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Original Article

Trends in hospital antibiotic utilization during the coronavirus disease 2019 (COVID-19) pandemic: A multicenter interrupted time-series analysis

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Abstract

Objective: To describe the evolution of respiratory antibiotic prescribing during the coronavirus disease 2019 (COVID-19) pandemic across 3 large hospitals that maintained antimicrobial stewardship services throughout the pandemic.

Design: Retrospective interrupted time-series analysis.

Setting: A multicenter study was conducted including medical and intensive care units (ICUs) from 3 hospitals within a Canadian epicenter for COVID-19.

Methods: Interrupted time-series analysis was used to analyze rates of respiratory antibiotic utilization measured in days of therapy per 1,000 patient days (DOT/1,000 PD) in medical units and ICUs. Each of the first 3 waves of the pandemic were compared to the baseline.

Results: Within the medical units, use of respiratory antibiotics increased during the first wave of the pandemic (rate ratio [RR], 1.76; 95% CI, 1.38–2.25) but returned to the baseline in waves 2 and 3 despite more COVID-19 admissions. In ICU, the use of respiratory antibiotics increased in wave 1 (RR, 1.30; 95% CI, 1.16–1.46) and wave 2 of the pandemic (RR, 1.21; 95% CI, 1.11–1.33) and returned to the baseline in the third wave, which had the most COVID-19 admissions.

Conclusions: After an initial surge in respiratory antibiotic prescribing, we observed the normalization of prescribing trends at 3 large hospitals throughout the COVID-19 pandemic. This trend may have been due to the timely generation of new research and guidelines developed with frontline clinicians, allowing for the active application of new research to clinical practice.

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The first case of coronavirus disease 2019 (COVID-19) in Canada was identified on January 23, 2020, in Toronto, Canada.[1] From that point forward, COVID-19 cases waxed and waned throughout the city, which is Canada's largest city by population and one of the country's epicenters during the COVID-19 pandemic. In Toronto, there have been 5 pandemic waves to date.[2] Since 2013, Antimicrobial Stewardship has been a required organizational practice for Canadian healthcare organizations accredited by Accreditation Canada.[3] Antimicrobial stewardship programs (ASPs) aim to optimize antimicrobial use to ultimately improve patient outcomes, decrease adverse drug events, and reduce or stabilize levels of antibiotic resistance.[4,5] However, at the outset of the pandemic, many ASPs worldwide temporarily halted or reduced their functions, due to many factors including staff redeployment.[6–8] At the beginning of the pandemic, increased antibiotic

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prescribing may have been caused by evolving COVID-19 diagnostic criteria and the unclear risk of concomitant bacterial pneumonia with a novel viral pathogen.

Our ASPs faced many challenges throughout the pandemic (eg, increasing admissions of patients with COVID-19 and strain on staff resources), but we continued with efforts to minimize unnecessary antibiotic use in conjunction with regional guidelines and emerging literature. Notably, a landmark systematic living review (first published by Langford et al[9] in July 2020) identified a 3.5% rate of coinfection with bacterial pathogens at the time of presentation to the hospital. Regional COVID-19 therapeutic guidelines were developed and updated in real time by local stakeholder groups. Over time, these evolved into a provincial advisory body, and included guidance on the appropriateness of antibiotics for bacterial coinfection.[9,10] These resources empowered ASPs to limit the use of antibiotics in patients admitted with COVID-19 using a variety of established stewardship strategies including audit and feedback, educational interventions, and development of local guidelines and order sets.

