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MAJOR ARTICLE

The Collapse of Infectious Disease Diagnoses Commonly Due to Communicable Respiratory Pathogens During the Coronavirus Disease 2019 Pandemic: A Time Series and Hierarchical Clustering Analysis

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Background. Nonpharmaceutical interventions such as physical distancing and mandatory masking were adopted in many jurisdictions during the coronavirus disease 2019 pandemic to decrease spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). We determined the effects of these interventions on incidence of healthcare utilization for other infectious diseases.

Methods. Using a healthcare administrative dataset, we employed an interrupted time series analysis to measure changes in healthcare visits for various infectious diseases across the province of Ontario, Canada, from January 2017 to December 2020. We used a hierarchical clustering algorithm to group diagnoses that demonstrated similar patterns of change through the pandemic months.

Results. We found that visits for infectious diseases commonly caused by communicable respiratory pathogens (eg, acute bronchitis, acute sinusitis) formed distinct clusters from diagnoses that often originate from pathogens derived from the patient's own flora (eg, urinary tract infection, cellulitis). Moreover, infectious diagnoses commonly arising from communicable respiratory pathogens (hierarchical cluster 1: highly impacted diagnoses) were significantly decreased, with a rate ratio (RR) of 0.35 (95% confidence interval [CI], .30–.40; $P < .001$) after the introduction of public health interventions in April–December 2020, whereas infections typically arising from the patient's own flora (hierarchical cluster 3: minimally impacted diagnoses) did not demonstrate a sustained change in incidence (RR, 0.95 [95% CI, .90–1.01]; $P = .085$).

Conclusions. Public health measures to curtail the incidence of SARS-CoV-2 were widely effective against other communicable respiratory infectious diseases with similar modes of transmission but had little effect on infectious diseases not strongly dependent on person-to-person transmission.

Keywords. COVID-19; healthcare delivery; infection; pandemic.

On 11 March 2020, the World Health Organization officially declared the coronavirus disease 2019 (COVID-19) pandemic, which has caused more than 250 million confirmed cases and 5 million deaths worldwide as of November 2021. Ontario, the most populous province in Canada, had approximately 182 000 confirmed cases and 4500 deaths from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by 31 December 2020 [1]. To slow the spread of SARS-CoV-2 in Ontario, the government marshalled extensive nonpharmaceutical and public health interventions that were being simultaneously enacted in many jurisdictions globally, including school and workplace closures, cancellation of public events, travel bans, restrictions on gatherings, mandated facial coverings/masks, and stay at home/shelter in place orders [2]. The Oxford COVID-19 Government Response Tracker (OxCGRT) reports "stringency index" scores in regions based on the extent of their lockdown policies on a scale of 0–100. The stringency index values for Ontario ranged from 60 to 80 throughout most of 2020, comparable to levels in countries like the United States and the United Kingdom [3]. The success

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of the stringent interventions enacted for reducing transmission of SARS-CoV-2 is well documented [4–6]. We therefore hypothesized that the nonpharmaceutical public health measures used to prevent COVID-19 would also reduce the spread of other communicable diseases. Assessing the general impact of marked reductions in contact rates can help inform our understanding drivers of transmission of communicable diseases at a population level, and what could be expected of future nonpharmaceutical interventions. To address these questions, we sought to employ population-level healthcare administrative data to examine changes in the distribution of outpatient infectious disease–relatedvisits to physicians from the prepandemic to the pandemic period.

METHODS

Study Design

We conducted a retrospective analysis of outpatient physician visits associated with 21 common infectious disease diagnoses in the province of Ontario, Canada, during the COVID-19 pandemic. We analyzed monthly outpatient (nonhospital) physician (general practitioners and specialists) visit data from January 2017 to December 2020, which captures the first 9 months of the pandemic and the previous 3 years for the control period. Ontario is the most populous province in Canada with a population of 14 733 506 at the conclusion of the study period. Citizens of Ontario benefit from universal health insurance, which ensures access to necessary physician and hospital services without out-of-pocket expense.

