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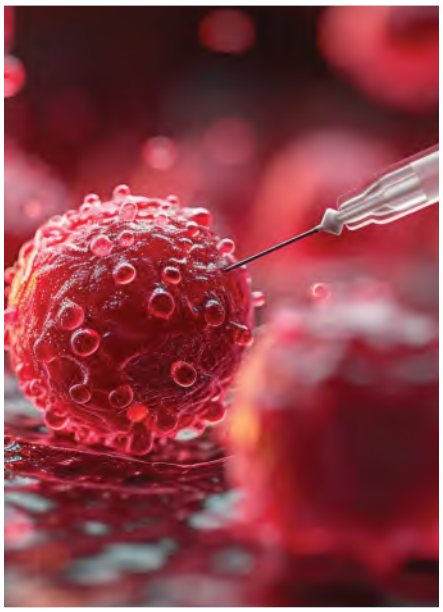

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Efficacy, effectiveness and immunogenicity of reduced HPV vaccination schedules: A review of available evidence

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Abstract

Background: Current National Advisory Committee on Immunization (NACI) guidance recommends human papillomavirus (HPV) vaccines be administered as a two or three-dose schedule. Recently, several large clinical trials have reported the clinical benefit of a single HPV vaccine dose. As a result, the World Health Organization released updated guidance on HPV vaccines in 2022, recommending a two-dose schedule for individuals aged 9–20 years, and acknowledging the use of an alternative off-label single dose schedule.

Objective: The objective of this overview is to provide a detailed account of the available evidence comparing HPV vaccination schedules, which was considered by NACI when updating recommendations on HPV vaccines.

Methods: To identify relevant evidence, existing systematic reviews were leveraged where possible. Individual studies were critically appraised, and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was used to assess the certainty of evidence.

Results: Available evidence suggests that a one, two, or three-dose HPV vaccine schedule may provide similar protection from HPV infection. While antibody levels against HPV vaccine types were statistically significantly lower with a single dose schedule compared to two or three doses, titres were sustained for up to 16 years. The clinical significance of lower antibody titres is unknown, as there is no established immunologic correlate of protection.

Conclusion: While the available evidence on single-dose HPV vaccination schedules shows a one-dose schedule is highly effective, continued follow-up of single-dose cohorts will be critical to understanding the relative duration of protection for reduced dose schedules and informing future NACI guidance on HPV vaccines.

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Keywords: HPV, vaccination, dose-reduction, dosing schedule, effectiveness, cancer, evidence review

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Introduction

Human papillomavirus (HPV) infections are the causative agent of several cancers, including virtually all cervical cancers, other anogenital cancers, as well as head and neck cancers and anogenital warts (AGW) (1,2). HPV vaccines were first authorized in 2006 and have been shown to be highly effective (3,4). In Canada, a two or three-dose schedule is recommended for healthy individuals aged 9–14 years, and a three-dose schedule is recommended for healthy individuals aged 15 years and over, and for immunocompromised individuals (5). Recently, the World Health Organization (WHO) released an updated position paper on HPV vaccination schedules, detailing that while a two-dose schedule is recommended for those over 9 years of age, an alternative off-label, single-dose schedule can be used in those aged 9–20 years (6). Several other jurisdictions, such as the United Kingdom, have since updated their HPV vaccination recommendations to include a single-dose schedule (7–9). This updated guidance was based on several factors, including emerging evidence indicating that a single dose of HPV vaccine provides similar levels of protection from HPV infection as multi-dose schedules (10).

Canadian provinces and territories have asked that the National Advisory Committee on Immunization (NACI) review the currently available evidence and potentially provide updated guidance on reduced HPV immunization schedules. The Public Health Agency of Canada (PHAC) has prepared this overview to review the available clinical evidence on reduced HPV vaccination schedules (with a focus on single-dose schedules), with an objective to help inform NACI evidence-informed recommendations and decision-making for vaccine programs in Canada.

Methods

Table 1 outlines eligibility criteria for studies included in this analysis. To identify relevant studies, an update of a 2022 systematic review (10) performed by Cochrane Response in collaboration with the Strategic Advisory Group of Experts on Immunization (SAGE) (which itself was a modified update of a previous Cochrane Response review (11)) was performed. The updated literature search allowed for identification of any additional studies published since 2022 or any available updated data from included studies (e.g., both recent publications and proceedings from international conferences).

For analyses comparing a single dose to zero, two, or three doses, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (12) was used to assess available evidence considered by NACI during guidance development. Following critical appraisal of individual studies, summary tables with ratings of the certainty of evidence using the GRADE methodology were prepared. For analyses comparing a two-dose to a three-dose HPV vaccine schedule, a methodology informed by A MeaSurement Tool to Assess

Table 1: Study eligibility criteria

Criteria	Eligibility (one vs. two/three doses)	Eligibility (two vs. three doses)
Population	Individuals ≥9 years of age	
Intervention	One dose of GARDASIL®9 or CERVARIX®. Considering limitations to evidence (e.g., limited follow-up time) on GARDASIL®9, indirect evidence from studies using GARDASIL®4 was also considered.	Two doses of GARDASIL®9 or CERVARIX®. Considering limitations to evidence (e.g., limited follow-up time) on GARDASIL®9, indirect evidence from studies using GARDASIL®4 was also considered.
Comparator	Two or three doses of GARDASIL®9 or CERVARIX® (with the interval between the first and last dose in the series being at least six months). Considering limitations to evidence (e.g., limited follow-up time) on GARDASIL®9, indirect evidence from studies using GARDASIL®4 was also considered. Note: While not directly comparing the clinical benefit of HPV vaccines by the number of doses, studies evaluating the immunogenicity or vaccine efficacy/effectiveness of a one-dose HPV vaccine schedule compared to no HPV vaccine were also included.	Three doses of GARDASIL®9 or CERVARIX®. Considering limitations to evidence (e.g., limited follow-up time) on GARDASIL®9, indirect evidence from studies using GARDASIL®4 was also considered.

Outcomes	Outcomes rated as critical for decision-making (deemed equally critical):
	• HPV-associated cancers
	• CIN2+
	• Histological and/or cytological abnormalities (including CIN1)
	• Infection with vaccine-associated serotypes
	  ◦ HPV vaccine type antibody titres
	Outcomes rated as important for decision-making (deemed equally important):
	• Anogenital warts
	  ◦ Juvenile onset recurrent respiratory papillomatosis (JORPP)	

Study design	Randomized controlled trials, non-randomized trials, and observational studies. Observational studies assessed to be at a serious or critical risk of bias were excluded.	

Abbreviations: CIN, cervical intraepithelial neoplasia; HPV, human papilloma virus

systematic Reviews (AMSTAR 2) (13) was used to assess available evidence considered by NACI during guidance development. Detailed information regarding the methodology used in the update of this review can be found elsewhere.

Results

Efficacy/effectiveness against HPV infection

A GRADE assessment of the available randomized controlled trial (RCT) evidence concluded that a one-dose HPV vaccine schedule resulted in a large reduction in persistent infection compared to no vaccine (high certainty of evidence; **Table 2**). Currently, the KENya Single-dose HPV-vaccine Efficacy (KEN SHE) trial represents the sole RCT evidence demonstrating the efficacy of a single-dose schedule (14). This trial randomized women aged 15–20 years (n=2,275) to one dose of either GARDASIL®9, CERVARIX®, or meningococcal vaccine. After three years of follow-up, vaccine effectiveness (VE) against persistent HPV16/18 infection was 97.5% (95% CI: 90.0%–99.4%) and 98.8% (95% CI: 91.3%–99.8%) for GARDASIL®9 and CERVARIX®, respectively. Similar results were seen in the non-RCT evidence, with a single dose probably resulting in reductions in persistent (15,16), incident (16,17), and prevalent (17,18) HPV infections compared to no vaccination (moderate certainty of evidence; Table 2, **Figure 1**).

