Incidence and outcomes of non-communicable pediatric diseases during the COVID-19 pandemic: An interrupted timeseries analysis

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Abstract

Background:

In response to the onset of the COVID-19 pandemic, many countries implemented public health interventions aimed at reducing the spread of the virus, such as social distancing and closure of all non-essential services, as well as closure of daycares and schools. Concerns have however been raised over the negative consequences of the COVID-19 pandemic and its associated interventions on healthcare systems and access to healthcare. Notably, worldwide reductions in pediatric emergency department (ED) visits were observed shortly after the onset of the pandemic. While this drop in ED visits has been attributed to a general reduction in infectious diseases other than SARS-CoV-2, concerns were raised over delayed treatment and worse prognosis for pediatric patients with chronic or non-communicable diseases. However, the impact of the pandemic on non-communicable pediatric diseases remains largely unknown.

Objective:

This study aimed to quantify whether there was a change in incidence of children (<18 years) presenting with 1) appendicitis and 2) confirmed or suspected cancers at the pediatric ED during the first year of the COVID-19 pandemic relative to prior to the pandemic in Quebec, as well as whether there were any changes in severity of pediatric patients with these diseases.

Design/Methods:

This retrospective cohort study made use of the computerized emergency and admissions database of the two large tertiary-care pediatric centers in Montreal, Quebec: The McGill University Health Center (MUHC) and the Centre hospitalier universitaire Sainte-Justine (CHU-SJ). The diagnoses of interest included children with appendicitis in the first manuscript and children with confirmed or suspected cancer in the second manuscript. Children who visited either pediatric ED with one

of the diagnoses of interest between May 2016 and May 2021 were eligible in this study. An interrupted timeseries design (ITS) was used to quantify the change in bi-monthly incidence of ED visits for the diagnoses of interest via Poisson regression or negative-binomial regression, as appropriate, adjusted for underlying baseline trend, seasonality, long term cycles, and hospital site. Outcomes of interests included the change in incidence at the onset of the COVID-19 pandemic (March-April 2020) and the change in bi-monthly trend throughout the first 14 months of the pandemic compared to the predicted incidence from a four-year historical control period (January 2016-February 2020).

In secondary analyses for the first manuscript, perforated appendix and/or surgical drainage were used as indicators for changes in severity of cases during the pandemic relative to previous years, quantified via binomial regression. Change in average length of hospital stay during the pandemic was used as a proxy for investigating changes in hospital utilization, quantified via linear regression. In secondary analyses for the second manuscript, a stratified Cox Proportional Hazards model was used to quantify the change in risk of multiple readmissions to the pediatric oncology ward during the first year of pandemic relative to the pre-pandemic period. .

Results:

There was evidence of a 14% increase in appendicitis diagnoses at the pediatric ED (Incidence Rate Ratio(IRR)= 1.14, 95% CI= 1.01 ; 1.28). This increase remained stable throughout the first 14 months of the pandemic (IRR=1.00 , 95% CI= 0.95 ; 1.04). There was evidence of a decrease in average LOS for appendectomies during the pandemic (-0.88 days 95% CI= -1.65 ; -0.12), but any change in risk of perforation or surgical drainage remained ambiguous (risk ratio= 0.83, 95% CI= 0.52 ; 1.32).

A 39% reduction in overall ED visits for children with suspected and confirmed cancers was observed at the onset of the pandemic (IRR= 0.65, 95% CI: 0.53, 0.79), followed by a gradual increase in cases to baseline throughout the pandemic (IRR=1.11, 95% CI: 1.05, 1.17). In secondary analyses, there was a 37% reduction in pediatric ED visits that resulted in a suspected cancer diagnoses at the onset of the pandemic (IRR=0.61, 95% CI=0.47 ; 0.77), followed by a gradual increase in cases to baseline throughout the pandemic (IRR=1.11, 95% CI=1.04 ; 1.19). In visits for suspected cancers, there was evidence of an increasing trend in pediatric ED visits for confirmed cancer patients (IRR=1.22, 95% CI=1.06 ; 1.41). There was evidence of a reduction in risk of multiple readmissions during the pandemic relative to the pre-pandemic risk (HR= 0.83, 95% CI= 0.74 ; 0.93). .

Conclusion:

This study found evidence of an increase in visits for appendicitis and a reduction in visits for suspected cancers at the pediatric ED during the COVID-19 pandemic relative to previous years. Potential associations between SARS-CoV-2 infection and onset of appendicitis should continue to be investigated. There was no indication of changes in severity of patients with appendicitis during the pandemic, indicating that delays in seeking medical treatment were not common or did not affect the prognosis of patients. The observed reduction in suspected cancer diagnoses and oncology ward admissions may be related to fewer non-SARS-CoV-2 viral transmissions during the first months of the pandemic, and/or in delays in seeking medical advice.

Abrégé

Context:

En réponse à la pandémie COVID-19, de nombreux pays ont mis des mesures de santé publique visant à réduire la propagation du virus, telles que la distanciation sociale et la fermeture de tous les services non essentiels, y compris les garderies et les écoles. Des inquiétudes ont été soulevées quant aux conséquences des interventions associées à la pandémie sur les systèmes de santé et l'accès aux soins de santé. Notamment, des réductions mondiales des visites aux urgences pédiatriques ont été observées peu après le début de la pandémie. Bien que cette baisse en nombre de visites aux urgences ait été attribuée à une réduction des maladies infectieuses, des inquiétudes ont été soulevées concernant le retard de traitement résultant en pire pronostic pour les patients pédiatriques atteints de maladies chroniques ou non transmissibles, mais l'impact de la pandémie sur ces maladies non transmissibles reste largement inconnu.

Objectif:

Cette étude visait à quantifier s'il y a eu un changement dans l'incidence des enfants (<18 ans) présentant avec 1) une appendicite et 2) des cancers confirmés ou suspectés à l'urgence pédiatrique au cours de la première année de la pandémie COVID-19 par rapport à la prépandémie au Québec, ainsi que s'il y a eu des changements dans la sévérité des patients pédiatriques atteints de ces maladies.

Méthodes:

Cette étude a utilisé la base de données informatisée des urgences et des admissions de deux grands centres pédiatriques de soins tertiaires à Montréal, Québec : le Centre universitaire de santé McGill (CUSM) et le Centre hospitalier universitaire Sainte-Justine (CHUSJ). Les diagnostics d'intérêt comprenaient les enfants atteints d'appendicite dans le premier manuscrit et des enfants atteints

d'un cancer confirmé ou suspecté dans le deuxième manuscrit. Les enfants qui ont visité l'un des deux urgence pédiatriques avec un des diagnostics d'intérêt entre mai 2016 et mai 2021 étaient éligibles. Une conception de séries chronologiques interrompues a été utilisée pour quantifier le changement de l'incidence bimensuelle des visites aux urgences via une régression de Poisson ou une régression binomiale négative, selon le cas, ajustée en fonction de la tendance séculaire, de la saisonnalité, des cycles à long terme et de l'hôpital. Les résultats d'intérêt comprenaient le changement d'incidence au début de la pandémie de COVID-19 (mars-avril 2020) et le changement de tendance bimensuelle tout au long des 14 premiers mois de la pandémie par rapport à l'incidence prévue à partir d'un historique de quatre ans. période de contrôle (janvier 2016-février 2020).

Dans les analyses secondaires du premier manuscrit, l'appendice perforé et/ou le drainage chirurgical ont été extraits des notes médicales et utilisés comme indicateurs de la sévérité des cas pendant la pandémie par rapport aux années précédentes, quantifiés par régression binomiale. Le changement de la durée moyenne du séjour à l'hôpital pendant la pandémie a été utilisé comme indicateur pour étudier les changements dans l'utilisation des hôpitaux, quantifiés par régression linéaire. Dans les analyses secondaires du deuxième manuscrit, un modèle stratifié de risques proportionnels de Cox a été utilisé pour quantifier le changement du risque de réadmissions multiples dans le service d'oncologie pédiatrique au cours de la première année de la pandémie par rapport à la période pré-pandémique.

Résultats:

Il y a eu une augmentation de 14 % des diagnostics d'appendicite au urgences pédiatrique (rapport des taux d'incidence (RTI) = 1,14, IC à 95 % = 1,01 ; 1,28). Cette augmentation est restée stable tout au long des 12 premiers mois de la pandémie (IRR = 1,00 , IC à 95 % = 0,95 ; 1,04). Il y avait aussi preuves d'une diminution de la durée moyenne de séjour pour les enfants atteints d’un appendicite pendant la pandémie (-0,88 jours, IC à 95 % = -1,65 ; -0,12), mais aucune preuve d'un changement du risque de perforation ou de drainage chirurgical (risque relatif = 0,83, 95 % IC = 0,52 ; 1,32).

Une réduction de 39 % du nombre total de visites aux urgences pour les enfants atteints de cancers suspectés et confirmés a été observée au début de la pandémie (IRR = 0,65, IC à 95 % : 0,53, 0,79), suivie d'une augmentation graduelle du nombre de cas par rapport au niveau de référence tout au long de la pandémie (TRI = 1,11, IC à 95 % : 1,05, 1,17). Dans les analyses secondaires, il y a eu une réduction de 37 % des visites pédiatriques aux urgences qui ont entraîné un diagnostic de cancer suspect au début de la pandémie (IRR = 0,61, IC à 95 % = 0,47 ; 0,77), suivie d'une augmentation graduelle des cas par rapport au niveau de référence tout au long de la pandémie (TRI = 1,11, IC à 95 % = 1,04 ; 1,19). Dans les visites pour des cancers suspects, il y avait des preuves d'une tendance à la hausse des visites pédiatriques aux urgences pour les patients atteints d'un cancer confirmé (IRR = 1,22, IC à 95 % = 1,06 ; 1,41).). Il y avait des preuves d'une réduction du risque de réadmissions multiples pendant la pandémie par rapport au risque pré-pandémique (RR = 0,83, IC à 95 % = 0,74 ; 0,93).

Conclusion:

Il y a eu une réduction des visites pour appendicite et cancers aux urgences pédiatriques pendant la pandémie de COVID-19 par rapport aux années précédentes. Cependant, il n'y a eu aucun indication de changement en sévérité pour ces maladies, ce qui indique que les retards dans les traitement médical n'ont pas eu d'effet majeur sur les résultats pour ces patients pédiatriques. Les associations potentielles entre l'infection par le SRAS-CoV-2 et l'apparition de l'appendicite doivent continuer à être étudiées, ainsi que la maladie COVID-19 chez les enfants atteints de cancer.

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Contributions of Authors

I, Francesca del Giorgio, as the first author of this thesis, wrote the initial thesis and approved the final version for submission. As first author of the first and second manuscript, I performed the analytical components of these studies, reviewed literature, drafted the manuscripts, and approved the final manuscript.

As a thesis co-supervisor, Olivier Drouin oversaw the thesis question, and revised and approved the final version of the thesis. For the first and the second manuscript, he reviewed and edited the draft versions, provided guidance interpreting the results, approved the final manuscript.

As a thesis co-supervisor, Jay Kaufman supervised the study design and provided guidance on methods and interpretations of results. He also reviewed and all versions of the manuscripts.

As a thesis co-supervisor, Joanna Merckx supervised the study design and provided guidance on methods and interpretations of results. She also reviewed and all versions of the manuscripts.

As a manuscript collaborator, Merieme Habti extracted data on severity of patients from medical records for the first manuscript. She also contributed to the literature review and writing the discussion section of the first manuscript.

As manuscript collaborator, Jocelyn Gravel provided access to and information on navigating the emergency department dataset at CHU-SJ, as well as clinical interpretation of the data and critical feedback to both manuscripts.

As manuscript collaborator, Esli Osmanlliu provided access to and information on navigating the emergency department dataset at MUHC, as well as clinical interpretation of the data and critical feedback to both manuscripts.

As manuscript collaborator, Nelson Piché provided clinical interpretation of the data and critical feedback to the second manuscript.

As manuscript collaborator, Sarah Mousseau provided clinical interpretation of the data and critical feedback to the second manuscript.

As manuscript collaborator, Thai Hoa Tran provided clinical interpretation of the data and critical feedback to the second manuscript.

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List of Abbreviations and Acronyms

WHO- World Health Organization

ED- Emergency Department

VOC- Variants of concern

NCD- Non-communicable disease

MUHC- McGill University Health Center and the

CHU-SJ - Centre hospitalier universitaire Sainte-Justine

ICD-10 - International Classification of Diseases, Tenth Revision,

LOS- Length of Stay

Paed-CTAS- Canadian Paediatric Triage and Acuity Scale

CI – Confidence Interval

RR – Rate ratio

OR- Odds Ratio

HR- Hazards Ratio

1 Introduction: Pediatric health during the COVID-19 pandemic

1.1 Emergence of the SARS-COV-2 Virus and the Onset of the COVID-19 Pandemic

The end of 2019 was marked by the discovery of a novel coronavirus now known as the SARS-CoV-2 virus, which causes COVID-19 disease [1]. Originally identified in the province of Wuhan in China after an abnormal number of patients presented with severe pneumonia-like symptoms, the virus spread rapidly across the country and subsequently across the globe, infecting more than 300,000 people worldwide only 3 months after its discovery [1]. Due to the high case-fatality rate and human-to-human transmission of the virus, on March 13th of 2020 the World Health Organization (WHO) declared the spread of the virus a global pandemic [1].

Almost two years later, the SARS-CoV-2 virus continues to impact countries worldwide, with over 5 million deaths attributed to COVID-19 disease [2]. Public health measures, such as social distancing measures and masks, as well as lock-down orders, were and continue to be common tactics used by governments to reduce the spread of the virus [3]. However, responses to the pandemic have varied by country, from minimal interventions to full closure of all non-essential services. The stringency index, developed by the Blavatnik School of Government at the University of Oxford, quantifies the extent to which public health measures are enforced by a country based on nine metrics: School closures; workplace closures; cancellation of public events; restrictions on public gatherings; closures of public transport; stay-at-home requirements; public information campaigns; restrictions on internal movements; and international travel controls [4]. Based on this index, Canada ranks as one of the countries with most prolonged stringent measures, alongside China, Italy, New Zealand and India.

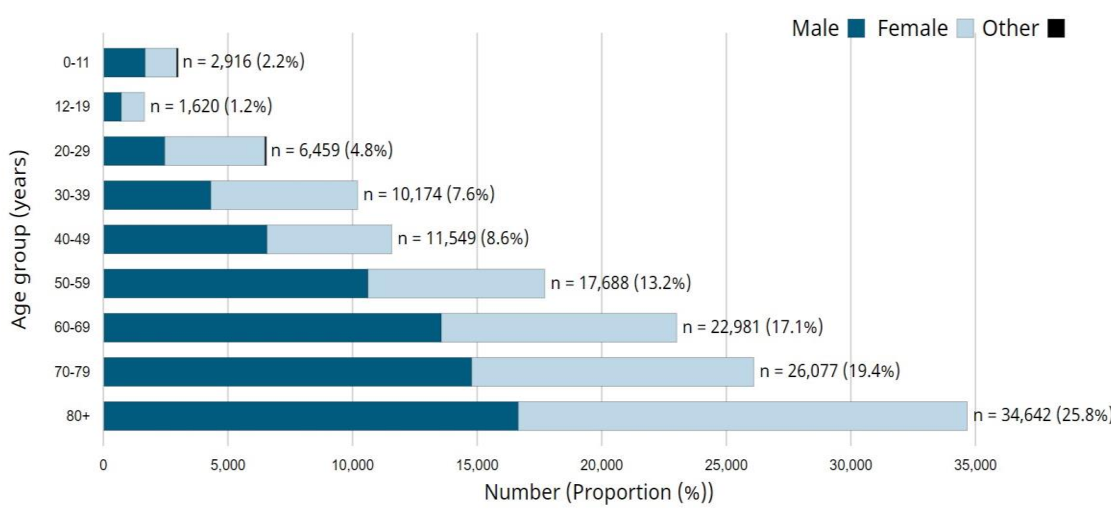
To-date, the pandemic in Canada has been characterized by six waves, or surges in number of cases, each driven by specific variants of concern (VOCs, as defined by the WHO): The Alpha variant, followed by the Beta variant, Gamma variant, Delta variant, and finally, the Omnicron variant and sub-variantS, in chronological order [1,5]. At the federal level, interventions most commonly involved border closures and travel restrictions, while provincially school closures were the most frequent public health intervention[6]. Québec was the first province in the Canada to declare a state of emergency on March 13th of 2020, and, over the following weeks enforced the first of many social distancing policies and closure of non-essential public places, including restaurants, bars, gyms, hair salons, daycares and schools [7].

As a result of the transmission of the SARS-CoV-2 and interventions enforced to control the spread of the virus, healthcare systems in Quebec and Canada more generally underwent changes in delivery of care. For example, a report by the Canadian Institute of Health Research (CIHR) summarizing changes in healthcare provision in Canada during the first 16 months of the pandemic found that a large portion of emergency department (ED) visits were shifted to virtual appointments, hospital resources were redirected towards treating patients with COVID-19 disease, and that there were mass delays in treatment for non-urgent medical conditions [8]. Such changes can lead to beneficial reductions in the spread of the SARS-CoV-2 virus, but also have indirect impacts that negatively impact access to care.

1.2 Differential prognosis of SARS-CoV-2 infection by age

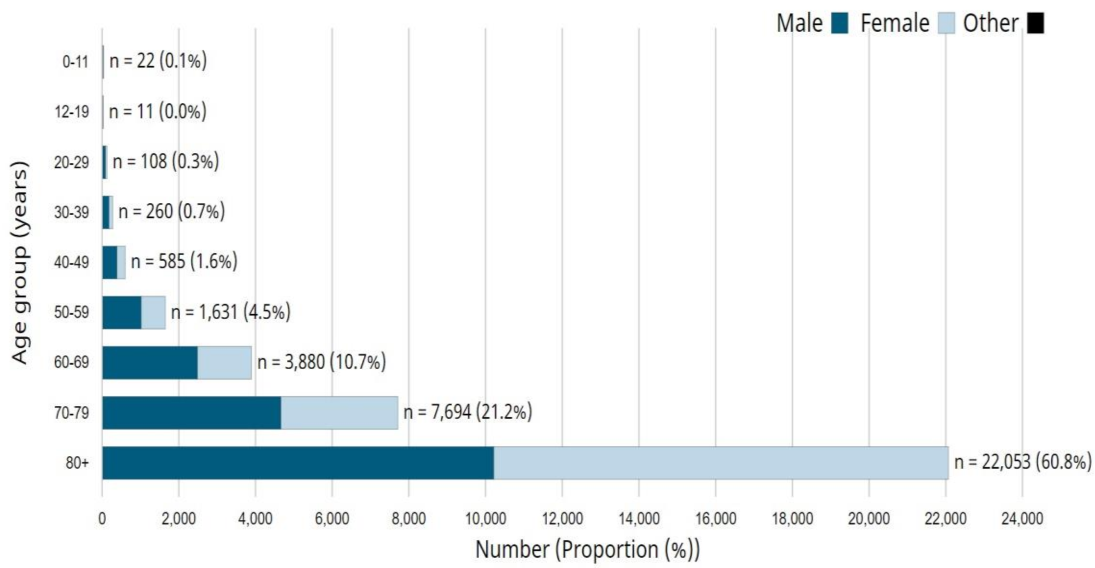
The clinical presentation of COVID-19 disease varies from mild symptoms, such as cough, fatigue, and loss of smell and taste, to progressive disease with pneumonia and respiratory failure and death [9,10]. During the early months of the COVID-19 pandemic, the case-fatality rate from SARS-CoV-2 infection was estimated between 7 to 17%. However, mortality related to the virus varied substantially by age, reaching up to 50% for patients older than 60 years of age but remaining virtually 0% for children under the age of 12 years [11]. In Canada, as of March of 2022, only 3.4% of hospitalized cases and less then 1% of deaths were in children and adolescents (0-19 years of age), whereas 25.8% of hospitalizations and over 60% of deaths were in adults over the age of 80 (Figures 1-2). Several hypotheses have been proposed to explain the reduced risk of severe infection in children, including fewer age-related comorbidities and risk factors, such as heart disease, obesity, and smoking, as well as differences in the innate and adaptive immunity systems[12,13].

