

The Impact of COVID-19 on Outpatient Antibiotic Prescriptions in Ontario, Canada; An Interrupted Time Series Analysis

Taito Kitano,^{1,2} Kevin A. Brown,^{2,3,4} Nick Daneman,^{2,4,5} Derek R. MacFadden,^{4,6} Bradley J. Langford,² Valerie Leung,^{2,7} Miranda So,^{8,9} Elizabeth Leung,^{9,10,11} Lori Burrows,¹² Douglas Manuel,^{4,6} Dawn M. E. Bowdish,¹³ Colleen J. Maxwell,^{4,14} Susan E. Bronskill,^{4,5,15,16} James I. Brooks,^{17,18} and Kevin L. Schwartz^{2,3,4,19}

¹The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada, ²Public Health Ontario, Toronto, Ontario, Canada, ³Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada, ⁴ICES, Toronto, Ontario, Canada, ⁵Sunnybrook Research Institute, Toronto, Ontario, Canada, ⁶Ottawa Hospital Research Institute, University of Ottawa, Ottawa, Ontario, Canada, ⁷Toronto East Health Network, Michael Garron Hospital, Toronto, Ontario, Canada, ⁸Sinai Health System-University Health Network Antimicrobial Stewardship Program, Toronto, Ontario, Canada, ⁹Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada, ¹⁰Unity Health Toronto, St. Michael's Hospital, Toronto, Ontario, Canada, ¹¹Li Ka Shing Knowledge Institute, Toronto, Ontario, Canada, ¹²Department of Biochemistry and Biomedical Sciences and the Michael G. DeGroot Institute for Infectious Disease Research, McMaster University, Hamilton, Ontario, Canada, ¹³Michael DeGroot Institute for Infectious Disease Research, McMaster Immunology Research Centre, Department of Medicine, McMaster University, Hamilton, Ontario, Canada, ¹⁴Schools of Pharmacy and Public Health Sciences, University of Waterloo, Waterloo, Ontario, Canada, ¹⁵Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Ontario, Canada, ¹⁶Women's College Hospital, Toronto, Ontario, Canada, ¹⁷Public Health Agency of Canada, Ottawa, Ontario, Canada, ¹⁸Division of Infectious Diseases, University of Ottawa, Ottawa, Ontario, Canada, and ¹⁹Unity Health Network, St. Joseph Health Centre, Toronto, Ontario, Canada

Background. The coronavirus disease 2019 (COVID-19) pandemic has potentially impacted outpatient antibiotic prescribing. Investigating this impact may identify stewardship opportunities in the ongoing COVID-19 period and beyond.

Methods. We conducted an interrupted time series analysis on outpatient antibiotic prescriptions and antibiotic prescriptions/patient visits in Ontario, Canada, between January 2017 and December 2020 to evaluate the impact of the COVID-19 pandemic on population-level antibiotic prescribing by prescriber specialty, patient demographics, and conditions.

Results. In the evaluated COVID-19 period (March–December 2020), there was a 31.2% (95% CI, 27.0% to 35.1%) relative reduction in total antibiotic prescriptions. Total outpatient antibiotic prescriptions decreased during the COVID-19 period by 37.1% (95% CI, 32.5% to 41.3%) among family physicians, 30.7% (95% CI, 25.8% to 35.2%) among subspecialist physicians, 12.1% (95% CI, 4.4% to 19.2%) among dentists, and 25.7% (95% CI, 21.4% to 29.8%) among other prescribers. Antibiotics indicated for respiratory infections decreased by 43.7% (95% CI, 38.4% to 48.6%). Total patient visits and visits for respiratory infections decreased by 10.7% (95% CI, 5.4% to 15.6%) and 49.9% (95% CI, 43.1% to 55.9%). Total antibiotic prescriptions/1000 visits decreased by 27.5% (95% CI, 21.5% to 33.0%), while antibiotics indicated for respiratory infections/1000 visits with respiratory infections only decreased by 6.8% (95% CI, 2.7% to 10.8%).

Conclusions. The reduction in outpatient antibiotic prescribing during the COVID-19 pandemic was driven by less antibiotic prescribing for respiratory indications and largely explained by decreased visits for respiratory infections.

Keywords. antimicrobial prescribing; antimicrobial stewardship; COVID-19; family physician; outpatient.

Health care services have been impacted by the coronavirus disease 2019 (COVID-19) pandemic. As a result of public health measures, the epidemiology of some communicable diseases and the number and type of contacts with the health care system have changed, which may result in associated changes in antibiotic prescribing behaviors [1–4]. Many community clinics shifted to provide more virtual care during the pandemic [5, 6]. The pandemic may have also affected patients' behavior for seeking health care, and certain patient subgroups faced more substantial barriers to accessing in-person or virtual care than

other groups [7]. These factors may have impacted antibiotic prescribing in the community.

Outpatient antibiotic prescribing has decreased during the pandemic in multiple jurisdictions [8–11]. However, few studies have explored possible explanatory factors, including the volume of patient visits and diagnoses [8, 11]. For example, a systematic review raised concerns about the potential for higher antibiotic prescribing rates in virtual visits than in face-to-face visits [12]. Outpatient antibiotic prescribing may also be associated with the prescriber's specialty, patient diagnosis, and patient demographics (eg, age and sex) [13, 14]. Evaluating factors influencing antibiotic prescribing during the COVID-19 pandemic may provide insights into stewardship opportunities and provide intervention targets in the post-COVID-19 period. Our objectives were to evaluate the impact of the COVID-19 pandemic on outpatient antibiotic prescriptions and antibiotic prescriptions/patient visits and to identify which factors,

Received 20 August 2021; editorial decision 13 October 2021; accepted 27 October 2021; published online 30 October 2021.

Correspondence: T. Kitano, MD, MPH, 555 University Ave, Toronto, ON, Canada, M5G 1X8 (tkitano1@jhu.edu).

Open Forum Infectious Diseases® 2021

Her Majesty the Queen in Right of Canada, as represented by the Public Health Ontario, 2021. <https://doi.org/10.1093/ofid/ofab533>

including prescriber's specialty, patient demographics, and patient conditions, may have influenced variations in prescribing behavior.

METHODS

Study Design and Setting

This was a retrospective cohort study evaluating outpatient antibiotic prescriptions in Ontario, Canada, between January 2017 and December 2020. We conducted an interrupted time series (ITS) analysis to evaluate the impact of the COVID-19 pandemic on antibiotic prescriptions. Ontario initially declared a state of emergency on March 17, 2020 [15]. We defined the period between March and December 2020 as the COVID-19 period, while the period between January 2017 and February 2020 was defined as the pre-COVID-19 period.