Table 2: Summary of findings comparing one dose to no doses of HPV vaccine

Number of studies	Study design	Number of events/ number of participants		Effect		Certainty of evidence	Comments
		Zero doses	One dose	Relative effect (95% CI)	Absolute effect (95% CI)		
Persistent HPV infection with vaccine types (follow-up ranging from 3–10 years)							
1 (14)	RCT[a]	72/757 (9.5%)	3/1,518 (0.2%)	RR 0.02 (0.01–0.07)	94 fewer per 1,000 (94 fewer to 88 fewer)	High	A single dose of HPV vaccine results in a large reduction in persistent HPV infections compared to no vaccine
2 (15,16)	Post-hoc RCT analysis	A small number of events in the intervention groups across studies (n=292–2,135); high VE was estimated in each study[b]				Moderate[c]	A single dose of HPV vaccine probably results in a large reduction in persistent HPV infections compared to no vaccine
Prevalent HPV infection with vaccine types (follow-up ranging from 6–11 years)							
2 (17,18)	1 post-hoc RCT analysis, 1 observational study	A small number of events in the intervention groups across studies (n=87–221); large reductions in infection prevalence associated with a single dose in each study[d]				Moderate[c]	A single dose of HPV vaccine probably results in reduction in prevalent HPV infections compared to no vaccine
Incident HPV infection with vaccine types (follow-up ranging from 10–11 years)							
2 (16,17)	Post-hoc RCT analysis	Number of events dissimilar between studies (n=112–2,858); however, similar reductions in risk compared to unvaccinated were observed[e]				Moderate[c]	A single dose of HPV vaccine probably results in reduction in incident HPV infections compared to no vaccine
Antibody titres (follow-up ranging from 4–10 years)							
3 (18–20)	Observational	Varying number of participants in each study (n=30–324), with differing lengths of follow-up and magnitudes of effect across studies; however, the direction of effect was consistent across studies[f]				High	A single dose of HPV vaccine results in an increased immune response compared to no vaccine
Anogenital warts (follow-up of approximately 2.5 years)							
1 (21)	Observational	523/52,779 (1.0%)	69/9,898 (0.7%)	aHR[g] 0.32 (0.20–0.52)	7 fewer per 1,000 (8 fewer to 5 fewer)	Moderate[h]	A single dose of HPV vaccine probably reduces the risk of anogenital warts compared to no vaccine
Juvenile-onset recurrent respiratory papillomatosis (JoRPP)							
N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Abbreviations: aHR, adjusted hazard ratio; aVE, adjusted vaccine effectiveness; CI, confidence interval; HPV, human papilloma virus; N/A, not applicable; RCT, randomized controlled trial; RR, relative risk; VE, vaccine effectiveness

[a] The groups receiving a single dose of GARDASIL®9 and CERVARIX® were collapsed into a single group for the purpose of the analysis

[b] Consistent results were observed across studies, with both included studies estimating single-dose VE to be similarly high. One study estimated VE at 95.1% (95% CI: 73.2%–99.8%) and the other estimated aVE (adjusted for disease-risk score) at 93.4% (95% CI: 81.1%–99.1%). The definition of persistent infection was similar across studies

[c] Downgraded by one level due to some concerns with bias due to confounding and selection of the reported result

[d] Consistent results were observed across studies. A post-hoc analysis of an RCT estimated single-dose VE at 82.1% (95% CI: 40.2%–97.0%). A retrospective observational study did not provide an estimate of VE; however, the adjusted prevalence ratio of HPV infections (adjusted for employment status and income) was 0.08 (95% CI: 0.01%–0.56%) compared to unvaccinated individuals. The definition of prevalent infection was consistent across studies

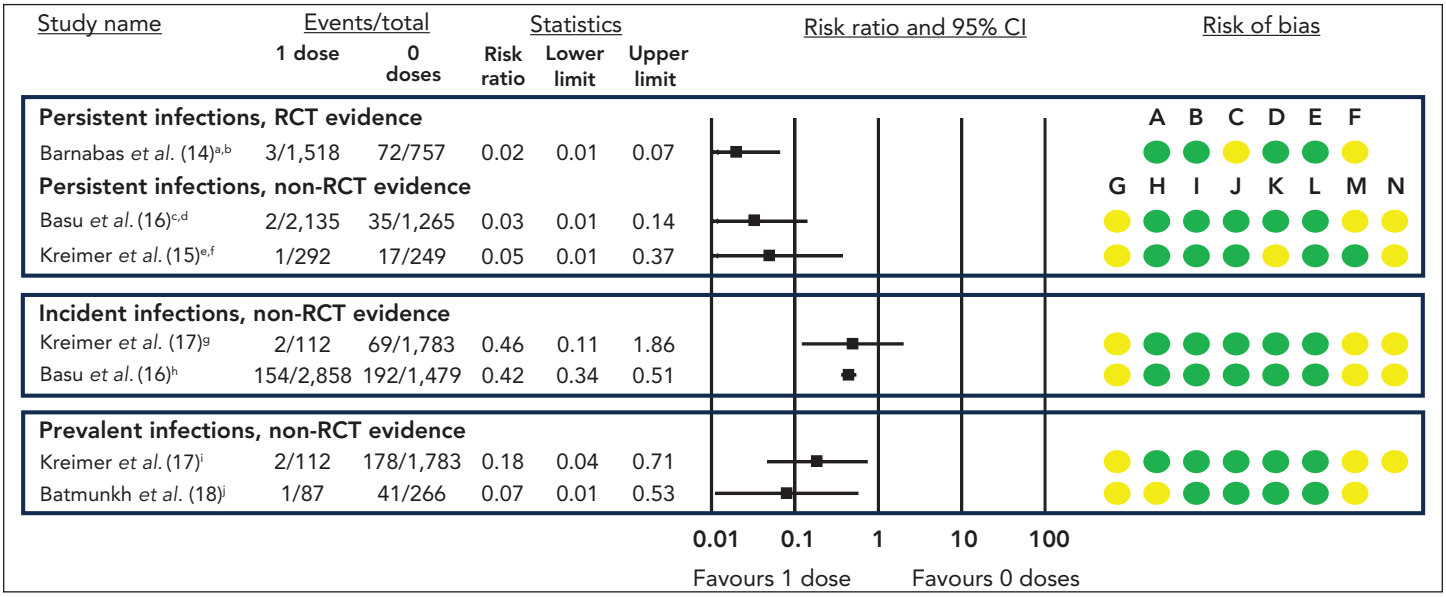
[e] Although the risk of incident infection with a single dose was dissimilar between the two included studies (1.8% vs. 5.4%), consistent reductions in risk were observed when compared to unvaccinated individuals. Both included studies estimated similar VE, with one study estimating VE at 53.9% (95% CI: −57.1%–92.4%) and the other estimating aVE (adjusted for disease-risk score) at 54.1% (95% CI: 41.8%–64.1%). The definition of incident infection was consistent across studies