Figure 1: Age and sex distribution of COVID-19 cases hospitalized in Canada as of March 4th, 2022



Source: Government of Canada: COVID-19 daily epidemiology update, from: https://health-infobase.canada.ca/covid-19/epidemiological-summary-covid-19-cases.html#a7

Figure 2: Age and sex distribution of COVID-19 cases deceased in Canada as of March 4th, 2022



Source: Government of Canada: COVID-19 daily epidemiology update, from: https://health-infobase.canada.ca/covid-19/epidemiological-summary-covid-19-cases.html#a7

As pediatric patients continue to have decreased risk of severe infection, much of the literature investigating COVID-19 disease to-date has focused on the adult population. However, certain comorbidities in young patients have been found to increase the risk of severe infection: There is now some evidence that children and adolescents with type-1 diabetes, obesity, chronic lung disease, cardiac and/or circulatory congenital anomalies may be at higher risk of severe COVID-19 disease compared to children with no comorbidities [14,15]. Children with acquired immune deficits, such as patients with cancer, may also be at higher risk for severe infection and mortality related to the virus, but this risk remains poorly quantified[14,16].

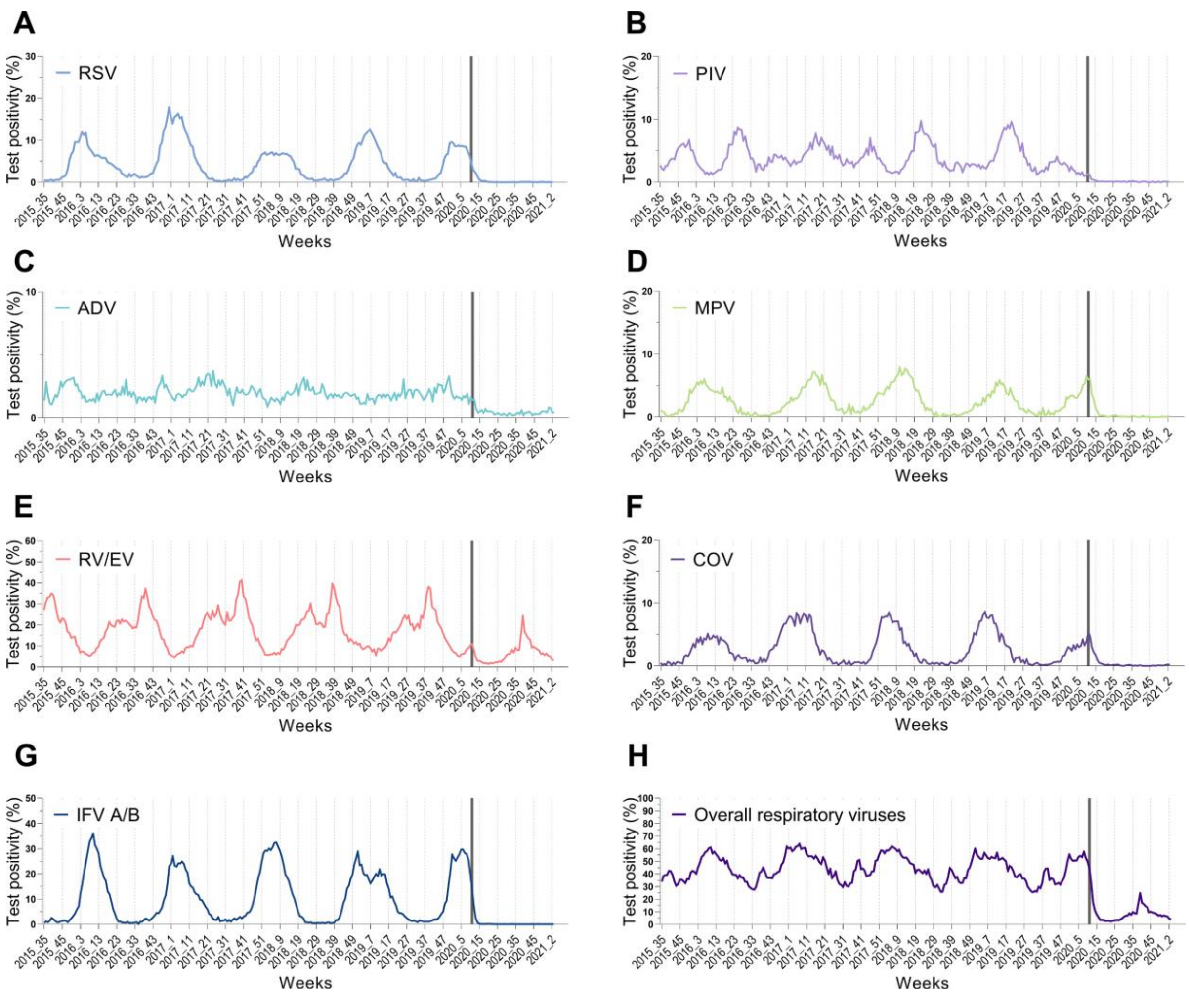
SARS-CoV-2 infection has also been associated with a novel acute pediatric hyperinflammatory syndrome, now commonly referred to as Multisystem Inflammatory Syndrome in Children (MIS-C), which most often presents with abdominal pain and diarrhea but can progress to hypotension, shock, and death [17,18]. Several case-studies have reported pediatric patients with

COVID-19 disease presenting with appendicitis, suggesting that there may be an association between SAR-CoV-2 infection and acute appendicitis in children [19,20]. Other studies have proposed that the overlapping clinical presentation between COVID-19 disease (or MIS-C, in more severe cases), and pediatric appendicitis may lead to more misdiagnosed cases of appendicitis [21,22]. As a 6th wave is ongoing in Canada and the SARS-CoV-2 virus is expected to become endemic, more robust studies are needed to quantify the COVID-19 disease in children, and potential associations with other acute conditions.

1.3 Indirect effects of the COVID-19 pandemic : Transmission of common viruses and access to healthcare systems

Public health measures have been found to effectively reduce the spread of the SARS-CoV-2 virus, especially when multiple interventions, such as enforced tele-work, school closures and cancellation of social activities (gatherings, stores, restaurants, and in-person activities) are enforced simultaneously (11). Unsurprisingly, these measures have also been associated with a

Figure 3: Test positivity of respiratory viruses based on weekly laboratory surveillance data in Canada.



The grey vertical bar indicates initiation of preventive measures against coronavirus disease 2019. Respiratory syncytial virus (RSV), parainfluenza virus (PIV), adenovirus (ADV), human metapneumovirus (MPV), human rhinovirus/enterovirus (RV/EV), seasonal human coronavirus (COV), and influenza A/B (IFV).
Source: Park et al.

reduction in prevalence of other infectious diseases. For example, in Canada a reduction in influenza and non-influenza respiratory viruses (including influenza A and B, Rhinovirus, Adenovirus, Human metapneumovirus, and seasonal coronaviruses) was observed during the first year of the pandemic (Figure 3) [23,24]. This reduction in non-SARS-CoV-2 respiratory viruses was also documented in other countries, including the United States, the United Kingdom, Japan, Korea, Australia, New-Zealand, and Thailand, amongst others [25–29]. In this regard, the COVID-19 pandemic and its associated interventions serve as a natural experiment by which mechanisms of viral transmission and the association between viral infections and health conditions may be better understood. For example, observed reductions in low birth weight and acute exacerbations for asthma during the pandemic have lead researchers to postulate a potential association of these conditions with viral infections [31–33]. Natural experiments, unlike other research designs, offer the benefit of providing data on exposures that are difficult and often unethical to assign [30].

On the other hand, lockdown measures are also associated with other indirect effects on the wellbeing of children and adolescents [34–37]. Notably, prolonged school closures and stay-at-home orders throughout the pandemic resulted in an estimated 1.5 billion children worldwide having been out of school during the first waves of the pandemic [34,38]. Increased cases of child abuse were documented in multiple countries during these stay-at-home order, likely due to reduced access to social services and signalling by social services that are normally provided through schools [34]. Furthermore, multiple studies have documented increased rates of suicide and self-harm in children and adolescents during the pandemic, implying that lockdown measures resulted may result in worse mental health [34–36,39].

A notable effect of the pandemic was the reduction in pediatric ED visits: At the onset of the COVID-19 pandemic in March of 2020 it is estimated that visits to the pediatric ED decreased anywhere between 30-89% [40]. In Canada, a 58% reduction in the number of expected pediatric ED visits was observed between March and April of 2020 relative to the same months in previous years [41,42]. Pediatric EDs differ from adult EDs in that most visits are for communicable or infectious diseases and traumas, and less so for chronic conditions. As such, the reduction in visits during the pandemic has been attributed to the decrease in infectious diseases resulting from confinement and sanitation measures [40,43,44]. Nonetheless, pediatric EDs also serve a crucial role in identifying and providing care for other acute pediatric conditions, such as appendicitis, diabetes dysregulation, and cancer related complications.

A large multi-center study conducted in the US found a decline in visits not only for communicable diseases at the pediatric ED, but also for other acute medical conditions such as appendicitis [45]. To explain this decrease, it has been suggested that fear of contracting the virus deterred parents from seeking medical care for their children. For example, a study investigating the reduction in pediatric ED visits in the UK found that delays in seeking medical attention occurred in approximately ¼th of all visits in April of 2020, with diabetic ketoacidosis, sepsis, malignancy, child protection, and appendicitis being the top conditions for which there were delays [46]. Importantly, delays in consulting for potentially severe pediatric conditions may lead to more severe illness for children with non-communicable diseases (NCDs) [47].

Currently there are some peer-reviewed publications investigating delays in visiting the pediatric ED with a focus on cases of appendicitis, as it is an acute condition that requires almost immediate medical intervention. For example, two studies, one conducted in Spain and the other in Australia, found an increased rate of complicated pediatric appendicitis during the first few months of the pandemic compared to previous years [48, 49]. These studies suggest that delays in presentation to the ED result in worse disease in children with appendicitis during the pandemic.

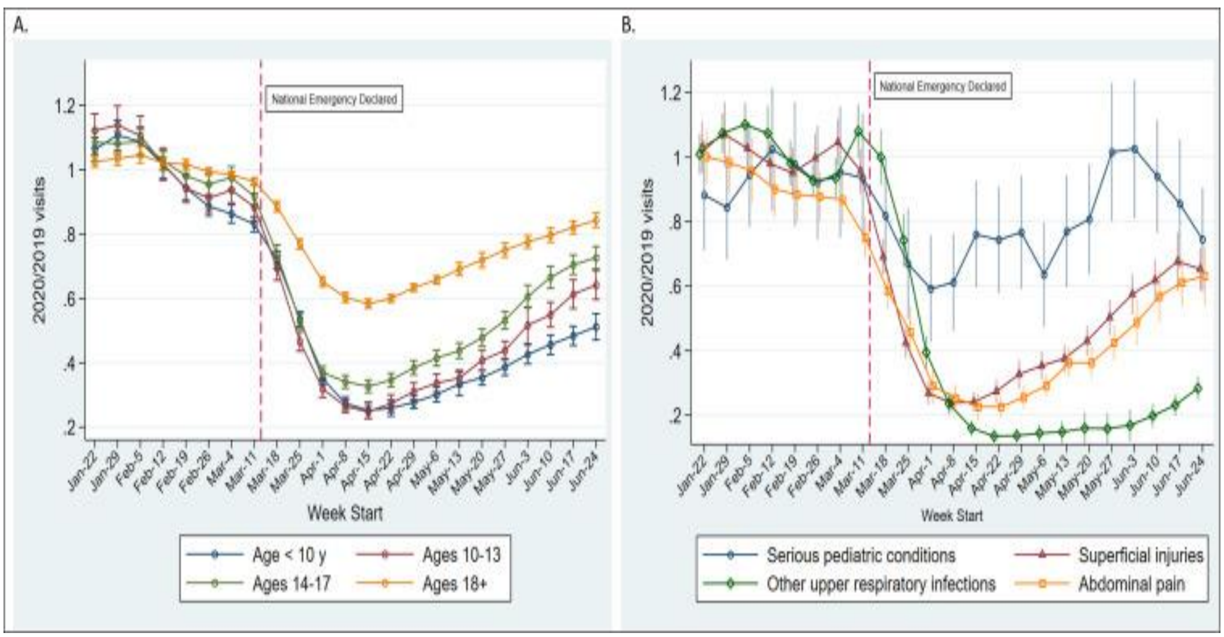
Indeed, a case-control study identified 7 children with complicated appendicitis resulting from parental concern of visiting the ED, telemedicine use, and insufficient evaluation [49]. However, studies to-date have relied on small patient-samples and been focused on changes in severity during the first months of the COVID-19 pandemic [48-51]. As such, there is need for more robust studies that investigate changes in incidence and severity of pediatric appendicitis throughout the duration of the COVID-19 pandemic. Furthermore, there is yet no study that has quantified changes in incidence or delays in seeking medical attention for pediatric patients with appendicitis in a Canadian context.

Even fewer studies have investigated delays in visiting the pediatric ED for other NCDs, such as cancers. A few case and cross-sectional studies conducted in Europe, USA, and Middle Easter regions found delays in medical care and diagnosis for pediatric cancers [52–55]. Pediatric EDs in Quebec and Canada more broadly play an important role in the initial detection of cancers and in providing emergency care to cancer patients. As such quantifying changes in incidence of visits provides important information on delayed diagnosis and treatment for pediatric cancers. However, no Canadian study to-date has quantified changes in hospital use of cancer patients during the pandemic.

The use of alternative pathways of care, such as telemedicine, may be a partial explanation of the reduction in pediatric ED visits as studies across different countries reported a large increase in use of virtual pediatric care [56–59]. Telemedicine in pediatric care has multiple benefits, including reducing contact moments that can lead to the spread of communicable diseases, reduced use of costly medical equipment, and greater healthcare accessibility to children in remote regions [56,59]. Although adult patient satisfaction with telemedicine has been documented to be high, especially for conditions concerning mental health, it remains unclear how the quality of care via telemedicine compares to more traditional forms of care, specifically in children [60]. Most pediatric NCDs, such as appendicitis and certain pediatric cancers, require rapid medical intervention, making use of telemedicine potentially harmful because traditional screening tools, such as blood tests and medical imagining, are not directly available and may be postponed.

Alternatively, a reduction in non-communicable diseases at the pediatric ED may result from fewer new cases compared to previous years. Emerging literature suggests a potential association between various pediatric NCDs and viral infections [61,62]. For example, there is

Figure 14: Weekly Facility Ratios of ED Visits 2020/2019 in 147 Facilities by Age (A) and Selected Pediatric Conditions (B) During the COVID-19 Pandemic



Note: Dotted vertical line separates pre-pandemic from pandemic period. Small vertical bars around each data point indicate 95% confidence interval, calculated using robust standard errors clustered at the facility-level. Trends in ages <3 were found to be nearly identical to trends in age 3–9 and were combined (<10 y). Serious pediatric conditions include appendicitis, sepsis, diabetic ketoacidosis, intussusception, and testicular torsion.
Source: Pines et al.

growing evidence of a potential association between viral infections and onset of pediatric leukemias, such that immaturity of the immune system due to lack of exposure during early childhood to common viruses may result in in-proper immune responses to infections later on, or that viral infections themselves are a potential trigger for specific pediatric cancers [63,64]. Type 1 diabetes and appendicitis have also been associated with viral infections: Infection can provoke a strong inflammatory response of the pancreatic islets (clusters of cells in the pancreas that produce hormones), which may act as an initial trigger in type 1 diabetes [65], and can cause inflammation of the appendix [66]. In fact, studies have observed a reduction in cases of acute appendicitis during the pandemic, attributing this to a reduction in microbial circulation [67,68]. If these hypotheses hold true, the reduction in viral transmission during the pandemic may have also resulted in a temporary absolute reduction of certain pediatric NCDs.

1.4 Gaps in the literature on the impact of the COVID-19 pandemic on pediatric non-communicable diseases

To summarize, there is evidence that the COVID-19 pandemic and associated public health measures have lead to changes in access to healthcare, nutrition, socialization, and other services normally available to children and adolescents [69,70]. One major effect of the pandemic was the global reduction in pediatric ED visits throughout the first year of the pandemic, which has in-part been attributed to a reduction in viruses resulting from confinement and sanitation measures. However, the extent to which the reduction in pediatric ED visits may be attributable to NCDs, and the reason and consequences behind any such reduction, remains unclear.

Appendicitis has been of interest during the pandemic because it is the most common reason for pediatric emergency surgery and delays can result in worse outcomes or death [48,51,71]. However, there is currently little evidence of the impact of the pandemic on severity and incidence of pediatric appendicitis in a Canadian context. Even fewer Canadian studies have investigated changing incidence for cancers in the pediatric population. As such, quantifying changes in incidence and severity of pediatric NCDs during the COVID-19 pandemic remains an essential task through which we can better our understanding of infectious pathogens and their association to pediatric NCDs, but also to understand the impact of COVID-19 disease and public health measures on health outcomes for pediatric patients.

2 Rationale and thesis objectives

It is well established that children and adolescents present with a reduced risk of severe SARS-CoV-2 infection compared to adults[13]. However, the worldwide reduction in pediatric ED visits during the COVID-19 pandemic led to concerns of worse prognosis for pediatric patients with non-communicable diseases. The goal of this thesis was to quantify the impact of the pandemic on pediatric patients with appendicitis and cancers in Canada to contribute to existing knowledge and gaps in the literature on pediatric NCDs during the COVID-19 pandemic. Specifically, the goals of this thesis were:

1. **To estimate the change in incidence and severity of appendicitis at two pediatric hospitals in Quebec, Canada.** Although the COVID-19 pandemic and associated reductions in common viral infections serve as a natural experiment by which we can explore potential triggers for pediatric appendicitis, few studies to-date have investigated absolute changes in cases of appendicitis. To fill this gap in knowledge, we investigated changes in bimonthly incidence of pediatric ED visits for appendicitis during the pandemic compared to 4 years prior to the pandemic. We also wanted to contribute to existing literature on changes in severity of cases of pediatric appendicitis in a Canadian context during the pandemic as measured by change in average length of hospital stay, change in risk of perforated appendix and/or requiring abscess drainage.
2. **To estimate the change in incidence and severity of pediatric cancers during the pandemic in Quebec, Canada.** Most studies to-date have been case-studies focusing on changes in severity of pediatric cancers resulting from delays in medical treatment. This study involved two large tertiary care pediatric centers, and as such will provide more robust estimates on the impact of the pandemic on pediatric cancers by investigating

changes in incidence of ED visits and oncology ward admissions. Such analyses provide relevant information on potentialchanges in incidence of pediatric cancers during the pandemic, changes in severity, and changes in hospital utilization.

