 million total prescriptions, approximately 29.1% were repeat prescriptions. For patients with same-day documented infections, lower rates of repeat prescribing were noted. Additionally, 8.6% of prescriptions were deemed potentially inappropriate based on the antibiotic type [28]. Despite the conditions of the pandemic, repeat prescribing rates did not significantly alter, highlighting the requirement for updated treatment guidelines and patient-specific information in light of the high and variable levels of repeat antibiotic prescribing observed. Although the English study focused on inappropriate antibiotic selection and repeat prescribing, our research distinctively investigated antibiotic appropriateness and AMS implementation in a secondary-care setting. The rise in inappropriate prescribing during the pandemic might be linked to the challenges faced by healthcare workers, including diagnostic uncertainties and increased patient loads. These issues, coupled with the evolving understanding of COVID-19 and its treatment protocols, influenced prescribing decisions, leading to a higher rate of non-adherence to established guidelines [28]. Our findings are in line with the broader context of AMR and antibiotic prescribing trends during the pandemic, emphasising the importance of robust AMS practices, particularly in times of healthcare crises.

Another 2021 study in England found that antibiotic prescribing patterns changed during the COVID-19 pandemic, with more early prescriptions. Different infection types were affected differently, and AMS was compromised. Future adaptations in infection management and stewardship are necessary [29]. The COVID-19 pandemic significantly influenced the number of patients admitted with RTIs. An increase in admissions in December 2019 could be attributed to the rapid spread of COVID-19 and its impact on respiratory health. Subsequent declines in March 2020 and June 2020 coincided with public health measures being put into place and the second national lockdown [13]. In England's 2021 winter season during the COVID-19 pandemic, there was a marked decrease in community antibiotic prescriptions for RTIs in primary care.

Contrary to previous winters, where such prescriptions typically increased, the 2020–2021 winter saw almost a 50% reduction compared to 2019–2020. This decline was not offset by increased prescriptions in secondary-care accident and emergency departments, suggesting fewer RTI cases and primary care visits, likely due to COVID-19 prevention measures [29]. In this study, we observed no substantial difference in appropriate antibiotic prescribing upon admission between 2019, prior to the pandemic, and 2020, during the COVID-19 pandemic. The prevalence of appropriate prescribing was 36% in 2019, compared to a similar 35% in 2020.

A nationwide cross-sectional study in Mexico in 2020 investigated the relationship between chronic conditions, comorbidities, and their impact on pneumonia and mortality in COVID-19 patients. The study revealed a clear association: chronic conditions such as cardiovascular diseases and chronic kidney disease heightened the risk of developing pneumonia. Similarly, these conditions, along with COPD, were linked to an increased likelihood of death in COVID-19 patients. Notably, the study found that the presence of multiple chronic conditions corresponded to a higher probability of either death or pneumonia in the patient sample, highlighting the critical impact of comorbidities on COVID-19 outcomes [30]. When comparing the prevalence of comorbidities PP and DP, significant differences were observed in chronic conditions. Cardiovascular diseases, such as heart failure, exhibited a notable increase during the pandemic (95% CI 1.23–3.52, $p = 0.007$), and hypercholesterolemia also demonstrated a significant rise (95% CI 1.14 to 3.20, p-Value = 0.014). Additionally, kidney diseases showed a statistically significant difference between the years PP and DP (95% CI 0.32 to 0.84, p-Value = 0.008). Liver diseases revealed a significant difference as well (95% CI 1.41–9.82, $p = 0.010$), while asthma was significantly different (95% CI 0.25 to 0.95, p-Value = 0.038). Furthermore, COPD was significantly different (95% CI 0.19 to 0.90, $p = 0.029$).

In a 2022 study conducted in Spain investigating the efficacy of chest X-rays in detecting COVID-19 pneumonia during the SARS-CoV-2 pandemic, it was determined that patients with low clinical suspicion and negative chest X-rays could be discharged with minimal risk of requiring consultation or developing severe COVID-19. The study also found that in patients who tested RT-PCR-positive for SARS-CoV-2, chest X-rays did not provide prognostic value [31]. Additionally, another 2021 study in England focusing on diagnosing COVID-19 from chest X-rays via a straightforward, rapid, and precise neural network revealed that it is feasible to accurately distinguish COVID-19 from other viral pneumonia and normal lung conditions in X-ray images. This method could aid clinicians in making more precise diagnostic decisions, underscoring the value of chest X-rays as an effective screening tool for the early and rapid identification of COVID-19 [32]. In this study, it was found that the prevalence of positive chest X-ray findings indicating pneumonia in 2021 was higher compared to 2019, as evidenced by an odds ratio of 1.75 (95% CI from 1.04 to 2.97, p-Value = 0.037). This indicates that patients were approximately 1.75 times more likely to have chest X-ray results positive for pneumonia during the pandemic in 2020 versus the pre-pandemic period in 2019. In a 2020 UK study, elevated CRP levels were found to predict bacterial and viral pathogens independently. However, their value, in addition to sputum purulence, was inconclusive [33]. Our study emphasises the importance of additional investigations like WBCs and chest X-rays to identify pneumonia patients who may benefit from antibiotics and ensure appropriate prescribing practices.