[f] Magnitude of effect differs across studies; however, this is potentially explained by the differences in study populations and differing lengths of follow-up. In addition, the direction of effect is consistent across studies

[g] Hazard ratio was adjusted for race/ethnicity, health plan (site), age at enrollment in the health plan, age at beginning of study period, age at first evidence of probable sexual activity (as defined by Healthcare Effectiveness Data and Information Set criteria), age at first dose of HPV vaccine (or proxy date), months enrolled in the health plan, Medicaid enrollment, oral contraceptive use, or history of tests for pregnancy, chlamydia or gonorrhea

[h] Downgraded by one level due to some concerns with bias, including due to confounding, selection of participants into the study and selection of the reported result

Figure 1: Risk ratios and 95% CI for persistent, prevalent, and incident HPV vaccine-type infections, one dose compared to no doses[a,b,c,d,e,f,g,h,i,j]



Abbreviations: CI, confidence interval; HPV, human papilloma virus; RCT, randomized controlled trial
[a] Persistent infection defined as detection of a vaccine-type HPV infection at two consecutive visits after the three-month visit, which were obtained no less than four months apart
[b] Three-year follow-up, nonavalent vaccine effectiveness (VE)=98.8% (95% CI: 91.3%–99.8%), bivalent VE=97.5% (95% CI: 90.0%–99.4%)
[c] Persistent infection defined as detection of vaccine-type infection in two consecutive samples taken at least 10 months apart
[d] 10-year follow-up, VE=95.4% (95% CI: 85.0%–99.9%)
[e] Persistent infection defined as two or more vaccine-type positive tests at least 300 days apart, with no intervening negatives
[f] Four-year follow-up, VE=95.1% (95% CI: 73.2%–99.8%)
[g] 11-year follow-up, VE=53.9% (95% CI: -57.1%–92.4%)
[h] 10-year follow-up, VE=63.5% (95% CI: 52.1%–73.1%)
[i] 11-year follow-up, VE=82.1% (95% CI: 40.2%–97.0%)
[j] Six-year follow-up; adjusted prevalence ratio 0.10 (0.01–0.73)
Risk of bias legend: A) risk of bias arising from the randomization process, B) risk of bias due to deviations from the intended interventions, C) risk of bias due to missing outcome data, D) risk of bias in measurement of the outcome, E) risk of bias in selection of the reported result, F) overall risk of bias, G) bias due to confounding, H) bias in selection of participants into the study, I) bias in classification of interventions, J) bias due to deviation from intended interventions, K) bias due to missing data, L) bias in measurement of outcomes, M) bias due to selection of reported result, N) overall risk of bias

A GRADE assessment of the available evidence concluded that, compared to two or three doses, there may be little to no difference in persistent, incident, or prevalent HPV infection risk with a one-dose HPV vaccine schedule (low certainty of evidence, **Table 3** and **Table 4**, **Figure 2** and **Figure 3**). Two RCTs evaluating the effectiveness of a two and/or three-dose HPV vaccine schedule have conducted post-hoc analyses to also estimate the VE of a one-dose schedule, with both studies reporting similar VE across all dosing schedules, up to 10 (16) or 11 years (17) (low certainty of evidence; Table 3 and Table 4, Figure 2 and Figure 3).

The Costa Rica Vaccine Trial (CVT) was originally designed to test the efficacy of a three-dose schedule of CERVARIX® in females aged 18–25 years (compared to control hepatitis A vaccine); however, approximately 20% of participants did not complete their three-dose schedule, primarily due to pregnancy or colposcopy referral, thus creating cohorts who received a one or two-dose schedule. After 11 years of follow-up, VE against prevalent HPV16/18 infection was similar among recipients of either one-dose (82.1%; 95% CI: 40.2%–97.0%), two-dose (83.8%; 95% CI: 19.5%–99.2%) or three-dose (80.2%; 95% CI: 70.7%–87.0%) schedules (17).

Similar results were also seen in the International Agency for Research on Cancer (IARC) study from India, which was originally designed to compare two and three doses of GARDASIL® in females aged 10–18 years. However, numerous participants did not complete their full vaccine schedule, as recruitment of girls into HPV trials was suspended by the Indian government in 2010. Vaccine effectiveness against persistent HPV16/18 infection was similar among women who received one (95.4%; 95% CI: 85%–99.1%), two (93.1%; 95% CI: 77.3%–99.8%) or three (93.3%; 95% CI: 77.5%–99.7%) doses after 10 years of follow-up (16).

Efficacy/effectiveness against cervical precancerous lesions

Among included studies, only the IARC trial (16) reported data on the effect of different HPV vaccine schedules on cervical precancers and HPV-related cancers. After 10 years of follow-up, 16/4,626 (0.3%) of unvaccinated women reported cervical intraepithelial neoplasia (CIN) grade 1, compared to 4/1,511 (0.3%), 1/1,128 (0.1%) and 1/1,037 (0.1%) in the one, two and three-dose groups, respectively. There were no cases of CIN2 or greater in any of the vaccine groups, regardless of the number of doses received, while 5/4,626 women (0.1%) in the unvaccinated group experienced CIN2 or greater. Additionally, there were no cases of HPV-related cancers in any of the groups.

Table 3: Summary of findings comparing one dose to two doses of HPV vaccine

Number of studies	Study design	Number of events/number of participants		Effect		Certainty of evidence	Comments
		Two doses	One dose	Relative effect (95% CI)	Absolute effect (95% CI)		
Persistent HPV infection with vaccine types (follow-up ranging from 4–10 years)							
2 (15,16)	Post-hoc RCT analysis	A small number of events in both the intervention (n=292–2,135) and control arms (n=611–1,452) across studies; high VE estimated for both arms in each study[a]				Low[b,c]	A single dose of HPV vaccine may result in little to no difference in persistent HPV infections compared to two doses
Prevalent HPV infection with vaccine types (follow-up of 11 years)							
1 (17)	Post-hoc RCT analysis	1/62 (1.6%)	2/112 (1.8%)	RR 1.11 (0.10–11.97)	2 more per 1,000 (15 fewer to 177 more)	Low[d,e]	A single dose of HPV vaccine may result in little to no difference in prevalent HPV infections compared to two doses
Incident HPV infection with vaccine types (follow-up ranging from 10–11 years)							
2 (16,17)	Post-hoc RCT analysis	Number of events dissimilar between studies (n [one dose]=112–2,858; n [two doses]=62–2,166), as the baseline risk of events varies across studies; however, VE estimates for each group are similar across studies[f]				Low[d,e]	A single dose of HPV vaccine may result in little to no difference in incident HPV infections compared to two doses
Antibody titres (follow-up ranging from 2–16 years)							
1 (22)	RCT	310	310	Ratio of GMTs ranging from 0.11 (0.09–0.14) to 0.21 (0.16–0.26)	N/A	High	A single dose of HPV vaccine results in a decreased immune response compared to two doses
2 (21,23)	Post-hoc RCT analysis	Dissimilar number of participants between intervention and control arms, across all studies; however, consistent magnitude and direction of effect across studies				High	A single dose of HPV vaccine results in a decreased immune response compared to two doses
Histological and cytological abnormalities (follow-up of 10 years)							
1 (16)	Post-hoc RCT analysis	1/1,128 (0.9%)	4/1,511 (2.6%)	RR 2.99 (0.33–26.80)	2 more per 1,000 (1 fewer to 23 more)	Low[b,e]	A single dose of HPV vaccine may result in little to no difference in cervical abnormalities compared to two doses
CIN2+ (follow-up of 10 years)							
1 (16)	Post-hoc RCT analysis	0/1,128 (0%)	0/1,511 (0%)	Not estimable	Not estimable	Low[b,g]	A single dose of HPV vaccine may result in little to no difference in CIN2+ compared to two doses
HPV-associated cancer (follow-up of 10 years)							
1 (16)	Post-hoc RCT analysis	0/1,128 (0%)	0/1,511 (0%)	Not estimable	Not estimable	Very low[b,h,i]	Data insufficient to determine association
Anogenital warts (follow-up of approximately 2.5 years)							
1 (21)	Observational	42/8,046 (0.5%)	69/9,898 (0.7%)	aHR[j] 0.74 (0.35–1.60)	2 more per 1,000 (5 fewer to 4 more)	Low[e,k]	A single dose of HPV vaccine may result in little to no difference in the risk of anogenital warts compared to two doses
Juvenile-onset recurrent respiratory papillomatosis (JoRPP)							
N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; CIN, cervical intraepithelial neoplasia; GMT, geometric mean titre; HPV, human papilloma virus; N/A, not applicable; RCT, randomized controlled trial; RR, relative risk; VE, vaccine effectiveness

