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ENTERIC DISEASES: A MAJOR HEALTH PROBLEM IN CANADA

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ccdr-rmtc@phac-aspc.gc.ca
613.301.9930

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The cover photo represents a woman using digital x-ray of human intestine holographic scan projection. The Public Health Agency of Canada estimates that each year roughly one in eight Canadians (four million people) get sick with a domestically acquired food-borne illness. The image was taken from Adobe Stock #323618743.

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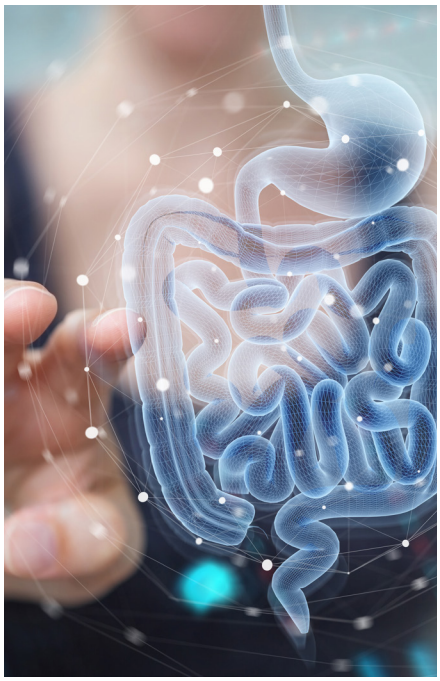

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EPIDEMIOLOGIC STUDY

Developing International Classification of Disease code definitions for the study of enteric infection sequelae in Canada

Eleni Galanis[1]*, Azita Goshtasebi[2], Yuen Wai Hung[3], Jonathan Chan[1], Douglas Matsell[1], Kristine Chapman[1], Gilaad Kaplan[4], David Patrick[1,2], Bei Yuan Zhang[1,3], Marsha Taylor[2], Dimitra Panagiotoglou[5], Shannon Majowicz[3]

Abstract

Background: Enteric infections and their chronic sequelae are a major cause of disability and death. Despite the increasing use of administrative health data in measuring the burden of chronic diseases in the population, there is a lack of validated International Classification of Disease (ICD) code-based case definitions, particularly in the Canadian context. Our objective was to validate ICD code definitions for sequelae of enteric infections in Canada: acute kidney injury (AKI); hemolytic uremic syndrome (HUS); thrombotic thrombocytopenic purpura (TTP); Guillain-Barré syndrome/Miller-Fisher syndrome (GBS/MFS); chronic inflammatory demyelinating polyneuropathy (CIDP); ankylosing spondylitis (AS); reactive arthritis; anterior uveitis; Crohn's disease, ulcerative colitis, celiac disease, erythema nodosum (EN); neonatal listeriosis (NL); and Graves' disease (GD).

Methods: We used a multi-step approach by conducting a literature review to identify existing validated definitions, a clinician assessment of the validated definitions, a chart review to verify proposed definitions and a final clinician review. We measured the sensitivity and positive predictive value (PPV) of proposed definitions.

Results: Forty studies met inclusion criteria. We identified validated definitions for 12 sequelae; clinicians developed three (EN, NL, GD). We reviewed 181 charts for 6 sequelae (AKI, HUS, TTP, GBS/MFS, CIDP, AS). Sensitivity (42.8%–100%) and PPV (63.6%–100%) of ICD code definitions varied. Six definitions were modified by clinicians following the chart review (AKI, TTP, GBS/MFS, CIDP, AS, reactive arthritis) to reflect coding practices, increase specificity or sensitivity, and address logistical constraints.

Conclusion: The multi-step design to derive ICD code definitions provided flexibility to identify existing definitions, to improve their sensitivity and PPV and adapt them to the Canadian context.

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Keywords: enteric infections, sequelae, administrative data, case definition

Affiliations

[1] Faculty of Medicine, University of British Columbia, Vancouver, BC

[2] British Columbia Centre for Disease Control, Vancouver, BC

[3] School of Public Health Sciences, University of Waterloo, Waterloo, ON

[4] Departments of Medicine & Community Health Sciences, University of Calgary, Calgary, AB

[5] Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montréal, QC

***Correspondence:**
eleni.galanis@ubc.ca

Introduction

Enteric infections are a major cause of disability and death globally and in Canada (1–3). In addition to the acute gastrointestinal manifestations, enteric infections can also lead to sequelae such as hemolytic uremic syndrome (HUS), inflammatory bowel disease, and Guillain-Barré Syndrome (GBS) (4–6). In separate but related work, we are conducting a retrospective population-based cohort study to determine the likelihood of developing sequelae following enteric infections, as well as their burden of illness and cost, in British Columbia (BC),

Canada (7). To do so, we require International Classification of Diseases (ICD) code definitions for the sequelae of interest.

Despite the increasing use of administrative health data in epidemiological research, there is a lack of verified ICD code-based case definitions broadly (8), and a lack of validated definitions for most enteric infection sequelae in the Canadian context. Our objective here was to identify, or develop and validate, ICD code-based case definitions for 15 sequelae of enteric infections (**Table 1**).

Table 1: Administrative case definitions for sequelae of enteric infections, showing International Classification of Diseases codes identified by study stage

Sequela	ICD codes identified, by study stage[a]			Final definition[a]	
	Literature review	Recommendation by clinical experts	Chart review	ICD codes	Timeframe
Acute kidney injury	ICD-9: 584 ICD-10: N17, Z99.2	ICD-9: 584 ICD-10: **N17.9**	ICD-9: N/A ICD-10: N17.9, **N17.8, N17.0**	ICD-9: 584 ICD-10: N17.0, N17.8, N17.9	One or more hospitalizations
Hemolytic uremic syndrome	ICD-9: 283.11 ICD-10: D59.3	ICD-9: 283.11 ICD-10: D59.3	ICD-9: N/A ICD-10: D59.3	ICD-9: 283.11 ICD-10: D59.3	Either (or both of): (a) one or more hospitalizations OR (b) more than two physician claims within a span of two years
Thrombotic thrombocytopenic purpura (misdiagnosed hemolytic uremic syndrome)[b]	ICD-9: 287.31, 287.33 ICD-10: M31.1, N08.5	ICD-9: **287.3** ICD-10: M31.1, N08.5	ICD-9: N/A ICD-10: M31.1, N08.5	ICD-9: **287,** 287.3 ICD-10: M31.1, N08.5 Together with: **ICD-9: 584** **ICD-10: N17.0, N17.8, N17.9**	Either (or both of): (a) one or more hospitalizations OR (b) one or more physician claims Together with: one or more hospitalizations or physician claims with an ICD code for acute kidney injury (see above) in the week before or after
Guillain-Barré syndrome/Miller Fisher syndrome	ICD-9: 357 ICD-10: G61.0	ICD-9: 357, **356+IVIG** ICD-10: G61.0	ICD-9: 356 ICD-10: G61.0	ICD-9: **356, 357** ICD-10: G61.0	Either (or both of): (a) one or more hospitalizations OR (b) two or more physician claims within a span of fewer than three months
Chronic inflammatory demyelinating polyneuropathy	ICD-9: 357.81 ICD-10: G61.8	ICD-9: 357.81, **356+IVIG** ICD-10: G61.8	ICD-9: **357,** 356+IVIG ICD-10: G61.8	ICD-9: **356, 357.81** ICD-10: G61.8	Either (or both of): (a) one or more hospitalizations OR (b) two or more physician claims occurring three or more months apart
Ankylosing spondylitis	ICD-9: 720 ICD-10: M45	ICD-9: 720, **720.0, 720.8, 720.9** ICD-10: M45	ICD-9: 720, 720.0 ICD-10: M45	ICD-9: 720, 720.0 ICD-10: M45	Either (or both of): (a) one or more hospitalizations OR (b) two or more physician claims within a span of two or fewer years
Reactive arthritis	ICD-9: 711 ICD-10: N/A	ICD-9: 711, **696, 714** ICD-10: M02	N/A	ICD-9: 711, 696, 714 ICD-10: M02	Two or more physician claims that are both: (a) two or more months apart AND (b) within a span of five or fewer years
Anterior uveitis	ICD-9: 364 ICD-10: H20.0	ICD-9: 364 ICD-10: H20.0	N/A	ICD-9: 364 ICD-10: H20.0	Either (or both of): (a) one or more hospitalizations OR (b) one or more physician claims

Table 1: Administrative case definitions for sequelae of enteric infections, showing International Classification of Diseases codes identified by study stage (*continued*)

Sequela	ICD codes identified, by study stage[a]			Final definition[a]	
	Literature review	Recommendation by clinical experts	Chart review	ICD codes	Timeframe
Crohn's disease	ICD-9: 555 ICD-10: K50	ICD-9: 555 ICD-10: K50	N/A	ICD-9: 555 ICD-10: K50	Either (or both of): (a) two or more hospitalizations OR (b) four or more physician claims within a span of two years
Ulcerative colitis	ICD-9: 556 ICD-10: K51	ICD-9: 556 ICD-10: K51	N/A	ICD-9: 556 ICD-10: K51	Either (or both of): (a) two or more hospitalizations OR (b) four or more physician claims within a span of two years
Irritable bowel syndrome	ICD-9: 564.1 ICD-10: K58.0, K58.9, F45.3	ICD-9: 564.1 ICD-10: K58.0, K58.9, F45.3	N/A	ICD-9: 564.1 ICD-10: K58.0, K58.9, F45.3	One or more physician claims or hospitalizations AND Either: (a) no Crohn's disease, ulcerative colitis or celiac disease OR (b) a second claim more than six months apart
Celiac disease	ICD-9: 579 ICD-10: K90.0	ICD-9: 579 ICD-10: K90.0	N/A	ICD-9: 579 ICD-10: K90.0	Either (or both of): (a) one or more hospitalizations OR (b) one or more physician claims
Erythema nodosum	-	ICD-9: 695.2, 729.3 ICD-10: L52, M79.3	N/A	ICD-9: 695.2, 729.3 ICD-10: L52, M79.3	Either (or both of): (a) one or more hospitalizations OR (b) one or more physician claims
Neonatal listeriosis	-	ICD-9: 771.2 ICD-10: P37.2	N/A	ICD-9: 771.2 ICD-10: P37.2	One or more hospitalizations
Graves' disease	-	ICD-9: 242.0, 242.01, 242.91, 242.9 ICD-10: E05.0, E05.90, E05.91	N/A	ICD-9: 242.0, 242.01, 242.91 ICD-10: E05.0	Either (or both of): (a) one or more hospitalizations OR (b) one or more physician claims

Abbreviations: ICD, International Classification of Diseases; N/A, not applicable
[a] Bolded text shows additions/changes at each stage of case definition development
[b] Thrombotic thrombocytopenic purpura is not a sequela of enteric infection; this definition was developed to capture historical misdiagnosis of hemolytic uremic syndrome as thrombotic thrombocytopenic purpura

Methods

We used a multi-step process to identify case definitions for the 15 sequelae (Table 1).

Literature review, clinician assessment

We searched MEDLINE (1946–July 2018) and EMBASE (1974–July 2018) databases for peer-reviewed studies published in English or French using the following terms: [([administrative OR hospital discharge OR health service OR physician] AND [data OR claim* OR record* OR database*]) OR (case definition* OR ICD-9 OR ICD-10 OR international classification of diseases)]; AND [(validity OR validate* OR validation OR agreement OR accuracy OR sensitivity OR specificity or predictive value)] AND [(search terms for sequelae of interest, as listed in **Supplemental material, Table S1**)].

We included studies with a case definition based on ICD-9 or ICD-10 coding of one or more of the sequelae validated against a gold standard that revealed at least one measure of validity (sensitivity, specificity, positive predictive value [PPV], or negative predictive value). Studies were evaluated for eligibility,

independently through title and abstract screening, and those that met the eligibility criteria underwent full text review. Disagreements were resolved by discussion and consensus. Where we identified multiple case definitions for a sequela, we selected those that were validated in Canada to ensure comparable coding practices or, if Canadian studies were not available, those with the highest measures of validity. Where we identified no relevant studies, clinicians proposed ICD-based case definitions based on expert opinion.

We invited clinician specialists in rheumatology, neurology, nephrology and gastroenterology with expertise in the sequelae of interest and based in BC or Alberta to participate in the study. They reviewed the case definitions from the literature review and revised them to reflect BC or Canadian coding practices.

Medical chart review

Setting, data sources, and ethics

We reviewed patients' charts from four tertiary care centres in Vancouver, BC, during the fall of 2018. Centres were selected based on the following criteria: most likely to see patients with sequelae of interest and sufficient numbers to meet sample size. Centres most likely to see the sequelae were selected based on whether the condition was more likely to be assessed in inpatient (e.g. acute kidney injury, AKI) or outpatient (e.g. ankylosing spondylitis, AS) settings and the age at which the condition is most likely to occur (e.g. thrombotic thrombocytopenic purpura [TTP] occurs mainly in adults and HUS, mainly in children). Vancouver Coastal Health and the British Columbia Children's Hospital granted operational approvals to access and review patient charts.

We conducted chart reviews for the following six sequelae: AKI, HUS, TTP, GBS/Miller-Fisher syndrome (MFS), AS, and chronic inflammatory demyelinating polyneuropathy (CIDP). Eligible charts included those for patients with at least one admission or visit between January 1, 2003, and December 31, 2016. We tailored our chart sampling strategy by sequelae and centre (**Table 2**), to accommodate facility differences. Chart reviews were not conducted for the other nine sequelae for the following reasons: 1) validated Canadian case definitions already existed (for Crohn's disease and ulcerative colitis); 2) clinical experts deemed further data were not required (for neonatal listeriosis [NL]); or 3) charts were not readily available (all other sequelae).

In the paediatric hospital, a randomized sample of patients with AKI and HUS were selected from a registry maintained by the nephrology department. Charts were reviewed, and ICD codes were retrieved from the health records database (Table 2). In the adult hospital, the Health Records Department converted the list of sequelae into ICD codes; a random sample of charts with one of these ICD codes for a given admission was reviewed. In the neurology clinic, charts were identified by the neurology co-author; we reviewed all MFS patients' charts, and a convenience sample of charts for patients with GBS or CIPD. In the rheumatology clinic, a convenience sample of charts from patients with AS was selected and reviewed from a registry maintained by the rheumatology co-author.

Diagnosis verification and data abstraction

We compared each ICD code against clinical criteria and/or the physician diagnosis. For AS, we used rheumatologist diagnosis as the gold standard as no diagnostic criteria existed. We developed clinical criteria (see Supplemental material, **Table S2**) using a literature review and clinical expert opinion, and created data abstraction forms for renal (AKI, TTP, HUS), neurological (GBS/MFS, CIDP), and rheumatologic (AS) sequelae. We piloted the forms with 4–5 charts each and included the pilot data in the final analysis.

Table 2: Patient charts and sequelae reviewed, by medical centre

Centre	Number of charts reviewed (% of all charts reviewed)	Sequelae assessed (Number of charts reviewed)	Patient registry	Type of charts reviewed	Source of ICD codes
Paediatric tertiary care hospital	20 (11%)	AKI (n=11) HUS (n=9)	Yes	Both electronic and paper	Hospital health records database
Adult tertiary care hospital	107 (59%)	AKI (n=31) HUS (n=11) TTP (n=14) GBS (n=26) MFS (n=3) CIDP (n=11) AS (n=11)	No	Both electronic and paper	Hospital health records database
Adult neurology referral clinic	27 (15%)	GBS (n=9) MFS (n=5) CIDP (n=13)	Yes	Electronic only	Electronic medical record
Adult rheumatology referral clinic	27 (15%)	AS (n=27)	Yes	Electronic only	Electronic medical record

Abbreviations: AKI, acute kidney injury; AS, ankylosing spondylitis; CIDP, chronic inflammatory demyelinating polyneuropathy; GBS, Guillain-Barré syndrome; HUS, hemolytic uremic syndrome; ICD, International Classification of Diseases; MFS, Miller-Fischer syndrome; TTP, thrombotic thrombocytopenic purpura

A medical chart abstractor reviewed the first visit/admission for each ICD code of interest. If the criteria were not met or diagnosis was not confirmed, the next visit/admission was reviewed. The abstractor evaluated all visits/admissions with the same ICD code or sequelae and abstracted all ICD codes recorded for the visit/admission and the diagnosis made by the attending physician on the discharge and/or consult note.

Analysis

We assessed agreement between the ICD codes and clinical criteria or physician diagnosis by calculating sensitivity (for the two clinics and paediatric hospital, where patients were identified based on diagnosis), and PPV (for the adult hospital, where patients were identified by ICD code), with 95% confidence intervals.

We developed case definitions using ICD-9 and ICD-10 codes given that during the study period (2005–2014) in BC, ICD-9 codes were used for physician billings and ICD-10 codes were used by hospitals.

Finalizing the case definitions

Clinicians with expertise in rheumatology, neurology, nephrology, gastroenterology and hematology reviewed the definitions resulting from the above steps to generate final definitions.

Results

Literature review and clinician assessment

Our search returned 1,414 articles; of which 39 met the inclusion criteria (9–47). One additional article, not uncovered through the search but meeting our eligibility criteria, was identified by a co-author for a total of 40 articles (48). For three sequelae (erythema nodosum [EN], NL and Graves' disease [GD]), no articles met our search criteria. Of the 40 articles, there were six from Canada, covering AS, ulcerative colitis, Crohn's disease, and celiac disease. Details on the 40 articles are in the Supplemental material, **Table S3**.

From these 40 articles, we derived initial case definitions for 12 sequelae (Table 1). Clinicians reviewed these and made minor changes to AKI, TTP, GBS/MFS, CIDP, AS and reactive arthritis to represent coding practices in BC. The use of intravenous immunoglobulin therapy was added to help identify cases of GBS/MFS and CIDP. For the three sequelae for which no articles were identified (EN, NL, GD), case definitions were proposed by clinicians (Table 1).

Medical chart review

We reviewed 181 charts from four medical centres (Table 2).

The agreement between the clinical criteria and physician diagnosis and the corresponding ICD codes is presented in **Table 3**. Sensitivity of the proposed AKI ICD codes was low (42.8%–44.4%), while sensitivity of the proposed ICD codes for

Table 3: Sensitivities and positive predictive values (with 95% confidence intervals) of International Classification of Diseases codes

Sequela	Sensitivity				Positive predictive value			
	ICD codes	Number of charts with sequela	Reference standard		ICD codes	Number of charts with ICD codes	Reference standard	
			Clinical criteria (95% CI)	Physician diagnosis (95% CI)			Clinical criteria (95% CI)	Physician diagnosis (95% CI)
Acute kidney injury	N17.0, N17.8, N17.9	11	44.4% (13.7–78.8)	42.9% (9.9–81.6)	N17.0, N17.8, N17.9	31	100.0% (89.0–100.0)	80.6% (63.7–90.8)
Hemolytic uremic syndrome	D593	9	100.0% (54.1–100.0)	85.7% (42.1–99.6)	D593	11	90.9% (62.3–98.4)	100% (74.1–100.0)
Thrombotic thrombocytopenic purpura	M31.1, N08.5	0	-[a]	-[a]	M31.1	14	100% (78.5–100.0)	100% (78.5–100.0)
Guillain-Barré syndrome	356	9	100.0% (63.4–100.0)	100.0% (63.4–100.0)	G610	26	68.0% (48.4–82.8)	92.5% (75.0–97.8)
Miller Fisher syndrome	356	5	100.0% (39.8–100.0)	100% (39.8–100.0)	G610	3	33.3% (6.1–79.2)	100% (43.9–100.0)
Chronic inflammatory demyelinating polyneuropathy	356, 357	13	100.0% (71.5–100.0)	100% (71.5–100.0)	G618	11	70% (39.7–89.2)	80% (49.0–94.3)
Ankylosing spondylitis	720	27	-[a]	92.5% (75.7–99.1)	M45	11	-[a]	63.6% (35.4–84.8)

Abbreviations: CI, confidence interval; ICD, International Classification of Diseases; -, no results are presented
[a] Charts identified using ICD codes, thus only positive predictive value could be calculated

HUS, GBS, MFS, CIDP and AS was high (85.7%–100%). The PPV varied by sequelae and reference standard, from 63.6% for AS to 100% for HUS, TTP and MFS.

Final administrative case definitions

Clinicians reviewed the chart review findings and provided final revisions and approval of case definitions (Table 1). Given that TTP was included in the study as a proxy for HUS, we combined codes for TTP and AKI to increase PPV. Given that the subsequent cohort study does not have access to intravenous immunoglobulin data, this was dropped from the GBS/MFS and CIDP definitions.

Discussion

This study identified, developed and validated ICD-based case definitions for 15 sequelae of enteric infections. These are now being used in a population-wide cohort study to determine the likelihood of developing sequelae following enteric infections and their burden in terms of illness and cost (7).

We used a multi-method approach that combined 1) a literature review, 2) clinician consultation, 3) chart reviews and 4) final clinician consultation to generate valid case definitions relevant to our study context, and we documented how each of these methods affected the final case definitions. This multi-method explicit approach is not common; most studies derive case definitions solely using medical chart reviews.