Data describing the effect of the COVID-19 pandemic on antimicrobial consumption trends are limited, but concern is increasing that the pandemic has exacerbated and accelerated the development of antimicrobial resistance worldwide.[11] Most of the published data on antimicrobial use during the pandemic describes outpatient trends.[12–15] Although some published data are available from the inpatient setting (generally demonstrating increased rates of antimicrobial prescribing during the first wave of the COVID-19 pandemic), most of these studies have only described early pandemic prescribing, and antibiotic use metrics were not always standardized to patient volumes or compared to baseline prescribing patterns.[16–19] Published data on the impact of the pandemic on ASPs, and how changes in ASPs may have affected antimicrobial consumption trends, are also limited. One study, which demonstrated a decrease in antimicrobial prescribing in COVID-19 units compared to historical controls, hypothesized that the ASP was responsible for the decreased rates of antimicrobial use. However, the intensity of their COVID-19–specific multidisciplinary ASP infrastructure may not be generalizable to many institutions, due to the human resources required to sustain such an intervention over a prolonged period.[19] In addition, different factors are likely to influence antimicrobial use in inpatient and outpatient settings (eg, in the outpatient setting, initial decreased visits were associated with decreased antimicrobial prescribing), and it is important to understand the effects of the pandemic on antimicrobial prescribing across the spectrum of care. The objective of this study was to describe the evolution of prescribing of antibiotics commonly used for community-onset respiratory infections during the COVID-19 pandemic across 3 large hospitals that maintained ASP services throughout the pandemic, despite significant strain on healthcare resources.

Methods

Study setting, design, and participants

This multicenter, retrospective study of antibiotics commonly used for community-onset respiratory infections was conducted within medical floors and intensive care units (ICUs), at St Michael's Hospital (463 beds, tertiary-care, academic hospital), St Joseph's Health Centre (372 beds, community teaching hospital) and Sunnybrook Health Sciences Centre (690 beds, tertiary-care academic hospital) located in Toronto, Ontario, Canada between March 2019 and June 2021. The medical floors and ICUs included in this study cared for patients admitted with COVID-19.

Antimicrobial stewardship programs

All 3 institutions had an active ASP during the entire study period, along with an intensive audit-and-feedback program that remained active throughout the pandemic. During the pandemic, our ASPs altered how services were provided locally (eg, staff redeployment and implementing teleconferenced clinical services to support physical distancing), resulting in variations and slight modifications of each study site's ASP activities. Details of each respective hospital's ASP services before and during the pandemic are outlined in Appendix 1. Overall, there were no major changes to clinical ASP services; examples of core ASP activities that were continued across all sites during the pandemic included prospective audit and feedback, educational interventions, and development of local guidelines and order sets.

Development of evidence and guidelines to guide use of antibiotics in COVID-19

Regional COVID-19 therapeutic guidelines were released in March 2020, which included guidance on the appropriateness of antibiotics for bacterial coinfection at time of presentation to hospital.[20] Recommendations were stratified based on severity of illness. In patients with mild-to-moderate disease, these guidelines recommended against the use of antibiotics "outside approved clinical trials or where other indications would justify its use." In critically ill patients, initial guidelines recommended antibiotics for all patients admitted with COVID-19; this guidance was updated on April 3, 2020, and antibiotics were recommended "if bacterial coinfection was suspected." Prior to the third wave of COVID-19, on February 25, 2021, the guidelines were updated further with an explicit recommendation to discourage the use of antibiotics upon hospital admission for critically ill patients; advising that "bacterial coinfection is uncommon in COVID-19 pneumonia at presentation. Do not add empiric antibiotics for bacterial pneumonia unless bacterial infection is strongly suspected."[10] These changes to the guideline were based on the landmark systematic review observing low bacterial coinfection rates by Langford et al[9] (in conjunction with the Toronto Antimicrobial Resistance Research Network).

Outcomes

The primary outcome of this study was the combined monthly rates of respiratory antibiotic use measured in days of therapy per 1,000 patient days (DOT/1,000 PD) in medical wards and medical-surgical ICUs across all 3 institutions for each pandemic wave. For this study, we defined "respiratory antibiotics" as antibiotics commonly used for respiratory infections: amoxicillin-clavulanic acid, azithromycin, ceftriaxone, cefuroxime, levofloxacin, and moxifloxacin. This list encompassed all recommended treatments for community-acquired lower respiratory tract infection across all study sites. The rate of respiratory antibiotic prescribing in DOT/1,000 PD for each wave was compared to the baseline period (March 2019–February 2020). Wave 1 occurred between March and June 2020; wave 2 occurred between October 2020 and February 2021; and wave 3 occurred between March and June 2021. We also measured the number of admissions with COVID-19 to each hospital during each wave of the pandemic. The number of COVID-19 admissions was standardized per

1,000 PD to account for fluctuations in hospital occupancy throughout the pandemic.

