Antiviral use among children admitted for influenza in Canadian pediatric tertiary care centers between 2010-2019

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ABSTRACT

Background

Seasonal influenza epidemics are an important cause of pediatric hospitalization and mortality. Randomized controlled trials have shown that early treatment (within 48 hours of symptom onset) with antivirals reduces illness duration in healthy children in the outpatient setting, and observational studies suggest improved outcomes in hospitalized cases. However, data on antiviral use amongst hospitalized children are scarce, and have primarily focused on the 2009 H1N1 pandemic period or earlier. Further, despite clinical practice guidelines recommending antiviral treatment for all hospitalized children, it is unknown why many children admitted to pediatric centers do not receive antiviral treatment.

Objectives

The objectives of this thesis were to describe antiviral use in children hospitalized for influenza in Canadian pediatric centers, and to identify factors associated with antiviral treatment.

Methods

We performed a retrospective cohort study of children (0-16 years) admitted for laboratory confirmed influenza infection between September 2010 and June 2019 at 12 IMPACT (Canadian Immunization Monitoring Program, ACTive) pediatric referral centers, ascertained through active surveillance. We excluded patients with hospital length of stay (LoS) <1 day, patients who received antivirals prior to admission to IMPACT hospital, and nosocomial cases. The primary outcome was in-hospital antiviral use. Exposure variables of interest included demographics, availability of a local influenza treatment guideline, timing of admission within influenza season, availability of laboratory confirmation of influenza infection relative to admission, presence of high-risk chronic health conditions, clinical characteristics, antibiotic prescription, and measures of illness severity (mortality, intensive care unit [ICU] admission, mechanical ventilation, and ICU and hospital length of stay). Descriptive statistics were calculated for the entire sample and by outcome. Univariable and multivariable logistic regression analyses were performed to identify factors associated with antiviral use.

Results

Amongst 7545 patients, 57.4% were male; median age was 3 years (IQR 1.1-6.3. Overall, 41.3% received antivirals; 72.8% received antibiotics. Antiviral utilization varied across sites (range, 10.2-81.1%) and influenza season (range, 19.9-59.6%). Children who received antivirals had increased markers of disease severity (median hospitalization duration 4 vs. 2 days, $p<0.001$; ICU admission, 27.8% vs. 8.7%, $p<0.001$; influenza-related mortality, 0.9% vs. 0.2%, $p<0.001$). On multivariable analysis, factors associated with antiviral use included older age [adjusted odds ratio (aOR) 1.04 (95% CI, 1.02-1.05)], more recent season [highest aOR 9.18 (6.70-12.57) for 2018-19], timing of admission [aOR 1.37 (1.19-1.58) for admission during peak season], availability of local treatment guideline [aOR 1.54 (1.17-2.02)], timing of availability of laboratory confirmation

[highest aOR 2.67 (1.97-3.61) for result availability prior to hospitalization], presence of chronic health conditions [highest aOR 4.81 (3.61-6.40) for cancer], radiographically-confirmed pneumonia [aOR 1.39 (1.20-1.60)], co-receipt of antibiotic therapy [aOR 1.51 (1.30-1.76)] and need for intensive care [aOR 3.62 (2.88-4.56)].

Conclusions

Antiviral medications are underutilized amongst children hospitalized for influenza in Canadian pediatric hospitals. However, an encouraging increase in utilization overall and in high-risk children was noted over time. A wide variation in prescribing practices was noted across the country, and a high rate of antibiotic use was also noted. We identified patient and hospital-level characteristics independently associated with antiviral prescribing. Taken together, these findings call for multifaceted hospital-based interventions to strengthen adherence to local and national influenza treatment guidelines, and improved antimicrobial stewardship practices.

RÉSUMÉ

L'utilisation des médicaments antiviraux parmi les enfants admis pour l'influenza en centre de soins tertiaires pédiatrique au Canada entre 2010 et 2019

Contexte
Les épidémies de grippe saisonnière causées par le virus de l'influenza sont une cause importante d'hospitalisation et de mortalité pédiatrique. Les données sur l'utilisation des antiviraux parmi les enfants hospitalisés sont rares. En outre, malgré les lignes directrices de pratique clinique qui recommandent un traitement antiviral pour tous les enfants hospitalisés, on ignore pourquoi nombreux n'en reçoivent pas.

Objectifs
Nous décrivons l'utilisation des antiviraux chez les enfants hospitalisés pour la grippe dans les centres pédiatriques canadiens, et d'identifions les facteurs associés au traitement antiviral.

Méthodes
Étude de cohorte rétrospective chez les enfants (0-16 ans) admis pour infection grippale confirmée en laboratoire, de septembre 2010 à juin 2019, dans les 12 centres pédiatriques du Programme canadien de surveillance active de l'immunisation (IMPACT), vérifiée par une surveillance active. Nous avons exclu les patients dont le séjour hospitalier < 1 jour, les patients ayant reçu des antiviraux avant leur admission et les cas nosocomiaux. Le résultat primaire était l'utilisation des antiviraux en hôpital. Les variables d'exposition comprenaient les données démographiques, la disponibilité de directives locales, le moment de l'admission pendant la saison grippale, le moment de confirmation virologique, la présence de conditions de santé chroniques à haut risque, les caractéristiques cliniques, la prescription d'antibiotiques et des mesures de sévérité (mortalité, admission dans l'unité des soins intensifs [USI], la ventilation mécanique, la longueur du séjour hospitalier et en USI). Les analyses de régression logistique univariées et multivariées ont été effectuées pour identifier les facteurs associés à l'utilisation d'antiviraux.

Résultats
Parmi les 7545 patients, étaient mâles. L'âge moyen était de 3 ans, (écart interquartile, 1.1-6.3) et 70.8% avaient une infection à l'influenza de type A. Dans l'ensemble, 41.3% ont reçu des antiviraux; 72.8% ont reçu des antibiotiques. L'utilisation des antiviraux variait selon les sites (fourchette, 10.2-81.1%) et la saison grippale (fourchette, 19.9-59.6%). Les enfants ayant reçu des antiviraux présentaient des marqueurs de sévérité plus élevés (durée médiane d'hospitalisation de 4 vs 2 jours, P<0.001; admission en USI, 27.8% vs. 8.7%, P<0.001; mortalité liée à l'influenza, 0.9% vs. 0.2%, P<0.001). Selon l'analyse multivariée, les facteurs associés à l'utilisation d'antiviraux comprenaient l'âge plus avancé [rapport de cotes ajusté (aRC) 1.04 (intervalle de confiance 95%, 1.02-1.05)], saison récente [aRC le plus élevé 9.18 (6.70-12.57) pour 2018-19], admission au pic saisonnier [aRC 1.37 (1.19-1.58)], disponibilité de directives locales [aRC 1.54 (1.17-2.02)], moment de confirmation en laboratoire [aRC le plus élevé 2.67 (1.97-3.61) pour résultats avant l'hospitalisation], présence de conditions de santé chroniques [aRC le plus élevé 4.81 (3.61-6.40) pour le cancer], pneumonie radiographique [aRC

1.39 (1.20-1.60)], réception d'antibiotiques [aRC 1.51 (1.30-1.76)] et admission à l'USI [aRC 3.62 (2.88-4.56)].

Conclusions

Les médicaments antiviraux sont sous-utilisés chez les enfants hospitalisés pour l'influenza dans les hôpitaux pédiatriques canadiens. Cependant, une augmentation encourageante de leur utilisation en général et chez les enfants à hauts risques a été constatée. Une large variation dans les pratiques de prescription a été remarquée à travers le pays, et un taux élevé d'utilisation d'antibiotiques a également été notée. Nous avons identifié les caractéristiques des patients et des hôpitaux associés à la prescription d'antiviraux. Dans l'ensemble, ces résultats appellent à des interventions hospitalières à multiples facettes pour renforcer le respect des directives en matière de traitement de la grippe.

PREFACE

This manuscript-based thesis describes antiviral use in children hospitalized for influenza in Canadian tertiary care centers and attempts to identify factors associated with influenza antiviral treatment in this population. It is presented in 6 chapters.

An introduction to antiviral use and outcomes amongst hospitalized children is given (Chapter 1). The rationale, hypotheses, and objectives for the study and the manuscript included in this thesis are then outlined (Chapter 1). Subsequently, a review of the literature on the various antivirals used to treat influenza, current treatment guidelines and outcomes associated with the use of antivirals among ambulatory and hospitalized patients (both adults and children) is given (Chapter 2). The methods used in this thesis are described in the manuscript (Chapter 4), however Chapter 3 describes the data source and statistical analyses in greater detail. The results of the study are presented as a manuscript and are reported in Chapter 4, which describes antiviral use in Canadian children hospitalized with influenza in the decade following the 2009 influenza A H1N1 pandemic. Chapter 5 provides a discussion of the main findings of the thesis. Finally, a summary and concluding remarks are given in Chapter 6.

I wrote all chapters of this thesis, and these were then reviewed critically and edited by my supervisor, Dr. Jesse Papenburg.

This thesis has been prepared according to the guidelines for a manuscript-based thesis,
and includes the following manuscript:

Mehta K, Morris SK, Bettinger JA, Vaudry W, Jadavji T, Halperin SA, Bancej C, Sadarangani M, Dendukuri N, Papenburg J, for the Canadian Immunization Monitoring Program Active (IMPACT) Investigators. Antiviral use among Canadian children hospitalized for influenza, 2010-2019.
Submitted to ***Pediatrics***.

Details of co-authors' contributions to each manuscript are outlined on page 45 of this thesis.

CONTRIBUTION OF AUTHORS

I developed the original research question and objectives for this thesis in collaboration with my thesis supervisor, Dr. Jesse Papenburg. With the guidance of my supervisor, I selected the design and the methods used in the study. I obtained the data used in this thesis from the IMPACT (Canadian Immunization Monitoring Program, ACTive) network and conducted all data processing and statistical analyses; and was responsible for the first interpretation of the results. After discussing the results with my supervisor, thesis committee members and co-authors, I wrote the manuscript, which was revised and edited by Dr. Papenburg as well as the co-authors. Finally, I wrote all chapters of this M.Sc. thesis.

Dr. Papenburg, as my primary supervisor, was involved in supervising all stages of this research. Dr. Dendukuri, as thesis committee member, provided advice on the choice and execution of the statistical methods, the interpretation of the results, and made editorial revisions to the manuscript.

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Lastly, and most importantly, I would like to thank my family, without whom I would not have been here. I thank my dear wife, Divya, for her sacrifices, support, counsel and for being my strongest cheerleader as well as greatest critic – you are my rock. My little 3-year-old son Dhruv, the sparkle in our lives. My dear brother Dhaval, whose love and wisdom are infinite. And my dear friend Adithya, for always being there, and for constantly reminding me of our larger purpose as health researchers.

I dedicate this work my beloved late parents Drs. Pankaj and Chaya Mehta, whose lives and mission continue to inspire many.

"In doing something, do it with love, or never do it at all."

Mohandas Karamchand Gandhi

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LIST OF ABBREVIATIONS

AIC	Akaike Information Criteria
AMMI	Association of Medical Microbiology and Infectious Disease (Canada)
aOR	Adjusted Odds Ratio
BMI	Body Mass Index
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CPS	Canadian Pediatric Society
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
ICD	International Classification of Diseases
ICU	Intensive Care Unit
IIV	Inactivated Influenza Vaccine
IMPACT	Canadian Immunization Monitoring Program, ACTive
ILI	Influenza-like Illness
IPD	Individual Participant Data
ITT	Intention to Treat
ITTi	Intention to Treat infected
IRR	Incidence rate ratio
IQR	Inter-quartile range
LAIV	Live Attenuated Influenza Vaccine
LoS	Length of Stay
LRI	Lower respiratory tract infection
NAI	Neuraminidase inhibitor
NNV	Number Needed to Vaccinate
OR	Odds Ratio
PCR	Polymerase Chain Reaction
PHAC	Public Health Agency of Canada
POC	Point of Care
RCT	Randomized Controlled Trial
RSV	Respiratory Syncytial Virus
RNA	Ribonucleic Acid
RR	Relative Risk
URI	Upper respiratory tract infection
USA	United States of America
VE	Vaccine effectiveness
WHO	World Health Organization

CHAPTER 1 - INTRODUCTION

1.1 Background

Globally, seasonal influenza epidemics are an important cause of pediatric hospitalization and mortality (1). Annual hospitalization rates are highest in young children, ranging from ~250 per 100,000 children <6 months old to ~6 per 100,000 for those 6-15 years old (2). In Canada, a 2006 modelling study estimated that 1.5% of all pediatric respiratory admissions could be attributed to influenza (18 admissions per 100,000 per year), with the largest burden in infants 6 to 11 months of age, with rates of 200 per 100,000 infants (3). An estimated 33 (95% CI 29-38) per 100,000 hospitalizations per year in Canada between 2003-2014 were attributed per year to influenza in the general population (4). Hospitalization risk is ~4 to 21 times greater in children with chronic medical conditions and they accounted for ~55% of pediatric influenza deaths during 2004-2012 in the U.S (5). While influenza vaccination is the cornerstone of prevention, antivirals, namely neuraminidase inhibitors, are the only specific treatment. The neuraminidase inhibitors oseltamivir and zanamivir are the only influenza antiviral treatments recommended for use in Canada (6). Randomized controlled trials show that early treatment with antivirals, i.e., within 48 hours of symptom onset, reduces illness duration in adults and healthy children with influenza in the outpatient setting, but efficacy in 'at risk' children remains to be proven (7-9). Despite an absence of randomized controlled trial data in the hospital setting, influenza guidelines recommend treatment of all cases requiring admission (10, 11). Observational studies in hospitalized adults support this notion, with early antiviral therapy associated with decreased disease severity outcomes (length of stay (LoS), intensive care unit admission and mortality) (12-15). However, data regarding antiviral use and outcomes of hospitalized children are scarce and have focused on the 2009 H1N1 pandemic period or earlier (14, 16).

1.2 Rationale

Data regarding the use of antivirals in Canadian children hospitalized with influenza are scarce. The Canadian Immunization Monitoring Program, ACTive (IMPACT) conducts active surveillance for vaccine-preventable diseases in children. The network consists of 12 tertiary care pediatric hospitals, accounting for ~90% of Canadian pediatric tertiary care beds (17). In crude analysis of unpublished data (2010-11 to 2015-16), it was found that an average of 715 influenza

cases per year are reported in IMPACT. In terms of severity outcomes, median LoS is typically 3 days (IQR, 2-5 days), ICU admission proportions range from 11% to 17% and there are 1-8 deaths per year. Antiviral use increased from 19% to 46% over that period.

From my initial literature review, I identified an important knowledge gap. Despite clinical practice guideline recommendations, and the availability of highly sensitive molecular assays facilitating prompt diagnosis, it is not known why most Canadian children admitted to pediatric centers do not receive antiviral treatment. This thesis attempts to better understand this guideline-practice gap.

In this thesis, I have used IMPACT data with the overall goal of assessing the extent of antiviral use and factors associated with antiviral use in pediatric seasonal influenza hospitalizations in Canada during the decade following the 2009 H1N1 pandemic (2010-11 to 2018-19).

I hypothesized that antiviral prescribing would vary considerably across IMPACT centers, would have increased over time, and could be associated with patient and hospital-level variables.

1.3 Objectives

The specific objectives of this thesis are as follows:

1. To describe antiviral use in children hospitalized for influenza in Canadian tertiary care centers, including differences across hospitals and over time.

2. To identify factors associated with influenza antiviral treatment in this population.

CHAPTER 2 – LITERATURE REVIEW

2.1 Influenza

2.1.1. Influenza virus: Virology and epidemiology

Influenza is an acute respiratory illness caused by influenza A or B viruses, and rarely influenza C viruses. These viruses belong to the Orthomyxoviridae family. Despite significant differences in genetic organization, structure, host range, epidemiology, and clinical characteristics between the three influenza virus types, all three viruses share certain features, including the presence of a host cell–derived envelope, envelope glycoproteins of critical importance in virus entry and egress from cells, and a segmented genome of negative-sense single-stranded RNA (18). Influenza A viruses are further classified into subtypes based on the antigenic properties of their two surface glycoproteins, haemagglutinin and neuraminidase. Sixteen haemagglutinin (H) and nine neuraminidase (N) subtypes of influenza A viruses have been isolated from birds (H1 to H16 and N1 to N9), and RNA of an additional two haemagglutinin and neuraminidase subtypes has been identified in bats (H17 and H18, and N10 and N11). A similar animal reservoir does not exist for influenza B viruses but two antigenically distinct lineages of influenza B viruses—Victoria and Yamagata— co-circulate in human beings (19).

Influenza typically occurs in annual outbreaks, primarily during the winter season, in temperate climates. Although influenza generally is an acute, self-limited, and usually uncomplicated disease in healthy children, it can be associated with severe morbidity and mortality. The influenza virus is transmitted from infected to susceptible persons by droplets. The basic reproductive number (mean number of secondary cases transmitted by a single index case to susceptible contacts) has been estimated to be 1.28 (IQR 1.19 to 1.37), and the median incubation period of seasonal influenza A illness, 1.4 days (95% CI 1.3 to 1.5 days) (20, 21). The attack rate of influenza in children (<18 years) varies from year to year, ranging between 10 and 40% during a typical influenza season (22). The estimated incidence of symptomatic influenza in children <18 years is approximately 9% (23). In the United States general population, between 2010 and 2018, seasonal influenza epidemics were associated with an estimated 4.3–23 million medical visits, 140,000–

960,000 hospitalizations, and 12000–79000 deaths annually (24). In Canada, influenza and pneumonia are ranked among the top 10 leading causes of death, and it is estimated that influenza causes approximately 12200 hospitalizations and 3500 deaths annually (25). A recent modeling study estimated that 291,243–645,832 seasonal influenza–associated respiratory deaths occur worldwide annually (24). The risks of complicated disease, causing serious illness, hospitalization or death are highest in infants (age <1 year), the elderly (age ≥65 years), and persons with underlying medical conditions (22, 26). Amongst the pediatric population, influenza virus infections are associated with increased frequency of outpatient visits, hospitalization, complications, antibiotic utilization, missed school days for the patient and patient's siblings, and missed workdays for the parent(s)(27-29).

