A Nationwide Pharmacoepidemiological Analysis of the Impact of Health Policy on Antimicrobial use in Critical Care Settings in India

Abstract

A nationwide multicentric pharmacoepidemiologic analysis of antimicrobial use in critical care settings over a 2 year period in India, revealed that 76.0% (22,920) received at least one antimicrobial with 36.6% (11,027) receiving multiple antimicrobials. When classified based on the WHO AWaRe stratification, Watch group antimicrobials were most frequently ordered (56.7%;17103 patients), with the joinpoint regression analysis indicating its peak use during the second COVID-19 wave (May 2021-December 2021: MPC=2.01, $p<0.05$) and significantly higher odds noted in patients with COVID-19 (aOR:6.73 (5.78-7.88)), APACHE-II >10 (aOR:1.60 (1.49-1.71)) and ventilation requirement (aOR:1.68 (1.55-1.83)), thus indicating their use as empiric antibiotic therapy particularly in severely ill COVID patients. Individual COVID-specific Antimicrobials (CSA) exhibited temporal and geographical variation congruent with the release of scientific literature and local treatment guidelines, reflecting proactive implementation of treatment protocols. Antimicrobials are used extensively in ICUs across India, but overall and individual trends were largely influenced by scientific literature and public health messaging.

Key words

Antimicrobial stewardship, Public Health, COVID-19, India, Antimicrobial, Pharmacoepidemiological study

INTRODUCTION

Antimicrobial resistance (AMR) and antimicrobial stewardship (AMS) have been prominent areas of focus in tropical settings with high rates of antimicrobial use, particularly in intensive care units (ICUs).[1–3] Multiple factors are at the core of this trend with the most recent factor being the COVID-19 pandemic that instigated antimicrobial treatment regimens that were often unsupported by evidence.[4–6] Additionally, several drug combinations previously unused for treating respiratory infections were promoted. Evidence-based guidelines have historically been imperative to ensuring reliable AMS practices. However, conflicting guidelines and policies that evolved over the course of the pandemic from different international research bodies,[7] and supply-chain issues limiting availability of antibiotics in different regions lead to inconsistent antimicrobial practices.

In India, stark differences between urban and rural settings continue to lead to discrepancies in treatment regimens. Apart from building meticulous community and hospital-based health surveillance systems in India, analysing ICU level data pertaining to antimicrobial use and its influence on outcomes, particularly in the COVID-19 context, is an important avenue to setting up reliable surveillance systems to guide policy making and investment in healthcare infrastructure. Nationwide ICU data and metrics are generally lacking in most tropical settings and therefore longitudinal datasets from diverse settings are imperative for advancement of health systems. In this pharmacoepidemiologic study, we analyse antimicrobial order trends from a combination of government funded, not-for-profit and corporate-run ICUs across 17 Indian states over a 25-month time-frame comprising two COVID-19 waves, the intervening period, and the post-vaccine deployment phase. We also identify risk factors and study the association between antimicrobial orders and outcomes.

METHODS

Study design and setting

This study met ethics exemption criteria after application to the relevant IRBs (Board Names: Boston Children's Hospital IRB, Cloudphysician IEC; Approval number P00040679, IEC N1-2022; Title: A multi-centric retrospective analysis of clinical and laboratory data among of critically ill patients in India, Approval date: March 1st 2022, April 1st 2022)
and was conducted in accordance with the STROBE guidelines as well as in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975 across 68 ICUs in 17 Indian states (***Figure 1A***) between March 2020-April 2022, which were part of a tele-ICU network that receives critical care expertise in a centralized manner. [8] The study period was divided into 'first COVID wave', 'intervening period', 'second COVID wave' and 'post-COVID period'. The states were classified into North/Central, South, West and East/Northeast zones for geographical trend analysis. (***Table S1).***

Patient selection, Data Collection, Extraction and Cleaning

All adult patients >14 years admitted to an in-network ICU were included. Patients who received $\geq$1 antimicrobial were the subjects while patients who received no antimicrobials were the comparator population. Further analyses involved comparing orders between COVID and non-COVID status and estimating patient risk factors for receiving non-bacterial antimicrobials (NBAs) and antimicrobials from the WHO's AWaRe categories. [9] (***Table S1,S2)*** Demographic data, clinical parameters, and disposition details were collected. (***Tables 1,2***) Although the APACHE-II score [10] is considered rudimentary in ICU care, it was found to be an appropriate standardized indicator of gauging severity for the purpose of this study, given the heterogeneity in patients and ICU settings.

Demographic data, clinical parameters, as well as disposition details were collected. (***Tables 1,2****)*. The data sets for the study analysis were extracted from the larger database system that is part of a custom-built and multidisciplinary interaction platform used by ICU teams within this tele-ICU network. The information was extracted from the cloud-infrastructure that accommodates the usage of software such as PostgreSQL and Python for querying and retrieval of data from the repositories. The extraction process involved using Python (version:3.6) which was part of a cloud-instance that facilitated the usage of database toolkit for PostgreSQL to extract the data including demographic and clinical information for each patient within the study duration, spread across multiple tables. This process generated two different datasets where the primary data consisted of unique patient observations and the secondary data comprising of single and multiple antibiotic orders along with other parameters pertaining to those unique observations. This data was imported into R (version: 3.5.0), an integrated development environment for R programming language, for data cleaning and feature engineering followed by analysis and visualization processes.

