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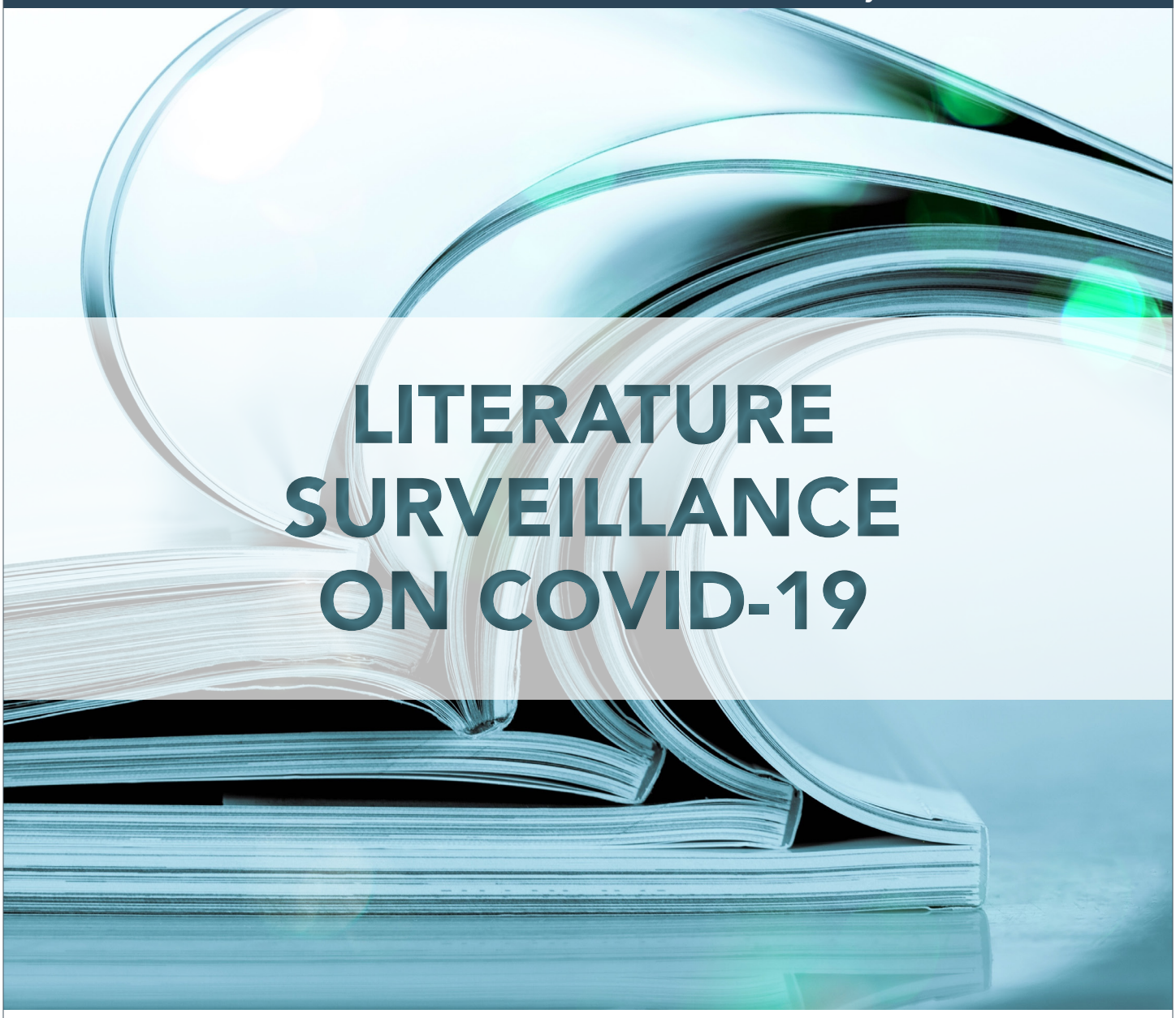

LITERATURE SURVEILLANCE ON COVID-19

Public Health Agency of Canada | Agence de la santé publique du Canada

Canada

CCDR
CANADA COMMUNICABLE DISEASE REPORT

The *Canada Communicable Disease Report* (CCDR) is a bilingual, peer-reviewed, open-access, online scientific journal published by the Public Health Agency of Canada (PHAC). It provides timely, authoritative and practical information on infectious diseases to clinicians, public health professionals, and policy-makers to inform policy, program development and practice.

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The cover photo represents a pile of open journals, illustrating the literature surveillance that became an integral part of the surveillance of new information from studies (epidemiology, clinical, and non-clinical) pertaining to the COVID-19 pandemic. This image was taken from Adobe Stock #268810733.

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LITERATURE SURVEILLANCE ON COVID-19

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RAPID COMMUNICATION

Rabies in an imported dog, Ontario, Canada, 2022

Paul Di Salvo[1]*, Maureen Anderson[2], Christine Fehlner-Gardiner[3], Francesca Di Mauro[4], Howard Shapiro[1], Anna Miranda[1], Heather McClinchey[5]

Abstract

Importation of rabies-infected dogs results in significant and costly public and animal health risks. In January 2022, a dog in Ontario, Canada, which was imported from Iran in June 2021, developed rabies, leading to an extensive public health investigation and administration of rabies post-exposure prophylaxis to 37 individuals. The dog was infected with a rabies virus variant known to circulate in Iran. This is the second reported case of a rabies-infected dog imported into Canada in 2021 from a high-risk country for canine mediated rabies. This case emphasizes the need for public education regarding the risks associated with importing dogs from high-risk countries for canine-mediated rabies and the benefits of establishing a public health team specializing in rabies exposure investigations.

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Keywords: imported dog, rabies, canine-mediated, risk assessment, animal importation, zoonoses

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Introduction

The rabies virus is primarily transmitted through saliva, most commonly via animal bites, and causes infection in mammals, including humans, that is almost invariably fatal, with the clinical course rarely lasting beyond seven days in humans (1–3). In humans, rabies causes an estimated 59,000 deaths annually worldwide (4). The majority of cases occur in rabies-endemic areas, with approximately 99% resulting from canine-mediated rabies (4,5). There are many variants of the virus, and these variants tend to be present in specific animal species and/or geographical locations (6).

Canine-mediated rabies was eliminated from the United States (US) in 2007 and has not been detected in Canada since rabies variant typing began in the 1980s (7). Animal importation, however, has the potential to introduce rabies and other zoonotic diseases into domestic animal and human populations. Countries such as Canada and the US have established control programs and regulations for rabies, which include rabies vaccination requirements for imported dogs, but these regulations do not always prevent the importation of infected dogs during their incubation phase: between 2015 and 2021, four dogs with canine-mediated rabies were imported into the US (8). In July 2021, a dog from Iran became the first reported case of canine-mediated rabies imported into Canada (9,10).

In July 2021, the US Centers for Disease Control and Prevention (CDC) implemented a temporary suspension of dogs entering the US from 113 countries considered high-risk for canine-mediated rabies, following a 52% increase in imported dogs from these countries being denied entry on arrival over the preceding years, mainly due to fraudulent rabies certificates (11,12). The temporary suspension was implemented while the CDC evaluated options to address the issue long term. It has been estimated that 23% of commercial dog imports to Canada from 2013 to 2019 originated from countries considered high-risk for canine-mediated rabies (*personal communication, Jillian Blackmore, March 11, 2022*).

In January 2022, a dog in Toronto, Canada, developed rabies following importation from Iran in June 2021. This is the second reported case of dog infected with canine-mediated rabies imported into Canada in 2021. Local public health units investigated the case and worked with human and animal health agencies to manage the risk to human health.

Public health investigation

The affected dog was imported into Canada on June 28, 2021, at approximately three months of age from Tehran, Iran—a country considered high-risk for canine-mediated rabies by the Canadian Food Inspection Agency (CFIA) (13). It was imported by an animal rescue organization, as a personally owned pet, with documentation of rabies vaccination in Iran dated June 2, 2021, meeting the importation requirements since there is no waiting period between vaccination and importation for personally owned pets. The dog had no observed exposures to bats or other wild animals while in Canada. On January 11, 2022, the dog developed mild neurological abnormalities that progressed rapidly despite intensive in-hospital care until the dog was euthanized on January 16, 2022. Details of the dog's clinical progression are presented in **Figure 1**.

On January 15, 2022, six Ontario public health units, led by Toronto Public Health, initiated a potential rabies exposure investigation, with the support of other agency partners, including the Ontario Ministry of Health, Ontario Ministry of Agriculture, Food and Rural Affairs, Canada Border Services Agency and CFIA.

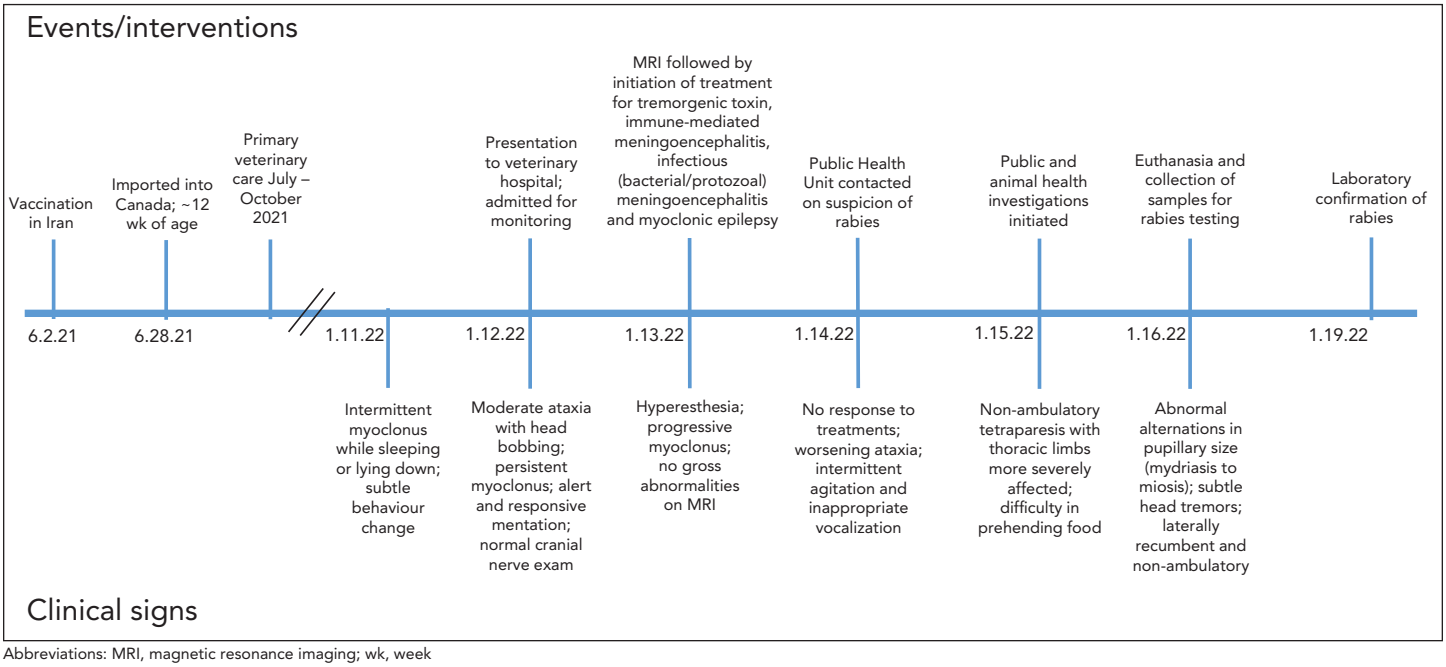
Tissues were submitted to the CFIA laboratory for rabies testing and a positive fluorescent antibody test result was confirmed on January 19, 2022. Further testing by indirect immunofluorescence assay and reverse transcription-polymerase chain reaction confirmed the initial rabies diagnosis. Partial sequencing of the nucleoprotein gene followed by phylogenetic analysis indicated that the infecting virus grouped with canine variant rabies viruses known to circulate in Iran and Iraq.