2.1.2 Clinical features

Infection due to influenza virus can be asymptomatic or range from mild, uncomplicated, and self-limited to the upper respiratory tract to a serious complicated illness dominated by a flare up of a comorbid, underlying medical condition or to severe viral or bacterial pneumonia with or without multiple organ failure (18). Typical uncomplicated influenza often begins with an abrupt onset of symptoms after an incubation period of 1 to 2 days (30). In adults, influenza typically begins with fever; respiratory symptoms such as a cough or sore throat; and systemic symptoms, such as myalgia, arthralgia, and headache (18). Gastrointestinal symptoms, notably diarrhea, have more commonly been described as manifestations of seasonal influenza A in children than in adults (22). Young children may not be able to vocalize their symptoms; they tend to have higher rates of fever, febrile seizures, less prominent respiratory findings, and more gastrointestinal complaints at the time of presentation (31). In general, influenza in otherwise healthy children is an acute, self-limited, and uncomplicated disease; however, more severe illness requiring hospitalization and, rarely, death may occur (22).

2.1.3 Complications

Complications of influenza are classified as pulmonary and non-pulmonary complications. Pulmonary complications most commonly include primary influenza viral pneumonia and secondary bacterial infection. In addition, less distinct and milder pulmonic syndromes often occur during an outbreak of influenza that may represent tracheobronchitis, localized viral pneumonia, or possibly mixed viral and bacterial pneumonia (18). Non-pulmonary complications include myositis, cardiac complications including myocarditis and pericarditis, toxic shock syndrome, Reye syndrome and central nervous system complications that include Guillain-Barré syndrome, transverse myelitis and encephalitis (18). The risk of complicated or severe influenza infection is increased in those with high-risk conditions, and such persons are priority groups for vaccination according to the Public Health Agency of Canada (PHAC) and the United States Centers for Disease Control Prevention (CDC), as summarized in table 1 below (26, 32, 33).

Table 1: Groups at high risk for serious influenza complications

- All pregnant women (especially in the second and third trimesters)
- Adults and children with the following chronic health conditions:
    i. cardiac or pulmonary disorders (includes bronchopulmonary dysplasia, cystic fibrosis, and asthma)
    ii. diabetes mellitus and other metabolic diseases
    iii. cancer, immune compromising conditions (due to underlying disease, therapy or both)
    iv. renal disease
    v. anemia or hemoglobinopathy
    vi. neurologic or neurodevelopmental conditions (includes neuromuscular, neurovascular, neurodegenerative and neurodevelopmental conditions and seizure disorders [for children, includes febrile seizures and isolated developmental delay], but excludes migraines and psychiatric conditions without neurological conditions)
    vii. morbid obesity [body mass index (BMI) of 40 and over]

viii. children 6 months to 18 years of age undergoing treatment for long periods with acetylsalicylic acid, because of the potential increase of Reye's syndrome associated with influenza

- People of any age who are residents of nursing homes and other chronic care facilities
- Adults 65 years of age and older
- All children 6–59 months of age (in particular, those aged 6-23 months)
- Indigenous peoples

2.1.4 Diagnosis of influenza: clinical and laboratory

Given the wide overlap in clinical presentation of various respiratory viral infections, it is challenging to accurately diagnose influenza in clinical practice; laboratory testing is required for definitive diagnosis (28, 34). The sensitivity and specificity of clinical diagnosis are influenced by various factors, including the case definition, host characteristics and the prevalence of influenza in the community (35, 36). Further, the clinical syndrome typically associated with influenza, termed 'influenza-like illness' (ILI), has been defined differently. In Canada, PHAC defines ILI as an "acute onset of respiratory illness with fever and cough and with one or more of the following - sore throat, arthralgia, myalgia, or prostration which is likely due to influenza" (37), whereas the U.S. CDC's definition is "fever (temperature of 100°F or greater) and a cough and/or a sore throat" (38). Other respiratory viruses that frequently co-circulate with influenza, such as respiratory syncytial virus (RSV), also often present as ILI (39). As a result, these definitions have been known to be associated with low sensitivity and specificity (40).

The laboratory diagnosis of influenza is based on the identification of the virus in a patient's respiratory secretions. The three main methods of laboratory diagnosis include molecular assays, antigen-based diagnostic tests, and virus isolation in culture. Molecular assays such as reverse-transcription polymerase chain reaction (RT-PCR) are now considered the gold standard due to their very high analytical and clinical sensitivity and specificity (34). However, even though these assays may need less than 2 hours of analytical time, turn-around time for results may be much longer. This is primarily because

specimens may need to be sent out to specialized laboratories and oftentimes testing may be performed in batches due to cost considerations. The antigen based diagnostic tests rely on the direct detection of viral antigen by immunofluorescence or rapid immunoassays. While immunofluorescence testing is fairly quick (analytical time, ~1hour), it requires substantial technical skill, and is also less sensitive (80-90%) compared to PCR. Rapid immunoassays are very attractive in that they are the fastest and simplest method and could potentially be performed at the site of care. However, the sensitivity (widely variable: 40-85%) and specificity (>95%) of such rapid immunoassays are the poorest of all techniques, especially when used outside of the pediatric population (41). Digital immunoassays use an instrument-based digital scan of the test strip to enhance antigen detection accuracy by eliminating the need for an operator to visualize and subjectively interpret test results. Further, they offer a moderately high sensitivity and high specificity (42). However, additional clinical experience is necessary to confirm their utility at the point of care. Virus isolation in culture historically used to be the gold standard method; but with the advent of RT-PCR and antigen detection techniques, this technique has fallen out of favor because of its lower sensitivity (80-90% vs. RT-PCR) and much longer turn-around times (28). Nevertheless, isolation of virus remains helpful in epidemiologic surveillance and to confirm the results of previous testing. In recent years, rapid molecular assays have been developed, which provide results in <30 minutes to inform clinical management and at the point of care (POC). Some of these utilize direct, unprocessed specimens, are easy to perform and have negligible chance of error, thus obtaining CLIA (Clinical Improvement Amendments of 1988) waivers. Examples include the Abbott ID Now (formerly Alere I influenza), Cepheid Xpert Xpress, BioFire RP EZ panel, Roche Cobas LIAT systems. The specificities of the assays for detection of influenza A and B viruses are greater than 97%. Sensitivities of various platforms range between 63.8–99.3% and 81.5-100% for influenza A and B viruses respectively for the Abbott ID Now system, to 98.6–100% and 96.3–97.9% for influenza A and B viruses respectively for the Xpert Xpress system (43). Thus, overall sensitivities are still lesser than those for traditional RT-PCR based tests. However, the few studies to date examining outcomes using molecular testing at the POC appear to show that diagnosis of influenza infection by POCT results in significantly higher rates of antiviral prescription and significantly shorter length of stay in the emergency departments (44).

Table 2: Comparison of methods used for the diagnostic testing of influenza (31, 42-44)

Test	Sensitivity	Turnaround time	Advantages	Disadvantages
Viral culture	Close to 100%	3–10 days	High sensitivity and specificity; virus available for characterization (recovery of new and divergent strains); ability to recover other viruses	Poor specimen quality might affect yield; results not available in time to inform clinical decision making; time and labor intensive; specialized laboratory facilities required
Antigen detection: direct fluorescent antibody	70–90%	1–4 hours	Rapid turnaround; can identify additional pathogens (different staining methods); can assess sample quality	Sensitivity and specificity dependent on expertise of technician; specialized equipment required; virus is not available for characterization of antigenicity
Rapid antigen detection: immunochromatogenic assay (Digital Immunoassays, DIA)	59–93%	<30 minutes	No specialized equipment or technical skill required; specialized specimen transport not required; rapid results	Least sensitive method; virus is not available for characterization of antigenicity
RT-PCR	Close to 100%	1–8 hours	High sensitivity and specificity; specimen quality	Expensive; specialized equipment and

			and handling have less impact on sensitivity; typing, subtyping, and sequencing possible; can be combined with Multiplex technology	trained personnel required; potential for cross-contamination; might miss divergent strains (dependent on primers)
CLIA waived rapid molecular assays	63-100%	15-60 mins	Rapid turn-around; can be employed at point of care, can identify additional pathogens such as RSV	Expensive; theoretical risk of environmental or amplicon contamination; often need dedicated space within crowded emergency rooms

2.1.5 Prevention of influenza

Vaccination

Vaccination is the most effective method for prevention and control of influenza infection (18). Universal vaccination of all individuals older than six months could potentially reduce influenza disease, influenza-related complications, medical resource use and influenza-related school or work absence (45, 46). Increasing the numbers of vaccinated individuals also may reduce influenza among unvaccinated contacts within the household and community (herd immunity) (47). Several inactivated influenza vaccines (IIV) and a live attenuated influenza vaccine (LAIV) are licensed for use in children. A comparison of IIV and LAIV is provided in the table below.

Table 3: Comparison of Live attenuated influenza vaccine (LAIV) and Inactivated influenza vaccine (IIV)(22)

	LAIV	IIV
Route of administration	Intranasal spray	Intramuscular injection

Type of vaccine	Live virus	Killed virus
Number of included virus strains	4 (2 influenza A, 2 influenza B)	3 (2 influenza A, 1 influenza B) or 4 (2 influenza A, 2 influenza B)
Approved age for use in Canada	Persons aged 2 to 49 years	Persons aged ≥6 months
Can be given to persons who have been given influenza antiviral medications within the previous 48 hours	No	Yes
Contraindications	Age < 2 years, individuals with immunocompromising conditions, severe asthma, children aged 2-17 years who are receiving chronic acetyl salicylic acid therapy, history of severe allergy to a previous dose of influenza vaccine (IIV or LAIV), pregnancy	Infants < 6 months of age, people who have experienced a severe (life threatening) allergy to a prior dose of a seasonal influenza vaccine or have severe allergy to a component of the IIV.

The components of the seasonal influenza vaccines vary with each season. The WHO makes recommendations on the composition of the next season's influenza vaccines based on surveillance, laboratory and clinical observations (48). This process occurs twice a year,

in February for the northern hemisphere and in September for the southern hemisphere. Annual vaccination for influenza is recommended mainly for two reasons. First, circulating influenza virus strains evolve over time and the contents of the vaccine are chosen yearly to reflect circulating strains. Second, even if circulating strains have not altered, protective antibody levels may wane, and re-vaccination leads to a booster response (18).

Vaccine effectiveness

Influenza vaccine effectiveness (VE), defined as the reduction in risk of influenza-associated disease in vaccinated compared to unvaccinated people under real-world conditions, varies from year to year. The protective effect of influenza vaccine is largely determined by the relationship between the vaccine strains and the viruses that circulate during influenza season (closeness of "fit" or "match") and the severity of circulating viruses (49-51). The 2018 Cochrane review by Demicheli *et al* (52) included 52 studies that addressed the effectiveness of the parenteral influenza vaccine in preventing infection in adults based on whether the patient was diagnosed clinically by a provider with influenza-like-illness (ILI) or empirically with laboratory confirmed illness by reverse transcriptase PCR (RT-PCR). Overall, the flu vaccine effectiveness in preventing ILI was found to be 16% (95% CI 5–25%; RR 0.84) and number needed to vaccinate (NNV) was 29. The vaccine effectiveness in laboratory confirmed illness was 59% (95% CI 53–64%; RR 0.41) with a NNV of 71. In the same population, live attenuated influenza vaccines were found to have an overall effectiveness corresponding to an NNV of 46 (52).

Amongst children, in a Cochrane review by Jefferson *et al* published in 2018 (53) that included 41 clinical trials (> 200,000 children) showed that compared with placebo or do nothing, live attenuated influenza vaccines probably reduce the risk of influenza infection in children aged 3 to 16 years from 18% to 4% (RR 0.22, 95% CI 0.11-0.41; 7718 children; moderate-certainty evidence), and they may reduce ILI by a smaller degree, from 17% to 12% (RR 0.69, 95% CI 0.60-0.80; 124,606 children; low-certainty evidence). The NNV to prevent one case of influenza was found to be 7, to prevent one child experiencing an ILI, the NNV was found to be 20. For inactivated vaccines, compared with placebo or no vaccination, inactivated vaccines were found to reduce the risk of influenza in children

aged 2 to 16 years from 30% to 11% (RR 0.36, 95% CI 0.28-0.48; 1628 children; high-certainty evidence), and they probably reduce ILI from 28% to 20% (RR 0.72, 95% CI 0.65-0.79; 19,044 children; moderate-certainty evidence). Five children would need to be vaccinated to prevent one case of influenza, and 12 children would need to be vaccinated to avoid one case of ILI (53).

In their recent review paper, Mameli *et al* (54) noted that for children older than 2 years, the trivalent IIV showed a higher VE against A/H1N1pdm09 (up to 70%) when compared to LAIV (up to 39%). However, both vaccines had similar effectiveness against influenza A/H3N2 and influenza B virus. The quadrivalent inactivated subunit-antigen vaccine showed a VE in preventing influenza illness ranging from 45 to 65% against any type of influenza, 51–71% against influenza A, and 32–34% against influenza B virus. For children aged between 6-24 months, VE ranged from 18 to 85% for trivalent IIV (54). Interim results from the Canadian 2019-20 season show that during a season characterized by early co-circulation of influenza A and B viruses, the 2019-20 influenza vaccine has provided substantial protection against medically attended influenza illness. Adjusted VE overall was 58% (95% CI 47-66%): 44% (95% CI 26-58%) for A(H1N1)pdm09, 62% (95% CI 37-77%) for A(H3N2) and 69% (95% CI 57-77%) for influenza B viruses, predominantly B/Victoria lineage (55).

2.2 Treatment of influenza

Influenza is the only respiratory virus with commercially available specific antiviral therapy. Three classes of antiviral drugs are available for the treatment of influenza, namely adamantanes, neuraminidase inhibitors and the recently approved selective inhibitors of influenza cap-dependent endonuclease.

2.2.1 Adamantanes: The adamantane class includes amantadine and rimantadine, agents that are only active against influenza A. The adamantane derivatives inhibit the matrix 2 ion channel of influenza A, but not B, viruses (18). Point mutations in the membrane spanning region of the matrix 2 protein confer resistance to both amantadine and

rimantadine while preserving viral fitness (56). All currently circulating seasonal influenza viruses are resistant to the adamantane derivatives and so the use of these agents is no longer recommended (10, 18, 31).

2.2.2 Neuraminidase inhibitors (NAIs): Oseltamivir, zanamivir, peramivir, and laninamivir are neuraminidase inhibitors, and this class of drugs is active against both influenza A and B viruses. Neuraminidase inhibitors inhibit the function of the influenza virus neuraminidase. They interfere with the release of progeny influenza virus from infected host cells, thereby preventing infection of new host cells and halting the spread of infection in the respiratory tract. Since replication of influenza virus in the respiratory tract reaches its peak between 24 and 72 hours after the onset of the illness, drugs such as the neuraminidase inhibitors that act at the stage of viral replication must be administered as early as possible (57). In Canada, oseltamivir (Tamiflu®, Hoffman-La Roche, Limited, Mississauga, ON, Canada) and zanamivir (Relenza®, GlaxoSmithKline Inc., Mississauga, ON, Canada) have been licensed for the treatment of influenza infection since 2000 (10). Since 2006, the NAIs are the only recommended first-line therapy for influenza because of widespread resistance to adamantanes (10). They are also used for pre- and post-exposure prophylaxis.

Oseltamivir

Amongst drugs used to treat influenza, oseltamivir is most often used. The US FDA first approved its use for the treatment of influenza in adults in 1999. Since then, it has become the mainstay of the treatment of influenza in both children and adults. While it was initially approved for the treatment of adults and thereafter children older than 1 year, during the 2009 H1N1 pandemic, Emergency Use Authorization (EUA) was granted for its use in the treatment of influenza in infants less than 1 year of age as well; subsequently it has been used in the infant age group as well. The following table summarizes key milestones in the development and approval of oseltamivir use.

Table 4: Key milestones in the development and approval of oseltamivir use

Year	Organization	Oseltamivir recommendation or approval
1999	FDA	Oseltamivir approved for treatment of influenza in adults
2000	FDA	Oseltamivir approved for the treatment of children >1 year of age with <48 hours of symptoms.
2000	PMDA	Oseltamivir was approved for the treatment of influenza in adults and adolescents in Japan
2000	Health Canada	Oseltamivir approved for the treatment of adults and children >1 year of age with <48 hours of symptoms.
2002	EMA	EMA approved oseltamivir for treatment of influenza in patients 1-year and older
2006	AMMI Canada	Oseltamivir approved for the treatment of influenza A and B virus infection in individuals one year of age or older
2009	FDA and Health Canada	Emergency use authorization during H1N1 pandemic approves oseltamivir use for patients <1 year of age. Oseltamivir use also approved in children with >2 days of symptoms.
2012	FDA	Treatment approved for children >2 weeks of age with symptoms for <48 hours.

Legend: AAP – American Academy of Pediatrics; AMMI - Association of Medical Microbiology and Infectious Disease (Canada); EMA – European Medicines Agency; FDA – Food and Drug Administration (USA); PMDA – Pharmaceutical and Medical Devices Agency (Japan).

In Canada, Oseltamivir (Tamiflu®) is authorized by Health Canada for the treatment of uncomplicated influenza A and B in patients aged 1 year or older within 48 hours of symptom onset (10). However, oseltamivir is approved by the FDA for children as young as 2 weeks of age (Table 4). Given preliminary pharmacokinetic data and limited safety data from the FDA, the AAP believes that oseltamivir can be used to treat influenza in both term and preterm infants from birth because benefits of therapy are likely to outweigh possible risks of treatment (22). The Health Canada stance is more conservative, and it endorses oseltamivir use in infants less than 1 year of age only on a case-by-case basis (10). This is primarily driven by concerns on multiple dose toxicity studies in animal models, that resulted in higher rates of mortality (58).

Treatment with oseltamivir should ideally begin within 48 hours of illness onset; however, initiation after 48 hours is recommended for patients with severe, complicated, or progressive illness; hospitalized patients; or those at increased risk for complications (59). The usual treatment does for adults is 75mg twice a day for 5 days; and a longer duration can be considered in severely ill or immunocompromised patients. Pediatric dosing is weight based for children <40 kg.

Oseltamivir is available as a capsule or powder for liquid suspension with good oral bioavailability. It is readily absorbed from the gastrointestinal tract, is converted by hepatic esterases to the active form of the compound (oseltamivir carboxylate) and is widely distributed in the body. The half-life of the drug is 6 to 10 hours. It is excreted primarily through the kidneys; thus, dosing must be modified in patients with renal insufficiency. No dose adjustment is required for patients with hepatic insufficiency. Oseltamivir achieves high plasma levels and thus can act outside the respiratory tract (57).