Data Analysis

Data analysis was split into 3 sections:

1. Patient analysis

The dataset containing unique patient observations were analyzed to establish demographics and baseline characteristics of the overall cohort and to compare them by COVID status. Risk factors for in-hospital mortality were calculated in the form of odds ratios (ORs) adjusted for demographic and clinical characteristics, geographical and temporal details and antimicrobial orders.

2. Antimicrobial order analysis

The antimicrobial orders dataset containing all antimicrobial orders from the study period (single and multiple per patient) were analysed to identify overall, temporal, and geographical trends. Antimicrobial orders associated with a patient COVID-positive status were compared with orders associated with a non-COVID status, and forest plots with unadjusted ORs were calculated. An antimicrobial order index was also calculated which used the number of times an antimicrobial was ordered divided by the number of patients.

3. Risk factors for multiple antimicrobial orders

The unique patient dataset was then used to identify those receiving single and multiple antimicrobial orders, and identify patient risk factors in receiving multiple orders, orders of different antimicrobial classes (Access, Watch, Reserve, Non-recommended, Non-bacterial and COVID-specific) and orders of specific CSAs (Azithromycin, HCQ, Oseltamivir, Ivermectin, Favipiravir and Remdesivir). These ORs were adjusted for patient characteristics including a COVID diagnosis, gender, markers of severity (APACHE-II score, ventilation requirement), geographical location during treatment as well as time-period of treatment.

Statistical analysis and outcomes

Continuous and categorical data were presented as mean (SD) and a number (percentage) respectively, and tested using Mann-Whitney U and chi-square tests respectively. Cochrane-Armitage test was employed while analysing categorical variables. For all prediction models, univariable and multivariable logistic regression models were used to explore associations of patient baseline demographic and clinical characteristics with the outcome of interest. Due to a host of several predictors and the study's exploratory nature, we did not attempt to pre-select variables a priori for multivariable logistic regressions. Data were presented as odds ratios (OR) and 95% confidence intervals (CI). Tests were 2-tailed, with $P<0.05$ considered significant. All tests were run using R version 4.1.2 (2021-11-01).

RESULTS

Demographic and clinical characteristics

There were 30,149 admissions during the study period of which 25,694 (85.2%) were non-COVID; 3,169 (10.5%) tested COVID-positive and 1,286 (4.3%) were COVID suspects (***Figure 1B***). The first COVID wave accounted for 16.2% (4,919) of all admissions, while the intervening period, second COVID wave and post-COVID period accounted for 13.9% (4,194), 28.5% (8,570) and 41.3% (12,470) respectively. Most admissions occurred in the Eastern/Northeastern zone (12,779;42.4%) followed by the Southern zone (9,810;32.5%). However, COVID-positive and suspected patients were more common than non-COVID patients in the southern (65.4% and 70.2% vs. 26.6%, $p<0.001$) and western zones (22.1% and 25.9% vs.14.8%, $p<0.001$). (***Table2***)

Overall, 16,283 (54.0%) were male, mean age was 53.6±17.5 years and median APACHE-II score was 8.0(IQR:4-13). Among the 7,855 (26.1%) ventilated patients, median ventilation duration was 25(IQR:11-66) hours, with 3,664 (12.2%) receiving invasive ventilation and 4,650 (15.4%) receiving non-invasive ventilation (NIV). The median length of hospital stay (LOHS) overall was 43(IQR:21-87) hours, and 3,164 (10.5%) patients died. COVID-positive patients were more often male, older and had a lower median APACHE-II score on admission. While NIV and High Flow Nasal Cannula (HFNC) usage rates were higher among COVID-positive and suspect patients, COVID-positive patients had lower invasive ventilation rates compared with non-COVID and COVID suspects. Median ventilation duration, HFNC, LOHS and adjusted mortality were higher in COVID-positive compared with COVID suspects and non-COVID patients (***Table1***).

Table 1: Distribution of COVID and non-COVID patients by Antimicrobial class, Geographical locations and admission time-period

Variables	**Non-COVID [n (%)]**	**COVID-positive [n (%)]**	**COVD suspected [n (%)]**	**Overall [n (%)]**	**P value**
Total patients	25698	3169	1286	30153	
Access antibiotic use	3959 (15)	161 (5)	69 (5)	4189 (14)	<0.001
Watch antibiotic use	14043 (55)	1982 (63)	1082 (84)	17107 (57)	<0.001
Reserve antibiotic use	1029 (4)	58 (2)	17 (1)	1104 (4)	<0.001
Non-Recommended antibiotic use	4854 (19)	173 (6)	64 (5)	5091 (17)	<0.001
Non-bacterial antimicrobial use	1313 (5)	1302 (41)	624 (49)	3239 (11)	<0.001
COVID-specific antimicrobial use	486 (2)	1241 (39)	606 (47)	2333 (8)	<0.001
North/Central zone Southern zone East/Northeastern zone Western zone	2509 (10) 6836 (27) 12560 (49) 3792 (15)	211 (7) 2072 (65) 186 (6) 699 (22)	14 (1) 903 (70) 36 (3) 333 (26)	2734 (9) 9811 (33) 12782 (43) 4824 (16)	<0.001
First COVID wave Intervening period Second COVID wave Post-COVID period	3056 (12) 3041 (12) 7283 (29) 12318 (48)	1206 (38) 682 (22) 1159 (37) 122 (4)	657 (51) 477 (37) 128 (10) 30 (2)	4919 (16) 4194 (14) 8570 (29) 12470 (41)	<0.001

Table 2: Clinical and Demographic characteristics of patients admitted to ICUs within this network