Six (HUS, AKI, TTP, GBS/MFS, CIDP, AS) conditions underwent all four steps (Table 1). Only the HUS definition underwent no changes from the initial literature review. Of the remaining five, all were slightly modified based on clinician input and three (AKI, GBS/MFS, CIDP) were further amended following the chart review. Of the nine conditions that did not undergo a chart review, only the reactive arthritis definition was modified based on clinician input. Five case definitions identified in the literature (anterior uveitis, Crohn's disease, ulcerative colitis, irritable bowel syndrome, celiac disease) remained unchanged throughout and three (EN, NL, GD) were entirely developed by clinicians.

Some of the clinician changes were made to reflect coding practices by hospitals (e.g. use of M79.3 for EN) or clinicians (e.g. use of 287 rather than 287.31 for TTP) in BC. Other changes were made to increase PPV (e.g. change from N17 to N17.0/8/9 for AKI) or sensitivity (e.g. add 696 and 714 for reactive arthritis). A final review addressed logistical constraints (e.g. the planned cohort study cannot assess intravenous immunoglobulin administration).

The findings from our chart review were varied. Sensitivity of the proposed case definitions was generally as high as, or higher than, that reported by others for the same or similar ICD codes (12,15,16,18,24–27). Exceptionally, we found low sensitivity (42.8%–44.4%) for AKI. Given that all our patients were selected from an AKI registry, we believe that they had AKI but were missing an AKI ICD code. Among those without an AKI code, five patients were admitted for other reasons and developed AKI while in hospital and two patients were coded as having chronic kidney injury rather than AKI. Interestingly, others also found low sensitivity for AKI-related ICD codes (9).

The PPV of our proposed case definitions was also generally as high as, or higher than the PPV reported by others (9,15,16). The chart review identified the use of two additional codes for AKI in hospitalized adults: N17.0, N17.9. The addition of these codes increased the PPV from 60.0% to 80.6%. The PPV of AS (63.6%) was lower than the one found by other studies (24,25,28); we found that four of 11 hospitalizations coded as M45 were for patients diagnosed with rheumatoid arthritis, not AS. The PPV of code G610 for MFS based on clinical criteria was low (33.3%) due to the lack of nerve conduction study results in two patient charts; however, all three patients were clinically diagnosed with MFS.

The main challenge in planning the chart review was determining the sample size to accurately estimate sensitivity and specificity and be representative of local coding practices. The literature on the ideal sample size to assess sensitivity and PPV is limited; authors typically review all charts within a period or at a given site (16). We decided to treat this as an exploratory or descriptive study where authors suggest 10–20 charts per question or variable of interest (49). We aimed for a minimum of 10 charts per sequelae, which seemed reasonable given the rarity of some of the conditions, the resources we had and the homogeneity of ICD coding in most instances.

Strengths and limitations

We conducted a chart review for only six of the 15 enteric infection sequelae. These six were selected based on clinician recommendations and because charts for these conditions were readily available. This convenience sample may not be entirely representative of coding practices across our entire study area; however, patients from BC who have the reviewed conditions are mostly cared for in the tertiary care centres included in the study. The sensitivity and PPV calculations were limited by a number of factors. For patients identified through a registry, if only a subset of their charts was reviewed, the code of interest may not be apparent. Clinical data to confirm a diagnosis may be incomplete or absent because patients were transferred from other hospitals or assessed in other settings. For some conditions (e.g. irritable bowel syndrome), the wide spectrum of illness and the large number of health care providers who encountered these patients likely lead to ICD-coding variability. For some conditions, multiple validated case definitions exist (e.g. inflammatory bowel disease) and we had to select among them (30,33,35,50).

Despite these limitations, there was relatively good concordance in ICD codes between the four methods used—the changes

we made to our case definitions were minor and the final definitions were very similar to those validated and used by other researchers. The main concern is the low PPV for ICD code M45, which will identify a substantial number of non-AS hospitalizations, and the low sensitivity of AKI codes, which will underestimate the number of AKI events. These issues need to be accounted for in our future analyses. Our approach allowed us to verify codes identified in the literature with local practices and local chart review validation and benefited from the knowledge of local clinicians.

Conclusion

The multi-step design to derive ICD-code based case definitions allowed us to identify previously validated definitions to adapt them to our study context, and to develop and validate definitions using clinical expertise and medical chart reviews. These findings will support future analyses to determine the likelihood, burden and cost of developing sequelae following enteric infections. They also provide Canadian researchers with validated ICD code definitions for 15 chronic conditions.

Authors' statement

EG — Conceptualization, funding acquisition, methodology, resources, project administration, supervision, writing–original draft, writing–review & editing
AG — Data curation, formal analysis, investigation, visualization, writing–original draft, writing–review & editing
YWH — Data curation, visualization, writing–original draft, writing–review & editing
JC — Investigation, resources, validation, writing–review & editing
DM — Investigation, resources, validation, writing–review & editing
KC — Investigation, resources, validation, writing–review & editing
GK — Investigation, validation, writing–review & editing
DMP — Validation, writing–review & editing
BYZ — Data curation, investigation, visualization, writing–review & editing
MT — Funding acquisition, validation, writing–review & editing
DP — Funding acquisition, methodology, validation, writing–review & editing
SEM — Conceptualization, funding acquisition, methodology, resources, project administration, supervision, visualization, writing–original draft, writing–review & editing

All authors read and approved the final manuscript.

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

Ethics approval was received from the University of British Columbia Clinical Review Ethics Board (H18-01664). EG and SEM report funding for this study as per the funding statement. At the time of the study, EG's spouse worked for an electronic medical records' company; this interest was not related to, or used in, this study. SEM reports other relationships though these interests were not used in this study: she has served as a paid expert on behalf of the Attorney General of Canada in legal proceedings, providing evidence on the public health risks and benefits of unpasteurised milk; she is an expert on the Joint FAO/WHO Expert Meetings on Microbiological Risk Assessment (JEMRA) Roster of Experts; she is a Member of the WHO Foodborne Disease Burden Epidemiology Reference Group. GK reports honoraria for speaking from AbbVie, Janssen, Pfizer, Amgen, Sandoz, and Pendophram; research support from Ferring; shared ownership of a patent: treatment of inflammatory disorders, autoimmune disease, and PBC. UTI Limited Partnership, assignee. Patent WO2019046959A1. PCT/CA2018/051098. 7 Sept. 2018; these interests were not related to, or used in, this study. JC reports research support from Pfizer and UCB for unrelated research; advisory board consulting fees from Abbvie, Organon, UCB, Novartis, Eli Lilly, Sandoz, Jansen, Pfizer, Roche, Merck, Viatris, and Fresenius Kabi; paid lectures from Eli Lilly, Viatris, Abbvie, Pfizer, Novartis, Fresenius Kabi, and UCB; support for attending ACR 2021 meeting from Jansen; unpaid leadership roles at Spondyloarthritis Research Consortium of Canada, Spondyloarthritis Research and Treatment Network, Group for Research and Assessment of Psoriasis and Psoriatic arthritis, and Assessment of Spondyloarthritis International Society; these interests were not related to, or used in, this study. KC reports board membership at CIDP Foundation of Canada, though this interest was not related to this study. All other authors declare no competing interests.

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Supplemental material

These documents can be accessed on the Supplemental material file.

Table S1: Search terms used in the literature review to identify International Classification of Diseases code-based case definitions for enteric infection sequelae
Table S2: Sequelae assessed during the chart review and their clinical criteria
Table S3: Results of the literature review to identify International Classification of Diseases code-based case definitions for enteric infection sequelae

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An Outbreak of *Salmonella* Typhimurium Infections Linked to Ready-To-Eat Tofu in Multiple Health Districts — Ontario, Canada, May–July 2021

Victoria Osasah[1,2]*, Yvonne Whitfield[1], Janica Adams[1], Affan Danish[1], Richard Mather[1], Mehdi Aloosh[1,3]

Abstract

From May to mid-August 2021, the Ontario, Canada provincial public health agency, Public Health Ontario, in collaboration with local public health authorities and federal food safety partners, investigated a spatiotemporal cluster of 38 patients with *Salmonella* Typhimurium infections across multiple public health districts in Ontario. Five (13%) patients were hospitalized; no deaths were reported. The outbreak was linked to consumption of ready-to-eat seasoned tofu from one manufacturer that was distributed to multiple Ontario restaurants. Isolates from the seasoned tofu were within one or fewer allele differences to the outbreak strain by whole genome sequencing. Evidence from food safety investigations conducted by local public health authorities and the Canadian Food Inspection Agency (CFIA), revealed that unsanitary conditions could have led to cross-contamination of the tofu, and insufficient heating of the tofu at the production level likely resulted in failure to eliminate the pathogen. The CFIA issued a food recall for the tofu at hotel, restaurant, and institution levels. Tofu was identified as a novel outbreak-associated food vehicle for *S.* Typhimurium in this outbreak. Interventions that target the production level and all parts of the supply chain and include additional safeguarding steps that minimize microbial growth are important.

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Affiliations

[1] Public Health Ontario, Toronto, ON, Canada

[2] Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD, United States

[3] Department of Health Research Methods, Evidence & Impact, McMaster University, Hamilton, ON, Canada

***Correspondence:**
vosasah1@jhmi.edu

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Epidemiologic investigation and findings

On July 5, 2021, Public Health Ontario (PHO) identified, via routine surveillance, three cases of *S.* Typhimurium infections across multiple public health districts (known as public health units) in Ontario, with four or fewer allele differences in isolates by whole genome multilocus sequence typing (wgMLST), suggesting a common exposure source. By July 9, six more cases were reported to PHO. In collaboration with local, provincial, and federal health authorities, PHO initiated an outbreak investigation. Cases continued to be reported across Ontario through mid-August; among 10 public health districts, incidence ranged from ≤0.2 to 2.9 cases per 100,000 persons. Although *S.* Typhimurium is one of the most common serovars in Ontario, the outbreak strain was not related to any existing clusters or isolates in PulseNet Canada, a national surveillance system that collects information on foodborne-related illnesses caused by specific pathogens. The project did not require ethics approval since the operations were within the purview of Public Health Ontario's legislated mandate.

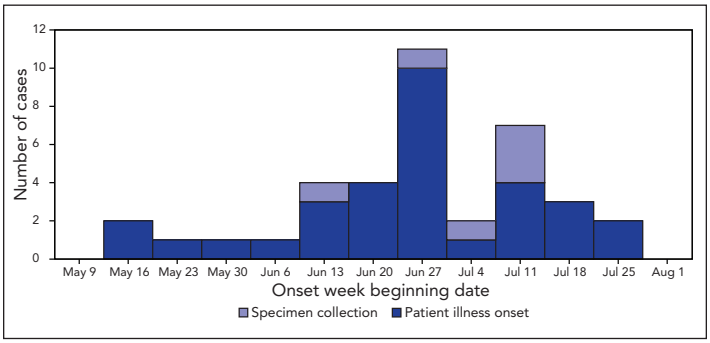
PHO defined a confirmed case as an infection with *S.* Typhimurium in a resident of or a visitor to Ontario occurring after April 30, 2021, with a genomic sequence pattern consistent with (≤10 wgMLST allele differences) the outbreak strain. Thirty-eight cases were reported across 10 of 34 public health districts in Ontario. Symptom onset dates ranged from May 16 to July 31, 2021. The median patient age was 27 years (range=1–87 years); 25 (66%) patients were aged ≥24 years, and 21 (55%) identified as female. Five (13%) patients were hospitalized, and no deaths were reported.

Patients with laboratory-confirmed *Salmonella* infections related to the whole genome sequencing (WGS) cluster were interviewed by local and provincial public health investigators in the 10 affected Ontario public health districts. Using standardized hypothesis-generating questionnaires, investigators recorded food exposure and other risk factors associated with animal and occupational exposure during the 7-day period preceding symptom onset. Information on restaurants and shops visited during the exposure period was collected to further identify any common food locations reported among the patients.

The proportions of reported risk factors were compared with corresponding reference values from the Foodbook report, a population-based telephone survey conducted in all Canadian provinces within a 1-year period during 2014–2015 that focused on describing foods eaten by Canadians during a 7-day period, to guide outbreak investigations and responses (1). An exact probability test was applied to measure the statistical significance of the consumption rates of patients with outbreak-confirmed illness when compared with the Foodbook reference values. Differences with associated *p*-values <0.05 were considered statistically significant.

Illness onset dates clustered from late June through mid-July (**Figure 1**), suggesting an ongoing common-source exposure. Thirty patients were interviewed (response rate=79%), and 19 (63%) reported being on a vegetarian or vegan diet. Among the 25 patients who provided a response for "consumption of tofu," 19 (76%) responded that they had consumed or probably consumed tofu, representing a significantly higher proportion than the proportion of the general population surveyed in the Foodbook report who reported eating tofu (3%; $p<0.001$). Other food items reported by patients that were statistically significantly more likely to be consumed were explored (such as non-dairy milk, vegetables, nuts, and avocado), but they lacked specificity by product type, brand name, and place of purchase. Among the 19 patients who reported consuming tofu, 16 purchased seasoned tofu either at one of 11 restaurant franchise locations or one of three nonfranchise restaurant locations across Ontario, before their illness onset.

Figure 1: Week of illness onset and specimen collection (N=6) for patients infected with a *Salmonella* Typhimurium outbreak strain (N=32) — Ontario, Canada, May–August 2021



Food safety and laboratory investigation and findings

All nonclinical specimens and isolates from clinical specimens were submitted to Public Health Ontario's laboratory (PHOL), a clinical and environmental reference laboratory in Ontario, for analysis. Isolates from all outbreak-confirmed cases underwent WGS at PHOL and the Public Health Agency of Canada's National Microbiology Laboratory. Isolates with four or fewer wgMLST allele differences were considered related by WGS. During the outbreak investigation, an isolate from a case in Québec closely related by WGS to the outbreak strain was identified in PulseNet Canada.

As a result of the epidemiologic evidence, local investigators and Canadian Food Inspection Agency (CFIA) authorities conducted investigations at restaurants where patients reported consuming seasoned tofu during the 7-day period before symptom onset. Additional investigations were conducted once a common manufacturer was identified. A total of 16 opened and closed specimens of the seasoned tofu product were collected from 10 restaurants and the manufacturer. After extensive food safety investigations, *S.* Typhimurium was isolated from three open specimens of seasoned tofu obtained from one of the restaurant franchise locations; the sequenced isolates were closely related by WGS to those from outbreak-confirmed cases. *Salmonella* was not detected in other food specimens produced by the manufacturer.

Food safety investigations revealed that seasoned tofu from the same manufacturer was served across all 14 restaurants. The tofu was identified as a ready-to-eat food product that was produced by a manufacturer in Ontario and commercially sold in 250-g (8.8-oz) and 500-g (17.6-oz) packages. Restaurants purchased the product as a 500-g vacuum-sealed package.

Food safety investigations identified the absence of a heat treatment process after the addition of seasoning to the packaged 500-g product, which was also sold online to other

provinces including Québec; the 250-g packaged product did undergo additional heat treatment. No illnesses were linked to the 250-g packaged product. Several infractions were observed at the manufacturing plant, including poor sanitation of the processing equipment and the absence of a food safety plan or a food sampling program.

Public health response

CFIA issued a food recall for the 500-g tofu product. Local public health inspectors ensured that existing products were removed from distribution and destroyed across implicated restaurants and the manufacturing plant. As a corrective action within the manufacturing facility, a heat treatment step after the addition of the seasoning before packaging was applied.

Discussion

Tofu was identified as the source of an outbreak of *S.* Typhimurium in Ontario in 2021. It was hypothesized that unsanitary conditions at the production facility could have led to contamination of the tofu after production and before packaging, but the absence of an additional heating step during production likely resulted in failure to eliminate the pathogen. Tofu is a novel outbreak-associated food vehicle for this pathogen and has not been implicated in previous outbreaks. Soy products, including tofu, are uncommon vehicles for foodborne illnesses. Among previously published outbreaks linked to soy products, only one outbreak involved *Salmonella* (*Salmonella enterica* paratyphi) (2). Although tofu has been implicated in outbreaks associated with other pathogens, there are no published reports of tofu-associated nontyphoidal *Salmonella* outbreaks (3,4); however, the growth or presence of *S.* Typhimurium on soy products has been detected in microbiological food studies (5,6).

Novel outbreak-associated food vehicles can emerge because of evolution of a pathogen or a change in dietary trends (7). This outbreak largely affected patients who had adopted a vegan or vegetarian diet. An estimated 5% of Canadians adhere to a plant-based diet (8). In addition, age and gender differences are apparent among persons adhering to plant-based diets such as vegetarianism, which is practiced more commonly among females and younger adults (9), consistent with the patient demographics in this outbreak.

The implication of detecting *S.* Typhimurium in tofu as a novel outbreak-associated food vehicle is of public health importance because of the global increase in the consumption of plant-based proteins and the associated high disability-adjusted life years associated with *S.* Typhimurium infection* (10). Improved guidance regarding the processing and handling of plant-based proteins in the supply chain is warranted to eliminate the growth and transmission of foodborne disease pathogens.

Competing interest

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No conflicts of interest were disclosed. The project did not require ethics approval since the operations were within the purview of Public Health Ontario's legislated mandate based on the Ontario Agency for Health Protection and Promotion Act, SO 2007, c 10.

Summary

What is already known about this topic?

Salmonella Typhimurium is a serovar commonly implicated in foodborne illnesses linked to animal product consumption.

What is added by this report?

During May–July 2021, an outbreak of *S.* Typhimurium involving 38 cases in 10 public health districts in Ontario, Canada was linked to consumption of tofu, suggesting a novel outbreak-associated *S.* Typhimurium food vehicle. Lapses in sanitation and recommended heat processing likely resulted in product contamination.

What are the implications?

Tofu has not been previously linked to nontyphoidal *Salmonella* outbreaks. Public health communications to consumers and food establishments should aim to increase awareness of the possible transmission of *Salmonella* through ready-to-eat soy products. In addition, interventions need to target production and all parts of the supply chain, with additional safeguarding steps that minimize growth of *Salmonella* in soy-based products.

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A *Burkholderia stabilis* outbreak associated with the use of ultrasound gel in multiple healthcare centres in Montréal, Canada, May–October 2021

Christine Arsenault[1,2]*, Josée Harel[3], Florence Doualla-Bell[3], Yiorgos Alexandros Cavayas[1,4], Xavier Marchand-Sénécal[2,5], Charles Frenette[6,7], Yves Longtin[7,8], Linda Lalande[1,9], L Marie-Paule Diby[1,9], Nadia Desmarais[1,9]

Abstract

Background: *Burkholderia stabilis* is a non-fermenting, gram-negative bacteria that has previously been implicated in multiple nosocomial outbreaks through the use of contaminated medical devices and substances. This article reports on an outbreak of *B. stabilis* infections and colonizations, involving 11 patients from five acute care hospitals in Montréal, Canada.

Methods: One sample was not available for testing, but the remaining 10 isolates (91%) were sent for phylogenetic testing. Medical materials and the patients' environments were also sampled and cultured. Samples were tested using pulsed field gel electrophoresis and multilocus sequence typing.

Results: The outbreak was found to be associated with the use of intrinsically contaminated non-sterile ultrasound gel. Relatedness of the gel's and the patients' *B. stabilis* strains was demonstrated using gel electrophoresis and multilocus sequence typing analyses. The investigation was concluded with a prompt recall of the product, and the outbreak was declared over by the end of October 2021.

Conclusion: Contaminated non-sterile gel caused infections and pseudo-infections in several patients.

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Affiliations

[1] Hôpital du Sacré-Cœur-de-Montréal, Montréal, QC

[2] Département de microbiologie, infectiologie et immunologie, Faculté de médecine, Université de Montréal, Montréal, QC

[3] Laboratoire de santé publique du Québec/Institut national de santé publique du Québec, Sainte-Anne-de-Bellevue, QC

[4] Département de médecine, Faculté de médecine, Université de Montréal, Montréal, QC

[5] Hôpital Maisonneuve-Rosemont, Montréal, QC

[6] McGill University Health Center, Montréal, QC

[7] Infectious Diseases Division, Faculty of Medicine and Health Sciences, McGill University, Montréal, QC

[8] Jewish General Hospital, Montréal, QC

[9] Service de prévention et contrôle des infections du CIUSSS du Nord de l'Ile de Montréal, Montréal, QC

***Correspondence:**
christine.arsenault.cnmtl@ssss.gouv.qc.ca

Introduction

On July 25, 2021, an unusually high number of requests for consultations (n=3) by the infectious diseases medical team were placed, seeking advice on *Burkholderia stabilis* bloodstream infections in the intensive care unit of the *Hôpital du Sacré-Coeur-de-Montréal*, a 440-bed teaching hospital in Montréal, Canada. It raised concerns about a possible outbreak and led to a formal investigation.

Burkholderia stabilis is a non-fermenting, oxidase-positive gram-negative bacillus, and is a ubiquitous environmental saprophyte. This member of the *B. cepacia* complex has been associated with nosocomial outbreaks of respiratory infections in patients with cystic fibrosis but can also cause non-respiratory infections in other populations through contamination of various medical devices. Washing gloves (1), chlorhexidine (2), alcohol-free mouthwash (3) and medication (4) have all been found to be sources of contamination in previous nosocomial outbreaks of *B. cepacia* complex. Although non-sterile, multi-use, ultrasound gel is appropriate for use on intact skin and on noncritical devices, it is known to support the growth of pathogenic bacteria (5) and has been associated with several outbreaks of *B. cepacia* complex in different settings (6–8).