Data Sources

We used linked databases from ICES (formerly the Institute for Clinical Evaluative Sciences), including the Ontario Health Insurance Plan (OHIP) Claims Database (all insured services including visit diagnostic codes) and the Registered Persons Database. These datasets were linked using unique encoded identifiers and analyzed at ICES. Stringency index (reflecting the severity of public health measures aimed at limiting people's behavior/close contacts) data for Ontario was collected from the Oxford COVID-19 Government Response Tracker Github repository on 25 August 2021.

Inclusion Criteria and Definitions

Physicians in Ontario who see a patient are required to submit a claim to OHIP to be reimbursed for their services. As a part of this process, physicians give a reason for the visit/presumptive diagnosis, which has a corresponding billing code. We considered the following diagnoses that are either always or frequently associated with underlying infection within our study: acute bronchitis, acute sinusitis, asthma, chronic sinusitis, common cold, dental conditions, epididymo-orchitis, eye infections, gastroenteritis, nonpurulent skin and soft tissue infections (SSTIs), otitis externa, otitis media, pharyngitis, pneumonia, prostatitis, purulent SSTIs, pyelonephritis, reproductive tract infections (RTIs), urinary tract infections (UTIs), miscellaneous bacterial infections, and miscellaneous nonbacterial infections. The specific *International Classification of Diseases, Ninth Revision* diagnostic codes are included in Supplementary Table 1 [7]. We restricted our analysis to only outpatient visits and assessments performed by general practitioners and specialist physicians for patients aged 1–105 years. Subgroup analysis was performed for the pediatric (patients aged 1–18 years) and adult (patients aged 19–105 years) populations. Data for pediatric prostatitis were not included due to very low visit numbers and to comply with the ICES privacy policy. Multiple visits/assessments for the same diagnosis on the same day were only counted once.

Heat Map, Hierarchical Clustering Analysis, and Calculation of Fold Change

The number of monthly visits in 2020 for each diagnosis was divided by the mean visits for the same month in the 2017–2019 period (pre–COVID-19) to generate a fold change (expressed as a % of the pre–COVID-19 mean). We employed hierarchical clustering analysis to highlight diagnoses with similar trends during 2020 [8]. This technique creates a distance matrix between all diagnoses and uses this to generate clusters of diagnoses without other specified a priori information, wherein diagnoses from within the same cluster have trends that are more similar to each other than those from other clusters. Hierarchical clustering was performed and visualized using R-project software package "pheatmap" (https://cran.r-project.org/web/packages/pheatmap/index.html) using Euclidean distance calculations and complete-linkage clustering.

Interrupted Time Series Analysis

Monthly data of outpatient visits ranging from January 2017 to December 2020 was obtained from ICES. Quarterly population estimates were obtained from Statistics Canada. Visits for each diagnosis were first normalized by the Ontario population in each quarter and expressed as visits per 100 000 population. We then conducted regression analysis using a quasi-Poisson model to allow for overdispersion, and harmonic terms (2 sine and cosine pairs with 12-month periods) to adjust for seasonality [9]. Given the abrupt impact of the pandemic, we hypothesized only a level change, and no slope term was included in the model. The validity of the model was assessed by visual inspection of the correlograms and residuals analysis. All statistical analyses were completed using R version 4.04 software (https://www.r-project.org).

RESULTS

We began by examining how the total number of outpatient visits changed over time for all healthcare visits in Ontario, not limited to infectious diseases (Figure 1*A*). Visits decreased