Data sources

Antibiotic use data were collected from the electronic medical records of each participating institution. Patient-day data and number of COVID-19 admission numbers were obtained from administrative data.

Statistical analysis

An interrupted time-series analysis was used to analyze the aggregate rate of respiratory antibiotic use in all 3 institutions. Two separate analyses were performed: one examining the monthly DOT/1,000 PD on medical wards and one for ICUs. A segmented regression analysis was performed that compared each wave of the pandemic to the baseline. A level-only model was chosen due to the short duration of each wave. Monthly data were modeled using Poisson regression with the total number of patient days set as the offset variable. Seasonality was accounted for by including the calendar month in the model. Testing for autocorrelation was carried out by inspecting the residuals from the autocorrelation and partial autocorrelation plots. No evidence of autocorrelation was detected. Weighted empirical adaptive variance estimators were used to account for heteroscedasticity. All statistical analyses were performed using R version 3.4.3 statistical software (R Foundation for Statistical Computing, Vienna, Austria).

Ethical considerations

This initiative was formally reviewed by the Review of Quality Improvement Studies (ReQuIST) at St Michael's Hospital and St Joseph's Health Centre and was evaluated using the Ethics Review Self-Assessment (ER-SAT) at Sunnybrook Health Sciences Centre. Both entities indicated that neither research ethics board approval nor written informed consent from participants was required.

Results

COVID-19 admissions

All 3 hospitals had large volumes of COVID-19 admissions during all 3 waves of the pandemic which were relatively well distributed (Table 1). With each successive wave, all hospitals saw an increase in the proportion of patients they cared for with COVID-19, with the exception of hospital 1, which had a slight decrease in the volume of patients they cared for in wave 2 (14.4 COVID-19 admissions per 1,000 PD) compared to wave 1 (19.9 COVID-19 admissions per 1,000 PD). All 3 hospitals saw the largest volumes of COVID-19 admissions in wave 3.

Baseline respiratory antibiotic use

All 3 institutions had comparable rates of respiratory antibiotic usage at baseline. In the medical wards, the monthly usage ranged from 98 to 210 DOT/1,000 PD. The baseline monthly means in medical wards for hospitals 1, 2, and 3 were 139, 150, and 138 DOT/1,000 PD, respectively. In ICUs, monthly usage ranged from 95 to 286 DOT/1,000 PD. The baseline monthly means in ICUs for hospitals 1, 2, and 3 were 162, 178, and 195 DOT/1,000 PD, respectively.

Table 1. COVID-19 Admissions Compared Between Study Sites

Variable	Wave 1 (Mar–Jun 2020)	Wave 2 (Oct 2020–Feb 2021)	Wave 3 (Mar–Jun 2021)
Total COVID-19 admissions	443	911	1,342
Hospital 1, no. (%)	151 (34)	196 (22)	383 (29)
Hospital 2, no. (%)	120 (27)	393 (43)	521 (39)
Hospital 3, no. (%)	172 (39)	322 (35)	438 (33)
Total COVID-19 admissions per 1,000 PD[a]	11.3	15.8	25.9
Hospital 1	19.9	14.4	32.4
Hospital 2	9.9	19.6	28
Hospital 3	8.9	13.4	20.6

Note. PD, patient days.
[a]Includes intensive care units and medical units.