The epidemiological investigation of the outbreak, the phylogenetic investigation, and the subsequent management are described to prevent further cases.

Method

Outbreak detection

On July 25, 2021, an outbreak of nosocomial bloodstream infections of an unknown source was suspected. An investigation was initiated by the infection control team to identify its source and to prevent exposure of additional patients. First, the laboratory information system was queried for previous positive culture specimens for either *B. stabilis* or *B. cepacia* complex. One previous positive blood culture (one or more bottle) for *B. stabilis* was identified on May 30, 2021, but the isolate had been discarded, in the meantime, as per laboratory protocol. This first case was considered as being part of the outbreak, although its isolate did not contribute to the analysis. Hence, a total of four patients were found to have at least one positive blood culture with *B. stabilis* over the course of six weeks, of which three isolates were available for further analysis. Three patients had their positive culture sampled 48 hours or more after admission, and one had a positive blood culture sampled on the day of admission. A preliminary case definition was established as a positive blood culture for *B. stabilis* sampled on the third day after hospital admission or later in the three-month period preceding July 25, 2021. This definition was used to be consistent with the case definition of a nosocomial bloodstream infection by the provincial surveillance program (9). Symptoms were not required to fit the case definition, and an infection diagnosis was not necessary for inclusion. When no symptom was attributed to the bacteria retrieved in a clinical specimen, it was considered either a contaminant or a colonizer. We defined a contaminant as an organism that is detected by culture but believed to be introduced in the process of sampling the bodily fluid or organ and absent in the fluid or organ itself. A colonizer is a saprophyte organism detected by culture but not causing disease.

A case definition for a possible case included any patient with a culture positive for *B. stabilis* or *B. cepacia* complex from any site (other than blood), either nosocomial or community-acquired in the three-month period preceding July 25, 2021.

Investigations

First observations were conducted in the intensive care unit department, where all four cases had been identified. On July 29 and July 30, infection control practitioners audited diverse care techniques provided to patients and related procedures including bathing with single-use gloves, oral hygiene, use of thermometers, central venous catheter manipulations, use of sterile water, handling of multi-use ultrasound gel bottles, and disinfection of noncritical devices.

Subsequently, sampling of clean and sterile material was performed and sent for culture. Indwelling central catheter insertion sites were also swabbed. Sampled material included opened and sealed non-sterile ultrasound gel, sterile ultrasound gel, single-use commercial washing gloves, chlorhexidine wipes, sterile water and mouthwash.

Cultures were incubated on 5% blood sheep agar and MacConkey agar for 48 hours at 37°C in ambient air conditions. Morphologically compatible colonies were submitted for identification using the VITEK MS system using Database v3.1 (bioMérieux, France).

Pulse field gel electrophoresis and multilocus sequence typing analyses

Molecular typing analysis of *B. stabilis* isolates was done by pulse field gel electrophoresis (PFGE) and multilocus sequence typing (MLST) (10,11). Pulse field gel electrophoresis was carried out at the *Laboratoire de santé publique du Québec*. Sequence typing of *B. stabilis* isolates was performed by the National Laboratory of Microbiology of Canada according to the protocol and primers specified in a public database of MLST sequence data (10–12).

Interventions

Positive cultures sampled from both opened and sealed ultrasound gel containers originating from the intensive care units were obtained on July 30. The use of all similar products was immediately discontinued at the intensive care units of the *Hôpital du Sacré-Coeur-de-Montréal* and affiliated hospitals. When additional positive cultures were obtained from ultrasound gel containers from other units, all gel bottles were discarded and replaced by an alternate product on August 2.

Montréal Public Health was notified on August 2 of a suspected contamination of ultrasound gel containers. A notice was sent to physicians and laboratories, and clinical specimens from other hospitals in the Montréal area were sent to the provincial public health laboratory.

Provincial health ministry was notified on August 4 and Health Canada was notified on August 6. A formal complaint was filed to the manufacturer on August 4 and the product was recalled the same day. To identify additional outbreak-related cases in other healthcare institutions in the province of Québec, a microbiology database search was conducted in several hospitals that used the same brand of ultrasound gel. Cultures from any sterile sites found to be positive with *B. stabilis* and *B. cepacia* complex were listed. The medical charts of patients with positive cultures were reviewed by local infectious disease consultants to determine whether the positive culture represented a true infection, a contaminant, or a colonization. Patients received care and antimicrobial treatment accordingly.

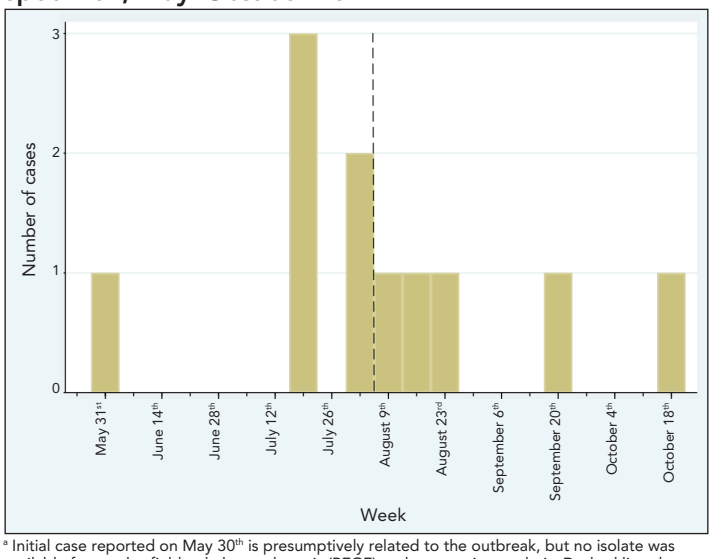
Results

Over the course of the outbreak, a total of 11 cases of infections and pseudo-infections (detection of a colonizer or contaminant in a specimen sent for culture) were found in five Montréal hospitals, of which 10 isolates were available for analysis; eight specimens were collected between July 16 and August 24 and the last two were collected on September 20 and October 18, 2021 (**Figure 1**). The 11th isolate had been discarded before the outbreak was declared.

The outbreak was considered over by the end of October 2021 as no further cases were reported and the identified source of the outbreak was no longer in operation.

The case definition used to initiate the investigation proved to be too restrictive, as specimens that were genetically related to the outbreak were sampled from both sterile and non-sterile sites. Consequently, the case definition was reviewed and updated on July 30 to include all cases of infection and pseudo-infections with a genetically related strain of *B. stabilis* recovered from any type of body specimen.

Figure 1: Cases of *Burkholderia stabilis* infections or pseudo-infections, by week of collection of first positive specimen, May–October 2021[a]



[a] Initial case reported on May 30th is presumptively related to the outbreak, but no isolate was available for a pulse field gel electrophoresis (PFGE) and sequencing analysis. Dashed line shows date of product recall (August 4th). First day of the week is used as label

Of the 33 specimens sampled from medical material and the patients' environment, six collected from different ultrasound gel bottles were positive for *B. stabilis*. Five of these bottles were factory sealed prior to sampling and one was already open and in use. *B. stabilis* was the only bacteria identified in culture. All other samples were negative. Isolates were sent to the public health reference laboratory for further analysis. All patients and gel isolates were clonal after sequencing analysis. All but one isolate was considered definitively related on PFGE analysis, displaying a unique PFGE pattern with restriction enzyme *SpeI* (pulsovar A). One was considered likely related to the outbreak strains, exhibiting a closely related *SpeI* pattern (pulsovar A2). In addition, all isolates shared the same MLST profile and were identified as MLST type ST51, confirming their relatedness.

No death has been attributed to an infection associated with this outbreak. While it is possible that medical care episodes were complicated by a positive blood culture, it was not possible to verify or quantify this impact. Patients presented with wide-ranging clinical profiles. The relevant clinical characteristics are reported in **Table 1**. Since no surgical site infection was reported, surgeries are not included in these reported data.

Table 1: Characteristics of patients with a positive culture with a clonal stain of *Burkholderia stabilis*

Hospital	Reason for admission	Procedures involving ultrasound gel prior to or at time of positive cultures	Type of specimens	Signification of culture result as per infectious disease consultant
1	Trauma	Central line insertion FAST ultrasound	Blood cultures	Infection
2	Cardiac arrest	Peripherally inserted central line, transthoracic echocardiogram	Endotracheal secretions	Colonization
2	Birth (newborn)	External fetal monitoring	Umbilical cord blood cultures	Contaminant
2	Fall	Peripherally inserted central line	Blood cultures	Infection
3	Trauma	Central line insertion FAST ultrasound	Blood cultures	Infection
3	Neurological condition	Peripherally inserted central line Venous cavography (using surface ultrasound)	Blood cultures	Infection
3	Neurological condition	Transthoracic cardiac ultrasound	Blood cultures	Infection
3	Trauma	Transthoracic cardiac ultrasound	Blood cultures	Infection
4	Orthopedic condition	Joint ultrasound	Synovial fluid	Contaminant
5	Congestive heart failure	Central line insertion, mesenteric angiogram and embolization, dialysis catheter insertion	Bronchoalveolar lavage	Infection

Abbreviation: FAST, Focused Assessment with Sonography in Trauma

Discussion

This report documents an outbreak of *B. stabilis* associated with the use of contaminated non-sterile ultrasound gel. Ten clinical isolates and six isolates from opened and sealed ultrasound gel containers showed relatedness by PFGE and MLST analyses, supporting the hypothesis of ultrasound gel being the cause of the outbreak. Most patients were hospitalized in the intensive care unit, and many had a central venous line in place or were intubated.

A similar investigation reporting 119 cases of *B. stabilis* infections acquired from ultrasound gel produced by the same manufacturer was performed in the United States during the same period (13); the results of this investigation are consistent with our findings and support our conclusions.

In this outbreak, intrinsic product contamination occurred at the manufacturing stage, as demonstrated by the presence of bacterial strains in sealed gel bottles. *Burkholderia cepacia* complex organisms are frequently involved in recalls of non-sterile products (14). These bacteria are often resistant to biocides used to prevent bacterial proliferation and can survive for prolonged periods in low-nutrient environments. They are a frequent cause of pharmaceutical compound contamination, which can occur because of contaminated surfaces and materials, but most often through the inclusion of contaminated water (14). While non-sterile products are vulnerable to contamination, sterile products are manufactured in bacteria-free environments using sterile materials and are therefore much less likely to result in a contaminated product.

The exact mechanism allowing the non-sterile contaminated gel to lead to bacteremia remains unclear and is likely multifactorial. Visual audits did not reveal noncompliance to central line insertion standards (15) or non-critical devices disinfection (16), but it was noted that ultrasound gel was sometimes removed swiftly using a dry cloth after a bedside examination. However, these audits are by nature limited to a handful of observations. Although non-sterile ultrasound gel is to be used only on intact skin (5), similar outbreaks related to contaminated gel have occurred (6–8). We hypothesize that contamination of the intact skin of vulnerable patients leads to changes in the skin microbiome and colonization with *B. stabilis*. *Burkholderia stabilis* is more likely to be a causative organism if these colonized patients subsequently develop a healthcare-associated infection. This suggests sterile gel should be preferred before an impending invasive procedure, as a simple intervention that should reduce the likelihood of similar events.

Most cases occurred over a short period of time, but two cases phylogenetically related to the outbreak occurred after the month of August, with the latest on October 18. While it was not possible to prove this hypothesis, one likely explanation is that some gel bottles were not discarded immediately after the recall and were still in use at the time of the last case. Implementing a temporary prospective surveillance following a product recall could help address this situation and ensure containment of the outbreak.

One strength of this investigation was the fast identification of the source, leading to a prompt recall of the contaminated product. The causal relationship between the cases and the

product is supported by the relatedness of the bacterial strains, demonstrated using multiple validated techniques. While it does not prove that the ultrasound gel caused all infections and pseudo-infections, it would be unlikely to observe such genetic similarity between bacteria retrieved in a product used on patients' skin and cultures due to chance alone, considering the rarity of this pathogen in the infectious disease practice. Although enough isolates were retrieved to support the association, the earliest case's isolate was not available to be analyzed. No systematic procedure was in place to refer *B. stabilis* isolates to the public health laboratory; therefore, our samples do not reflect the entire outbreak's magnitude. We believed that enough data supported the association between the ultrasound gel and the positive cultures of clinical specimens, so no formal case-control study was performed.

This article describes an outbreak of infections and pseudo-infections with *B. stabilis*, attributed to intrinsically contaminated ultrasound gel. Non-sterile ultrasound gel is vulnerable to contamination with bacterial pathogens at the time of manufacturing, and from human cross-contamination after introduction into clinical use. Healthcare centres must remain aware of the potential for contamination of these products that could lead to multicenter outbreaks. The universal use of sterile single-use ultrasound gel containers could provide a theoretical advantage, but our study cannot determine whether switching to sterile gels could improve patient outcomes. Still, our study supports the generally accepted notion that single use sterile gels should be preferred over multiuse non-sterile gel in at-risk contexts, such as invasive procedures, procedures that involve sterile equipment and for procedures on mucous membranes or non-intact skin (5).

Authors' statement

CA — Writing original draft, investigation, review and editing
JH — Investigation, writing–review and editing
FDB — Investigation, writing–review and editing
YAC — Writing–review and editing
XMS — Investigation, writing–review and editing
CF — Investigation, writing–review and editing
YL — Investigation, writing–review and editing
LL — Investigation, writing–review and editing
LMPD — Investigation, writing–review and editing
ND — Investigation, writing–review and 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

YL has received research support from Syneos Health for work unrelated to the current study.

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Portrait of French-speaking minorities with respect to vaccination against COVID-19

Chloé Desjardins[1], Jennifer Lacroix Haraysm[1], Joseph Abdoulnour[2], Manon Denis-LeBlanc[2,3], Daniel Hubert[1], Salomon Fotsing[1,2,3], Diane Bouchard Lamothe[1], Sylvain Boet[2,4,5,6,7,8]*

Abstract

Background: The coronavirus disease 2019 (COVID-19) vaccination campaign highlighted the requirement to better understand the needs of different populations. French-speaking minorities (FSMs) have greater difficulty accessing quality care in French, and this problem was exacerbated during the COVID-19 pandemic.

Objective: The aim of this survey was to develop a descriptive portrait of the health needs of FSMs in relation to the COVID-19 vaccination campaign by describing their vaccination status, attitudes and beliefs compared with English-speaking majorities.

Methods: A survey was conducted among eligible participants using convenience sampling. Data measurement includes a descriptive statistical comparison using analysis of the variance, univariate logistic regressions and a two-proportions z-test.

Results: Of the 1,505 respondents (554 FSMs vs. 951 English speakers), the FSMs have an average age of 51.4 years and 89.2% are Canadian citizens. Vaccination of children was preponderant among English speakers (74.2% vs. 86.3%), including against COVID-19 (58.6% vs. 73.9%). A higher proportion of FSMs had gotten vaccinated in order to obtain a vaccine passport (39% vs. 29.3%). Among the unvaccinated, FSMs were more likely to question the efficacy of vaccines (60% vs. 36.4%). Canadian citizen FSMs with higher education could be divided in relation to the vaccine regimen.

Conclusion: This survey revealed differences between FSMs and the English-speaking majority in their perceptions of vaccine efficacy, particularly vaccination of children, and a polarization of attitudes/beliefs among FSMs according to certain sociodemographic factors.

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Keywords: vaccines, vaccine hesitancy, Francophone minorities, community survey

Affiliations

[1] Francophone Affairs, Faculty of Medicine, University of Ottawa, Ottawa, ON

[2] Institut du Savoir Montfort, Ottawa, Ottawa, ON

[3] Department of Family Medicine, University of Ottawa, Ottawa, ON

[4] Faculty of Education, University of Ottawa, Ottawa, ON

[5] Department of Anesthesiology and Pain Medicine, University of Ottawa, Ottawa, ON

[6] Department of Innovation in Medical Education, University of Ottawa, Ottawa, ON

[7] Clinical Epidemiology Program, The Ottawa Hospital Research Institute, Ottawa, ON

[8] Keenan Research Centre at the Li Ka Shing Knowledge Institute, Toronto, ON

***Correspondence:**
jlacroi9@uottawa.ca

Introduction

The coronavirus disease 2019 (COVID-19) vaccination campaign highlighted the requirement to better understand the needs of different Canadian populations during a pandemic. The lack of data on the needs of linguistic minorities (1–3) had a significant impact on vaccine uptake and trust in healthcare institutions (4,5).

French-speaking minorities (FSMs) have greater difficulty accessing quality care in French (6–12), which is one of the problems exacerbated during a pandemic (8,12,13). However, vaccine uptake is influenced by multiple factors linked to the sociocultural context, including values, morality, accessibility and therapeutic experience, requiring adapted medical practices (14–17). This study is necessary to fill the knowledge gap on the subject and improve the active offer.

Given the fragmented nature of Canadian Francophonie (18), it is difficult to establish an overall picture of the needs of FSMs

based on up-to-date evidence. An existing survey (19) explores some relevant areas, but does not provide a breakdown by language, at least not in publicly available data. This survey, carried out between May 1 and June 30, 2022, aims to describe the health needs of FSMs in relation to the COVID-19 vaccination campaign through the lens of vaccination status, attitudes and beliefs, and provides for a comparison with English-speaking majorities.

Methods

This article was written according to the guidelines of Improving the Quality of Web Surveys: The Checklist for Reporting Results of Internet E-Surveys (CHERRIES) (20).

Population, time and place

The survey was conducted over an eight-week period ending on June 30, 2022, among FSMs and English speakers outside Québec, Canada. The study defines FSMs as residents outside Québec whose preferred language is French, and Anglophones as residents outside Québec whose preferred language is English. Given the rapid evolution of the pandemic, convenience sampling was used.

Link to the research objective

The descriptive portrait of FSMs vis-à-vis the COVID-19 vaccination campaign includes the collection of sociodemographic data, vaccination status, attitudes and beliefs.

Development of the survey questionnaire

The questionnaire (**Supplemental material**, **Survey**) was designed by the research team based on a validated survey (19) by Statistics Canada. To meet the requirements of the study, questions dealing with language, attitudes and beliefs were added before conducting a pilot study with 30 participants drawn from the mailing list of Léger Marketing Inc.

Sampling technique

Participants were recruited primarily via the sampling strategy, the mailing list of Léger Marketing Inc. and Canadian Francophone organizations (Supplemental material, **Survey invitation letter**). The sample was created taking into account the response rates for each age category and the quotas required to obtain a representative sample. Representative quotas were established for age, gender and province. The sample was sent out strategically to ensure representativeness. For example, attention was focused on the 18 to 24 age group, as these respondents are generally harder to reach, while less attention was paid to the 65+ age group, as they are conversely much easier to reach. This required constant attention to the quotas defined in the survey platform, while ensuring random selection. An invitation letter, a consent form and the questionnaire were distributed to those who met the inclusion criteria.

Informed consent

The study was approved by the University of Ottawa Research Ethics Board (H-02-22-7648). A consent form had to be completed by participants prior to conducting the survey.

Optimizing response rates

The survey was made available on FocusVision Decipher (Forsta, 2022) and on the LEO mobile app (Léger Marketing Inc., 2020), in addition to being widely distributed via the social networks of the University of Ottawa Faculty of Medicine's Francophone Affairs. Participants were invited to share the survey, allowing snowball sampling to be used to optimize the response rate.

Measurement

Data measurement was carried out in accordance with two research questions designed to identify 1) the vaccination status, attitudes and beliefs of FSMs compared with English speakers, and 2) the sociodemographic characteristics of FSMs in relation to vaccination status, attitudes and beliefs.

Sociodemographic data includes: province/territory of residence, age, gender, income, education, marital status, ethnicity, citizenship and health status. Vaccination status includes COVID-19 vaccine doses, willingness to follow the recommended vaccine regimen, and vaccination of children (ages 5 to 11 years). Attitudes include reasons for uptake and hesitancy, as well as trusted sources of information. Beliefs include vaccine safety, perceived risks and efficacy, health practices and social responsibility.

Analysis

Descriptive statistics were calculated and analyzed using SPSS (version 22.0). Continuous variables were presented as means and standard deviations, and categorical variables as totals and/or percentages. Analyses of variance (ANOVA) were performed to examine significant differences in continuous variables. Univariate logistic regressions were performed to determine the associations between FSMs and English speakers, and also sociodemographic variables with vaccination status and belief. The findings are presented as odds ratios (OR) with 95% confidence intervals (CI), as well as the likelihood chi-squared statistic. A two-proportions z-test was performed for multiple-response questions to compare proportions between groups; the Bonferroni correction was used for multiple comparisons. A *p*-value of less than 0.05 indicates a statistically significant difference.

Findings

The sample comprised 1,505 participants: 554 FSMs and 951 English speakers. The findings include a 100% response rate for each participant, giving n=554 (FSMs) and n=951 (English speakers). The sociodemographic data are presented below (**Table 1**).