3 Methods

3.1 Date source

Data was retrospectively extracted from the emergency department and admissions database, as well as electronic medical charts at the Centre hospitalier universitaire Sainte-Justine (CHUSJ) and the McGill University Health Centre (MUHC). These are two tertiary care centers on the island of Montréal, Québec, and have a combined census of 164,000 ED visits per year. The following variables were available from the emergency department databases: Date of arrival (defined as the date the patient was registered at the hospital), reason for consult, triage category (ranging from 1 to 5 with 1 being highest priority), age (in years), length of stay (in hours, from the time of arrival to the time of leave or admission), and diagnosis (ICD-10 codes at the MUHC and a drop down list of 600 possible diagnoses at the CHUSJ).

3.2 Participants

In all analyses, patients who arrived at either hospital between April 2016 and March 2021 were included in the analysis. In the first manuscript, cases of appendicitis were identified via ICD-10 codes K35-K37 and K38.9 at MUHC, and via the diagnosis of 'Appendicite, App' at CHUSJ. In secondary analyses, patients admitted to the hospital with a primary or secondary diagnosis of appendicitis were identified via ICD-10 codes K35-K37 at both hospitals, and information on the diagnosis, interventions, demographics (age, sex, and date of birth), as well as MRN were extracted from the electronic medical archives. The MRN, in combination with the date of birth, was used to identify the medical record of patients with appendicitis at both hospitals, and medical notes were used to identify whether the patient had a perforated appendix and/or required abscess drainage.

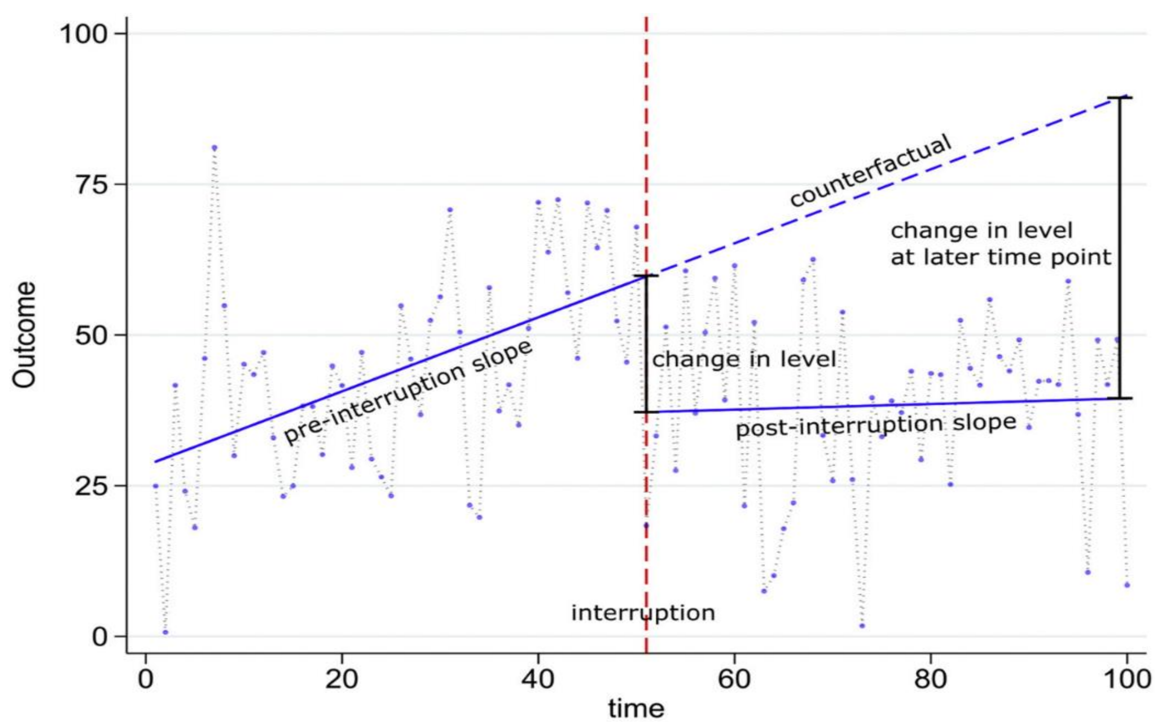
In the second manuscript ICD-10 codes for oncological conditions C00-C98 were used to identify children with cancer at the MUHC pediatric ED. Children with cancer were identified from the drop down list of diagnostic criteria at the CHUSJ (see Appendix 1). In secondary analyses, all children admitted to the oncology at MUHC and CHUSJ during the study period were extracted using electronic medical archives of the oncology wards.

3.3 Analysis

3.4 Introduction to Interrupted Time Series Analysis

In this study, an interrupted time series (ITS) analysis was used to estimate the effect of the pandemic on incidence and outcomes for specific pediatric non-communicable diseases. ITS analysis relies on repeated and consistent aggregate measures over time, with the goal of estimating the impact of a well defined intervention by quantifying the change in trend and level in an outcome after the intervention to the expected trend had the intervention not occurred [72]. Figure 5 by Turner et al. depicts a typical ITS design, where the vertical dotted red line indicates the

Figure 5: Commonly used interrupted time series effect measures and components



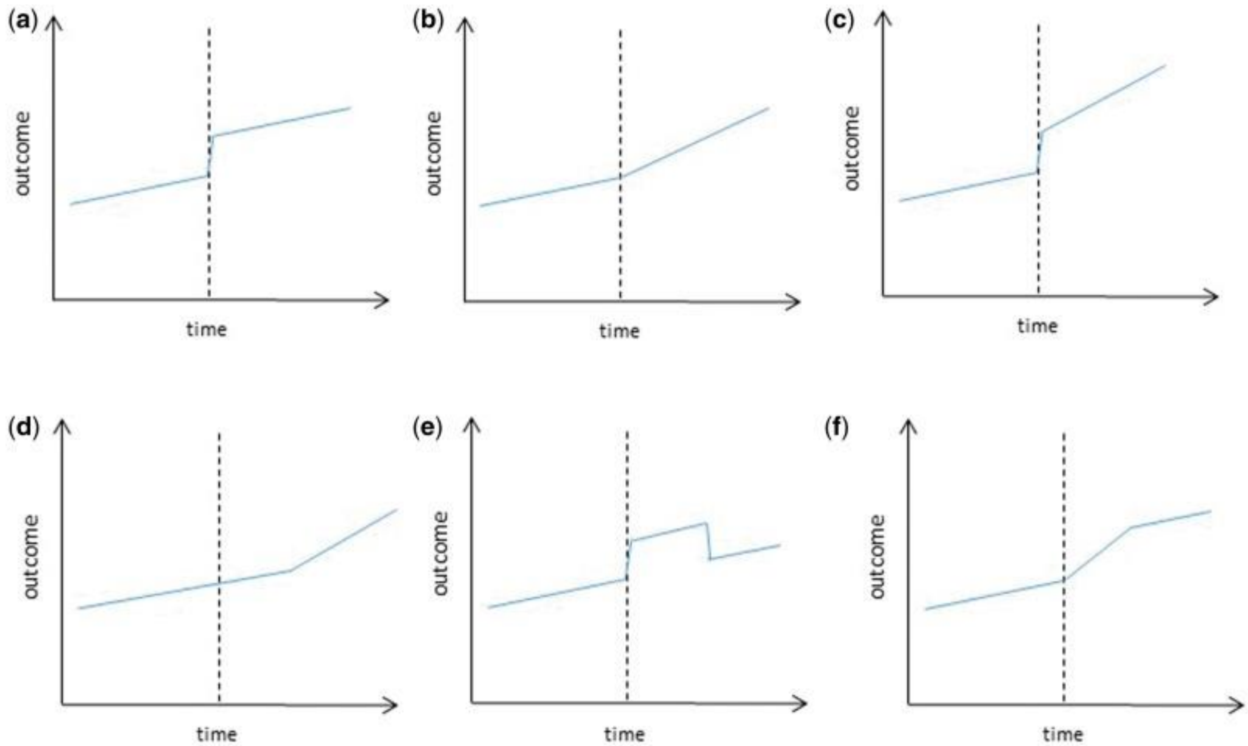
Source: Turner et al.

intervention, the blue line represents the fitted values, and the dotted blue lines represents the counterfactual.

This type of analysis falls under the umbrella of quasi-experimental methods, which are considered strong alternate options to experimental designs when assignment of the exposure is unethical or impossible [73,74]. Unlike experimental designs, in quasi-experiments researchers cannot randomize participant but instead rely on the natural occurrence of an exposure (usually a policy intervention), making it more plausibly random than purely observational studies [75,76]. The use of aggregate data at the population level makes individual-level confounding unlikely and allows for easy investigation of differential impact on subgroups of the population. Furthermore, the results of an ITS can be easily interpreted graphically, making it ideal to communicate the impact of an intervention to a broader audience compared to other more analytical methods [77].

In simple terms, the effect of the intervention in ITS analysis can be expressed as the difference in trend and level between the counterfactual estimate and the observed trend in the post-intervention period. Figure 6 by Bernal et al. depicts different effect estimates in ITS analysis: A level-shift refers to the change in intercept at the onset of the intervention (Figure 6.a), whereas a slope-change refers to a change in trend post-intervention relative to the pre-intervention trend (Figure 6.b). Both a level shift and slope change can be observed simultaneously (Figure 6.c). It is also important to consider potential lags in the effect of an intervention, non linear effects, and the duration of the effect through the post-intervention period (Figure 6.d-f) [78].

Figure 6: Effect estimates in interrupted time-series analysis



Examples of impact models used in ITS (a) Level change; (b) Slope change; (c) Level and slope change; (d) Slope change following a lag; (e) Temporary level change; (f) Temporary slope change leading to a level change.

Source: Bernal et al.

There are multiple modelling techniques in ITS analysis, such as the AutoRegressive Integrated Moving Average (ARIMA) and segmented regression models, amongst others [79,80]. Choosing a model largely depends on the type of outcome, the presence of autocorrelation, access to a control group, the type of co-variates, and trends in the data such as seasonality [81]. ARIMA models are often used in timeseries with complex trends, but are not suitable to small counts [82]. On the other hand, segmented regression (also known as piecewise regression) is often used when the data exhibit weak autocorrelation and simple trends that can be easily modelled [78]. Segmented regression is defined as a regression analysis where the independent variable, usually time, is divided into one or more segments [83]. Poisson regression is typically used as it is appropriate to count data. However, Poisson regression assumes that the mean of the data is equal to its variance, an assumption that is often not upheld in timeseries data. Overdispersion can be tested using the dispersion test in R statistical software [84] and corrected for by adding a scale parameter to the regression, or using quasi-Poisson regression or negative binomial regression[85,86].

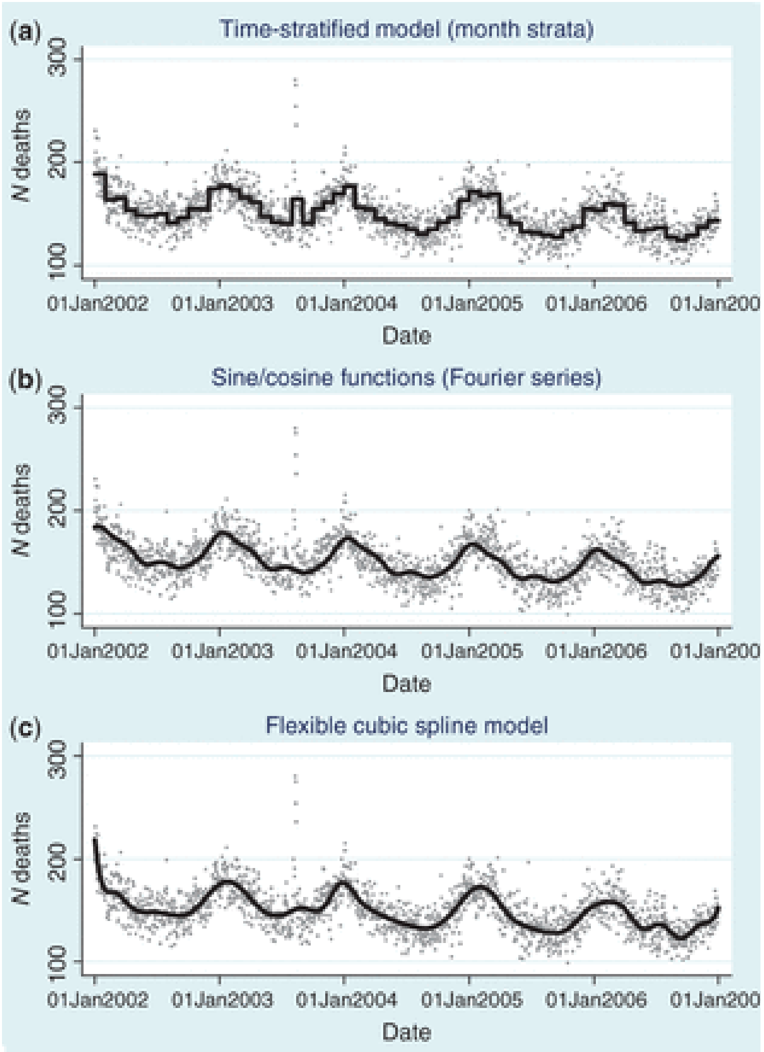
3.5 Modelling considerations and threats to validity

Although ITS analysis is considered a strong quasi-experimental methods, it faces certain challenges owing to the serial nature of the design [74]. As mentioned above, individual level confounders are unlikely, but time-varying confounders such as changes in socio-demographic characteristics of the study population, secular time-trends, seasonality, or other cyclical trends, pose threats to the validity of ITS analyses. Ideally, an external comparison population that represents the study population is used as a control, which can help account for secular trends, seasonality, but also for co-occurring events (events that coincide with the intervention) that may bias the effect estimate. In many cases, however, an external control group is not available, and thus the ITS analysis relies on the assumption that extrapolation of the pre-intervention trend serves as an accurate counterfactual making it crucial to accurately model the pre-intervention trend [74].

One issue often faced in ITS analysis that must be examined and accounted for is autocorrelation, which refers to correlation in datapoints that are nearer in time compared to those further in time resulting in the violation of the assumption of independence required in statistical modelling [79]. A plot of residuals versus time can help visually detect autocorrelation in a regression model. More commonly, the autocorrelation function (ACF) is used to detect autocorrelation, which plots the correlation between data-points with k-lag and a corresponding 95% confidence interval, where k is the gap between datapoints [79]. For example, k=1 refers to the correlation between adjacent data points, whereas k=2 refers to the correlation between datapoints that are 2 time-points apart [87,88]. A partial autocorrelation function (PACF) plots the correlation between points with k-lag after accounting for the correlation explained by data-points residing in-between (k-1 lag data-points), and can be helpful in identifying seasonality [82]. For a stationary series, the autocorrelation in the ACF plot should decay quickly; with a non-stationary series, the ACF will decay slowly(30). Statistical tests often used to identify autocorrelation include the Durbin Watson statistic and the Ljung-Box chi-square statistic, which detect autocorrelation in a regression analysis at specific lag points [74,89]. Often, autocorrelation is minimized when seasonality or secular trends are adequately accounted for in the model.

Another common and related issue that must be considered in ITS analysis is non-stationarity. This refers to situation where the mean and/or variance of a timeseries are time-dependent, which occurs, for example, when seasonality or secular time-trends are present [82,90]. Such timeseries cannot be used for forecasting and must be transformed into stationary processes via differencing or explicit modelling of the trends in the data [82]. In segmented regression analysis, secular time-trends can be accounted for by adding a linear (that is, $\mu t = \beta_0 + \beta_1 t$) or non-linear (for example, a quadratic trend, $\mu t = \beta_0 + \beta_1 t + \beta_2 t^2$) slope parameter, with the assumption that this trend applies to the entirety of the timeseries [91]. Figure 7 by Bernal at al. graphically depicts these three methods for modelling seasonality in regression analysis. Seasonality can be modelled via seasonal indicator variables, which are easy to interpret but increase the number of model parameters and assumes unrealistic jumps between time periods (Figure 7.a). Alternatively, cubic splines, which are piecewise polynomials joined together to make a single smooth curve,

Figure 7: Modelling seasonality in timeseries



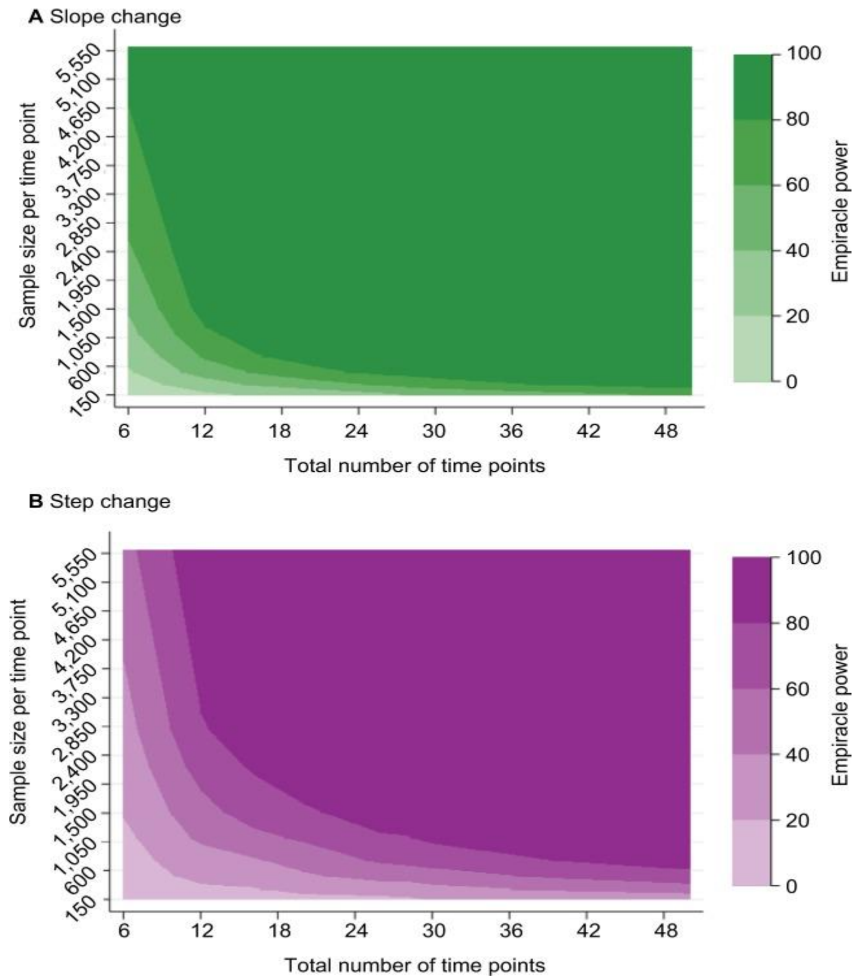
Source: Bhaskaran et al.

can capture unstable seasonality and long-term trends, but are mathematically complex and make interpretation of parameters difficult (see Figure 7.c). Finally, Fourier terms are functions of sine and cosine pairs that model very regular seasonal patterns and involve fewer parameters compared to indicator terms but may be too restrictive for timeseries data with unstable seasonality (see Figure 7.b) [78,90].