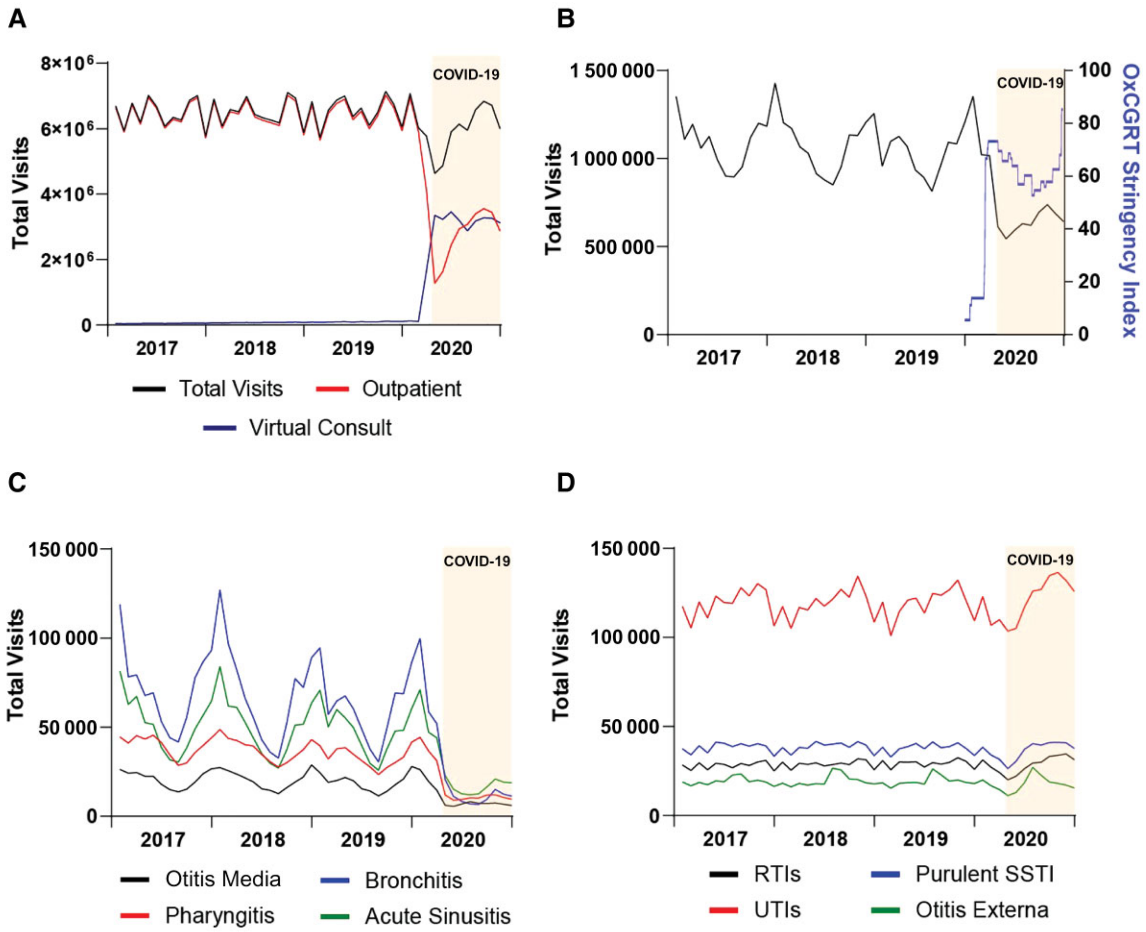

Figure 1. Time series data for primary physician visits, 2017–2020. *A*, All visits to eligible physicians during the study period. *B*, Visits for all infectious disease diagnoses during the study period. Oxford Coronavirus Disease 2019 (COVID-19) Government Response Tracker (OxCGRT) stringency index values for Ontario are shown in blue. *C*, Trend in visits for select diagnoses from the "highly impacted" cluster, which fell during the COVID-19 period. *D*, Trend in visits for select diagnoses from the "minimally impacted" cluster, which remained constant during the COVID-19 period. Abbreviations: COVID-19, coronavirus disease 2019; OxCGRT, Oxford COVID-19 Government Response Tracker; RTI, reproductive tract infection; SSTI, skin and soft tissue infection; UTI, urinary tract infection.

by 11.3%, 28.9%, and 25.2% for the months of March, April, and May, respectively, immediately following the COVID-19–related closures. Total healthcare utilization recovered to almost preclosure levels by June. Similar to previously reported figures, virtual consultations in Ontario increased 40.7 fold from 78 577 visits per month from January 2017 to February 2020 to 3 195 888 visits per month from June 2020 to December 2020 [10]. The number of in-person visits decreased by 51.7% from 6 431 218 to 3 104 768 visits per month over the same time period. Although there were major shifts in how care was accessed, the total number of physician visits rebounded quickly following the initial stages of the pandemic from 6 509 796 visits per month in January 2017–February 2020 to 6 300 656 visits per month in June 2020–December 2020.