Table 1: Sociodemographic characteristics of French-speaking minority participants and English-speaking participants

Characteristics	% FSM (n=554)	% English speakers (n=951)
Age (years)		
Mean; standard deviation	51.4; 16.9	48.1; 17.4
Median	53.0	47.0
18–24	4.7	11.1
25–34	17.0	15.3
35–44	14.6	17.0
45–54	17.5	20.1
55–64	20.9	17.5
65–74	17.5	9.3
≥75	7.8	9.6
Gender		
Female	61.2	50.2
Male	38.8	49.8
Other	0.0	0.0
Prefer not to answer	0.0	0.0
Province		
Ontario	47.1	50.4
New Brunswick	33.4	2.4
British Columbia	6.5	17.8
Alberta	6.5	14.2
Manitoba	2.7	4.9
Saskatchewan	1.4	4.1
Nova Scotia	1.4	3.7
Nunavut	0.4	0.0
Newfoundland and Labrador	0.2	2.1
Prince Edward Island	0.2	0.4
Yukon	0.2	0.0
Income		
≤$30,000	12.4	13.2
$30,000 to $60,000	23.4	23.6
$60,000 to $90,000	20.7	22.0
$90,000 to $120,000	17.4	17.9
$120,000 to $150,000	11.3	9.8
>$150,000	14.8	13.5
Education		
Less than a high school diploma or equivalent	3.1	1.2
High school diploma or certificate of equivalence	15.6	18.2
Trade certificate or diploma	5.6	6.9
College, CEGEP or other non-university certificate or diploma	20.0	22.4
University certificate or diploma below bachelor level	5.1	6.8

Table 1: Sociodemographic characteristics of French-speaking minority participants and English-speaking participants (*continued*)

Characteristics	% FSM (n=554)	% English speakers (n=951)
Education (*continued*)		
Bachelor's degree	30.0	30.5
University certificate, diploma or degree above bachelor level	20.5	14.0
Marital status		
Single	23.4	24.1
Couple	49.5	34.9
Family	27.2	40.9
Indigenous status		
North American First Nation	1.3	2.1
Métis	2.5	2.0
Inuk (Inuit)	0.0	0.3
Ethnicity		
Arab	0.9	1.4
Southeast Asian	1.6	0.5
West Asian	0.7	0.2
Caucasian	70.8	91.5
Chinese	8.8	1.3
Korean	0.6	0.0
Japanese	0.5	0.0
Latin American	1.5	0.5
African American	1.8	2.5
Filipino	1.3	0.0
South Asian	6.6	0.5
Other	4.7	1.6
Citizenship status		
Canadian citizen by birth	89.2	77.2
Canadian citizen by naturalization	7.6	18.6
Permanent resident	2.5	2.7
None	0.7	1.5
State of health		
Obesity	9.4	9.2
Heart and/or vessel disease	4.7	4.7
Diabetes	10.1	6.3
Liver disease	0.7	0.4
Chronic kidney disease	0.0	0.7
Alzheimer's disease	0.2	0.0
Immunodeficiency	3.3	3.3
Lung disease	7.2	6.7
None of these health problems	64.3	68.7

Abbreviation: FSM, French-speaking minority

Vaccination status

Differences between French-speaking minorities and English speakers

According to the univariate regression values, FSMs were less willing to have their children vaccinated against preventable diseases (74.2% vs. 86.3%) (χ^2[1, N=440]=7.069, p=0.008; OR=0.455 [95% CI: 0.259–0.799]), against COVID-19 (58.6% vs. 73.9%) (χ^2[1, N=436]=7.531, p=0.006; OR=0.500 [95% CI: 0.306–0.815]) or to follow the recommended vaccine regimen (0.0% vs. 22.0%) (χ^2[3, N=126]=16.879, p=0.001) (**Table 2**).

Table 2: Vaccination status among French-speaking minorities and English speakers

Vaccination status	% FSM (n=554)	% English speakers (n=951)	Likelihood chi-squared	Approx. sig. (bilateral)[a]	OR	95% CI	
Adult vaccinated against COVID-19							
Yes	93.60	91.80	1.763	0.184	0.756	0.500	1.144
No	6.40	8.20			N/A	N/A	N/A
COVID-19 vaccination doses							
1 dose	0.80	1.30	5.758	0.124	0.472	0.144	1.549
2 doses	19.50	23.50			0.640	0.429	0.953
3 doses	66.70	65.20			0.790	0.559	1.116
4 doses	13.00	10.10			N/A	N/A	N/A
Plausibility of following the recommended full vaccine regimen (vaccinated adult)							
Very likely	62.20	62.60	2.463	0.482	0.881	0.559	1.390
Somewhat likely	20.10	22.50			0.792	0.483	1.300
Unlikely	11.10	9.10			1.082	0.623	1.879
Very unlikely	6.60	5.90			N/A	N/A	N/A
Plausibility of following the recommended full vaccine regimen (unvaccinated adult)							
Very likely	2.90	6.40	4.523	0.210	0.354	0.039	3.194
Somewhat likely	5.70	17.90			0.253	0.053	1.200
Unlikely	17.10	16.70			0.817	0.277	2.405
Very unlikely	74.30	59.00			N/A	N/A	N/A
Previous vaccination for children (against other diseases)							
Yes	74.20	86.30	7.069	0.008	0.455	0.259	0.799
No	25.80	13.70			N/A	N/A	N/A
Children vaccinated against COVID-19							
Yes	58.60	73.90	7.531	0.006	0.500	0.306	0.815
No	41.40	26.10			N/A	N/A	N/A
COVID-19 vaccination doses							
1 dose	29.20	17.20	3.382	0.184	2.064	0.784	5.433
2 doses	54.20	62.60			1.053	0.446	2.486
3 doses	16.70	20.30			N/A	N/A	N/A
Plausibility of following the recommended full vaccine regimen (children)							
Very likely	0.0	22.0	16.879	0.001	6.84E-10	6.84E-10	6.84E-10
Somewhat likely	28.6	34.10			0.473	0.180	1.247
Unlikely	28.6	19.8			0.815	0.296	2.246
Very unlikely	42.9	24.2			N/A	N/A	N/A

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; FSM, French-speaking minority; N/A, not applicable; OR, odds ratio
[a] Approx. sig. (bilateral) is a p-value of less than 0.05 for univariate analyses is considered significant

Differences according to sociodemographic data

Compared with those born outside the country, Canadian-born FSMs are more inclined to not follow the recommended vaccine regimen (85.2% vs. 37.5%) (χ^2[3, N=35]=10.714, p=0.013; OR=7.667 [95% CI: 1.035–56.770]), but have more doses (67.7% and 13.6% vs. 56.9% and 7.8%) (χ^2[3, N=513]=9.848, p=0.020; OR=15.750 [95% CI: 1.736–142.882]). Among those, individuals with a college/certificate education are less inclined to agree with the vaccine regimen compared with those with a higher education (52.7% vs. 75.7%) (χ^2[9, N=509]=22.968, p=0.006; OR=0.313 [95% CI: 0.109–0.903]). More FSMs are vaccinated in Ontario (96.2% vs. 86.2% [West] and 93.8% [Atlantic]) (χ^2[2, N=547]=10.317, p=0.017; OR=4.012 [95% CI: 1.695–9.497]) receive more doses compared with other regions (20% vs. 8.6% [West] and 5.6% [Atlantic]) (χ^2[6, N=511]=43.713, p<0.001). Men (18.9% vs. 9.3%, women) (χ^2[3, N=514]=14.229, p=0.003; OR=2.044 [95% CI: 1.203–3.471]) and older individuals (52.2 ± 16.1 and 68.8 ± 11.2 years vs. 40.8 ± 18.3 and 40.9 ± 12.2 years; F(3, 510)=46.58, p<0.001) more often had 3–4 doses. Among FSMs with vaccinated children, a high income was preponderant (87% [>$120,000] vs. 56.8% [$60,000 to $120,000] vs. 34.6% [<$60,000]) (χ^2[2, N=86]=14.963, p=0.001; OR=12.593 [95% CI: 2.931–54.107]).

Attitudes

Differences between French-speaking minorities and English speakers

There are two significant differences: a greater proportion of FSMs had gotten vaccinated to obtain the vaccine passport (39% vs. 29.3%, p<0.001); among the unvaccinated, more FSMs questioned the efficacy of the COVID-19 vaccine (60.0% vs. 36.4%, p=0.019) (**Table 3**).

Table 3: Vaccination attitudes between French-speaking minorities and English speakers

Vaccination attitudes	FSMs		English speakers		Statistical z-test[a]	*p*-value
	n	%	n	%		
Reasons for vaccination (vaccinated adult)[b]						
Vaccination is mandated by my workplace	112	21.7%	163	18.8%	−1.34	0.1811
Vaccination passport	201	39.0%	254	29.3%	−3.72	0.0002
I want to protect myself against serious illness	395	76.7%	686	79.0%	−1.02	0.3099
Return to normal life	275	53.4%	433	49.9%	−1.26	0.2064
I want to protect others	329	63.9%	574	66.1%	−0.85	0.3964
Leisure	179	34.8%	288	33.2%	−0.60	0.5487
Other	14	2.7%	22	2.5%	−0.21	0.8355
Reasons for vaccine hesitancy (unvaccinated adult)[c]						
The vaccine is not recommended for me	5	14.3%	7	9.1%	−0.83	0.4088
I do not have the necessary information to make a decision	4	11.4%	8	10.4%	−0.17	0.8688
I know too many people who have had side effects	12	34.3%	32	41.6%	−0.73	0.4642
I'm afraid	5	14.3%	9	11.7%	−0.39	0.6994
I am not at a great risk of contracting COVID-19	9	25.7%	17	22.1%	−0.42	0.6720
If I get COVID-19, I won't be very sick	6	17.1%	17	22.1%	0.60	1.4517
We do not know the long-term side effects	22	62.9%	44	57.1%	−0.57	0.5681
I don't know who to believe	3	8.6%	8	10.4%	−0.30	0.7640
I don't know how, when or where to get vaccinated	0[d]	0.0%	1	1.3%	N/A[d]	N/A[d]
I should be given a choice	18	51.4%	36	46.8%	−0.46	0.6456
There was a problem with the appointment	0[d]	0.0%	2	2.6%	N/A[d]	N/A[d]
I didn't have time	0[d]	0.0%	4	5.2%	N/A[d]	N/A[d]
I've already had COVID-19	3	8.6%	15	19.5%	−1.46	0.1446
I don't want to get vaccinated at this time	14	40.0%	25	32.5%	−0.78	0.4370
In general, I don't believe in vaccines	4	11.4%	10	13.0%	−0.23	0.8169
The vaccine I want is not available or has not been offered to me	0[d]	0.0%	2	2.6%	N/A[d]	N/A[d]
I don't trust the vaccine offered to me	10	28.6%	20	26.0%	−0.29	0.7731
I don't trust the health system	5	14.3%	10	13.0%	−0.19	0.8513

Table 3: Vaccination attitudes between French-speaking minorities and English speakers (*continued*)

Vaccination attitudes	FSMs		English speakers		Statistical z-test[a]	*p*-value
	n	%	n	%		
Reasons for vaccine hesitancy (unvaccinated adult)[c] (*continued*)						
Cultural, philosophical or religious reasons	5	14.3%	7	9.1%	−0.83	0.4088
I'm pregnant or plan to become pregnant	1	2.9%	3	3.9%	−0.28	0.7833
I'm not sure that vaccines against COVID-19 are effective	21	60.0%	28	36.4%	−2.34	0.0194
Other	1	2.9%	10	13.0%	−1.67	0.0947
Reasons for hesitancy concerning vaccination of children[e]						
The vaccine is not recommended for them	7	20.0%	29	32.2%	−1.35	0.1754
I do not have the necessary information to make a decision	8	22.9%	11	12.2%	−1.49	0.1370
I know too many people who have had side effects	5	14.3%	14	15.6%	−0.18	0.8591
I'm afraid and/or my children are afraid	2	5.7%	6	6.7%	−0.20	0.8451
My children are not at high risk of contracting COVID-19	4	11.4%	11	12.2%	−0.12	0.9024
If they contract COVID-19, my children won't be very sick	8	22.9%	10	11.1%	−1.68	0.0931
We do not know the long-term side effects of the vaccine that was offered to me for them	11	31.4%	27	30.0%	−0.16	0.8761
I don't know who to believe	3	8.6%	3	3.3%	−1.23	0.2187
I don't know how, when or where to get my children vaccinated	0[d]	0.0%	1	1.1%	N/A[d]	N/A[d]
I should be given a choice	8	22.9%	16	17.8%	−0.65	0.5174
There was a problem with the appointment	1	2.9%	2	2.2%	−0.21	0.8350
I didn't have time	2	5.7%	2	2.2%	−1.00	0.3192
They've already had COVID-19	6	17.1%	10	11.1%	−0.91	0.3648
I don't want my children to get vaccinated at this time	5	14.3%	19	21.1%	−0.87	0.3844
In general, I don't believe in vaccines	0[d]	0.0%	6	6.7%	N/A[d]	N/A[d]
The vaccine I want for my children is not available or has not been offered to me	1	2.9%	3	3.3%	−0.14	0.8920
I don't trust the vaccine offered to me	4	11.4%	10	11.1%	−0.05	0.9597
I don't trust the health system because of a bad experience	3	8.6%	5	5.6%	−0.62	0.5362
Cultural, philosophical or religious reasons	0[d]	0.0%	3	3.3%	N/A[d]	N/A[d]
I'm not sure that vaccines against COVID-19 are effective	5	14.3%	21	23.3%	−1.12	0.2631
In general, the risks associated with vaccines are greater than the benefits	6	17.1%	15	16.7%	−0.06	0.9490
Other	0[d]	0.0%	4	4.4%	N/A[d]	N/A[d]
Trusted sources of information on COVID-19 vaccination[f]						
Friends, family members or acquaintances	51	9.3%	132	13.9%	−2.64	0.008
My physician	379	69.0%	657	69.4%	−0.14	0.890
My pharmacist	238	43.4%	380	40.1%	−1.23	0.220
Other healthcare professionals (e.g. nurses)	228	41.5%	439	46.4%	−1.82	0.069
Community leaders	17	3.1%	35	3.7%	−0.61	0.540
Politicians	24	4.4%	18	1.9%	−2.80	0.005
Social media	23	4.2%	26	2.7%	−1.52	0.129
Alternative medicine professionals	32	5.8%	48	5.1%	−0.63	0.527
Public health authorities	335	61.0%	529	55.9%	−1.95	0.051
Health scientists and researchers	352	64.1%	593	62.6%	−0.58	0.561
World Health Organization (WHO)	267	48.6%	437	46.1%	−0.93	0.351
Pharmaceutical companies	24	4.4%	70	7.4%	−2.34	0.020
Other	29	5.3%	59	6.2%	−0.75	0.451

Table 3: Vaccination attitudes between French-speaking minorities and English speakers (*continued*)

Vaccination attitudes	FSMs		English speakers		Statistical z-test[a]	*p*-value
	n	%	n	%		
Means of validating COVID-19 vaccination information[g]						
Confirm with other sources	338	61.6%	558	59.1%	−0.94	0.3481
Click on the link to read the full article	230	41.9%	461	48.8%	−2.59	0.0095
Check the date of the information	204	37.2%	354	37.5%	−0.13	0.8949
Check the number of likes or shares	6	1.1%	29	3.1%	−2.47	0.0134
Research the author or source	242	44.1%	407	43.1%	−0.36	0.7154
Read the comments or take note of the discussions on the subject	93	16.9%	164	17.4%	−0.21	0.8300
Consult friends and family	59	10.7%	142	15.0%	−2.33	0.0196
Check the credibility of the URL	203	37.0%	339	35.9%	−0.41	0.6785
Other	60	10.9%	86	9.1%	1.15	1.7482

Abbreviations: COVID-19, coronavirus disease 2019; FSM, French-speaking minority; N/A, not applicable
[a] Statistical z-test results are based on bilateral tests with a significance level of 0.05. The tests are adjusted for all pairwise comparisons within a row of each innermost sub-table, using the Bonferroni correction
[b] Total N for FSMs=35 and for English speaking=77
[c] This category is not used in the comparisons as its proportion of columns is equal to zero
[d] Total N for FSMs=515 and for English speaking=868
[e] Total N for FSMs=35 and for English speaking=90
[f] Total N for FSMs=549 and for English speaking=947
[g] Total N for FSMs=549 and for English speaking=944

Differences according to sociodemographic data

French-speaking minorities who are Canadian citizens by birth are mainly vaccinated for a return to normal life (55% vs. 39%, p=0.034) and protection against serious illness (79% vs. 59%, p=0.002). To obtain information on COVID-19, they mainly consulted family and friends (10% vs. 20%, p=0.015), pharmacists (45% vs. 30%, p=0.026) and public health authorities (63% vs. 47%, p=0.016). Ontarians are more confident in the safety and efficacy of vaccines/health measures (58.1% vs. 38.9% [West] and 42.7% [Atlantic]) (χ^2[6, N=545]=19.141, p=0.004; OR=1.829 [95% CI: 0.786–4.255]). This confidence is also preponderant among men (58.4% vs. 43.4%, women) (χ^2[3, N=548]=12.337, p=0.006; OR=1.724 [95% CI: 0.804–3.695]) who are more willing to get vaccinated to protect themselves against serious illness (83% vs. 72.6%, p<0.001). The higher the level of education, the more likely it was that article publication dates would be consulted to validate information (40% vs. 24%, p=0.008) and that scientific professionals would be regarded with confidence (76% vs. 56%, p<0.001).

Beliefs

Differences between French-speaking minorities and English speakers

FSMs frequently disagreed with the efficacy of herd immunity (**Table 4**).

Table 4: Vaccination beliefs among French-speaking minorities and English speakers

Vaccination beliefs	% FSM (n=554)	% English speakers (n=951)	Likelihood chi-squared	Approx. sig. (bilateral)	OR	95% CI	
Vaccines are safe despite the risks							
Strongly agree	52.00	51.40	5.561	0.135	3.009	1.023	8.854
Agree	40.60	39.70			2.971	1.114	7.923
Disagree	4.90	5.60			1.876	0.692	5.084
Strongly disagree	2.50	3.30			N/A	N/A	N/A
COVID-19 vaccines are safe, despite the risks							
Strongly agree	49.30	48.50	6.656	0.084	0.290	0.089	0.943
Agree	36.70	36.90			0.258	0.090	0.743
Disagree	8.00	9.00			0.342	0.134	0.875
Strongly disagree	6.00	5.70			N/A	N/A	N/A

Table 4: Vaccination beliefs among French-speaking minorities and English speakers (*continued*)

Vaccination beliefs	% FSM (n=554)	% English speakers (n=951)	Likelihood chi-squared	Approx. sig. (bilateral)	OR	95% CI	
I distrust COVID-19 vaccines because they were developed too quickly							
Strongly agree	10.30	9.60	1.981	0.576	0.692	0.366	1.310
Agree	15.90	16.40			0.763	0.468	1.245
Disagree	39.80	38.60			0.816	0.588	1.134
Strongly disagree	34.00	35.40			N/A	N/A	N/A
By getting the COVID-19 vaccine, I am protecting myself against severe forms of this disease							
Strongly agree	52.60	50.30	3.161	0.367	1.614	0.622	4.188
Agree	35.60	36.70			1.251	0.501	3.124
Disagree	7.10	7.40			1.556	0.642	3.772
Strongly disagree	4.70	5.60			N/A	N/A	N/A
Physical distancing, frequent hand washing and wearing a mask are effective methods of slowing the spread of COVID-19							
Strongly agree	58.00	56.10	3.332	0.343	0.734	0.295	1.828
Agree	34.60	35.60			0.616	0.250	1.514
Disagree	4.50	6.20			0.517	0.197	1.353
Strongly disagree	2.90	2.10			N/A	N/A	N/A
Physical distancing, frequent hand washing and wearing a mask are enough to protect me against COVID-19							
Strongly agree	13.60	11.60	1.311	0.727	0.853	0.537	1.356
Agree	28.50	29.50			0.795	0.529	1.196
Disagree	43.20	43.30			0.896	0.625	1.284
Strongly disagree	14.70	15.70			N/A	N/A	N/A
Only those at risk of becoming seriously ill due to COVID-19 need to be vaccinated							
Strongly agree	6.90	6.00	3.537	0.316	0.822	0.469	1.443
Agree	12.90	12.20			1.012	0.613	1.670
Disagree	36.70	35.40			0.771	0.550	1.080
Strongly disagree	43.60	46.40			N/A	N/A	N/A
By getting vaccinated against COVID-19, I'm helping to protect the health of others in my community							
Strongly agree	57.50	56.10	3.842	0.279	1.862	0.817	4.244
Agree	30.50	29.20			1.564	0.701	3.490
Disagree	6.50	8.60			1.032	0.464	2.297
Strongly disagree	5.50	6.00			N/A	N/A	N/A
I prefer to develop immunity to COVID-19 by catching the disease than through the vaccination							
Strongly agree	9.40	7.10	48.820	0.000	5.716	2.997	10.901
Agree	15.60	14.70			3.693	2.207	6.181
Disagree	40.60	29.30			2.918	2.060	4.134
Strongly disagree	34.40	48.90			N/A	N/A	N/A
Those who have already had COVID-19 do not need to get vaccinated							
Strongly agree	5.60	6.50	13.088	0.004	0.522	0.253	1.077
Agree	12.00	12.80			0.961	0.560	1.647
Disagree	49.00	39.00			1.489	1.079	2.055
Strongly disagree	33.40	41.70			N/A	N/A	N/A

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; FSM, French-speaking minority; N/A, not applicable; OR, odds ratio

Differences according to sociodemographic data

French-speaking minorities with high incomes, >$120,000, were not wary of the rapid development of the vaccines (47.2% [>$120,000] vs. 32.2% [$60,000 to $120,000] and 25.0% [<$60,000]) (χ^2[6, N=546]=33.064, p<0.001; OR=6.381 [95% CI: 2.454–16.592]), did not believe in the stand-alone efficacy of physical distancing (21.7% [>$120,000] vs. 12.5% [$60,000 to $120,000] vs. 11.9% [<$60,000]) (χ^2[6, N=544]=15.805, p=0.015; OR=3.836 [95% CI: 1.671–8.805]), or herd immunity (46.8% [>$120,000] vs. 30.8% [$60,000 to $120,000] vs. 29.1% [<$60,000]) (χ^2[6, N=545]=20.787, p=0.002; OR=5.789 [95% CI: 2.080–16.112]) and that a previous diagnosis would result in less serious illness (42.6% [>$120,000] vs. 30.9% [$60,000 to $120,000] vs. 29.1% [<$60,000]) (χ^2[6, N=544]=15.185, p=0.019; OR=5.965 [95% CI: 1,659–21,449]).