3.6 Power considerations in interrupted time-series analysis:

In general, increasing the number of pre-intervention time-points increases the predictive accuracy of the pre-intervention trend by capturing secular trend and seasonal or longer cycles in the data that may otherwise be missed[78]. Hawley et al. simulated power calculations for time-series

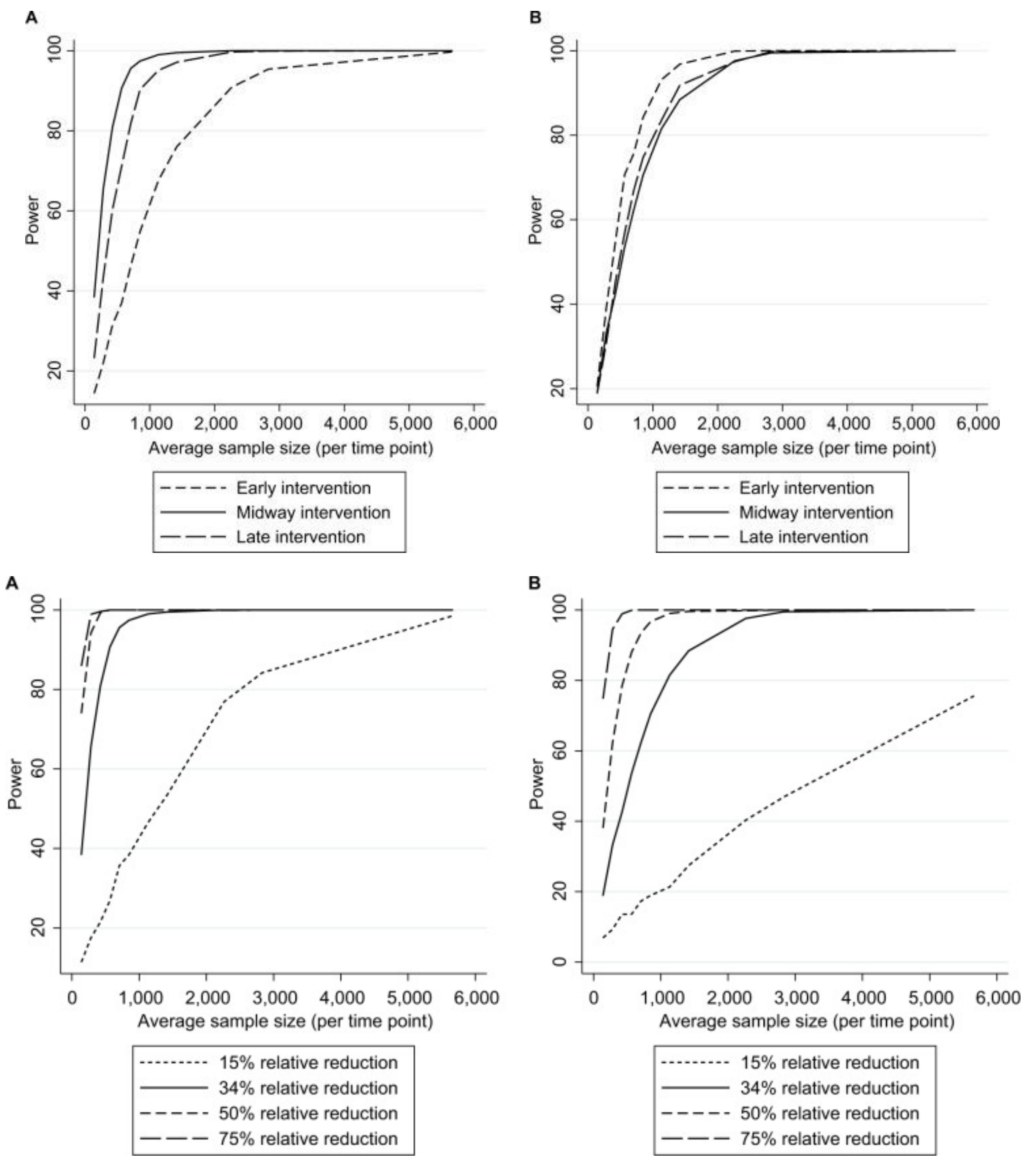
Figure 8: Empirical power to detect a relative 34% reduction in outcome, where mean pre-intervention incidence is 3.5%: by the number of time points and mean sample size per time point: (A) slope change (B) step change.



Source: Hawley et al.

analysis demonstrates that increasing the number of datapoints above 24 is beneficial to increase the power of ITS analysis in timeseries with small counts (<600 counts per datapoint). However, the frequency of events per datapoint itself has an even greater effect on the power of the analysis to detect the intervention effect [92]. Figure 9 displays the effect of count-size by effect-size and intervention location on power to detect a slope change (graphs A) and level-shift (graphs B), demonstrating that increasing count is particularly important for smaller effect sizes, whereas intervention location has less of an effect on the analysis. We can also see from these graphs that the slope-change parameter typically has more power than the corresponding level-shift parameter especially in scenarios when the change in incidence is smaller than 15%. To

Figure 9: Empirical power of ITS analysis stratified by effect size and intervention location resulting in (A) a slope change or (B) step change



Source: Hawley et al.

summarize, the effect of an intervention on a rare outcome and with a small effect size (<15%) will be difficult to capture in an ITS analysis with small counts and fewer timepoints [92].

3.7 Interrupted Time-Series analysis with multiple sites

A timeseries often involves aggregate counts from different sites. For example, the monthly incidence of a disease may be extracted from multiple hospitals. Multi-site studies should be accounted for in the ITS model to control for potential heterogeneity between sites [76]. Causes for heterogeneity involve different intervention times by site or different responses to the intervention. One method for accounting for multiple sites is the pooled analysis technique, which involves running a separate segmented Poisson regression model for each site and pooling the estimates by creating a weighted average for each site based on the variance of the estimate from the individual regression models [76]. Alternatively, a stacked analysis involves fitting a single model with a coefficient for each site, which has the benefit of potentially increasing power of the analysis to detect the effect of the intervention by using the aggregate counts of all sites [93]. However, this method may not be feasible in instances when there are many sites, or if the duration of the timeseries varies by site [76].

3.8 Selection of the final model

Selection of the final should rely on a combination of model fit and known confounders. For example, the parameter for secular time trends is often retained in the model even if it is not significant because secular trends often pose threats to the validity of the analysis. However, increased number of parameters often results in decreased power to detect the effect of the intervention. As such, parameters that are not significant and are not suspected or known confounders in the analysis are often dropped from the model. The most common method for model selection involves a backwards stepwise search using the Bayesian information criterion (BIC) criteria as an estimate of model fit, which accounts for the number of parameters in the model. This search begins with the model including all confounder and effect measures of interest, such as the level-shift and slope change parameters and ends at the model with the lowest BIC value. The final model may not include all effect estimates if one or more is not improving the fit of the model [83]. The residuals of the final model should follow a Poisson distribution and be randomly distributed.

3.9 Applications of interrupted time-series analysis to this study

In this study, all analyses were performed using R version 1.3.1073 and tests of fit and model specification were evaluated at alpha=0.05. This study was approved by the ethics review boards of both hospital sites (MP-21-2021-2930) and participant consent was waived. The intervention was defined as March-April of 2020 as it coincides with the onset of the COVID-19 pandemic and of its associated public health measures in Canada. Based on the results of similar studies [40,41,43], it was hypothesized that the effect of this intervention on incidence of pediatric ED visits and admissions for the diagnoses of interest would be immediate and would be followed by a 'catch-up' period or return to the pre-pandemic trend by the end of the first year. No co-occurring events were identified or suspected since lockdown measures overrode all other intervention. Thus, we expected to observe both a level shift and slope change in the incidence of pediatric ED visits for the diagnoses of interest (Figure 6. c).

Considering that power in ITS analysis increases by the number of time-points and the counts per time-point, the incidence of ED visits and admissions for the diagnoses of interest were extracted up to 4 years preceding the onset of the COVID-19 pandemic to ensure sufficient time points to adequately model the pre-intervention trends. Knowing that the diagnoses of interest in this study are rare and that the effect of the pandemic was not expected to be greater than 15%, it was decided a-priori that timeseries with counts (n) below 200 would be aggregated bimonthly to increase the power of the analysis. In such cases, incidence was measured at 24 data points (48 months) in the pre-period and 6 data points (12 months) in the pandemic period.

Prior to modelling the data, descriptive analyses were conducted: Simple monthly and bimonthly timeseries plots were used to detect low counts and potential seasonality. Bar plots for frequency and proportion by year interval (each year spanned from March to February), site (MUHC versus CHU-SJ), age category (defined as: <1, 1-2, 3-4, 5-11, and +12+ years) and triage category (ranging from 1 to 5, with 1 being highest priority) for the pre-pandemic and pandemic period were created for both manuscripts.

Segmented Poisson regression was used to estimate the level shift and slope change parameters. Segmented regression was chosen over other modelling techniques due to small counts in the outcome and for interpretability of parameters. The critical distributional assumption of Poisson regression was verified using a dispersion test [84] and, in positive cases, accounted for via negative-binomial regression. The basic regression equation was as follow:

Equation 1: $\mathbf{Y(t) \sim \beta_0 + \beta_1 X + \beta_2 L + \beta_3 S + \beta_4 H + \beta_5 H{*}L + \beta_5 H{*}S + \varepsilon t}$

Where $\boldsymbol{\beta_0}$ is the intercept in the absence of the intervention, $\boldsymbol{\beta_1}$ is the slope of the pre-intervention, $\boldsymbol{\beta_2}$ is the level shift at the onset of the COVID-19 pandemic (D is coded as a binary indicator; 0 in the pre-intervention period and 1 in the intervention period), $\boldsymbol{\beta_3}$ is the difference in the intervention period relative to the pre-intervention period (set to 0 pre-intervention and coded as continuous time since the onset of the intervention), $\boldsymbol{\beta_4}$ is the difference in count by site (S is set as a binary indicator for site, reference=MUHC, 1=CHU-SJ), and $\boldsymbol{\beta_4}$ and $\boldsymbol{\beta_4}$ are interaction terms between the outcomes of interest and site to account for heterogeneity by site. Finally, εt is the time-varying error.

Equation 1 assumes a linear trend in the pre-intervention period. However, as mentioned, it is important to consider seasonality or cyclical trends. The ‘decompose’ function in R statistical software performs a time series decomposition [94], which was used to identify the three major components of a timeseries: Seasonality, secular trends, and random noise. When present, Fourier terms were introduced to model seasonality as they provide a more accurate representation than seasonal indicators and are more interpretable than splines. Fourier terms can be easily integrated into the regression model as follows:

Equation 2: Y(t) ~ $\beta_0 + \beta_1 X + \beta_2 L + \beta_3 S + \beta_4 H + \beta_5 H*L + \beta_5 H*S$ + **sin(2*pi*b*X/6) + cos(2*pi*b*X/6) +** εt

Where b defines the sine-cosine pair (1,2,3, etc.), and X defines the number of time points in the series, typically divided by 12 to capture monthly seasonality. However, as the timeseries in this study were aggregated bimonthly, the time component was X was divided by 6 rather than 12. The number of sine and cosine pairs should reflect the number of seasonal points divided by 2 (S/2), meaning that for 6 seasonal points there should be 3 sine-cosine pairs [95].

Finally, we used a backwards search strategy using change-in-estimate criteria for covariate selection and the lowest Bayesian information criterion value (BIC) as an indicator of model fit [96]. It was decided a-priori that the coefficient for linear long-term trend in the pre-pandemic period would be retained in the model regardless of significance as it is known that pediatric ED visits in Montreal have increase yearly since 2016. After accounting for seasonality and secular trends, remaining autocorrelation was verified using the Durbin-Watson test and by visual inspection of the autocorrelation function (ACF) and partial autocorrelation function plots (PACF) [78,97]. The final model was displayed in table format and graphically.

4 Results

4.1 Preface for Manuscript 1

In this first manuscript, our goal was to investigate changes in incidence of pediatric appendicitis in Canada during the COVID-19 pandemic. This was done by quantifying the change in incidence of visits for appendicitis at two large pediatric EDs in Quebec during the first year of the pandemic, relative to four years preceding the pandemic. We were also interested in investigating changes in severity for pediatric patients with appendicitis in Canada, as it has been noted in several other studies that delays in seeking medical attention resulted in more severe disease. We used two well-known indicators of severity for appendicitis: Perforated appendix and requiring abscess drainage. We also measured changes in average length of hospital stay during the pandemic relative to previous years, as it is an indicator of hospital utilization. The results were displayed graphically and in table format. This manuscript was submitted to the World Journal of Pediatrics (WJP).

4.2 Manuscript 1: Investigating Changes in Incidence and Severity of Pediatric Appendicitis During the COVID-19 Pandemic in Canada: An Interrupted Time Series Analysis

Title: Investigating Changes in Incidence and Severity of Pediatric Appendicitis During the COVID-19 Pandemic in Canada: An Interrupted Time Series Analysis

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Abstract:

Purpose:

This study aimed to quantify changes in incidence and severity of pediatric appendicitis during the first year of the COVID-19 pandemic in Montreal relative to the pre-pandemic trend.

Methods:

An interrupted time-series analysis was used to estimate the change in bimonthly incidence of appendicitis cases at two pediatric emergency departments (ED) during the first year of the pandemic (April 2020- March 2021) relative to a 4-year historical control period (April 2016-March 2020). In secondary analyses, change in disease severity was assessed by quantifying changes in length of hospital stay (LOS) via multivariable linear regression, and risk of perforated appendix and need for surgical drainage via multivariable binomial regression.

Results:

There was evidence of a 14% increase in incidence of pediatric ED visits for appendicitis during the first year of the pandemic (incidence rate ratio = 1.14, 95% CI= 1.01 ; 1.28). There was evidence of a reduction in average hospital LOS (-0.88 days 95% CI= -1.65 ; -0.12), but no change in risk of perforated appendicitis (risk ratio= 0.94, 95% CI= 0.68 ; 1.30), or of requiring abscess drainage (risk ratio= 0.83, 95% CI= 0.52 ; 1.32) during the pandemic relative to the pre-pandemic period.

Conclusion:

There was a sustained increase in pediatric ED visits for appendicitis during the pandemic, but there were no changes in severity of patients, suggesting that there were no major delays in seeking

treatment for pediatric appendicitis. Potential explanations for this increase are an increase or change in triggers for appendicitis or a shift towards tertiary care hospitals for care during the pandemic.

Key Words: COVID-19, Appendicitis, Pandemic, Pediatric, Interrupted Time-Series, Emergency Department

Statements and Declarations:

Conflict of Interest: The first author (Francesca del Giorgio) was funded was funded by the Canada Graduate Scholarships-Master's (CGS M) awarded from the Canadian Institutes of Health Research (CIHR), and Fonds de Recherche Santé du Québec (FRQS) Master's Award.

The corresponding author (Olivier Drouin) was also supported by a Clinical Research Scholar Junior 1 Award from the Fonds de recherche du Québec – Santé

Availability of data and material: On request

Code availability: On request

Authors' contributions

As first author, Francesca del Giorgio ran the analysis, conducted literature reviews, and wrote the majority of the paper (introduction, methods, discussion, limitations, and conclusion).

As second author, Merieme Habti extracted data on severity of patients from medical records and helped clean data. She also contributed to the literature review and writing the discussion section.

As co-author, Joanna Merckx provided guidance on the method, reviewed and provided detailed revisions in all versions of the paper.

As co-author, Jay Kaufman provided guidance on the methods and reviewed all versions of the paper.

As co-author, Jocelyn Gravel provided access to and information on navigating the emergency department data-set at CHU-SJ, as well as clinical interpretation of the data and feedback to the manuscript.

As co-author, Nelson Piché provided clinical interpretation of the data and feedback to the manuscript.

As co-author, Esli Osmanlliu provided access to and information on navigating the emergency department data-set at MUHC, as well as clinical interpretation of the data and feedback to the manuscript.

As corresponding author, Olivier Drouin provided guidance conducting statistical analyses, and gave detailed feedback on the content and structure of the paper in all versions of the manuscript.

Ethics approval (include appropriate approvals or waivers): MP-21-2021-2930

Consent to participate (include appropriate statements): Participant consent was waved by the institutional review boards (McGill IRB and CHU-SJ ethics board)

Consent for publication (include appropriate statements): Not applicable

Abbreviations:

CHU-SJ- Centre hospitalier universitaire Sainte-Justine

CI- Confidence Interval

CTAS- Canadian Triage and Acuity Scale

ED- Emergency Department

IQR= Inter-Quartile Range

IRR- Incidence Rate ratio

LOS- Length of Stay

MUHC- McGill University Health Centre

OR- Odds Ratio

Acknowledgments:

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Clinicians capsule

What is known about the topic?

At the onset of the pandemic, delays in diagnosis for pediatric appendicitis have been documented worldwide, resulting in worse prognosis. A possible association between COVID-19 disease and onset of pediatric appendicitis has also been noted, along with misdiagnoses of appendicitis resulting from overlapping symptoms with COVID-19 disease.

What did this study ask?

This study asked whether there were changes in incidence of appendicitis at tertiary care hospitals in Quebec throughout the first year of the COVID-19 pandemic, and whether children faced worse prognosis relative to previous years.

What did this study find?

The interrupted time series analysis showed evidence of a 14% increase in cases of appendicitis at the pediatric ED throughout the first year of the pandemic, but no changes in severity for patients with appendicitis relative to previous years.

Why does this study matter to clinicians?

There were no changes in severity of pediatric patients with appendicitis in Quebec during the first year of the pandemic, but clinicians should be aware of overlapping symptoms between COVID-19 disease and appendicitis, as well as a possible association with COVID-19 disease and onset of pediatric appendicitis.

Introduction:

At the onset of the COVID-19 pandemic in the early spring of 2020, pediatric emergency department (ED) visits decreased worldwide by an estimated 30-89% [1]. In Canada, a 58% reduction in the number of expected pediatric ED visits was observed between March and April of 2020 relative to the same months in previous years [2,3]. Studies have shown that a large portion of the observed reduction in pediatric ED visits during the pandemic was attributable to a decrease in prevalence of other infectious diseases resulting from confinement and public health measures [1,4,5]. It is also hypothesized that delay or avoidance in seeking medical treatment and/or use of alternative pathways of care (such as telemedicine) may explain in part the observed decrease in pediatric ED visits [6]. However, the collateral effect of the COVID-19 pandemic and associated public health measures on specific pediatric diseases and population subgroups remains unclear.

Appendicitis is among the most common reasons for emergency surgery in children, representing an estimated 20% of all pediatric surgical admissions [7]. Although its etiology remains poorly understood, there is evidence that it may be triggered by diet and both viral or bacterial, infections [8]. Children with appendicitis generally require rapid clinical assessment and often surgical intervention within 24 hours from the onset of symptoms, making abstaining from seeking medical attention or management via telemedicine unlikely [7,9,10]. Nonetheless, short-term delays in seeking medical attention can occur and may result in more severe presentation, including appendix rupture, leading to more invasive interventions, such as abscess drainage and longer length of stay (LOS) [11]. As there were concerns over delays in treatment during the pandemic, the published literature to-date on pediatric appendicitis has focused on changes in severity of patients during the early months of the pandemic, largely finding increased rates of perforated appendix [12–15].

The acute nature of pediatric appendicitis implies that any change in incidence over longer time-periods (>30 days) indicates increases/decreases in triggers for appendicitis, or changes in patient distribution between hospitals. The COVID-19 pandemic and its associated reduction in viral infections presents an opportunity to investigate triggers for appendicitis. However, few large studies and no Canadian study have investigated concomitantly the change in incidence and severity of pediatric cases of appendicitis brought about by the COVID-19 pandemic. As such, the objectives of this study were to 1) quantify whether there was a change in incidence of appendicitis diagnosed in the pediatric ED and 2) investigate whether children with appendicitis presented with more severe disease during the first year of the COVID-19 pandemic relative to previous years.