Next, we examined the trend in infectious diseases visits, which fell by 42.8% and 48.5% for April 2020 and May 2020, from 1 020 460 to 583 865 and 1 016 693 to 523 138, respectively, compared to the same months from 2017 to 2019 (Figure 1*B*). Average visits for infectious diseases partially recovered in June 2020–December 2020, but were still 34.2% less, from 962 190 to 633 212, than the same periods in 2017–2019. Furthermore, the aggregate trend for visits did not match what we observed for each individual diagnoses. For instance, diagnoses corresponding to otitis media, acute bronchitis, pharyngitis, and acute sinusitis fell dramatically during COVID-19 and visits for these conditions stayed depressed for the remainder of 2020 (Figure 1*C*). Conversely, we note that the volume of RTI, UTI, purulent SSTI, and otitis externa visits remained consistent with historical levels throughout the pandemic, apart from a brief decline in April and May (Figure 1*D*). Time series data for all diagnoses are available in Supplementary Figure 1. To summarize the trends observed across all diagnoses, we expressed the 2020 monthly data in

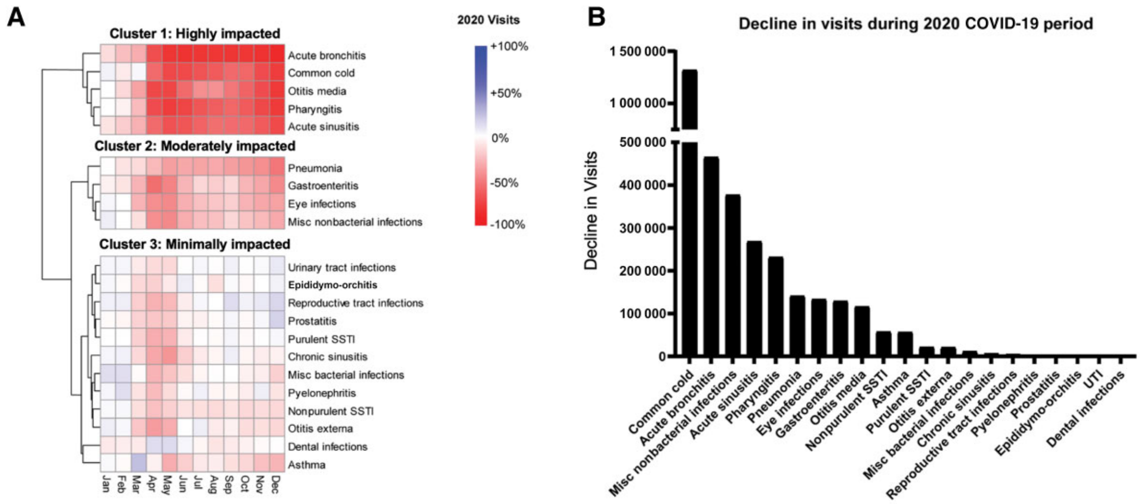

Figure 2. Outpatient visits for many infectious disease diagnoses fell during the coronavirus disease 2019 pandemic. *A*, Heat map depicting the percentage change in visits observed for 2020 compared to the mean of the same time period during the previous 3 years. Hierarchical clustering was performed by diagnoses, clustering diagnoses with similar 2020 trends together. Three clusters emerged, which we termed cluster 1: highly impacted; cluster 2: moderately impacted; and cluster 3: minimally impacted. *B*, Decline in visits during April–December 2020 for each diagnosis, relative to the average number of visits in the corresponding time period from 2017 through 2019. Abbreviations: COVID-19, coronavirus disease 2019; Misc, miscellaneous; SSTI, skin and soft tissue infection; UTI, urinary tract infection.