Discussion

Summary of key findings

The survey highlights three findings of interest: a polarization of attitudes/beliefs according to citizenship and education, vaccine uptake for a return to normal, and significant hesitancy concerning vaccination of children.

Comparative analysis

Compared with English speakers, FSMs show a polarization of attitudes/beliefs according to certain sociodemographic characteristics. Among FSMs, Canadian-born citizens with a higher education were more likely to completely disagree or agree with the recommended vaccine regimen. This trend is noted by other studies in high-income countries (17). The literature indicates that mixed attitudes may stem from inconsistent information from official sources (21–24), becoming a risk to communication and patient disregard for medical care (25).

According to the literature, the prospect of a "return to normal" is strong motivation for vaccine uptake (4,21). Although FSMs generally doubted its efficacy, they mainly got vaccinated to obtain the vaccine passport and to protect themselves against serious illness, especially in the case of men. Given the inconsistency of information, also felt among healthcare professionals (25), FSMs were not always able to count on the news and relied on the recommendations of government agencies, promising a return to normality thanks to vaccination (24,26).

Although FSMs are often described as an older population (7,27), this survey was designed to be representative of all FSM generations. Despite the low representation of French-speaking parents with young children, vaccination hesitancy for children is of particular interest. Vaccine hesitancy (COVID-19 and other diseases) for children is more pronounced among FSMs, who are less likely to follow the vaccine regimen, unless they have a high income. In a broader context, the efficacy of COVID-19 vaccines in children has been widely disputed in literature (17,28).

The problem of childhood vaccination, which existed prior to the emergence of COVID-19 (17) and led to parental vaccine hesitancy during this pandemic (28), could be caused by sub-optimal physician-patient communication (4,29). The finding of this study could indicate greater inaccessibility for linguistic minorities. We hypothesize that the current shortage of family physicians in rural and urban settings (30,31), and by extension a lack of accessibility to bilingual health professionals, could contribute to an exacerbation of the problem of vaccination of children during a health crisis. Vaccination of children and parental hesitancy should be the subject of further research to pursue this line of thought and optimize access to care.

Strengths and weaknesses

Considering the rapid evolution of the virus and of health recommendations, the study has some conceptual and methodological limitations. Media saturation and collective exhaustion made participation less appealing and influenced the sampling technique that was selected, resulting in a sampling bias caused by a convenience sample. Despite the strategy employed by Léger Marketing Inc., it is difficult to ensure the representativeness of FSMs and English speakers, as well as the potential for statistical generalization of the findings. Furthermore, the survey presents a portrait of FSMs for a given period, rather than according to a specific situation during the pandemic. The time elapsed between the data collection period and the comparative analysis must also be considered a bias for the representativeness of the findings. Despite this, the study met its objective and thus contributed to the active offering of French-language health services.

Impact

This survey provides health professionals with the relevant information they need to tailor their communication with patients who are faced with a vaccination choice. The findings also point to the need for new studies establishing a portrait of FSMs in order to better address their vaccine needs.

Next steps

By filling the knowledge gap regarding vaccination against COVID-19, this data could help improve access to information and, consequently, help adapt the training of health professionals for a therapeutic alliance based on trust.

Conclusion

Although difficult to generalize, this survey did reveal significant differences between FSMs and English speakers in their perceptions of vaccine efficacy, particularly vaccination of

children, as well as a polarization of the attitudes/beliefs of FSMs according to certain sociodemographic factors. The findings imply a requirement to better understand the overall needs of FSMs in order to improve access to information and care in French.

Authors' statement

CD — Participation in study design, writing–original draft, data interpretation, writing–revision and editing, final approval
JLH — Participation in study design, writing–original draft, data acquisition, data interpretation, writing–revision and editing, final approval
JA — Data analysis, writing–revision and editing, final approval
MDL — Participation in study design, writing–revision and editing, final approval
DH — Participation in study design, writing–revision and editing, final approval
SF — Participation in study design, writing–revision and editing, final approval
DBL — Participation in study design, final approval
SB — Participation in study design, writing–revision and editing, final approval

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

No conflicts of interest were declared.

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Supplemental material

These documents can be accessed on the Supplemental material file

Survey, data collection tool
Survey invitation letter and distribution list

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SYSTEMATIC REVIEW

Communicating effectively with patients about vaccination: A systematic review of randomized controlled trials

Chloé Desjardins[1], Manon Denis-LeBlanc[1,2,3], Christine Paquette Cannalonga[1], Malek Rahmani[1], Teresa A Gawargy[1], Pierre-Marc Dion[1], Jennifer Lacroix Harasym[1], Salomon Fotsing[1,2,3], Maria Cherba[4], Nigèle Langlois[5], Sylvain Boet[1,3,6,7,8,9,10]*

Abstract

Background: Good communication between healthcare professionals and their patients is essential to enlighten the benefits and risks of vaccination. Despite the availability of effective vaccines, reluctance prevails, sometimes fuelled by sub-optimal communication leading to a lack of trust. An evaluation of the effectiveness of a communication strategy for which healthcare professionals are trained has yet to be carried out.

Objective: Systematic review of studies with a randomized controlled trial (RCT) to define and evaluate the impact of healthcare professionals' communication on patients' vaccine adherence.

Methods: We performed a structured search on Medline, Embase, CENTRAL, PsycINFO and CINAHL. The studies selected include those involving healthcare professionals authorized to administer vaccines according to Canadian guidelines. Primary outcomes include vaccination rate or vaccine hesitancy rate.

Results: Nine articles were included. Five studies (n=5) reported intervention effectiveness according to vaccine adherence. The results are largely represented by parental vaccine hesitancy for human papillomavirus (HPV) or childhood vaccination, while three studies (n=3) target the general population. The risk of bias relative to the studies is either low (n=7) or of some concern (n=2).

Conclusion: The effectiveness of communication varies according to the studies and knowledge acquired through training. Future studies will need to examine communication with healthcare professionals in order to establish a consensus on optimal and appropriate training.

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Keywords: communication, randomized controlled trials, vaccines, vaccine hesitancy

Affiliations

[1] Francophone Affairs, Faculty of Medicine, University of Ottawa, Ottawa, ON

[2] Department of Family Medicine, University of Ottawa, Ottawa, ON

[3] Institut du Savoir Montfort, Ottawa, ON

[4] Department of Communication, Faculty of Arts, University of Ottawa, Ottawa, ON

[5] Health Sciences Library, University of Ottawa, ON

[6] Faculty of Education, University of Ottawa, Ottawa, ON

[7] Departments of Anesthesiology and Pain Medicine, University of Ottawa, Ottawa, ON

[8] Department of Innovation in Medical Education, University of Ottawa, Ottawa, ON

[9] Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ottawa, ON

[10] Keenan Research Centre, Li Ka Shing Knowledge Institute, Toronto, ON

***Correspondence:**
sboet@uottawa.ca

Introduction

Vaccination is effective in preventing many diseases and their serious forms. However, some patients are reluctant to be vaccinated, despite the potentially harmful consequences for their health and that of the population as a whole. This hesitancy stems from multiple, complex and sometimes interconnected factors (1–7). Possible reasons include a lack of trust in healthcare professionals and institutions, healthcare professionals' lack of patient communication skills (4,5,7), or difficulties in navigating the sometimes contradictory information available (1–3,5).

Physician-patient communication is defined in the literature as a key component of the therapeutic relationship, enabling the development of a bond of trust that leads to optimal care (5,7–9). The bond of trust is important when discussing vaccination, since the decision-making process has an impact on individual and community safety (1). Given the importance of communication in healthcare decision-making, it is possible that a communication intervention with healthcare professionals could influence vaccine adherence. Given the coronavirus disease 2019 (COVID-19) pandemic and its repercussions, including the lack of educational resources in patient communication skills, a communication intervention is all the more important to address the limitations of healthcare institutions and mistrust of the COVID-19 vaccine. In the absence of intervention, current limitations may lead to mistrust of future vaccines in times of health crisis. The effectiveness of intervention has yet to be systematically evaluated.

Objectives

We conducted a systematic review of randomized controlled trials (RCTs) to define and evaluate the impact of healthcare professionals' communication on patients' vaccine adherence.

Methods

Protocol and registration

This systematic review was conducted in accordance with AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews) standards (10) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (11). The protocol has been registered with the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42022330645).

Eligibility criteria

All RCTs in which participants were healthcare professionals authorized to administer vaccines (doctors, nurses, pharmacists and resident physicians) were eligible. We included studies in which communication on vaccine adherence was the main intervention. We excluded studies in which the healthcare professionals were medical, nursing or pharmaceutical students (not authorized to administer vaccines according to Canadian guidelines). We also excluded studies where the intervention was aimed at patients rather than healthcare professionals. Non-peer-reviewed articles, conference abstracts, letters, editorials and commentaries were not eligible.

Information sources

Two electronic search reviews (12) were carried out, a Medline search strategy and a translation of the CINAHL RCT Filter search. MEDLINE® ALL via Ovid, Embase Classic + Embase via Ovid, Cochrane Central Register of Control Trials via Ovid, APA PsycINFO via Ovid and CINAHL via EBSCO were consulted.

Search

The search strategy (**Supplemental material A**) was developed by an information specialist with the research team and revised by a second information specialist as suggested in the Peer Review of Electronic Search Strategies (PRESS) guide (12). Eligibility criteria (**Box 1**) included no language or publication date limits. A filter for published RCTs was applied (13). The search strategy was developed in Medline and then translated into the other databases. Key search concepts included MeSH terms related to vaccine adherence, healthcare professionals and communication. Only studies published and available in French or English were considered. The list of references cited in the included studies was also searched. The final list of included studies was reviewed by content experts to confirm their relevance.

Selection of studies

Studies were uploaded to a web-based software program, Covidence (version 2.0, Veritas Health Innovation, Melbourne, Australia) (14), and duplicates were removed. A pilot assessment tool, developed by the research team and tested on 30 randomly selected articles (**Supplemental material B**), was refined until subjectively acceptable agreement was established among the judges. Evaluation of each level of inclusion was carried out by pairs of independent reviewers, and conflicts were resolved by a third party.

Box 1: Search strategy eligibility criteria

Population: healthcare professionals authorized to administer vaccines (physicians, nurses, pharmacists and resident physicians)
Intervention: communication training for healthcare professionals to be used during vaccination consultations only
Comparison: a control group of healthcare professionals who received no communication intervention
Outcome: vaccine adherence, defined as receiving, intending to receive or being less reluctant to receive the series of disease-preventing vaccines according to the schedule suggested by the national immunization authority
Study date: no limit
Method: randomized controlled trial
Publication language: no initial limit
Publication date: no limit

Data extraction

A data extraction grid (**Supplemental material C**), developed by the research team, was tested by the same reviewers. Extraction was performed in duplicate by pairs of reviewers and consensus by a third party. Extracted data include publication characteristics (name of lead author, year of publication, data collection sites), study characteristics (objective, study design and context, number of healthcare professionals, outcomes), type of healthcare professional, intervention details and results.

Risk of bias inherent in each study

Pairs of reviewers assessed included studies for risk of bias according to the Risk of Bias Tool 2 for Randomized Controlled Trials (RoB 2) (15). The tool assesses the risk of bias attributed to study design, conduct and data reporting. For each area, a questionnaire is used to establish the level of risk as "low," "some concern" or "high." All areas must be predominantly low risk for the study to be considered reliable (15).

Data summary

A description of all included studies is presented in tables containing information on demographic, clinical and methodological quality. The results are summarized qualitatively, given the heterogeneity of the included studies.

Results

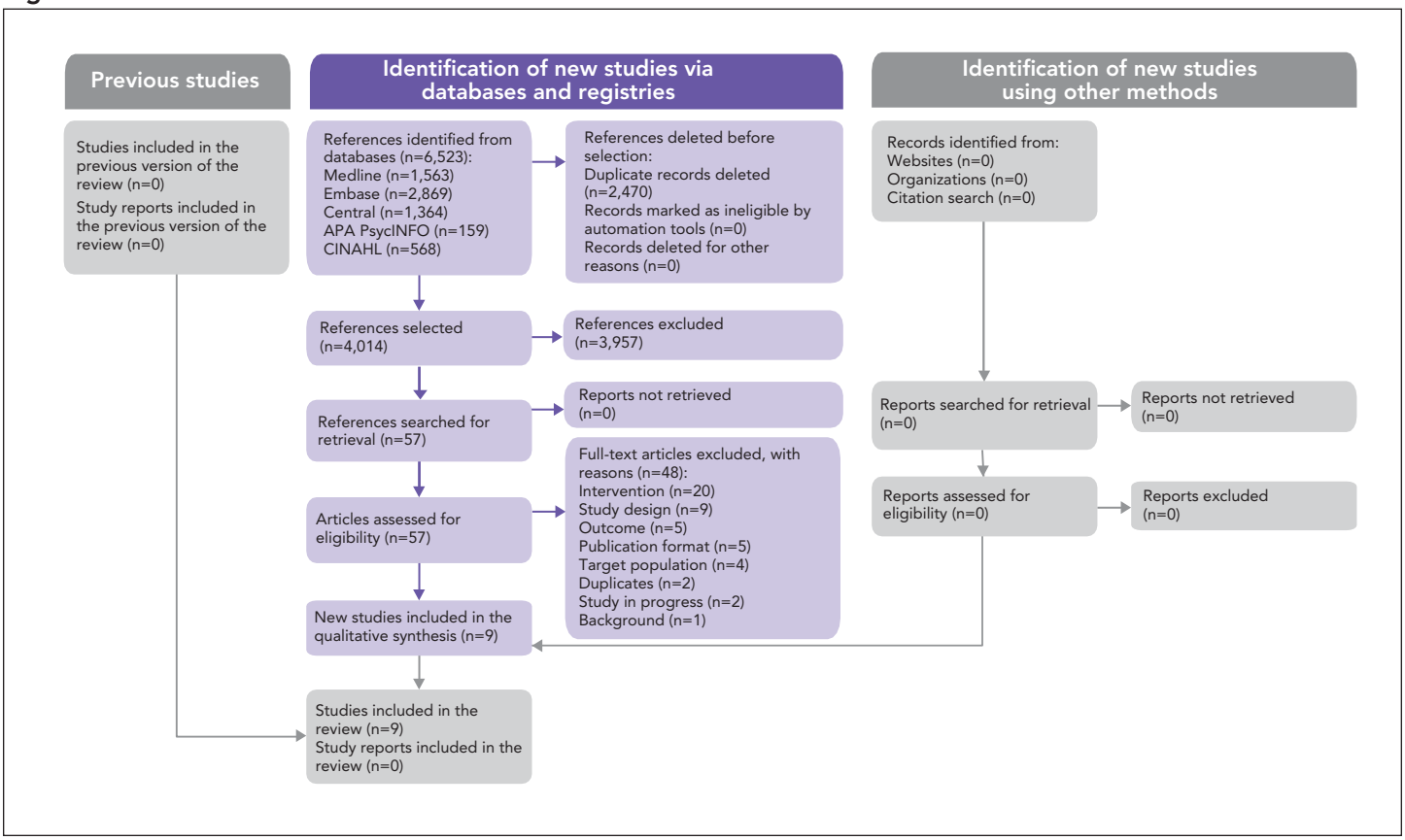
Selection of studies

The search identified 6,484 studies. After eliminating duplicates, 4,014 studies were assessed for eligibility, including 57 full-text articles, 48 excluded studies and 9 included studies (**Figure 1**).

Characteristics of selected studies

The included studies (n=9) employed communication training in a variety of formats targeting different knowledge areas, including understanding the virus, how the vaccine works, assertive communication, effective recommendations and the patient perspective. The vaccination context was childhood diseases (n=2), pneumonia/influenza (n=3), or human papillomavirus (HPV) (n=4). Six studies (16–21) focused on parental vaccine hesitancy, and three on adult vaccine hesitancy (22–24). General characteristics are shown in **Table 1**.

Figure 1: PRISMA 2020[a] Flow Chart



Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses
[a] Page *et al.* (11)

Table 1: Key features of included studies

First author, year	Country of data collection	Type of study	Background	Sample size (n), Age/sex (%)	Population	Study duration and format	Study objective(s)	Risk of bias
Abdel-Qader, 2022 (22)	Jordan	RCT	Private practice of pharmacists and physicians	320 practitioners Age: NR Gender: 56 F vs. 43 M (intervention); 55 F vs. 45 M (control)	Doctors; pharmacists	16 online training sessions	To study vaccine hesitancy and evaluate the effectiveness of a collaborative physician-pharmacist intervention to improve adult COVID-19 vaccine hesitancy.	Some concern
Boom, 2010 (16)	United States	RCT	Community practices in paediatric and family medicine	189 practitioners Age: NR Gender: NR	Doctors	One year; training one hour/day during lunch break	To evaluate the effectiveness of a university-based continuing education intervention aimed at increasing childhood vaccination rates in paediatric and family medicine practices in a large metropolitan area.	Low risk
Brewer, 2017 (17)	United States	RCT	Paediatric and family medicine clinics	30 clinics (number of practitioners NR) Age: NR Gender: NR	Doctors; nurses; unspecified (i.e. health professionals or authorized personnel)	Four one-hour clinical training sessions	To determine the effectiveness of training providers to improve their recommendations using presumptive announcements or participatory conversations for HPV vaccine coverage.	Low risk
Dempsey, 2018 (18)	United States	RCT	Primary care practices	16 clinics/188 practitioners Age: NR Gender: NR	Doctors; nurses; unspecified (i.e. health professionals or authorized personnel)	Series of two training sessions at team development meetings over six months	To evaluate the effect of a 5-component HPV vaccine communication intervention conducted by healthcare professionals on adolescent HPV vaccination.	Low risk
Gatwood, 2021 (23)	United States	RCT	Two regional community pharmacy chains	96 pharmacies (number of practitioners NR) Age: NR Gender: NR	Pharmacists	Duration of training not reported; results were counted for a period of six months pre-intervention and post-intervention	To evaluate the impact of a communication training program to improve pharmacist promotion of pneumococcal vaccine among high-risk adults in Tennessee. The aim was to make it easier for pharmacists to address each patient's beliefs and attitudes toward vaccination, particularly adults with chronic illnesses that put them at high risk of invasive pneumococcal infection.	Low risk

Table 1: Key features of included studies (*continued*)

First author, year	Country of data collection	Type of study	Background	Sample size (n), Age/sex (%)	Population	Study duration and format	Study objective(s)	Risk of bias
Gilkey, 2019 (19)	United States	RCT	Cook Children's outpatient clinics	25 clinics/77 practitioners Age: NR Gender: NR	Doctors	One hour of clinical training	To evaluate the efforts of a paediatric health system to improve HPV vaccination coverage among adolescent patients. The objectives were to assess the extent to which a quality improvement (QI) program reached clinics and physicians, and the program's impact on HPV vaccination coverage.	Low risk
Henrikson, 2015 (20)	United States	RCT	Outpatient paediatric and family medicine clinics	56 clinics/526 practitioners Age: NR Gender: 68 F vs. 32 M (intervention); 64 F vs. 36 M (control)	Doctors	45-minute training session; 10-month intervention	To test whether a new communication intervention targeting physicians can improve physician confidence in communication and reduce vaccine hesitancy among mothers of infants.	Some concern
Muñoz-Miralles, 2021 (24)	Spain	RCT	Urban and rural primary healthcare centres	57 practitioners Age: NR Gender: NR	Doctors; nurses	Duration of training not reported; one-year intervention	To determine the effectiveness of a brief intervention to increase influenza vaccination coverage compared with the usual advice in people who refuse it, and to record the main reasons for refusing to be vaccinated.	Low risk
Szilagyi, 2021 (21)	United States	RCT	Paediatric primary care practices	48 clinics/234 practitioners Age: NR Gender: NR	Doctors	Three 20–30 minute online training modules; 6-month intervention	To evaluate the effect of online communication training for clinicians on missed HPV vaccination opportunities overall and during healthcare visits, acute and chronic illness visits, and on adolescent HPV vaccination rates.	Low risk

Abbreviations: COVID-19, coronavirus disease 2019; F, female; HPV, human papillomavirus; M, male; NR, not reported; RCT, randomized controlled trial

Summary of results

Among the studies (n=9) included, the effectiveness of the interventions varied greatly according to the training format (5 effective (17,18,21,22,24); 3 no significant difference (16,19,20); 1 ineffective (23)). A descriptive analysis of the communication adopted and its results are presented below. The measurement tools, primary outcomes and results with statistical significance are summarized in **Table 2**.