Variables	**Non-COVID (n= 25698)**	**COVID-positive (n=3169)**	**COVD suspected (n=1286)**	**Overall (n=30153)**	**P value**
Male Female	13456 (52) 9979 (39)	1996 (63) 1017 (32)	833 (65) 435 (34)	16285 (54) 11431 (38)	<0.001
Age (years) [Mean (±SD)]	53 (± 18)	54 (± 18)	55 (± 16)	54 (± 18)	<0.001
APACHE-II [Median (IQR)]	8 (5-14)	5 (2-9)	7 (4-10)	8 (4-13)	<0.001
LOHS (hours) [Median(IQR)]	39 (20-71)	131 (53-228)	60 (27-132)	43 (21-87)	<0.001
Ventilation duration (hours) [Median (IQR)][#]	21 (10-51)	60 (22-132)	43 (15-92)	25 (11-66)	<0.001
Invasive ventilation duration (hours) [Median (IQR)][$]	23 (12-59)	28 (10-67)	24 (7-55)	23 (12-60)	0.433
NIV duration (hours) [Median (IQR)][@]	16 (7-35)	49 (18-102)	32 (12-78)	20 (8-46)	<0.001
HFNC duration (hours) [Median (IQR)][&]	12 (2-50)	40 (14-105)	27 (11-70)	26 (7-80)	<0.001
Ventilated [n (%)]	6132 (24)	1153 (36)	571 (44)	7856 (26)	<0.001
HFNC [n (%)]	341 (1)	428 (14)	215 (17)	984 (3)	<0.001
Death Transfer out Discharge	2128 (8) 3261 (13) 20309 (79)	659 (21) 379 (12) 2131 (67)	377 (29) 156 (12) 753 (59)	3164 (11) 3796 (13) 23193 (77)	<0.001

**2437 (8.1%) did not have a coded gender, [#]7856 received ventilation, [$]3665 received invasive ventilation, [@]4650 received NIV, [&]984 received HFNC*

Mortality risk factor analysis

Mortality odds were higher among patients with COVID (aOR:3.90(3.37-4.50)), an APACHE-II≥10 (aOR:2.18(1.94-2.44)) and ventilation requirement (aOR:4.05(3.08-5.28) all p<0.001) but decreased with LOHS>44 hours (aOR:0.36(0.32-0.40)). Compared with patients in other regions, odds of mortality were lower in East/Northeast India. Compared with the first wave, odds of mortality were lower during the intervening period (aOR:0.79(0.68-0.92), p=0.003) and the post-COVID period (aOR:0.78(0.67-0.91), p=0.001). The odds of mortality were lower with both single antimicrobial orders (aOR:0.38(0.31-0.48)) and multiple orders (aOR:0.50(0.38-0.65), both <0.001). However, there were higher mortality odds with Watch group (aOR:2.00(1.64-2.44), p<0.001), Reserve group (aOR:1.88(1.56-2.27), p<0.001) and NBAs (aOR:2.05(1.77-2.38), p<0.001), and lower odds with the use of CSAs (aOR:0.57(0.49-0.67), p<0.001), Access group (aOR:0.63(0.54-0.74), p<0.001) and non-recommended antimicrobials (aOR:0.85(0.72-0.99), p=0.043). (***Table S5***)

Overall antimicrobial orders

The 46,795 antimicrobial orders during the study period were classified into 'Access' (5,458;11.7%), 'Watch' (28,200;60.3%), 'Reserve' (1,845;3.9%) (AWaRe), 'Non-Recommended' (5,475;11.7%) and 'Non-bacterial antimicrobial (NBA)' (5,817;12.4%) groups. COVID-specific antimicrobial (CSA) orders (7,425;15.9%) included either of the following: Azithromycin, Hydroxychloroquine (HCQ), Ivermectin, Oseltamivir, Favipiravir, Remdesivir, Molnupiravir and Lopinavir/Ritonavir combination. The most prescribed antimicrobials irrespective of diagnosis included Ceftriaxone (7,881;16.8%), Piperacillin-Tazobactam (6,431;13.7%), Meropenem (3379;7.2%), Azithromycin (3,264;7.0%) and Amoxicillin-Clavulanic acid (3,019;6.5%). Watch group antibiotics were consistently the most ordered class of antimicrobials throughout, (***Figure 3***) accounting for over half of all antimicrobial orders.

COVID-associated antimicrobial orders

Among all antimicrobial orders, 21.4% (10,018) were for COVID patients. Among these COVID-associated orders, 2.9% (293) were Access, 59.0% (5,912) were Watch, 1.2% (116) were Reserve and 2.7% (273) were Non-Recommended antimicrobials. The most prescribed antimicrobials for COVID were Remdesivir (16.6%;n=1663), Azithromycin (16.1%;n=1617), Ceftriaxone (15.8%;n=1583), Piperacillin-Tazobactam (13.7%;n=1375) and Oseltamivir (7.7%;n=769) over the study duration. Comparing antimicrobial orders between COVID and non-COVID status showed lower unadjusted ORs for COVID- associated orders - Access (OR:0.23(0.10-0.54)), Watch (OR:0.33(0.18-0.61)), Reserve (OR:0.23(0.14-0.37)) and Non-Recommended (OR:0.19(0.07-0.54)) antimicrobials. (***Figure S1***)