Data Source

The Geographic Prescription Monitor (GPM) database from IQVIA was used for the monthly absolute number of antibiotic prescriptions. The GPM database was created from ~60% of prescriptions dispensed by outpatient pharmacies in the province. IQVIA then uses insurance claims and sales data in a proprietary geospatial projection algorithm to project 100% of antibiotic prescribing [16]. IQVIA is a source of data containing a variety of prescription drug databases, including antibiotic prescribing. This IQVIA database and extrapolation algorithm have been previously validated [17]. This database was linked by month to aggregated outpatient visit data based on Ontario Health Insurance Plan (OHIP) billings from ICES (formerly the Institute for Clinical Evaluative Sciences). These data sets were linked using unique encoded identifiers and analyzed at ICES. ICES is an independent nonprofit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze health care and demographic data, without consent, for health system evaluation and improvement. The patient visits were divided into face-to-face and virtual visits. Virtual visits included both video and telephone interactions.

Outcomes

The primary outcomes of interest were the monthly absolute number of total outpatient antibiotic prescriptions and total outpatient antibiotic prescriptions per 1000 patient visits. Outpatient antibiotic prescriptions included all pharmacy prescriptions for oral antibiotics in Ontario, excluding inpatient antibiotic prescriptions. The visit data were obtained from family physicians and physician subspecialists (ie, all non-family medicine physician subspecialties) via the linked ICES databases; therefore, analyses using antibiotic prescriptions per 1000 patient visits were restricted to antibiotics prescribed by family physicians and physician subspecialists only (both the numerator and the denominator of antibiotic prescriptions/1000 visits are restricted by family physicians and physician subspecialists

only). As secondary outcomes, we also divided antibiotics into 13 classes according to the anatomical therapeutic classification of the World Health Organization (Supplementary Table 1) [18] and grouped them by approximate indication (antibiotics indicated for respiratory, urinary tract, and skin and soft tissue infections) based on the most common indications for use [16]. The overall magnitude of the impact of COVID-19 on outpatient antibiotic prescribing was presented as the adjusted relative change.

Covariates

Covariates in this study included prescriber specialty (family physician, subspecialist physician, dentist, and other nonphysician, nondentist prescribers [ie, nurse practitioners, midwives, nonphysician lab directors, optometrists, osteopaths, chiropractors, and chiropractists]), patient age and sex (male <18 years, female <18 years, male 18–64 years, female 18–64 years, male 65 years or older, or female 65 years or older), type of visit (face-to-face or virtual), and diagnosis. Prescriber's specialty, patient age, and sex grouping for antibiotic prescriptions were obtained from IQVIA, while patient age and sex grouping for patient visits and the type of visit were obtained from ICES. Diagnosis was based on OHIP billing codes. In this study, they were categorized as respiratory infection, urinary tract infection, or skin and soft tissue infection. The ICES data were only available for physicians (family physicians and subspecialist physicians).

Statistical Analysis

The characteristics in the pre-COVID-19 period and the COVID-19 period were compared using nonparametric tests to calculate unadjusted relative changes. The unadjusted relative change refers to the relative change in each outcome in the COVID-19 period compared with the pre-COVID-19 period (without accounting for the nature of time series data). Mann-Whitney *U* tests and Spearman's rank correlation tests were conducted to calculate unadjusted *P* values.

The impact of the COVID-19 pandemic was measured by the adjusted relative change in the number of antibiotic prescriptions, number of patient visits, and rate of antibiotic prescriptions/1000 patient visits. For the ITS analysis of the number of antibiotic prescriptions and patient visits, we used negative binomial regression models, with the number of antibiotic prescriptions or patient visits as the outcome given the overdispersion of our data. For the ITS analysis of antibiotic prescriptions/1000 patient visits, the log of patient visits as an offset term was added to the negative binomial regression models. A level change model was used to evaluate the adjusted relative change in each observed outcome during the COVID-19 period compared with the expected outcome. Model outputs were presented as adjusted relative change with 95% CIs and were calculated by comparing the overall expected and overall observed number

of antibiotic prescriptions during the COVID-19 period in the level change model.

A level and slope change model was also investigated to evaluate a potential gradual impact on the health care system during the COVID-19 period and to produce the expected monthly outcome assuming no impact of the COVID-19 pandemic. In the level and slope change model, the slope change refers to average monthly adjusted relative change in the outcome during the COVID-19 period. Therefore, while adjusted relative changes with 95% CIs that represent the overall magnitude of the impact during the COVID-19 period were calculated by the level change model, the monthly expected outcomes during the COVID-19 period were plotted in figures using the level and slope model. The ITS models were adjusted for seasonality with a categorical variable of calendar month as well as secular trends over all study months.

The subgroup analyses were conducted by stratifying the outcomes by antibiotic class, by patient age and sex groupings, by prescriber's specialty (family physicians vs subspecialists), and by diagnostic condition (respiratory, urinary, and skin and soft tissue infections in [Supplementary Table 2](#)) [19].

We plotted the monthly observed outcomes and compared them with the expected outcomes created by the level and slope change model with the assumption of no COVID-19 pandemic in the period following March 1, 2020. The difference in the number of antibiotic prescriptions during the COVID-19 period (observed vs expected) was calculated to evaluate the magnitude of the effect of COVID-19 on antibiotic prescriptions. All statistical analyses were conducted using Stata 14.1 (College Station, TX, USA).

Patient Consent

ICES is a prescribed entity under Ontario's Personal Health Information Protection Act (PHIPA). Section 45 of PHIPA authorizes ICES to collect personal health information, without consent, for the purpose of analysis or compiling statistical information with respect to the management, evaluation, or monitoring of the allocation of resources to or planning for all or part of the health system. Projects that use data collected by ICES under section 45 of PHIPA and use no other data are exempt from research ethic board (REB) review. The use of the data in this project was authorized under section 45 and approved by ICES' Privacy and Legal Office.

RESULTS

During the study period between January 2017 and December 2020, there were 306 742 226 outpatient visits and 32 663 825 total outpatient oral antibiotic prescriptions written. [Table 1](#) shows that the average number of monthly total antibiotic prescriptions was 731 325 in the pre-COVID-19 period (from January 2017 to February 2020) and 487 346 during the COVID-19 period (from March to December 2020). In contrast, the average number of

monthly total visits, for any reason, was 6 509 795 in the pre-COVID-19 period and 5 937 003 during COVID-19. Virtual visits accounted for 1.2% of total visits in the pre-COVID-19 period and 51.6% in the COVID-19 period ([Table 1](#)).