terms of its fold change in comparison to the average of the past 3 years and expressed this as a heat map with hierarchical clustering by diagnoses (Figure 2*A*). The pandemic responsive public health measures were not present in January and February, and visits were accordingly close to the yearly average. In April and May (and to a lesser extent March), there was a decline in visits across all diagnoses, except for dental conditions, which rose slightly during this period. After May, diagnoses followed 1 of 3 general patterns revealed by hierarchical clustering. Cluster 1 contained diagnoses that fell precipitously in 2020 (by 40%–70%), cluster 2 diagnoses showed a more mild decline (20%–30%), and diagnoses in cluster 3 returned to levels close to the historical average for the duration of the COVID-19 period. Based on these features, we have termed cluster 1 as "highly impacted diagnoses," cluster 2 as "moderately impacted diagnoses," and cluster 3 as "minimally impacted diagnoses." To understand the relative difference of the impact of COVID-19 on visits for each diagnostic cluster, we measured the difference in visits from April to December 2020 compared to the average visits in these months from the previous 3 years (Figure 2*B*). Visits with a diagnosis of common cold declined the most, with approximately 1.2 million fewer healthcare visits during the COVID-19 period. Despite a more modest fold change in diagnoses, physicians in Ontario saw approximately 350 000 fewer patients diagnosed with "miscellaneous nonbacterial infections," which comprise a number of disparate diagnoses including herpesviruses, mononucleosis, and other fungal and viral infections (Supplementary Table 1). Although there was a large fold change decrease in visits for otitis media, the lower incidence of this diagnosis translates to a modest decline in absolute number of visits.

We next completed interrupted time series regression on each diagnosis [9] (Figure 3). The diseases are then presented in table format to include rate ratios (RRs) of diagnoses postintervention compared to preintervention, and have also been categorized based on disease site, common modes of transmission, and disease etiology (Table 1). Cluster 1 (highly impacted diagnoses) demonstrated substantial reductions in visits (RR, 0.35 [95% confidence interval {CI}, .30–.40]; $P < .001$) and largely represented infectious diagnoses associated with communicable respiratory pathogens. Cluster 2 (moderately impacted diagnoses) demonstrated modest reductions in visits (RR, 0.70 [95% CI, .64–.76]; $P < .001$) and represented a variety of underlying infectious etiologies. Cluster 3 (minimally impacted diagnoses) demonstrated no major changes in visits (RR, 0.95 [95% CI, .90–1.01]; $P = .085$) and represented infectious diagnoses typically arising from endogenous flora. Visits for some specific diseases, such as acute bronchitis (RR, 0.23 [95% CI, .18–.29]; $P < .001$) and common cold (RR, 0.35 [95% CI, .30–.41]; $P < .001$) showed marked reductions during the postintervention period, while visits for other diseases such as RTIs (RR, 0.98 [95% CI, .89–1.07]; $P = .648$) and UTIs (RR, 1.02 [95% CI, .97–1.07]; $P = .509$) did not change following the COVID-19 restrictions (Figure 3*A*–*F*). To determine if decreased healthcare access in the months of April and May of 2020 influenced the relative rates of visits for these diseases for the remainder of the year, we performed another interrupted time series analysis omitting April and May and also