Respiratory antibiotic use during the pandemic

All 3 institutions observed a statistically significant increase (rate ratio [RR], 1.76; 95% confidence interval [CI], 1.38–2.25) in respiratory antimicrobial use during the first wave of the pandemic in their medical wards (Fig. 1 and Table 2). The rates did not significantly differ when compared to the pre–COVID-19 baseline period for the following 2 waves, despite having more patients admitted with COVID-19. This change was temporally associated with the publication of the systematic review by Langford et al.[9]

A similar trend was observed in the ICUs. Respiratory antibiotic use increased by 30% in wave 1 (RR, 1.30; 95% CI, 1.16–1.46). This increase persisted in the second wave of the pandemic (RR, 1.21; 95% CI, 1.11–1.33). After regional COVID-19 therapeutic guidelines were modified to discourage the use of antibiotics in critically ill patients admitted with COVID-19, respiratory antibiotic use returned to the baseline in the third wave, which saw the highest number of admitted patients with COVID-19 (Fig. 2 and Table 2).

Discussion

We examined the use of antibiotics commonly used for community-onset respiratory infections throughout the first 3 waves of the COVID-19 pandemic in Toronto, Ontario. In the medical wards, a 76% increase in respiratory antibiotic prescribing was observed in wave 1 but not in waves 2 or 3, despite higher numbers of patients admitted to the hospital with COVID-19 in the latter 2 waves. In ICUs, respiratory antibiotic use increased by 30% and 21% in waves 1 and 2, respectively; however, respiratory antibiotic use returned to the baseline in wave 3. Respiratory antibiotic use was similar between institutions (Figs. 1 and 2), and antibiotic use data were compared to a baseline period to adjust for seasonal and institution-specific prescribing trends.

Throughout the COVID-19 pandemic, significant healthcare resource strain has been described, leading to reduced or suspended ASP interventions.[6–8] However, data describing the use of antibiotics in hospitalized patients throughout the many waves of the current pandemic are limited, especially in North America. In our study, clear prescribing trends evolved similarly in 3 large, acute-care hospitals that continued core ASP activities and followed the same regional COVID-19 therapeutic guidelines. Similar to existing publications, we noted an increased use of antibiotics during the pandemic.[16–19] Compared to existing publications, our antibiotic use metrics were normalized with the use of