[a] Consistent results observed across studies, with both included studies estimating one and two-dose VE to be similarly high. One study estimated VE at 93.4% (95% CI: 81.1%–99.1%) and 93.7% (95% CI: 78.9%–99.8%) and the other estimated VE at 95.1% (95% CI: 73.2%–99.8%) and 89.6% (95% CI: 68.9%–97.5%) for one and two-dose groups, respectively. The definition of persistent infection was similar across studies

[b] Downgraded one level due to some concerns with bias due to confounding and selection of the reported result

[c] Downgraded one level due to imprecision, few events and a 95% CI that encompasses a potential benefit, no effect, and a potential harm

[d] Downgraded one level due to some concerns with bias due to confounding

[e] Downgraded one level due to imprecision and a 95% CI that encompasses a potential benefit, no effect, and a potential harm

[f] The baseline risk of incident infection for both one and two doses was dissimilar across the two included studies. However, VE estimated for both the one and two-dose arms of the trials was similar across studies, with one study reporting VE of 54.1% (95% CI: 41.8%–64.1%) and 59% (95% CI: 46.9%–69.1%) and the other reporting VE of 53.9% (95% CI: −57.1%–92.4%) and 58.4% (95% CI: −110.9%–97.9%) for one and two-dose groups, respectively

[g] Downgraded by one level due to imprecision, as the optimal information size was not met

[h] Downgraded by two levels due serious concerns over indirectness, due to a small number of events, owing to the follow-up period. A 10-year follow-up is insufficient to determine the effect on cancer incidence

[i] Downgraded by one level due to some concerns over imprecision. There are no events and the optimal information size was not met

[j] Hazard ratio was adjusted for race/ethnicity, health plan (site), age at enrollment in the health plan, age at beginning of study period, age at first evidence of probable sexual activity (as defined by Healthcare Effectiveness Data and Information Set criteria), age at first dose of HPV vaccine (or proxy date), months enrolled in the health plan, Medicaid enrollment, oral contraceptive use, or history of tests for pregnancy, chlamydia, or gonorrhea

[k] Downgraded by one level due to some concerns with bias, including due to confounding, selection of participants into the study and selection of the reported result

Table 4: Summary of findings comparing one dose to three doses of HPV vaccine

Number of studies	Study design	Number of events/number of participants		Effect		Certainty of evidence	Comments
		Three doses	One dose	Relative effect (95% CI)	Absolute effect (95% CI)		
Persistent HPV infection with vaccine types (follow-up ranging from 4–10 years)							
2 (15,16)	Post-hoc RCT analysis	A small number of events in both the intervention (n=292–2,135) and control (n=1,460–11,104) arms across studies; high VE estimated for both arms in each study[a]				Low[b,c]	A single dose of HPV vaccine may result in little to no difference in persistent HPV infections compared to three doses
Prevalent HPV infection with vaccine types (follow-up of 11 years)							
1 (17)	Post-hoc RCT analysis	27/1,365 (2.0%)	2/112 (1.8%)	RR 0.90 (0.22–3.75)	2 fewer per 1,000 (15 fewer to 54 more)	Low[d,e]	A single dose of HPV vaccine may result in little to no difference in prevalent HPV infections compared to three doses
Incident HPV infection with vaccine types (follow-up ranging from 10–11 years)							
2 (16,17)	Post-hoc RCT analysis	Number of events dissimilar between studies (n [one dose]=112–2,858; n [two doses]=1,365–2,019), as the baseline risk of events varies across studies[f]				Low[d,e]	A single dose of HPV vaccine may result in little to no difference in incident HPV infections compared to three doses
Antibody titres (follow-up ranging from 2–16 years)							
1 (22)	RCT	310	310	Ratio of GMTs ranging from 0.06 (0.05–0.07) to 0.19 (0.15–0.24)	N/A	High	A single dose of HPV vaccine results in a decreased immune response compared to three doses
2 (21,23)	Post-hoc RCT analyses	Dissimilar number of participants between intervention and control arms, across all studies; however, consistent magnitude and direction of effect across studies				High	A single dose of HPV vaccine results in a decreased immune response compared to three doses
Histological and cytological abnormalities (follow-up of 10 years)							
1 (16)	Post-hoc RCT analysis	1/1,037 (0.9%)	4/1,511 (2.6%)	RR 2.75 (0.31−24.53)	2 more per 1,000 (1 fewer to 23 more)	Low[b,e]	A single dose of HPV vaccine may result in little to no difference in cervical abnormalities compared to three doses
CIN2+ (follow-up of 10 years)							
1 (16)	Post-hoc RCT analysis	0/1,037 (0%)	0/1,511 (0%)	Not estimable	Not estimable	Low[b,g]	A single dose of HPV vaccine may result in little to no difference in CIN2+ compared to three doses
HPV-associated cancer (follow-up of 10 years)							
1 (16)	Post-hoc RCT analysis	0/1,037 (0%)	0/1,511 (0%)	Not estimable	Not estimable	Very low[b,h,i]	Data insufficient to determine association
Anogenital warts (follow-up of approximately 2.5 years)							
1 (21)	Observational	91/57,287 (0.2%)	69/9,898 (0.7%)	aHR[j] 0.63 (0.37−1.09)	3 more per 1,000 (1 fewer to 4 more)	Low[e,k]	A single dose of HPV vaccine may result in little to no difference in the risk of anogenital warts compared to three doses
Juvenile-onset recurrent respiratory papillomatosis (JoRPP)							
N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; CIN, cervical intraepithelial neoplasia; GMT, geometric mean titre; HPV, human papilloma virus; N/A, not applicable; RCT, randomized controlled trial; RR, relative risk; VE, vaccine effectiveness

[a] Consistent results observed across studies, with both included studies estimating one and three-dose VE to be similarly high. One study estimated VE at 93.4% (95% CI: 81.1%–99.1%) and 90.3% (95% CI: 71.9%–98.5%) and the other estimated VE at 95.1% (95% CI: 73.2%–99.8%) and 87.0% (95% CI: 83.7%–89.7%) for one- and three-dose groups, respectively. The definition of persistent infection was similar across studies