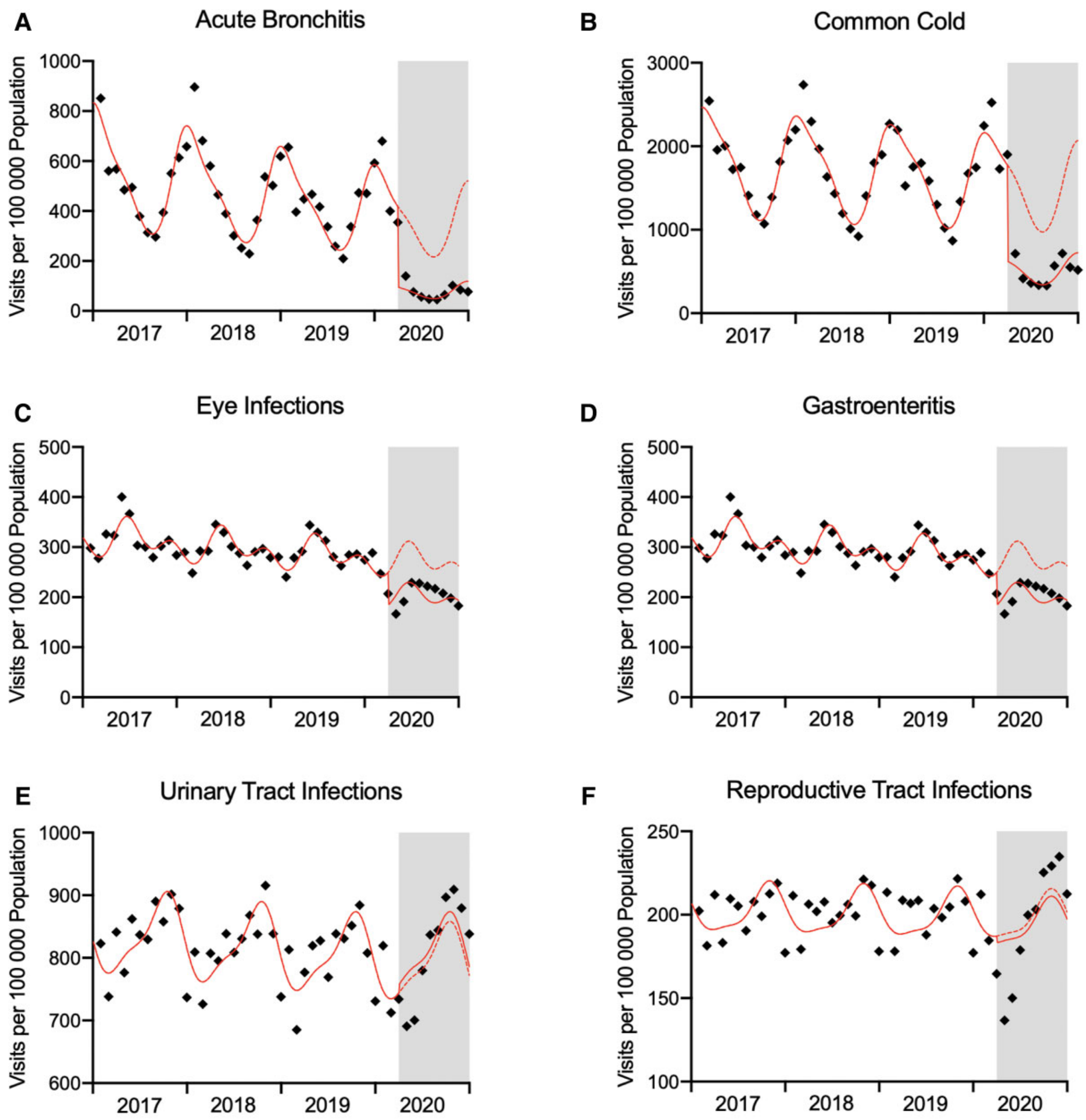

Figure 3. Interrupted time series regression for selected infectious diseases in Ontario. Monthly outpatient visit data are plotted as visits per 100 000 population in Ontario. Red line reflects seasonally adjusted quasi-Poisson regression. Counterfactual is represented by the dotted red line. White areas of the graphs represent the preintervention period (January 2017–March 2020); gray areas reflect the postintervention period (April–December 2020). Time series analysis reflects diagnoses from "highly impacted" (*A* and *B*), "moderately impacted" (*C* and *D*), and "minimally impacted" (*E* and *F*) clusters.

compiled the absolute decline in visits during these months (Supplementary Table 1, Supplementary Figure 2). Data for pediatric prostatitis were not included due to very low visit numbers and to comply with ICES privacy policy. Exclusion of April and May did not result in any striking changes in the RR of any diagnosis, except for a slight increase in number of visits for RTIs and UTIs. Last, we stratified the data into the pediatric and adult populations and reran the interrupted time series analysis. We found that for most diagnoses, visits by pediatric age groups declined at a higher rate than those by adults (Supplementary Tables 2 and 3). We also generated a heatmap with the RR of each diagnoses using the different interrupted time series analyses methods to facilitate comparisons (Supplementary Figure 6). Graphs for regression analysis for all diagnoses, including the age-stratified data, are also included in Supplementary Figures 3–5.