Antimicrobial orders: Temporal trends

Overall and class-wise antimicrobial order frequency revealed a steady rise over the study duration. (***Table S3***) Based on model selection, the Joinpoint Regression identified three significant joinpoints each for the monthly mean percentage of Access and Watch group order trends and only one joinpoint for Reserve group antimicrobials. (***Figure S2***). Watch group orders fell during the first wave and intervening periods (March 2020-February 2021:MPC=-0.42; February 2021-May 2021:MPC=-2.88), significantly increased during the second wave (May 2021-December 2021:MPC=2.01), and then significantly reduced during the post-COVID period (December 2021-April 22:MPC=-2.47). A similar trajectory was noted with the Access group- a fall during the first wave (March 2020-August 2020:MPC=-2.18) followed by a rise in orders during the intervening period (August 2020-February 2021:MPC=1.47) and another fall during the post-COVID period (October 2021-April 2022:MPC=-0.87). Only one joinpoint was observed in September 2020 for the reserve group, with a steady, significant increase (MPC=0.28) until April 2022.

Geographical trends

Most antimicrobial orders were seen in the East/Northeast (16,598;35.5%) followed by the South (15,965;34.1%). In terms of antimicrobial classes, the East/Northeastern regions had the highest rates of Access (15.6% vs. 9.5%, p<0.001) and Watch group orders (65.9% vs. 57.2%, p<0.001) compared with other regions. Reserve group (5.9% vs. 3.7%, p<0.001) and Non-Recommended antimicrobials (17.8% vs. 10.9%, p<0.001) were most prescribed in North/Central regions compared with other zones. NBA and CSA orders were most frequent in the South compared with other regions (18.5% vs. 9.3%, p<0.001) and (27.5% vs. 9.9%, p<0.001) respectively. ***(Table S4)***.

An Antimicrobial Order Index (***Table S1)*** was calculated to determine regions with a high burden of antimicrobial orders relative to patient-bed days. The highest aggregate index was noted in the East/Northeastern zone (7549.7) followed by the South (6173.5). (***Figure 1A***) Compared with non-COVID orders, there were lower odds of COVID-associated antimicrobial orders in the East/Northeast (OR:0.16(0.09-0.27)) and North/Central (OR:0.31(0.19-0.52)) regions, whereas the South and West showed no significant differences between the two groups. Overall, COVID-associated antimicrobial orders were less likely (OR:0.49(0.37-0.65)). (***Figure S3***).

Risk factor analysis

Patients receiving any antimicrobials

Odds for antimicrobial orders were lower among men (aOR:0.87(0.82-0.93), p<0.001) and among COVID patients (aOR:0.68(0.62-0.75), p<0.001), and higher among those with APACHE-II≥10 (aOR:2.03(1.89-2.18), p<0.001), requiring ventilation (aOR:1.77(1.63-1.94), p<0.001), or located in North/Central India (aOR:2.41(2.11-2.77), p<0.001) and West India (aOR:1.13(1.03-1.24), p=0.012). Higher odds for antimicrobial orders were seen for the intervening period (aOR:1.86(1.65-2.09), p<0.001) and lower odds for the post-COVID period (aOR:0.90(0.82-0.99), p=0.035). (***Table S6)***

Patients receiving specific antimicrobial classes and antimicrobials

Men had higher odds of receiving AWaRe and NBA orders compared to women. There were higher odds of Watch group orders in patients with COVID (in addition to CSA orders) and APACHE-II≥10 (along with Reserve antimicrobials). Ventilated patients were associated with the orders from the AWaRe classes as well as CSAs except for HCQ. Compared with all other regions, patients in the East/Northeast zones were less likely to receive Remdesivir, Favipiravir and Oseltamivir. Additionally, patients in the South were less likely to receive AWaRe antimicrobials and Ivermectin, and more likely to receive Azithromycin and HCQ. All these risk factors were associated with multiple antimicrobial orders. (***Figure 2***)

Compared with the first wave, Watch group and CSA orders (Azithromycin, HCQ and oseltamivir) had lower odds for patients in all subsequent time-periods, while Ivermectin, Favipiravir and Remdesivir had higher odds for patients in the intervening period and second wave. The odds of receiving Ivermectin fell from the second wave to post-COVID period. (***Figure 2***) ***Supplementary tables S7-S19*** contain the crude and adjusted ORs for the above risk factors.

DISCUSSION:

This multicentric ICU study of antimicrobial order trends in the context of the COVID-19 pandemic illustrates the importance of timely publication of treatment guidelines and strong leadership to ensure adherence to it. Over half the study population received $\geq$1 antimicrobial. NBA orders were the only group that corresponded with both COVID waves (***Figure 3)*** while order trends of individual CSAs fluctuated in accordance with the release of published data and/or local guidelines.

Watch group antimicrobials were consistently the most ordered class of antimicrobials throughout, (***Figure 3***) accounting for over half of all antimicrobial orders and four of the five most ordered antimicrobials, thus alluding to its position as the empiric antibiotic drug of choice in ICUs, consistent with reports from low- and middle-income settings. [3] Furthermore, it's easy availability and lower cost, together with the lack of rapid diagnostics particularly in low-resource settings have contributed to its sustained growth in orders and sales compared with Access group antimicrobials. [1,2]