There was a marked discrepancy between the observed and expected numbers of monthly total antibiotic prescriptions in the COVID-19 period ([Figure 1](#); [Supplementary Table 3](#)). The observed total number of antibiotic prescriptions from March to December 2020 was 2 211 822 fewer than the expected number of total antibiotic prescriptions (−31.2%; 95% CI, −35.1% to −27.0%; $P < .001$ of adjusted relative change).

The largest discrepancy between the observed and expected total numbers of antibiotic prescriptions by prescriber specialty was observed for family physicians, at −37.1% (95% CI, −41.3% to −32.5%; $P < .001$ of adjusted relative change), followed by all non-family medicine subspecialist physicians (−30.7%; 95% CI, −35.2% to −25.8%; $P < .001$), other nonphysician, nondentist prescribers (−25.7%; 95% CI, −29.8% to −21.4%; $P < .001$), and dentists (−12.1%; 95% CI, −19.2% to −4.4%; $P = .003$) ([Figure 2](#)). Although the reduction in the number of antibiotic prescriptions from family physicians and subspecialists was sustained during the COVID-19 period, the number of antibiotic prescriptions among dentists recovered in the next 3 months to a level similar to the pre-COVID-19 period. The reduction in the observed antibiotic prescriptions, compared with the expected antibiotic prescriptions during the COVID-19 period, was larger in children aged 0–17 (adjusted relative change in males, −62.8%; 95% CI, −68.4% to −56.3%; $P < .001$; adjusted relative change in females, −57.4%; 95% CI, −63.1% to −50.9%; $P < .001$) than in adults aged 18–64 (adjusted relative change in males, −28.0%; 95% CI, −31.3% to −24.4%; $P < .001$; adjusted relative change in females, −25.4%; 95% CI, −21.9% to −28.8%; $P < .001$) and adults aged ≥65 (adjusted relative change in males, −25.5%; 95% CI, −29.3% to −21.6%; $P < .001$; adjusted relative change in females, −24.2%; 95% CI, −27.8% to −20.5%; $P < .001$) ([Supplementary Figure 1](#)).

We observed the largest reductions in macrolides (adjusted relative change, −59.6%; 95% CI, −64.7% to −53.6%; $P < .001$), second- or third-generation cephalosporins (−45.9%; 95% CI, −51.1% to −40.2%; $P < .001$), and penicillins without a beta-lactamase inhibitor (−40.5%; 95% CI, −45.9% to −34.5%; $P < .001$) ([Supplementary Figure 2](#)). We observed the largest reductions for antibiotics indicated for respiratory infections (adjusted relative change, −43.7%; 95% CI, −48.6% to −38.4%; $P < .001$). Antibiotics indicated for urinary tract infections had a −9.9% adjusted relative change (95% CI, −12.5% to −7.3%; $P < .001$), and antibiotics indicated for skin and soft tissue infections had a −11.1% adjusted relative change (95% CI, −13.5% to −8.7%; $P < .001$) ([Supplementary Figure 3](#)).

The monthly absolute number of outpatient visits showed a significant decrease initially in the COVID-19 period compared with the pre-COVID-19 period, but subsequently

Table 1. The Average Monthly Number of (and Unadjusted/Adjusted Percent Change in) Antibiotic Prescriptions and Visits in Pre-COVID-19 and COVID-19 Periods

	Pre-COVID-19 Period	COVID-19 Period	Unadjusted Relative Change [95% CI], %	P Value	Adjusted Relative Change [95% CI], %	P Value
Total antibiotic prescriptions	731 325 ± 75 023	487 346 ± 60 181	-33.4 [-37.9 to -28.4]	<.001	-31.2 [-35.1 to -27.0]	<.001
Total patient visits	6 509 795 ± 411 235	5 937 003 ± 725 928	-8.8 [-13.6 to -3.7]	.001	-10.7 [-15.6 to -5.4]	<.001
Antibiotic prescriptions/1000 visits	90.8	60.2	-33.7% [-39.4% to -27.4%]	<.001	-27.5 [-33.0 to -21.5]	<.001
Antibiotic prescriptions or patient visits by patient age and sex grouping						
<18 y male						
Antibiotics prescriptions	59 916 ± 13 769	20 027 ± 8522	-66.6 [-71.9 to -60.2]	<.001	-62.8 [-68.4 to -56.3]	<.001
Patient visits	367 994 ± 30 815	246 829 ± 46 827	-32.9 [-38.0 to -27.4]	<.001	-32.0 [-37.7 to -25.8]	<.001
Antibiotic prescriptions/1000 visits	141.1	60.6	-57.0 [-63.5 to -49.4]	<.001	-52.4 [-59.2 to -44.6]	<.001
<18 y female						
Antibiotics prescriptions	60 207 ± 12 855	23 054 ± 7730	-61.7 [-67.2 to -55.3]	<.001	-57.4 [-63.1 to -50.9]	<.001
Patient visits	382 020 ± 31 410	247 892 ± 48 495	-35.1 [-40.1 to -29.7]	<.001	-34.2 [-39.7 to -28.1]	<.001
Antibiotic prescriptions/1000 visits	136.6	71.1	-47.9 [-54.6 to -40.4]	<.001	-42.1 [-48.6 to -34.8]	<.001
18-64 y male						
Antibiotics prescriptions	158 361 ± 15 002	110 543 ± 11 767	-30.2 [-34.5 to -25.6]	<.001	-28.0 [-31.3 to -24.4]	<.001
Patient visits	2 327 442 ± 144 873	2 200 192 ± 257 802	-5.5 [-10.3 to -0.3]	.037	-6.2 [-11.3 to -0.7]	.027
Antibiotic prescriptions/1000 visits	51.1	33.2	-35.1 [-40.5 to -29.2]	<.001	-29.1 [-34.5 to -23.2]	<.001
18-64 y female						
Antibiotics prescriptions	266 143 ± 22 748	195 300 ± 21 126	-26.6 [-34.5 to -25.6]	<.001	-25.4 [-28.8 to -21.9]	<.001
Patient visits	1 544 976 ± 87 441	1 406 511 ± 153 453	-9.0 [-13.3 to -4.4]	.003	-9.6 [-14.2 to -4.7]	<.001
Antibiotic prescriptions/1000 visits	138.8	102.7	-26.0 [-31.1 to -20.6]	<.001	-21.4 [-26.8 to -15.6]	.001
>64 y male						
Antibiotics prescriptions	73 848 ± 7335	54 819 ± 4875	-25.8 [-30.4 to 20.8]	<.001	-25.5 [-29.3 to -21.6]	<.001
Patient visits	1 028 349 ± 89 364	1 001 241 ± 130 464	-2.6 [-8.9 to 4.1]	.434	-8.2 [-13.3 to -2.7]	.004
Antibiotic prescriptions/1000 visits	57.4	41.1	-28.3 [-34.6 to -21.3]	<.001	-20.8 [-25.9 to -15.4]	<.001
>64 y female						
Antibiotics prescriptions	108 195 ± 9756	81 113 ± 6837	-25.0 [-29.4 to -20.4]	<.001	-24.2 [-27.8 to -20.5]	<.001
Patient visits	859 012 ± 72 331	834 339 ± 103 283	-2.9 [-8.9 to 3.6]	.374	-9.0 [-13.9 to -3.8]	.001
Antibiotic prescriptions/1000 visits	104.7	77.0	-26.5 [-32.3 to -20.2]	<.001	-18.1 [-23.2 to -12.7]	.004
Antibiotic prescriptions by prescriber's specialty						
Family physicians	481 112 ± 61 733	278 951 ± 48 177	-42.5 [-47.4 to -37.1]	<.001	-37.1 [-41.3 to -32.5]	<.001
Subspecialist physicians	104 642 ± 9355	73 463 ± 9732	-29.8 [-34.4 to -24.8]	<.001	-30.7 [-35.2 to -25.8]	<.001
Dentists	88 521 ± 6989	88 328 ± 16 453	-0.2 [-7.6 to 7.8]	.956	-12.1 [-19.2 to -4.4]	.003
Other prescribers ^a	53 050 ± 7333	46 604 ± 5618	-12.2 [-19.6 to -4.0]	.004	-25.7 [-29.8 to -21.4]	<.001
Antibiotic prescriptions by antibiotic class						
Penicillin without β-lactamase inhibitors	244 203 ± 35 470	137 744 ± 24 533	-43.6 [-49.1 to -37.5]	<.001	-40.5 [-45.9 to -34.5]	<.001
Penicillin with β-lactamase inhibitors	47 323 ± 7841	36 983 ± 5698	-21.8 [-29.9 to -12.9]	<.001	-33.1 [-37.3 to -28.6]	<.001
First-generation cephalosporins	70 964 ± 8069	66 494 ± 7338	-6.3 [-13.2 to 1.2]	.098	-14.4 [-16.5 to -12.2]	.099
Second- or third-generation cephalosporins	30 635 ± 7001	13 112 ± 4403	-57.2 [-63.6 to -49.7]	<.001	-45.9 [-51.1 to -40.2]	<.001
Second-generation fluoroquinolones	42 283 ± 3564	31 537 ± 2067	-25.4 [-29.5 to -21.1]	<.001	-14.3 [-17.1 to -11.3]	<.001