Although no disease was diagnosed more frequently throughout the entire duration of the postintervention period,

Table 1. Summary of Interrupted Time Series Regression Analysis of Infectious Diseases in Ontario, Canada, Comparing Healthcare Visits in January 2017–March 2020 With Visits in April–December 2020

Diagnosis	Mode of Transmission[a]	Etiology[b]	Disease Site[c]	RR (95% CI)	*P* Value
Cluster 1: Highly impacted	…	…	…	**0.345 (.297–.403)**	**<.001**
Acute bronchitis	D	V, B	P	0.229 (.178–.294)	<.001
Common cold	D	V	P	0.351 (.299–.412)	<.001
Pharyngitis	D, C	V, B	P	0.353 (.315–.396)	<.001
Otitis media[d]	E, D	V, B	HN	0.414 (.355–.482)	<.001
Acute sinusitis	D	V, B	HN	0.428 (.369–.497)	<.001
Cluster 2: Moderately impacted	…	…	…	**0.698 (.644–.757)**	**<.001**
Pneumonia	D	V, B	P	0.442 (.382–.513)	<.001
Gastroenteritis	C	V, B	S	0.719 (.641–.807)	<.001
Misc nonbacterial infections	N	V, O	S	0.724 (.668–.784)	<.001
Eye infections	D, C	V, B	HN	0.737 (.681–.797)	<.001
Cluster 3: Minimally impacted	…	…	…	**0.954 (.904–1.006)**	**.085**
Misc bacterial infections	N	B	S	0.796 (.734–.864)	<.001
Asthma[d]	D	V	P	0.866 (.795–.945)	.001
Chronic sinusitis[d]	N	B, O	HN	0.889 (.811–.974)	.012
Nonpurulent SSTI	E, C	B	S	0.895 (.858–.932)	<.001
Pyelonephritis	E	B	U	0.897 (.848–.948)	<.001
Otitis externa	E, C	B	HN	0.908 (.818–1.008)	.070
Purulent SSTI	E, C	B	S	0.974 (.902–1.052)	.499
RTI	E, C	B	U	0.979 (.894–1.072)	.648
Epididymo-orchitis	E, C	B	U	1.017 (.951–1.087)	.631
UTI	E	B	U	1.018 (.965–1.074)	.509
Prostatitis	E	B	U	1.071 (.992–1.156)	.080
Dental conditions	E	B	HN	1.077 (1.023–1.134)	.005

Bold values reflect aggregate statistics for each disease cluster.

Abbreviations: CI, confidence interval; Misc, miscellaneous; RR, rate ratio; RTI, respiratory tract infection; SSTI, skin and soft tissue infection; UTI, urinary tract infection.

[a]Mode of transmission: C, direct/indirect contact; D, droplet/airborne; E, endogenous flora; N, not classified due to variety of conditions.

[b]Etiology: B, bacterial; O, fungal and other; V, viral.

[c]Disease site: HN, head and neck; P, pulmonary; S, systemic and other; U, urogenital.

[d]Where conditions may be precipitated or exacerbated by underlying infection.

visits for dental conditions increased substantially in the months immediately following the COVID-19 restrictions in 2020 compared to the same months in 2017–2019 (Supplementary Figure 3). The statistically significant increase in visits was driven by the surge in visits during the months of April and May (Table 1, Supplementary Table 1).

DISCUSSION

In this article, we have shown that outpatient assessments for many different infection-related diagnoses declined dramatically and in a sustained fashion during the pandemic period across a complete large province-wide sample. Diagnoses due to communicable respiratory pathogens were most significantly impacted, whereas diagnoses related to infections typically arising from the patient's own flora were more minimally impacted. Our findings highlight the massive and ongoing impact of COVID-19 on the underlying mechanisms of infection transmission in populations and the changes in healthcare assessments for infectious diseases. These observations reflect the potential effects of nonpharmaceutical interventions against COVID-19 on the incidence of other infectious diseases.

Diseases with a sustained decline in incidence during the months of June–December 2020 were typically due to communicable respiratory pathogens, and this observation aligns with published literature demonstrating declines in seasonal respiratory viruses during the COVID-19 pandemic [11–14]. The decline was more apparent in the pediatric population, especially for visits for acute bronchitis, pneumonia, and asthma exacerbations, which could be due to school closures throughout this time period. Public health recommendations for frequent hand washing, along with mobility/contact-mitigating policies, may have also contributed to modestly decreased visits for diagnoses such as gastroenteritis and eye infections, which are driven by both contact/droplet modes of transmission. A decline in norovirus outbreaks (a common cause of viral gastroenteritis) during 2020 has been documented in both the United States and Australia [15, 16]. Diseases that often arise from endogenous flora, such as SSTIs and UTIs, did not show a sustained decrease in incidence. This strongly suggests that person-to-person transmission may not play a major role in the incidence of many of the cluster 3 (minimally impacted) diagnoses such as UTI and cellulitis. We also observed a significant increase in visits for dental conditions in April and May 2020, which was likely caused by dental office closures from the COVID-19 governmental response [17].