Commonest adverse effects experienced after the use of oseltamivir include nausea, vomiting, and headache. Occasional post marketing reports of serious skin reactions and sporadic, transient neuropsychiatric events have been noted (59). Resistance to oseltamivir is rare, but has been described, mainly through the H275Y mutation (a histidine to tyrosine substitution at amino acid 275 of the influenza A N1 neuraminidase) in H1N1 viruses (from 2007 to 2009, but rarely among 2009 pandemic and post-pandemic seasonal H1N1 influenza A viruses) and the I223 and the S247N mutations which offer low levels of resistance in H1N1 viruses (60, 61). In H3N2 viruses, the most frequent mutations conferring resistance to oseltamivir are E119V and R292K (62). The National Microbiology Laboratory (NML), which tests influenza viruses received from Canadian laboratories for antiviral resistance, reported that during the 2019-2020 influenza season, 733 influenza viruses [164 A(H3N2), 283 A(H1N1) and 286 B] were tested for resistance to oseltamivir, and all influenza A(H3N2) and B viruses were sensitive to oseltamivir. Among the A(H1N1) viruses tested, 282 (99.6%) were sensitive to oseltamivir; one virus was resistant to oseltamivir with the H275Y mutation in the neuraminidase gene (63).

Zanamivir

Zanamivir (Relenza®) is authorized by Health Canada for the treatment of uncomplicated influenza A and B in patients aged 7 years or older who have been symptomatic for no more than 2 days (10). It is also authorized for the prevention of influenza A and B in patients aged 7 years or older (10). Zanamivir is not bioavailable orally and is marketed as a dry powder for inhalation. It is delivered directly to the respiratory tract through an inhaler that holds small pouches of the drug. Zanamivir is highly concentrated in the respiratory tract; 10 to 20 percent of the active compound reaches the lungs, and the rest is deposited in the oropharynx. The concentration of the drug in the respiratory tract has been estimated to be more than 1000 times as high as the 50 percent inhibitory concentration (IC50) for neuraminidase; in addition, the inhibitory effect starts within 10 seconds — two favorable features in terms of reducing the likelihood of emergence of drug-resistant variant viruses. Zanamivir is excreted unchanged in the urine, and no dose reductions are recommended for any patient population. The recommended dose is 10 mg per inhaled dose twice daily for 5 days. However, zanamivir is not recommended for the treatment of hospitalized patients because of limited data in patients with severe influenza, and in patients with severe underlying airway disease because of the risk of serious adverse events, including bronchospasm, decline in respiratory function, and respiratory arrest (10). The threshold for resistance is much higher than with oseltamivir, and very little zanamivir resistance has been observed to date. The majority of cases of oseltamivir resistance have not resulted in cross-resistance to zanamivir (59). All the 733 influenza viruses [164 A(H3N2), 283 A(H1N1) and 286 B] tested for resistance at the National Microbiology Laboratory during the 2019-2020 influenza season were found to be susceptible to zanamivir (63).

Other NAIs

Peramivir is an intravenously administered neuraminidase inhibitor that is licensed in the United States for treatment of influenza in patients ≥2 years who have been ill for ≤2 days, however it is not yet licensed in Canada (10). Laninamivir is a long-acting inhaled neuraminidase inhibitor. Its use remains investigational in the United States and many other countries, but it is available for the treatment and prevention of influenza in Japan. In

Canada, peramivir and laninamivir may be accessed through Health Canada's Special Access Program (10).

2.2.3 Selective inhibitors of influenza cap-dependent endonuclease

Baloxavir is a cap-dependent endonuclease inhibitor that interferes with viral RNA transcription and blocks virus replication (64). In October 2018, this drug was approved by the US FDA for treatment of acute uncomplicated influenza, and later the drug was approved by Health Canada for use in the treatment of uncomplicated influenza in people aged 12 years and more (65). It has activity against both influenza A and B viruses (64). In a phase 3, randomized, double-blind, controlled trial involving otherwise healthy outpatients with acute uncomplicated influenza, it was found that baloxavir reduced the duration of flu-like symptoms by about one day, from an average of 80.2 hours to 53.7 hours (64). Further, patients who started baloxavir within 24 hours of symptom onset had a greater benefit from the drug compared to those who started later. Currently, this drug is licensed in Japan for use in children ≥12 years and children <12 years who weigh at least 10 kg and in the United States for the treatment of influenza in people ≥12 years of age (including high-risk individuals). Baloxavir needs to be initiated within 48 hours of influenza symptom onset, and administered as a single dose (64). Baloxavir is currently not recommended for the treatment of hospitalized patients with influenza, due to limited data in patients with severe influenza. Results from a phase 3, randomized, double-blind placebo-controlled clinical trial of baloxavir treatment of influenza in hospitalized patients are awaited (66).

2.3 Benefits of antiviral treatment

There is a growing body of evidence that NAI use (mostly oseltamivir) for the treatment of influenza is associated with improved clinical outcomes. In ambulant, outpatient settings, randomized controlled trials have shown a reduction in the duration of illness but have not reliably shown a reduction in the rate of complications or hospitalization. However, several observational studies conducted after the 2009 H1N1 pandemic have demonstrated lower rates of hospitalization, reductions in the duration of illness,

complications associated with influenza, and overall health care costs attributable to influenza when early treatment is initiated for adult patients treated with NAIs. Similarly, observational studies including a very large and well-controlled meta-analysis from the H1N1 2009 pandemic suggests a reduction in mortality with NAI use in hospitalized adults (67). While data amongst pediatric populations is scarcer, similar benefits of treatment have been demonstrated, in both ambulant and hospitalized patients. These data are presented in the sections below.

2.3.1 Impact of NAI use in adults

2.3.1.1 Non-hospitalized/ "healthy" adults

Duration of symptoms

Large, randomized placebo-controlled trials of healthy adults have shown that NAI treatment within 48 hours of influenza illness onset shortens illness duration by 1 to 2 days (68-71). Most of these trials were conducted in the late 1990s - early 2000s and showed that in addition to reductions in illness duration, there was also less viral shedding, improved health, and quicker return to usual activity. Several studies conducted thereafter also showed similar findings, with reduction in the duration of illness ranging from 0.5-4 days (57). RCTs conducted in the post pandemic era have also shown similar benefits. In a recent randomized, open-label trial that involved 3266 patients from 209 European primary care practices during three consecutive influenza seasons (2016-18), it was found that oseltamivir significantly shortened mean duration of flu-like symptoms by 1 day (5.7 days vs. 6.7 days, $p<0.05$). In the no-oseltamivir group, mean duration of symptoms was longer in patients who were 65 or older, had more severe disease, had relevant comorbidities, or had been ill for longer than 48 hours at presentation (72).

Incidence of complications

Several studies have shown that the treatment of healthy adults with NAIs reduced the development of secondary bacterial complications, including pneumonia, bronchitis, and sinusitis, (68, 70) and the use of antibiotics (68, 70, 71). However, data on the effectiveness

of neuraminidase inhibitors in the prevention of influenza-related complications are variable. A 2014 Cochrane review (9), which examined data from 46 trials (20 oseltamivir and 26 zanamivir studies) found no decrease in the risk of hospital admissions (risk difference 0.15%; 95% CI 0.78-0.91) or serious complications with oseltamivir treatment (risk difference 0.07%; 95% CI 0.78-0.44). In that review, data analysis was done in an intention-to-treat (ITT) group without accounting for the results of influenza testing. To overcome this shortcoming, a subsequent meta-analysis, by Dobson and colleagues, for the Multiparty Group for Advice on Science (MUGAS) study group (73) grouped individuals into 2 groups - an ITT group and an ITT infected (ITTi) group, in which influenza infection was confirmed by testing. The study estimated a risk reduction of 44% (RR 0.56; 95% CI 0.42–0.75; p=0.0001) in lower respiratory tract complications and a 63% risk reduction (RR 0.37 [0.17–0.81]; p=0.013) in hospital stay for the ITTi group that received oseltamivir (73). The Cochrane review found that oseltamivir made no significant difference to hospitalization rate compared to placebo (RR 0.92 [95% CI 0.57 to 1.50]) (9). In the MUGAS review, the treatment of all patients with ILI (the intention to treat [ITT] population) also showed no statistically significant reduction in the subsequent all-cause hospitalization of patients treated for non-severe influenza in the community (RR 0.61 [95% CI 0.36-1.03; p=0.066]): 25/2402 randomized to oseltamivir compared to 35/1926 randomized to placebo), but in the sub-group with confirmed influenza infection there was a 63% risk reduction (RR 0.37 [95% CI 0.17 to 0.81], 9/1591 patients randomized to oseltamivir compared to 22/1302 patients randomized to placebo) (73).

Need for hospitalization

Preadmission NAI treatment has been found to reduce the odds of hospitalization. A meta-analysis of observational studies from the H1N1 2009 pandemic using individual participant data from 3376 patients, evaluated the effect of NAI treatment on hospital admission in patients with influenza (91% of which was laboratory confirmed) in the community and outpatient settings (74). After adjustment for preadmission antibiotics and NAI treatment propensity, preadmission NAI treatment was associated with decreased odds of hospital admission compared to no NAI treatment (aOR, 0.24; 95% CI 0.20-0.30). The meta-analysis further showed that earlier treatment (<48 h of symptoms duration) with

NAIs was more beneficial than later treatment. This finding was also confirmed in an RCT study design. Fry and colleagues enrolled 1190 participants in a double-blind, randomized, controlled trial in Kamalapur, Bangladesh (75). They found that in patients with mild uncomplicated influenza infection who did not have risk factors for severe or complicated illness, antiviral therapy initiated within 48 hours of symptom onset reduced symptom duration compared with placebo, but therapy initiated after 48 hours of symptoms did not (75).

2.3.1.2 Hospitalized adults

In contrast to the evidence base for NAI efficacy in the community setting (availability of RCT data), data in hospitalized patients are limited to observational studies, which need to be interpreted cautiously given the inherently higher risk of bias by virtue of an observational study design.

Mortality

Most pre-pandemic studies suggested that NAI treatment in hospitalized adults was associated with a reduction in mortality. Similar conclusions were seen in studies conducted in the post-pandemic era as well; in a study that included adult patients hospitalized with severe laboratory-confirmed influenza in Spain spanning 6 influenza seasons (2010–2016), it was shown that when started early after the onset of symptoms (≤48 hours or ≤5 days), NAI treatment was associated with a reduction in influenza-associated deaths (aOR, 0.37; 95% CI, 0.22 to 0.63, and aOR, 0.50; 95% CI, 0.32 to 0.79, respectively for the two timeframes) (76). McGeer *et al* undertook a prospective cohort study to assess the impact of antiviral therapy on outcomes of patients hospitalized with influenza in southern Ontario between January 2005 and May 2006 and found that treatment with antiviral drugs active against influenza was associated with a significant reduction in mortality (OR 0.21; 95% CI 0.06–0.80; p=0.03) (13). In further exploratory analyses, considering only adults aged ≥65 years, the OR for mortality associated with oseltamivir therapy was 0.24 (95% CI, 0.06–0.92); considering only influenza A virus infections, the OR was 0.13 (95% CI, 0.03–0.63); considering only oseltamivir therapy

initiated >48 hours after symptom onset, the OR was 0.24 (95% CI, 0.05–1.14); excluding deaths that occurred within 48 hours after admission to the emergency department, the OR was 0.41 (95% CI, 0.10–1.7); including only deaths assessed by all reviewers as due to influenza, the OR was 0.24 (95% CI, 0.06–0.85); and considering deaths that occurred within 30 days after symptom onset, the OR was 0.41 (95% CI, 0.14–1.2) (13). Hsu and colleagues undertook a systematic review and meta-analysis of data including 74 observational studies of hospitalized patients with seasonal influenza and concluded that oseltamivir may be associated with reduced mortality compared with no antiviral treatment in high-risk populations (OR 0.23 [95% CI, 0.13 -0.43]). They did caution that the overall quality of the evidence, however, was low because of the risk of confounding, selection and publication bias (77). Other observational data from the 2009 H1N1 pandemic reported by the Post-pandemic Review of anti- Influenza Drug Effectiveness (PRIDE) consortium showed that treatment with NAIs at any time was associated with a reduction in any cause mortality of hospitalized patients (aOR for death 0.81 [95% CI 0.70 to 0.93]) (78). In the same study, the authors also described significant reductions for early treatment (≤48 hours after symptom onset) versus late (OR 0.38 [95% CI 0.27–0.53]) and for early treatment versus none (OR 0.35 [95% CI 0.18–0.71]). NAI treatment (at any time) versus none was associated with an elevated risk of severe outcome (OR 1.76 [95% CI 1.22–2.54]), but early versus late treatment reduced the likelihood (OR 0.41 [95% CI 0.30–0.56]). The authors attributed the lack of an observed mortality benefit with NAI treatment vs. none to confounding by indication - whereby severely unwell patients were more likely to receive NAI treatment than the rest. They also noted a high degree of heterogeneity among included studies and a likely publication bias. The same authors performed a subsequent meta-analysis using individual participant data from nearly 30,000 patients (including adults and children) hospitalized with pandemic H1N1 2009 influenza (14). Propensity scoring was used to adjust for confounding variables. In this rigorous analysis, a significant reduction in mortality was observed with NAI treatment at any time vs. no NAI treatment (aOR 0.81; 95% CI 0.70-0.93; p=0.0024). Compared with later treatment, early treatment (within 2 days of symptom onset) was associated with a reduction in mortality risk (aOR 0.48; 95% CI 0.41-0.56; p<0.0001). Early treatment versus no treatment was also associated with a reduction in mortality (aOR 0.50; 95% CI 0.37-0.67; p<0.0001). The

mortality benefit of NAI treatment was not seen with commencement after 48 hours of symptoms duration in the main cohort but was maintained beyond 48 hours of symptoms duration in patients admitted to critical care units, suggesting continued benefits even with late administration in more severely unwell patients.

Need for ICU admission

With regards to the need for intensive care, some observational studies have shown that NAI use was associated with statistically significant reductions in the need for ICU stay amongst hospitalized adults (79, 80). Other observational studies have also presented statistically significant comparisons in favor of earlier NAI treatment for the outcome of ICU admission (81-83). In a prospective national cohort study from the UK involving pregnant women, treatment within 2 days of symptom onset was associated with an 84% reduction in the odds of admission to an intensive therapy unit (OR 0.16, 95% CI 0.08-0.34) (82). In a case–control study carried out to estimate risk factors associated with hospitalizations and severe outcomes (ICU admission or death) among patients with laboratory-confirmed 2009 pandemic H1N1 infection during the first wave of activity in the province of Quebec, it was found that antiviral use prior to hospitalization was associated with reduced odds (OR 0.3, 95% CI 0.1-0.8) of ICU admission or death (12).

Length of stay

Amongst adult patients, a literature search yielded four studies that have addressed the question of whether antiviral treatment was associated with a decrease in the length of hospital stay. A study of 356 adult patients hospitalized with laboratory-confirmed seasonal influenza in Hong Kong showed that early oseltamivir treatment was associated with a reduced LoS in both unadjusted and multivariable analyses compared with no or later treatment, with the median LoS decreasing from 6 to 4 days (84). In contrast, a Canadian study of adult patients with seasonal influenza found that oseltamivir treatment was not associated with the LoS among surviving patients (13). In Europe, a study in 13 Spanish hospitals involving 538 patients with laboratory-confirmed A(H1N1)pdm09 infection noted that the LoS increased by 7% (OR 1.07), after adjustment for confounders, if NAI treatment was initiated <48 hours after symptom onset; however, this was of borderline

statistical significance (85). A recent study from the United States analyzed data on 201 adult patients with laboratory-confirmed seasonal influenza at two Michigan hospitals during the 2014-15 and 2015-16 influenza seasons (86). Although NAI treatment was not associated with the LoS overall, it was associated with a reduced LoS among vaccinated individuals (hazard ratio of discharge, 1.6; 95% CI, 1.0–2.4; p = 0.04) (86). In an important study published in 2020, Venkatesan et al conducted a one-stage individual participant data (IPD) meta-analysis exploring the association between NAI treatment and LoS in patients hospitalized with 2009 influenza A(H1N1) virus (A[H1N1]pdm09) infection (15). They analyzed data on 18309 patients from 70 clinical centers in 36 countries and excluded patients with a length of stay less than 1 day and individuals who died while hospitalized. After adjustment, NAI treatment initiated at hospitalization was associated with a 19% reduction in the LoS among patients with clinically suspected or laboratory-confirmed influenza A(H1N1)pdm09 infection (IRR 0.81; 95% CI 0.78–0.85), with a median decrease of 1.19 days, compared with later or no initiation of NAI treatment. Additionally, NAI treatment on the day of admission was associated with an 8% reduction in the length of stay among patients who were not admitted to the ICU (15).

2.3.2 Impact of NAI use in children

While certain aspects of influenza treatment in adults can be generalized to children, there are several areas in which specific pediatric considerations are essential. However, fewer data are available to guide the management of care for children, most particularly young infants, than are available for adults.

2.3.2.1 Non-hospitalized/ "healthy" children

Duration of symptoms

Early studies of NAI antiviral treatment were conducted in healthy children with influenza in the outpatient setting to acquire approval by regulatory agencies. In a multicenter, double blind, placebo-controlled, industry-sponsored (FDA reviewed) study conducted almost two decades ago, 452 healthy children with laboratory-confirmed influenza infection who

presented within 48 hours of symptom onset, were randomized to receive either oral oseltamivir or placebo for 5 days (87). It was found that children treated with oseltamivir had a duration of illness that was 36 hours (26%) shorter than children who received placebo, which was statistically significant ($p<0.0001$) (87). Another early study that employed a similar design included 98 healthy children aged 1–3 years with laboratory confirmed influenza infection, and it was found that the duration of illness in children who received oseltamivir was 1.4 days (34 hours) shorter than children who received placebo (88). Subsequent trials also showed similar findings. In children with confirmed influenza, one trial with zanamivir and another with oseltamivir showed significant reductions in the median time to resolution of influenza symptoms from 5.25 to 4.0 days (difference 1.25 days, 95% CI 0.5 - 2.0 days, $p<0.001$) and from 4.2 to 2.6 days (difference 1.5 days, 0.25 - 2.5 days, $p<0.001$), respectively (89). The Cochrane review on this topic included only one relatively small trial of oseltamivir use in previously healthy children. This showed a benefit in the time to first alleviation of symptoms of 29.4 hours (95% CI, 47.0 - 11.8 hours; n=669), although no benefit compared to a placebo was seen in children with asthma in another relatively small trial (n=660), and no difference in hospitalizations was observed. No statistically significant effect of zanamivir was seen in the same review (n = 723; time to first alleviation of symptoms reduced by 1.08 days; 95% CI: a reduction of 2.32 days to an increase of 0.15 days) (9). The recent 2018 individual patient data (IPD) meta-analysis of published and unpublished pediatric oseltamivir treatment studies in children by Malosh *et al* included 1598 children less than 18 years with uncomplicated influenza also reported similar benefits of early oseltamivir treatment (7). This meta-analysis included five RCTs of early oseltamivir treatment (initiated within 2 days of illness onset) of ILI and uncomplicated influenza in pediatric outpatients. Three included RCTs enrolled otherwise healthy children and those with chronic conditions, and two RCTs were conducted among children with asthma. This meta-analysis reported that early treatment was associated with reduced duration of illness by approximately 17.6 hours. In children without asthma the effect was more pronounced, with a reduction in illness duration of 29.9 hours. Among the ITTi population, there was a 34% reduction in risk of otitis media with oseltamivir treatment versus placebo (7).