Methods:

2.1. Study Design

This is a retrospective cohort using the computerized ED and admissions databases of the two large tertiary care pediatric hospitals in Montreal, Canada: the CHU Saint-Justine (CHUSJ) and the Montreal Children's Hospital (MUHC), with an estimated combined 160,000 ED visits per year prior to the COVID-19 pandemic. These are the only two pediatric hospitals of the city and are responsible for most pediatric appendicitis surgeries in the Montreal region. The pediatric ED databases have been previously used for research and accrued extensive quality checks [16,17].

2.2. Data source and Participants

Patients 0-17 years inclusively who consulted either pediatric ED between March 2016 and May 2021, and whose primary ED diagnosis was appendicitis, were included in the primary analysis. International Classification of Diseases 10th Revision (ICD-10) codes were used to identify cases of appendicitis at the pediatric ED of the MUHC (codes K35-K37, and K38.9). The CHUSJ pediatric ED database does not include ICD-10 codes, and as such appendicitis cases were identified from the previously validated drop-down menu of 632 diagnostic criteria. The selected diagnostic category ('Appendicite, App') was verified by two ED physicians.

In secondary analyses, children with a primary or secondary diagnosis of appendicitis were identified from medical archives at both hospitals via ICD-10 codes K35-K37 during the same period. The MRN and date of birth of children of eligible patients available from medical archives was used to identify the medical charts of these patients.

2.3. Intervention

The intervention was defined as the onset of the COVID-19 pandemic, which was defined as April/May of 2020 as it coincides with both the first wave of the COVID-19 pandemic and the first set of public health measures in Quebec, Canada [18]. In secondary analyses, the outcomes of interests were having a perforated appendix and/or requiring abscess drainage. *2.4. Outcome Measures*

The outcomes of interest in the primary analysis were 1) the level-shift, defined as the change in bi-monthly incidence of appendicitis at the pediatric ED at the intervention, and 2) the slope change, defined as the change in trend during the first year of the COVID-19 pandemic (April 2020- March 2021) relative to the pre-pandemic trend. In secondary analyses, the outcomes of interest were the change in average LOS (in days), and the change in risk of perforation and/or abscess drainage (identified via revision of physician notes in the medical charts) during the first year of the pandemic relative to the average risk in the four years preceding the pandemic.

2.5. Data Analysis

In primary analysis, participants were stratified by age group (defined as: <1, 1-2, 3-4, 5-11, and 12+ years), Canadian Paediatric Triage and Acuity Scale (Paed-CTAS, ranging from 1 to 5 with 1 being highest priority)[16], and site (MUHC or CHUSJ). Segmented multi-variable Poisson regression was used to estimate the change in incidence of appendicitis diagnoses at the pediatric ED. The 4 years preceding the pandemic (March 2016 to March 2020) were used as historical control to predict the expected number of appendicitis visits during the first year of the pandemic.

Due to low counts of ED visits for appendicitis, incidence was measured bimonthly to increase power to detect the outcomes of interest, leading to 24 data points (48 months) in the pre-pandemic and 6 data points (12 months) in the pandemic period (April 2020- May 2021) [19]. Seasonality and long-term cyclical trends were accounted for via Fourier transformations [20]. The distributional assumption of Poisson regression was verified using a dispersion test [21]. A backwards stepwise selection strategy was used with change-in-estimate criteria for covariate selection using the lowest Bayesian information criterion value (BIC) as an indicator of model fit [22]. It was decided a-priori that the coefficient for linear long-term trend in the pre-pandemic period would be retained in the model regardless of significance as it is known that pediatric ED visits in Montreal have increase yearly since 2016.

In secondary analyses, linear regression was used to estimate the change in average LOS (in days) of children admitted to the hospital with appendicitis. Although the distribution of LOS is typically right-skewed, the large sample size in this study implies that the assumption of normality can still be assumed via the central limit theorem [23]. Binomial regression was used to estimate the change in proportion of perforated appendicitis and patients requiring abscess drainage between the pre-pandemic and the pandemic periods. All regression analyses were adjusted for sex, site and age group and included interaction terms between the period (pandemic versus pre-pandemic period) and the covariates.

All tests of fit and model specification were evaluated at alpha=0.05. All analyses were performed using R version 1.3.1073. This study was approved by the ethics review boards of both hospital sites (MP-21-2021-2930) and participant consent was waved.

Results:

3.1. Characteristics of study subjects

There were a total of 2532 children with a diagnosis of appendicitis seen in either one of the pediatric ED during the pre-pandemic period (average of 588 per year), and 770 children during the pandemic period. In both the pre-pandemic and pandemic period, over 90% of cases occurred in patients 5 years and older and 74% were classified as CTAS level 3 (Urgent) (Table 1).

In secondary analysis, there were 2326 patients admitted with appendicitis in the pre-pandemic period (average of 592 visits per year), and 736 admitted in the pandemic period. The average LOS was 3.2 days in the pre-pandemic period (median=1 day, IQR=1-4 days), and 3 days in the pandemic period (median=1 day, IQR=1-4 days) (Fig 2 in supplementary material). The distribution of age and sex were similar in both periods (Table 2). Approximately 35% of patients admitted had a perforated appendix, and 15% required abscess drainage, with both proportions being similar in both periods (Fig 3 in supplementary material). There were slightly fewer admissions to the hospital for appendicitis than ED visits for appendicitis in the pre-pandemic period, although during the pandemic this trend reversed (Fig 4 in supplementary material).

3.2. Primary analysis: Appendicitis diagnoses at the pediatric ED

Table 3 summarizes the output of regression models, and Figure 1 shows the fitted values against the predicted values during the pandemic period using the final model. Hospital site and seasonality were not retained in the final model. There was evidence of no slope-change in any of the models (from final model: IRR=1.00; 95% CI= 0.95 ; 1.04). From the final model, there was evidence of a 14% increase in appendicitis diagnoses at the onset of the pandemic (level shift: IRR= 1.14, 95% CI=1.01 ; 1.28) (Table 2, Model 3).

3.3. Secondary analyses: severity

Table 4 summarizes the regression outputs for the secondary outcomes. In multi-variate analysis, there was evidence of a reduction in LOS (-0.88 days, 95% CI=-1.65 ; -0.12) (Fig 4 in supplementary material). There was evidence that patients under the age of 5 years stayed longer at the hospital (7.07 days, 95% CI=5.57 ; 8.57) and that the average LOS was lower at MUHC compared to CHUSJ in the pre-pandemic period (-0.68 days, 95%CI= -1.08 ; -0.27), but there were no changes in LOS by site or age during the pandemic (Table 4).

In multi-variable regression, there was no evidence of a change in risk of having a perforated appendix (RR= 0.94, 95% CI= 0.68 ; 1.30) or in requiring abscess drainage (RR=0.86, 95% CI= 0.58 ; 1.28) during the pandemic compared to the pre-pandemic risk. There was also no change in risk of perforation or abscess drainage by site or sex in either period. Infants (<5 years) had increased risk of experienced perforation and requiring abscess drainage in the pre-pandemic period compared to older patients, and this trend remained the same during the pandemic (Table 4).

Discussion:

In this study, we found evidence of a 14% increase in incidence of appendicitis at the onset of the COVID-19 pandemic in Montreal. This increase was sustained throughout the first year of the pandemic, indicating that the incidence of appendicitis never returned to the pre-pandemic level (Fig 1). We found evidence of a reduction in LOS, but there was no change in risk of requiring abscess drainage or having a perforated appendix during the pandemic compared to the pre-pandemic risk.

Due to the relatively short post intervention period and low counts, it was not possible to measure changes in incidence of appendicitis using narrower time-periods of the pandemic or by other co-variates. As data used in this study were obtained directly from the emergency database records, electronic medical archives, and patient medical records, it is possible that there was misclassification of appendicitis. However, we do not expect this possible misclassification to differ between study periods. Furthermore, limitations in data availability made it impossible to verify if patients admitted with appendicitis simultaneously had COVID-19 disease or had been transferred from secondary care centers.

World-wide reductions in pediatric ED visits during the COVID-19 pandemic raised concerns about the potential impact of lockdown measures on patient outcomes for pediatric non-communicable diseases. Some publications have since reported evidence of a rise in severity of pediatric patients with appendicitis during the COVID-19 pandemic relative to previous years [14,15,24–28]. Hypotheses for this increase in severity of cases include delayed patient care at the hospital [24], delayed presentation to the ED due to parental fears associated to the COVID-19 pandemic, or use of telemedicine resulting in misdiagnoses and delayed care[15,25]. In the current study, we found no change in severity of appendicitis during the pandemic, as measured by perforated appendix or abscess drainage, suggesting that delayed presentation to the ED was likely not common in our study population. However, we found an overall reduction in average LOS, which may indicate changes in healthcare provision. For example, to reduce the risk of COVID-19 infection, surgeries may have been scheduled earlier compared to prior to the pandemic, reducing in-person time at the hospital.

Despite its frequency, triggers for appendicitis remain incompletely understood. Low fiber intake and/or viral or bacterial infections may trigger appendicitis by causing blockage or swelling of the appendix [8]. The COVID-19 pandemic and associated public health measures may serve as a natural experiment to further our understanding of triggers for pediatric appendicitis. To-date, most studies investigating the impact of the COVID-19 pandemic on pediatric appendicitis have focused on quantifying changes in severity resulting from delays in medical treatment. Fewer studies have investigating changes in overall incidence of appendicitis at the pediatric ED, but those that have found evidence of a reduction in acute appendicitis during the first months of the pandemic, hypothesizing that this decrease could be related to reduced exposure to microbes and changes in dietary habits during domestic quarantine, or spontaneous resolution in a larger proportion of cases [29–31].

In contrast, our study found evidence of a sustained increase in incidence of appendicitis diagnosed at the pediatric ED during the first year of the pandemic. The known gastrointestinal involvement of COVID-19 disease in children indicates a possible association between SARS-CoV-2 infection and appendicitis [32]. More specifically, case-studies have reported children presenting with appendicitis following or during SARS-CoV-2 infection, indicating that COVID-19 disease may be a trigger for appendicitis [33,33–36]. Other case-studies have found that the novel Multisystem Inflammatory Syndrome in Children (MIS-C) associated to SARS-CoV-2 infection mimics the clinical presentation of appendicitis, potentially resulting in mis-diagnosed appendicitis [37–39]. As such, the overlap in clinical presentation between appendicitis and COVID-19 disease in children may explain the increase in ED visits, as well as the absence of increased severity during the pandemic.

Alternatively, the apparent increase in pediatric appendicitis may be due to a shift in patient care between general and tertiary care pediatric hospitals. For example, a study in France found a 77% increase in cases of pediatric appendicitis during the COVID-19 pandemic but concluded that this was largely attributable to increased transfer patients from other hospitals during the pandemic [40]. In this study, there were slightly more admissions that ED visits during the pandemic, meaning that there may have been more transfers during the pandemic. However, this does not explain the increase in diagnoses of appendicitis at pediatric ED. In the province of Quebec, almost all children under the age of 5 years are treated at MUHC or CHUSJ, although older children may be treated in adult and community hospitals. Parental anxiety relating to exposure to the virus has been well documented and may have resulted in parents opting to go directly to pediatric tertiary care centers to avoid exposure to the virus at secondary care hospitals where adults were being treated. However, there were no notable changes in age distribution for hospital admissions. Nonetheless, a change in patient distribution and not a higher absolute number of cases could, in-part, explain the observed increased incidence of pediatric appendicitis.

Conclusion:

In this study, we found evidence of an increased incidence of appendicitis diagnosed at the pediatric ED at the onset and throughout the first year of the COVID-19 pandemic in Canada. However, there was no change in severity of cases during the pandemic relative to previous years. More research is needed to determine whether a pathophysiological link exists between appendicitis and SARS-COV-2 and the frequency of misdiagnoses of appendicitis due to COVID-19 disease in pediatric patients. Nonetheless, physicians should be aware of the overlapping symptoms between appendicitis and severe SARS-CoV-2 infection in children.

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Tables and Figures:

Table 1 Characteristics of pediatric patients diagnosed with appendicitis at the pediatric ED

Characteristics, n (%)	**Pre-Pandemic period n (%)**	**Pandemic period n (%)**
Total cases, N	2397	725
Age		
<1 year	0 (0.0)	1 (0.1)
1-2 years	38 (1.6)	7 (1.0)
3-4 years	148 (6.2)	31 (4.3)
5-11 years	1287 (53.7)	379 (52.3)
+12 years	924 (38.5)	307 (42.3)
Paed-CTAS level [a]		
1- Resuscitation	1 (0.0)	0 (0.0)
2- Emergency	230 (9.6)	53 (8.9)
3- Urgent	1782 (74.3)	445 (74.4)
4- Less Urgent	371 (15.5)	93 (15.6)
5- Non-Urgent	13 (0.5)	7 (1.2)

ED: Emergency department; Pre-pandemic period: April 2016-March 2020; Pandemic period: April 2020 to March 2021; Paed-CTAS level= Canadian Paediatric Triage and Acuity Scale

[a] Among all children who were diagnosed with appendicitis at the ED during the pandemic period, there were 127 who were missing Pead CTAS level.

Table 2 Demographic information of children admitted with appendicitis at the pediatric hospital, pre-pandemic period versus pandemic period[a].

Characteristics, n (%)	**Pre-pandemic period n (%)**	**Pandemic period n (%)**
Total cases, N	2326	736
Age		
<1 year	2 (0.1)	3 (0.4)
1-2 years	43 (1.8)	7 (1.0)
3-4 years	140 (6.0)	33 (4.5)
5-11 years	1262 (54.3)	389 (52.9)
+12 years	879 (37.8)	304 (41.3)
Sex		
Female	893 (38.4)	309 (42.0)
Male	1433 (61.6)	427 (58.0)
Perforated appendix	875 (37.7)	262 (35.6)
Abscess drainage	353 (15.2)	101 (13.7)

[a] The pre-pandemic period spans from April 2016 to March 2020, the pandemic period spans from April 2020 to March 2021.

Table 3 Model output incidence rate ratios for ITS analysis of appendicitis diagnoses at the pediatric ED, estimated with segmented Poisson regression [a,b]

Coefficient	***Complete model***	**Model 1** RR (95% CI)	**Model 2** RR (95% CI)	**Model 3** RR (95% CI)
	BIC= 420.52	BIC= 414.29	BIC= 222.40	BIC= 219.04
Pre-pandemic linear time-trend	1.00 (1.00 ; 1.01)	1.00 (1.00 ; 1.01)	1.00 (1.00 ; 1.01)	1.00 (1.00 ; 1.01)
Level-shift	1.28 (1.03 ; 1.57)	1.15 (0.99 ; 1.34)	1.15 (0.99 ; 1.34)	1.14 (1.01 ; 1.28)
Slope-change	0.97 (0.91 ; 1.04)	1.00 (0.95 ; 1.04)	1.00 (0.95 ; 1.04)	--
Site (ref: CHU-SJ)	1.29 (1.19 ; 1.40)	1.26 (1.18 ; 1.35)	--	--
Segment*Site	0.83 (0.63 ; 1.08)	--	--	--
Segment*Site*Slope-change	1.04 (0.96 ; 1.14)	--	--	--

ITS= Interrupted Time-Series; ED= Emergency department; BIC= Bayesian information criterion; Pre-pandemic period=April 2016- March2020; Pandemic period=April 2020 to March 2021; 2020; MUHC= McGill University Health Centre ; CHU-SJ=Centre hospitalier universitaire Sainte-Justine; CI= Confidence Interval

[a] The analysis includes the MUHC and CHU-SJ pediatric hospitals
[b] In the complete model, the coefficients for seasonality were excluded as there was no evidence of seasonality and it decreased the fit of the model. Model 1 represents the best fit including both outcomes of interest. In Model 2, the coefficient for site was removed from the model to demonstrate that it had no effect on the remaining coefficients. Model 3 is the model with the lowest BIC and is the final model.

Table 4 Model outputs for analyses on severity of pediatric patients with appendicitis [a]

Coefficient	Analysis		
	Length of Stay[b] mean (95% CI)	**Perforation**[c] RR (95% CI)	**Abscess Drainage** [c] RR (95% CI)
Intercept	3.46 (3.09 ; 3.83)*	0.64 (0.55 ; 0.75)*	0.17 (0.13 ; 0.20)*
Pandemic period (vs. pre-pandemic)	-0.88 (-1.65 ; -0.12)*	0.94 (0.68 ; 1.30)	0.86 (0.58 ; 1.28)
Female (vs. Male)	0.05 (-0.37 ; 0.46)	1.14 (0.96 ; 1.36)	1.12 (0.92 ; 1.36)
MUHC (vs. CHU-SJ)	-0.68 (-1.08 ; -0.27)*	0.84 (0.71 ; 1.00)	1.14 (0.94 ; 1.38)
Age category (ref=5-11 years)			
<1 year[d]	NA	NA	NA
1-2 years	7.07 (5.57 ; 8.57)*	8.16 (3.60 ; 18.49)*	2.18 (1.42 ; 3.35)*
3-4 years	1.61 (0.75 ; 2.48)	3.88 (2.65 ; 5.68)*	1.73 (1.29 ; 2.34)*
+12 years	-0.37 (-0.79 ; 0.06)	0.67 (0.55 ; 0.80)*	0.72 (0.57 ; 0.90)*
Site * Period	0.41 (-0.42 ; 1.23)	0.91 (0.63 ; 1.30)	1.10 (0.73 ; 1.65)
Sex * Period	0.58 (-0.26 ; 1.41)	1.00 (0.70 ; 1.44)	0.86 (0.57 ; 1.31)
Age * Period			
<1 year[d]	NA	NA	NA
1-2 years	-3.78 (-7.77 ; 0.21)	1.24 (0.13 ; 12.17)	2.01 (0.90 ; 4.49)
3-4 years	0.32 (-1.64 ; 2.28)	1.72 (0.67 ; 4.42)	0.91 (0.32 ; 1.96)
+12 years	0.69 (-0.17 ; 1.55)	1.14 (0.78 ; 1.66)	1.26 (0.80 ; 1.98)

RR= Risk Ratio; CI= Confidence Interval; MUHC= McGill University Health Centre ; CHU-SJ=Centre hospitalier universitaire Sainte-Justine; Pre-pandemic period=April 2016- March 2020; Pandemic period=April 2020 to March 2021

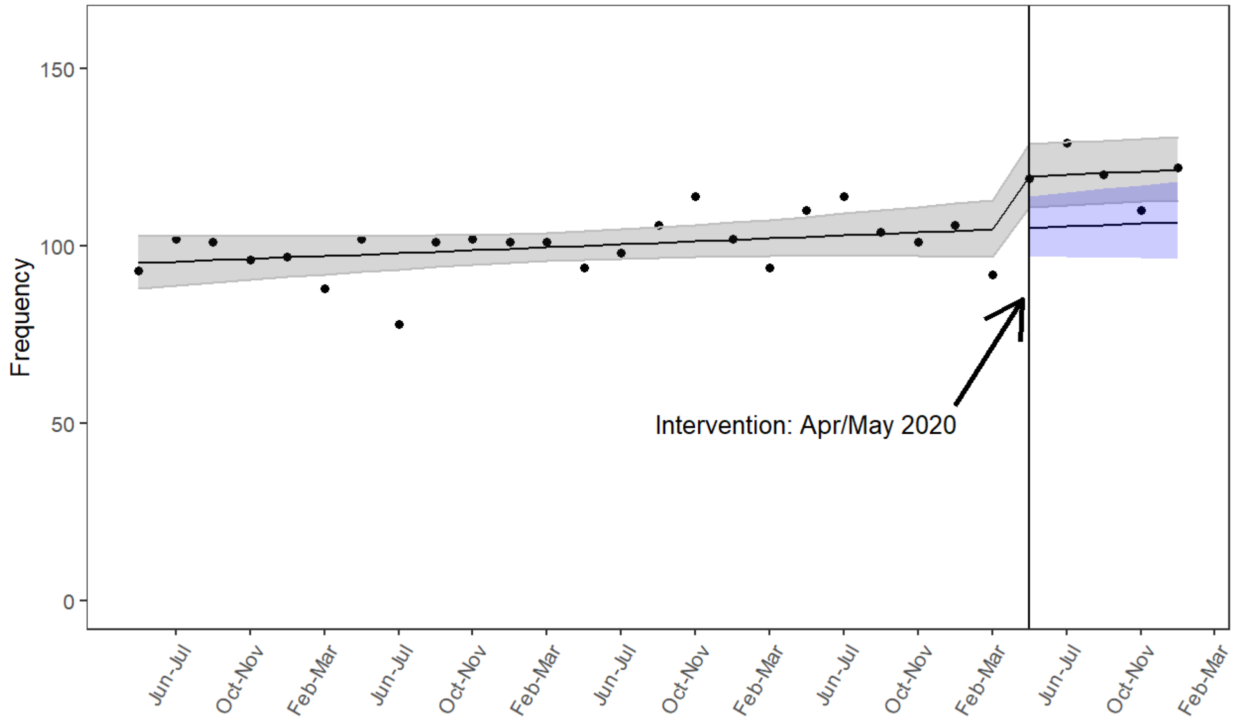
[a] Analyses include the MUHC and the CHU-SJ pediatric hospitals

[a] Estimated via linear regression

[b] Estimated via binomial regression

[d] Counts for children <1 were too low to include in the analysis There were 2 and 3 patients in the pre-pandemic and pandemic period respectively, and as such the age category <1 year was excluded.