Table 1. Continued

	Pre-COVID-19 Period	COVID-19 Period	Unadjusted Relative Change [95% CI], %	P Value	Adjusted Relative Change [95% CI], %	P Value
Third-generation fluoroquinolones	21 630 ± 5094	8993 ± 3056	-58.4 [-64.7 to -51.0]	<.001	-50.2 [-54.7 to -45.2]	<.001
Macrolides	112 233 ± 29 766	38 648 ± 21 224	-65.6 [-72.0 to -57.7]	<.001	-59.6 [-64.7 to -53.6]	<.001
Trimethoprim and/or sulfonamides	28 297 ± 1915	25 222 ± 1671	-10.9 [-14.9 to -6.6]	<.001	-6.2 [-8.8 to -3.5]	<.001
Tetracyclines	25 952 ± 2703	24 853 ± 2118	-4.2 [-10.6 to 2.6]	.216	-18.3 [-21.0 to -15.4]	<.001
Lincosamides	20 757 ± 1761	18 556 ± 2523	-10.6 [-16.4 to -4.4]	.001	1.0 [-5.2 to 7.7]	.749
Nitrofurantoin	50 696 ± 4951	48 698 ± 2485	-3.9 [-9.5 to 2.0]	.189	-9.4 [-13.7 to -5.0]	<.001
Metronidazole	25 858 ± 4065	23 419 ± 1971	-9.4 [-18.0 to 0.0]	.051	-32.3 [-36.7 to -27.6]	<.001
Other oral antibiotics	10 495 ± 2138	13 086 ± 822	24.7 [9.3 to 42.3]	.001	-18.4 [-22.8 to -13.8]	<.001
Patient visits by visit type						
Face-to-face	6 431 218 ± 407 184	2 875 687 ± 877 725	-55.3 [-60.0 to -50.0]	<.001	-56.7 [-62.4 to -50.3]	<.001
Virtual	78 577 ± 21 312	3 061 316 ± 516 544	3795.9 [3164.8 to 4549.1]	<.001	2115.8 [1949.9 to 2295.2]	<.001
Respiratory infection	541 833 ± 135 330	240 631 ± 115 831	-55.6 [-63.5 to -46.0]	<.001	-49.9 [-55.9 to -43.1]	<.001
Urinary tract infection	124 229 ± 8169	126 863 ± 12 515	2.1 [-2.9 to 7.4]	.417	0.1 [-3.7 to 4.1]	.958
Skin and soft tissue infection	99 239 ± 10 539	92 201 ± 14 154	-7.1 [-14.3 to 0.7]	.073	-9.7 [-13.7 to -5.5]	<.001

The pre-COVID-19 period is between January 2017 and February 2020. The COVID-19 period is between March and December 2020. The visit data were obtained from family physicians and subspecialists. Antibiotics prescribed by family physicians and subspecialists were only included to calculate antibiotic prescription/1000 visits. The monthly absolute number of antibiotic prescriptions and patient visits is presented as mean ± SD. The monthly rate of antibiotic prescriptions per 1000 patient visits is presented as mean. While unadjusted relative change refers to the relative change in each outcome in the COVID-19 compared with the pre-COVID-19 period (without accounting for the nature of time series data), adjusted relative changes with 95% CIs were obtained from the levels of the level change model in the interrupted time series analysis described in the "Methods" section.

Abbreviation: COVID-19, coronavirus disease 2019.

^aOther prescribers included nurse practitioners, pharmacists, nonphysician lab directors, optometrists, osteopaths, chiropractors, and chiroprudists.

returned to prepandemic levels (Supplementary Figures 4–7, Supplementary Table 4). The number of visits with diagnosis of respiratory infection during the COVID-19 period showed a sustained significant reduction (adjusted relative change, -49.9%; 95% CI, -55.9% to -43.1%; *P* < .001), while the number of visits with diagnosis of urinary tract infection (adjusted relative change, 0.1%; 95% CI, -3.7% to 4.1%; *P* = .958) and skin

and soft tissue infection (adjusted relative change, -9.7%; 95% CI, -13.7% to -5.5%; *P* < .001) returned to prepandemic levels, following an initial drop at the beginning of the pandemic (Supplementary Figure 7, Supplementary Table 4).