A 2021 study from Manchester showed that short and long antibiotic courses are equally effective in treating acute infections, indicating that shorter courses may help reduce antimicrobial resistance without leading to increased complications [34]. While this study did not investigate the effectiveness of different antibiotic course lengths, it was found that the proportion of patients receiving short ($\leq$3 days) versus longer ($\geq$6 days) courses of antibiotics was similar in the two years analysed PP and DP (2019 and 2020).

Across the six study sites in the USA, it was found that 12.5% of empirical antimicrobials were escalated, 21.5% were narrowed or discontinued, and 66.4% were unchanged. Narrowing or discontinuation was more likely when cultures were collected at the start of therapy (adjusted OR 1.68, 95% CI 1.05–2.70). Escalation was associated with multiple infection sites (2.54, 1.34–4.83) and a positive culture (1.99, 1.20–3.29) [35]. Furthermore, a study investigating AMS interventions during the COVID-19 pandemic discovered that 'de-escalation' and 'IV-to-Oral Switch' were significant interventions employed in acute-care settings during the pandemic period [6]. This study revealed statistically significant differences between the two AMS interventions when comparing 2019 and 2020. The odds of continuing antibiotics were 3.36 times higher in 2020 than 2019 (95% CI 1.30–9.25, p = 0.015). Additionally, the odds of de-escalating antibiotics were 2.77 times higher in 2020 (95% CI 1.37–5.70, p = 0.005). In contrast, other interventions, such as escalation, IV-to-oral switch, and stopping antibiotics, showed no significant differences between the two years (p > 0.05). Specifically, the odds ratios for escalation, IV-to-oral switch, and stopping antibiotics were 0.97 (0.48–1.96, p = 0.928) and 0.86 (0.44–1.71, p = 0.659), respectively. The COVID-19 pandemic impacted the implementation of AMS interventions. With the release of the National Institute for Health and Care Excellence (NICE) guidelines for pneumonia management in high-COVID-19-prevalence settings, the practices of intravenous-to-oral antibiotic switches (IVOS) and stopping unnecessary antibiotics decreased in 2020 compared to 2019 [36]. This highlights an urgent need to improve awareness and deliver further education on appropriate AMS interventions, with an emphasis on utilising IVOS, de-escalation, and antibiotic cessation aligned with individual patient factors and conditions. Focused efforts on these evidence-based AMS practices can help curb inappropriate antibiotic usage during public health crises. The COVID-19 pandemic has emphasised the economic and societal impact of uncontrolled infectious diseases, resembling predictions about AMR. Understanding the effects of changed antibiotic use, health-seeking behaviours, and infection control on AMR is crucial to promoting good practices and prioritising research [37]. Stewardship programs should prioritise core strategies and focus on their effectiveness before incorporating supplemental approaches. Quality indicators and improvement projects help maintain the sustainability of antimicrobial stewardship implementation, especially during the pandemic [6]. While healthcare professionals are dealing with the challenges of COVID-19, the ongoing crisis of AMR should not be neglected. Addressing AMR proactively can prevent future reactivity, similar to our response to COVID-19 [38]. In a 2022 Lancet study, the antibiotic review kit intervention method reduced antibiotic use among adult acute general medical inpatients. The COVID-19 pandemic likely influenced the inconsistent effects on mortality [39]. Hospitals should adopt the antibiotic review kit to curb antibiotic overuse. Although there was no significant difference in the day of antibiotic review before and during the pandemic, most reviews occurred after four days in both periods. This highlights the significance of multidisciplinary team ward rounds by the AMS team for proper antibiotic review and decision making for patients. SSTF audits yielded significant outcomes and valuable insights for other hospitals, resulting in improved antibiotic prescribing practices. Furthermore, incorporating other quality improvement methods can effectively sustainably enhance antibiotic prescribing [40,41].