Incidence of complications

In the FDA reviewed, industry sponsored, multicenter, double-blind placebo-controlled trial described above, it was found that oseltamivir treatment was associated with a 44% reduction in the risk of developing otitis media, from 21% in children who received placebo to 12% in children treated with oseltamivir. Physician-prescribed antibiotic usage was 24% lower in children receiving oseltamivir (p=0.03) (87). Many of these treatment-related benefits were replicated in another prospective, double-blind, industry-sponsored, placebo-controlled study of 98 healthy children aged 1–3 years with laboratory confirmed influenza infection (88). Children who were treated with oseltamivir within 12 hours of symptom onset were found to be 85% less likely to develop otitis media. Parental and children's absence from work and daycare, respectively, was reduced by 2 days in the oseltamivir-treated group (88). The recent 2018 individual patient data (IPD) meta-analysis of published and unpublished pediatric oseltamivir treatment studies in children by Malosh *et al* found that there were fewer cases of lower respiratory tract complications >48 hours after starting oseltamivir treatment versus placebo in the ITTi population, however, this difference was not statistically significant (7).

Need for hospitalization

A recent global meta-analysis of observational data for 1747 pediatric outpatients aged <16 years with comorbidities who were considered to be at high risk for influenza complications and had laboratory-confirmed influenza A(H1N1)pdm09 virus infection reported that NAI treatment (mostly oseltamivir) was associated with reduced odds of hospital admission versus no treatment (aOR 0.25, 95% CI, 0.18–0.34, $p < 0.001$) (74). The meta-analysis found that the clinical benefit was greatest (except for children with asthma) when oseltamivir treatment was started within 24 hours after illness onset, highlighting the importance of starting treatment soon after illness onset. However, despite such findings, there remain challenges to implementing such timely administration of oseltamivir treatment to children with influenza. Recent studies in the United States reported that persons who experience acute respiratory illness and are at high risk for influenza complications, including young children, often do not present to medical care within 2 days of illness onset (90, 91). Other studies have shown treatment benefit even

after this window. In a post hoc analysis of participants that were enrolled 3 days after illness onset in an RCT conducted among participants (median age 5 years) in urban Bangladesh, the duration of major signs or symptoms in those treated with oseltamivir was significantly shorter by 1 day compared with placebo (75). For participants enrolled 3 days after illness onset, the proportion of patients with influenza virus isolated on days 2 and 4 after illness onset was significantly lower in those treated with oseltamivir compared with placebo (75). Such findings suggest that there is still benefit of initiating oseltamivir treatment for influenza patients 3 days or perhaps more after illness onset, especially if they have underlying risk factors for severe disease.

2.3.2.2 Hospitalized children

There are fewer pediatric studies than adult studies exploring the effectiveness of antiviral among hospitalized patients. Data from various observational studies, summarized in table 5 below, have shown that antiviral treatment is associated with improved outcomes, including shorter hospital length of stay, decreased mortality, and lower risk of ICU admission and mechanical ventilation. All available evidence comes from observational studies; the only randomized placebo-controlled trial of oseltamivir treatment in hospitalized children with influenza had to be terminated early with only 21% of the targeted population enrolled due to lower than anticipated participant accrual (92).

Mortality

Several observational studies amongst children hospitalized with influenza have suggested mortality benefit associated with antiviral use, especially when started early during the course of hospitalization. In a study of 437 critically ill pediatric patients admitted to a pediatric ICU in Argentina for acute lower respiratory tract infections, 147 were diagnosed with influenza A H1N1 infection. Of these, 84% required mechanical ventilation, and 39% died within 28 days of admission. Oseltamivir administration within 24 hours of hospital administration was significantly associated with decreased odds of mortality (OR 0.2, 95% CI 0.07-0.54) (93). A 2013 study based on surveillance data from California included 784 influenza cases aged<18 years hospitalized in ICUs, and showed that in a multivariate

model that included receipt of mechanical ventilation and other factors associated with disease severity, the estimated risk of death was reduced in NAI-treated cases (aOR 0.36, 95% CI 0.16-0.83) (94). However, in their seminal 2014 meta-analysis of individual participant data, Muthuri *et al* found that after stratification for children, after treatment with NAIs, mortality benefits were not statistically significant: children under age 16: aOR 0.82 (95% CI 0.58-1.17; p=0.28); children in critical care: aOR 0.70 (95% CI 0.42-1.16; p=0.17) (14).

Need for ICU admission

In a study of 345 hospitalized children with 2009 influenza A (H1N1) from the United States, it was found that those who received antiviral treatment within 48 hours of symptom onset were at lower risk of ICU admission and/or death (95). A retrospective cohort study involving 127 children admitted with pandemic H1N1 2009 infection in Barcelona, Spain found that patients who received oseltamivir > 72 hours after admission had higher odds of ICU admission [aOR 3.7 (1.1–11.7)] (96). A large retrospective cohort study that included close to 20,000 children hospitalized with influenza from 43 pediatric hospitals in the United States found that early hospital treatment with influenza antiviral medications was associated with decreased initiation of mechanical ventilation on hospital day ≥3 in the seasonal influenza (OR 0.66; 95% CI, 0.45–0.97) and pH1N1 (OR 0.23; 95% CI, 0.16–0.34) periods (97).

Length of stay

A retrospective cohort study of 104 children hospitalized with influenza at a large Canadian pediatric tertiary care center between January and July 2009 found that LoS was significantly shortened to 3.7 days for individuals who had pandemic (H1N1) 2009 influenza and who received empiric oseltamivir on admission to the hospital, compared with 12.0 days for patients for whom treatment was delayed (p = 0.02) (98). In a 2011 retrospective cohort study of children with influenza infection admitted to a pediatric intensive care unit during 6 consecutive winter seasons (2001-2007), multivariable analysis of 252 oseltamivir-treated patients and 252 propensity score-matched untreated patients demonstrated that patients treated with oseltamivir experienced an 18% reduction in total

hospital days (time ratio: 0.82, p = 0.02), whereas intensive care unit stay, in-hospital mortality, and readmission rates did not differ (99). More lately, an important 2018 multicenter retrospective cohort study from the United States that included children with tracheostomies who were hospitalized with influenza, after matching 772 unique admissions by propensity score, it was found that LoS was shorter for the cohort receiving early anti-influenza medications (6.4 vs 7.5 days; p = 0.01) without increase in revisit rate (27.5% vs 24.1%; p = 0.28) (100). In the recent Venkatesan *et al* individual participant data (IPD) meta-analysis exploring the association between NAI treatment and LoS in patients hospitalized with 2009 influenza A(H1N1) virus (A[H1N1]pdm09) infection (15), early NAI treatment was associated with a 7% overall reduction in the LoS (aIRR, 0.93 [95% CI, 0.87–0.99]; median decrease, 0.40 days [IQR, 0.36–0.45 days]), compared with no NAI treatment; however, this association was not statistically significant in children (15).

Table 5: Summary of key studies describing the impact of antiviral use amongst hospitalized children

Reference	Study design	Population/Setting	Key findings
Louie, 2010(95)	Retrospective cohort study	345 children (age <18 years) hospitalized with laboratory confirmed 2009 influenza A/ H1N1 in California, USA between April 23 to August 11, 2009	Receipt of antiviral treatment within 48 hours of symptom onset associated with lower risk of ICU admission and/or death (27% vs 21%, p=0.01).
Farias, 2010(93)	Prospective cohort study	437 patients with acute lower respiratory infection admitted in 17 PICUs in Argentina between 15 June and 31 July 2009, of which 147 had 2009 influenza A/ H1N1	Oseltamivir administration within 24 hours of hospital administration was significantly associated with decreased odds of mortality (OR 0.2, 95% CI 0.07-0.54).
Fanella, 2011(98)	Retrospective cohort study	104 children hospitalized with influenza at a large Canadian pediatric	LoS was significantly shortened to 3.7 days for individuals who had pandemic (H1N1) 2009 influenza

		tertiary care center between January and July 2009.	and who received empiric oseltamivir on admission to the hospital, compared with 12.0 days for patients for whom treatment was delayed (*p* = 0.02).
Coffin, 2011(99)	Retrospective cohort study	1257 children with influenza infection admitted to a pediatric ICU in the United States during 6 consecutive winter seasons (2001–2007)	Patients treated with oseltamivir experienced an 18% reduction in total hospital days (time ratio: 0.82, p = 0.02); no change in ICU stay, in-hospital mortality, readmission rates.
Launes, 2011(96)	Retrospective cohort study	127 children admitted with pandemic H1N1 2009 infection in Barcelona, Spain in 2009	Patients who received oseltamivir > 72 hours after admission had higher odds of ICU admission [aOR 3.7 (1.1–11.7)].
Eriksson, 2012(97)	Retrospective cohort study	10,173 children hospitalized with seasonal influenza and 9,837 with presumed pH1N1 across 43 US hospitals between July 2006 – December 2009	Early hospital treatment with influenza antiviral medications was associated with decreased initiation of mechanical ventilation on hospital day ≥3 in the seasonal influenza (OR 0.66; 95% CI, 0.45–0.97) and pH1N1 (OR 0.23; 95% CI, 0.16–0.34) periods.
Louie, 2013(94)	Retrospective cohort study	784 children (age <18 years) hospitalized in ICUs in California, USA between April 2009 and September 2012	Estimated risk of death was reduced in NAI-treated cases (OR 0.36, 95% confidence interval: 0.16–0.83). Treatment within 48 hours of illness onset was significantly associated with survival (p = 0.04).
Bueno, 2013(101)	Retrospective cohort study	287 children hospitalized with influenza in Madrid, Spain between September 2010 and June 2012	No significant differences between treated and untreated patients in days of fever after admission (1.7 ± 2; 2.1 ± 2.9, p > 0.05), length of stay (5.2 ± 3.6; 5.5 ± 3.4, p >0.05), days of hypoxia (1.6 ± 2.3; 2.1 ± 2.9, p > 0.05), diagnosis of bacterial pneumonia (10%; 17%, p > 0.05), intensive care admission (6.5%;

			1.5%, p > 0.05) or antibiotic prescription (44%; 51%, p > 0.05).
Muthuri, 2014(14)	Meta-analysis of individual participant data	29,234 patients from 78 studies of patients hospitalized between Jan 2009, and March 2011 worldwide. This sample included 9218 children (age < 16 years)	After stratification for children, mortality benefits of NAI treatment were not statistically significant: children under 16: aOR 0.82 (95% CI 0.58-1.17; p=0.28); for children in critical care: aOR 0.70 (95% CI 0.42-1.16; p=0.17).
Brogan, 2014(102)	Retrospective cohort study	8899 children (≤ 18 years) hospitalized with influenza between May 2 and December 11, 2009 across 42 freestanding children's hospitals in the United States	Patients with complicated index hospitalizations who received oseltamivir had lower all-cause 30-day readmissions [aOR 0.70 (0.53–0.91)] and influenza-related complications [aOR 0.54 (0.37–0.78)].
Miyakawa, 2018(100)	Retrospective cohort study	889 children (age < 19 years) with tracheostomies hospitalized for influenza between October 2007 and September 2015.	LoS shorter for the cohort receiving early (on day 0 or 1 of hospitalization) anti-influenza medications (6.4 vs 7.5 days; P = 0.01) without an increase in revisit rate (27.5% vs 24.1%; p = 0.28).
Venkatesan, 2020(15)	Meta-analysis of individual participant data	18309 patients from 70 clinical centers hospitalized with 2009 influenza A(H1N1) virus (A[H1N1]pdm09) infection.	Early NAI treatment was associated with a 7% overall reduction in the LoS (aIRR, 0.93 [95% CI, 0.87–0.99]; median decrease, 0.40 days [IQR, 0.36–0.45 days]), compared with no NAI treatment; however, this association was not statistically significant in children.

2.4 NAI prescribing: Practices amongst hospitalized children

Although antiviral treatment of children hospitalized with influenza infection has been consistently recommended by the American Academy of Pediatrics (22), Infectious Disease Society of America (11) and AMMI-Canada (10) for several years, a significant number of hospitalized children with influenza still do not receive antiviral treatment.

In a retrospective cohort study that included around 36,000 children hospitalized with influenza during the 2007–2015 influenza seasons in the United States, only 69% received treatment with an antiviral agent. Further, in children deemed to be high risk, only 70% received antiviral treatment. (103). This study was however limited by its use of ICD-9-CM codes to identify cases of influenza (limited sensitivity could have resulted in under detection) and children with high-risk conditions (which may have not been validated). Further, antiviral use prior to hospital admission was not captured. Another retrospective observational cohort of hospitalized Canadian children with laboratory confirmed influenza in southern Ontario hospitals for the 2004-05 to 2013-14 seasons found that percentage treated increased from 29% pre-pandemic to 74% during the pandemic, decreased to 55% in 2011-12 and then increased to 65% in 2013-14 (104). Using surveillance data from the Centers for Disease Control and Prevention (CDC) Influenza Surveillance Network (FluSurv-NET), Garg and colleagues showed that during the 2010–2011 influenza season, antiviral treatment of children and adults hospitalized with laboratory-confirmed influenza declined significantly compared with treatment during the 2009 pandemic (children, 56% vs 77%; adults, 77% vs 82%; both $p < 0.01$) (105). Data from Europe have also shown similarly low prescription rates. A prospective cohort study amongst children hospitalized with the pandemic A/H1N1v influenza 2009 from Belgium which included 215 children enrolled during the pandemic showed that only 24% of the children received oseltamivir (106). Another study from Spain showed that only 32% of 287 children hospitalized with influenza in 10 hospitals in Madrid between September 2010 and June 2012 received antivirals (101).

Amongst critically ill patients too, prescribing rates historically have not been optimal. Louie *et al* described a cohort of 784 influenza cases aged <18 years hospitalized in ICUs in California between 2009-2012, and found that 90% (532/591) of cases during the 2009 H1N1 pandemic (April 3, 2009-August 31, 2010) received NAI treatment compared with 63% (121/193) of cases in the post-pandemic period (September 1, 2010-September 30, 2012; $p < 0.0001$) (94).

The reasons for lower antiviral prescribing rates amongst hospitalized children are thought to be several. For many children with an ILI, neuraminidase inhibitor treatment is often only considered after a specific diagnosis of influenza is made, either by clinical judgment or after laboratory confirmation. In earlier years, the turnaround times of diagnostic tests were longer than what is seen today, and prescribing rates were lower. Further, the symptoms of influenza infection overlap significantly with other respiratory viruses; healthcare workers who rely exclusively on clinical judgment may unfortunately fail to suspect or diagnose influenza, and subsequently prescribe antivirals. This is postulated to contribute to lower utilization rates amongst hospitalized children. Moreover, guideline recommendations for treatment of patients hospitalized with influenza are based only on observational data. Randomized clinical trials of NAIs among outpatients have shown modest benefits, but with accompanying risk of adverse events, primarily gastro-intestinal side-effects. The perception of a questionable risk-benefit profile has also been postulated to lead to hesitancy in prescribing antivirals among some clinicians (103).

Recent data, however, have been more encouraging with regards to better antiviral utilization proportions. Using population-based surveillance data collected as a part of the Influenza Hospitalization Surveillance Network (FluSurv-NET) during the 2010–2011 through 2014–2015 influenza seasons (37239 adults, 6469 children), Appiah *et al* demonstrated that antiviral treatment significantly increased during the study period: 72% in 2010–2011, 75% in 2011–2012, 83% in 2012–2013, 87% in 2013–2014, and 89% in 2014–2015 (p for trend <0.001) (107). Specifically, children aged <1 year had the greatest overall treatment increase across seasons, from 51% to 82% (107). Another retrospective cohort study published in 2016 that included 395 inpatients with PCR–confirmed influenza admitted at the Children's Hospital Colorado between December 2010 to April 2014 found that 323/395 children (82%) received oseltamivir (108). In Japan, a multicenter prospective cohort evaluation of hospitalized patients with laboratory-confirmed influenza, found that of 1345 patients with influenza (766 pediatric, 579 adult), excluding those aged < 1 year (who were not approved for antiviral therapy), as many as 97.7% (1224/1253) received antiviral therapy (109).

2.5 Predictors of NAI use amongst children hospitalized with influenza

Very few studies describe the predictors of antiviral use amongst hospitalized children. A 2016 retrospective cohort study of 395 inpatients with PCR–confirmed influenza admitted at the Children's Hospital Colorado between December 2010 to April 2014 found that oseltamivir use was associated with admission within 48 hours of symptom onset (89% vs 77%), ICU admission (88% vs 79%), longer length of stay (90% for >6 days vs 77% for ≤2 days), and influenza A H1N1 infection ($p < 0.05$ for all). On multivariate logistic regression analysis, longer length of stay, illness during the 2013-14 season, and admission within 48 hours of symptom onset were associated with higher odds of oseltamivir use (108). Another retrospective observational cohort that included both adult and pediatric patients hospitalized with laboratory confirmed influenza in southern Ontario hospitals for the 2004-05 to 2013-14 seasons found amongst the pediatric population (which they defined as 0-14 years, n=368), age [OR 1.08(1.02-1.15)], suspicion of influenza at admission [OR 3.41 (1.90-6.09)] and duration between symptom onset and diagnostic testing ≤ 48 hours [OR 2.24 (1.43-3.51)] were associated with increased odds of receiving antiviral therapy (104).

2.6 Current influenza treatment recommendations

Table 6: Summary of current North American influenza treatment recommendations, with a focus on children

Year	Organization	Recommendations
2018	IDSA (11)	Clinicians should start antiviral treatment as soon as possible for adults and children with documented or suspected influenza, irrespective of influenza vaccination history, who meet the following criteria: • Persons of any age who are hospitalized with influenza, regardless of illness duration prior to hospitalization • Outpatients of any age with severe or progressive illness, regardless of illness duration.