Any person or domestic animal that had contact with the infected dog during the potential (ten days) viral shedding period, from December 31, 2021, to January 16, 2022, was interviewed to determine their rabies exposure risk. Rabies exposure risk assessments were conducted by the public health units in accordance with the Ontario Rabies Prevention and Control Protocol, 2020 in consultation with the potentially exposed persons and their healthcare providers, as necessary (14). A total of 37 individuals were administered rabies post-exposure prophylaxis.

A total of 42 individuals were interviewed due to having contact with the infected dog during the at-risk period, of which 41 were family or friends of the animal owners (n=16) or staff at the veterinary clinic (n=25). There was one initially unidentified Toronto resident (and their pet dog) who had contact with the infected dog during the risk period but for whom the animal owners had no means of contact. Toronto Public Health and an adjacent health unit undertook strategies to locate this individual, including animal control database searches, door-to-door canvassing over a 13-block area and a neighbourhood poster campaign. Ultimately, a media campaign was successful in reaching the individual who came forward on January 26, nearly two weeks following the exposure.

Public health staff identified seven dogs associated with individuals who were assessed for potential exposure to the rabid dog. Two of the dogs did not have any contact with the rabid dog during the risk period for virus shedding. Exposure of the other five dogs, all of which were currently vaccinated for rabies, was assessed by their primary care veterinarians and Ontario Ministry of Agriculture, Food and Rural Affairs veterinary

Figure 1: Timeline of events and clinical progression of imported rabid dog in Ontario, Canada, June 2021 to January 2022



Abbreviations: MRI, magnetic resonance imaging; wk, week

staff. Three dogs had only minor casual contact with the infected dog and were not considered at risk for rabies exposure. Two of the remaining dogs had potential non-bite exposure to the infected dog's saliva. One was revaccinated within seven days of exposure and was placed under observation for 45 days. Because the seventh dog was not identified until two weeks after the exposure, it was placed under a precautionary confinement period for three months following booster vaccination. None of the in-contact dogs developed rabies.

Conclusion

This is the second reported case of a rabies-infected dog imported into Ontario, Canada in 2021. This case emphasizes the need for countries to be vigilant with animal importation regulations, and for owners of imported dogs from high-risk countries to understand that the risk of these dogs developing rabies can persist for weeks to months after arrival. While this dog arrived with documented rabies vaccination and appeared healthy, further investigation revealed significant inconsistencies that cast doubt on the validity of the documentation and likely efficacy of the reported vaccination. Federal import requirements for dogs have been under review in Canada for several years; in May 2021 various changes were made to importation requirements for commercial dogs under eight months of age (15). This review should continue for all categories of dogs, with the aim of preventing animals infected with rabies from entering Canada. In June 2022, the CFIA announced that as of September 28, 2022, commercial dogs from countries at high-risk for dog rabies will no longer be permitted entry into Canada, regardless of age (13).

This investigation highlights the need for public health agencies to ensure fulsome rabies exposure risk assessments are conducted for every reported exposure, including scrutinizing vaccination certificates and travel history of pets. Based on the animal's estimated age at the time of rabies vaccination in Iran, the use of a vaccine product not licensed for use in Canada and provincial rabies vaccination regulations, this dog should have been revaccinated for rabies upon arrival in Ontario. It is unknown whether re-vaccination on arrival would have prevented the onset of rabies infection in this dog, particularly given the abnormally long incubation period of over six months.

Toronto Public Health led this investigation with four Public Health inspectors from a slightly larger team of Public Health inspectors with specialty training in rabies investigations. This small team was very efficient and effective at conducting patient consultations, complex risk assessments and contact tracing. This allowed other team members to focus on other routine investigations and negated the need to utilize non-specialist Public Health inspectors, despite the large number of individuals who required assessments. Where possible, public health agencies should consider establishing specialized teams of public health officials for investigating potential rabies exposures.

This investigation also highlights the ongoing need to raise awareness with healthcare providers, veterinarians, animal rescue organizations and the public, regarding the risk of rabies in imported dogs. This will help rescue organizations and animal owners to make more informed decisions on selection of animals for import and adoption, and help healthcare providers and veterinarians to better manage their respective patients. Additional actions that should be considered include ongoing work to identify high-risk rabies countries, implementing timely and legislated rabies immunization of animals and improving both qualitative and quantitative assessment of canine imports to Canada.

Authors' statement

PD — Writing–original draft, writing–review & editing, investigation, conceptualization, supervision
MA — Investigation, writing–review & editing
CFG — Investigation, writing–review & editing
FD — Investigation, writing–review & editing
HS — Investigation, writing–review & editing
AM — Investigation, writing–review & editing
HM — Investigation, writing–review & editing

The content and view expressed in this article are those of the authors and do not necessarily reflect those of the Government of Canada.

Competing interests

None.

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COVID-19 literature surveillance—A framework to manage the literature and support evidence-based decision-making on a rapidly evolving public health topic

Tricia Corrin[1]*, Dima Ayache[1], Austyn Baumeister[1], Kaitlin Young[1], Kusala Pussegoda[1], Rukshanda Ahmad[2], Lisa Waddell[1]

Abstract

Background: The coronavirus disease 2019 (COVID-19) pandemic has led to a rapid surge of literature on severe acute respiratory syndrome coronavirus 2 and the wider impacts of the pandemic. Research on COVID-19 has been produced at an unprecedented rate, and the ability to stay on top of the most relevant evidence is top priority for clinicians, researchers, public health professionals and policymakers. This article presents a knowledge synthesis methodology developed and used by the Public Health Agency of Canada for managing and maintaining a literature surveillance system to identify, characterize, categorize and disseminate COVID-19 evidence daily.

Methods: The Daily Scan of COVID-19 Literature project comprised a systematic process involving four main steps: literature search; screening for relevance; classification and summarization of studies; and disseminating a daily report.

Results: As of the end of March 2022 there were approximately 300,000 COVID-19 and pandemic-related citations in the COVID-19 database, of which 50%–60% were primary research. Each day, a report of all new COVID-19 citations, literature highlights and a link to the updated database was generated and sent to a mailing list of over 200 recipients including federal, provincial and local public health agencies and academic institutions.

Conclusion: This central repository of COVID-19 literature was maintained in real time to aid in accelerated evidence synthesis activities and support evidence-based decision-making during the pandemic response in Canada. This systematic process can be applied to future rapidly evolving public health topics that require the continuous evaluation and dissemination of evidence.

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Keywords: COVID-19, evidence-based decision-making, literature surveillance, evidence synthesis, knowledge synthesis, SARS-CoV-2

Introduction

The rapid spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19), across the globe in early 2020 sparked an immediate urgency for evidence to understand the virus and how to combat it. Although evidence was scarce at the beginning of 2020, it was anticipated that a rapid surge of research would emerge based on recent experience with the Zika pandemic (1,2). As the pandemic began to unfold, there

was a swift influx of evidence on COVID-19, which varied in breadth from clinical epidemiology to the impact of public health interventions. Staying on top of the most recent evidence was extremely important to keep researchers and decision-makers up-to-date as fast as possible on what was both known and unknown.

With the world looking for answers about the evolving COVID-19 pandemic, it was evident there was an urgent need for an efficient literature surveillance system to identify, manage, synthesize and disseminate this evidence daily. The aim of this article is to report the process developed by the Public Health Agency of Canada (PHAC) to manage and maintain a COVID-19 literature surveillance system on a predictable 24-hour cycle to meet the evidence needs of several research and policy groups while reducing redundancies in search and retrieval efforts.

Methods

Role of the Public Health Agency of Canada in response to the COVID-19 pandemic

The Public Health Agency of Canada is responsible for preparing and responding to public health emergencies (3). In response to the pandemic, an Emerging Sciences Group was created within PHAC consisting of employees at the Agency with a variety of expertise in infectious disease modelling, epidemiology, clinical care, diagnostics, virus research and knowledge synthesis expertise. The role of the Emerging Sciences Group was to help coordinate and share information across disciplines within the Agency and COVID-19 literature surveillance was a key priority identified by this group. In collaboration with Emerging Sciences Group members, a knowledge synthesis team with extensive experience in infectious diseases within PHAC took the lead in developing and maintaining a COVID-19 literature surveillance system to aid in the COVID-19 pandemic response.

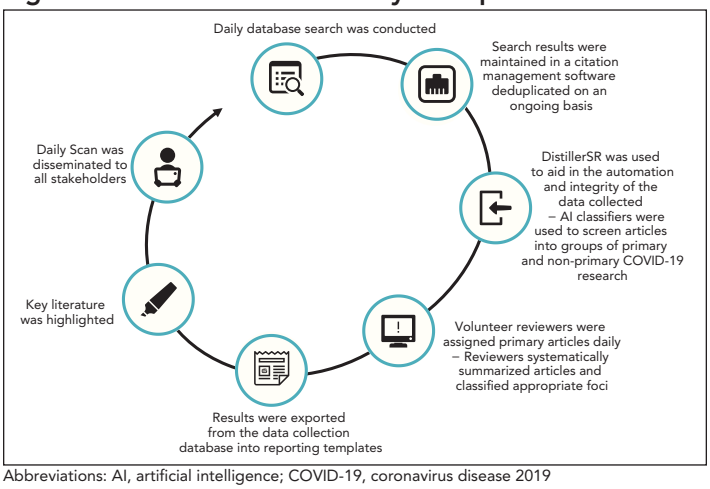
Purpose and scope of the project

The literature surveillance project was initiated in January 2020, with the main goal of creating and maintaining a central repository of COVID-19 literature to aid in evidence synthesis activities, promote the use of up-to-date evidence by researchers and policymakers through daily updates on new evidence, and support evidence-based decision-making across the Agency. This project was named the Daily Scan of COVID-19 Literature (referred to as the Daily Scan).

At its inception, there were no other repositories anywhere in the world that compiled the literature on COVID-19. Over time, several COVID-19 repositories were created (e.g. Cochrane, LOVE, LitCOVID, WHO COVID literature database), each with its own focus and methods for mapping the COVID-19 literature (4–7). This Daily Scan project differs in that 1) articles were searched and retrieved from preprint databases, which required manual extraction of citations, 2) all COVID-19 literature was included without restriction, 3) the search was conducted each morning from Monday to Friday (24-hour cycle) and 4) the literature was compiled and disseminated to end users daily.

The Daily Scan was developed based on well-known and established knowledge synthesis methodologies that employ systematic methods to identify, collect, map and report on evidence underpinning a broad topic, while also addressing the need for a real-time living evidence base that could be tapped into to monitor the evolution of priority topics (8–12). The Daily Scan comprised a systematic process involving four main steps: searching the literature, relevance screening; classification and summarization of studies; and disseminating evidence in a daily report (**Figure 1**). A high-level overview of each step in this process is described below and additional details can be found in **supplemental material**.