Azithromycin, a CSA, accounted for a significant proportion of Watch group orders, which were significantly associated with COVID patients, particularly those with higher APACHE-II scores and admissions during the first COVID wave. (***Figure 2;Table S8)*** This indicates that Watch group antimicrobials, notably Azithromycin and Cefotaxime, were likely employed as empiric agents in COVID-19, especially in severely ill patients. This could be due to the early pandemic misconception of the similar risk of bacterial co-infections and associated high mortality rates between COVID-19 and influenza, leading many physicians and contemporary local treatment guidelines [11,12] to consider empiric bacterial coverage with watch group antimicrobials in severe illness/septic shock as appropriate, although all state and national guidelines recommended the judicious use of antimicrobials as needed. [13] Increased antibiotic use in ICUs for COVID-19 were reported by both developed and developing countries, [4–6,14–18] with many ICUs reporting Watch group antimicrobials as the most prescribed, [4,5,14,17,18] including when not recommended by institutional guidelines. [16] Most of these studies found that antibiotic order rates were higher than confirmed infection rates [5,6,14,16,19] with one showing a 40% inappropriate order rate. [19] Even though COVID-19 bacterial co-infections were associated with increased mortality rates, [6,20] so was increased antibiotic use. [6,14] Furthermore, indiscriminate antibiotic use substantially increased the risk of emergence of Multi-Drug Resistant (MDR) bacterial strains as evidenced by the higher prevalence of MDR strains in COVID patients and its associated higher mortality compared with pre-pandemic periods. [15,20]

Another explanation for empiric antibiotic use was the syndromic approach to critically ill COVID-19 patients adopted by many physicians particularly during the early pandemic and low-resource settings where there was limited availability of testing kits and delayed testing turn-around times. While AMS programs to ensure timely and appropriate empiric antimicrobial use would reduce the likelihood of indiscriminate antimicrobial use, the pandemic posed unique challenges to AMS including barriers to diagnosing bacterial/fungal superinfections among other resource-constrained related issues. [21] Yet, with suitable considerations, successful AMS programs can be set up. [22]

As more aggregate data demonstrating the low risk of bacterial co-infections surfaced, removing all justification for empiric antibiotic use in COVID-19, [23,24] a corresponding decline in Watch group orders, particularly between waves, was noted in our trend analysis. Although Reserve group antibiotic orders remained relatively low, the sustained rise in orders over time (***Figure S2)*** along with a fall in COVID cases (***Figure 3).*** Given its utility in critically ill patients, e increase in orders along with the fall in COVID cases may be an indirect indicator for the delivery of critical care services with the help of the tele-ICU resources, in an area that previously did not have access to extensive critical care services.

Multiple antimicrobials were ordered for half of all admissions with higher odds for patients with COVID and invasive ventilation requirement. They were common for CSAs, with the composition changing over time and region, reflecting the emergence of evidence and/or local guidelines recommending/discouraging the use of different antimicrobials in the treatment of COVID-19.

Azithromycin, HCQ and Oseltamivir orders among COVID patients spiked during the first wave - presumably a result of published data demonstrating the anti-SARS-CoV-19 effect of AZT and HCQ in vitro [25,26] and all three drugs clinically, [27,28] - and then demonstrated a fall in orders correlating with the advent of data demonstrating a low safety profile and lack of clinical benefit in COVID-19 (***Figure 4***). [29–33] This also explains the higher likelihood of COVID-associated orders for these three antimicrobials during the first wave compared with the second wave. (***Figure S4)*** Support for the use of azithromycin and HCQ in local southern guidelines[34,35] also explains its higher odds of being ordered in the South compared with other regions. (***Figure 2;Table S13-15*****)**

While the proportion of Ivermectin orders remained low, its use in COVID-19 gained popularity during the intervening period and second wave with the release of supportive data and local guidelines [12,36–39]. Its subsequent decline in the post-wave period coincides with the emergence of more data highlighting its incompetence in COVID-19 (***Figures 2,4;Table S16***). [40,41] Favipiravir orders exhibited little geographical and temporal variation throughout the study period. The mild fluctuation exhibited coincides with the publication of supportive [42,43] and unsupportive data [44] respectively (***Figure 4).*** The relatively low proportion of Favipiravir orders sustained throughout may be due to its high cost and/or limited availability that resulted from a combination of pandemic-related manufacturing and supply chain disruptions and pharmaceutical hoarding.

Remdesivir demonstrated a unique biphasic pattern, with its initial spike appearing after the publication of data indicating a shorter recovery period in COVID-19. [45,46] While its use temporarily dipped after the SOLIDARITY trial demonstrated no significant benefit in COVID-19, [30] Remdesivir use in ICUs continued to rise and peaked during the second wave and post-COVID periods. (***Figure 4, S4)*** This variation may be attributed to the influence of local guidelines in determining institutional treatment protocols as Remdesivir was consistently mentioned as a limited therapeutic option for severely ill patients in multiple national and local guidelines. [12,38,47,48] While trials advocating the use of Dexamethasone appeared early on during the pandemic, [49,50] it did not seem to influence the overall frequency of antimicrobial orders, empiric or COVID-19 specific. Vaccine deployment also likely had a prominent impact in reducing NBA use between waves, but further analysis was not possible due to lack of high-resolution data of vaccine coverage and issues with statistical power analysis. (***Figure 3)***

Overall, antimicrobial trends in these ICUs across India were influenced by literature (***Figures 4,S5-7)***, local guidelines and largely uniformly implemented treatment policies, all of which were possible due to the centralized structure of this tele-ICU network. Since the bedside physician is the final decision-maker in this network's modus operandi, some regional variations are to be expected. Yet, overall, these results indicate that even in the absence of adequate diagnostic resources, access to good-quality literature, strong leadership and an effective implementation system are sufficient for judicious antimicrobial use during a pandemic.