[b] Downgraded one level due to some concerns with bias due to confounding and selection of the reported result

[c] Downgraded one level due to imprecision, few events and a 95% CI that encompasses a potential benefit, no effect, and a potential harm

[d] Downgraded one level due to some concerns with bias due to confounding

[e] Downgraded one level due to imprecision and a 95% CI that encompasses a potential benefit, no effect, and a potential harm

[f] The baseline risk of incident infection for both one and three doses was dissimilar across the two included studies, as was the estimated VE for one of the included studies. The VE estimated for the one and two-dose arms of the trials was 54.1% (95% CI: 41.8%–64.1%) and 54.7% (95% CI: 40.9%–65.0%) in one study and 53.9% (95% CI: −57.1%–92.4%) and 84.9% (95% CI: 69.8%–93.2%) in the other, for one- and two-dose groups, respectively. The difference in VE reported can be at least partially explained by the small number of events and participants in the one-dose group

[g] Downgraded by one level due to imprecision, as the optimal information size was not met

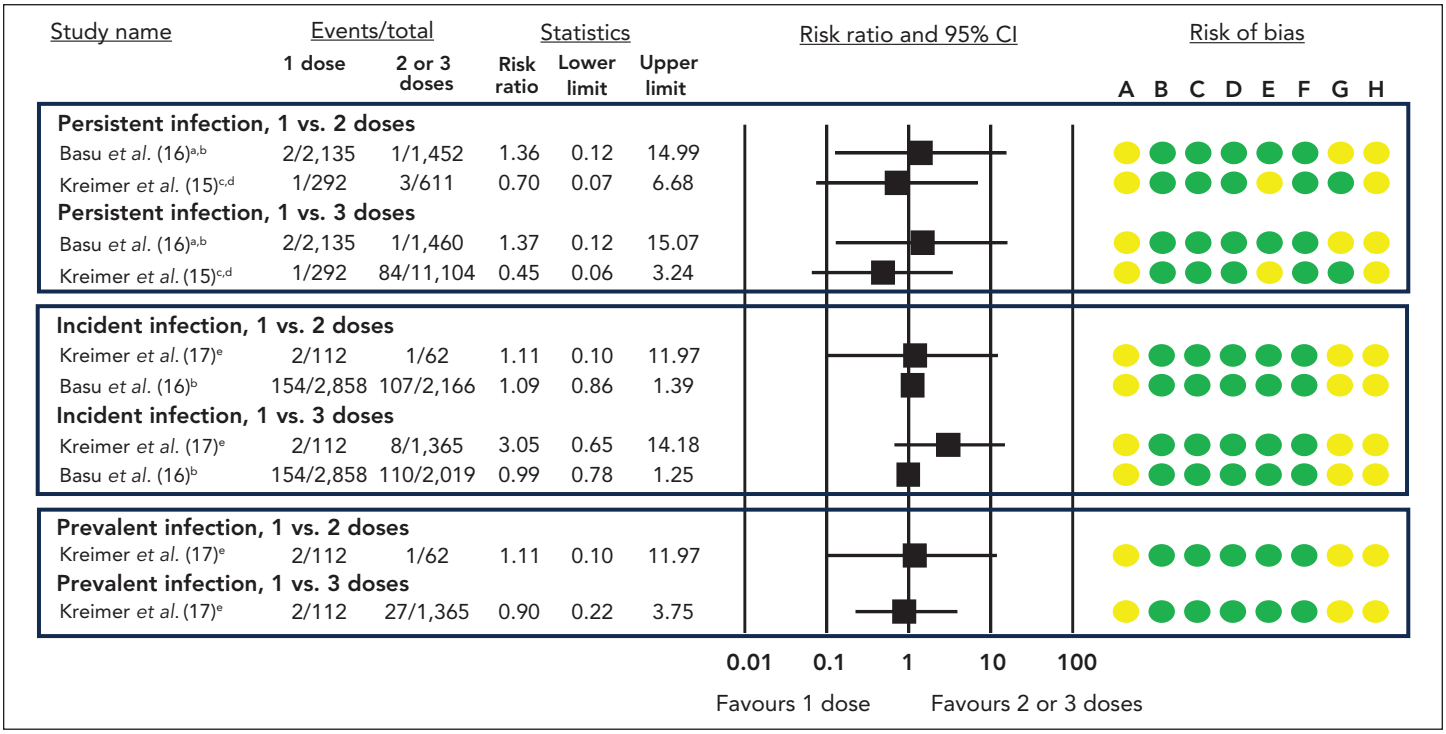
[h] Downgraded by two levels due serious concerns over indirectness, due to a small number of events, owing to the follow-up period. A 10-year follow-up is insufficient to determine the effect on cancer incidence

[i] Downgraded by one level due to some concerns over imprecision. There are no events, and the optimal information size was not met

[j] Hazard ratio was adjusted for race/ethnicity, health plan (site), age at enrollment in the health plan, age at beginning of study period, age at first evidence of probable sexual activity (as defined by Healthcare Effectiveness Data and Information Set criteria), age at first dose of HPV vaccine (or proxy date), months enrolled in the health plan, Medicaid enrollment, oral contraceptive use, or history of tests for pregnancy, chlamydia or gonorrhea

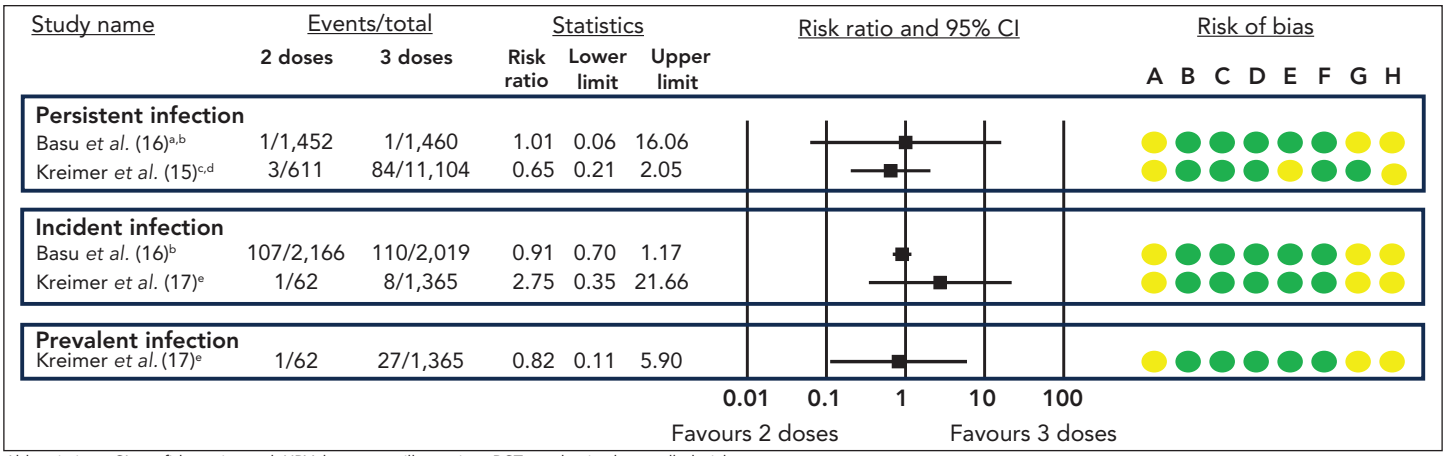
[k] Downgraded by one level due to some concerns with bias, including due to confounding, selection of participants into the study and selection of the reported result