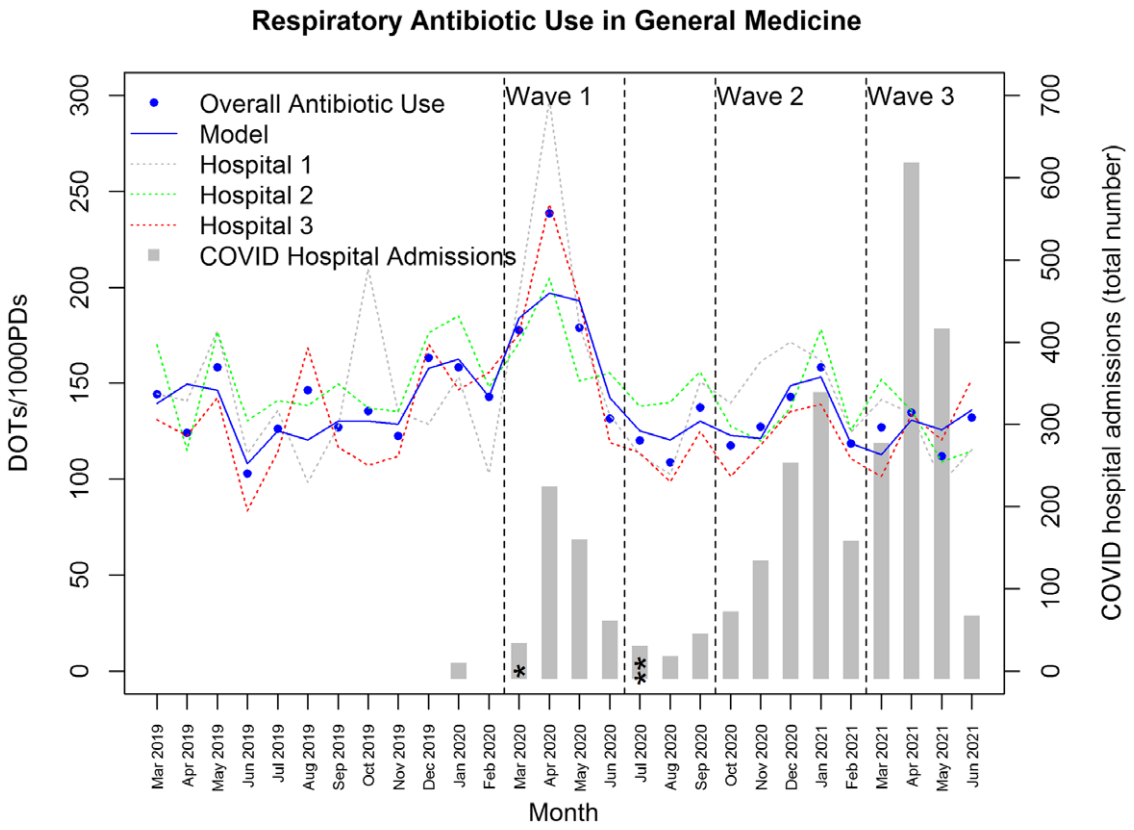

Fig. 1. Respiratory antibiotic use in general medicine. *Regional COVID-19 therapeutic guidelines were released that recommended against antibiotic use in patients with mild-to-moderate disease[20] **Langford et al[9] was published identifying a low rate of bacterial coinfection on admission.

patient day data, and we adjusted for prior antibiotic prescribing trends and seasonality with the use of an interrupted time-series analysis. We also analyzed antibiotic use between different pandemic waves to examine the evolution of antibiotic prescribing as new publications and guidelines were developed throughout the first 3 waves of the pandemic.

In this study, we observed a large initial increase in respiratory antibiotic prescribing, followed by reduced prescribing in subsequent pandemic waves even though COVID-19 admissions increased with every wave. All authors were involved in the clinical care of COVID-19 patients during the pandemic, and through our experiences, we identified several potential mechanisms and drivers of appropriate antibiotic prescribing. Firstly, the generation of timely scientific research to inform clinical practice and to develop evidence-based guidelines was essential. For example, the systematic living review published in July 2020[9] was the first large-scale meta-analysis describing the low incidence of bacterial coinfection in patients with COVID-19. Secondly, ASPs benefitted from the rapid development of regional COVID-19 treatment guidelines, which began as an informal initiative among hospitals in the Greater Toronto Area and later was incorporated into an advisory body to the government (Ontario COVID-19 Science Advisory Table). In contrast to some major international guidelines,[21,22] the Ontario COVID-19 Science Advisory Table guidelines include explicit recommendations against the use of antibiotics unless there is a specific concern for bacterial coinfection. Contributors to these regional consensus guidelines included frontline healthcare clinicians across the province, with diverse backgrounds regarding practice setting (rural and urban centers) and clinical specialty (infectious diseases, antimicrobial stewardship, critical care, ambulatory care, and patient partners). Finally, involvement of ASPs in regional guideline development and as local content experts facilitated knowledge translation and implementation of evidence-based guidelines. This process occurred both at the individual patient level via prospective audit and feedback and at the system level via interventions such as order sets and institution-wide continuing education initiatives. Each of these potential mechanisms are closely linked and act in tandem; new research is needed to inform the development of evidence-based guidelines, which then empowers individual ASP initiatives to optimize antibiotic use.