The most prominent limitation of this study is the absence of microbiological data and confirmation of non-COVID infections which makes the determination of the appropriateness of antimicrobial orders, the distinction between empiric orders and targeted antibiotic therapy as well as the determination of early discontinuation of antimicrobials in the confirmed absence of bacterial infections/positive COVID-19 results, impossible. Secondly, a comprehensive list of comorbidities for patients and use of additional therapies such as steroids/other immunomodulatory therapies are also lacking. Thus, establishing the effect of antibiotic use on adverse outcomes (for example, mortality) was not possible. However, our large cohort from multiple varied centres across India not only provide insight into the antimicrobial order practices during the COVID-19 pandemic in the absence of adequate diagnostic resources, but also highlights the role of scientific literature as well as a strong system for implementation of guidelines that determine these practices.

CONCLUSION

Antimicrobials were used extensively in ICUs for COVID-19 infections during the pandemic, with order trends reflecting local guidelines and changing data on effectiveness of drugs in

COVID-19. In the absence of rapid diagnostics, a syndromic approach to treating severe illness can contribute to AMR emergence. Investment in rapid diagnostics and strict AMS is warranted to ensure low mortality and to reduce the risk of AMR.

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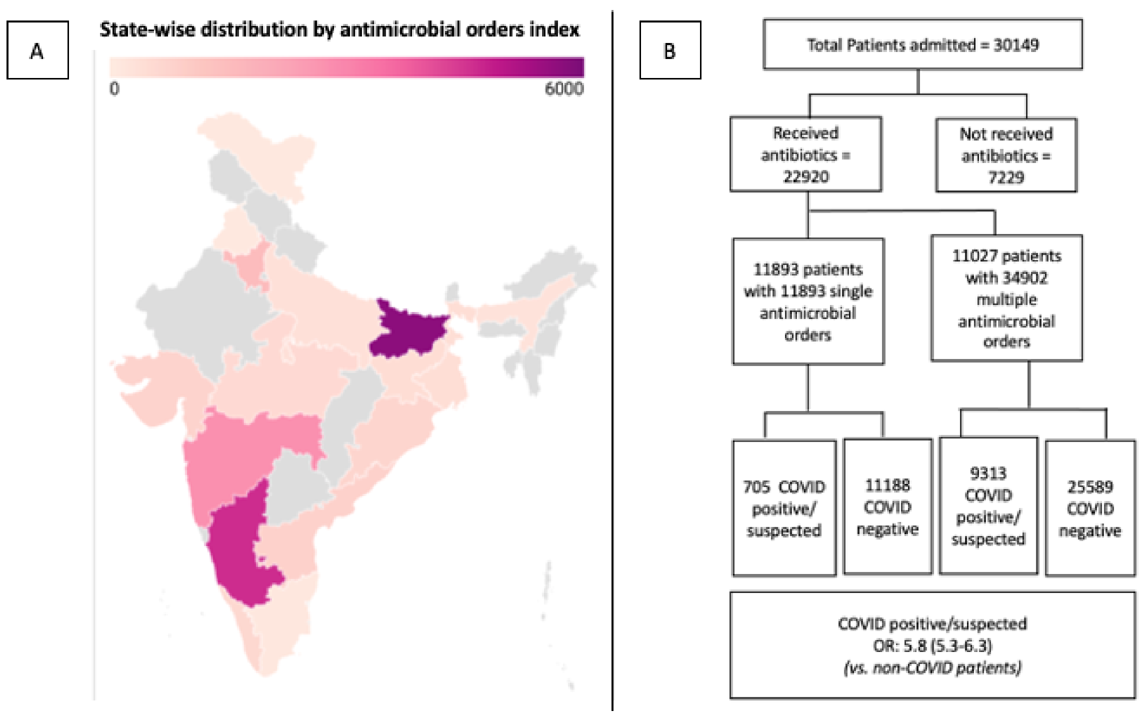
Figure Legends

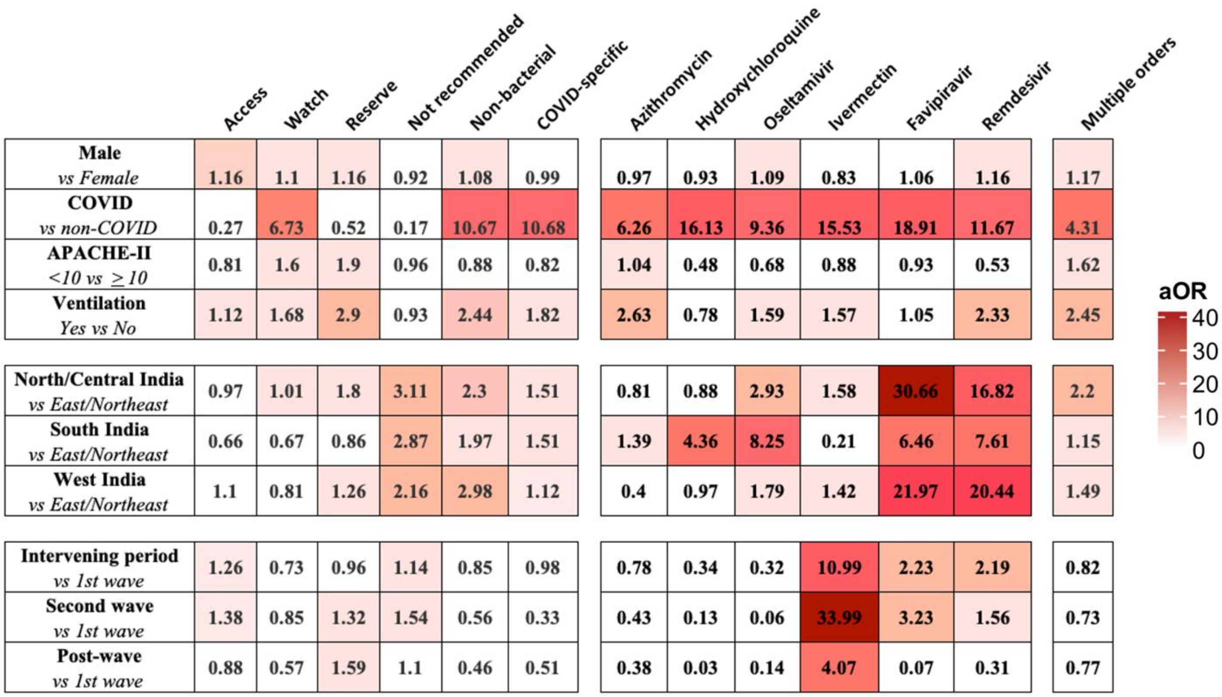
Figure 1: Fig 1A : State-wise representation of total antimicrobial orders ; 1B : Distribution of total admissions based on receipt of antimicrobials, single/multiple antibiotic order and COVID status