As demonstrated in Figure 3 and Supplementary Table 5, the total antibiotic prescriptions/1000 patient visits showed a significant reduction during the COVID-19 period (adjusted

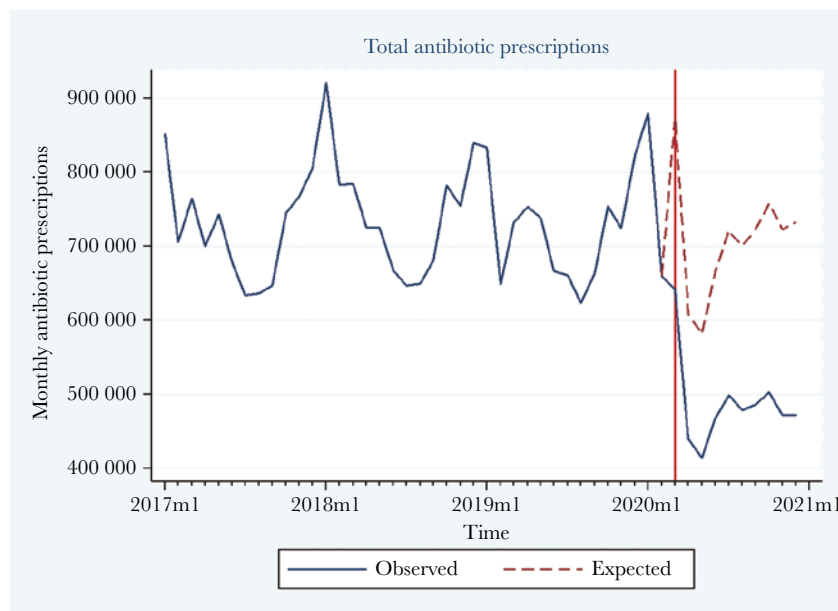


Figure 1. Total antibiotic prescriptions. The first month of the year (January) is presented as m1.

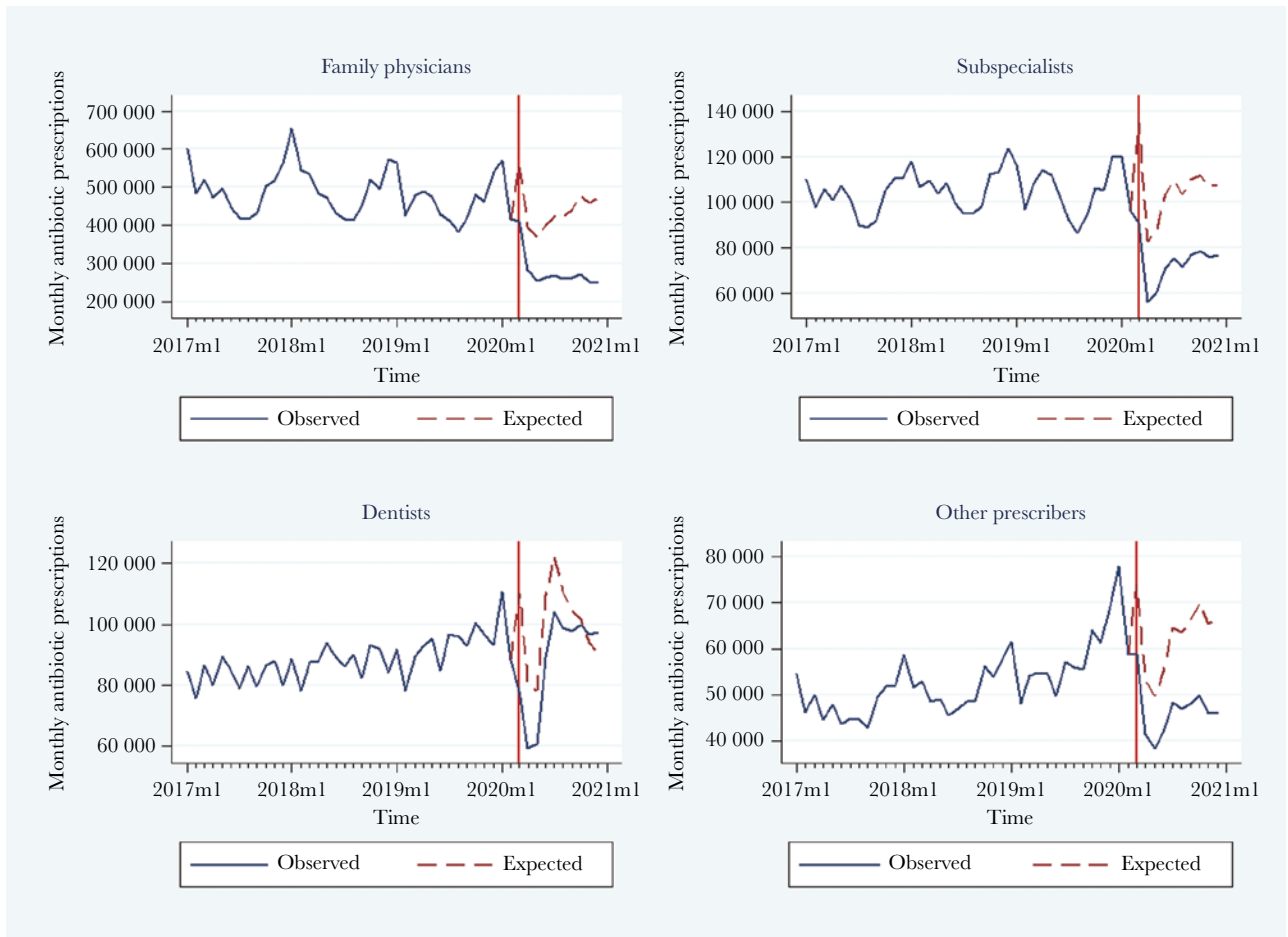


Figure 2. Antibiotic prescriptions by prescriber. The first month of the year (January) is presented as m1.