		• Outpatients who are at high risk of complications from influenza, including those with chronic medical conditions and immunocompromised patients. • Children younger than 2 years and adults ≥65 years. • Pregnant women and those within 2 weeks postpartum. Clinicians can consider antiviral treatment for adults and children who are not at high risk of influenza complications, with documented or suspected influenza, irrespective of influenza vaccination history, who are either: • Outpatients with illness onset ≤2 days before presentation. • Symptomatic outpatients who are household contacts of persons who are at high risk of developing complications from influenza, particularly those who are severely immunocompromised. • Symptomatic healthcare providers who care for patients who are at high risk of developing complications from influenza, particularly those who are severely immunocompromised.
2018	CPS (110)	• Treat all children with underlying risk factors for severe disease and all requiring hospitalization, irrespective of age • For 1-5 year olds with mild illness and no risk factors, antivirals may be considered but not routinely required
2019-2020	AAP (22)	Regardless of influenza vaccination status, antiviral treatment should be offered as early as possible to: • Any hospitalized child with suspected or confirmed influenza disease, regardless of duration of symptoms. • Any child, inpatient or outpatient, with severe, complicated, or progressive illness attributable to influenza, regardless of duration of symptoms. • Influenza virus infection of any severity in children at high risk of complications of influenza, regardless of symptom duration Antiviral treatment may be considered in any previously healthy, symptomatic outpatient not at high risk for influenza complications in whom an influenza diagnosis is confirmed or suspected on the basis of clinical judgment, if treatment can be initiated within 48 hours of illness onset.
2019-2020		• Treatment should be considered for adults and children at high risk of serious influenza complications or in

AMMI Canada (6, 10)	individuals with progressive, severe, or complicated illness, regardless of vaccine receipt • Otherwise healthy patients with relatively mild influenza are not likely to benefit from antiviral therapy initiated more than 48 hours after illness onset. • Effectiveness is reduced when treatment is initiated >48 hours after illness onset but should still be considered if the illness is progressive, severe, or complicated, regardless of previous health status, or if the individual belongs to a group at high risk for severe disease.

Legend: AAP – American Academy of Pediatrics; AMMI - Association of Medical Microbiology and Infectious Disease (Canada); CPS – Canadian Pediatric Society; IDSA – Infectious Diseases Society of America

Canadian guidance regarding antiviral use for influenza: AMMI Canada recommendations specific to children (10)

Children with mild disease, and no risk factors other than age:

a) *Aged younger than 1 year:* NAIs are currently not approved in Canada for the routine treatment of seasonal influenza illness; antiviral use may be considered on a case-by-case basis.
b) *Aged 1 year to younger than 5 years:* Although children aged younger than 5 years are classified as a high-risk group (with those aged younger than 2 years at highest risk), those who are otherwise healthy and have mild disease not requiring hospitalization do not routinely require antiviral therapy.
c) *Aged 5 years or older:* Antiviral therapy is not routinely recommended for children and youth who are otherwise healthy and have mild disease not requiring hospitalization.

Children with mild disease and risk factors other than age:

a) *Aged younger than 1 year:* NAIs are currently not approved in Canada for the routine treatment of seasonal influenza illness. Such use may be considered on a case-by-case basis.
b) *Aged 1 year and older, for illness of less than 48 hours' duration:* Treatment with oseltamivir or, if age appropriate, inhaled zanamivir is recommended.
c) *Aged 1 year and older, for illness of more than 48 hours' duration:* Treatment with oseltamivir or, if age appropriate, inhaled zanamivir may be considered on a case-by-case basis.

Treatment of infants, children, and youth with moderate, progressive, severe, or complicated influenza illness with or without risk factors

AMMI Canada recommends starting treatment immediately with oseltamivir or zanamivir (if age appropriate). Further, the guidelines recommend that treatment with these agents be started even if the interval between symptom onset and initial administration of antiviral is longer than 48 hours.

Antivirals for children aged less than 1 year:

With regards to the treatment of children aged < 1 year, the guidelines mention that although oseltamivir was approved temporarily for use in infants aged younger than 1 year on the basis of a favorable risk-to-benefit ratio during the recent 2009 H1N1 pandemic and is now authorized in the United States, it is not authorized in Canada for the routine treatment of seasonal influenza illness in infants aged younger than 1 year. Such use in this population for seasonal influenza should be handled on a case-by-case basis, based on severity of illness. Guidance from the Canadian Pediatric Society mirrors that of AMMI Canada for the treatment of children less than 1 year of age (110). In contrast, oseltamivir has been approved by the FDA for children as young as 2 weeks of age. Given preliminary pharmacokinetic data and limited safety data, the American Academy of Pediatrics (AAP) suggests that oseltamivir can be used to treat influenza in both term and preterm infants from birth because benefits of therapy are likely to outweigh possible risks of treatment (22).

CHAPTER 3 - METHODS

3.1 Overview, study setting and design

In this thesis, I describe antiviral use in children hospitalized for laboratory-confirmed influenza, ascertained through active surveillance for laboratory-confirmed influenza between September 1, 2010, to June 30, 2019 at 12 tertiary care pediatric hospitals participating in the Canadian Immunization Monitoring Program, ACTive (IMPACT). This is a retrospective cohort study. All participating centers have institutional ethics approval for surveillance.

3.2 Source of data

The Canadian Immunization Monitoring Program, ACTive (IMPACT), is a national surveillance initiative managed by the Canadian Pediatric Society (CPS) and carried out by the IMPACT network of Infectious Disease specialists and nurse monitors. It is a pediatric hospital-based national active surveillance network for adverse events following immunization, vaccine failures and selected infectious diseases that are, or will be, vaccine preventable. Presently, the vaccine preventable diseases for which active surveillance occurs include *Haemophilus influenzae*, *Neisseria meningitides*, Pertussis, *Streptococcus pneumoniae*, Varicella, Herpes Zoster, Influenza, Rotavirus, and Polio-Acute Flaccid Paralysis surveillance. The participating centers admit over 75,000 children annually, account for ~90% of pediatric tertiary care beds in the country, receive referrals from all provinces and territories, and serve a population of ~50% of Canada's children. The 12 IMPACT centers are Alberta Children's Hospital, Calgary, Alberta; B.C. Children's Hospital, Vancouver, British Columbia; Le Centre Mère-Enfant de Québec City, Quebec; Children's Hospital of Eastern Ontario, Ottawa, Ontario; CHU-Sainte-Justine, Montreal, Quebec; IWK Health Centre, Halifax, Nova Scotia; Eastern Health Janeway Child Health and Rehabilitation Centre, St. John's, Newfoundland; The Montreal Children's Hospital, Montreal, Quebec; Royal University Hospital, Saskatoon, Saskatoon; Stollery Children's Hospital, Edmonton, Alberta; The Hospital for Sick Children, Toronto, Ontario and the Children's Hospital, Winnipeg, Manitoba. Surveillance is supported financially by the Public Health Agency of Canada (PHAC). The information collected complements existing national surveillance systems, supports public health action, informs policy dialogue with federal, provincial and territorial governments and other national stakeholders, and assists in meeting Canada's international immunization commitments (111).

Since the time of its inception, the IMPACT network has published 7 research papers and has had 13 peer-reviewed presentations related to influenza. None of the work so far has looked into the specific aspects related to antiviral use amongst pediatric patients hospitalized with influenza in Canada.

3.3 Influenza case definition and data collection

Cases included are those when hospital admission is attributable to influenza infection or a complication of infection (i.e. admitted for influenza or a complication of influenza such as febrile convulsion, pneumonia), with laboratory confirmation of influenza by positive culture, positive immunoassay, RT-PCR or serial serologic testing. Patients are aged between 0-16 years; nosocomial cases (with symptom onset ≥72 hours after admission to acute care hospital) or those cases in which influenza was incidental, unrelated to the real reason for admission are excluded from the database (112). For this study, we excluded patients whose LoS < 1 day, since such admissions may have only been precautionary, and those who received antivirals prior to admission to the IMPACT hospital. At each IMPACT center, a trained nurse monitor screens daily laboratory results for eligible cases. Data collected include demographics, pre-existing medical conditions, influenza vaccination history, influenza type, clinical manifestations, treatment, complications, level of care required, duration of hospital stay, and outcome. Case details are abstracted from medical charts by using electronic standardized data collection forms (Daciforms, Dacima Software, Inc, Montreal, Quebec, Canada).

The methods specific to the conduct of this study are laid out in the methods section of the manuscript (Chapter 4). I describe the study population, study design, variables of interest and statistical analyses therein. However, in this chapter, I additionally discuss model selection for multivariable logistic regression analyses in greater detail.

3.4 Considerations regarding the development of the multivariable logistic regression model

For the multivariate models we considered all variables which were statistically significant on univariable analyses (with an α of 0.05) and further, we included variables thought to be plausible confounders a priori based on previous literature or clinical experience. We did not include some specific variables like hospital LoS and death since these events necessarily occurred after our outcome (antiviral treatment). Certain exposure variables like pregnancy, chronic anemia, receipt

of acetylsalicyclic acid, prematurity and obesity had very few occurrences, and were not significant on univariable analyses, and so we did not include them in the model. Model selection was guided by the Akaike Information Criteria (AIC), using backward selection. Age was considered as a continuous variable in the final multivariable model, since the continuous variable led to a better model fit compared to the categorical variable. We do however present the age breakdown in our univariable analyses, because we considered that the age categorization could be clinically meaningful; to describe the proportion of children < 6 months of age in our cohort, who would not be eligible for receipt of the seasonal influenza vaccine, and those aged between 6-23 months and 24-59 months who would be at increased risk for hospitalization and severe outcomes.

We attempted to study interaction between age and time (since influenza treatment guidelines and antiviral prescribing practices could have evolved over time with regards to children < 1 year old) and time and IMPACT center (since local influenza treatment guidelines and antiviral prescribing practices could have evolved over time), however due to the complexity of the model, multiplicity of variables and sub-categories, introducing an interaction term into the multivariable model was not possible. To account for these interactions, however, we sent out an email survey to all participating centers seeking information about the availability of a local influenza treatment guideline, and if such a guideline was available, when specifically during the timeframe of this study it became available. We included this composite variable (availability of a local guideline at the admitting IMPACT center for the season of the admission) into our multivariable model.

The possibility of representing the association between the exposure and outcome variable as relative risks (RR) was also explored. Unfortunately, as is often the case when the incidence of the outcome is high, the model did not converge on multivariable log binominal analyses (113). We further explored obtaining adjusted RRs through Poisson regression with robust standard error variance. This method, however, is known to produce variable results, that would need to be interpreted with caution, especially since such a model may yield individual predicted probabilities above 1 (113). Our findings on this model did not change the interpretation of our results. We have therefore used univariable and multivariable logistic regression analyses (a more tried-and-tested methodology, with familiar interpretation) to identify factors associated with antiviral use, and have been cautious in our interpretation of these associations as odds ratios (ORs) and not as relative risks (RRs).

CHAPTER 4 – MANUSCRIPT

4.1 PREAMBLE

Several observational studies suggest that early antiviral therapy in patients hospitalized with influenza is associated with improved outcomes; however, pediatric data are scarce. Despite guidelines recommending treatment, it is unknown why many children admitted to pediatric centers do not receive antivirals. Notably, data regarding the extent and factors associated with antiviral use in the context of hospitalized Canadian children are lacking.

This manuscript is aimed at bridging these important knowledge gaps. Here, we describe the extent of antiviral use amongst pediatric patients hospitalized for influenza in Canada, including differences across hospitals and over time, and identify factors associated with antiviral use amongst Canadian children hospitalized with influenza in the decade following the 2009 H1N1 influenza pandemic.

This manuscript has been formatted for submission to the journal ***Pediatrics***, the official journal of the American Academy of Pediatrics.

4.2 MANUSCRIPT

Antiviral use among Canadian children hospitalized for influenza, 2010-2019

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Dr. Papenburg reports grants from BD Diagnostics, grants from MedImmune, grants from Sanofi Pasteur, grants and personal fees from Seegene, grants and personal fees from Janssen Pharmaceutical, grants and personal fees from AbbVie, outside the submitted work.
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The other authors have no conflicts of interest to disclose.

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Role of Funder/Sponsor: PHAC provided input into the study design and was involved in the review and approval of the manuscript.

Abbreviations:

CI	Confidence Interval
ICU	Intensive Care Unit
IMPACT	Canadian Immunization Monitoring Program, ACTive
ILI	Influenza-like Illness
IQR	Inter-quartile range
LoS	Length of stay
LRI	Lower respiratory tract infection
NAI	Neuraminidase inhibitor
OR	Odds Ratio

PCR	Polymerase Chain Reaction
PHAC	Public Health Agency of Canada
URI	Upper respiratory tract infection

Table of Contents Summary

This article explores the extent and factors associated with antiviral use amongst Canadian children hospitalized with influenza in the decade following the 2009 H1N1 pandemic.

What's Known on This Subject

Observational studies suggest that early antiviral therapy in patients hospitalized with influenza is associated with improved outcomes; however, pediatric data are scarce. Despite guidelines recommending treatment, it is unknown why many children admitted to pediatric centers do not receive antivirals.

What This Study Adds

There was limited and variable antiviral use for Canadian children hospitalized with influenza. An increase in utilization overall and in high-risk children was noted temporally. Those receiving antivirals had increased disease severity markers. Patient and hospital-level characteristics influenced antiviral use.

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Contributors' Statement Page

Dr. Mehta participated in the design of the study, carried out the analysis, and drafted the initial manuscript; Drs. Vaudry, Bettinger, Halperin, Jadavji, Sadarangani, Bancej, and Morris contributed to study conception and design, and reviewed and revised the manuscript; Dr. Dendukuri contributed to the study design, oversaw the analysis, and reviewed and revised the manuscript; Dr Papenburg conceptualized and designed the study, oversaw the analysis, and reviewed and revised the manuscript; all authors approved the final manuscript as submitted.

ABSTRACT

Objectives

Antivirals are recommended for children hospitalized with influenza but are underutilized. We describe antiviral prescribing during influenza admissions in Canadian pediatric centers after the 2009 pandemic and identify factors associated with antiviral use.

Methods

We performed active surveillance for laboratory-confirmed influenza hospitalizations among children ≤16 years old at the 12 Canadian Immunization Monitoring Program Active hospitals, from 2010-11 to 2018-19. Logistic regression analyses were used to identify factors associated with antiviral use.

Results

Amongst 7545 patients, 57.4% were male; median age was 3 years (IQR 1.1-6.3). Overall, 41.3% received antivirals; 72.8% received antibiotics. Antiviral use varied across sites (range, 10.2-81.1%) and influenza season (range, 19.9-59.6%), and was more frequent in children with ≥1 chronic health condition (52.7% vs 36.7%; p<0.001). On multivariable analysis, factors associated with antiviral use included older age [adjusted odds ratio (aOR) 1.04(1.02-1.05)], more recent season [highest aOR 9.18(6.70-12.57) for 2018-19], admission during peak influenza period [aOR 1.37(1.19-1.58)], availability of local treatment guideline [aOR 1.54(1.17-2.02)], timing of laboratory confirmation [highest aOR 2.67(1.97-3.61) for result available prior to admission], presence of chronic health conditions [highest aOR 4.81(3.61-6.40) for cancer], radiographically-confirmed pneumonia [aOR 1.39(1.20-1.60)], antibiotic treatment [aOR 1.51(1.30-1.76)], respiratory support [1.57(1.19-2.08)] and intensive care unit admission [aOR 3.62(2.88-4.56)].

Conclusions

Influenza antivirals were underutilized in Canadian pediatric hospitals, including among children with high-risk chronic health conditions. Prescribing varied considerably across sites, increased over time, and was associated with patient and hospital-level characteristics. Multifaceted hospital-based interventions are warranted to strengthen adherence to influenza treatment guidelines and antimicrobial stewardship practices.

INTRODUCTION

Seasonal influenza epidemics are an important cause of pediatric hospitalization and mortality[1]. Annual hospitalization rates are highest in young children, ranging from ~250 per 100,000 children <6 months old to ~4.6 to 6 per 100,000 for those 5-16 years old[2,3]. Hospitalization risk is ~4 to 21 times greater in children with chronic medical conditions and they accounted for ~55% of pediatric influenza deaths during 2004-2012 in the United States[4,5]. The neuraminidase inhibitors oseltamivir and zanamivir are the only influenza antiviral treatments recommended for pediatric use in Canada[6]. Randomized controlled trials show that early treatment with neuraminidase inhibitors, i.e., within 48 hours of symptom onset, reduces illness duration and frequency of complications in adults and healthy children with influenza in the outpatient setting, but efficacy in 'at risk' children remains to be proven[7-9]. Despite a paucity of trial data in the hospital setting[10], clinical practice guidelines, including those from Canada, recommend antiviral treatment for hospitalized children with suspected or confirmed influenza, especially those with chronic health conditions[11,12]. Observational studies in hospitalized adults support this guidance, with early antiviral therapy associated with decreased disease severity outcomes (length of stay [LoS], intensive care unit [ICU] admission and mortality)[13-16]. However, data on antiviral use amongst hospitalized children are scarce, and have primarily focused on the 2009 H1N1 pandemic period or earlier[17,18]. Further, despite availability of guidelines recommending treatment, many children admitted to pediatric centers for influenza do not receive antivirals[17,19].

We describe antiviral use in children hospitalized with laboratory-confirmed influenza between 2010-11 and 2018-19 in Canadian pediatric centers, and identify factors associated with influenza antiviral treatment in this population. We hypothesized that antiviral use would vary considerably

across sites, would increase over time, and would be associated with patient and hospital-level variables.

METHODS

Study population

The study population comprised patients aged 0-16 years ascertained through active surveillance for laboratory-confirmed influenza admissions from September 1, 2010 to June 30, 2019 at the 12 tertiary care pediatric hospitals participating in the Canadian Immunization Monitoring Program, ACTive (IMPACT)[20]. These centers admit over 75000 children annually, account for ~90% of pediatric tertiary care beds in the country, receive referrals from all provinces and territories, and serve a population of ~50% of Canada's children[21]. During the study period, all centers routinely tested children admitted with acute respiratory infection for influenza. Patients with hospital LoS <1 day, receipt of antivirals prior to admission to the IMPACT hospital, and nosocomial cases (symptom onset ≥72 hours after admission) were excluded from this study. Institutional ethics approval was obtained at each center.