Fig 1 Fitted versus predicted values of bi-monthly incidence of pediatric ED appendicitis diagnoses during the COVID-19 Pandemic, estimated via segmented Poisson regression [a]



[a]Grey zone indicates 95% confidence interval of fitted values, blue zone indicates 95% confidence interval of predicted values.

Fig 2 Length of hospital stay for patients admitted to the pediatric hospital for appendicitis by year interval

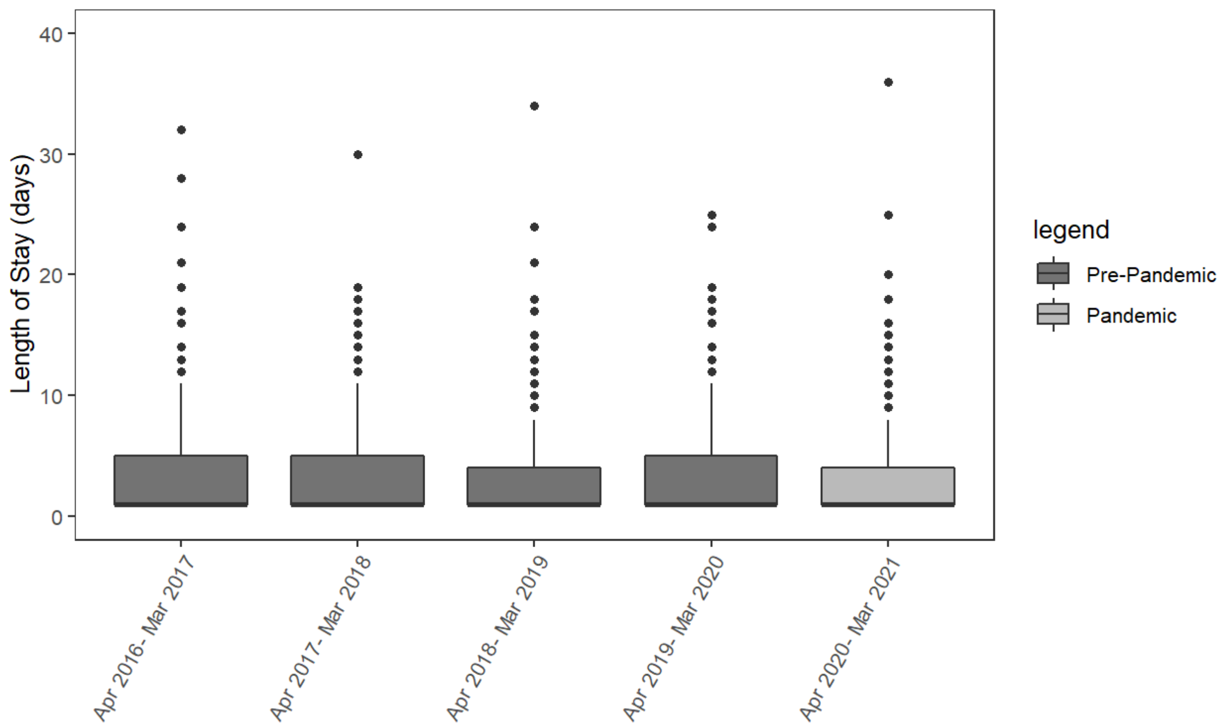
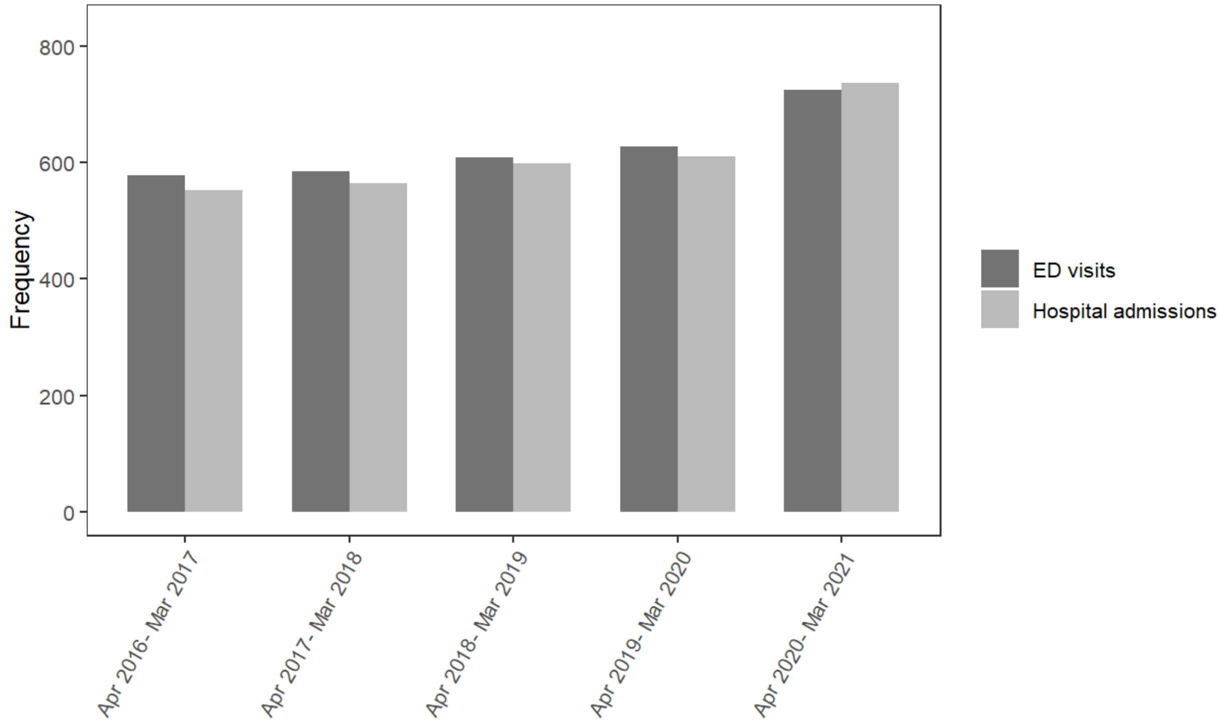


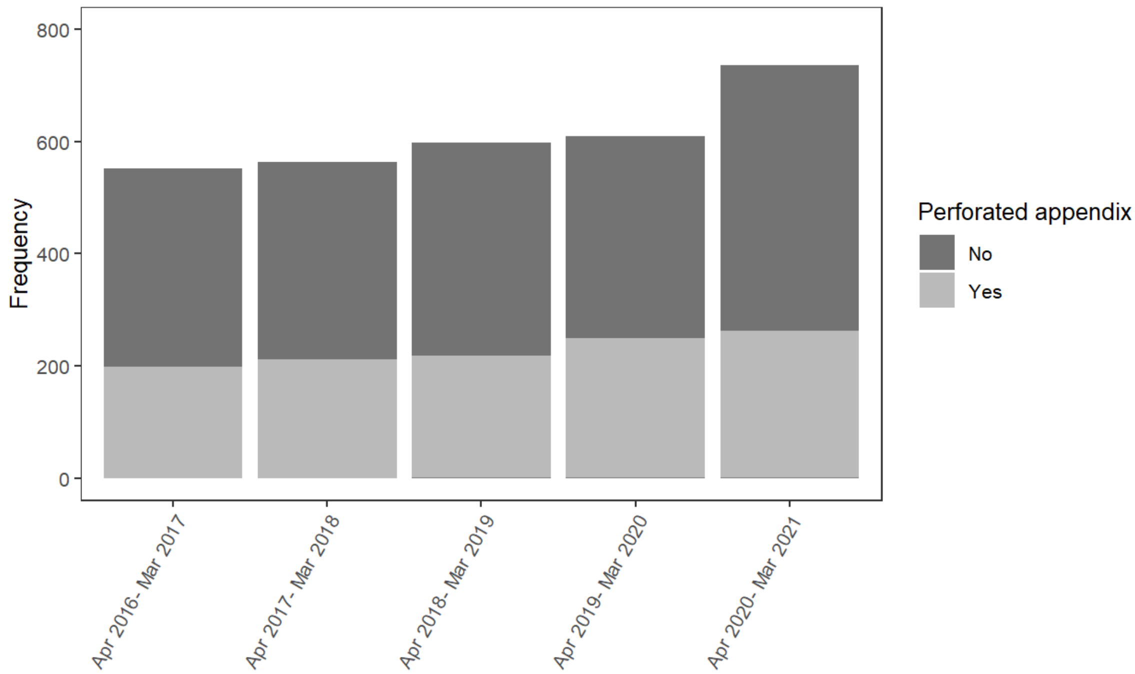
Fig 3 Frequency of ED visits and hospital admissions for appendicitis by year interval



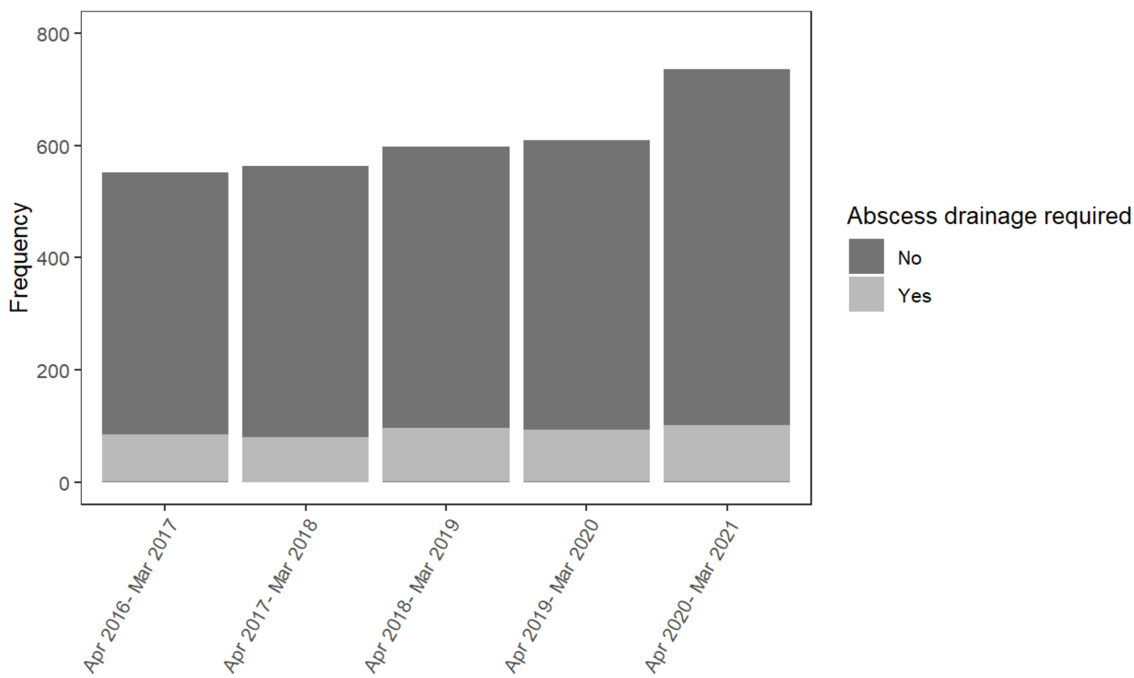
ED= Emergency department

Fig 4 Frequency of hospital admissions for appendicitis resulting in perforated appendix (Graph A) and requiring abscess drainage (Graph B) by year interval

Graph A)



Graph B)



[a] The pandemic period spans from April 2020 to March 2021.

4.3 Preface for Manuscript 2

The goal of this second manuscript was to quantify any changes in incidence of visits to the pediatric ED for children with a clinical presentation of cancer (suspected cancer) and children with a previous confirmed cancer diagnosis during the first year of the COVID-19 pandemic. We also quantified changes in severity resulting from delays in diagnosis or in treatment via changes in incidence of pediatric oncology ward admissions.

Pediatric EDs play an important role in the initial detection of cancers, although often official diagnoses are given at a later date. On the other hand, children with a confirmed cancer diagnosis will often be admitted directly at the oncology ward for health complications, although some will also go to the pediatric ED. As such, we quantified the impact of the pandemic on ED visits for confirmed cancer patients versus suspected cancers separately. We were also interested in verifying whether there were changes in incidence of new cancer diagnoses, although data for this is not yet available and thus is not part of the current manuscript. The results were displayed graphically and in table format.

4.4 Manuscript 2: Incidence and Outcomes of Pediatric Cancers During the COVID-19 Pandemic in Canada: An Interrupted Time-Series Analysis

Title: Incidence and Outcomes of Pediatric Cancers During the COVID-19 Pandemic in Montreal, Canada: An Interrupted Time Series Analysis

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Background: The worldwide reduction in pediatric emergency department (ED) visits during the COVID-19 pandemic led to concerns of worse prognosis for pediatric conditions resulting from delays in diagnosis and treatment of pediatric conditions. This study aimed to quantify whether there was a change in incidence of children with suspected and already confirmed cancer at the pediatric ED, and secondly whether there was a change in oncology ward admissions during the first year of the COVID-19 pandemic relative to the pre-pandemic incidence in Quebec.

Methods: Children diagnosed with cancer or suspected cancer conditions at either of two pediatric emergency departments between May 2016 and May 2021 were eligible. A negative binomial segmented regression was used to quantify the change in incidence of cancer diagnoses at the pediatric ED at the onset of the COVID-19 pandemic (March-April 2020) and throughout the first year of the pandemic (March 2020- May 2021) compared to the predicted number of visits from a four-year historical control, adjusted for underlying baseline trend, seasonality, and hospital site. In secondary analysis, a stratified Cox Proportional Hazards model was used to estimate the change in risk of readmission to the oncology ward during the pandemic compared to prior to the pandemic, including covariate of age, sex, and hospital site.

Results: There was evidence of a 39% reduction in suspected and confirmed cancers at the pediatric ED at the onset of the pandemic (IRR=0.61, 95% CI=0.48 ; 0.78), followed by an increasing trend throughout the first year of the pandemic (IRR=1.11, 95% CI=1.04 ; 1.19). In secondary analyses, there was a 37% reduction in pediatric ED visits that resulted in a suspected cancer diagnoses at the onset of the pandemic (IRR=0.63, 95% CI=0.48 ; 0.82), followed by a gradual increase in cases to baseline throughout the pandemic (IRR=1.08, 95% CI=1.00 ; 1.17). There was evidence of an increasing trend in pediatric ED visits for confirmed cancer patients (IRR=1.22, 95% CI=1.06 ; 1.41). There was a reduction in rate of readmission during the pandemic relative to prior to the pandemic (HR= 0.83, 95% CI= 0.74 ; 0.93).

Conclusion: It is probable that the reduction in viral infections during the pandemic led to fewer visits to the ED and to the oncology ward related to infections . This study found an increase in ED visits for patients that already had a confirmed cancer diagnosis during the pandemic, although more robust data is needed to determine ED utilization for pediatric cancer patients during the COVID-19 pandemic.

Key Words: COVID-19, Cancer, Pandemic, Pediatrics, Interrupted Time-Series, Health Services Research

Statements and Declarations:

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This work was also supported by a Clinical Research Scholar Junior 1 Award from the Fonds de recherche du Québec – Santé [OD]

Conflict of Interest: The authors have no conflict of interest relevant to this article to disclose

Availability of data and material: On request

Code availability: On request

Ethics approval (include appropriate approvals or waivers): MP-21-2021-2930

Consent to participate (include appropriate statements): Participant consent was waved by the institutional review boards (McGill IRB and CHU-SJ ethics board)

Consent for publication (include appropriate statements): Not applicable

Abbreviations:

CHU-SJ- Centre hospitalier universitaire Sainte-Justine

CI- Confidence Interval

CTAS- Canadian Triage and Acuity Scale

ED- Emergency Department

IQR= Inter-Quartile Range

IRR- Incidence Rate ratio

MUHC- McGill University Health Centre

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Introduction:

In the early months of the COVID-19 pandemic, there was a significant decrease in pediatric emergency department (ED) visits in many parts of the world,ranging from 45% to 79% [1–4]. This phenomenon was mainly attributed to the reduced transmission rate of other infectious diseases, a by-product of the public health measures issued by governments to limit the spread of the SARS-CoV-2 virus [5]. Parental concern over the risk of exposure to the SARS-CoV-2 virus at healthcare facilities may also have played a role in this decrease in ED visits [5]. The current literature, however, offers limited insight into the effect of the pandemic on specific non-communicable pediatric diseases.

The pediatric ED plays an essential role in the diagnosis of pediatric cancers and in the management of cancer-related conditions. Prompt patient evaluation, referral, and treatment, which are particularly crucial to pediatric cancers, have been staggered by the pandemic [6]. For example, a recent study conducted in Italy described a reduction in ED visits for pediatric patients with cancer as well as a reduction in newly diagnosed cancers during the peak of the pandemic [7]. There has yet to be a study describing this phenomenon in Canada.

In this study, we aimed to investigate whether there was a change in the incidence of patients visiting the pediatric ED that resulted in a suspected or confirmed cancer diagnosis during the first year of the pandemic and to assess whether there was a change in the number of admissions to the oncology ward during the same period relative to a 4-year control period.