Figure 1: Flow chart of the Daily Scan process



Abbreviations: AI, artificial intelligence; COVID-19, coronavirus disease 2019

Daily Scan team

Since the inception of this project, the National Microbiology Laboratory knowledge synthesis team has coordinated the contributions of more than 50 people from across PHAC. A search specialist and three scan leads managed and coordinated day-to-day project activities with oversight by a manager. Each day approximately 10–15 reviewers contributed to reviewing, categorizing and summarizing the literature on a part-time basis (1–3 hours a day).

Search strategy

A search of the literature (published and pre-published) was conducted daily Monday through Friday. Searches to retrieve relevant COVID-19 literature were conducted in seven databases: PubMed, Scopus, BioRxiv, MedRxiv, ArXiv, SSRN and Research Square. ArXiv, SSRN and Research Square required a manual citation extraction process.

Database management

Search results were managed in citation management software, Endnote (EndNote X8, Clarivate Analytics). To facilitate access to the citation database by end users, the citations were transferred to another citation management software, RefWorks (RefWorks, ProQuest LLC). The citations were then imported into the web-based systematic review management software DistillerSR® (Evidence Partners Inc., Ottawa, Canada). Duplicates were identified and removed in each software.

Management of citations for screening, characterizing, and data extraction was conducted using DistillerSR. This platform allowed a large number of reviewers to work on the project simultaneously across the Agency.

Categorization of COVID-19 literature

After the daily search results were imported into DistillerSR, two artificial intelligence classifiers (DistillerAI) were applied to automatically categorize the COVID-19 literature into three pre-defined groups: synthesis research (e.g. systematic reviews, meta-analyses, scoping reviews); primary research; and non-primary articles (e.g. narrative reviews, commentaries, letters to editors). The primary research then proceeded to a data collection level for further categorization and summarization.

Each morning, the primary literature was divided and distributed within DistillerSR to a team of reviewers. A data collection form designed at the beginning of the project was used to collect information for each primary research article in DistillerSR. The form allowed a reviewer to provide a brief synopsis of the evidence, classify it into predetermined foci (e.g. epidemiology, transmission) and ensure that there was a working article link to the article so it could be readily accessed. The reviewers also identified any primary literature that was noteworthy in their assigned articles to include in the "highlights section" of the Daily Scan email report to draw end-user attention to new research on priority COVID-19 topics. One reviewer filled out the data collection form for each article. The scan leads conducted frequent spot checks to verify results and ensure consistency.

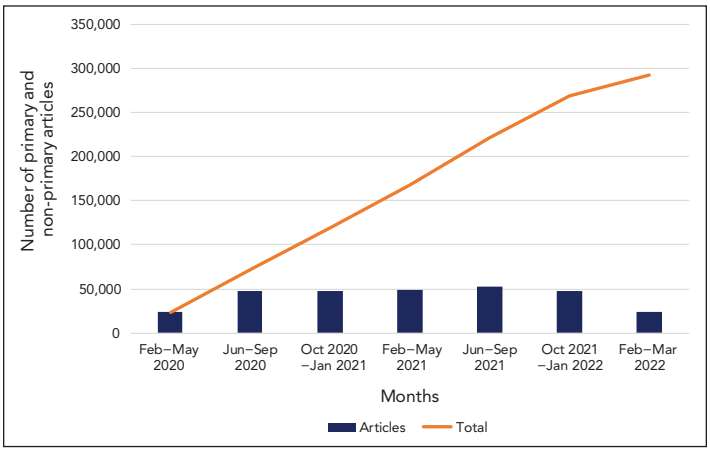
Results

Volume and focus of literature

Initially there were fewer than 50 citations identified daily, which increased quickly through the winter of 2020 to a median of 700 citations per day. After the first six months of the pandemic (January–June 2020) the volume of research being produced stabilized at approximately 50,000 articles per six-month period (**Figure 2**). At of the end of March 2022 there were approximately 300,000 COVID-19 and pandemic-related citations in the database.

Although there was a median of 700 citations identified daily, the range was 200–2,500 citations. Generally, 50%–60% of

Figure 2: Volume of COVID-19 literature February 2020–March 2022



the citations were primary research and the others were non-primary articles (e.g. literature reviews, science news, conference proceedings).

Reviewers tagged each primary research article with one or multiple pre-determined foci that were addressed by the outcomes in the article. At the end of March 2022, the total number of articles by foci included clinical data (n=48,179), epidemiology (n=42,622), healthcare response (n=17,559), public health response (n=15,505), coronavirology (n=14,480), mental health (n=11,261), modelling (n=11,184), therapeutics (n=10,946), diagnostics (n=10,532), immunology (n=10,357), public health interventions (n=8,737), vaccine research (n=8,373), transmission (n=4,547), long-term sequelae (n=2,376), animal model (n=2,358), infection prevention and control (n=1,935), randomized controlled trials (n=1,547), surveillance (n=1,291), economics (n=1,020), zoonoses/COVID-19 in animals (n=419) and other COVID-19/pandemic impact research not covered by other foci (n=15,811).

Dissemination of the Daily Scan

The data was then compiled each day to produce the Daily Scan. The data was first exported out of DistillerSR into a Microsoft Excel template that was developed to automatically organize the data into the format required for the report. A Microsoft Word template was then populated with each article, foci(s) and summary. Finally, this report was placed in an email along with the literature highlights for the day and a link to both the citation database and Microsoft Excel spreadsheet accessible through Google Drive that contained a searchable list of all the literature with their foci categorizations and summaries. The mailing list for the Daily Scan included over 200 recipients and groups including federal, provincial and local public health agencies, and academic institutions.

Database maintenance

As pre-published articles (preprints) underwent peer review and were published, they were picked up in the search and flagged. A process was developed to remove preprints from the

databases once an article was published to ensure that preprint articles were not accidentally used in place of published articles by end users. The search specialist identified published articles that were previously preprints and proceeded to quarantine them in Refworks, DistillerSR and the Excel sheets.

Utilization of the Daily Scan

The results of the Daily Scan were used in a variety of ways by end users across PHAC and other organizations. First, the daily report and highlights were used extensively by groups working on the pandemic response to keep apprised of key new research relevant to their work. As our database covered all COVID-19 literature, including wider consequences of the pandemic, it was a resource that met the needs of a wide range of end users responding to the pandemic.

Second, evidence synthesis teams across PHAC have capitalized on this database resource to rapidly respond to urgent requests for evidence, conduct rapid evidence syntheses on priority questions, and to streamline evidence into other domain-focused projects (e.g. vaccines, therapeutics, public health measures). The knowledge synthesis team that led this project has also conducted over 150 rapid evidence syntheses on high-priority COVID-19 topics since February 2020. An up-to date and searchable repository was a key feature of this project for producing these evidence synthesis products rapidly. Other groups also utilized the repository for evidence synthesis reviews, reporting evidence highlights to senior management, populating predictive models, creating guidelines, web content and answering media requests.

In November 2021, a short survey was sent to all the Daily Scan recipients to gain additional insight on how the Daily Scan was being utilized and to assess the need to continue this project. The survey reported a consensus that the Daily Scan remained a valuable and necessary tool for the ongoing pandemic response within and outside of PHAC. Several teams indicated that they would be negatively affected should it be discontinued and reported that they would have to allocate resources to search the literature to continue with their ongoing COVID-19 projects and activities.

Discussion

The breadth of this project, the inclusion of all COVID-19 literature, and the 24-hour update cycle are unique to this project and key to its usefulness to the extensive needs of researchers and decision makers within and outside PHAC. Keeping dedicated expertise on the COVID-19 literature facilitated rapid response work and ongoing assessment of knowledge gaps during the pandemic.

Limitations

There were several limitations to this methodology. First, this project was created and implemented within a very short timeframe using existing resources. Different software and further automation of searching, screening, classification of articles and reporting could have made this process more efficient. However, time and resource constraints with this project and other COVID-19 priority projects limited the capacity to keep the Daily Scan running while making significant changes that may have improved the efficiency of the process.

The process was developed to be feasible to conduct on a 24-hour cycle. This meant that while the search was thorough, we may have missed citations due to language or omission by the search strategy (Supplemental material). There was always the potential for human error in conducting the search, reviewing and classifying articles, and maintaining and updating the database.

Current and future applications

Given the urgent need for evidence-based public health decisions during a public health emergency such as the COVID-19 pandemic, the rapid and systematic gathering and synthesis of evidence is extremely important. At the time of writing, this database continues to be maintained and remains an essential resource to multiple departments throughout PHAC for use in the continued COVID-19 response.

To be prepared for the next public health emergency, post-pandemic planning will be essential to improve upon our existing literature surveillance framework. A priority will be to increase automation and efficiency at different stages of the literature surveillance process by acquiring the software and expertise to embed more automation within the process. Development of a web interface or dashboard for the Daily Scan would reduce the amount of time spent creating and disseminating the reports. This would allow end users to directly access and interact with the COVID-19 literature database, eliminating many report preparation steps in the current process. As artificial intelligence technologies are rapidly evolving, future literature surveillance may be able to work towards automated study summarization, significantly reducing the human resources required to run the project. Any of the above possible improvements will increase efficiency of the process, making it more feasible to implement for the next public health emergency.

Conclusion

This paper provides insight into a process for developing and maintaining a literature surveillance system to manage the surge of COVID-19 research during the pandemic. Despite the unprecedented amount of literature on the pandemic, the literature surveillance process identified, characterized, summarized and disseminated evidence daily for over two years and facilitated the use of evidence in decision-making by PHAC and external stakeholders. This framework could be applied to

any public health emergency with a rapidly evolving evidence base that requires ongoing real-time monitoring for use in decision-making.

Authors' statement

TC — Project lead, contributed to design updates, wrote manuscript
DA — Project lead, contributed to design updates, contributed to results section of manuscript
AB — Project lead, contributed to design updates
KY — Worked on project, contributed to design updates
KP — Worked on project, contributed to design updates
RA — Conceptualization of project, worked on project
LW — Conceptualization, design and initiation of the project, supervisor

All authors approved the final version for publication.

Competing interests

None.

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Supplemental material

These documents can be accessed on the Supplemental material file.

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National influenza mid-season report, 2022–2023: A rapid and early epidemic onset

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Abstract

Canada's 2022–2023 national influenza epidemic was declared in epidemiological week 43 (week ending October 29, 2022), relatively early in comparison to historical seasons. This year marks the return to pre-pandemic-like influenza circulation, following the brief and delayed influenza epidemic declared in the spring of the 2021–2022 season. To date this season, 59,459 detections of influenza have been reported out of 456,536 tests; both values exceeding historical averages. This epidemic is being fundamentally driven by influenza A, with influenza A(H3N2) accounting for 94% of subtyped detections. This season to date has had a significant impact on adolescents and young children, with a high proportion of detections occurring in those aged 0–19 years (42%). Provinces and territories have reported higher than usual influenza-associated hospitalizations, intensive care unit admissions, and deaths in comparison with previous seasons; in particular, paediatric hospitalization incidence was persistently far above historical peak levels for several weeks. The return of seasonal influenza circulation highlights the importance of sustained vigilance with regard to influenza and employment of available mitigation measures, especially of annual seasonal influenza vaccination.

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Keywords: influenza, epidemic, surveillance, paediatric, influenza A(H3N2), Canada

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Introduction

This surveillance report summarizes the first 18 weeks of the 2022–2023 influenza season in Canada based on FluWatch data reported by the Public Health Agency of Canada from August 28 to December 31, 2022 (1). The national influenza epidemic began in epidemiological week 43 (week ending October 29, 2022), when the percentage of influenza tests positive exceeded the seasonal threshold of 5%. Following the brief influenza epidemic in the spring of 2022, this season is the first re-emergence of pre-pandemic influenza circulation patterns in Canada (2–4).