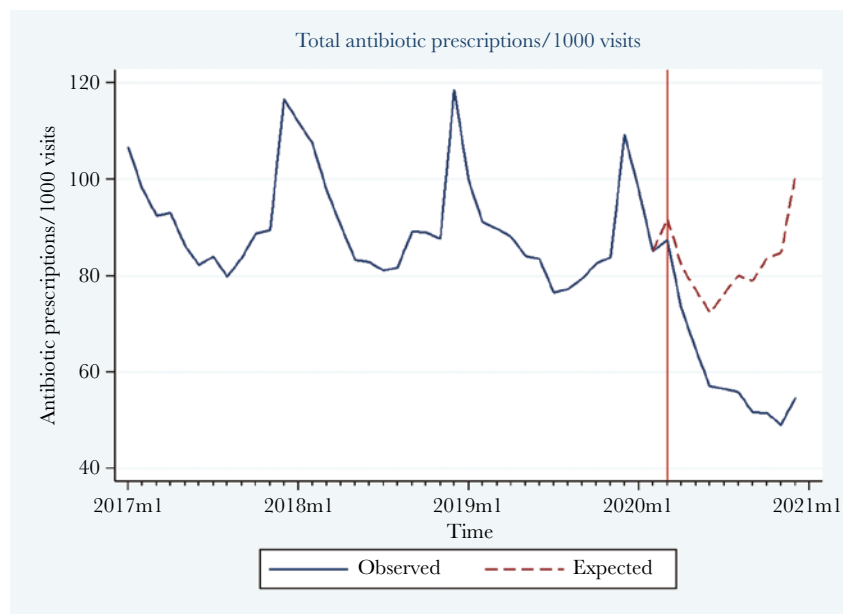


Figure 3. Total antibiotic prescriptions/1000 patient visits. The first month of the year (January) is presented as m1.

relative change, -27.5%; 95% CI, -33.0% to -21.5%; $P < .001$). For subgroup analyses (Supplementary Figures 8 and 9), a reduction in antibiotic prescriptions/1000 patient visits during the COVID-19 period was observed both in family physicians (adjusted relative change, -28.9%; 95% CI, -34.7% to -22.6%) and in subspecialist physicians (adjusted relative change, -22.2%; 95% CI, -26.5% to -17.7%). The adjusted relative changes were -6.8% (95% CI, -10.8% to -2.7%; $P = .001$) in antibiotics indicated for respiratory infections/1000 visits with respiratory infections, -11.0% (95% CI, -14.3% to -7.6%; $P < .001$) in antibiotics indicated for urinary tract infections/1000 visits with urinary tract infections, and -4.7% (95% CI, -8.2% to -1.1%; $P = .012$) in antibiotics indicated for skin and soft tissue infections/1000 visits with skin and soft tissue infections, respectively. The adjusted relative changes were -5.5% (95% CI, -8.1% to 2.8%; $P < .001$) in antibiotics indicated for any of respiratory, urinary tract, or skin and soft tissue infections/1000 visits with any diagnosis of respiratory, urinary tract, or skin and soft tissue infections (Supplementary Figure 10).

DISCUSSION

The study highlights the significant reduction (-31.2%; 95% CI, -35.1% to -27.0%; adjusted relative change) in total outpatient antibiotic prescriptions issued during the COVID-19 period in Ontario, Canada. The magnitude of the reduction in the number of antibiotic prescriptions was larger in children, in antibiotics for respiratory infections, and for family physician prescribers. Although the number of total visits recovered from May 2020 onward, the trend of reduced total antibiotic prescriptions was sustained, which led to a reduction in total antibiotic prescriptions/1000 visits.

The reduced total antibiotic prescriptions observed during the COVID-19 period may be explained, in part, by the reduced visits for respiratory infections (adjusted relative change, -49.9%) due to the implementation of public health measures in Ontario, including school closures, restrictions on gatherings, hand hygiene, mask wearing, and physical distancing [20, 21]. The visits for respiratory infections showed a sustained reduction throughout the COVID-19 period, while visits with urinary tract infections and skin and soft tissue infections in the later COVID-19 period returned to prepandemic levels. The actual rate of prescribing of antibiotics indicated for respiratory infections for visits with respiratory infections declined by only 6.8% during the COVID-19 period; thus a change in prescribing rate does not fully explain the 43.7% reduction in antibiotics indicated for respiratory infections. These observations suggest that the sustained reduction in antibiotic prescription during the COVID-19 period was driven by the reduction of respiratory infections rather than by altered prescribing rates among those with infections. Similarly, the data also suggest that there was no increase in prescribing related to the shift to virtual care.

Difficult access to medical visits (including both in-person and virtual case visits) could potentially be another reason for the reduced antibiotic prescriptions [22]. Virtual care may present diagnostic challenges; however, several studies have identified similar or reduced antibiotic prescribing practices compared with in-person care [9, 23–25]. However, our study could not evaluate the direct causality between the increasing trend of virtual visits and the reduction of antibiotic prescriptions.

While various impacts of the first wave of COVID-19 in March 2020 on outpatient antibiotic prescriptions have been reported, from a sustained reduction to a transient increase in antibiotic prescribing [26–28], our study showed a remarkable reduction of antibiotic prescriptions in March 2020. This may be explained by a variety of reasons, including differences in the overall number of COVID-19 cases or intensity of mitigation measures, epidemiology of infectious diseases, and access to health care services in the first wave of the COVID-19 pandemic. Patients with COVID-19 may often receive antibiotics. A recent study reported increased prescriptions of amoxicillin-clavulanate during the COVID-19 pandemic related to prescribing in patients with COVID-19 [9]. A retrospective study initially reported a potential positive impact of azithromycin on COVID-19 outcome, which was negated by randomized trial data [29, 30]. We observed a marked reduction in macrolide prescribing during the COVID-19 period, similar to a report published by the Centers for Disease Control and Prevention [28]. The observed large reduction in macrolide use is likely related to frequent use for respiratory indications, which are often viral and, as such, macrolides are unnecessary [31]. Ongoing monitoring of antibiotic prescribing in the community is important to monitor trends given the dynamic feature of the COVID-19 pandemic.

In our study, the magnitude of the reduced antibiotic prescriptions was lower among dentists compared with family physicians or subspecialist physicians. An Australian study demonstrated a reduction of antibiotic prescriptions among dentists [32], while a UK study showed an increased trend of dental antibiotic prescriptions [33]. Early in the pandemic, there was decreased access to dental care and likely increased antibiotic prescribing for dental conditions. This highlights that access to appropriate dental care likely influences overall outpatient antibiotic prescribing and subsequently is an important component of outpatient antimicrobial stewardship.

While a reduction of antibiotic prescriptions was observed during the COVID-19 period for all patient age and sex groups, the magnitude of the reduced impact was larger in children compared with older adults. This potentially reflects the larger reduction in respiratory infections among children in the COVID-19 period. Schools in Ontario were closed for a considerable period of time beginning in March 2020 [34]. School closure and a subsequent reduction in respiratory infections may explain the larger antibiotic reduction among children [35–38]. Given the

fact that there was only a small reduction in respiratory antibiotic prescriptions/1000 visits with respiratory infections in our study, one possible explanation is that antibiotic prescribing behaviors may not have changed substantially between the pre-COVID-19 and COVID-19 periods, and the reduction of antibiotic prescribing may have been driven by there being fewer, predominately viral, respiratory infections [39–41]. Therefore, we may expect antibiotic prescribing to increase back to pre-COVID-19 pandemic levels without further intervention. On the other hand, the reduction in antibiotic prescribing during the COVID-19 period also may provide a reasonable approximate target for outpatient stewardship interventions if unnecessary antibiotics for viral infections have been the issue [42].