Figure 2: Risk ratios and 95% CI for persistent, prevalent and incident HPV vaccine-type infections, one dose compared to either two or three doses[a,b,c,d,e]



Abbreviations: CI, confidence interval; HPV, human papilloma virus; RCT, randomized controlled trial
[a] Persistent infection defined as detection of vaccine-type infection in two consecutive samples taken at least 10 months apart
[b] 10-year follow-up
[c] Persistent infection defined as two or more vaccine-type positive tests at least 300 days apart, with no intervening negatives
[d] Four-year follow-up
[e] 11-year follow-up
Risk of bias legend: A) bias due to confounding, B) bias in selection of participants into the study, C) bias in classification of interventions, D) bias due to deviation from intended interventions, E) bias due to missing data, F) bias in measurement of outcomes, G) bias due to selection of reported result, H) overall risk of bias

Figure 3: Risk ratios and 95% CI for persistent, prevalent and incident HPV infections, two doses compared to three doses[a,b,c,d,e]



Abbreviations: CI, confidence interval; HPV, human papilloma virus; RCT, randomized controlled trial
[a] Persistent infection defined as detection of vaccine-type infection in two consecutive samples taken at least 10 months apart
[b] 10-year follow-up
[c] Persistent infection defined as two or more vaccine-type positive tests at least 300 days apart, with no intervening negatives
[d] Four-year follow-up
[e] 11-year follow-up
Risk of bias legend: A) bias due to confounding, B) bias in selection of participants into the study, C) bias in classification of interventions, D) bias due to deviation from intended interventions, E) bias due to missing data, F) bias in measurement of outcomes, G) bias due to selection of reported result, H) overall risk of bias

A GRADE assessment of the available evidence concluded that there may be little to no difference in the risks of cervical abnormalities or CIN2+ between one and either two or three-dose schedules (low certainty of evidence; Table 3 and Table 4).

Efficacy/effectiveness against anogenital warts

There is currently no clinical trial evidence comparing the effect of a single dose to either two or three doses on the risk of AGW. However, an observational study from the United States (n=64,517) compared the risk of AGW in female participants who received one dose to those who received no, two, or three doses of GARDASIL® (21). Propensity score-weighted incidence rates were 761.9 (95% CI: 685.5–849.1), 256.6 (95% CI: 161.8–432.3), 194.2 (95% CI: 108.0–386.4), and 161.8 (95% CI: 124.4–214.6) per 100,000 person-years in the unvaccinated, one, two and three-dose groups, respectively. Propensity score-weighted hazard ratios (HRs) demonstrated no statistically significant difference between the groups, with HRs of 0.74 (95% CI: 0.35–1.60) and 0.63 (95% CI: 0.37–1.09) for two and three doses (compared to one), respectively (no direct comparison of the two and three-dose groups).

A GRADE assessment of the available evidence concluded that a single dose of HPV vaccine probably reduces the risk of AGW compared to no vaccine (moderate certainty of evidence; Table 2), and that there may be little to no difference in risk, compared to a two or three-dose schedule (low certainty of evidence; Table 3 and Table 4).

Antibody titres

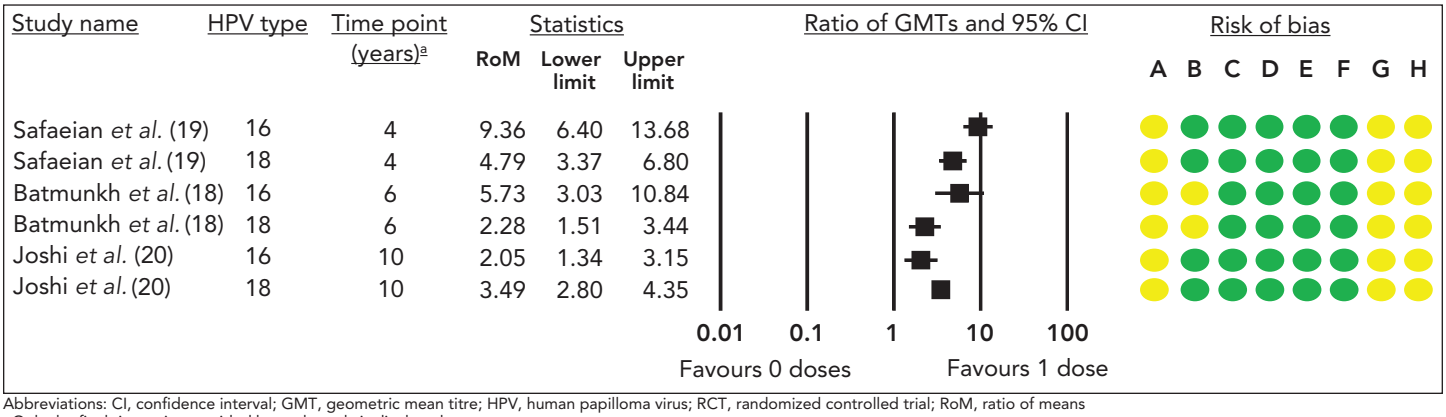
A GRADE assessment of the available evidence concluded that a single dose of HPV vaccine results in an increased immune response compared to no vaccine (18–20) (high certainty of evidence; Table 2, **Figure 4**), and a decreased immune response compared to two or three doses (high certainty of evidence; Table 3 and Table 4, **Figure 5**).

The Dose Reduction Immunobridging and Safety study (DoRIS) from Tanzania randomized females aged 9–14 years (n=930) to receive one, two, or three doses of CERVARIX® or GARDASIL®9 (22). Antibody titres were statistically significantly lower for one-dose recipients compared to two or three-dose recipients for both vaccines (Figure 5). However, while lower titres were observed for the one-dose schedule, the antibody response was sustained through year two (end of study). In individuals who received two doses of GARDASIL®9, antibody titres were non-inferior compared to those who received three doses; however, they were significantly lower (and non-inferiority was not met) for those receiving two doses of CERVARIX® (**Figure 6**).

Two post-hoc analyses of the CVT and IARC trials (data up to 16 (23) and 10 (21), respectively) have produced similar results to the DoRIS study, with a single-dose schedule producing inferior but sustained antibody titres (high certainty of evidence; Table 3 and Table 4, Figure 5).