Although our results do not prove causation, our findings may indicate that local and regional ASP initiatives and resources were successful in reducing unnecessary antibiotic use in patients with COVID-19. Despite the pandemic-associated challenges for each institution's ASP, all programs maintained some form of prospective audit and feedback (the gold standard, and guideline-recommended approach/cornerstone for ASPs)[23] throughout the pandemic, and we observed that prescribing trends changed similarly across all study sites despite the local variations in ASP activities. Thus, we hypothesize that the combinations of a variety of ASP approaches were successful at changing prescribing behavior and that regional guidelines also contributed to improving antibiotic prescribing practices throughout the pandemic. Notably, a Public Health Ontario survey of all hospitals in the province reported that the pandemic may have had less adverse impact on core ASP activities and ASP funding in Ontario, compared to programs in other jurisdictions.[24]

Although our study observed similar trends of local respiratory antibiotic prescribing during the pandemic, it had several

Table 2. Segmented Regression Analysis of Combined Respiratory Antibiotic Days of Therapy (DOT) per 1,000 Patient Days (PD) during the First Three Pandemic Waves Compared to the Baseline

Variable	Level Rate Ratio (95% CI)	*P* Value
Medical wards		
Wave 1 (Mar–Jun 2020)	1.76 (1.38–2.25)	<.001
Wave 2 (Oct 2020–Feb 2021)	1.02 (0.96–1.08)	.56
Wave 3 (Mar–Jun 2021)	1.01 (0.88–1.16)	.92
Intensive care units		
Wave 1 (Mar–Jun 2020)	1.30 (1.16–1.46)	<.001
Wave 2 (Oct 2020–Feb 2021)	1.21 (1.11–1.33)	<.001
Wave 3 (Mar–Jun 2021)	0.93 (0.75– 1.15)	.51

Note. CI, confidence interval.

limitations. Although our results are hypothesis generating, our descriptive study could not identify the causative factors specifically responsible for the initial increase, and subsequent normalization of respiratory antibiotic prescribing during the first 3 waves of the COVID-19 pandemic across our institutions. We only included antibiotics recommended for community-acquired lower respiratory infection to best capture the direct impact of COVID-19 on antimicrobial prescribing. We did not have access to indications for antimicrobial therapy, thus our utilization data may have included antibiotics used for indications other than respiratory tract infection and may have excluded some patients who received broader antimicrobial coverage for bacterial coinfection. We were also unable to identify and exclude a small amount of study-related antibiotic prescribing (eg, REMAP-CAP[25]). In addition, we were not able to restrict our study population solely to patients with COVID-19, due to limitations of administrative data. Thus, we selected a nonconventional metric of COVID-19 admissions per 1,000 PD. Our selected study units were chosen because they represent the admitting units for most COVID-19 patients at our institutions. Another factor that may have influenced our study results is the possible change in patient demographics across our study units throughout the pandemic (eg, surgical units may have taken patients who would usually be admitted to a medicine ward for bed-spacing purposes). Patient demographics may also have varied between our institutions, which could have contributed to variances from observed baseline antibiotic prescribing patterns. We attempted to control for these variances by including a local baseline use period and adjustment for seasonality, which provided a local historical comparator. Our chosen metric (DOT/1,000 PD) did not specifically assess appropriateness of antibiotic prescribing; however, the continuation of our local prospective audit-and-feedback programs regularly assessed antibiotic appropriateness in real time throughout the pandemic. Furthermore, as all 3 sites had comprehensive ASPs consisting of a variety of interventions (both prior to and during the pandemic), we were not able to directly identify which specific ASP intervention(s) may have driven our observations or whether additive or synergistic effects exist with multiple ASP interventions. Finally, it is unclear whether our