An important strength of this study was the use of ITS analysis with linked prescription and aggregate physician visit data, allowing us to evaluate the magnitude of changes in antibiotic prescriptions (and whether these changes were sustained) not only for total antibiotic prescriptions, but also by key patient and prescriber strata. This allowed for a greater understanding of why antibiotic prescribing may have changed. There are a few limitations to this study. First, we could not evaluate the magnitude of impact of increased virtual visits during the COVID-19 period because we could not link the individual types of visits to the antibiotic prescriptions. Second, we could not obtain individual data regarding COVID-19. A study of UK family physicians revealed that ~30% of patients with SARS-CoV-2 infections received at least 1 antibiotic prescription [11]. Third, the geospatial projection algorithm of the IQVIA data was not validated during the COVID-19 period. Finally, while data from other jurisdictions support that a reduction in respiratory infections drove the observed change in visit behavior, this study did not examine infectious etiology directly [43, 44].

In conclusion, our study showed a significant reduction in overall outpatient antibiotic prescribing during the COVID-19 pandemic in Ontario. The sustained reductions in observed antibiotic prescriptions appear to have been driven by implementation of public health measures that reduced respiratory infection transmission [20, 21, 45]. However, we observed a modest reduction in antibiotic prescriptions/visits with respiratory infection. This may suggest that antibiotic prescribing behaviors did not change or improve during the COVID-19 period. Further study is needed to understand the implications of these changes in antibiotic prescribing on antimicrobial resistance. Ongoing vigilance in monitoring antibiotic prescribing is crucial for the implementation of timely and effective stewardship interventions during and following the COVID-19 pandemic.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Acknowledgments

We sincerely thank Ms. Sarah Muir from Public Health Ontario for reviewing our manuscript.

Disclaimer. The opinions, results and conclusions reported in this paper are those of the authors and are independent from the funding sources. No endorsement by ICES, CIHI, or the Ontario MOH and MLTC is intended or should be inferred.

Financial support. This study was supported by ICES, which is funded by an annual grant from the Ontario Ministry of Health (MOH) and the Ministry of Long-Term Care (MLTC). Parts of this material are based on data and/or information compiled and provided by the Canadian Institute for Health Information (CIHI).

Potential conflicts of interest. All authors: no reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Huang QS, Wood T, Jelley L, et al; NPISImpactOnFlu Consortium. Impact of the COVID-19 nonpharmaceutical interventions on influenza and other respiratory viral infections in New Zealand. *Nat Commun* **2021**; 12:1001.
2. Olsen SJ, Winn AK, Budd AP, et al. Changes in influenza and other respiratory virus activity during the COVID-19 pandemic - United States, 2020-2021. *MMWR Morb Mortal Wkly Rep* **2021**; 70:1013-9.
3. Janapatla RP, Chen CL, Dudek A, et al. Serotype transmission dynamics and reduced incidence of invasive pneumococcal disease caused by different serotypes after implementation of non-pharmaceutical interventions during COVID-19 pandemic. *Eur Respir J*. **In press**.
4. Kitano T. The estimated burden of 15 vaccine-preventable diseases from 2008 to 2020 in Japan: a transition by the COVID-19 pandemic. *J Infect Chemother* **2021**; 27:1482-8.
5. Khairat S, Meng C, Xu Y, et al. Interpreting COVID-19 and virtual care trends: cohort study. *JMIR Public Health Surveill* **2020**; 6:e18811.
6. Webster P. Virtual health care in the era of COVID-19. *Lancet* **2020**; 395:1180-1.
7. Czeisler ME, Marynak K, Clarke KEN, et al. Delay or avoidance of medical care because of COVID-19-related concerns - United States, June 2020. *MMWR Morb Mortal Wkly Rep* **2020**; 69:1250-7.
8. King LM, Lovegrove MC, Shehab N, et al. Trends in U.S. outpatient antibiotic prescriptions during the COVID-19 pandemic. *Clin Infect Dis* **2021**; 73:e652-60.
9. Miller LE, Bhattacharyya N. Antibiotic prescribing for acute rhinosinusitis: in-person versus virtual visits during Covid-19. *Laryngoscope* **2021**; 131:E2121-4.
10. Buehrle DJ, Nguyen MH, Wagener MM, Clancy CJ. Impact of the coronavirus disease 2019 pandemic on outpatient antibiotic prescriptions in the United States. *Open Forum Infect Dis* **2020**; 7:XXX-XX.
11. Zhu N, Ailin P, Rawson T, et al. Investigating the impact of COVID-19 on primary care antibiotic prescribing in North West London across two epidemic waves. *Clin Microbiol Infect* **2021**; 27:762-8.
12. Han SM, Greenfield G, Majeed A, Hayhoe B. Impact of remote consultations on antibiotic prescribing in primary health care: systematic review. *J Med Internet Res* **2020**; 22:e23482.
13. Hashimoto H, Matsui H, Sasabuchi Y, et al. Antibiotic prescription among outpatients in a prefecture of Japan, 2012-2013: a retrospective claims database study. *BMJ Open* **2019**; 9:e026251.
14. Hicks LA, Bartoces MG, Roberts RM, et al. US outpatient antibiotic prescribing variation according to geography, patient population, and provider specialty in 2011. *Clin Infect Dis* **2015**; 60:1308-16.
15. Government of Ontario. Archived - COVID-19: government service changes and public closures. Available at: <https://www.ontario.ca/page/covid-19-government-service-changes-and-public-closures>. Accessed 28 May 2021.
16. Schwartz KL, Achonu C, Brown KA, et al. Regional variability in outpatient antibiotic use in Ontario, Canada: a retrospective cross-sectional study. *CMAJ Open* **2018**; 6:E445-52.
17. Hong M, Dutil L, Bhatia T, et al. Assessing antimicrobial consumption using two different methodologies in British Columbia. *Can J Infect Dis Med Microbiol* **2007**; 18:35.
18. WHO Collaborating Centre for Drug Statistics and Methodology. Guidelines for ATC Classification and DDD Assignment 2021. World Health Organization; **2020**. Available at: https://www.whooc.no/filearchive/publications/2021_guidelines_web.pdf. Accessed 21 July 2021.
19. Ontario Ministry of Health and Long-Term Care. Ontario Health Insurance Plan: Schedule of Benefits. Ontario Ministry of Health and Long-Term Care; **2015**.