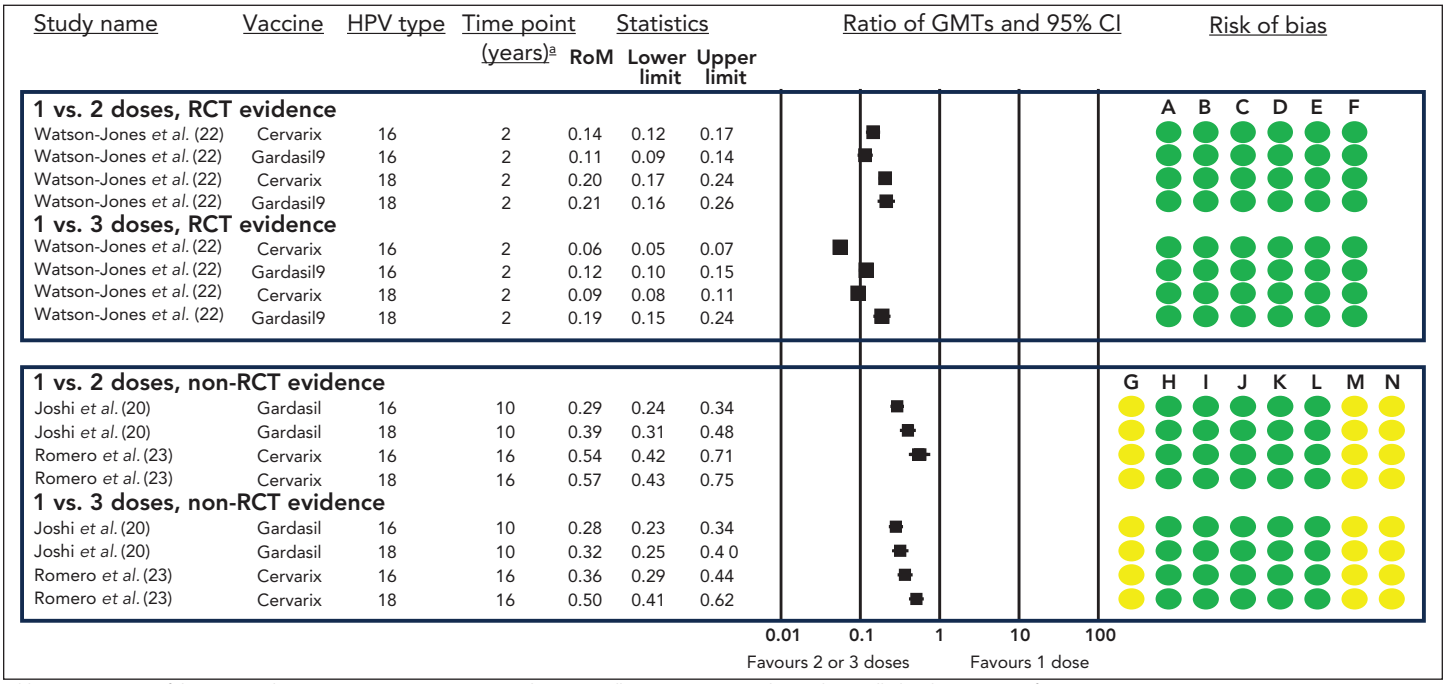
Several RCTs provide data comparing the antibody titres of a two-dose versus three-dose schedule (Figure 6). The long-term follow-up of a Canadian RCT in girls aged 9–13 years receiving GARDASIL® demonstrated a non-inferior antibody response with two doses for HPV6, HPV11 and HPV16, ten years following vaccination (non-inferiority not met for HPV18) (24). Another RCT of girls aged 9–14 years receiving GARDASIL® demonstrated a non-inferior immune response for HPV16 and HPV18, three years following vaccination (25). In a multinational RCT using GARDASIL®9, girls aged 9–14 years were randomized to receive two (six or 12 months apart) or three doses (six months apart), while boys aged 9–14 years were randomized to receive two doses six or 12 months apart. While the individuals receiving two doses six months apart had generally lower/similar antibody levels compared to those receiving three doses, those receiving two doses 12 months apart generally had higher/similar antibody

Figure 4: Ratio of geometric mean titres and 95% CI comparing one dose to zero doses[a]



Abbreviations: CI, confidence interval; GMT, geometric mean titre; HPV, human papilloma virus; RCT, randomized controlled trial; RoM, ratio of means
[a] Only the final timepoint provided by each study is displayed
Risk of bias legend: A) bias due to confounding, B) bias in selection of participants into the study, C) bias in classification of interventions, D) bias due to deviation from intended interventions, E) bias due to missing data, F) bias in measurement of outcomes, G) bias due to selection of reported result, H) overall risk of bias

Figure 5: Ratio of geometric mean titres and 95% CI comparing one dose to either two or three doses[a]

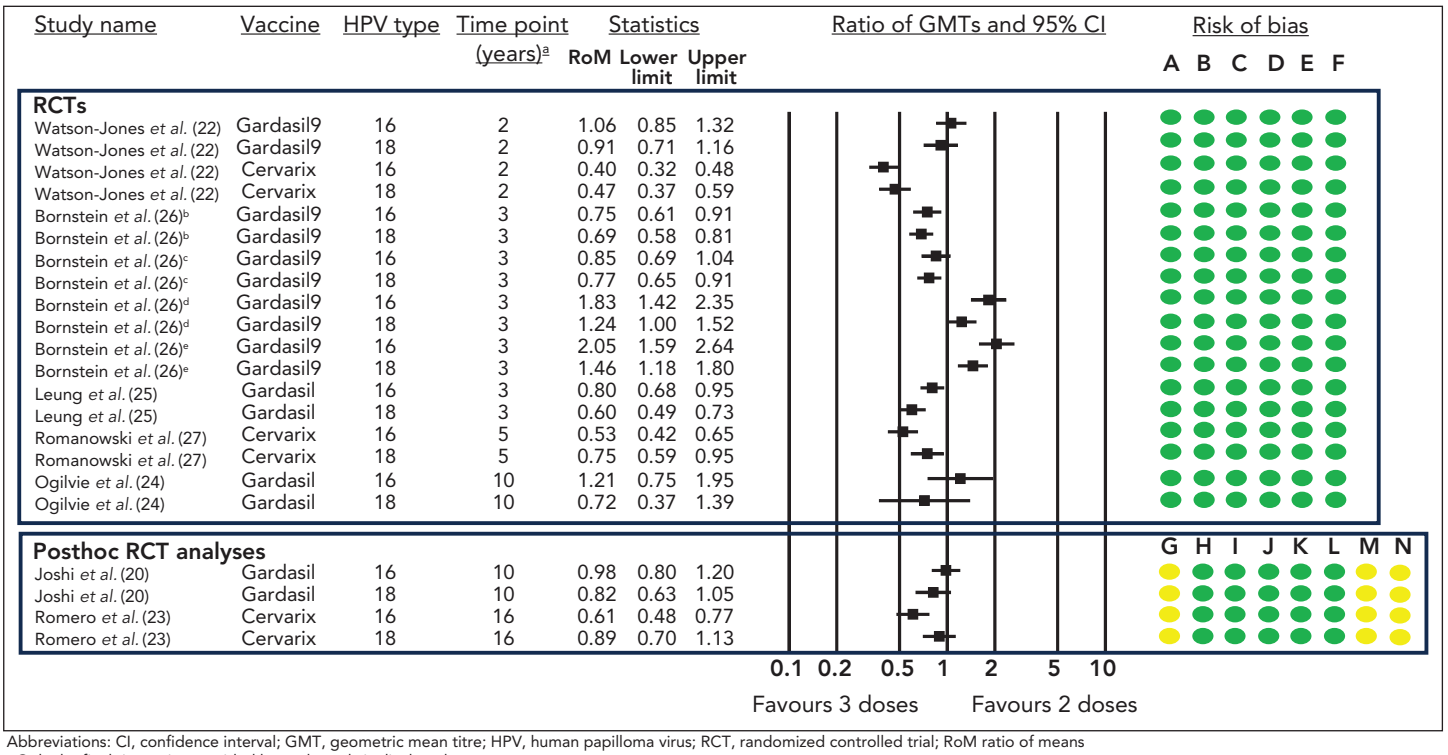


Abbreviations: CI, confidence interval; GMT, geometric mean titre; HPV, human papilloma virus; RCT, randomized controlled trial; RoM, ratio of means