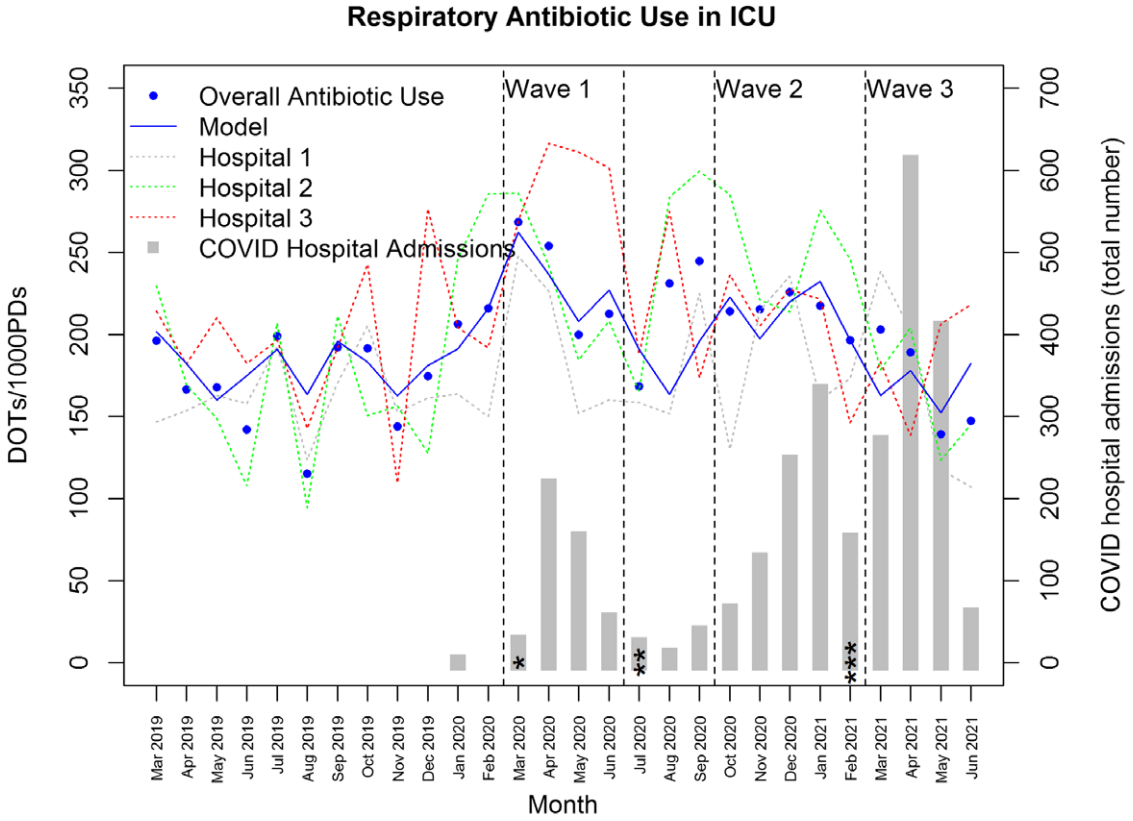

Fig. 2. Respiratory antibiotic use in intensive care units. *Regional COVID-19 therapeutic guidelines were released that recommended antibiotic use in critically ill patients when bacterial coinfection was suspected.[20] **Langford et al[9] was published identifying a low rate of bacterial coinfection on admission. ***Regional COVID-19 therapeutic guidelines were revised to highlight the low rate of bacterial coinfection on admission and recommended against antibiotic use in critically ill patients unless bacterial coinfection was strongly suspected.[10]

observations are representative of other regional or international institutions, which may have had differing prepandemic ASP resources and may have faced different pandemic-related limitations or local pressures.

In summary, after an initial surge in respiratory antibiotic prescribing, we observed the normalization of prescribing trends at 3 large hospitals throughout the first 3 waves of the COVID-19 pandemic in Toronto, Ontario. Although exact causation could not be established, our results suggest that our ASPs were successful at decreasing respiratory antibiotic use by maintaining core antimicrobial stewardship activities, despite significant resource strains throughout the pandemic. Timely generation of new research and evidence, and rapid knowledge translation into guidelines with the involvement of frontline clinicians and local stakeholders, may have contributed to the success of our ASPs. Our study illustrates the essential nature of ASPs for both monitoring and influencing antibiotic prescribing trends; therefore, it is important to support the growth and development of ASPs, especially in situations in which the overuse of antibiotics is likely to occur.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/ash.2022.268

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Conflicts of interest. E.L., J.L., L.T., M.E., M.W., and P.W.L. are members of the Toronto Antimicrobial Resistance Research Network (TARRN). E.L. is a voting member of the Ontario COVID-19 Science Advisory Table's Clinical Practice Guidelines Working Group.

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