Methods

FluWatch is Canada's influenza surveillance system which monitors the national spread of influenza and influenza-like-illness (ILI) through core surveillance indicators based on global epidemiological standards (5). FluWatch consists of seven key areas of surveillance: syndromic surveillance; virological surveillance; geographic spread; outbreak surveillance; severe outcome surveillance; influenza strain characterization; and vaccine monitoring. Detailed methods, including surveillance indicator definitions, data sources and statistical analyses, can be found in the 2021–2022 National Influenza Annual Report (2). Pre-pandemic seasonal averages are computed using data from 2017–2018 to 2019–2020 unless stated otherwise. **Table 1** summarizes seasonal indicators up until week 52, compared with recent pre-pandemic seasons.

Laboratory detections

To date this season, a total of 59,459 influenza detections (from 456,536 tests) have been reported across the country, virtually all of which were influenza A (**Figure 1**). The number of detections at this point in the season was significantly higher than the pre-pandemic seasonal average (n=11,757) when average testing volumes were much lower (93,572 tests). Influenza A(H3N2) accounted for almost all influenza A detections (94%). Among the 37,670 detections for which detailed age information was provided, no significant differences in strain distribution were observed among age groups; however, the high proportion of detections among those younger than 19 years of age early in

Table 1: Season indicators reported up to week 52 compared to recent pre-pandemic seasons, 2017–2018 to 2019–2020

Indicator		2022–2023	2019–2020	2018–2019	2017–2018
Epidemic onset		Week 43	Week 47	Week 43	Week 45
Onset to peak		5 weeks	14 weeks	8 weeks	14 weeks
1st report of localized activity		Week 35	Week 40	Week 38	Week 36
Peak percent positivity week (%)		Week 47 (23.8%)	Week 6 (29.7%)	Week 52 (28.9%)	Week 7 (32.5%)
Dominant circulating influenza type (%)		Influenza A (99%)	Influenza B (51%)	Influenza A (99%)	Influenza A (74%)
Dominant circulating influenza A subtype (%)		H3N2 (94%)	H3N2 (68%)	H1N1 (93%)	H3N2 (96%)
Proportion of detections among ages 65 years and older (%)		26	21	16	44
Proportion of detections among ages 19 years and younger (%)		42	44	41	19
Provincial and territorial severe outcomes[a]	Cumulative hospitalization rate (per 100,000)	41	7	13	19
	Hospitalizations	3,411	618	1,064	1,493
	ICU admissions	301	73	151	114
	Deaths	182	22	27	34
Paediatric severe outcomes[b]	Hospitalizations	1,505	264	414	195
	ICU admissions	183	57	71	35
	Deaths	6	0	fewer than 5	fewer than 5
Outbreaks	Total outbreaks	534	146	86	288
	Proportion of outbreaks in LTCFs (%)	54	58	43	57

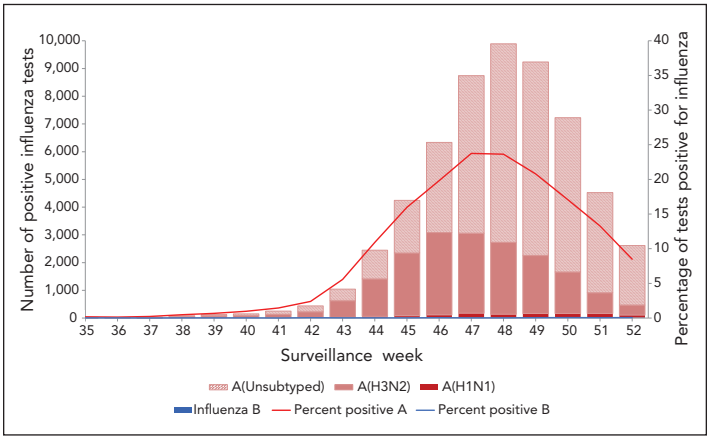
Abbreviations: ICU, intensive care unit; LTCFs, long-term care facilities
[a] Influenza-associated hospitalizations are reported by Alberta, Manitoba, New Brunswick, Newfoundland and Labrador, Northwest Territories, Nova Scotia, Prince Edward Island and Yukon. Only hospitalizations that require intensive medical care are reported by Saskatchewan
[b] Paediatric influenza-associated severe outcomes are reported by the Immunization Monitoring Program Active (IMPACT) network. The IMPACT paediatric sentinel hospital network consists of 12 paediatric hospitals across Canada, located in Alberta, British Columbia, Quebec, Ontario, Nova Scotia, Newfoundland and Labrador, Saskatchewan and Manitoba

the season was a notable feature of this season. To date, 42% of detections occurred among those aged 0–19 years, compared with an average of 35% in previous pre-pandemic years and detections among those aged 65 years and older are within proportions previously seen.

In week 43, influenza activity surpassed the epidemic threshold, and an influenza epidemic at the national level was declared. This season's onset occurred earlier than the historical average (week 45); however, it was not unprecedented, with the 2018–2019 national influenza epidemic also beginning in week 43. Since onset, influenza percent positivity increased sharply week to week, reaching a peak level of 23.8% (week 47), before beginning to decrease steeply in week 48. This season's five week duration of onset to peak appears to be shorter than historical averages (12 weeks).

Among the small sample of influenza viruses submitted to the National Microbiology Laboratory (n=168) from provincial/territorial public health laboratories for antigenic characterization, all were similar to the 2022–2023 recommended Northern Hemisphere influenza vaccines, and all were sensitive to the antivirals oseltamivir and zanamivir.

Figure 1: Number of positive influenza tests and percentage of tests positive, by type, subtype and report week, Canada, 2022–2023 influenza season to date, weeks 35 to 52



Syndromic surveillance

To date this season, all FluWatch syndromic surveillance indicators correlated with the early increases in activity reported through virologic surveillance with activity either above average levels or above expected levels typically seen in the fall and early winter. The general increase in cough and fever reported by volunteer FluWatcher participants began in week 37. To date, an average of 10,957 FluWatchers responded on a weekly basis, and the percentage of FluWatchers reporting a cough and fever remained above expected levels for five weeks (weeks 43 to 47).

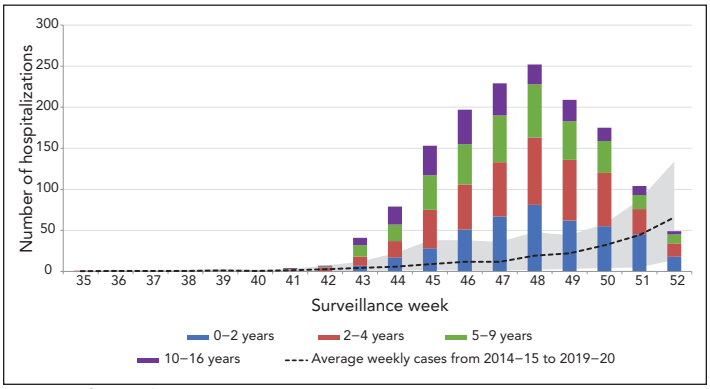
The general increase in ILI activity reported by sentinel primary healthcare providers started week 42 and remained above average levels for six weeks (weeks 45 to 50); thereafter, ILI activity remained elevated but within pre-pandemic seasonal respiratory norms. Thus, ILI activity from the co-circulation of respiratory viruses including influenza, respiratory syncytial virus and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was comparable to the elevated levels seen during a typical pre-pandemic respiratory season (6). A weekly average of 46 sentinel primary care providers reported to the ILI surveillance system, seeing a weekly average of 3,276 patients.

Severe outcomes

To date this season, 3,411 influenza-associated hospitalizations have been reported by the nine participating provinces and territories, the overwhelming majority of which have been linked to influenza A. The number of hospitalizations to date was well above the historical numbers reported at this time of year (n=1,058). Among these hospitalizations, heterogeneity exists between age groups. The highest cumulative hospitalization rates were among those aged 0–4 years (n=112/100,000 population) followed by those aged 65 years and older (n=109/100,000 population). These rates significantly exceeded both the cumulative rates among remaining age groups and the overall cumulative hospitalization rate this season (n=41/100,000 population). This season has also been marked by increased intensive care unit (ICU) admissions and deaths (301 ICU admissions and 182 influenza-associated deaths) relative to historical pre-pandemic seasons (average of 113 ICU admissions and 28 deaths), as reported by from nine participating provinces and territories. Over half (60%) of ICU admissions this season have been among persons aged 45 years and older and 75% of deaths have occurred among persons aged 65 years and older.

To date this season, paediatric influenza-associated hospitalizations reported by the Immunization Monitoring Program Active (IMPACT) were far above historic levels ever reported through the program, with 1,505 hospitalizations (**Figure 2**). The number of weekly hospitalizations began to spike in week 42 before reaching a peak of 252 in week 48. Weekly incidence counts reported from week 45 onward (range 153–252 hospitalizations) exceeded the all-time season peak previously reported (n=151 in week 9 of the 2015–2016 season) for six consecutive weeks. Cumulatively, the number of paediatric influenza-associated hospitalizations at mid-season exceeded all prior annual/full-season numbers. Virtually all hospitalized cases were due to influenza A, and among subtyped cases (n=584), 94% were associated with influenza A(H3N2). The largest proportion of hospitalized cases was among children between the ages of two and four years (32%), followed closely by children between the ages of five and nine years (24%). Paediatric ICU admissions to date were also above historical averages, with 183 reported this season compared to an average of 54 in previous seasons. Approximately 12% of hospitalizations resulted in an ICU admission this season and children between the ages of two and four years and five and nine years accounted for 31% and 22% of paediatric ICU admissions respectively. Influenza-associated paediatric deaths were also higher than previous seasons, with six influenza-associated paediatric deaths being reported thus far.

Figure 2: Number of paediatric[a] hospitalizations reported by the Immunization Monitoring Program Active network, by age group, by week, Canada, 2022–2023 influenza season to date, weeks 35 to 52[b]



[a] 16 years of age and younger
[b] Shaded area represents the maximum and minimum numbers of paediatric hospitalizations reported by Immunization Monitoring Program Active (IMPACT) by week from seasons 2014–2015 to 2019–2020

Outbreaks

To date this season, 534 laboratory-confirmed influenza outbreaks have been reported. The number of outbreaks reported was higher than historical numbers reported at this time of year (n=173). All but one outbreaks reported were due to influenza A. Outbreaks reported in long-term care facilities accounted for the highest proportion of outbreaks (54%), followed by facilities classified as "other" (28%) (3). Among the 231 ILI outbreaks reported, nearly 99% occurred in schools/daycares.

Discussion

Following the short and delayed influenza A(H3N2)-dominant 2021–2022 influenza season, Canada has seen a return of late fall influenza activity resulting in a seasonal epidemic. This season, which began early relative to historical seasons, has since

demonstrated a steep progression and significant impacts on the paediatric population.

The length of the season is difficult to infer based on the timing of onset, as historical data points to differing trajectories. Factors such as the timing of the peak as well as the proportion of influenza A and B circulating have a bearing on the duration of the influenza epidemic. On average, historical pre-pandemic seasons have peaked at 30.4% between week 52 and week 7, in contrast to what has been seen so far this year. To date, the seasonal epidemic has been driven by influenza A(H3N2), with minimal circulation of influenza B. Contrary to previous pre-pandemic seasons, we have yet to see an increase in the relative proportion of influenza B detections. It is currently unknown whether Canada will see a typical late season wave of influenza B.