Study design

Trained nurse monitors prospectively screened daily laboratory results and admission lists for eligible cases. Audits of hospital discharge abstract databases were performed yearly to ensure case ascertainment completeness. Data regarding demographics, pre-existing medical conditions, influenza vaccination, influenza type, clinical manifestations, treatment, complications, level of care required, hospital LoS, and outcome at discharge were abstracted from medical charts using

electronic standardized data collection forms (Daciforms, Dacima Software, Inc, Montreal, Canada).

Variables of interest

The primary outcome was receipt of anti-influenza antiviral treatment during hospitalization. The secondary outcome was timing of receipt of antiviral during admission. Exposure variables included demographics, health status (by chronic conditions known to be risk factors for complicated infection[22]), influenza season (e.g., 2010-11), admitting center, availability of local influenza treatment guidelines during that season at the admitting center, timing of admission within influenza season ("peak" season defined as the period within each season during which the national influenza test positivity proportion was at least 15%, as reported by the Public Health Agency of Canada[23]), test method used for diagnosis, timing of availability of laboratory confirmation of influenza infection in relation to admission, influenza vaccination status for that season, antibiotic prescription, and measures of illness severity (mortality, ICU admission, respiratory support [CPAP, BiPAP, conventional or high-frequency ventilation, and ECMO], ICU and hospital length of stay).

Statistical analyses

Data were analyzed using R, version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was assessed using 2-tailed tests, with an α of 0.05. Descriptive statistics were calculated, medians of continuous variables were compared across strata using the Wilcoxon rank sum test, and proportions were compared using the Pearson's Chi square test. The Mann Kendall test was used to analyze temporal trends in antiviral utilization. Correction for

multiple hypothesis testing was not performed. Logistic regression analyses were used to determine crude and adjusted odds ratios (ORs) and corresponding 95% confidence intervals (95% CI) for factors associated with antiviral use. Given the substantial proportion of missing data for ethnicity (47%) and vaccination status (16.8%), no inferential statistics were performed on these variables. For the multivariate model, we considered all variables which were statistically significant on univariable analyses, and further included variables thought to be plausible confounders *a priori* based on previous literature or clinical experience. Model selection was guided using the Akaike Information Criteria (AIC), using backward selection.

RESULTS

During the study period, 7946 laboratory-confirmed influenza admissions were recorded at the 12 IMPACT centers. Amongst these, 276 had a hospital LoS <1 day, 103 had received antivirals prior to hospitalization at the IMPACT center and for 22 cases, data regarding receipt of antivirals were unknown. After these exclusions, we included 7545 cases in this study (Fig. 1).

Patient characteristics

Median patient age was 3.0 years (IQR 1.1-6.3) and 57.4% were male (Table 1). Median number of cases admitted per influenza season was 680 (range 561-1298). The total number of cases at each IMPACT center during the study ranged from 185 to 1132. Eight IMPACT centers (75%) had local influenza treatment guidelines, and onset of guideline availability ranged from prior to 2010-11 season to 2016-17 season. Amongst patients with known vaccination status, only 690/5402 (12.8%) had documented receipt of influenza vaccine that season.

Virus characteristics

Influenza A virus was detected in 5345 cases (70.8%), and influenza B in 2165 cases (28.7%). Amongst the 1926 type A isolates that underwent subtyping, 50.3% were A/H3N2 and 45.9% A/H1N1 2009. Seventy-three percent of infections were detected using PCR.

Clinical characteristics

The median duration of symptoms prior to presentation was 3 days (IQR 2-5). At least one chronic health condition was found in 3434 (45.4%) children. Radiographically confirmed pneumonia was noted in 2212 children (29.3%). Seventy-two percent received antibiotics, but laboratory confirmed bacterial infections (positive tissue, aspirate, blood, CSF and/or urine culture) were noted in only 508 (6.7%) patients. ICU admission was reported in 1252 (16.5%) cases, and 795 (63.5%) of these patients required respiratory support. The median hospital LoS was 3 days (IQR 2-5). Forty-two patients (0.5%) died due to influenza related complications.

Antiviral use

Overall, 3122 patients (41.3%) were prescribed antivirals, 3118 (99.9%) of whom received oseltamivir. Antiviral use increased from 19.9% in the 2010-11 season to 59.6% in the 2018-19 influenza season (p for trend = 0.001) (Fig. 2). Prescribing varied widely across sites (range 10.2-81.1%). Almost all cases (93%) had influenza test results available within 48 hours of admission. Among patients who received antivirals, 2551 (81.7%) received them within 2 days of admission (Supplementary figure 1). The proportion treated decreased with time from symptom onset to admission (<2 days, 48.3%; 2-4 days, 44%; >4 days, 35%). Antiviral use increased with age, from 32% in 0-5 months old to 48.6% in >5 years old. Children with ≥1 chronic health condition were

more likely to receive antiviral therapy (52.7% vs. 36.7%; p<0.001); this was also seen across most individual medical conditions (Table 2). The median time to treatment after admission did not differ significantly between those with or without an underlying chronic health condition (2±1.32 vs. 2±1.02 days; p=0.06). Antiviral prescribing increased similarly over time for patients with or without a chronic health condition (Fig. 3) and across age groups (Fig. 4). Patients with influenza B virus infection were less likely to receive antiviral therapy compared to those with influenza A (34.4% vs. 44.2%; p<0.001). Prescription of antibiotics was more frequent in children who received antivirals (77.3% vs. 69.6%; p<0.001). Cases which received antivirals had increased markers of disease severity (median hospital LoS 4 vs. 2 days, p<0.001; ICU admission, 27.8% vs. 8.68%, p<0.001; median ICU LoS 3 vs. 2 days, p<0.001; influenza-related mortality, 0.9% vs. 0.2%, p<0.001).

Factors associated with antiviral use: multivariable analysis

Multivariable logistic regression modeling identified an increased odds of receipt of antiviral therapy with advancing age [aOR 1.04(1.02-1.05)], more recent season [highest aOR 9.18(6.70-12.57) for 2018-19 season], admission during peak season [aOR 1.37(1.19-1.58)], availability of a local treatment guideline during that influenza season at that center [aOR 1.54(1.17-2.02)], and with the timing of availability of laboratory confirmation of influenza infection [highest aOR 2.67(1.97-3.61) for result availability prior to admission]. Among chronic health conditions, cancer was most strongly associated with antiviral therapy, [aOR 4.81(3.61-6.40)]. Influenza B virus infection demonstrated lower odds [aOR 0.81(0.70-0.94)] of receiving antiviral therapy, whereas radiographic pneumonia [aOR 1.39(1.20-1.60)], co-receipt of antibiotic therapy [aOR

1.51 (1.30-1.76)], ICU admission [aOR 3.62(2.88-4.56)] and respiratory support [aOR 1.57 (1.19-2.08)] were associated with antiviral therapy.

DISCUSSION

North American influenza clinical practice guidelines, including those of the Infectious Diseases Society of America[12], American Academy of Pediatrics[24] and the Canadian Pediatric Society[25] recommend antiviral treatment for all children hospitalized with influenza. These longstanding recommendations pre-date the 2009 H1N1 pandemic. Despite this, in our study of Canadian children admitted for laboratory confirmed influenza using a country-wide hospital-based active surveillance network with data from over 7500 hospitalizations across 9 post-pandemic seasons found that the overall utilization of antivirals was only 41% since 2010-11. Prescribing increased over time, demonstrated wide variation across participating centers, was associated with the timing of admission relative to peak influenza circulation, timing of availability of laboratory confirmation of influenza infection, and availability of local influenza treatment guidelines. Furthermore, we identified patient-level factors associated with antiviral use which included older age, presence of underlying chronic health conditions that are risk factors for severe illness, infecting virus type, radiographic pneumonia, co-receipt of antibiotics and need for intensive care and respiratory support.

The use of neuraminidase inhibitors in adults and children in randomized placebo-controlled trials of the treatment of influenza in outpatients has been demonstrated to reduce duration of illness, duration of viral shedding, and risk of influenza-associated complications[7,26]. The evidence base for antiviral treatment of influenza in the hospital setting is weaker. The only published pediatric

controlled trial that evaluated neuraminidase inhibitors among children admitted with influenza was terminated early with only 21% of the targeted population enrolled[10]. However, mounting evidence from observational studies in children and adults suggests clinical benefit (including decreased length of stay, health care costs, ICU admission and mortality) of treatment with neuraminidase inhibitors, especially in high-risk populations and when initiated early (within 48 hours of illness onset or of hospitalization)[27-34]. Despite this, our study and others show that a substantial number of hospitalized children with influenza do not receive antiviral treatment. In a retrospective cohort study[19] that included ~36,000 children hospitalized with influenza during 2007–2015 in the United States, 69% received antiviral treatment. Further, in children deemed to be high risk, 30% were not treated[19]. A retrospective cohort of hospitalized patients (adults and children) with laboratory confirmed influenza in southern Ontario hospitals for the 2004-05 to 2013-14 seasons found that the percentage treated increased from 29% before the 2009 H1N1 pandemic to 74% during the pandemic, decreased to 55% in 2011-12 and then increased to 65% in 2013-14[35]. Similarly, we found that utilization rates increased over time, climbing to almost 60% during 2018-19; this trend was observed across centers and patient sub-populations. Antiviral use among children most likely to benefit from treatment, those with chronic health conditions, more than doubled over the study period to nearly 70% in 2018-19.

Guidelines recommend initiation of antiviral treatment within 48 hours of onset of illness in outpatients, since optimal benefits are obtained with early treatment[11,36,37]. In this study, only a quarter of children presented within this time interval; delayed presentation, i.e., more than 48 hours, may have led some clinicians not to use antivirals. Antiviral prescriptions may also be affected by rapidity of influenza test result availability[38]. In our cohort almost 75% of diagnoses

were based on highly accurate laboratory-based PCR tests, and ~94% of results were available within 48 hours of hospital admission. Specimens for PCR must be sent to the laboratory, and testing is done in batches, which can result in long turnaround times. Integrating novel rapid and accurate molecular assays for influenza diagnostic algorithms in the emergency department, especially for at-risk children being hospitalized, may facilitate early diagnosis and treatment[39].

We observed wide variation of antiviral use across IMPACT centers (range, 10.2 to 81.1%). Similarly, Stockmann *et al* found that among 46 freestanding U.S. children's hospitals, antiviral use ranged from 42-90% across centers during 2007-2015[19]. While most IMPACT centers had local guidelines for antiviral use, such guidelines were not always in place during earlier seasons. Additional hospital-level factors not evaluated in this study, such as the population served, referral patterns, and the presence of an antimicrobial stewardship program may also influence local prescribing cultures. Moreover, guideline recommendations for treatment of patients hospitalized with influenza are based only on observational data. Randomized clinical trials of neuraminidase inhibitors among outpatients have shown modest benefits, but with accompanying risk of adverse events, primarily gastro-intestinal side-effects. The perception of a questionable risk-benefit profile may lead to hesitancy to prescribe antivirals among some clinicians[19,28].

It is concerning that antibiotics were used much more frequently than antivirals in this cohort of children admitted with laboratory confirmed influenza; almost 70% of patients received antibiotics. Although the IMPACT dataset is limited in its ability to provide some important antibiotic treatment details (spectrum of activity; timing and duration of use; complete vs. incomplete courses), only 6.7% of children had a laboratory-confirmed concomitant or secondary

bacterial infection and we presume that most physicians were empirically treating pneumonia and/or acute otitis media, which rarely have a laboratory-confirmed etiology. Our findings are similar to those from other studies evaluating antimicrobial use in hospitalized influenza cases [35,40], and highlight the difficulty clinicians face distinguishing bacterial vs. viral causes of severe lower respiratory tract infections because of overlap in presentations, risk of bacterial superinfection, and challenges in obtaining samples from the lower respiratory tract for microbiologic testing[41,42]. Multifaceted interventions using combinations of education, rapid viral testing, biomarkers, and audit with feedback may be needed to reduce antibiotic overuse in influenza-associated hospitalizations[43-45].

Our study and others[35,36] have observed lower antiviral use in patients with influenza B infection compared to influenza A. Researchers have attempted to attribute this to differences in illness severity and in the interval between symptom onset and admission[36]. A recent study that included both pediatric and adult patients demonstrated that those with influenza A infection were more likely to meet standard case definitions than those with influenza B[46]. However, morbidity and mortality associated with pediatric influenza B infection can be greater than that of influenza A[17]; and thus, antiviral use is recommended equally for both influenza types[47].

We found that older age was associated with antiviral use. More "classic" presentation among older children[46], lack of approval of oseltamivir use by Health Canada in infants <12 months of age, and evolving guidance on oseltamivir use in younger children[40] could be reasons for antiviral use increasing with older age. Reports of neurotoxicity from animal models when oseltamivir was used in the infant rats[48] had raised concerns for its use in young children; however, no such

neurotoxicity has been observed in human studies[11]. Neuraminidase inhibitors are not currently authorized in Canada for the treatment of seasonal influenza in infants aged younger than 1 year, and oseltamivir use in infants is recommended on a case-by-case basis, based on illness severity[11].

The presence of chronic conditions known to be risk factors for complicated infection were significantly associated with antiviral use in a multivariable logistic regression model. Children with these comorbidities may present more severe disease, which may partly explain greater antiviral use in this population; nevertheless, after adjustment for requirement for intensive care and respiratory support, these conditions remained associated with antiviral prescription. This suggests that clinicians recognize that these children are at greater risk of severe outcomes and potentially benefit most from antiviral treatment.

Our study is limited by its retrospective design. Although case reporting was conducted prospectively by nurse monitors using a standardized reporting form, data were collected from the medical chart and could not capture clinical decision-making processes. Data regarding the receipt of influenza vaccine and ethnicity were frequently missing. Clinical data were limited regarding the timing of the appearance of specific signs or symptoms during the course of illness. Moreover, while were we not able to include or control for measures of severity at presentation or admission to hospital, we attempted to overcome this limitation by including need for ICU admission and respiratory support as proxies for disease severity in our multivariable model. Finally, the external validity of this study is limited by the fact that IMPACT conducts surveillance in tertiary care centers in Canada; the management of pediatric influenza associated admissions in community hospitals may be different. Despite these limitations, our study is strengthened by its representation

of a nationwide active surveillance cohort of children hospitalized with laboratory confirmed influenza admitted over almost a decade, and it is one of the largest such studies in the post pandemic period.

CONCLUSIONS

Antiviral medications are underutilized amongst children hospitalized for influenza in Canadian pediatric hospitals. Moreover, nearly half of children with chronic health conditions placing them at risk for severe outcomes were not treated. However, an increase in utilization overall and in high-risk children was noted over time. Despite national clinical practice guidelines, there is a wide variation in antiviral prescribing practices across the country, and a high rate of antibiotic use was noted. We also identified patient and hospital-level characteristics independently associated with antiviral prescribing. Taken together, these findings call for multifaceted interventions to strengthen adherence to local and national influenza treatment guidelines and antimicrobial stewardship practices.

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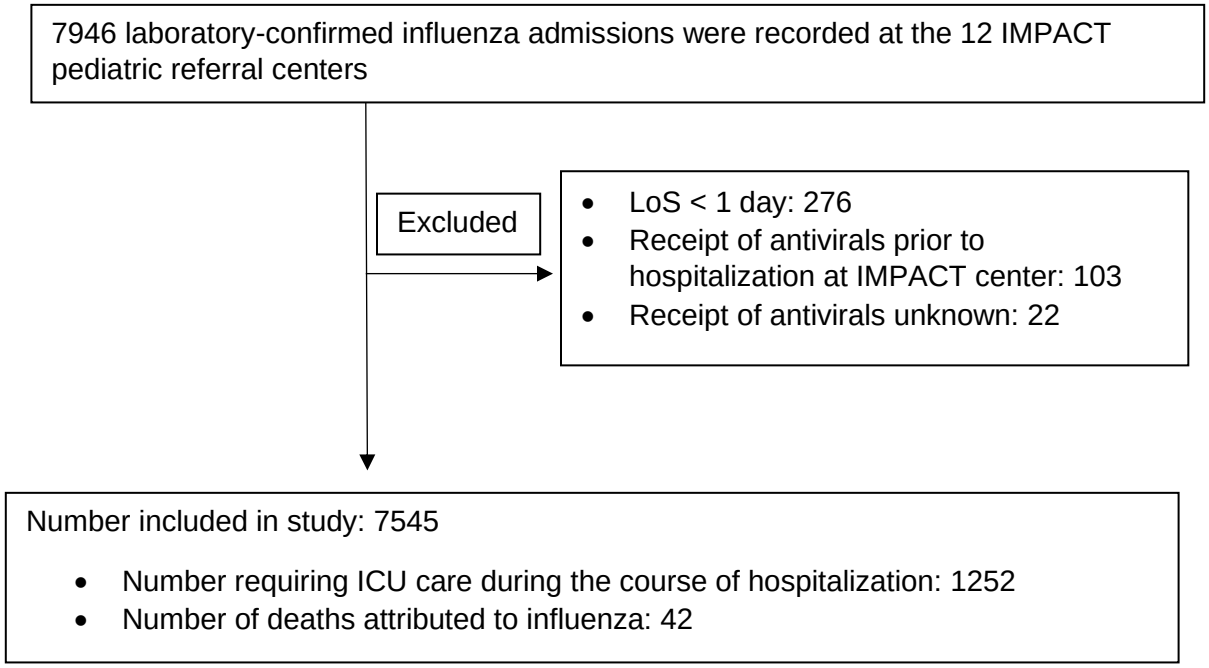
Figure 1. Study flow diagram



Legend: LoS: Length of stay; IMPACT - Canadian Immunization Monitoring Program, ACTive; ICU – Intensive care unit.