Although the ICES datasets are population-wide and encompass most publicly funded health services, there are several limitations to this study. The relationship between disease incidence and healthcare visits may not be direct, as patients may have been more hesitant to visit a healthcare practitioner during the COVID-19–related closures. Indeed, initial hesitancy to access healthcare may have contributed to the short-lived, systematic decline in healthcare visits observed during the months of March–May 2020. We also could not measure disease severity, as patients with less severe disease may have chosen to not use the healthcare system during the COVID-19 restrictions. In addition, some of the analyzed diagnoses overlap in symptomology with COVID-19; therefore, patients may be required to complete COVID-19 screening before being seen by a physician. For some self-limiting conditions, such as the common cold, the symptoms may have resolved before the results of the COVID-19 tests were made available. This phenomenon could account for some of the observed decline in the analyzed diagnoses.

Several observations within our data suggest that an inability or reluctance to access care is not entirely responsible for the decline in diagnoses. First, we can use the example of otitis media and otitis externa. Both present with overlapping spectrum of symptoms (eg, ear pain, fever), and hence one might expect similar care seeking as a result of symptoms, but each had different trends during the peripandemic period. Visits for otitis media, which often arise as a complication of a cold or other upper respiratory tract infection, fell by 58.6% (RR, 0.41 [95% CI, .36–.48]; $P < .001$), whereas visits for otitis externa, usually triggered by external bacterial infection of the ear, did not decline significantly in the peripandemic period (RR, 0.91 [95% CI, .82–1.0]; $P = .07$). Second, diagnoses in cluster 3 (minimally impacted) almost uniformly declined at the onset of the pandemic, followed by a rapid return to baseline. This observation suggests that changes in care seeking or access occurred initially but quickly resolved. Third, our hypothesis-free clustering approach groups diagnoses based solely on peripandemic changes in incidence. Based on the results, the underlying common element in each cluster is likely to be a similar infectious etiology as opposed to similarities in care seeking/access across a diverse spectrum of syndromes.

Our study provides evidence on the magnitude of effect that widely adopted nonpharmaceutical interventions can have on some common infections. These results can be used to inform improvements to public health strategy (including updates to public health policy) that have the potential to sustain these reductions into the postpandemic era. Additionally, what we learned from the differences in diagnoses can help us understand future impacts of this pandemic, both on aspects of immunogenicity (eg, due to reductions in viral-related diagnoses) as well as antibiotic resistance (eg, reduction and maintained indications for antibiotic prescriptions, such as pharyngitis and UTIs, respectively). We also better understand what to expect in future epidemics or pandemics necessitating major changes in human interaction, and which diagnoses may decline and persist. According to the OxCGRT stringency index, Ontario's public health measures are comparable to much of the world, particularly the United States, the United Kingdom, and Europe [3]. Vaccines only became widely available in Ontario in the spring of 2021, meaning the nonpharmaceutical interventions were relied upon during our study period. For these reasons, we believe that the results of our study are widely generalizable to many other countries/regions.

In summary, we found that nonpharmaceutical interventions aimed at curtailing the spread of COVID-19 have also resulted in a decreased diagnosis of other highly transmissible respiratory diseases, whereas infectious diagnoses arising from direct contact or from the patient's own flora did not markedly change in incidence. Future studies should aim to further identify the effects of demographic factors such as patient age, geographical location, and mode of access (ie, telemedicine or in-person visit) on visits for specific infectious diseases.

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.

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Author contributions. Conceptualization: D. M., A. Z., and M. D. S. Methodology: A. Z. and M. D. S. Formal analysis: A. Z. and M. D. S. Data curation: R. M., D. G. M., R. T., N. D., D. M. Original draft: D. M., A. Z., and M. D. S. Critical review and editing: All authors.

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Patient consent statement. 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 of, 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 REB review. The use of the data in this project is authorized under section 45 and approved by ICES' Privacy and Legal Office.

Potential conflicts of interest. The 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.

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