To date this season, trends in the severity of influenza cases have been heterogeneous between age groups. Paediatric hospitalizations reported by the IMPACT network were far above historically seen levels. Explanations behind this phenomenon are complex and difficult to untangle. The coronavirus disease 2019 (COVID-19) pandemic response disrupted seasonal respiratory virus transmission across the nation and resulted in a large unexposed cohort of young children who may be more vulnerable to severe infection. For instance, the IMPACT network reported no paediatric hospitalizations, ICU admissions or deaths throughout the 2020–2021 season (7). The cessation of previously mandated non-pharmaceutical interventions, such as mask wearing, may have facilitated the increase of transmission in the community (8,9). The lifting of travel and border measures may have allowed the re-introduction of seasonal influenza to Canada from regions where community circulation was occurring (10). When looking at the relative proportions of hospitalizations by age group, it is interesting to note that distributions are unusual given the predominance of influenza A(H3N2), a pattern that carries on from the late, short 2021–2022 season. Similar to the short epidemic experienced in the spring of the 2021–2022 season, to date, a higher proportion of detections and activity were among children and teenagers, who have typically experienced a lower proportion of detections and activity during influenza A(H3N2)-dominant seasons (2).

The beginning of seasonal vaccination campaigns coincided with the early onset of the seasonal influenza epidemic. Regardless of the timing of this season's peak percent positivity, influenza circulation is expected to persist for many weeks. In previous seasons, the progressive decline to levels below the epidemic threshold after reaching the peak has taken an average of 20 weeks (2016–2017 to 2018–2019). It remains important to seek vaccination in the face of the ongoing epidemic. Antigenic and genetic characterization results received to date suggest that the circulating strains of influenza A(H3N2), A(H1N1) and B are similar to the recommended Northern Hemisphere vaccine components for the 2022–2023 season. The vaccine effectiveness (VE) of the 2021–2022 vaccine against the current circulating A(H3N2) sub-clade was moderate (36%); however, this season's H3N2 component appears to be more antigenically similar to currently circulating strains (11). Although antigenic similarity is not a consistent predictor for vaccine effectiveness, which is dependent on several factors (12), preliminary findings from the Canadian Sentinel Practitioners Surveillance Network (SPSN) based on data up to week 50 indicate that the risk of medically-attended H3N2 illness was approximately halved among recipients of the current season's vaccine compared to unvaccinated individuals (13).

The early and relatively intense resurgence of influenza highlights the importance of continued seasonal influenza surveillance. The systematic collection of influenza surveillance data has enabled the situational awareness to respond to the current influenza season in the context of the ongoing COVID-19 pandemic. Additionally, the use of the same indicators as those used prior to the COVID-19 pandemic has allowed for the interpretation of both the magnitude and the spread of influenza in the 2022–2023 season. Ongoing, timely surveillance is crucial to Public Health Agency of Canada's ability to respond to influenza trends, monitor changes in circulation patterns, and facilitate preparedness for and planning of mitigation measures within the influenza season.

Authors' statement

The FluWatch team in the Centre for Immunization and Respiratory Infectious Diseases developed the first draft collaboratively; all authors contributed to the conceptualization, writing and revision of the manuscript.

Competing interests

None.

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Novel six-month all oral treatment of pre-extensively drug-resistant tuberculosis in Canada: New treatment options present new implementation challenges

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Abstract

Drug-resistant tuberculosis (TB) is a major global health challenge in part because there are fewer effective treatments and these treatments have been prolonged and more toxic. The evidence base for more effective, shorter, standardized treatments is evolving rapidly. Herein, we report the first case of pre-extensively drug-resistant pulmonary TB treated with a novel six-month all oral bedaquiline, pretomanid and linezolid (BPaL) regimen in Canada. Recent clinical trial data supporting BPaL therapy is presented in the context of current and evolving clinical guidelines. In this article, we highlight significant implementation challenges and make recommendations for what needs to be addressed to ensure safe programmatic use of BPaL in Canada. Key recommendations include the development of infrastructure for timely access to novel TB drug susceptibility testing, streamlining access to novel TB drugs, and cautious use of such drugs in collaboration with care teams with expertise in drug-resistant TB management.

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Keywords: tuberculosis, pretomanid, bedaquiline, linezolid, extensively drug-resistant tuberculosis, multi-drug-resistant tuberculosis, Canada

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Introduction

Drug-resistant tuberculosis (TB) is associated with disproportionate morbidity and mortality related to prolonged, more toxic, and less effective treatments. In 2020, the World Health Organization (WHO) estimated 10 million people developed TB disease, including 500,000 people with rifampin-resistant/multi-drug-resistant TB (RR/MDR) (1). In recent years, a series of clinical trials evaluating novel (bedaquiline, pretomanid) and repurposed (linezolid, clofazimine, fluoroquinolones) oral anti-TB drugs have demonstrated the potential for shorter, less toxic and highly effective treatment of drug-resistant forms of TB (2–5). Informed by accumulating clinical evidence, the WHO recently released updated clinical guidance endorsing the use of a novel all oral short course (6–9 month) regimen of bedaquiline, pretomanid and linezolid (BPaL) for RR/MDR and pre-extensively drug-resistant (pre-XDR) TB (**Table 1**) (6). While this represents a major advancement in TB treatment, it also presents important operational challenges, including timely access to resistance testing and drug procurement. We present our experience treating a person with pre-XDR TB with BPaL—the first patient to complete this regimen in Canada—and highlight key implementation challenges.

Table 1: Updated World Health Organization drug-resistant tuberculosis definitions, 2021[a]

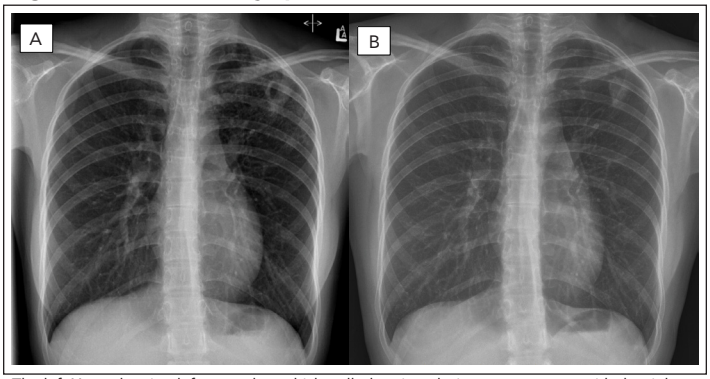
Type of drug resistance	Definition
Mono/poly-drug-resistant	Single or multi-drug resistance not meeting MDR/XDR criteria
MDR[b]	Concurrent rifampin and isoniazid resistance
Pre-XDR	MDR criteria plus fluoroquinolone resistance[c]
XDR	Pre-XDR criteria plus bedaquiline or linezolid resistance

Abbreviations: MDR, multi-drug-resistant; pre-XDR pre-extensively drug-resistant; XDR, extensively drug-resistant
[a] Taken from reference (7)
[b] WHO classifies both rifampin-resistant (RR) and MDR TB as clinically similar in management and RR/MDR is combined in global surveillance data
[c] Either levofloxacin or moxifloxacin

Case report

In March 2021, an 18-year-old female was referred to a provincial TB program with a five-month history of cough and several weeks of night sweats. Chest radiograph revealed left upper lobe cavitation (**Figure 1**). Sputum samples demonstrated acid-fast bacilli on smear, which was confirmed as *Mycobacterium tuberculosis* complex by polymerase chain reaction assay targeting the IS6110 and *mpt*64 genes. The patient was born in China and had moved to Canada three years prior to her TB diagnosis. She had no known prior TB exposure or treatment, was a non-smoker and was on no medications. Baseline investigations were negative for human immunodeficiency virus, hepatitis B/C and diabetes.

Figure 1: Chest X-ray (posterior-anterior film)[a]

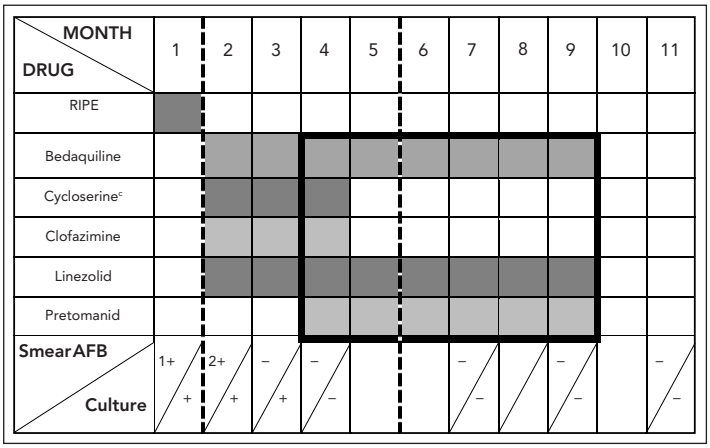


[a] The left X-ray showing left upper lung thick walled cavitary lesion pretreatment with the right X-ray showing improvement on follow-up six-month post completion of treatment

A week following referral, she was initiated on standard first-line, four-drug anti-TB therapy, and continued home isolation. Three weeks later, first-line drug phenotypic susceptibility testing indicated the possibility of multi-drug resistance, further confirmed by both genotypic and repeat phenotypic testing (**Table 2**). The isolate was sent to the National Reference Centre for Mycobacteriology (Winnipeg, Manitoba) and the National Jewish Hospital Laboratory (Denver, Colorado) for second-line drug testing. The patient was admitted to the provincial hospital-based TB Unit to establish therapy geared towards pre-XDR TB and continue isolation. Three months post-diagnosis, two months into hospitalization, phenotypic second-line drug susceptibility results were finalized by the National Reference Centre for Mycobacteriology (Table 2), but phenotypic drug susceptibility testing for bedaquiline and pretomanid were not available in any of the North American labs we contacted.

Treatment is summarized in **Figure 2**. In hospital, treatment was initially modified to four presumed effective medications (bedaquiline, clofazimine, cycloserine, linezolid) once Health Canada Special Access Program (SAP) approval and medication procurement completed. Based on recent reports of effective use of combination therapy with pretomanid (3), SAP approval was sought from Health Canada. While SAP approval for use of pretomanid was obtained quickly, it took three weeks from approval to initiate therapy due to manufacturer delays related to establishing an account to order and purchase the drug. Once the patient was established on pretomanid, a consensus decision among TB Unit physicians was made to stop clofazimine and cycloserine and proceed with a BPaL six-month regimen adhering to operational research conditions outlined by WHO (8). This decision was informed by the limited extent of TB disease and desire to limit toxicity and social disruption in this young, school-aged patient. The patient provided informed consent to proceed with treatment. Given her small body habitus (45 kg) and concern about high rates of linezolid-associated adverse events at 1,200 mg daily dosing used in the published BPaL regimen (3), the dose was reduced to 600 mg daily after one month informed by published pharmacokinetic parameters. Peak and through linezolid serum drug levels were performed via Infectious Disease Pharmacokinetics Laboratory (Gainesville, Florida) confirming adequate drug exposure at 600 mg daily (9).