Methods:

Study design and data source:

This is a retrospective cohort study using the electronic pediatric emergency and oncology ward admissions databases at two large tertiary care pediatric center in Montreal, Quebec: the McGill

University Health Centre (MUHC), and the Centre hospitalier universitaire Sainte-Justine (CHUSJ).

Participants:

Patients younger than 18 years of age with cancer diagnosis or who received a suspected cancer diagnosis (defined as a diagnosis compatible with cancer) at either of the pediatric EDs between April 2016 and April 2021 were eligible. ICD-10 codes C00-C96 were used to identify confirmed cancer diagnoses, and ICD-10 codes R59.9, I88.0, I88.9, I89, R19.0, R22.2 were used to identify suspected cancer diagnoses at MUHC [8,9]. As CHUSJ does not use ICD-10 codes at the pediatric ED, a dropdown menu of all diagnoses (>600 diagnoses) was used to identify confirmed and suspected cancers. The selected diagnostic criteria for confirmed and suspected cancers were verified by 2 physicians (Table 5-6 in supplementary material).

Secondary analyses included patients <18 years of age admitted to the oncology ward at either hospital during the same study period. Oncology ward admissions were identified from electronic medical archives.

Independent variable:

The primary independent variables of interest for the analysis of pediatric ED visits and oncology ward admissions were the change in bi-monthly incidence at the onset of the pandemic in March/April 2020, and the change in number of bi-monthly incidence throughout the first year of the pandemic (March 2020- May 2021) compared to the pre-pandemic trend. The onset of the pandemic was defined in relation to the first lock-down measures and school closures in Montreal and in North America more generally [10].

Analysis:

In descriptive analyses of ED visits, patients were stratified by age category, Pediatric Canadian Acuity and Triage scale (Pead- CTAS, ranging from 1 to 5, with 1 being highest priority) [11], and site (MUHC or CHUSJ) for each time period (pre-pandemic and pandemic period). In secondary analysis investigating oncology ward admissions, patients were stratified by age category, sex, and site.

Segmented Poisson regression was used to estimate the change in incidence of visits at the pediatric ED. The crucial assumption of Poisson regression was verified using the dispersion test from the Applied Econometrics with R (AER) statistical software package [12], and negative binomial regression was used when the assumption was violated [13,14]. A 4 year historical control period (May 2016 to February 2020) was used to predict the expected number of visits during the first year of the pandemic (March 2020 - May 2021). Given that monthly incidence for all analyses resulted in fewer than 200 cases per time-point, incidence was measured bimonthly to increase the power to detect the outcomes of interest [15]. As a result, there were 24 data points (48 months) in the pre-period and 6 data points (12 months) in the pandemic period for all analyses. The date of arrival to the pediatric ED was used to aggregate visits bi-monthly.

Seasonality and long-term cyclical trends were accounted for in the ITS analysis via Fourier transformations [16], and interaction terms between site and secular time-trend as well as site and the outcomes of interest were included to account for differences in the effect of the pandemic by site. The coefficient for secular time-trend in the pre-pandemic period was retained regardless of significance to account for the known increase in hospital visits in Montreal since 2016. A backwards change-in-estimate selection strategy using Bayesian information criterion (BIC) as an indicator of model fit was used to select the final model [17].

In secondary analysis investigating the change in rate of readmission to the oncology ward, a stratified Cox Proportional Hazards model developed by Prentice, Williams, and Peterson (often referred to as the PWP Total Time model) was used to account for multiple readmissions to the oncology ward [18-19]. Admissions were also stratified by time period (pre-pandemic versus pandemic), and since information of death or remission was unavailable patients were assumed to be at risk for the length of that time period, after which they were right censored. For example, a patient whose final readmission was in March of 2017 would be considered at risk for readmission until the start of the pandemic (March 14th, 2020). Age categories, sex, and site were included as covariates in the model. Patients admitted more than 25 times during each period were excluded in the analysis due to insufficient number of patients in this readmission category. The crucial assumption of proportion hazards was verified using the Schoenfeld test [20-22]. All tests of fit and model specification were evaluated at alpha=0.05. All analyses were performed using R version 1.3.1073. This study was approved by the ethics review boards of both hospitals (MP-21-2021-2930).

Results:

Patient characteristics:

A total of 2576 pediatric ED visits had a discharge diagnosis compatible with either a confirmed or suspected cancer; 2161 in the pre-pandemic period (average of 536 visits per year) and 415 in the pandemic period. Suspected cancers represented over 85% of cases in both the pre-pandemic and pandemic period (Fig 5 in supplementary material). Table 1 summarizes the characteristics of ED visits meeting inclusion criteria by study period. Overall, there was a small shift in the age distribution of visits towards older children during the pandemic period. There was also a small change in the acuity of visits during the pandemic with a decrease in CTAS level 3 (Urgent) and increase in CTAS level 2 (Emergency) cases (Table 1).

During the same period, there was a total of 7674 admissions at either oncology wards: 5836 at MUHC and 1838 at CHUSJ. The majority of admissions were for patients over the age of 5 years in both pre-pandemic and pandemic period. The CHUSJ had on average fewer admissions in the pre-pandemic and pandemic period compared to MUHC(Table 2, Fig 1).

Results of the regression analysis:

Table 3 summarize the regression output for the final model investigating changes in incidence for pediatric ED visits for confirmed and suspected cancer patients. Overall, there was evidence of a 39% reduction in visits at the onset of the pandemic (level shift IRR=0.61, 95% CI=0.47 ; 0.77), followed by an increasing trend throughout the first year of the pandemic (Slope change IRR=1.11, 95% CI=1.04 ; 1.19). There was also evidence of seasonality in the pre-pandemic period (Fig 2, Table 3).

Table 4 summarizes the final model for secondary analyses of the pediatric ED. In confirmed cancer ED visits, there was evidence of an increasing trend throughout the first year of the pandemic (IRR=1.22, 95% CI=1.06 ; 1.41), but there was insufficient power to detect a level-shift (IRR=0.61, 95% CI=0.35 ; 1.06) (Fig 3). In suspected cancer ED visits, there was evidence of a 37% reduction at the onset of the pandemic, (IRR= 0.63, 95% CI=0.48 ; 0.82) as well as an increasing trend throughout the pandemic (IRR=1.08, 95% CI=1.00 ; 1.17).

Table 5 summarizes the results for the analysis of oncology ward admissions. There was evidence of a 17% reduction in the rate of re-admissions during the pandemic relative to prior to the pandemic period (HR= 0.83, 95% CI= 0.74 ; 0.93) at both sites. CHUSJ had overall a lower rate of re-admissions compared to MUHC in both the pre-pandemic and pandemic period (HR=0.69, 95% CI= 0.62 ; 0.77). There was no difference in the rate of readmission by site or sex during the pre-pandemic and pandemic period and as such these coefficients were excluded from the final model (Table 5).

Discussion:

In Canada, pediatric EDs are essential in the initial detection of new cancers and in providing immediate care for acute complications in patients with known cancers. As such, investigating changes in incidence of pediatric ED visits may shed light on delays in diagnosis for pediatric cancers and in emergent care for already confirmed cancer patients. This study found evidence of a 39% reduction in pediatric ED visits for suspected and confirmed cancers at the onset of the pandemic in March-April of 2020, followed by a return to the predicted trend by the end of the first year of the pandemic. The observed reduction in ED visits was largely explained by visits for suspected cancers, as opposed to confirmed cancers, and was not followed by a substantial catch-up in later months of the pandemic, implying that there were overall fewer suspected cases during the pandemic relative to previous years.

The clinical presentation of pediatric cancers will often overlap with that of infections. For example, swollen lymph nodes (lymphadenopathy) is a clinical feature of lymphoma, but more often is caused by infections [18,19]. As such, the reduction in viruses during the COVID-19 pandemic may have led to a filtering of non-cancer related visits to the pediatric ED that would have, in previous years, resulted in a diagnosis similar to cancer. Alternatively, studies have now established a potential relationships between infectious diseases and pediatric cancers, proposing that immaturity of the immune system due to lack of exposure during early childhood to common viruses may result in in-proper immune responses to infections later on, or that viral infections themselves are potential trigger for pediatric cancers, especially in leukemias [20,21]. Since most pediatric cancers cannot go undiagnosed for more than a couple weeks after the onset of symptoms, there may have been a reduction in new pediatric cancers during the COVID-19 pandemic.

The initial reduction in suspected cancer visits during the first month of the pandemic followed by an increase at the pediatric ED may also indicate some delay in diagnosis and treatment. A study conducted in the UK found that two thirds of caregivers of pediatric cancer patients felt unsafe at the hospital due to fear that their child might contract the SARS-CoV-2 virus [22]. Multiple other studies have also documented anxiety related to COVID-19 disease in pediatric cancer patients or caregivers, which can result in delays in seeking medical advice/treatment [23–27]. Shortages in healthcare providers and changes in hospital management during the pandemic have also been associated to delays in diagnosis and treatment [6,28,29]. A study conducted in Saudi Arabia found that over 60% of cancer patients at a pediatric tertiary care center experienced delays in treatment during the early months of the pandemic due to appointment cancellations by the hospital [30].

On the other hand, the trend in pediatric ED visits for patient with previously confirmed cancer diagnoses showed a slight increase in visits during the end of 2020. Children with cancer have suppressed immunity and will most often visit the ED due to viral or bacterial infections. As immunosuppression is a known risk factor for severe viral infections, this peak may also be related to a resurgence in viral transmission, including COVID-19 disease, in children during this time [31]. Indeed, a surge in cases of COVID-19 diseases during the winter holidays of 2020 may explain increased pediatric ED visits for children with cancer [32]. However, a study conducted in Canada on pediatric risk-factors for severe COVID-19 disease found no increased risk in pediatric cancer patients, suggesting that the observed increase in pediatric ED visits for cancer patients may be related to resurgence of non-SARS-CoV-2 viruses [33]. Furthermore, the small sample size in this analysis makes the observed trend inconclusive.

In any case, the analysis investigating changes in oncology ward admissions showed evidence of a reduction in rate of readmissions during the pandemic relative to previous years. Children with cancer most often receive treatment through outpatient clinics at both hospitals, whereas multiple admissions to the oncology ward can indicate health complications resulting from treatment or infection. As such, the reduction in rate of readmission may indicate the pediatric cancer patients were less sick during the pandemic, or that more children were receiving care through alternate means of care such as telehealth. It is, however, unlikely that severely sick children would be treated virtually due to the limitation of at home medical treatment. e

Strengths and Limitations:

The two participating hospitals in this study are part of a universal single payer health system, implying that there are no financial access barriers as in other countries. Furthermore, these hospitals are the only two centers that provide care to pediatric cancer patients in Montreal, implying that all pediatric cancer patients in Montreal were captured in this study.

A limitation in this study was the different disease classification systems between the two pediatric EDs. Although clustering was accounted for in the regression models, the validity of the primary analysis was likely reduced due to these differences. Furthermore, as data in the primary analysis was obtained directly from the emergency database records, it is possible that there was misclassification in the selected diagnoses. Due to data limitations, it was impossible to verify which suspected cancer diagnoses at the pediatric ED resulted in cancer. Finally, although counts were aggregated bimonthly, the frequency of ED visits for confirmed cancers per time-point was small, meaning that there was very low power to detect the outcomes of interest and that the observed trends may be coincidental.

Conclusion:

This study saw a 39% decrease in both suspected cancers and known cancers at the pediatric ED during the first two months of the pandemic. However, this trend was largely explained by suspected cancers: A large reduction in pediatric ED visits for patients with clinical presentations compatible with cancer at the onset of the pandemic was observed. Reduced viral transmission during the first months of the COVID-19 pandemic due to public health measures may have resulted in fewer children with viral infections presenting with symptoms shared with new cancers. Children with cancer had on average fewer readmissions to the pediatric oncology ward during the pandemic relative to before the pandemic, which may also be related to reduced viral infections in children during this time.

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Tables and Figures:

Table. 1 Characteristics of pediatric ED visits for suspected and confirmed cancer

Characteristics	Pre-Pandemic period (May 2016-Feb 2020) n (%)			Pandemic period (March 2020-Feb 2021) n (%)		
	Confirmed	Suspected	Total	Confirmed	Suspected	Total
Total cases, N	275	1886	2161	79	336	415
Age						
<1 year	12 (4.4)	145 (7.7)	157 (7.3)	1 (1.3)	26 (7.7)	27 (6.5)
1-2 years	38 (13.8)	401 (21.3)	439 (20.3)	14 (17.7)	53 (15.8)	67 (16.1)
3-4 years	44 (16.0)	372 (19.7)	416 (19.3)	13 (16.5)	45 (13.4)	58 (14)
5-11 years	110 (40.0)	697 (37)	807 (37.3)	30 (38)	128 (38.1)	158 (38.1)
+12 years	71 (25.0)	271 (14.4)	342 (15.8)	21 (26.6)	84 (25)	105 (25.3)
Paed CTAS level[a]						
1- Resuscitation	9 (3.3)	2 (0.1)	11 (0.5)	4 (5.4)	0 (0.0)	4 (1)
2- Emergency	160 (58.2)	103 (5.5)	263 (12.2)	41 (55.4)	24 (7.8)	65 (17)
3- Urgent	78 (28.4)	629 (33.6)	707 (32.7)	20 (27)	85 (27.5)	105 (27.4)
4- Less Urgent	21 (7.6)	897 (47.6)	918 (42.3)	7 (9.5)	160 (51.8)	167 (43.6)
5- Non-Urgent	7 (2.6)	225 (13.5)	262 (12.1)	2 (2.7)	40 (12.9)	42 (11.0)

ED= Emergency department; Paed CTAS level= Pediatric Canadian Triage and Acuity Scale

[a] Among children with confirmed diagnoses of cancer at the pediatric, there were 5 missing priority level in the pre-pandemic period. Among all children with suspected cancer diagnoses, 27 were missing priority level in the pandemic period.

Table. 2 Characteristics of patients admitted to the pediatric oncology ward by hospital site

Variable	Pre-Pandemic, n (%)[1]			Pandemic, n (%)[2]		
	MUHC	CHU-SJ	Total	MUHC	CHU-SJ	Total
Total cases, N	2749	3087	5836	925	913	1838
Age[3]						
<1 year	52 (1.9)	166 (5.4)	218 (3.7)	23 (2.5)	46 (5.0)	69 (3.8)
1-2 years	261 (9.5)	385 (12.5)	646 (11.1)	112 (12.1)	154 (16.9)	266 (14.5)
3-4 years	456 (16.6)	443 (14.4)	899 (15.4)	174 (18.8)	171 (18.7)	345 (18.8)
5-11 years	1107 (40.4)	894 (29.0)	2001 (34.3)	346 (37.4)	299 (32.7)	645 (35.1)
+12 years	864 (31.5)	1199 (38.8)	2064 (35.4)	270 (29.2)	243 (26.6)	513 (27.9)
Sex						
Female	1203 (43.9)	1487 (48.2)	2690 (46.2)	408 (44.1)	379 (41.5)	787 (42.8)
Male	1537 (56.1)	1600 (51.8)	3137 (53.8)	517 (55.9)	534 (58.5)	1051 (57.2)

ED= Emergency Department; CHU-SJ= Centre hospitalier universitaire Sainte-Justine; MUHC= McGill University Health Centre; Pre-pandemic period=May 2016-February 2020; Pandemic Period=March 2020 to February 2021

Table. 3 Results of multivariate regression model for interrupted time series analysis for suspected and confirmed cancers at the pediatric ED[1,2]

Final model	Incidence Rate Ratio (95% CI)
Level-shift	0.61 (0.47 ; 0.77)
Slope-change	1.11 (1.04 ; 1.19)
Secular time-trend	0.98 (0.97 ; 0.99)
Site (REF=MUHC)	2.33 (2.01 ; 2.69)
Site*slope-change	1.02 (1.01 ; 1.03)

ED= Emergency Department; CI= Confidence Interval; REF= Reference; CHU-SJ= Centre hospitalier universitaire Sainte-Justine; MUHC= McGill University Health Centre

[1]Negative binomial regression was used to account for overdispersion in the data

[2]Fourier terms were included in the model to account for seasonality

Table. 4 Analysis type and regression output of the final model for secondary analyses of the pediatric emergency department

Analysis	Coefficient	IRR (95% CI)
Pediatric ED visits for confirmed cancer patients[1]	Secular time trend (pre-pandemic)	1.00 (0.98 ; 1.02)
	Level-shift	0.61 (0.35 ; 1.06)
	Site (ref= MUHC)	3.35 (2.60 ; 4.31)
	Slope-change	1.22 (1.06 ; 1.41)
Pediatric ED visits for suspected cancer patients[1,2]	Secular time-trend	0.98 (0.97 ; 0.99)
	Level-shift	0.63 (0.48 ; 0.82)
	Site (ref=MUHC)	2.17 (1.85 ; 2.55)
	Slope-change	1.08 (1.00 ; 1.17)
	Interaction term - Site*Slope-change	1.02 (1.01 ; 1.03)

IRR= Incidence Rate Ratios; CI= Confidence Interval; ITS= Interrupted Time-Series; ED= Emergency Department; CHU-SJ= Centre hospitalier universitaire Sainte-Justine; MUHC= McGill University Health Centre

[1] Estimated via segmented Poisson regression

[2]The model included Fourier terms to account for seasonality

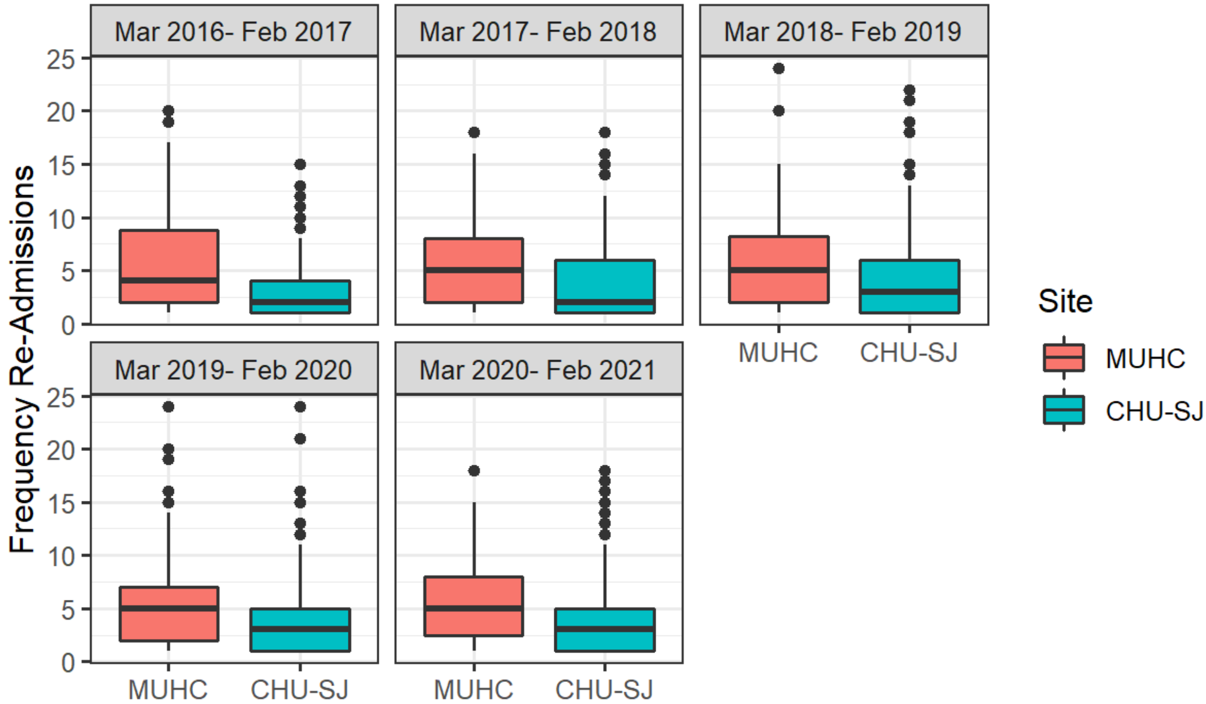
Table. 5 Regression output of the final model of oncology ward re-admission