- Available at: <https://londonreferral.files.wordpress.com/2018/02/2015-ohip-dx-codes.pdf>. Accessed 11 July 2021.
20. Public Health Ontario. Respiratory diseases. Available at: <https://www.publichealthontario.ca/en/diseases-and-conditions/infectious-diseases/respiratory-diseases/novel-coronavirus/public-health-measures>. Accessed 4 July 2021.
 21. Government of Canada. Annual influenza reports. Available at: <https://www.canada.ca/en/public-health/services/diseases/flu-influenza/influenza-surveillance/annual-reports.html>. Accessed 28 July 2021.
 22. Canadian Medical Association. Virtual Care Task Force report. Available at: <https://www.cma.ca/sites/default/files/pdf/virtual-care/ReportoftheVirtualCareTaskForce.pdf>. Accessed 28 July 2021.
 23. Yao P, Clark S, Gogia K, et al. Antibiotic prescribing practices: is there a difference between patients seen by telemedicine versus those seen in-person? *Telemed J E Health* **2020**; 26:107–9.
 24. Johnson KM, Dumkow LE, Burns KW, et al. Comparison of diagnosis and prescribing practices between virtual visits and office visits for adults diagnosed with sinusitis within a primary care network. *Open Forum Infect Dis* **2019**; 6:XXX–XX.
 25. Johnson KL, Dumkow LE, Salvati LA, et al. Comparison of diagnosis and prescribing practices between virtual visits and office visits for adults diagnosed with uncomplicated urinary tract infections within a primary care network. *Infect Control Hosp Epidemiol* **2021**; 42:586–91.
 26. Rezel-Potts E, L'Esperance V, Gulliford MC. Antimicrobial stewardship in the UK during the COVID-19 pandemic: a population-based cohort study and interrupted time-series analysis. *Br J Gen Pract* **2021**; 71:e331–8.
 27. Malcolm W, Seaton RA, Haddock G, et al. Impact of the COVID-19 pandemic on community antibiotic prescribing in Scotland. *JAC Antimicrob Resist*. **In press**.
 28. Center for Disease Control and Prevention. The intersection of antibiotic resistance (AR), antibiotic prescribing (AU), and COVID-19 for the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria. Available at: <https://www.hhs.gov/sites/default/files/antibiotic-resistance-antibiotic-prescribing-covid-19-paccarb.pdf>. Accessed 4 July 2021.
 29. Million M, Lagier JC, Gautret P, et al. Early treatment of COVID-19 patients with hydroxychloroquine and azithromycin: a retrospective analysis of 1061 cases in Marseille, France. *Travel Med Infect Dis* **2020**; 35:101738.
 30. Furtado RHM, Berwanger O, Fonseca HA, et al; COALITION COVID-19 Brazil II Investigators. Azithromycin in addition to standard of care versus standard of care alone in the treatment of patients admitted to the hospital with severe COVID-19 in Brazil (COALITION II): a randomised clinical trial. *Lancet* **2020**; 396:959–67.
 31. Hersh AL, Shapiro DJ, Pavia AT, Shah SS. Antibiotic prescribing in ambulatory pediatrics in the United States. *Pediatrics* **2011**; 128:1053–61.
 32. Mian M, Teoh L, Hopcraft M. Trends in dental medication prescribing in Australia during the COVID-19 pandemic. *JDR Clin Trans Res* **2021**; 6:145–52.
 33. Shah S, Wordley V, Thompson W. How did COVID-19 impact on dental antibiotic prescribing across England? *Br Dent J* **2020**; 229:601–4.
 34. Ontario COVID-19 Science Advisory Table. COVID-19 and education disruption in Ontario: emerging evidence on impacts. Available at: <https://covid19-sciencetable.ca/sciencebrief/covid-19-and-education-disruption-in-ontario-emerging-evidence-on-impacts/>. Accessed 4 July 2021.
 35. Kishimoto K, Bun S, Shin JH, et al. Early impact of school closure and social distancing for COVID-19 on the number of inpatients with childhood non-COVID-19 acute infections in Japan. *Eur J Pediatr* **2021**; 180:2871–8.
 36. Raucci U, Musolino AM, Di Lallo D, et al. Impact of the COVID-19 pandemic on the emergency department of a tertiary children's hospital. *Ital J Pediatr* **2021**; 47:21.
 37. Huang QS, Wood T, Jelley L, et al; NPIsImpactOnFlu Consortium. Impact of the COVID-19 nonpharmaceutical interventions on influenza and other respiratory viral infections in New Zealand. *Nat Commun* **2021**; 12:1001.
 38. Jackson ML, Hart GR, McCulloch DJ, et al; Seattle Flu Study Investigators. Effects of weather-related social distancing on city-scale transmission of respiratory viruses: a retrospective cohort study. *BMC Infect Dis* **2021**; 21:335.
 39. Hara M, Takao S, Fukuda S, et al. Human metapneumovirus infection in febrile children with lower respiratory diseases in primary care settings in Hiroshima, Japan. *Jpn J Infect Dis* **2008**; 61:500–2.
 40. Inagaki A, Kitano T, Nishikawa H, et al. The epidemiology of admission-requiring pediatric respiratory infections in a Japanese community hospital using multiplex PCR. *Jpn J Infect Dis* **2021**; 74:23–8.
 41. Tsagarakis NJ, Sideri A, Makridis P, et al. Age-related prevalence of common upper respiratory pathogens, based on the application of the FilmArray Respiratory panel in a tertiary hospital in Greece. *Medicine (Baltimore)* **2018**; 97:e10903.
 42. Marra F, Patrick DM, Chong M, Bowie WR. Antibiotic use among children in British Columbia, Canada. *J Antimicrob Chemother* **2006**; 58:830–9.
 43. Kuitunen I, Artama M, Mäkelä L, et al. Effect of social distancing due to the COVID-19 pandemic on the incidence of viral respiratory tract infections in children in Finland during early 2020. *Pediatr Infect Dis J* **2020**; 39:e423–7.
 44. Kang S, Ahn TK, Seo YH, et al. Comparison of emergency department utilization trends between the COVID-19 pandemic and control period. *Medicine (Baltimore)* **2021**; 100:e26847.
 45. Groves HE, Piché-Renaud PP, Peci A, et al. The impact of the COVID-19 pandemic on influenza, respiratory syncytial virus, and other seasonal respiratory virus circulation in Canada: a population-based study. *Lancet Reg Health Am* **2021**; 1:100015.