Figure 2: Treatment timeline and details[a,b]



Abbreviations: AFB, acid-fast bacilli; RIPE, rifampin, isoniazid, pyrazinamide, ethambutol at standard weight-based dosing
[a] Drug dosing (weight: 45 kg): bedaquiline 400 mg PO OD x 2 weeks then 200 mg 3 times per week, cycloserine 250 mg PO BID, linezolid 1,200 mg PO OD month 2 then 600 mg PO OD months 3 to 9, clofazimine 100 mg PO OD, pretomanid 200 mg PO OD
[b] Dark line/box: BPaL (bedaquiline pretomanid, linezolid), dashed line; hospital admission and discharge
[c] Together with pyridoxine (B6) 100 mg

Table 2: Sputum mycobacterial culture drug susceptibility test results

Drug	MIC (mg/L)	Interpretation	Testing method	Testing laboratory
Rifampin	At least 1	Resistant	MGIT	Provincial
Isoniazid	At least 0.4	Resistant	MGIT	Provincial
Pyrazinamide	At least 100	Resistant	MGIT	Provincial
Ethambutol	At least 5	Resistant	MGIT	Provincial
Moxifloxacin	At least 0.25	Resistant	MGIT	Provincial
Rifabutin	At least 0.5	Resistant	MGIT	National
Amikacin[a]	At least 0.1	Resistant	MGIT	National
Ethionamide	At least 5	Resistant	MGIT	National
Linezolid[b]	1	Susceptible	MGIT	National
para-Aminosalicylic acid	4	Susceptible	MGIT	National
Clofazimine	0.12 or less	Tentative susceptible	Agar dilution	US
Cycloserine	60	Susceptible	Agar dilution	US

Abbreviations: MGIT, Mycobacteria Growth Indicator Tube; US, United States
[a] Also resistant to kanamycin, capreomycin and streptomycin
[b] Extended incubation was required; result did not conform to the standard protocol recommended by Clinical and Laboratory Standards Institute

Unable to home isolate, the patient remained hospitalized until sputum culture was confirmed negative (month 5) (**Figure 3**). Outpatient treatment was via daily observed dosing either in-person or via asynchronous video-assisted directly observed therapy (Figure 3). Monthly blood work, including complete blood counts, kidney function, liver enzymes and lipase levels, along with electrocardiogram, demonstrated no adverse treatment effects that required modification. During the third month of treatment, the patient developed a non-progressive multifocal pruritic papular rash without systemic symptoms that responded symptomatically to topical corticosteroids and resolved with cessation of clofazimine and cycloserine.

One month after hospitalization and treatment optimization, all TB symptoms had resolved and sputum smears and cultures were consistently negative. Serial follow-up chest imaging demonstrated improvement. In November 2021, BPaL regimen treatment was stopped. More than six months post treatment the patient remained symptom free with negative sputum cultures and improved chest imaging (Figure 2 and Figure 3).

Figure 3: Photo of daily BPaL medications[a]

[a] Medication submitted along with video of pill ingestion by the patient as asynchronously daily video-assisted directly observed therapy

Discussion

Canadian guidelines currently recommend MDR/pre-XDR TB treatment with individualized all oral regimens consisting of at least four effective medications for at least 20 months (10,11). However, the evidence base for shorter standardized treatment, such as BPaL, has evolved rapidly since the publication of the guidelines (6). This case illustrates the safe and effective use of the novel BPaL regimen to treat pre-XDR TB in Canada. It also highlights key implementation challenges: timely and accessible TB drug susceptibility testing; medication access; and program-level knowledge about appropriate use.

The evidence base for BPaL comes from three recent clinical trials. The open label, single group Nix-TB trial published

in 2020, first evaluated six-month BPaL treatment of MDR/pre-XDR pulmonary TB and demonstrated a remarkable 90% of participants experienced favourable outcomes. This is in dramatic contrast to the consistently fewer than 70% favourable outcomes with prior guideline-based regimens. However, participants in Nix-TB experienced significant toxicity; with a linezolid dose of 1,200 mg daily, more than 80% of participants reported adverse effects, and 71% required linezolid treatment interruption (3). To validate these findings and evaluate toxicity mitigation strategies, the multinational phase II/III TB-PRACTECAL trial compared six-month BPaL using variable linezolid dosing (600 mg daily for four months then 300 mg or 600 mg three times per week for two months) with or without moxifloxacin or clofazimine, against locally accepted standard of care (12). While the multinational, partially blinded phase III ZeNIX trial compared six-month BPaL using variable linezolid dose (1,200 mg or 600 mg) and duration (two or six months) (4,13). Results from these trials demonstrate that more than 80% of participants experienced successful treatment outcomes with improved tolerability at reduced linezolid doses (600 mg daily); however, final results of the TB-PRACTECAL trial have not yet been published (4,12).

Based on these findings, BPaL regimens were recently endorsed by the WHO as potential treatment options for highly drug-resistant TB (6). To preserve effectiveness and ensure safety, careful patient selection and treatment oversight must be central to programmatic use. To this end, the WHO outlined potential BPaL patient eligibility criteria in their 2020 consolidated guidelines on drug-resistant tuberculosis treatment (8). The central criteria for patient selection are as follows: informed consent; side effect monitoring; and TB susceptibility to medications used. It should also be underscored that there is currently a lack of evidence for use of BPaL in children (younger than 15 years of age) and for extra-pulmonary TB. For Canadian clinicians and pharmacists who may have limited familiarity with the novel drugs in BPaL, the recently updated Canadian Tuberculosis Standards 8th Edition provides a useful overview of these medications (9).

Despite increasing prevalence of resistance—including to BPaL drugs—and recommendations that susceptibility to treatment drugs be laboratory-confirmed in all people with TB, the ability to perform drug susceptibility testing for novel TB drugs, like pretomanid and bedaquiline, remains limited globally and currently unavailable in Canada (6,8,15). Clinical and Laboratory Standards Institute guidelines—a common set of laboratory standards used worldwide—do not provide recommendations for test performance or interpretation to either of these drugs. While breakpoints for susceptibility testing to bedaquiline and delamanid (a nitroimidazooxazine class drug like pretomanid) are available through European Committee on Antimicrobial Susceptibility Testing guidelines, shortages of drug available for test set up (in the case of delamanid) and lack of readily available well-characterized organisms for validation and standardization impede implementation. These factors contributed to lack of bedaquiline and pretomanid susceptibility testing for our case. Even when drug susceptibility testing is available for a drug, delayed results impact timely decision-making and clinical utility. In our case it took three months to obtain finalized linezolid susceptibility results due to specimen shipment delays, testing capacity limitations, and isolate specific incubation/growth issues. As such, expanded treatment regimens should be considered while awaiting susceptibility testing results and BPaL regimens may not be appropriate if there is concern for constituent drug resistance and susceptibility testing unavailability. Borrowing from non-BPaL treatment recommendations, additional medications such as moxifloxacin, clofazimine and cycloserine could be included while awaiting susceptibility testing results (6,10).

Recommendations

Safe and effective use of BPaL for treatment of persons with drug-resistant TB in Canada presents multiple significant implementation challenges. To address these challenges, we recommend the following:

- Prioritizing validated and accessible preferred drug-resistant TB drug (bedaquiline, pretomanid, clofazimine, linezolid, cycloserine) susceptibility testing via collaboration between regional labs and national and international reference and research centres
- Streamlining access to novel TB medicines by using shared, standardized eligibility criteria as well as harmonized priority application and procurement pathways with Health Canada SAP and drug suppliers
- Limiting this regimen to operational research conditions that reflect eligibility criteria and implementation guidelines similar to those outlined by the WHO (8), particularly in the absence of documented drug susceptibility to BPaL drugs (specifically the now more widely used linezolid and bedaquiline)

Alongside these needed system improvements, in accordance with national and international best practice guidelines, case-by-case management of people with drug-resistant TB should occur in close collaboration with a team of experienced physicians, nurses and pharmacists (7,10,11).

Conclusion

New treatment options for drug-resistant TB represent a major advancement for global TB elimination efforts. However, system improvements and continued close operational oversight will be required for sustainable effective integration of these new treatments into TB care in Canada.

Authors' statement

WC — Conceptualized this report, contributed to drafting and revising the paper
VC — Contributed to drafting and revising the paper
JJ — Contributed to drafting and revising the paper
IS — Contributed to drafting and revising the paper
CN — Contributed to drafting and revising the paper

The content and view expressed in this article are those of the authors and do not necessarily reflect those of the Government of Canada.

Competing interests

None.

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Pertussis epidemiology in Canada, 2005–2019

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Abstract

Background: Pertussis, also known as whooping cough, is an endemic vaccine-preventable disease that affects the respiratory tract and is caused by the bacterium *Bordetella pertussis*. Between 1999 and 2004, the adolescent booster dose of pertussis was introduced across Canada. This report describes the epidemiology of pertussis in Canada from 2005 to 2019, the period after adolescent acellular vaccination was recommended.

Methods: We analyzed pertussis incidence by year, age groups, sex and geographic region using national surveillance data from the Canadian Notifiable Disease Surveillance System. Hospitalization data from the Discharge Abstract Database was used to investigate pertussis hospitalizations by sex and age. Deaths from pertussis were explored using Statistics Canada's vital statistics data. Vaccination coverage data was gathered from the 2019 Childhood National Immunization Coverage Survey and 2018–2019 Seasonal Influenza Vaccination Coverage Survey.

Results: Between 2005 and 2019, there were a total of 33,481 pertussis cases with the average annual incidence rate of 6.4 cases per 100,000 population. The highest average age-specific incidence rate was among infants under one year of age (n=68.7 cases per 100,000 population). There were a total of 1,593 pertussis hospitalizations; nearly 80% of these hospitalizations were infants under one year of age. Hospitalization rates were 8.2 times higher in infants three months or younger compared to infants four to 11 months of age. There were 17 deaths; all among infants under one year of age.

Conclusion: The highest morbidity and fatality of pertussis were among infants under one year of age. It is important to take measures to reduce transmission to infants who are too young to be vaccinated. Increasing vaccine coverage in children and pregnant women are important to reduce the burden of disease.

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Keywords: pertussis, whooping cough, Canada, epidemiology, surveillance, vaccination

Introduction

Pertussis, also known as whooping cough, is an infectious disease affecting the respiratory tract and is caused by the bacterium *Bordetella pertussis* (1). Although pertussis is a vaccine-preventable disease, it is endemic worldwide, including in Canada. Pertussis has been under national surveillance in Canada since 1924. Since 1943, national childhood vaccination programs have been available and have contributed to a significant reduction in the incidence of pertussis (1). Currently, there are publicly funded routine vaccination programs for infants, adolescents, pregnant women and adults across Canada; however, there are differences in vaccine products administered and the recommended vaccination schedules between some provinces and territories (2,3). Between 1999 and 2004, the adolescent booster dose of pertussis, at 14 to 16 years of age, was introduced across Canada (4). In 2018, the National Advisory Committee for Immunization recommended a dose of the tetanus, diphtheria and pertussis (Tdap) vaccination be offered with every pregnancy, as immunization during pregnancy is a method to provide passive protection through antibody transfer to the infant (5). The purpose of this report is to provide

a summary of the epidemiology of pertussis in Canada between 2005 and 2019; the period following the implementation of the adolescent acellular pertussis vaccination programs.

Methods

National case reports

Nationally reported confirmed cases of pertussis from 2005 to 2019 were extracted from the Canadian Notifiable Diseases Surveillance System (CNDSS) database in June 2021 (6). National pertussis case definitions were updated in 2009 (7). Between 2000 and 2008, a confirmed pertussis case was defined as laboratory confirmation of infection or an epidemiological link to a laboratory-confirmed cases and the presentation of at least one of a list of clinical symptoms (8). In 2009, the case definition was further refined to require those cases in which *B. pertussis* deoxyribonucleic acid was detected to also have clinically compatible symptoms (7).