Panel A – State-wise representation of total antimicrobial orders relative to total patient-days in the ICUs (Antimicrobial Order Index). The highest aggregate index was noted in the East/Northeastern zone (7549.7), followed by the South (6173.5), the West (3491.2) and then the North/Central zone (2590.9). The 3 states with the highest burden were Bihar (5709.7), followed by Karnataka (4611.9) and Maharashtra (2741.9).

Panel B – Distribution of total admissions based on receipt of antimicrobials, single/multiple antibiotic order and COVID status. COVID positive patients were more likely to receive multiple antimicrobial orders than non-COVID patients.

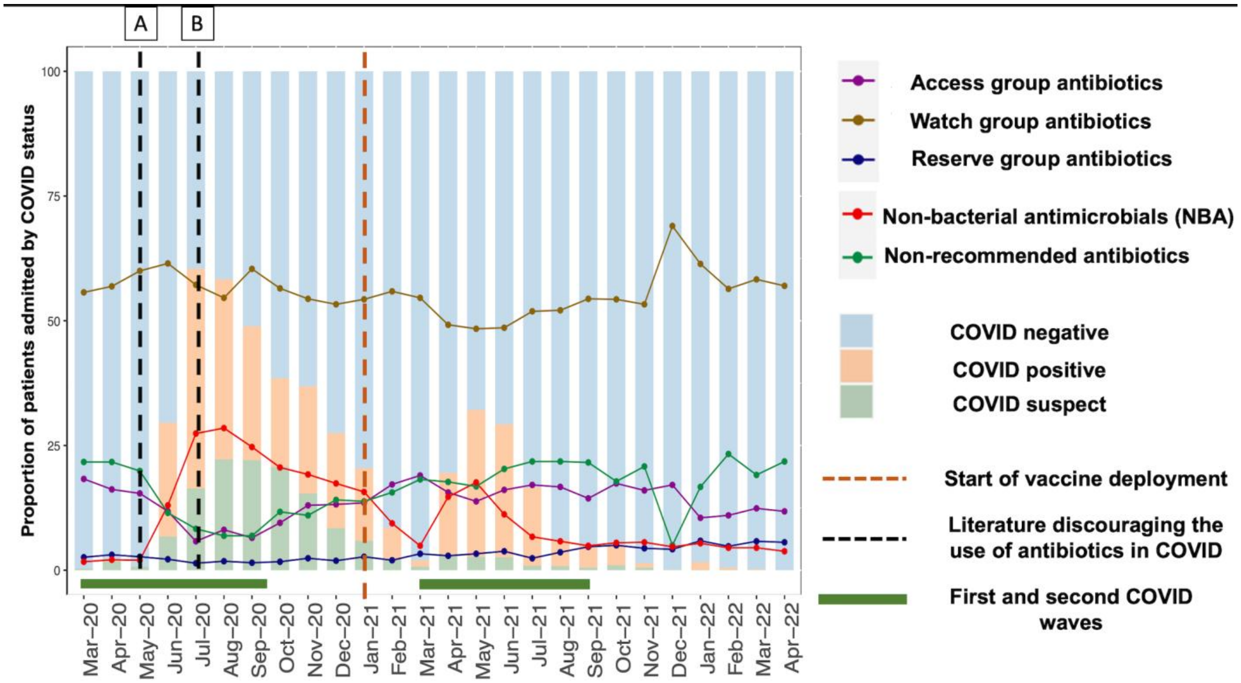
Figure 2: Heatmap of all patient risk factors and their adjusted odd ratios for receiving orders of different antimicrobial classes