Figure 2: Percentage of patients treated with antivirals across 12 Canadian IMPACT pediatric hospital centers by influenza season, 2010-11 to 2018-19. (n=7545)

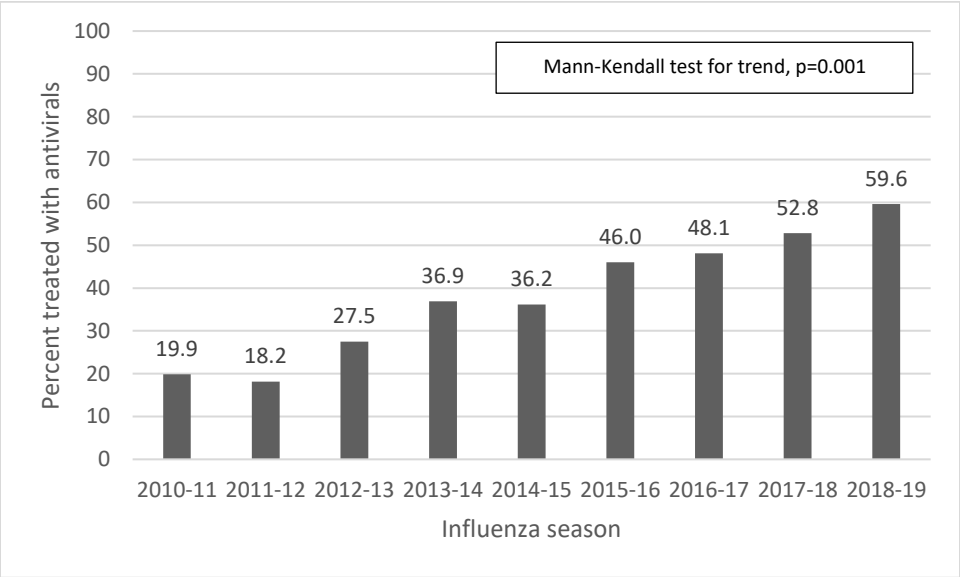


Figure 3. Percentage of patients treated with antivirals across 12 Canadian IMPACT pediatric hospital centers by influenza season, stratified by the presence/absence of an underlying chronic health condition

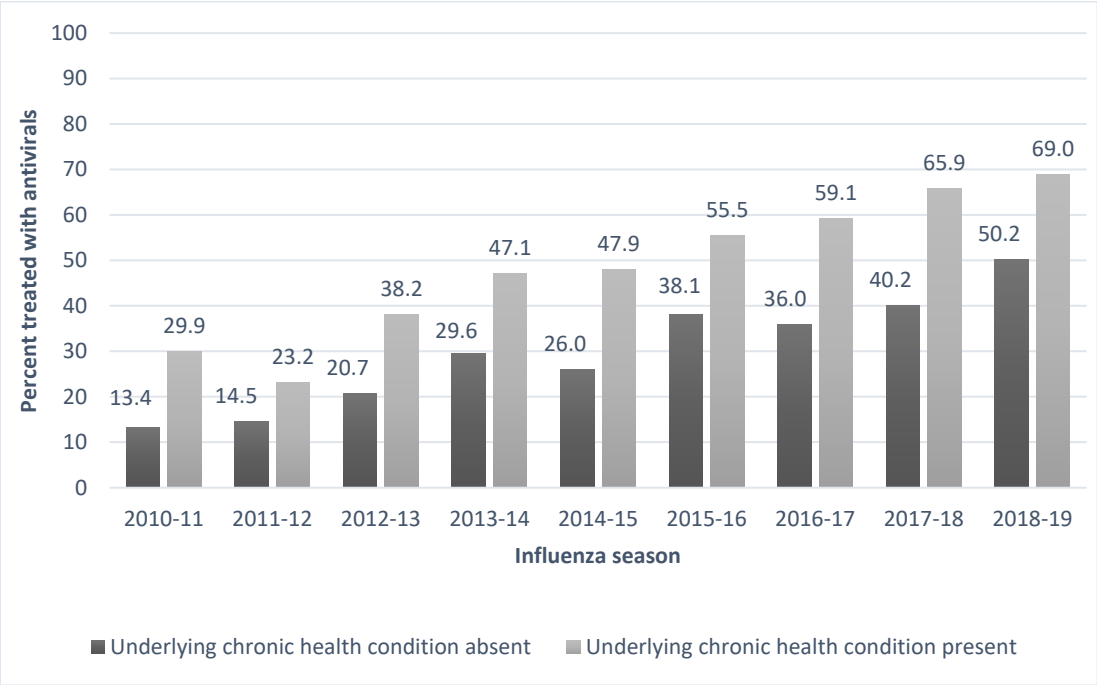


Figure 4. Percentage of patients treated with antivirals across 12 Canadian IMPACT pediatric hospital centers by influenza season, stratified by age group

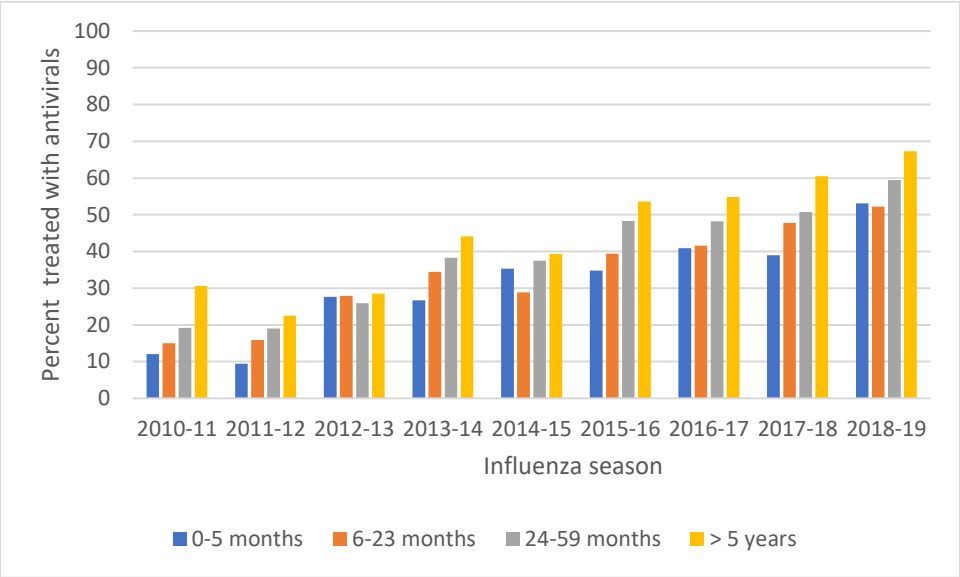


Table 1. Characteristics of children admitted for influenza across 12 Canadian IMPACT pediatric hospital centers, 2010-11 to 2018-19 (n=7545)

Characteristics	n (%)
Demographic data	
Age (in years)	
Mean ± SD	4.30 ± 4.10
Median (IQR)	3.0 (1.08-6.33)
Age group	
0-5 months	1053 (13.9)
6-23 months[a]	1841 (24.4)
24-59 months	2100 (27.8)
≥ 5 years	2551 (33.9)
Sex	
Male	4332 (57.4)
Ethnicity	
Caucasian	2141 (28.3)
Asian	418 (5.5)
Middle Eastern/Arabic	333 (4.4)
Black	390 (5.1)
Latin, Central and South American	111 (1.4)
North American Indigenous	472 (6.2)
Other/Mixed	129 (1.7)
Unknown	3551 (47.0)
Influenza season	
2010-11	636 (8.4)
2011-12	561 (7.4)
2012-13	836 (11.0)

2013-14	675 (8.9)
2014-15	680 (9.0)
2015-16	1298 (17.2)
2016-17	563 (7.4)
2017-18	1011 (13.3)
2018-19	1285 (17.0)
Timing of admission within influenza season	
Admitted during "peak" season[b]	4845 (64.2)
IMPACT center	
A	218 (2.8)
B	1132 (15.0)
C	1068 (14.1)
D	494 (6.5)
E	492 (6.5)
F	679 (8.9)
G	682 (9.0)
H	657 (8.7)
I	185 (2.4)
J	853 (11.3)
K	762 (1.0)
L	323 (4.2)
Availability of a local influenza antiviral treatment guideline[c]	
Treatment guideline available	3978 (52.7)
Vaccination status (n=6492)[d]	
Received influenza vaccine for that season	690 (10.6)
Did not receive influenza vaccine for that season	4712 (72.6)
Vaccination status unknown	1090 (16.8)

Laboratory data	
Influenza virus type	
A	5345 (70.8)
B	2165 (28.7)
Both A and B	35 (0.5)
Test used to make the diagnosis	
PCR	5512 (73.1)
EIA	234 (3.1)
DFA	1082 (14.3)
Viral culture	693 (9.2)
Unknown	24 (0.3)
Timing of availability of report of laboratory confirmation of influenza infection	
Result available prior to IMPACT center admission	782 (10.4)
Result available on first day of admission	4660 (61.8)
Result available within second day of admission	1632 (21.6)
Result available after second day of admission	471 (6.2)
Clinical data	
Presence of underlying chronic health condition	
Any underlying risk factor	3434 (45.4)
Chronic heart disorders	365 (4.8)
Chronic lung disorders	1403 (18.5)
Diabetes mellitus or other metabolic disorders	263 (3.4)
Cancer	318 (4.2)
Immunodeficiency[e]	270 (3.5)
Immunosuppression[f]	297 (3.9)
Chronic renal disease	169 (2.2)

Chronic anemia	102 (1.3)
Hemoglobinopathy	256 (3.3)
Chronic acetylsalicylic acid therapy	16 (0.2)
Residence in institutional setting and other chronic care facilities	28 (0.3)
Neurologic or neurodevelopment disorders	855 (11.3)
Pregnancy	2 (0.0)
Obesity	41 (0.5)
Prematurity (if < 1 year old)	140 (1.8)
Duration of symptoms prior to admission at IMPACT hospital (days)	
Mean ± SD	3.68 ± 3.10
Median (IQR)	3 (2-5)
Presence of radiographically confirmed pneumonia	2212 (29.3)
Presence of a lab-confirmed bacterial infection	508 (6.7)
Co-receipt of antibiotic therapy	5494 (72.8)
Need for intensive care	1252 (16.5)
Need for respiratory support[g]	795 (10.5)
Hospital length of stay (days)	
Mean ± SD	4.81 ± 7.51
Median (IQR)	3 (2-5)
Outcome at hospital discharge	
Survived	7501 (99.4)
Died of reported influenza infection	42 (0.5)

Died of other cause	2 (0)

PCR – Polymerase chain reaction, EIA – Enzyme immunoassay test, DFA – Direct fluorescent antibody test, SD - standard deviation, IQR - interquartile range, IMPACT - Canadian Immunization Monitoring Program, ACTive.

[a]Includes 630 children aged 6-11 months, such that the total number of infants (age <1 year) = 1683; and children aged 12-23 months = 1211. Age categories chosen are reflective of AMMI Canada guidance on antiviral use, those between 0-5 months are ineligible to receive an influenza vaccine and 6-23 months are at risk for severe disease.

[b]Admitted when the national testing positivity proportion was at least 15%, as reported by the Public Health Agency of Canada.

[c]Availability of a local guideline at the admitting IMPACT center for the season of the admission.

[d]1053 children were < 6 months of age, and therefore not eligible to receive the influenza vaccine.

[e]Includes chronic or intermittent neutropenia, HIV, anatomic or functional asplenia, and genetically determined immune disorders such as defects in immunoglobulin production, complement levels and cell-mediated (T-lymphocyte) immunity defects.

[f]Includes corticosteroids and/or other immunosuppressive medications (like cyclosporine, azathioprine, methotrexate, infliximab etc.), bone marrow or solid organ transplants and immunosuppressive asthma treatment (i.e. daily oral steroids).

[g]Includes CPAP, BiPAP, conventional and high-frequency ventilation, and ECMO.

Table 2: Factors associated with antiviral use among children hospitalized with influenza across 12 Canadian IMPACT pediatric hospital centers, 2010-11 to 2018-19 (n=7545)

Exposure variable	**Received antivirals (n=3122) n (%)[†]**	**Did not receive antivirals (n=4423) n (%)[†]**	**OR (95% CI)**	**adjusted OR[a] (95% CI)**
Demographic data				
Age in years[b]				
Mean ± SD	4.96 ± 4.38	3.83 ± 3.83		1.04 (1.02-1.05)
Median (IQR)	3.66 (1.41-7.41)	2.58 (0.91-5.75)	p<0.05	
Age group				
0-5 months	337 (32.0)	716 (68.0)	Reference	NI[c]
6-23 months	674 (36.6)	1167 (63.4)	1.22 (1.04-1.44)	NI[c]
24-59 months	870 (41.4)	1230 (58.6)	1.50 (1.28-1.75)	NI[c]
≥ 5 years	1241 (48.6)	1310 (51.4)	2.01 (1.73-2.34)	NI[c]
Sex				
Male	1783 (41.1)	2549 (58.9)	0.97(0.89-1.07)	0.94 (0.83-1.06)
Influenza season				
2010-11	127 (20.0)	509 (80.0)	Reference	Reference
2011-12	102 (18.2)	459 (81.8)	0.89 (0.66-1.18)	1.27 (0.89-1.81)
2012-13	230 (27.5)	606 (72.5)	1.52 (1.18-1.94)	1.79 (1.32-2.43)
2013-14	249 (36.9)	426 (63.1)	2.34 (1.82-3.00)	2.97 (2.15-4.10)
2014-15	246 (36.2)	434 (63.8)	2.27 (1.77-2.91)	2.76 (2.00-3.81)
2015-16	597 (46.0)	701 (54.0)	3.41 (2.73-4.26)	4.46 (3.27-6.07)
2016-17	271 (48.1)	292 (51.9)	3.71 (2.88-4.80)	4.34 (3.07-6.13)

2017-18	534 (52.8)	477 (47.2)	4.48 (3.56-5.64)	5.83 (4.24-8.01)
2018-19	766 (59.6)	519 (40.4)	5.91 (4.72-7.40)	9.18 (6.70-12.57)
Timing of admission within influenza season				
Admitted during "peak" season[d]	2249 (46.4)	2596 (53.6)	1.81 (1.64-2.00)	1.37 (1.19-1.58)
Availability of a local influenza antiviral treatment guideline[e]				
Treatment guideline available	2097 (52.7)	1881 (47.3)	2.76 (2.51-3.04)	1.54 (1.17-2.02)
Laboratory data				
Influenza virus type				
A	2363 (44.2)	2982 (55.8)	Reference	Reference
B	746 (34.4)	1419 (65.5)	0.66 (0.59-0.73)	0.81 (0.70-0.94)
Both A and B	13 (37.1)	22 (62.9)	0.74 (0.37-1.48)	0.65 (0.25-1.68)
Timing of availability of report of laboratory confirmation of influenza infection				
Result available prior to IMPACT center admission	295 (37.7)	487 (62.3)	1.04 (0.82-1.32)	2.67 (1.97-3.61)
Result available on first day of admission	1972 (42.3)	2688 (57.7)	1.26 (1.03-1.53)	2.63 (2.06-3.37)
Result available within second day of admission	682 (41.8)	950 (58.2)	1.23 (1.00-1.52)	1.78 (1.37-2.31)
Result available after second day of admission	173 (36.7)	298 (63.3)	Reference	Reference
Clinical data				
Presence of underlying chronic health condition				
Chronic heart disorders	205 (56.2)	160 (43.8)	1.87 (1.51-2.31)	1.82 (1.39-2.38)

Chronic lung disorders	709 (50.5)	694 (49.5)	1.57 (1.40-1.77)	1.51 (1.30-1.77)
Diabetes mellitus or other metabolic disorders	121 (46.0)	142 (54.0)	1.21 (0.94-1.55)	NI[f]
Cancer	197 (61.9)	121 (38.1)	2.39 (1.90-3.01)	4.81 (3.61-6.40)
Immunodeficiency[g]	186 (68.9)	84 (31.1)	3.27 (2.51-4.25)	2.74 (1.98-3.80)
Immunosuppression[h]	212 (71.4)	85 (28.6)	3.71 (2.87-4.80)	3.52 (2.54-4.86)
Chronic renal disease	101 (59.7)	68 (40.3)	2.14 (1.56-2.92)	1.50 (1.01-2.21)
Chronic anemia	50 (49.0)	52 (51.0)	1.36 (0.92-2.02)	NI[f]
Hemoglobinopathy	147 (57.4)	109 (42.6)	1.95 (1.51-2.51)	2.33 (1.70-3.20)
Chronic acetylsalicylic acid therapy	3 (18.7)	13 (81.3)	0.32 (0.09-1.14)	NI[f]
Residence in institutional setting and other chronic care facilities	17 (60.7)	11 (39.3)	2.19 (1.02-4.69)	2.14 (0.84-5.45)
Neurologic or neurodevelopment disorders	482 (56.4)	373 (43.6)	1.98 (1.71-2.28)	1.22 (1.01-1.47)
Pregnancy	1 (50.0)	1 (50.0)	1.41 (0.08-22.66)	NI[f]
Obesity	17 (41.4)	24 (58.6)	1.00 (0.53-1.87)	NI[f]
Prematurity (if < 1 year old)	62 (44.2)	78 (55.8)	1.12 (0.80-1.58)	NI[f]
Duration of symptoms prior to admission at IMPACT hospital (days)[b]				
Mean ± SD	3.34 ± 3.04	3.92 ± 3.11		0.92 (0.90-0.94)
Median (IQR)	3 (1-5)	3 (2-5)	p<0.05	
Presence of radiographically confirmed pneumonia	1074 (48.5)	1138 (51.5)	1.51 (1.36-1.67)	1.39 (1.20-1.60)

Presence of a lab-confirmed bacterial infection	228 (44.9)	280 (55.1)	1.16 (0.97-1.39)	NI[f]
Co-receipt of antibiotic therapy	2413 (43.9)	3081 (56.1)	1.48 (1.33-1.64)	1.51 (1.30-1.76)
Need for intensive care	868 (69.3)	384 (30.7)	4.05 (3.55-4.61)	3.62 (2.88-4.56)
Need for respiratory support[i]	559 (70.3)	236 (29.7)	3.86 (3.29-4.54)	1.57 (1.19-2.08)
Hospital length of stay (days) [b]				
Mean ± SD	6.41 ± 9.69	3.68 ± 5.18		NI[j]
Median (IQR)	4 (2-7)	2 (1-4)	p<0.05	
Outcome at hospital discharge				
Survived	3903 (52.0)	4408 (48.0)	Reference	NI[j]
Died of reported influenza infection	29 (69.0)	13 (31.0)	3.17 (1.65-6.12)	NI[j]
Died of other cause	0 (0.0)	2 (100.0)	NA	NI[j]

SD - standard deviation, IQR - interquartile range, IMPACT - Canadian Immunization Monitoring Program, ACTive, NI - not included, NA – not applicable.

[a]Multivariable logistic regression model included age, sex, influenza season, IMPACT center, timing of admission relative to peak influenza activity within season, availability of local guideline, presence of underlying chronic health conditions shown above, influenza virus type, timing of availability of influenza laboratory test result relative to hospital admission, duration of symptoms prior to admission, presence of radiographically confirmed pneumonia, co-receipt of antibiotic therapy, need for intensive care unit admission and respiratory support. ORs for IMPACT center not shown in the table above.