Hospitalizations

Hospitalization data from 2005 to 2019 were obtained from the Canadian Institute for Health Information's Discharge Abstract Database (DAD) and were extracted in November 2021 (9). The International Classification of Diseases, Tenth Modification (ICD-10) was used for coding diagnoses. Records in DAD with the most responsible diagnosis code of either A37.0 (Whooping cough due to *Bordetella pertussis*) or A37.9 (Whooping cough, unspecified) were included. Hospital transfers and readmissions that occurred within six weeks of admission were excluded. The DAD includes pertussis hospitalizations of all acute hospital discharges in Canada, with the exception of Québec (9).

Deaths

Mortality data were obtained from Statistics Canada's Death Database; a national mortality database collected annually (10). Deaths with an underlying cause of pertussis were identified using the same ICD-10 codes listed above.

Vaccinations

The 2019 Childhood National Immunization Coverage Survey was used to obtain national childhood vaccination coverage data. This survey is conducted on a biennial basis by Statistics Canada on behalf of the Public Health Agency of Canada to estimate national uptake for all publicly funded routine childhood vaccinations, including tetanus, diphtheria and acellular pertussis vaccines (11). The 2019 survey included the Survey on Vaccination during Pregnancy, in which the biological mothers of children born from September 1, 2018, to March 1, 2019, were surveyed regarding pertussis vaccination during their pregnancy (12). National adult vaccination coverage estimates were from the 2018–2019 Seasonal Influenza Vaccination Coverage Survey, which includes adult vaccination coverage for the TdaP vaccine booster (13).

Analysis

Incidence rates and hospitalization rates of pertussis were calculated per 100,000 population using Statistics Canada population data (14). To explore geographic distributions, Canada was divided into four main regions—Northern, Atlantic, Western and Central. The Northern region included Yukon, Northwest Territories and Nunavut. The Atlantic region included New Brunswick, Nova Scotia, Prince Edward Island and Newfoundland and Labrador. The Western region included British Columbia, Alberta, Saskatchewan and Manitoba. Lastly, the Central region included Ontario and Québec. Age-standardized incidence rates were used to compare geographic regions. These rates were calculated using the direct method with the 2011 Canadian population as the standard. Cases with missing age were excluded from the age standardization. Fewer than 2% of cases had missing ages.

As hospitalization numbers did not include the province of Québec, the proportion of cases hospitalized and hospitalization rates were calculated excluding the cases and population of Québec, respectively. For hospitalization rates of infants under one year of age, age groups were created in accordance with National Advisory Committee for Immunization's recommendations to administer a pertussis vaccine at two, four, six and 12–23 months (15). Thus, the age groupings for infants under one year were as follows: under two months, two to three months, four to five months and six to 11 months. Population estimates for one-month interval ages for infants under one year of age were not available to calculate hospitalization rates; therefore, the denominator for each one-month age interval was estimated by dividing the population under one year of age by 12, resulting in each infant contributing one month to the rate.

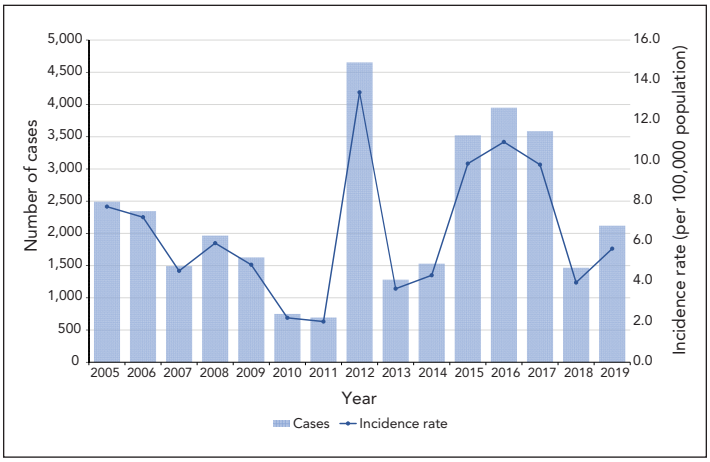
Negative binomial regression was used to estimate the association between rates, sex, age groups, and time periods. Statistical significance was considered at a confidence level of 95%. All statistical analyses were conducted using SAS 9.4.

Results

Cases and incidence

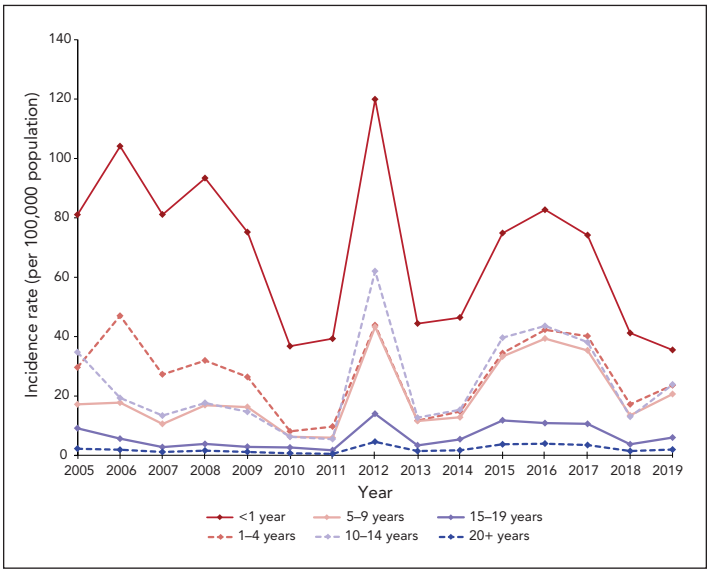
From 2005 to 2019, a total of 33,481 cases of pertussis were reported, with an average annual incidence rate per 100,000 population of 6.4 (range: 2.0 in 2011 to 13.4 in 2012) (**Figure 1**). Pertussis incidence peaked in the years 2012 and 2015 to 2017. During this 15-year period, females accounted for an average of 54.2% of cases while males accounted for 45.7% of cases. The difference in incidence rates between sex was not statistically significant (*p*-value=0.40).

Figure 1: Reported cases and incidence rate, per 100,000 population, of pertussis in Canada by year, 2005–2019



Infants under one year of age had the highest average incidence rate per 100,000 population by age group (n=68.7) and accounted for 13.1% of cases. Following the under one year age group, the highest average annual incidence rates were among the one to four years of age (n=27.2), 10 to 14 years of age (n=24.0), and five to nine years of age (n=20.1). The average incidence rate was lower in the 15 to 19-year age group (n=6.3) and the lowest average rate was among adults over 20 years of age (n=2.1). The trends in pertussis incidence were similar in age groups covering children under 15 years of age, with peaks in 2012 and 2015–2017 (**Figure 2**). There were also peaks in incidence that were specific to age groups such as a peak in the years 2005 to 2009 for the under one-year age group and a peak in 2006 for the one to four-year age group.

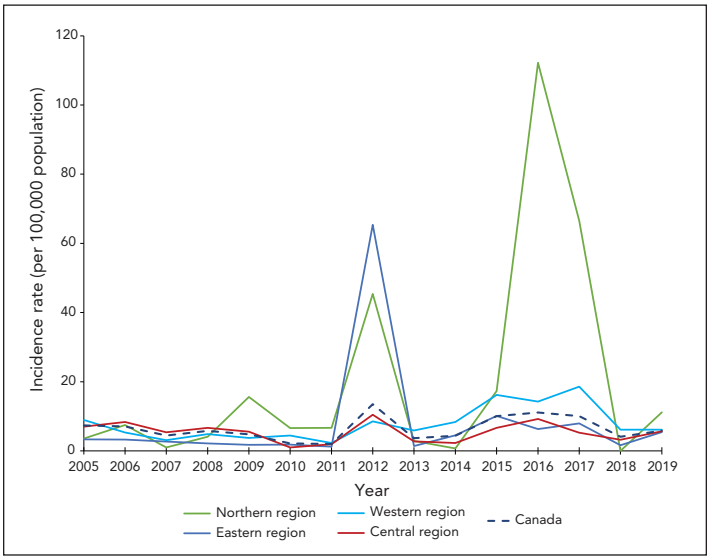
Figure 2: Incidence rate, per 100,000 population, of pertussis reports in Canada by age group[a] by year, 2005–2019



[a] Age group in years

Variations in pertussis age-standardized incidence among the four geographic regions of Canada were observed (**Figure 3**). The average annual age-standardized incidence of each region is not statistically different from the other regions nor from the national incidence. The age-standardized incidence rate per 100,000 population of pertussis fluctuated less in the Central region, where the average was 5.4 (95% CI: 3.9–7.0) and the Western region, where the average was 7.8 (95% CI: 5.1–10.5). The greatest fluctuations in pertussis incidence and the highest peaks occurred in the Northern region, where the average was 20.1 (95% CI: 2.7–37.5). The Atlantic region observed fairly steady incidence rates with an average incidence rate of 7.9 (95% CI: -1.0–16.9), with the exception of 2012. In 2012, the Atlantic region observed a 55-fold increase in the incidence rate compared to the previous year when the region accounted for 31% of the nation's cases.

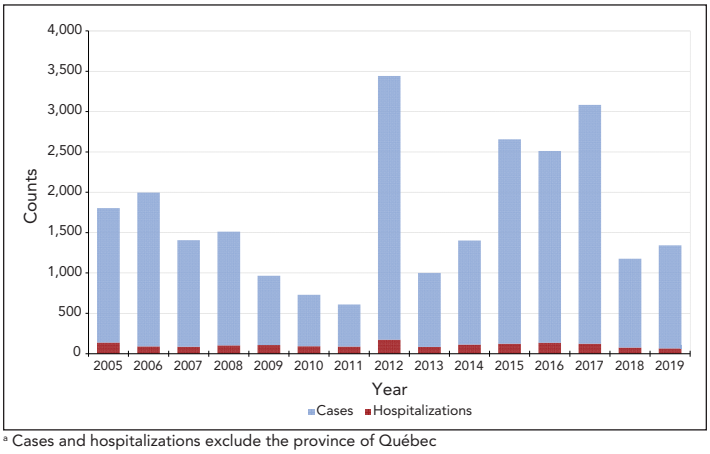
Figure 3: Trends in annual age-standardized incidence rate of pertussis, per 100,000 population, by geographic region and nationwide, 2005–2019



Hospitalizations

From 2005 to 2019, there were a total of 1,593 acute care pertussis hospitalizations, averaging 106.2 hospitalizations each year (range: 66 in 2019 to 173 in 2012) (**Figure 4**). The average hospitalization rate per 100,000 population was 0.4 per year (range: 0.2 in 2019 to 0.6 in 2012). Although case data from CNDSS and hospitalization data from DAD cannot be linked, the proportion of pertussis cases that were hospitalized was estimated as less than 10% for this 15-year period. The trends in hospitalizations followed the trends in pertussis cases as the peaks in hospitalization counts occurring in 2012 and 2015 to 2017 coincided with the peaks in cases. During this period, females accounted for an average 57.7% of hospitalizations while males accounted for 48.5%; a difference that was not statistically significant (*p*-value=0.96).