	Access	Watch	Reserve	Not recommended	Non-bacterial	COVID-specific	Azithromycin	Hydroxychloroquine	Oseltamivir	Ivermectin	Favipiravir	Remdesivir	Multiple orders
Male *vs Female*	1.16	1.1	1.16	0.92	1.08	0.99	0.97	0.93	1.09	0.83	1.06	1.16	1.17
COVID *vs non-COVID*	0.27	6.73	0.52	0.17	10.67	10.68	6.26	16.13	9.36	15.53	18.91	11.67	4.31
APACHE-II *<10 vs ≥ 10*	0.81	1.6	1.9	0.96	0.88	0.82	1.04	0.48	0.68	0.88	0.93	0.53	1.62
Ventilation *Yes vs No*	1.12	1.68	2.9	0.93	2.44	1.82	2.63	0.78	1.59	1.57	1.05	2.33	2.45
North/Central India *vs East/Northeast*	0.97	1.01	1.8	3.11	2.3	1.51	0.81	0.88	2.93	1.58	30.66	16.82	2.2
South India *vs East/Northeast*	0.66	0.67	0.86	2.87	1.97	1.51	1.39	4.36	8.25	0.21	6.46	7.61	1.15
West India *vs East/Northeast*	1.1	0.81	1.26	2.16	2.98	1.12	0.4	0.97	1.79	1.42	21.97	20.44	1.49
Intervening period *vs 1st wave*	1.26	0.73	0.96	1.14	0.85	0.98	0.78	0.34	0.32	10.99	2.23	2.19	0.82
Second wave *vs 1st wave*	1.38	0.85	1.32	1.54	0.56	0.33	0.43	0.13	0.06	33.99	3.23	1.56	0.73
Post-wave *vs 1st wave*	0.88	0.57	1.59	1.1	0.46	0.51	0.38	0.03	0.14	4.07	0.07	0.31	0.77

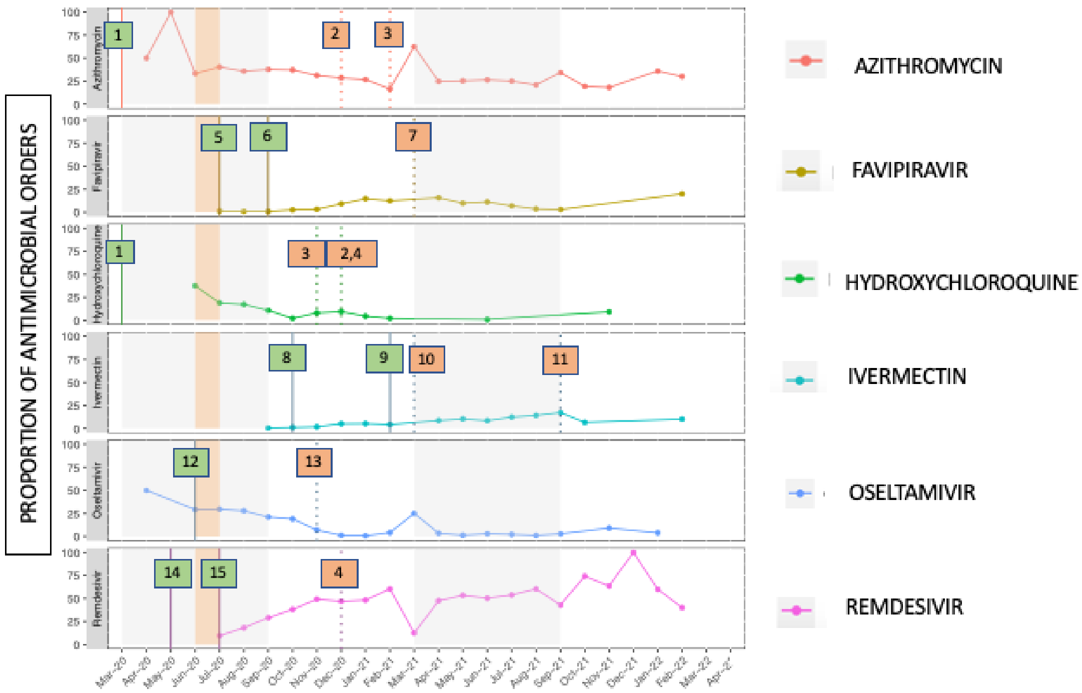
Heatmap of all patient risk factors and their adjusted odd ratios for receiving orders of different antimicrobial classes (AWaRe, NBAs, CSAs), individual CSAs (Azithromycin, HCQ, Oseltamivir, Ivermectin, Favipiravir and Remdesivir) as well as multiple antimicrobial orders. Risk factors were demographic (Male, COVID positive diagnosis), indicators of severity (APACHE-II ≥ 10, ventilation requirement), Geographical location (North/Central, South or West zones) or time-period (Intervening period, second COVID wave and post-COVID period). Adjusted ORs are mentioned for each risk factor and outcome.

Figure 3: Distribution of total admissions by COVID status as well as receipt of antimicrobial class during admission between March 2020 – April 2022.



Distribution of total admissions by COVID status as well as receipt of antimicrobial class during admission between March 2020 – April 2022. Publishing of literature discouraging the use of antimicrobials in COVID-19 (A- Rawson et al; B- Langford et al) appears to have little effect on the AWaRe antibiotic order trends.

Figure 4: Temporal trends of individual COVID-specific antimicrobial orders associated with COVID status



Temporal trends of individual COVID-specific antimicrobial orders associated with COVID status over the study period in light of literature supporting its use (solid line) or dissuading its use (dotted line) in COVID-19. References: (1) Gautret et al; (2) Ghazy et al; (3) RECOVERY trial; (4) SOLIDARITY trial; (5) Nasir et al; (6) Shrestha et al; (7) Ozlusen et al; (8) Rajter et al; (9) Chowdhury et al; (10) Lopez-medina et al; (11) Lawrence et al; (12) Coenen et al; (13) Tan et al; (14) Beigel et al; (15) Davies et al.