[b]Medians compared using Wilcoxon rank sum test

[c]Age treated as a continuous variable in the multivariable logistic regression model

[d]Admitted when the national testing positivity rate was at least 15%, as reported by the Public Health Agency of Canada

[e]Availability of a local guideline at the admitting IMPACT center for the season of the admission

[f]Not included in the multivariable model because not significantly associated in univariable analysis

[g]Includes chronic or intermittent neutropenia, HIV, anatomic or functional asplenia, and genetically determined immune disorders such as defects in immunoglobulin production, complement levels and cell-mediated (T-lymphocyte) immunity defects.

[h]Includes corticosteroids and/or other immunosuppressive medications (like cyclosporine, azathioprine, methotrexate, infliximab etc.), bone marrow or solid organ transplants and immunosuppressive asthma treatment (i.e. daily oral steroids).

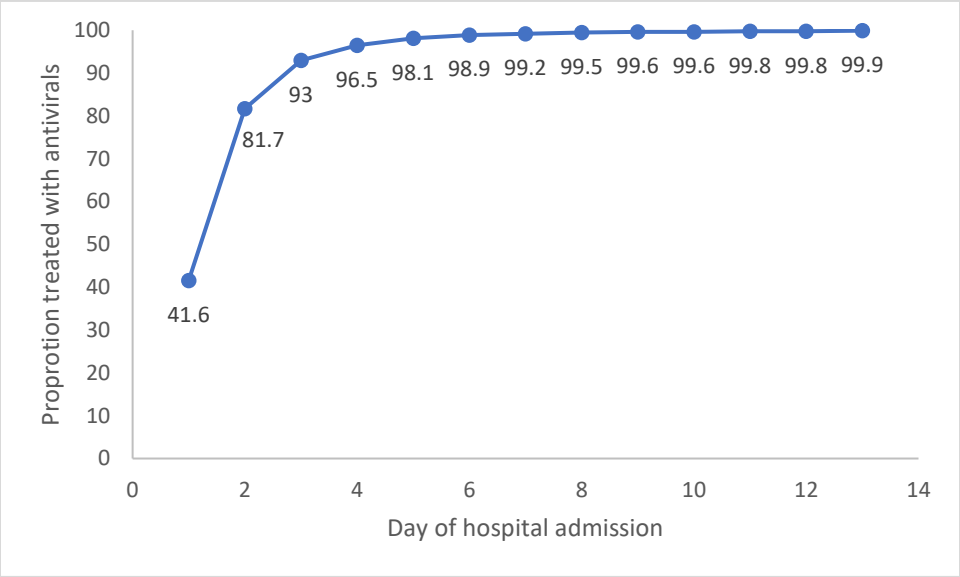
[i]Includes CPAP, BiPAP, conventional and high-frequency ventilation and ECMO.

[j]Not included in the multivariable model because these variables necessarily occurred after antiviral treatment decisions, i.e., at the end of the hospitalization.

†Data are *n (row %)* unless otherwise indicated.

Supplementary material

Supplementary Figure 1. Cumulative proportion treated with antivirals, by day of IMPACT hospital admission, amongst children who received antivirals (n=3122)



APPENDICES

Appendix 1: Additional figures

Figure 1: Percentage of patients treated with antivirals at each IMPACT center by influenza season, 2010-11 to 2018-19

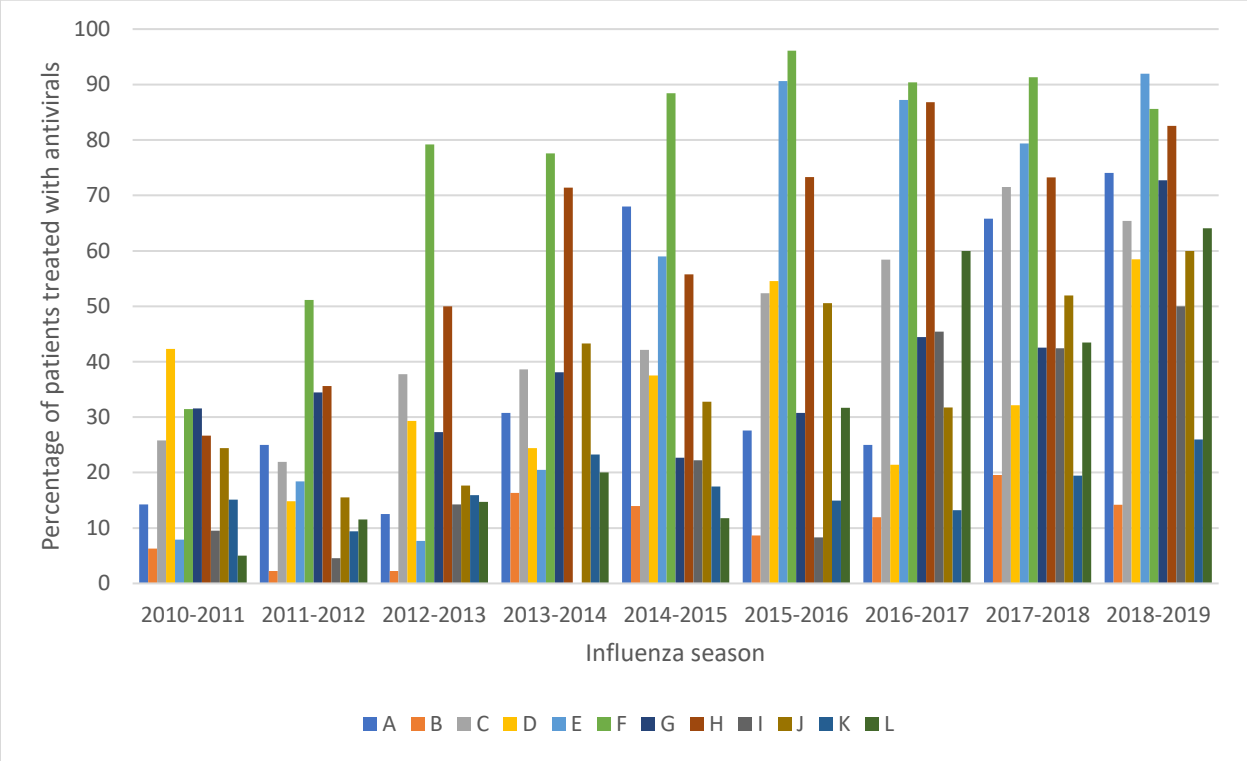
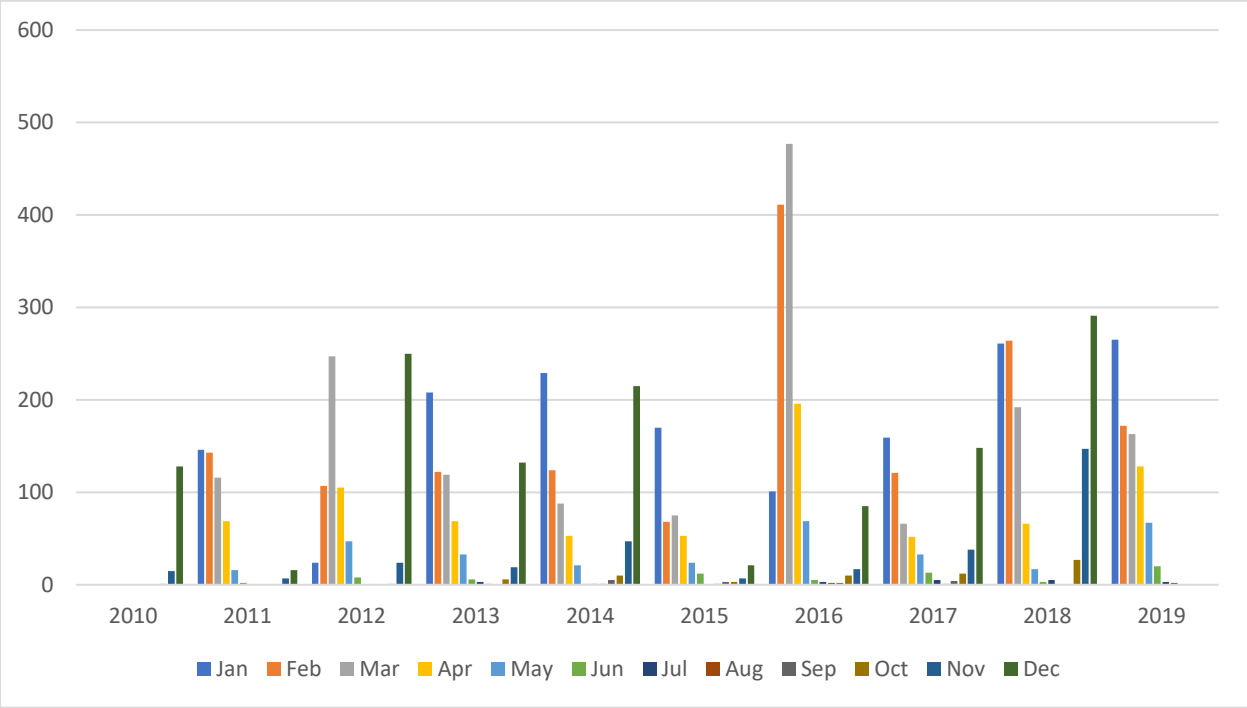


Figure 2: Number of cases admitted per month across the 9 influenza seasons, at the 12 IMPACT centers, 2010-11 to 2018-19



Appendix 2: Additional tables

Table 1: Availability of local influenza treatment guidelines at IMPACT centers, 2011-2019

Centre number	Local guideline available	Year local guideline became available
A	Yes	2016
B	No	NA
C	Yes	2013
D	Yes	2009
E	Yes	2014
F	Yes	2016
G	Yes	2014
H	No	NA
I	No	NA
J	Yes	2009
K	No	NA
L	Yes	2009

NA – local treatment guideline not available

CHAPTER 5 - DISCUSSION

In this thesis, I evaluated antiviral utilization amongst Canadian children hospitalized with influenza during the decade following the 2009 H1N1 pandemic. I analyzed over 7500 admissions for pediatric laboratory confirmed influenza using a country-wide hospital-based active surveillance network found that the overall utilization of antivirals was only 41%. Although utilization has increased over time, there is still a wide variation across participating centers. The discussion of the results of this study has already been presented in the manuscript (Chapter 4), and I will mainly focus on the interpretations and implications of my findings in this chapter, and mainly explore the reasons behind poor utilization of antivirals in the treatment of influenza.

The problem of low rates of utilization of antivirals for the treatment of influenza, in spite of recommendations from several professional societies (Table 6) is concerning. Low rates of utilization of antivirals for the treatment of influenza amongst hospitalized patients have been shown in several studies across the world (presented in Chapter 2). This implores us to question why rates of utilization continue to remain low, despite guidance and availability of sophisticated testing methods with quick turn-around times.

This question inevitably propels us to revisit history. Oseltamivir was approved for seasonal influenza by US FDA in 1999, after a number of randomized controlled trials, systematic reviews, and meta-analysis emphasized a favorable efficacy and safety profile. Majority of these initial trails were industry sponsored; and Roche first marketed and promoted this drug. In 2005 and 2009, the looming fear of pandemic influenza led to recommendations by prominent regulatory bodies such as World Health Organization, Centers for Disease Control and Prevention, European Medicines Agency and others for its use in treatment and prophylaxis of influenza, and its stockpiling as a measure to tide over the crisis. However, serious adverse events, especially neuropsychiatric events associated with the drug started getting reported leading to a cascade of questions on clinical utility of this drug (67).

Reviews from the Cochrane collaboration did not raise any major issues over safety and efficacy of oseltamivir until 2009. However, in 2009, a Japanese pediatrician questioned the Cochrane team regarding the results of their review by suggesting that their report mainly drew inferences from a meta-analysis done by Kaiser *et al* (114), who had based their review on 10 RCTs, of which only 2 were peer-reviewed. In view of the emerging safety issues and these specific objections, the

Cochrane collaboration decided to undertake a complete analysis of the clinical trial data set. The subsequent 2014 review examined data from 46 trials and found extremely modest reductions in the time to alleviation of symptoms (less than a day), and no decrease in the risk of hospital admissions, or serious complications (67). It not only questioned the risk-benefit ratio of the drug, but also raised doubts about the regulatory decision of approving it. The validity of this review was subsequently questioned, given that data analysis was done in an intention-to-treat (ITT) group without accounting for the results of influenza testing (ITTi) group. This shortcoming was subsequently overcome by the MUGAS study group, which demonstrated reductions in lower respiratory tract complications hospital stay for the ITTi group that received oseltamivir (73). Several observational studies and meta-analyses of individual patient data (described in this thesis) have subsequently demonstrated that NAI use has been associated with lower rates of hospitalization, reductions in the duration of illness, complications associated with influenza, and overall health care costs attributable to influenza (Chapter 2).

Nevertheless, there is a perceived lack of efficacy of NAIs amongst providers. Merely modest reductions in the duration of influenza symptoms, and relatively small benefit in a condition that is usually self-limiting and only rarely leads to serious complications, along with gastro-intestinal side effects seem to contribute to provider hesitancy in NAI use (103). Previously, concerns were raised about neuropsychiatric events among children treated with oseltamivir, but these were later found by the US FDA to be most likely related to an increased awareness of influenza-associated encephalopathy, increased access to oseltamivir among that population, and a coincident period of intensive monitoring for adverse events (115). No serious side effects have been associated with NAI use, and oseltamivir has been found to be generally well tolerated in adults and children. Another common perception is the need for early treatment. A recent quality improvement endeavor demonstrated that many providers were unaware that influenza treatment was recommended beyond 48 hours of symptom onset (116). As described in this thesis, several studies have demonstrated the utility of NAI treatment even after start of therapy > 48 hours of symptom onset. For many children with an ILI, neuraminidase inhibitor treatment is often only considered after a specific diagnosis of influenza is made, either by clinical judgment or after laboratory confirmation. In the past, the turnaround times of diagnostic tests were longer than what is seen today, and prescribing rates were lower. Further, the symptoms of influenza infection overlap significantly with other respiratory viruses; healthcare workers who rely exclusively on clinical

judgment may unfortunately fail to suspect or diagnose influenza, and subsequently prescribe antivirals. Consequently, clinical dilemmas also contribute to low antiviral utilization rates.

Additionally, the lack of availability of RCT data of NAI use in hospitalized patients contributes to lack of confidence in the utility of this therapy. In a recent survey conducted in the United Kingdom in 2017, 50 senior clinicians actively involved in the care of adult patients hospitalized with severe respiratory infections and/or respiratory infection research were asked their opinion on the evidence for benefit of NAIs in influenza, and their current practice in relation to testing for influenza, treating empirically with NAIs, and prescribing NAIs when influenza was virologically confirmed (117). Only 31% respondents agreed that NAIs are effective at reducing influenza mortality; 40% disagreed and the remainder neither agreed nor disagreed. Only 64.5% said that they would prescribe NAIs if influenza infection was confirmed, 89% clinicians agreed that a placebo-controlled clinical trial should be conducted and 85% said that they would participate in such a trial (117). Despite observational data being generally at a higher risk of bias than RCTs; they offer their own value. While RCTs are normally better at determining efficacy, observational data can better reflect the effectiveness of an intervention in usual care and identify rarer outcomes (118). In formulating policy and guidance, it can therefore be appropriate to use observational data, particularly when data from large, pragmatic RCTs are not available (118).

Perhaps the only way to settle the debate about oseltamivir treatment benefit in hospitalized influenza patients is to conduct a large placebo-controlled RCT. There are particular difficulties inherent to the design and conduct of clinical trials of treatment or prophylaxis of influenza, and to the interpretation and application of their results in clinical and public health practice (119). This is especially complicated by the fact that oseltamivir has been recommended as standard of care for the treatment of influenza, and therefore a RCT would raise ethical challenges. Further, specific to designing RCTs studying children, since the duration of hospitalization is shorter and in-hospital mortality is low among most children with influenza in comparison with adults, different endpoints, outcomes, and numbers of estimated participants will be needed for studies in children than in adults (120). Choosing an appropriate study population of interest in the oseltamivir treatment RCTs is also complicated. Although some studies have focused upon all participants with a nonspecific influenza-like illness syndrome (ITT population), most studies have considered the findings for the ITTi (laboratory confirmed influenza) population. Oseltamivir is

not known to have any antiviral effects against non-influenza respiratory viruses that can cause influenza-like illness. As a result, reporting of ITT results is biased against finding clinical benefit because any treatment effect for influenza virus infection would be diminished by including participants who tested negative for influenza (119). Given all these challenges in RCT conduct and design, consideration should also be given to novel approaches for clinical trials, such as pragmatic or adaptive designs, drawing from experience in other disease areas, for example, assessments of cancer therapies and the treatment of Ebola (121).

In addition to strengthening the evidence base and its quality through elegant research methods, there is also a need for multifaceted interventions to strengthen adherence to influenza treatment guidelines. Such attempts have previously demonstrated success. Using quality improvement methods, Murphy *et al* sought to increase influenza testing and treatment of children admitted to a 271-bed, freestanding children's hospital in Nashville, Tennessee during the 2014-15 influenza season (116). Interventions included awareness modules, biweekly flyers, and failure tracking. Following the rollout of the intervention, appropriate testing and treatment increased from a baseline mean of 65% to 91% within 3 months, and these gains were sustained in the subsequent season as well (116). Adoption of similar approaches, as well as advocating for adherence to guidelines will go a long way in increasing overall utilization rates of antivirals and improved outcomes in children hospitalized with influenza.

CHAPTER 6 – SUMMARY AND CONCLUSIONS

In summary, in this thesis, I have explored the extent of antiviral use and factors associated with antiviral use amongst Canadian children hospitalized with influenza in the decade following the 2009 H1N1 influenza pandemic. This study is the first of its kind to explore and present such trends in antiviral utilization amongst Canadian children hospitalized with influenza, using data from a nationwide active surveillance network, and one of the largest such studies globally in the post 2009 H1N1 pandemic period. I have found that the rate of utilization of antivirals for the treatment of influenza in hospitalized children in Canada was low overall. Despite national clinical practice guidelines, utilization is poor, and there is a wide variation in antiviral prescribing practices across the country. However, a recent trend towards increased utilization is noted across centers located across Canada. I have also been able to identify patient and hospital-level characteristics that go on to influence prescribing practices. Effectively increasing the utilization of antivirals for influenza amongst hospitalized Canadian children will require multifaceted interventions to strengthen adherence to influenza treatment guidelines and antimicrobial stewardship practices.

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