Effectiveness of communication training

Effective training

First, we note some training courses that proved effective in the HPV context. These included educational resources and patient-adapted recommendations. Following a self-guided webinar and two group sessions (18), the application of motivational interviewing during physician-patient interactions improved HPV vaccine adherence in adolescents. Similar training consisting of a webinar with three interactive modules and weekly encouragement to reveal common patient questions also improved vaccine adherence (21).

Table 2: Detailed results of included studies

First author, year	Results measurement tool(s)	Name of primary outcome(s)	Conclusion of primary results
Abdel-Qader, 2022 (22)	Pre and post-intervention self-report survey assessing vaccine hesitancy and resistance from a physician's perspective. Pre and post-intervention self-report survey assessing vaccination status. Pre and post-intervention self-report survey assessing knowledge, attitude and beliefs about COVID-19 vaccines.	The impact of collaborative physician-pharmacist training on COVID-19 vaccine hesitancy and resistance. Proportion of patients vaccinated before and after intervention.	The proportions of COVID-19 vaccine hesitancy and resistance were significantly reduced (20.1% and 7.8% vs. 64.3% and 35.7%, $p<0.05$), including one month after training (3.3% vs. 11.1%). The proportion of subjects vaccinated increased considerably (51.6% vs. 0.0%) one month after training. There was no significant difference in the proportion of patients vaccinated between the intervention and control groups.
Boom, 2010 (16)	The Clinical Assessment Software Application (CASA) produced by the CDC (data entry and vaccination database).	Immunization rate for children aged 12 to 23 months.	There was no significant difference in the mean percentage of up-to-date vaccination for the control and intervention groups (19–23 months) (44% vs. 51%, $p<0.05$). After one year, there was a significant difference between the mean percentages of up-to-date vaccination for the control practices (41%) and the intervention practices (52%, $p<0.05$).
Brewer, 2017 (17)	Data on vaccine coverage, specialty, number of patients, patient gender and patient eligibility for state-funded vaccines according to NCIR (The North Carolina Immunization Registry).	HPV vaccination rate in patients aged 11 to 17 years.	Presumptive announcement training showed a significant increase in HPV vaccination initiation at 6 months in 11 and 12-year-old adolescents vs. the control group (5.4% difference, 95% CI: 1.1%–9.7%). There was no significant difference for the conversation training. There was no significant difference in the 13 to 17-year-olds in the two groups.
Dempsey, 2018 (18)	Vaccination data were extracted from each practice's electronic medical record. To ensure completeness, this data was supplemented by data from the Colorado Immunization Information System.	HPV vaccine series initiation (one dose).	HPV vaccine initiation was significantly higher in adolescents in intervention practices (aOR: 1.46; 95% CI: 1.31–1.62) as was vaccine dose completion (aOR: 1.56; 95% CI: 1.27–1.92) compared to the control groups.
Gatwood, 2021 (23)	Vaccine distribution records (pneumococcus, influenza, herpes zoster) provided by Walgreens in the Memphis and Nashville, Tennessee areas. Community vaccination beliefs and behaviours were compiled through an online survey facilitated by QuestionPro (Austin, Texas).	Increase in the rate of pneumococcal vaccination.	Compared to the Nashville area, people in the Memphis area showed less agreement that vaccines are a good way to protect against disease (73.8% vs. 79.7%, $p<0.05$), indicating a lower likelihood of following vaccine recommendations (73.4% vs. 78.3%, $p<0.05$) and more concern about side effects (47.1% vs. 35.8%, $p<0.0001$). Between the 6-month periods in 2018 and 2019, pneumococcal vaccine rates administered (on all patients) decreased in both regions.
Gilkey, 2019 (19)	EMR to assess vaccine coverage. Vaccination in patients aged 12 to 14 years using standardized EMR queries.	HPV coverage (minimum one dose) for: 1) Model 1 (an intention-to-treat analysis of all doctors randomly assigned to the intervention and control groups); 2) Model 2 (a sensitivity analysis that excluded 6 doctors (2 in the intervention group and 4 in the control group).	In the overall sample (Model 1), HPV vaccination coverage increased by 8.6 percentage points (intervention) and 6.4 percentage points (control). The treatment effect was not statistically significant according to a hierarchical linear model and an unstandardized coefficient (b) (b=0.023; SE=0.018; $p<0.05$). There was considerable variance in HPV vaccination coverage between physicians and clinics in Model 1, with the majority of the total variance lying with physicians (74%) vs. clinics (74%) vs. clinic level (14%).

Table 2: Detailed results of included studies (*continued*)

First author, year	Results measurement tool(s)	Name of primary outcome(s)	Conclusion of primary results
Henrikson, 2015 (20)	Mother's score on the "Parental attitudes to childhood vaccines" test. Childhood vaccines by PACV percentage of mothers reluctant to vaccinate. Six single-item self-efficacy questions on communicating with parents about childhood vaccines (email survey).	Maternal vaccine hesitancy at 6 months (dichotomous). Maternal vaccine hesitancy at 6 months (ORDINAL measure).	The intervention had no effect on the mother's vaccine hesitancy (p=0.78). Adjustment for baseline PACV score and race yielded similar results (OR: 1.22; 95% CI: 0.47–2.68; OR: 1 indicates no difference between the two groups).
Muñoz-Miralles, 2021 (24)	Electronic medical records.	Vaccination rate.	The intervention was effective overall (OR: 2.48 [1.61–3.82], p<0.001) and in people aged 60 and over (in good health, OR: 2.62 [1.32–5.17]; and with risk factors, OR: 2.95 [1.49–5.79]). There was no statistically significant difference in the efficacy of the intervention in people under 60 with risk factors, or between different diseases.
Szilagyi, 2021 (21)	Electronic medical records.	Percentage of office visits with a missed HPV vaccination opportunity for vaccine initiation. Total number of missed opportunities for HPV vaccination. Proportion of adolescents receiving HPV vaccination.	The rate of missed opportunities decreased in intervention vs. control practices by 6.8% (95% CI: 3.9–9.7) for HPV vaccination initiation. No significant difference was observed for subsequent vaccination. The rate of missed opportunities decreased between the start of the study and the intervention period by 2.4% (95% CI: 1.2–3.5) in intervention vs. control practices. For adolescents with at least one office visit during the intervention period, HPV vaccine initiation was 3.4% (95% CI: 0.6–6.2) higher in intervention vs. control practices. No significant difference was observed for subsequent vaccination.

Abbreviations: aOR, adjusted odds ratio; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COVID-19, coronavirus disease 2019; EMR, electronic medical records; HPV, human papillomavirus; PACV, Parental Attitudes on Childhood Vaccines score; OR, odds ratio; SE, standard error

We also observed that good physician-patient communication includes a good understanding of the virus, the vaccine and the reasons for vaccine hesitancy. The study by Muñoz-Miralles *et al.* (24) shows a positive effect in patients aged 60 and over following a brief standardized intervention in the context of influenza. Although this communication depended on a directive guide, doctors and nurses were encouraged to adapt their communication by using empirical evidence to address the reasons for vaccine hesitancy, gathered beforehand.

This example can be enriched by the intervention proposed by Abdel-Qader *et al.* (22), who integrated the patient-partner perspective into the training material. The training, organized in 16 virtual sessions in a private Facebook group, invited pharmacists to be trained by eight doctors and eight pharmacists. However, the training sessions particularly included testimonials from patients discussing their experiences with the health crisis and vaccination. The patient-partner perspective justified the importance of patient-adapted communication. This study shows a significant reduction in vaccine hesitancy and an increase in vaccination rates. It should be noted, however, that the self-reported results of this study may be biased.

Training courses based on assertive communication cannot be overlooked. Brewer *et al.*'s study (17) demonstrated improved HPV vaccine adherence using an announcement, i.e., a vaccine recommendation given on the day of the consultation. The same study also evaluated the effectiveness of a conversation with the patient to present the vaccine for shared decision-making, but this intervention noted no significant difference.

Risk of relative and cross-study bias

Seven studies (16–19,21,23,24) have low risk and two studies (20,22) are of some concern (see **Table 3**). A follow-up bias is present, as the healthcare professionals would have been aware of the result of randomizing to an intervention or control group. We consider this risk unavoidable, based on ethical considerations of informed consent, despite the fact that it may have had an impact on study results. The second bias (20,22) (measurement bias) is taken into account, since self-reported surveys were used, which can influence the validity of the results.

Table 3: Summary of risk of bias for included studies

Study - Cochrane RoB 2	Randomization bias	Follow-up bias	Attrition bias	Measurement bias	Evaluation and selection biases	Overall risk of bias
Abdel-Qader, 2022 (22)	Low risk	Some concern	Low risk	Some concern	Low risk	Some concern
Boom, 2010 (16)	Low risk	Some concern	Low risk	Low risk	Low risk	Low risk
Brewer, 2017 (17)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Dempsey, 2018 (18)	Low risk	Some concern	Low risk	Low risk	Low risk	Low risk
Gatwood, 2021 (23)	Low risk	Some concern	Low risk	Low risk	Low risk	Low risk
Gilkey, 2019 (19)	Low risk	Some concern	Low risk	Low risk	Low risk	Low risk
Henrikson, 2015 (20)	Low risk	Some concern	Low risk	Some concern	Low risk	Some concern
Muñoz-Miralles, 2021 (24)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Szilagyi, 2021 (21)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Abbreviation: RoB 2, Risk of Bias Tool 2 for Randomized Controlled Trials

Discussion

Summary of levels of evidence

Randomized controlled trials evaluating the effectiveness of communication training for healthcare professionals are few in number and show mixed results in terms of vaccine adherence. Studies showing positive results have often adopted a communication approach aimed at formulating optimal recommendations and raising awareness of patients' specific needs.

Interpretations

The effectiveness of interventions does not seem to depend simply on the presence of communication that adopts epidemiological and medical knowledge, but also on communication that is adapted to the patient, understanding the factors that influence the vaccination decision. The most effective interventions (24,25) focused on HPV and targeted parents of minor patients. These studies have potentially been built on a better understanding of parental vaccine hesitancy, since the reasons for vaccine hesitancy and HPV have previously been addressed through research, improved communication and the development of quality recommendations (25). An adapted intervention, such as motivational interviewing (18), is consequently viewed favourably in the literature and by healthcare professionals (6,26–28). Infant vaccination (excluding HPV), on the other hand, seems to require more research, as indicated by studies by Brewer *et al*. and Henrikson *et al*. (17,20).

Contradictory results on the effectiveness of communication training can raise questions about the wider potential role of communication skills. In fact, communication in the therapeutic relationship is not limited exclusively to the transfer of medical knowledge about vaccination in clinical consultations. Both parties—the healthcare professional and the patient—are also influenced by societal communication, including socio-political and cultural factors that may be disseminated by public health authorities and popular rhetoric. In the case of HPV, linked to the sensitive subject of adolescent sexuality and gender (29–31), several socio-political factors have prompted a change in the public's approach to vaccination (32). Social and medical perception seems to depend on multiple variables including ideology, customs, understanding of health, collective responsibility, trust and accessibility to healthcare (33).

Given the complexity of vaccine hesitancy, we would like to hypothesize that effective communication must take into account the above variables. The literature points to the inefficiency of a universal algorithm. In 2015, a systematic review on vaccine hesitancy demonstrated the need for a call for strategies tailored to the target population, the reasons for hesitancy and their context (34). We note in particular that effective studies tended to form recommendations with subjectivity according to the patient's concerns, but the integration of all these variables remains to be applied to establish a bond of trust with patients. Further socio-culturally adapted communication interventions would be needed to study this topic.

Limitations

There are several limitations to note. Other diversified studies would have enabled a better scope of conclusions, as well as a meta-analysis to understand the relationship between different groups of healthcare professionals, different diseases and vaccines, and then different communication training. Studies may be missing given the broad scope of the search strategy, the exclusion of articles published neither in English nor French, and the fact that only studies involving healthcare professionals authorized to administer the vaccine in Canada were included. Some studies also included different clinical locations and determining variables that may have been ignored or absent, such as regional infection rates, the context of the intervention (e.g. a national or regional vaccination program) and the demographics of specific patient groups. RCTs only were included in the study because of their rigorous methodology. It would also have been possible to include cohort studies with the same type of intervention.

Conclusion

The effectiveness of vaccination-related communication varies according to the studies and knowledge acquired through training. This systematic review confirms the need for studies that focus on communication with healthcare professionals to build consensus around optimal, tailored training that increases trust in healthcare institutions. There is thus a need for studies that take into account initiatives that include the patient perspective in communication with healthcare professionals.

Author's statement

CD — Participation in study design, writing–original draft, data acquisition and evaluation, data analysis, writing–revision and editing, final approval
MD-L — Participation in study design, writing–revision and editing, final approval
CPC — Data acquisition and evaluation, writing–revision and editing, final approval
MR — Data acquisition and evaluation, writing–revision and editing, final approval
TAG — Data acquisition and evaluation, writing–revision and editing, final approval
P-MD — Data acquisition and evaluation, writing–revision and editing, final approval
JLH — Participation in study design, writing–revision and editing, final approval
SF — Participation in study design, writing–revision and editing, final approval
MC — Participation in study design, writing–revision and editing, final approval
NL — Search strategy development, writing–revision and editing, final approval
SB — Participation in study design, development of search strategy, data analysis, writing–revision and editing, final approval

Competing interests

No conflicts of interest have been declared.

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Supplemental material

These documents are available in the Supplemental material file.

Supplemental material A: Search strategy
Supplemental material B: Effective communication strategies
Supplemental material C: Data extraction grid

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Invasive group A streptococcal (iGAS) surveillance in Island Health, British Columbia, 2022

Andrea Nwosu[1,2]*, Andrea Schut[2], Christie Arlotti Wood[2], Christine Urquhart[2], Claudia Bachman[2], Katelyn Thompson[2], Julia Evans[2], Kathleen Mills[2], Lisa Wenstob[2], Theresa Restemeyer[2], Trista Galbraith[2], Shannon Mason[2], Stephanie Gabriel[2], Twyla Gasper[2], Cheryl Broeren[2], Francine Lewis[2], Dee Hoyano[2], Sandra Allison[2], Pamela Kibsey[2], Angela Reid[2], Maritia Gully[2], Carl Swanson[2]

Abstract

Background: Invasive group A streptococcal disease (iGAS) is caused by *Streptococcus pyogenes* group A bacteria. In 2022, multiple disease alerts for iGAS in the Island Health region, in the context of increased infections in the paediatric population in Europe and the United States, prompted further investigation into local trends. This surveillance study summarizes epidemiological trends of iGAS in the region covered by Island Health, a regional health authority in British Columbia, in 2022.

Methods: In British Columbia, iGAS is a reportable disease; all confirmed cases are reported to the regional authority and the provincial health authority (BC Centre for Disease Control). Island Health's iGAS surveillance system is passive and collects information on cases that are identified through laboratory testing. Surveillance data were summarized for 2022 and compared with historical data from 2017–2021.

Results: In 2022, the incidence rate was 11.4 cases per 100,000 population (n=101), the highest observed rate in the last six years. The median age of cases was 53 years, with a range of 0–96 years, and 64% of cases were male. The highest risk of infection was reported in men 40–59 years of age, with an incidence rate of 21.3 cases per 100,000 population. The most common *emm* types were *emm*92 (n=14), *emm*49 (n=13), and *emm*83 (n=12). Overall, 85% (n=86) of cases were hospitalized, 21% (n=21) were admitted to the intensive care unit, and 6% (n=6) died.

Conclusion: This study highlights that the incidence of iGAS in the Island Health region continued to increase throughout the coronavirus disease 2019 (COVID-19) pandemic, reaching its highest annual rate in 2022. In contrast to reports from Europe and the United States, there was no notable increase in infections in the paediatric population. Given the sustained increase in iGAS activity, continued monitoring and description of the epidemiology of these cases on a regular basis is imperative.

Affiliations

[1] Canadian Field Epidemiology Training Program, Public Health Agency of Canada, Ottawa, ON

[2] Island Health, Victoria, BC

***Correspondence:**
andrea.nwosu@phac-aspc.gc.ca

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Keywords: iGAS, group A streptococcus, *Streptococcus pyogenes*, *emm*, surveillance, British Columbia, Canada

Introduction

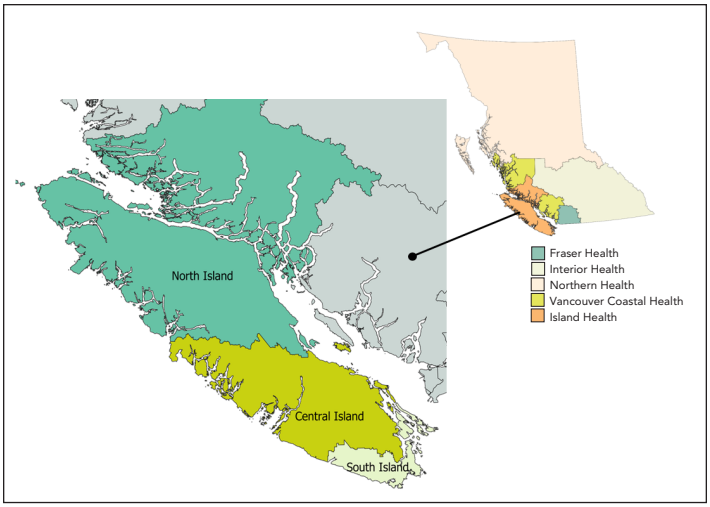
Group A streptococcal disease (GAS) is caused by *Streptococcus pyogenes* group A bacteria (1). A GAS infection is considered invasive when bacteria is detected at a sterile site within the body (1). Invasive group A streptococcus (iGAS) causes severe and in some cases life-threatening illness (1). In 2022, multiple disease alerts for iGAS in Island Health, a regional health authority in British Columbia, in the context of reports of increased infections in the pediatric population in Europe and the United States, prompted further investigation into local trends (2,3). The following surveillance report summarizes epidemiological trends of iGAS in Island Health, British Columbia in 2022.

Methods

Population

Island Health is one of five regional health authorities in British Columbia. The Island Health region has a population of about 860,000 people, which includes residents of Vancouver Island, the Islands in the Salish Sea and the Johnstone Straight, and the mainland communities north of Powell River and south of Rivers Inlet (**Figure 1**) (4). The region is divided into three health service delivery areas (HSDAs): North, Central and South Island.

Figure 1: Island Health Region of British Columbia



Case definitions

Confirmed case

Laboratory confirmation of infection with or without clinical evidence of invasive disease: isolation of group A streptococcus (*S. pyogenes*) from a normally sterile site, or demonstration of *S. pyogenes* DNA by an appropriately validated nucleic acid test from a normally sterile site (5).

Probable case

Clinical evidence of invasive disease in the absence of another identified etiology and with non-confirmatory laboratory evidence of infection: isolation of group A streptococcus from a non-sterile site, or positive group A streptococcus antigen detection (5).

Surveillance methods

In British Columbia, iGAS is a reportable disease; all confirmed cases are reported to the regional health authority and then to the BC Centre for Disease Control (BCCDC). Island Health's iGAS surveillance system is a passive case-based system that relies on the collection of information about cases that are identified through laboratory testing. Laboratory testing of iGAS is conducted locally at Island Health laboratories. Positive bacterial cultures are then sent to the BCCDC Public Health Laboratory for confirmatory testing. Subtyping (*emm* typing) of all isolates is conducted by the Canadian National Microbiology Laboratory (NML). Information on case demographics, clinical progression of illness, and risk factors are collected using a standardized surveillance form.

Island Health case-level data were extracted from BCCDC's Public Health Reporting Data Warehouse on February 1, 2023, at 12:00 p.m. PST. The case line list included episode date and information on age, sex, risk factors, and outcomes. The episode date is equal to the onset date if available. If the onset date is not available, then the clinical diagnosis date is used, followed by the earliest of specimen collection date, laboratory result date, or report date.