Coefficient[1]	**HR (95% CI)**
Site (ref= MUHC)	0.69 (0.62 ; 0.77)
Age (ref= 5-11 years)	
<1 year	0.55 (0.43 ; 0.70)
1-2 years	0.91 (0.80 ; 1.04)
3-4 years	0.95 (0.84 ; 1.08)
+12 years	0.89 (0.80 ; 1.00)
Interaction term- **Age*Site**	
<1 year	1.75 (1.33 ; 2.31)
1-2 years	1.01 (0.84 ; 1.21)
3-4 years	1.01 (0.85 ; 1.20)
+12 years	1.24 (1.06 ; 1.44)
Segment (ref= Pre-Pandemic period)	0.83 (0.74 ; 0.93)

HR= Hazard Ratio; CI= Confidence Interval; CHU-SJ= Centre hospitalier universitaire Sainte-Justine; MUHC= McGill University Health Centre; Pre-pandemic period=May 2016-February 2020; Pandemic Period=March 2020 to March 2021

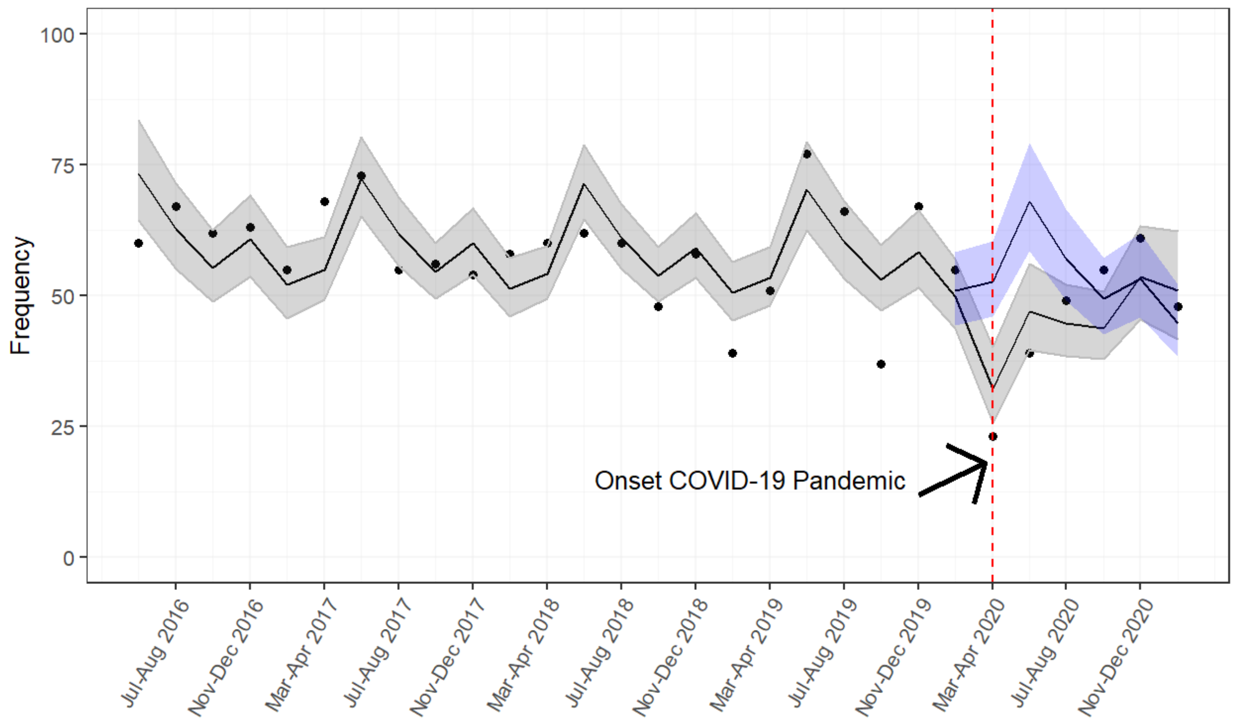
[1] A stratified Cox proportional hazards model was used to estimate the change in rate of re-admissions

Fig. 1 Frequency of readmissions to the pediatric oncology ward by site and year interval



MUHC= McGill University Health Centre; CHU-SJ= Centre hospitalier universitaire Sainte-Justine

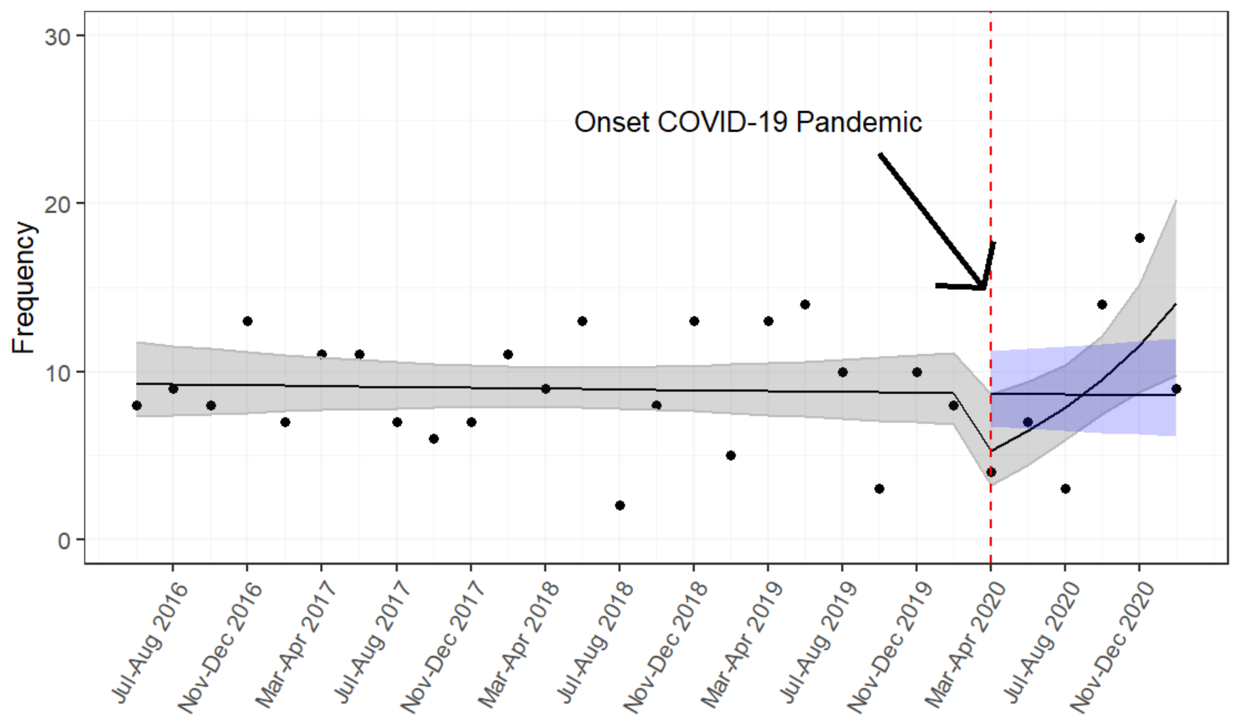
Fig. 2 Interrupted timeseries analysis for bi-monthly incidence of pediatric emergency department visits for children with confirmed or suspected cancer at the CHU Sainte-Justine[1]



ED= Emergency department;

[1] Grey zone indicates 95% confidence interval of fitted values, blue zone indicates 95% confidence interval of predicted values.

Fig. 3 ITS analysis of bimonthly incidence for confirmed cancer patients at the pediatric ED[1,2]

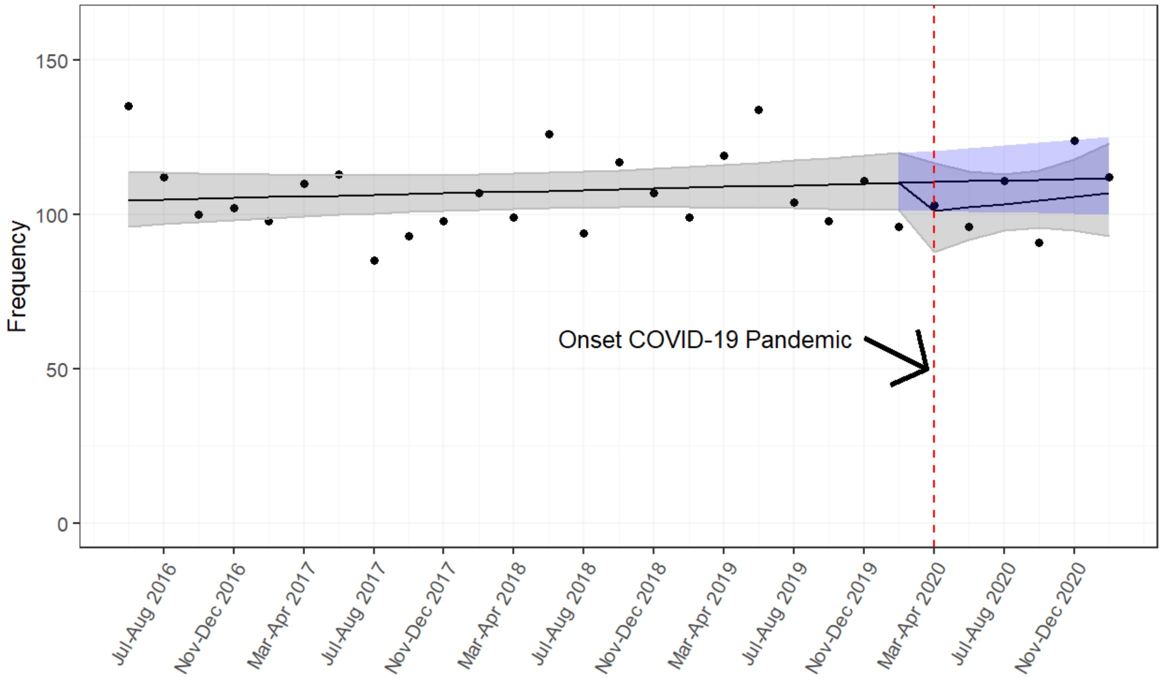


ITS= Interrupted Time-Series; ED= Emergency department; CHU-SJ= Centre hospitalier universitaire Sainte-Justine; MUHC= McGill University Health Centre

[1]Results are for CHU-SJ

[2] Grey zone indicates 95% confidence interval of fitted values, blue zone indicates 95% confidence interval of predicted values.

Fig. 4 ITS analysis of bi-monthly incidence of oncology admissions at MUHC and CHU-SJ [1,2]



ITS= Interrupted Time-Series; ED= Emergency department; CHU-SJ= Centre hospitalier universitaire Sainte-Justine; MUHC= McGill University Health Centre

[1]Results are for CHU-SJ

[2] Grey zone indicates 95% confidence interval of fitted values, blue zone indicates 95% confidence interval of predicted values.

Supplementary Material:

Table S 1: Pediatric ED diagnostic criteria for confirmed cancers

Categories	**CHU-SJ** identified via a drop-down menu	**MUHC** identified via icd-10 code
Leukemia/ Hematologic Tumor	'Leucemie', 'Leucemie lymphoide aigue, LLA'	'Leukaemia', 'Neoplasm hematologic other'
Brain And Cranial Tumors	'Tumeur cerebrale'	'Malignant neoplasm of brain unspecified' , 'Neoplasm of head, face & neck'
Bone Tumor	'Tumeur osseuse'	NA
Kidney And Renal Tumor	'Tumeur renale, neoplasie renale', 'Wilms, Tumeur Wilms'	NA
Testicular/Gynecological Tumors	NA	'Neoplasm of testicle', 'Neoplasm gynecologic',
Skin Tumors	NA	'Neoplasm of skin',
Breast Tumors	NA	'Neoplasm of breast',
Neuroblastoma	'Neuroblastome'	NA
Sarcomas	'Oteosarcome', 'Sarcome'	NA
Unknown/Other Cancers	'Cancer Autres', 'Immunodeprimes (sous chimio)', 'Oncologie', 'Neoplasie, cancer, Neo', 'Tumeur'	'Tumor of unknown behaviour'

ED= Emergency Department; CHU-SJ= Centre hospitalier universitaire Sainte-Justine ; MUHC= The McGill University Health Centre

Table S 2: Pediatric ED diagnostic criteria for suspected cancers

Categories	CHU-SJ Identified By a Drop-Down Menu	MUHC Identified By ICD-10 Codes
Thoracic Mass	'Masse thoracique',	‘Localized swelling, mass and lump, trunk’
Cervical Mass	'Masse cervicale',	NA
Abdominal Mass	'Masse abdominale',	‘Intra-abdominal and pelvic swelling, mass and lump’
Unspecified Mass	‘Masse’	‘Swelling, mass and lump ‘
Pancytopenia	'Pancytopenie',	NA
Adenopathy, Lymph Nodes	'Adenopathies, ganglions',	‘Lymphadenoapthy’, ‘Nonspecific mesenteric’, ‘Lymphadenitis’, ‘Lymphangitis’
Immunosuppressed	'Immunosupprimes',	NA

CHU-SJ= Centre hospitalier universitaire Sainte-Justine ; MUHC= The McGill University Health Centre ; ED= Emergency Department

5 Conclusion

In this thesis, we examined changes in incidence and severity for two pediatric NCDs during the COVID-19 pandemic in Quebec: Appendicitis and cancers. In doing so, we aimed to quantify the impact of public health measures on health care utilization and disease occurrence, as well as effects SARS-CoV-2 infection, for these diseases. We found evidence of a 14% increase in pediatric ED visits for appendicitis, and a 37% reduction in visits for suspected cancers at the onset of the pandemic. While the observed initial increase in visits for appendicitis remained constant, there was an increased rate of visits for suspected cancers at the pediatric ED throughout the first year of the pandemic. In contrast, we found an increase in visits for already confirmed cancer patients at the pediatric ED during the winter of 2020.

A change in incidence in pediatric NCDs can be attributable to multiple factors, such as increased use of telemedicine, delays in seeking medical attention due to inaccessibility of health care during the pandemic (such as lockdown measures) or fears in visiting the pediatric ED due to the SARS-CoV-2 virus. It can also indicate increases/decreases in the onset of new NCDs resulting from changes in exposure to triggers of these diseases. Acute appendicitis requires almost immediate medical attention, making longer delays very unlikely, but this also means that almost all cases will go through the pediatric ED before being admitted for treatment. As such, the observed increase in visits at the pediatric ED resulted either from an absolute increase in cases of pediatric appendicitis during the pandemic, or more parents going directly to tertiary care centers to avoid exposure to the SARS-CoV-2 virus at secondary care centers that also treat adults. In relation to the former, the potential association between COVID-19 disease and onset of pediatric appendicitis should continue to be explored.

Pediatric EDs serve as the initial site of detection for most pediatric cancers. However, the majority of suspected cancers are attributable to infections. As such, the observed reduction in visits at the pediatric ED during the first year of the pandemic for suspected cancers could have resulted from either an absolute reduction in new cancers, increased use of telemedicine, or more likely, a reduction in visits that were not for cancers. On the other hand, there was an increase in visits for patients that already had a formal cancer diagnosis during the winter of 2020, although, due to the small sample size, the results of this analysis remain inconclusive and should be verified using larger datasets.

We were also interested in quantifying changes in severity of patients with appendicitis and cancers during the first year of the pandemic. This was measured via changes in risk for perforated appendix and requiring surgical drainage in cases of appendicitis, and changes in incidence of oncology ward admissions for cancers. Unlike other studies investigating acute appendicitis that found increased severity of patients due to delays in seeking medical treatment, we did not find evidence of a change in severity of patients, indicating that delays were not common. Furthermore, we found a slight reduction in average LOS, meaning that patients were being discharged faster than previous years. In oncology ward admissions, we found a reduction in risk of readmission during the pandemic for 5-11 year olds compared to the pre-pandemic period, which suggests that children were not ask sick, or were receiving treatment through alternate means (such as telemedicine).

In conclusion, the pandemic impacted the incidence of children with appendicitis and cancers at two pediatric EDs in Quebec. In future studies, the potential association between COVID-19 disease and onset of pediatric appendicitis should continue to be explored as it is a possible explanation for the observed increase in incidence of appendicitis during the first year of the pandemic. The reduction in viral transmission likely had an impact of pediatric ED visits for diagnosis overlapping with the clinical presentation of cancer patients and oncology admissions, but more studies are needed to conclude how this affected ED visits for children with a previously confirmed cancer diagnosis.

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7 Appendices

Appendix 1: Pediatric ED diagnostic criteria for confirmed cancer patients

Categories	CHU-SJ identified via a drop-down menu	MUHC identified via icd-10 code
Leukemia/ Hematologic Tumor	'Leucemie', 'Leucemie lymphoide aigue, LLA'	'Leukaemia', 'Neoplasm hematologic other'
Brain And Cranial Tumors	'Tumeur cerebrale'	'Malignant neoplasm of brain unspecified' , 'Neoplasm of head, face & neck'
Bone Tumor	'Tumeur osseuse'	NA
Kidney And Renal Tumor	'Tumeur renale, neoplasie renale', 'Wilms, Tumeur Wilms'	NA
Testicular/Gynecological Tumors	NA	'Neoplasm of testicle', 'Neoplasm gynecologic',
Skin Tumors	NA	'Neoplasm of skin',
Breast Tumors	NA	'Neoplasm of breast',
Neuroblastoma	'Neuroblastome'	NA
Sarcomas	'Oteosarcome', 'Sarcome'	NA
Unknown/Other Cancers	'Cancer Autres', 'Immunodeprimes (sous chimio)', 'Oncologie', 'Neoplasie, cancer, Neo', 'Tumeur'	'Tumor of unknown behaviour'

ED= Emergency Department; CHU-SJ= Centre hospitalier universitaire Sainte-Justine ; MUHC= The McGill University Health Centre

Appendix 2: Pediatric ED diagnostic criteria for suspected cancers

Categories	**CHU-SJ** Identified By a Drop-Down Menu	**MUHC** Identified By ICD-10 Codes
Thoracic Mass	'Masse thoracique',	‘Localized swelling, mass and lump, trunk’
Cervical Mass	'Masse cervicale',	NA
Abdominal Mass	'Masse abdominale',	‘Intra-abdominal and pelvic swelling, mass and lump’
Unspecified Mass	‘Masse’	‘Swelling, mass and lump ‘
Pancytopenia	'Pancytopenie',	NA
Adenopathy, Lymph Nodes	'Adenopathies, ganglions',	‘Lymphadenoapthy’, ‘Nonspecific mesenteric’, ‘Lymphadenitis’, ‘Lymphangitis’
Immunosuppressed	'Immunosupprimes',	NA

CHU-SJ= Centre hospitalier universitaire Sainte-Justine ; MUHC= The McGill University Health Centre ; ED= Emergency Department