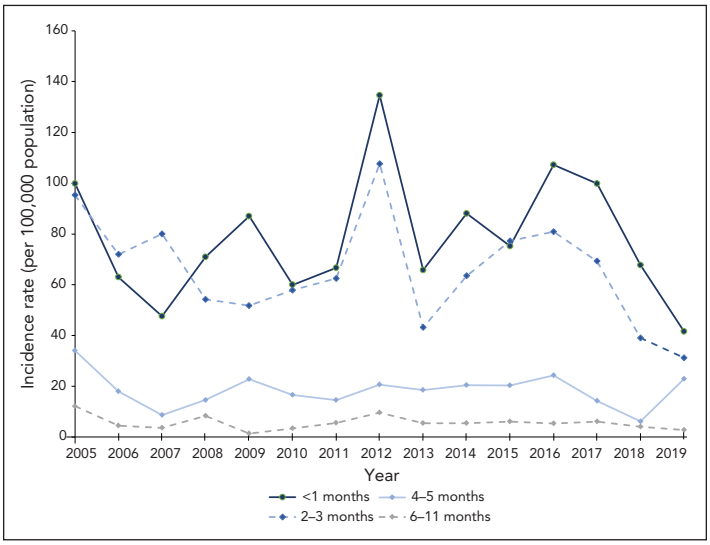
Figure 4: Number of pertussis cases and hospitalizations[a] in Canada by year, 2005–2019



[a] Cases and hospitalizations exclude the province of Québec

Infants under one year of age accounted for over 80% of all hospitalizations and had an average hospitalization rate per 100,000 population of 29.9 (range: 17.3 in 2019 to 48.6 in 2012). Focusing specifically on the under one year of age population, the hospitalization rate was 8.2 times higher (95% CI: 6.4–10.4; *p*-value <0.01) in infants under four months of age compared to infants four to 11 months of age over the 15-year period (**Figure 5**).

Figure 5: Hospitalization rate of infants under one year of age, by age group, 2005–2019



In 2019, following the 2018 recommendation for pertussis vaccination during pregnancy, there was a decline in hospitalization rates among younger infants, compared to the period of 2005 to 2018; the years before the recommendation. There was a two-fold decline in the hospitalization rate in 2019 compared to the mean hospitalization rate in the period of 2005 to 2018 among infants under two months of age (95% CI: 1.1–3.4; *p*-value=0.02) and among infants between two and three months of age (95% CI: 1.3–4.0; *p*-value=0.01). In contrast, the decline was not significant among infants between four and five months of age (*p*-value=0.51) and six to 11 months of age (*p*-value=0.24).

Deaths

From 2005 to 2019, Statistics Canada reported 17 deaths with pertussis listed as the leading cause of death, with zero to three deaths reported each year. All 17 deaths were infants under one year of age. Nine deaths occurred in females (52.9%) and eight deaths in males (47.1%); a difference that was not significant (*p*-value=0.81).

Vaccination

The 2019 Canadian Childhood National Immunization Coverage Survey estimated the vaccine coverage rate for at least four doses of the tetanus, diphtheria, and pertussis vaccine administered by two years of age was 78%, for at least five doses by seven years was 78%, and for one booster dose by 17 years was 95% (11). This survey also revealed that, of the mothers who knew whether or not they had been vaccinated against pertussis during their pregnancy, 44% had been vaccinated (12). The coverage among adults was lower, with only 33% of adults over 18 years of age having received a pertussis booster in adulthood, as estimated by the 2018–2019 Seasonal Influenza Vaccination Coverage Survey (13).

Discussion

Since the introduction of the pertussis vaccine and routine pertussis vaccination programs in Canada in 1943, the national incidence rate of pertussis decreased overall (16). Our study shows that since 2004, when the vaccination recommendation of at least one adult dose was introduced, there was not a steady increase or decrease in the pertussis incidence, but rather fluctuations with peaks on a national and regional level. Importantly, the greatest burden of pertussis was observed among the under one year of age population, which consistently had the highest annual incidence rate, accounting for nearly 80% of hospitalizations, and all 17 pertussis-related deaths during this 15-year period. In contrast, adults over 20 years of age had the lowest annual incidence rate each year.

Sporadic peaks in pertussis incidence were observed in each geographic region. Although data available on pertussis cases does not include outbreak information, peaks in incidence in a geographic region can be connected to outbreaks occurring at a regional level. For example, in 2012, a 55-fold increase in the incidence rate in the Atlantic region was associated with a large outbreak declared in New Brunswick, involving 1,421 confirmed cases, in which 2% of the cases were hospitalized. Over half of the cases were among school-aged children, with the 10 to 14-year-old age group followed by the five to nine-year-old age group having the highest age-specific incidence rates. Province-wide school-based immunization campaigns were implemented

in spring and fall of 2012 to battle this large outbreak (17). From 2005 to 2019, the highest regional peaks in incidence occurred in the Northern region, which can be attributed to large outbreaks that were further accentuated by the smaller population in the territories compared with the other geographic regions. The spike in incidence, in the Northern region in 2016 and 2017, was connected to a large outbreak in Nunavut occurring in May 2016 to April 2017, which spread to 11 communities with 163 confirmed cases and a second smaller outbreak occurring in September to November of 2017 (6,18). Sporadic peak years in pertussis activity have been reported in other countries including the United States, Greece, Finland and Singapore, to name a few, in the past several decades (19,20). Studies have hypothesized that the cyclic nature of this disease could be attributable to low vaccination numbers, waning vaccine immunity and changes in *Bordetella pertussis* (21–23).

Hospitalization data obtained from DAD does not include the province of Québec. According to the *Maintenance et exploitation des données pour l'étude de la clientèle hospitalière* (Med-Echo), a clinical administrative Québec database, a total of 710 pertussis hospitalizations were recorded in Québec between April 1, 2006, and March 31, 2020 (24). During the same period, 1,448 hospitalizations were recorded in DAD. While the population of Québec accounts for about 23% of Canada's population, approximately 33% of pertussis hospitalizations in Canada occurred in Québec during this study period and were not captured in this study.

The greatest burden of disease was among infants under one year of age. Hospitalization rates were over eight times higher in infants under four months of age than infants between four and 11 months, which coincides with the first dose of the pertussis vaccine administered at two months of age. Three different studies, including a Canada-wide study by Desai *et al.* (25), a study covering British Columbia and Québec by Skowronski *et al.* (26) and a study in the United States by Masseria *et al.* (27), all reported similar findings showing pertussis hospitalizations were highest in infants under three months of age. The lower hospitalization rates among infants between four and 11 months of age, compared to infants under four months of age, can be attributed to less severe disease in older infants and to vaccinations. This highlights the importance of timely childhood immunization.

The 2019 national vaccination coverage estimates show that childhood vaccine uptake could be improved, as both childhood vaccine coverage goals of 95% coverage of four or more doses by two years of age and 95% coverage of five or more doses by seven years of age have not been reached (28). In contrast, the national coverage goal of 90% coverage for the adolescent booster by 17 years of age was met (11,28).

Adult vaccine coverage for pertussis in 2019 was also low, with only 33% of all adults having received a pertussis booster, which was the lowest among all vaccines covered by publicly funded programs, despite national recommendations to receive a booster dose of a pertussis-containing vaccine (13). Findings from a 2015 study surveying over 1,000 healthcare providers across Canada indicated low levels of knowledge among healthcare providers about Tdap recommendations in adults, resulting in a low likelihood of providing Tdap recommendations to patients in accordance with national recommendations (29). Although the incidence rate per 100,000 of pertussis among adults was low at 2.1, pertussis is a highly communicable disease resulting in a significant risk of transmission from infected adults to infants under one year of age who are at highest risk of pertussis-related complications, hospitalizations and death (1). This indicates a need to improve awareness of adult vaccinations among healthcare providers and the public to improve adult vaccination uptake. It is anticipated that higher vaccine coverage among children and adults could decrease pertussis activity within the vaccinated population and also decrease transmission of infection to young infants who are unimmunized and have the greatest morbidity and mortality from the disease (30).

In February 2018, Tdap vaccination was recommended in every pregnancy and by November 2019, all provinces and territories except for Ontario and British Columbia implemented publicly funded pertussis vaccination with each pregnancy (5,31). Within a year following this recommendation, vaccine coverage among pregnant women was low at 44%, but coverage rates are expected to increase with time as more provinces and territories fund maternal vaccination and the recommendation becomes more well known (12,31). As of April 2022, all provinces and territories have publicly funded Tdap vaccination during each pregnancy (2,32). Although more time is needed to evaluate the potential benefits of maternal pertussis vaccination during pregnancy in Canada, our analysis shows early signs of a significant decrease in pertussis hospitalization rates among infants under four months of age in 2019 compared to the mean hospitalization rates in 2005 to 2018. In addition, in 2019, there was a decrease in pertussis hospitalization rates among infants under four months of age, despite a national increase in hospitalization rates for all ages, compared to the previous year. Further insight can be gained from other countries with maternal vaccination. A 2020 study in Brazil by Friedrich *et al.* found a 47.7% decrease in the mean annual incidence of pertussis in children under one month of age in the period after maternal pertussis vaccination was implemented compared to the period before maternal vaccination (33). As the greatest burden of pertussis is among young infants who are too young to be vaccinated, it is important to couple vaccination coverage numbers with strong surveillance data to assess the impact of recommendations for immunization during pregnancy.

Limitations

There are several limitations to these findings as data collected from these surveillance systems have constraints. Due to the passive nature of CNDSS, there is a likelihood of underreporting

of cases (6). A diagnosis of pertussis requires a high level of clinical suspicion, resulting in many cases in both children and adults being undiagnosed. It is likely that the incidence of pertussis is higher among adults than reported, as symptoms are generally milder, and testing for *B. pertussis* among adults is infrequent. Furthermore, trends of incidence rates must be interpreted with caution because of changes in case definition, provincial and territorial reporting and laboratory technologies.

In addition, the pertussis-related hospitalizations are coded based on the physician's diagnosis and do not necessarily match the national case definition. As a result, the number of pertussis-related hospitalizations from DAD featured in this report may be an underestimate of the actual burden. Furthermore, DAD does not include the province of Québec, which accounts for an estimated one third of pertussis hospitalizations in Canada. However, we speculate that the pertussis hospitalizations in Québec would not change the overall interpretations.

The 2016 to 2019 data on deaths obtained from Statistics Canada's Death Database were considered preliminary because there were improvements in methodology and timeliness resulting in a shortened data collection period compared with previous years. Thus, there may be fewer deaths captured. In addition, death data for Yukon from 2017 to 2019 were not available (10).

Vaccination coverage surveys undergo methodology changes, so coverage estimates cannot be compared between iterations. Furthermore, Childhood National Immunization Coverage Survey data are collected from parent-held vaccination records in which some information may be incomplete, erroneous or missing, leading to an underestimate of vaccination coverage (34). Neither the CNDSS nor DAD data includes vaccination history of cases or patients, so analysis of vaccine efficacy was limited.

Conclusion

Following the period after the implementation of an adolescent pertussis booster, pertussis remained an endemic disease in Canada that affected individuals of all ages. However, the greatest burden continued to be among infants under one year of age, especially infants three months and younger who are too young to be vaccinated or have only received one dose of the vaccine. Thus, it is important to prevent transmission of infection by increasing vaccine coverage to protect those at highest risk of severe outcomes. It will be important to monitor the effect of the maternal pertussis vaccination recommendation on epidemiology of infants under four months of age. Enhanced surveillance systems that capture vaccine history, pertussis strains and outbreak information would provide a more comprehensive understanding of pertussis epidemiology that can be used to assess vaccine recommendation changes and to inform further public health action.

Authors' statement

DB — Conceptualization, methodology, software, formal analysis, investigation, writing–original draft, writing–review and editing, visualization
MS — Methodology, writing–review and editing
GH — Methodology, writing–review and editing
FRD — Conceptualization, methodology, writing–review and editing
SGS — Conceptualization, methodology, writing–review and editing
MIS — Writing–review and editing
YAL — Conceptualization, methodology, writing–review and editing

Competing interests

None.

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