Strengths and Limitations

Our study stands out for its comprehensive analysis of AMS in the context of the COVID-19 pandemic at an English NHS Trust, offering valuable empirical data on antibiotic prescribing practices and their seasonal variations. The robustness of our methodology, underpinned by rigorous follow-up and an established retrospective review process, coupled with a validated data extraction tool, ensures a thorough and reliable quantitative examination of AMS. However, the study is not without limitations. Its generalisability is restricted, being conducted in an acute-care setting within a secondary-care hospital, and primarily focusing on adult patients aged 75–84, excluding those under 25 and children. This limits the breadth of demographic applicability. The study's focus on RTIs also narrows its relevance to other infection types. Despite the sample size of 640 records, the examination was confined to the first and second courses of antibiotics, excluding longer courses. This might have left out vital information, especially considering the noted reduction in the maximum length of stay from 2019 to 2020. The systematic sampling methodology, while structured, might have inadvertently overlooked certain patient groups or unique cases, thereby not fully capturing the diversity in antibiotic prescribing practices. While our study provides significant insights into the practices of AMS prior to and during the pandemic, it is crucial to interpret its findings in light of these outlined limitations. The study paves the way for further research to broaden the understanding of healthcare professionals' perspectives on antibiotic prescribing in acute-care settings during the pandemic.

The study's limitations are noteworthy. It was conducted in an acute-care setting within a secondary-care hospital, which, coupled with the exclusion of children under 12 and challenges in calculating patient days, could impact the assessment of antibiotic usage and narrow its demographic scope. Moreover, its focus on RTIs limits its relevance to other infection types. Moreover, the study's limited timeframe does not fully explore ongoing changes in AMR and antibiotic stewardship. Additional research is necessary to better understand these ongoing developments and their impact on healthcare. Another major limitation arises when comparing data across seasons, considering the study's relatively short duration, the evolving virulence of SARS-CoV-2 variants, increasing treatment experience, and evolving AMR prevention measures. The analysis, based on 640 records, covers only the first and second antibiotic courses, potentially missing vital data, especially considering the reduced hospital stays from 2019 to 2020. The study's sampling approach may not fully capture the spectrum of antibiotic prescribing practices. As a retrospective, cross-sectional study, it may not precisely gauge the varied health conditions of patients and their adherence to prescribing guidelines. These limitations underscore the need for further research in this area.

Our study suggests that antimicrobial stewardship programs in acute-care settings should prioritise monitoring prescription patterns to enhance adherence to guidelines and mitigate AMR. A clear and specific diagnosis, particularly in cases of CAP, which predominated in our indications, significantly influences appropriate antibiotic selection and reduces AMR. Applying relevant severity scoring tools such as CURB-65 when initiating antimicrobial therapy and interpreting results appropriately is vital for ensuring proper antibiotic prescribing [34]. Maintaining AMS interventions, particularly 'De-escalation', is vital during antibiotic reviews in order to align with local guidelines and consider the severity of the infection. The study identified no significant difference between longer and shorter antibiotic durations PP and DP, suggesting that shorter courses of antibiotics could be considered in line with local guidelines. This consistency could be a key consideration in emergencies or crises but should always be balanced with local guidelines and clinical data, including lab results, cultures, and other diagnostic tests.

5. Conclusions

This retrospective study evaluates the impact of the COVID-19 pandemic on antibiotic prescribing and AMS practices, emphasising the pivotal role of AMS in healthcare, particularly in combating AMR. It highlights the importance of monitoring antibiotic use in accordance with local guidelines. It emphasises the importance of accurate diagnoses, such as in cases of community-acquired pneumonia, to select the appropriate antibiotics and mitigate AMR. Implementing sustainable AMS interventions, particularly 'De-escalation', is essential during emergencies like a pandemic. Additionally, the study emphasises the importance of considering chronic conditions in antibiotic decision-making for COVID-19 patients. It advocates for ongoing AMS efforts and the implementation of effective and comprehensive AMS programmes during the post-pandemic era, focusing on integrating immediate patient care with long-term strategies for fighting AMR in sustainable public healthcare.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/covid4010010/s1, Figure S1: Mind map organises data extraction for antimicrobial stewardship.; Figure S2: Framework used for data analysis used in this retrospective study; Table S1: Data extraction tool in this retrospective study.

Author Contributions: R.A.E. was responsible for data acquisition, with the study design and conceptualisation developed collaboratively by R.A.E., N.U. and Z.A.; R.A.E. carried out the literature review under N.U.'s and Z.A.'s supervision and further extracted relevant electronic data from patient records. The project dataset was constructed by R.A.E., who also verified, accessed, and analysed the data, guided significantly by N.U. and Z.A.; R.A.E. produced the initial draft of the study, guided by N.U. and Z.A. All authors contributed to data interpretation and the preparation and revision of the manuscript, sharing equal responsibility for the final decision to submit and approval of the final manuscript. Z.A. acted as the guarantor for the overall content of the research. Data were anonymised before analysis and securely stored within the University of Hertfordshire's (UH) dual secure system. R.A.E. analysed the anonymised data using UH's dual secure system. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The datasets presented in this article are not readily available, according to the institution's policy. Requests to access the datasets should be directed to r.a.elshenawy@herts.ac.uk.

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