Data analysis

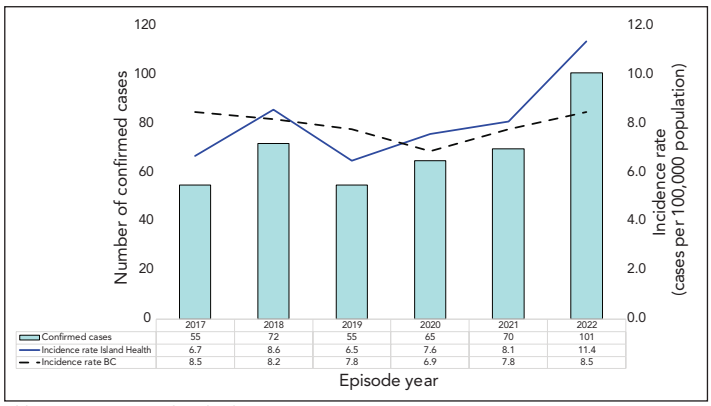
All analyses were performed using R version 4.1.1 and RStudio version 1.4.1717. Trends in case counts, incidence rates, geographic distribution, demographics, severity, and risk factors were summarized for 2022 and compared with historical data from 2017–2021. Population denominators were used to calculate rates.

Results

Trends in case counts and rates

Incidence rates of iGAS in the Island Health region have been increasing since 2019 (**Figure 2**). From 2017 to 2022, incidence rates ranged from 6.7 cases to 11.4 cases per 100,000 population. In 2022, 101 confirmed cases of iGAS were reported in the Island Health region. The incidence rate was 11.4 cases per 100,000 population, which was

Figure 2: Invasive group A streptococcal disease cases and incidence rates by year, Island Health, 2017–2022 (n=418)



Abbreviation: BC, British Columbia
Note: The provincial incidence rates provided in this figure are preliminary as of January 27, 2023. They are subject to change after the data reconciliation process has been completed by BC Centre for Disease Control

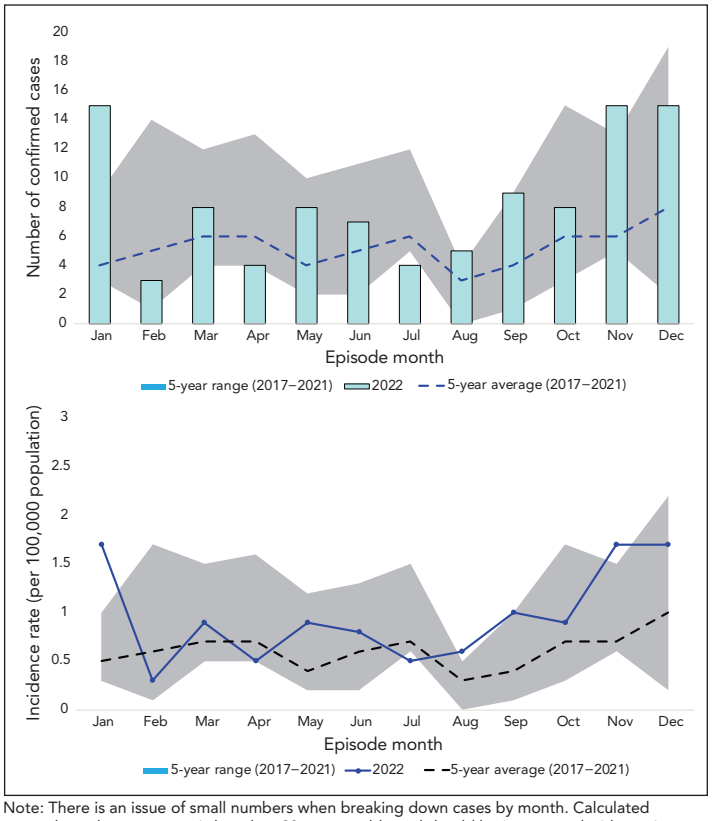
above the preliminary annual provincial rate (8.5 cases per 100,000 population) and the highest observed incidence in the last six years.

The number of reported cases ranged from 3–15 cases per month (incidence range: 0.3 cases to 1.7 cases per 100,000 population) (**Figure 3**). The highest observed cases and monthly incidence rates were in January, November, and December (15 cases, incidence rate: 1.7 cases per 100,000 population). In January and November, the number of cases and incidence rate exceeded the maximum cases and incidence seen in the previous five years. The number of cases in these months were 2.5 times and 1.9 times the maximum number of cases reported in the previous five years.

Geographic distribution

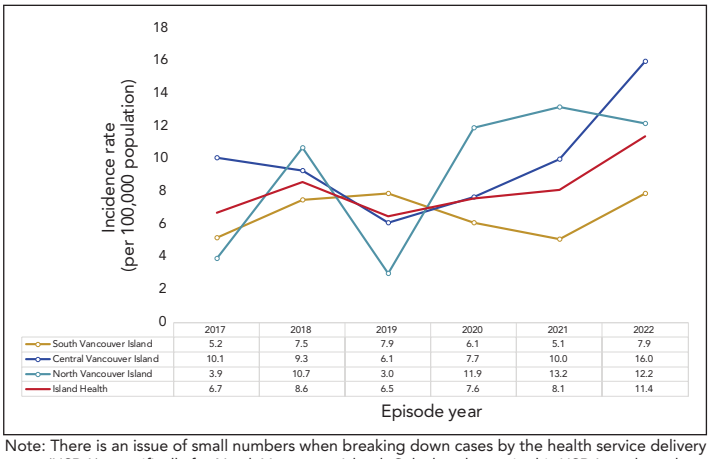
The incidence rates in 2022 ranged from 7.9 to 16.0 cases per 100,000 population in the three HSDAs (**Figure 4**). The incidence rates in both North and Central Island exceeded the rates for the entire Island Health Region. Since 2019, the incidence rates in Central Island have been increasing. In North Island, the incidence rates increased from 2019 to 2021 and decreased in 2022. In South Island, the incidence rates decreased from 2019 to 2021 and increased in 2022. In 2022, the highest incidence rate occurred in Central Island at 16.0 cases per 100,000 population. Forty-nine cases were reported from Central Island, which is an increase of 19 cases (63% increase) compared to the number reported in the previous year.

Figure 3: Invasive group A streptococcal disease cases and incidence rates by month, Island Health, 2022 compared to 2017–2021



Note: There is an issue of small numbers when breaking down cases by month. Calculated rates where the numerator is less than 20 are unstable and should be interpreted with caution. Fluctuations in these values may indicate random variation rather than significant change in the rate

Figure 4: Invasive group A streptococcal disease incidence rates by health service delivery area and year, Island Health, 2017–2022

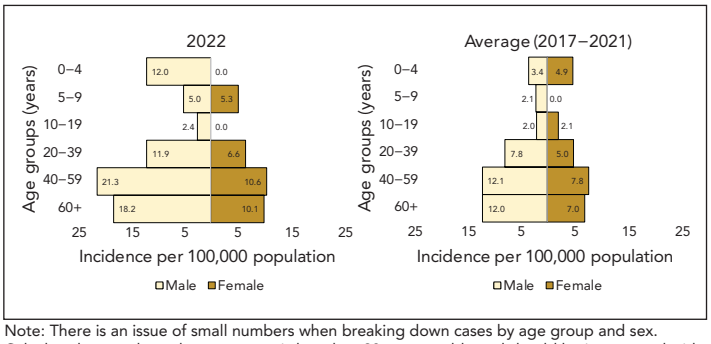


Note: There is an issue of small numbers when breaking down cases by the health service delivery areas (HSDA), specifically for North Vancouver Island. Calculated rates in this HSDA are based on numerators with fewer than 20 cases. Therefore, these rates are unstable and should be interpreted with caution. Fluctuations in these values may indicate random variation rather than significant change in the rate

Demographic distribution

The median age of cases was 53 years, with a range of 0–96 years and 64% of cases were male. The distribution and risk of infection were the highest in men (distribution: 64%, incidence: 15.0 cases per 100,000 population) and individuals 40 years of age and older (distribution: 76%, incidence: 14.7 cases per 100,000 population) (**Table 1**). The highest incidence was reported in men 40–59 years of age (21.3 cases per 100,000 population) (**Figure 5**).

Figure 5: Invasive group A streptococcal disease cases and incidence rates by age and sex, Island Health, 2022 compared to 2017–2021



Note: There is an issue of small numbers when breaking down cases by age group and sex. Calculated rates where the numerator is less than 20 are unstable and should be interpreted with caution. Fluctuations in these values may indicate random variation rather than significant change in the rate

Emm typing

In 2022, there was no single dominant *emm* type. The three most common reported *emm* types were *emm*92 (n=14), *emm*49 (n=13), and *emm*83 (n=12) (**Table 2**).

Severity

Twenty-seven percent of cases reported in 2022 were clinically classified as severe (**Table 3**). Severe cases are defined as cases of streptococcal toxic shock syndrome (STSS), soft-tissue necrosis (including necrotizing fasciitis, myositis, or gangrene), meningitis, GAS pneumonia, or death directly attributable to GAS infection (6). Overall, 85% of cases were hospitalized, 21% were admitted to the intensive care unit (ICU), and 6% died (**Table 4**). The proportion of cases admitted to the hospital and ICU was below the average number admitted in the previous five years (hospitalizations: average=90%, range=85%–93%; ICU admissions: average=23%, range=15%–32%). The case fatality rate was the same as the average case fatality rate reported in the previous five years (average=6%, range=4%–8%). The deaths reported in 2022 occurred in men and women 52–89 years of age (median age=73 years, 67% female). All cases had multiple risk factors reported (median number of reported risk factors=4, range=2–5). Five different *emm* types were prevalent amongst these fatal cases: 74, 81, 83, 92, and 43.

There was no dominant *emm* type reported among severe cases. For both severe and non-severe cases, the most common *emm* types were the same (**Figure 6**).

Risk factors

The most common reported risk factors among cases were having a skin infection, 47% (n=47) and having a wound, 46% (n=46) (**Table 5**). Compared to the previous five years, skin infections, wounds, alcohol use disorder, unstable housing, chronic cardiac conditions, chronic respiratory conditions, and immunocompromised conditions were reported more frequently in 2022, while injection drug use was reported less frequently. Among severe cases (n=27), the most common reported risk factors were having a wound, 52% (n=14); using substances, 52% (n=14); or having a skin infection, 44% (n=12) (**Table 6**). For non-severe cases (n=74), the most common reported risk factors were having a skin infection, 47% (n=35) or having a wound, 43% (n=32).

Table 1: Invasive group A streptococcal disease cases, distribution, and incidence by age and sex, 2022 compared to 2017–2021

Demographics	2022			Average (2017–2021)		
	Number of cases	Distribution	Incidence rate (per 100,000 population)	Number of cases	Distribution	Incidence rate (per 100,000 population)
Age group (years)						
0–4	2	2%	6.1	1	2%	4.1
5–9	2	2%	5.1	0	1%	1.1
10–19	1	1%	1.2	2	3%	2.1
20–39	20	20%	9.3	13	21%	6.4
40–59	35	35%	15.8	22	34%	9.9
60+	41	41%	13.9	25	40%	9.3
Sex						
Female	36	36%	8.0	25	40%	5.9
Male	65	64%	15.0	38	60%	9.2

Note: There is an issue of small numbers when breaking down cases by age group and sex. Calculated rates where the numerator is less than 20 (i.e. for age groups younger than 20 years of age) are unstable and should be interpreted with caution. Fluctuations in these values may indicate random variation rather than significant change in the rate

Table 2: Distribution of *Streptococcus pyogenes* *emm* types by year, Island Health, 2017–2022

Emm type	2017	2018	2019	2020	2021	Average (2017–2021)	2022
*emm*92	1	0	0	0	8	2	14[a]
*emm*49	0	0	0	1	15[a]	3	13[a]
*emm*83	0	2	4	4	2	2	12[a]
*emm*74	0	0	1	0	1	0	9
*emm*59	0	0	0	5	6	2	8
*emm*43	0	0	0	0	2	0	6
*emm*76	1	16[a]	2	5	1	5	4
*emm*53	3	3	4	4	1	3	3
*emm*12	0	1	0	1	0	0	3
*emm*11	1	0	1	0	2	1	2
*emm*77	4	0	3	2	4	3	2
*emm*82	6[a]	2	1	1	1	2	2
*emm*1	3	11	6	1	0	4	1
*emm*101	2	2	3	7[a]	3	3	1
*emm*22	1	0	0	0	0	0	1
*emm*41	7[a]	16[a]	10[a]	4	1	8	1
*emm*89	4	2	0	1	1	2	1
*emm*81	0	3	1	3	0	1	1
*emm*114	0	0	0	0	0	0	1
*emm*104	1	0	0	0	0	0	0
*emm*2	3	0	0	0	0	1	0
*emm*28	2	1	1	1	0	1	0
*emm*3	1	0	0	0	0	0	0
*emm*4	1	1	2	0	0	1	0
*emm*73	1	0	0	0	0	0	0
*emm*87	1	0	0	0	0	0	0
*emm*91	1	3	1	0	0	1	0
*emm*118	0	0	1	0	0	0	0
*emm*78	0	0	1	1	0	0	0
*emm*6	0	0	0	5	0	1	0
*emm*68	0	0	0	2	0	0	0
*emm*9	0	0	0	1	0	0	0
*emm*51	0	0	0	0	1	0	0
*emm*75	0	0	0	0	2	0	0
Unknown	11	9	13	16	19	14	16

[a] Highlighted values indicate the most common *emm* types for each year

Table 3: Invasive group A streptococcal disease cases and distribution by severity, 2022 compared to 2017–2021

Severity	2022		Average (2017–2022)	
	Cases	Distribution	Cases	Distribution
Severe	27	27%	13	21%
Non-severe	74	73%	38	60%
Unknown	0	0%	12	19%

Table 4: Invasive group A streptococcal disease cases and distribution by outcomes, 2022 compared to 2017–2021

Outcomes	2022		Average (2017–2022)	
	Cases	Distribution	Cases	Distribution
Hospitalizations	86	85%	57	90%
ICU admissions	21	21%	15	23%
Deaths	6	6%	4	6%

Abbreviation: ICU, intensive care unit

Figure 6: Distribution of streptococcal pyogenes *emm* types by severity, Island Health, 2022

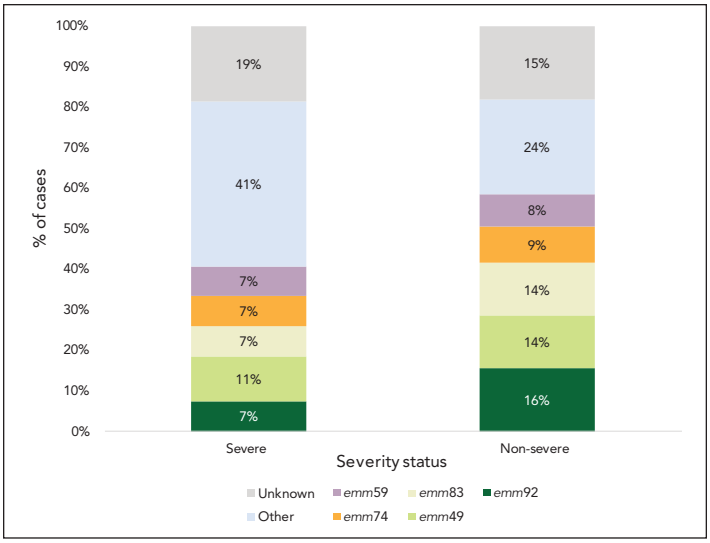


Table 5: Risk factors reported among cases of invasive group A streptococcal disease cases, Island Health, 2022 compared to 2017–2022

Risk factors	2022		Average (2017–2022)	
	Cases	Distribution	Cases	Distribution
Skin infection	47	47%	24	38%
Wound	46	46%	22	34%
Substance use[a]	40	40%	25	39%
Chronic cardiac condition	31	31%	13	21%
Homeless/underhoused	27	27%	14	23%
Alcohol use disorder	26	26%	14	22%
Chronic respiratory condition	21	21%	9	14%
Diabetes	19	19%	11	17%
Injection drug use	17	17%	14	22%
Immunocompromised	12	12%	5	8%
Substance use, other[b]	2	2%	1	2%
Tobacco use	1	1%	1	1%

[a] Substance is a composite variable that includes alcohol use disorder, injection drug use, tobacco use, and substance use, other
[b] Substance use, other is a variable used to capture any other type of substance use than the ones available for selection in the online data reporting system (i.e. alcohol use disorder, tobacco use and injection drug use)

Table 6: Risk factors reported among cases of invasive group A streptococcal disease cases, by severity status, Island Health, 2022

Risk factors	Severe (n=27)	Non-severe (n=74)
Wound	52%	43%
Substance use[a]	52%	35%
Skin infection	44%	47%
Chronic cardiac condition	37%	28%
Alcohol use disorder	37%	22%
Chronic respiratory condition	30%	18%
Diabetes	26%	16%
Homeless/underhoused	26%	27%
Immunocompromised	22%	8%
Injection drug use	19%	16%
Tobacco use	0%	1%
Substance use, other[b]	0%	3%

[a] Substance is a composite variable that includes alcohol use disorder, injection drug use, tobacco use, and substance use, other
[b] Substance use, other is a variable used to capture any other type of substance use than the ones available for selection in the online data reporting system (i.e. alcohol use disorder, tobacco use and injection drug use)

Discussion

In 2022, 101 confirmed cases of iGAS were reported in the Island Health region, corresponding to an incidence rate of 11.4 cases per 100,000 population; the highest rate reported in the last six years and above the preliminary annual provincial rate (8.5 cases per 100,000 population). Since 2019, the incidence of iGAS has been increasing in the Island Health region. This includes throughout the pandemic period when implemented non-pharmaceutical containment measures were also associated with a decrease in invasive respiratory diseases worldwide (7). Provincially, in British Columbia, rates of iGAS have been higher than expected since 2017, with the incidence in the last six years remaining stable (8). Globally, an increase in the incidence of iGAS over time has also been observed in many countries, including Canada (9–12). Previous analyses have hypothesized that the observed increase is linked to both the increase in genetic diversity of circulating *emm* types and compounding societal risk factors, such as homelessness and substance use (10,13–17). Although the factors associated with the increased incidence seen in the Island Health region since 2019, and particularly in 2022, are not completely clear, it is likely that multiple factors have contributed to the observed trends. This includes increased circulation of respiratory viruses, an increase in the diversity in circulating *emm* types, and the impact of the coronavirus disease 2019 (COVID-19) pandemic on community services, specifically an increased demand paired with reduced capacity and availability.

In December 2022, several European countries and the United States reported recent increases in infections of iGAS in children (2,3). Similar to the provincial picture in British Columbia, demographic analysis of Island Health cases showed no notable increase in infections among the paediatric population (8). The highest risk of infection was observed in men 40 years of age and older. While men 40 years of age and older appear to be at a higher risk for iGAS in 2022, further analysis on iGAS in this demographic group would contribute to understanding whether this is a confounding factor, since other risk factors, such as substance use, are known to be higher in this population (18–20).

In 2022, no single dominant *emm* type was identified in the Island Health region. The three most common reported *emm* types were *emm*92 (n=14), *emm*49 (n=13), and *emm*83 (n=12). Prior to 2021, these *emm* types were uncommon in the Island Health region and British Columbia, representing on average 0.4%–4% and 1% of subtyped cases reported from 2016 to 2020, respectively (8). Nationally, *emm*1 has been the dominant *emm* type for the last decade (21). Since 2014, the prevalence of *emm*1 has been decreasing nationally and was surpassed by *emm*76 in 2019 and *emm*49 in 2020 (9,22–24). To date in the available literature, *emm* types 49, 83, and 92 have not been associated with more life-threatening illness. *Emm* types 1 and 3 have been associated with more life-threatening illness, but only represented 1% of cases subtyped in the Island Health region in 2022 (25–27). Overall, indicators of severity in the Island Health region were either below the average or within range of the values reported in the previous five years.

Limitations

When breaking down case numbers by subgroups, cell sizes become small. Calculated rates where the numerator is less than 20 are unstable and should be interpreted with caution. The descriptive analyses where cases are broken down by month, by HSDA (applies to North Island), by age (applies to age categories younger than 20 years of age), and by age and sex are affected by small cell sizes. Fluctuations in these values may indicate random variation rather than significant change in the rate. As well, information on risk factors is predominantly collected through chart reviews. These reviews may not capture the full medical or social history of each case, therefore risk factors among iGAS cases may be under-reported. The regional data presented in this report have undergone data quality assessment by Island Health, but data reconciliation processes for the provincial data are underway for cases reported for 2019 through 2022. The provincial rates shown are based on preliminary numbers, and final numbers and rates for the province may change. Lastly, this report includes data from pandemic response years and an analysis on the impact of the response on the completeness and trends of respiratory surveillance data in the Island Health region has not yet been conducted. It is likely that due to the response, both burden of disease and data completeness decreased, therefore, observed trends during these years might have been higher than reported in this publication. This would affect the interpretation of observed trends in 2022 in comparison to the previous five years. Despite these limitations, this summary contributes descriptive epidemiology that is important for understanding iGAS in the Canadian context.

Conclusion

Overall, this surveillance study characterizes cases of iGAS in the Island Health region in 2022 and compares these cases to those reported over the last five years. The study highlights that incidence of iGAS in the Island Health region continued to increase throughout the COVID-19 pandemic, reaching its highest annual rate in 2022. In contrast to reports from Europe and the United States, there was no notable increase in infections in the paediatric population. The findings of this report contribute to the epidemiological characterization of iGAS in Canada. Given the continued local, provincial, and national increase in incidence of iGAS, it is imperative that the epidemiology of these cases continues to be monitored and described annually.

Authors' statement

AN — Formal analysis, data curation, visualization, writing–original draft, review and editing of final version
AS — Data collection, writing–review and editing
CAW — Data collection, writing–review and editing
CU — Data collection, writing–review and editing
CB — Data collection, writing–review and editing
KT — Data collection, writing–review and editing
JE — Data collection, writing–review and editing
KM — Data collection, writing–review and editing
LW — Data collection, writing–review and editing
TR — Data collection, writing–review and editing
TGalbraith — Data collection, writing–review and editing
SM — Data collection, writing–review and editing
SG — Data collection, writing–review and editing
TGasper — Data collection, writing–review and editing
CB — Data collection, resources, methodology, writing–review and editing
FL — Data collection, resources, methodology, writing–review and editing
DH — Resources, methodology, writing–review and editing
SA — Resources, methodology, writing–review and editing
PK — Data collection, resources, laboratory validation and methodology, writing–review and editing
AR — Resources, methodology, supervision, writing–review and editing
MG — Resources, methodology, supervision, writing–review and editing
CS — Resources, writing–review and editing

Competing interests

None.

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Nirmatrelvir-ritonavir use among adults hospitalized with COVID-19 during the Omicron phase of the COVID-19 pandemic, Canadian Nosocomial Infection Surveillance Program

Robyn Mitchell[1]*, Diane Lee[1], Linda Pelude[1], Jeannette Comeau[2], John Conly[3], Chelsey Ellis[4], Jennifer Ellison[5], John Embil[6], Gerald Evans[7], Lynn Johnston[8], Jennie Johnstone[9], Kevin Katz[10], Pamela Kibsey[11], Bonita Lee[12], Marie-Astrid Lefebvre[13], Yves Longtin[14], Allison McGeer[9], Dominik Mertz[15], Jessica Minion[16], Stephanie Smith[17], Jocelyn Srigley[18], Kathryn Suh[19], Jen Tomlinson[6], Alice Wong[20], Nisha Thampi[21], Charles Frenette[13]

Affiliations

*See full list of affiliations in the Appendix

***Correspondence:**
robyn.mitchell@phac-aspc.gc.ca

Abstract

Background: Recent studies have demonstrated the effectiveness of nirmatrelvir-ritonavir in reducing the risk of progression to severe disease among outpatients with mild to moderate coronavirus disease 2019 (COVID-19); however, data are limited regarding the use and role of nirmatrelvir-ritonavir among hospitalized patients. This study describes the use and outcomes of nirmatrelvir-ritonavir among adults hospitalized with COVID-19 in a sentinel network of Canadian acute care hospitals during the Omicron variant phase of the pandemic.

Methods: The Canadian Nosocomial Infection Surveillance Program conducts surveillance of hospitalized patients with COVID-19 in acute care hospitals across Canada. Demographic, clinical, treatment and 30-day outcome data were collected by chart review by trained infection control professionals using standardized questionnaires.

Results: From January 1 to December 31, 2022, 13% (n=490/3,731) of adult patients (18 years of age and older) hospitalized with COVID-19 in 40 acute care hospitals received nirmatrelvir-ritonavir either at admission or during hospitalization. Most inpatients who received nirmatrelvir-ritonavir, 79% of whom were fully vaccinated, had at least one pre-existing comorbidity (97%) and were of advanced age (median=79 years). Few were admitted to an intensive care unit (2.3%) and among the 490 nirmatrelvir-ritonavir treated inpatients, there were 13 (2.7%) deaths attributable to COVID-19.

Conclusion: These findings from a large sentinel network of Canadian acute-care hospitals suggest that nirmatrelvir-ritonavir is being used to treat adult COVID-19 patients at admission who are at risk of progression to severe disease or those who acquired COVID-19 in hospital. Additional research on the efficacy and indications for nirmatrelvir-ritonavir use in hospitalized patients is warranted to inform future policies and guidelines.

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Keywords: nirmatrelvir-ritonavir, COVID-19, hospitalized patients, Omicron

Introduction

Vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) remains the most effective intervention to prevent severe coronavirus disease 2019 (COVID-19) related illness and death (1–6). For those who become infected, antiviral therapies such as nirmatrelvir-ritonavir are valuable tools to improve patient outcomes and reduce the burden on healthcare systems. A recent randomized controlled trial demonstrated that treatment with nirmatrelvir-ritonavir among unvaccinated, non-hospitalized adults during the pre-Delta and Delta pandemic phases resulted in an 89% reduction in hospitalization or death (7). Recent observational studies have shown the benefit of nirmatrelvir-ritonavir in reducing the risk of hospitalization and death among outpatients with mild or moderate COVID-19 who are at risk for progression to severe disease (8–11).

Nirmatrelvir-ritonavir was approved for use by Health Canada on January 17, 2022, for treating adults with mild to moderate COVID-19 infection who are at high risk for progression to severe disease, including hospitalization and death (12). A recent observational study from Ontario, Canada, found that outpatient use of nirmatrelvir-ritonavir during an Omicron-dominant period between April and August 2022 was associated with a significant reduction in the odds of hospital admission from COVID-19 or all-cause mortality. The largest benefits were observed among those who were under-vaccinated or unvaccinated and those 70 years of age or older (13). Information regarding the use of nirmatrelvir-ritonavir among hospitalized patients with mild to moderate disease during the Omicron phase of the pandemic is limited. To help inform future policies and guidelines, we sought to describe the use and outcomes of nirmatrelvir-ritonavir among adult patients hospitalized with COVID-19 in a sentinel network of Canadian acute care hospitals.

Methods

The Canadian Nosocomial Infection Surveillance Program (CNISP) is a collaboration between the Public Health Agency of Canada, the Association of Medical Microbiology and Infectious Disease Canada and sentinel hospitals across Canada (14). The CNISP conducts surveillance of healthcare-associated (HA) infections among hospitalized adult and paediatric patients, including HA viral respiratory infections. In March 2020, surveillance was expanded to include patients of all ages hospitalized with COVID-19, in addition to patients with HA viral respiratory infection. Beginning on January 1, 2022, eligibility for the inclusion of patients with COVID-19 was restricted to those who were admitted due to COVID-19 or acquired COVID-19 while in hospital.

Demographic, clinical, treatment and 30-day outcome data were collected by trained infection control professionals by chart review and submitted to the Public Health Agency of Canada through a secure online platform, the Canadian Network for Public Health Intelligence, using a standardized protocol and data collection form. Information on initiation of nirmatrelvir-ritonavir was collected between January 1 and December 31, 2022. Data on initiation of nirmatrelvir-ritonavir prior to admission were not systematically recorded in the patient chart; therefore, patients who started nirmatrelvir-ritonavir prior to admission were excluded from the analysis. Outcomes were identified at 30 days from the date of the first positive reverse transcription-polymerase chain reaction test. Attributable mortality was defined as COVID-19 being the cause of death or contributing to death. A HA case was defined as a patient 1) with symptom onset or positive test seven or more calendar days after admission to hospital, or 2) who was readmitted with a positive test within less than seven days after discharge from hospital, or 3) who was most likely a HA case based on best clinical judgment (e.g. symptom onset prior to the seventh day but known epidemiological link to a positive inpatient or staff case).

The primary analysis describes adult patients, 18 years of age and older, who received nirmatrelvir-ritonavir at admission or during hospitalization. A subgroup analysis was conducted among HA COVID-19 adult patients to compare treated to non-treated patients. Paediatric patients, younger than 18 years, were excluded from the analysis. Chi-squared test or Fisher's exact test were used to compare proportions and the Kruskal-Wallis rank sum test was used to compare medians. Missing and incomplete data for individual variables were excluded from analyses, therefore denominators may vary. Provinces were grouped into three regions: Western (British Columbia, Alberta, Saskatchewan and Manitoba); Central (Ontario and Québec); and Eastern (Nova Scotia, New Brunswick, Prince Edward Island and Newfoundland and Labrador). Analyses were conducted using R version 4.0.5.

Results

From January 1, 2022, to December 31, 2022, 40 CNISP-participating hospitals in nine provinces submitted data on 3,731 adult inpatients with laboratory-confirmed COVID-19 for whom information on receipt of nirmatrelvir-ritonavir was available. During this period, 13% (n=490/3,731) were prescribed nirmatrelvir-ritonavir either at admission or during hospitalization. Among all inpatients hospitalized with COVID-19, the proportion who received nirmatrelvir-ritonavir either at admission or during hospitalization was significantly higher in Eastern Canada (28%), followed by Central (18%) and Western Canada (3%) ($p<0.001$) (**Table 1**).

Table 1: Summary of participating hospitals that provided detailed patient information, January 1–December 31, 2022

Region	Reporting hospitals (n=40)	Adults who received nirmatrelvir-ritonavir among patients hospitalized with COVID-19 (n=3,731)	
		n	%
Western Canada[a]	15	43/1,370	3.1%
Central Canada[b]	19	397/2,180	18.2%
Eastern Canada[c]	6	50/181	27.6%

Abbreviation: COVID-19, coronavirus disease 2019
[a] Western refers to British Columbia, Alberta, Saskatchewan and Manitoba
[b] Central refers to Ontario and Québec
[c] Eastern refers to Nova Scotia, New Brunswick, Prince Edward Island, and Newfoundland and Labrador

The median age of treated patients was 79 years (IQR: 68–87) and 53% (n=261/488) were male. Among those who were treated, nearly all (97%, n=469/486) had at least one pre-existing comorbidity. Hypertension (56%, n=273/486), chronic heart disease, excluding hypertension (37%, n=180/486) and diabetes (33%, 160/486) were the most reported conditions. Most treated inpatients (84%, n=388/463) were symptomatic and the most frequently reported symptoms were cough (49%, n=227/463), fever (30%, n=137/463) and weakness (29%, n=135/463). Of those who were asymptomatic, the majority (89%, n=67/75) had a HA COVID-19 infection. The median time from symptom onset to initiation of nirmatrelvir-ritonavir was two days (IQR: 1–4).

The median time from the date of a positive test to initiation of nirmatrelvir-ritonavir was one day (IQR: 0–1). Nearly half of treated patients (49%, n=226/464) acquired COVID-19 while in hospital. Five percent of inpatients (n=25/489) who received nirmatrelvir-ritonavir were admitted from a long-term care facility; of those, 64% (n=16/25) received nirmatrelvir-ritonavir within one day of admission.

The majority of treated patients (79%, n=282/356) had received two or more doses of a COVID-19 vaccine, while 6% (n=20/356) had received only one dose and 15% (n=54/356) were unvaccinated. The median time from the date of last COVID-19 vaccination to initiation of nirmatrelvir-ritonavir was 183 days (IQR: 120–304). The most common additional treatments among patients who received nirmatrelvir-ritonavir were corticosteroids (21%, n=101/487) and remdesevir (12%, n=60/484). Among inpatients with COVID-19 who received nirmatrelvir-ritonavir, 2.3% (n=11/481) were admitted to an intensive care unit (ICU), 1.1% (n=5/461) received mechanical ventilation and 6.1% (n=30/490) died (all-cause 30-day in-hospital death) (**Table 2**). Thirteen deaths (2.7%) among the 490 inpatients treated with nirmatrelvir-ritonavir were attributable to COVID-19; COVID-19 contributed to the death of seven patients and COVID-19 was the cause of death for six patients (1.2%) (Table 2).

Table 2: Frequency of 30-day outcomes among adults hospitalized with COVID-19 who received nirmatrelvir-ritonavir, January 1–December 31, 2022

30-day outcome	Adults hospitalized with COVID-19 who received nirmatrelvir-ritonavir (n=490)	
	n	%
ICU admission	11/481	2.3%
Mechanical ventilation	5/461	1.1%
Pulmonary embolism	4/483	0.8%
CPAP/BiPAP	2/460	0.4%
Dialysis initiated for COVID-19 complications	1/488	0.2%
Stroke	0/486	0%
Extracorporeal membrane oxygenation	0/459	0%
Patient died (all cause)	30/490	6.1%
Death attributed to COVID-19	**13/490**	**2.7%**
COVID-19 contributed to death	7/490	1.4%
COVID-19 was the cause of death	6/490	1.2%

Abbreviations: COVID-19, coronavirus disease 2019; CPAP/BiPAP, continuous positive airway pressure/bilevel positive airway pressure; ICU, intensive care unit

A subgroup analysis among HA patients found that the characteristics (e.g. age, sex, at least one pre-existing comorbidity and vaccination status) of untreated HA patients were similar to those of treated HA patients; however, ICU admissions were higher among untreated HA patients (8.3%, n=63/755) compared to treated HA patients (2.2%, n=5/223, p=0.002). Similarly, all-cause 30-day mortality was also higher among untreated HA patients (16%, n=18/226) compared to treated HA patients (8.0%, n=122/774, p=0.003) (**Table 3**).

Discussion

Findings from a sentinel network of Canadian acute care hospitals found that, during the Omicron phase of the pandemic, 13% of adults hospitalized with COVID-19 received nirmatrelvir-ritonavir either at admission or during hospitalization. Nearly all inpatients, of whom 79% were fully vaccinated, had at least one pre-existing comorbidity and were of advanced age, which put them at increased risk of progression to severe disease or death. The proportion of severe outcomes (e.g. ICU admission and death attributable to COVID-19) at 30 days was low. Significant regional variation was observed in the use of nirmatrelvir-ritonavir, which is most likely related to differences in provincial policies and/or prescriber patterns, and possibly regional drug availability. However, it is difficult to attribute regional treatment differences to regional differences in patient populations, suggesting the need for more data on treatment indications for inpatients from which national treatment guidelines can be developed.

Table 3: Patient characteristics and outcomes in adult inpatients with healthcare-associated COVID-19 by receipt of nirmatrelvir-ritonavir, January 1–December 31, 2022

Patient characteristics	Inpatients who received nirmatrelvir-ritonavir (n=226)		Inpatients who did NOT receive nirmatrelvir-ritonavir (n=774)		*p*-value
	n	%	n	%	
Region					
Western Canada[a]	8/226	3.5%	201/774	26.0%	<0.001
Central Canada[b]	188/226	83.2%	535/774	69.1%	<0.001
Eastern Canada[c]	30/226	13.2%	38/774	4.9%	<0.001
Demographics					
Median age (years)	77	68, 86	76	67, 85	0.62
Male sex	113/226	50.0%	423/770	54.9%	0.19
At least one pre-existing comorbidity	218/224	97.3%	745/764	97.5%	0.87
Vaccination status					
Unvaccinated	22/170	12.9%	65/659	9.9%	0.24
1 dose	9/170	5.3%	24/659	3.6%	0.33
2 or more doses	139/170	81.8%	570/659	86.5%	0.12
Treatment					
Anticoagulant	45/223	20.2%	338/756	44.7%	<0.001
Corticosteroid	25/225	11.1%	467/770	60.6%	<0.001
Remdesivir	22/223	9.9%	763/774	98.6%	<0.001
30-day outcomes					
ICU admission	5/223	2.2%	63/755	8.3%	0.002
Mechanical ventilation	2/224	0.9%	32/766	4.2%	0.018
Pulmonary embolism	0/223	0.0%	14/754	1.9%	0.049
CPAP/BiPAP	0/223	0.0%	29/756	3.8%	0.003
Dialysis initiated for COVID-19 complications	0/226	0.0%	5/767	0.7%	0.59
Stroke	0/225	0.0%	5/760	0.7%	0.59
Extracorporeal membrane oxygenation	0/223	0.0%	2/764	0.3%	>0.99
Patient died (all cause)	18/226	8.0%	122/774	15.8%	0.003
Death attributed to COVID-19	7/226	3.1%	68/774	8.8%	0.03

Abbreviations: COVID-19, coronavirus disease 2019; CPAP/BiPAP, continuous positive airway pressure/bilevel positive airway pressure; ICU, intensive care unit
[a] Western refers to British Columbia, Alberta, Saskatchewan and Manitoba
[b] Central refers to Ontario and Québec
[c] Eastern refers to Nova Scotia, New Brunswick, Prince Edward Island, and Newfoundland and Labrador

Few studies have evaluated the effectiveness of nirmatrelvir-ritonavir among hospitalized patients. However, a cohort study in Hong Kong during the Omicron pandemic phase demonstrated that initiation of nirmatrelvir-ritonavir treatment within five days of symptom onset among hospitalized patients 60 years of age and older or younger patients with at least one chronic disease was associated with a lower risk of in-hospital death compared to controls (15). A Chinese study suggested the potential role of early nirmatrelvir-ritonavir treatment for high-risk patients who are immunocompromised, including those who are hospitalized, to facilitate viral eradication (16). A retrospective cohort study of hospitalized patients with COVID-19 who did not initially require supplemental oxygen found that early initiation of nirmatrelvir-ritonavir was associated with significant reductions in risk of all-cause mortality and disease progression (17).

Our subgroup analysis found that HA COVID-19 adult inpatients who received nirmatrelvir-ritonavir were less frequently admitted to an ICU or less frequently died (30-day all-cause mortality) compared to non-treated HA COVID-19 adult inpatients. These results should be interpreted with caution as eligibility to receive nirmatrelvir-ritonavir was not determined (e.g. data on contraindications for nirmatrelvir-ritonavir were not collected) and due to the small sample size, a multivariable analysis was not conducted. Nonetheless, these preliminary results warrant further study. In addition to the treatment benefits among hospitalized patients reported in other recent studies, our findings suggest a role for nirmatrelvir-ritonavir treatment for adult patients with mild to moderate symptoms who are hospitalized for reasons unrelated to COVID-19 or who acquired COVID-19 in-hospital who are at high risk for progression to severe disease.

Limitations

Our study has several limitations. This report describes early findings of the epidemiology of COVID-19 among inpatients who received nirmatrelvir-ritonavir in a subset of Canadian acute care hospitals; these findings may change as additional data become available. These analyses were descriptive in nature, and we cannot draw any causal inferences. Specifically, our findings should be interpreted with caution as there is potential for selection bias, given that our surveillance methodology did not identify eligibility of patients to receive treatment. Due to the regional variation in data submission and of nirmatrelvir-ritonavir use, our results may not be generalizable to all adult patients hospitalized in Canada. In addition, our cohort was limited to those with a positive test result for SARS-CoV-2 by polymerase chain reaction test and did not include inpatients with positive test result by only rapid antigen test, which may also limit the generalizability of our findings. Finally, we did not collect data on indications or drug contraindications to nirmatrelvir-ritonavir.

Conclusion

Among adult patients hospitalized with COVID-19, we found that 13% received nirmatrelvir-ritonavir. Further study to monitor the use and effectiveness of nirmatrelvir-ritonavir among COVID-19 inpatients and other high-risk populations (e.g. long-term care residents) is critical to inform future policies and guidelines.

Authors' statement

DL and RM analyzed the data. RM drafted the original manuscript. NT and CF contributed equally and are considered co-supervisors of this work.

All authors contributed to the conception of this work and acquisition of the data. All authors contributed to the interpretation of the data and review of the manuscript.

Competing interests

A McGeer reported receiving research grants to the Sinai Health System from the COVID-19 Immunity Task Force, the Canadian Institutes of Health Research, Merck, Pfizer and Sanofi Pasteur; and receiving personal fees from AstraZeneca, GlaxoSmithKline, Janssen, Medicago, Merck, Moderna, Novavax, Pfizer and Sanofi Pasteur outside the submitted work.

J Conly reported receiving research grants and funding from the Canadian Institutes for Health Research. He has participated in World Health Organization-funded studies outside of the submitted work. He was the primary local investigator for a study funded by Pfizer for which all funding was provided to the University of Calgary. Outside of the submitted work, he has received travel support from the Centers for Disease Control and Prevention and bioMérieux Canada. Outside of the submitted work, he is involved in multiple World Health Organization groups for which no funding is received. No other disclosures were reported.

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Appendix: List of affiliations

[1] Public Health Agency of Canada, Ottawa, ON
[2] IWK Health Centre, Halifax, NS
[3] University of Calgary, Calgary, AB
[4] The Moncton Hospital, Moncton, NB
[5] Alberta Health Services, Calgary, AB
[6] Health Sciences Centre, Winnipeg, MB
[7] Queen's University, Kingston, ON
[8] QEII Health Sciences Centre, Halifax, NS
[9] Sinai Health, Toronto, ON
[10] North York General Hospital, Toronto, ON
[11] Royal Jubilee Hospital, Victoria, BC
[12] Stollery Children's Hospital, Edmonton, AB
[13] McGill University Health Centre, Montréal, QC
[14] SMBD-Jewish General Hospital, Montréal, QC
[15] McMaster University and Hamilton Health Sciences, Hamilton, ON
[16] Saskatchewan Health Authority, Regina, SK
[17] University of Alberta Hospital, Edmonton, AB
[18] BC Women's and BC Children's Hospital, Vancouver, BC
[19] The Ottawa Hospital, Ottawa, ON
[20] Royal University Hospital, Saskatoon, SK
[21] Children's Hospital of Eastern Ontario, Ottawa, ON

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Public Health Agency of Canada
130 Colonnade Road
Address Locator 6503B
Ottawa, Ontario K1A 0K9
ccdr-rmtc@phac-aspc.gc.ca

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