[a] Only the final timepoint provided by each study is displayed

Risk of bias legend: A) risk of bias arising from the randomization process, B) risk of bias due to deviations from the intended interventions, C) risk of bias due to missing outcome data, D) risk of bias in measurement of the outcome, E) risk of bias in selection of the reported result, F) overall risk of bias, G) bias due to confounding, H) bias in selection of participants into the study, I) bias in classification of interventions, J) bias due to deviation from intended interventions, K) bias due to missing data, L) bias in measurement of outcomes, M) bias due to selection of reported result, N) overall risk of bias

Figure 6: Ratio of geometric mean titres and 95% CI comparing two doses to three doses[a,b,c,d,e]



Abbreviations: CI, confidence interval; GMT, geometric mean titre; HPV, human papilloma virus; RCT, randomized controlled trial; RoM ratio of means

[a] Only the final timepoint provided by each study is displayed

[b] Boys, six-month interval

[c] Girls, six-month interval

[d] Boys, 12-month interval

[e] Girls, 12-month interval

Risk of bias legend: A) risk of bias arising from the randomization process, B) risk of bias due to deviations from the intended interventions, C) risk of bias due to missing outcome data, D) risk of bias in measurement of the outcome, E) risk of bias in selection of the reported result, F) overall risk of bias, G) bias due to confounding, H) bias in selection of participants into the study, I) bias in classification of interventions, J) bias due to deviation from intended interventions, K) bias due to missing data, L) bias in measurement of outcomes, M) bias due to selection of reported result, N) overall risk of bias

levels compared to those given three doses within six months, three years after vaccination (26), suggesting the interval between doses may be more important than the number of doses. Lastly, in an RCT of females aged 9–25 years receiving CERVARIX®, HPV16 and HPV18 antibody titres appeared slightly higher after a three-dose schedule compared to a two-dose schedule, regardless of age strata (9–14 and 15–25 years), five years following vaccination. However, no test of non-inferiority was performed (27).

Discussion

The effectiveness/efficacy and immunogenicity of various HPV vaccine schedules were reviewed. Available evidence suggests that single-dose VE against HPV infection may be similar to that of two or three doses. Antibody titres, however, indicate a lower immune response with a single dose compared to two or three doses. Currently, there is no established correlate of protection for HPV, and therefore the clinical relevance of this decreased immune response is unknown. The interpretation of results from other clinical outcomes, such as the risks of CIN and abnormal cytology, remain challenging due to limitations of the included studies. In addition to the currently available evidence outlined above, which includes follow-up for up to 16 years post-immunization depending on the study and clinical protection outcome, longer follow-up data are expected in the coming years from multiple key studies. As trials continue to accrue data, follow-up will remain important as trial participants reach the age of increased baseline risk of cervical abnormalities and associated cancers, as data for these outcomes is currently limited. Two additional RCTs from Costa Rica are underway and are expected to produce estimates of single dose VE in females 12–16 years and 18–30 years of age by 2025 and 2026, respectively (28,29).

Limitations

There are several limitations to the current data. Data are predominately limited to female adolescents and young women, with a primary focus on cervical HPV infection and cervical cancer precursors. However, several additional cancers are attributable to HPV infections (i.e., other anogenital, and head/neck cancers) (2), for which there are currently no data. While there is no clinical trial data on VE of a single vaccine dose in males, several retrospective observational studies include both biological sexes. However, only two studies report results stratified by sex, with neither study reporting a difference in HPV infection risk between dosing schedules in males (30,31). Neither study was eligible for inclusion, however, as both were considered at serious risk of bias. It is possible that different antibody levels or immunologic factors are required for protection in the female versus male genital tract, and for protection against warts and head/neck/anal cancer. Future research on the effect of single dose HPV vaccination and other HPV-related cancers, including trials where clinical outcomes are assessed among male populations, will be important for public health decision-making. Data are also currently lacking on the effect of a one-dose schedule in immunocompromised individuals. Only one observational study that provided data for this group was identified, with no difference in the incidence of abnormal cervical cytology observed between dosing schedules in HIV-positive females. This study was, however, considered at serious risk of bias and therefore not eligible for inclusion (32).

Conclusion

Current clinical data on reduced HPV dosing schedules are promising. Longer-term follow-up of clinical trial participants, as well as monitoring real-world outcomes in countries where the change to single-dose schedules have already taken place, can help better understand the duration of protection against HPV infection conferred from reduced dosing schedules. In addition, when considering population-level programmatic changes, several additional factors will likely require consideration, including impacts of a program change on acceptability and uptake of the HPV vaccine, as well as on health inequities and access to the vaccine.

Authors' statement

JM — Conceptualization, methodology, formal analysis, data curation, writing–original draft
NF — Conceptualization, methodology, formal analysis, data curation, writing–review & editing
MS — Conceptualization, methodology, data curation, writing–review & editing, supervision
VD — Conceptualization, methodology, writing–review & editing, supervision
SA — Conceptualization, methodology, formal analysis, data curation, writing–review & editing
AJ — Conceptualization, methodology, formal analysis, data curation, writing–review & editing
CY — Conceptualization, data curation, writing–review & editing
KG — Conceptualization, data curation, writing–review & editing
KY — Conceptualization, methodology, writing–review & editing, supervision
MT — Conceptualization, methodology, writing–review & editing, supervision

Competing interests

None.

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Healthcare-associated infections and antimicrobial resistance in Canadian acute care hospitals, 2018–2022

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Abstract

Background: Healthcare-associated infections (HAIs) and antimicrobial resistance (AMR) continue to contribute to excess morbidity and mortality among Canadians.

Objective: This report describes epidemiologic and laboratory characteristics and trends of HAIs and AMR from 2018 to 2022 (*Candida auris*, 2012–2022) using surveillance and laboratory data submitted by hospitals to the Canadian Nosocomial Infection Surveillance Program (CNISP) and by provincial and territorial laboratories to the National Microbiology Laboratory.

Methods: Data collected from 88 Canadian sentinel acute care hospitals between January 1, 2018, and December 31, 2022, for *Clostridioides difficile* infections (CDIs), carbapenemase-producing *Enterobacterales* (CPE) infections, methicillin-resistant *Staphylococcus aureus* (MRSA) bloodstream infections (BSIs) and vancomycin-resistant *Enterococcus* (VRE) BSIs. *Candida auris* (*C. auris*) surveillance was initiated in 2019 by CNISP and in 2017 (retrospectively to 2012) by the National Microbiology Laboratory. Trend analysis for case counts, rates, outcomes, molecular characterization and AMR profiles are presented.

Results: From 2018 to 2022, decreased rates per 10,000 patient days were observed for CDIs (7% decrease; 5.42–5.02) and MRSA BSIs (2.9% decrease; 1.04–1.01). Infection rates for VRE BSIs increased by 5.9% (0.34–0.36). Infection rates for CPE remained low but increased by 133% (0.06–0.14). Forty-three *C. auris* isolates were identified in Canada from 2012 to 2022, with the majority in Western and Central Canada (98%).

Conclusion: From 2018 to 2022, the incidence of MRSA BSIs and CDIs decreased and VRE BSI and CPE infections increased in the Canadian acute care hospitals participating in a national sentinel network (CNISP). Few *C. auris* isolates were identified from 2012 to 2022. Reporting standardized surveillance data to inform the application of infection prevention and control practices in acute care hospitals is critical to help decrease the burden of HAIs and AMR in Canada.

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Keywords: healthcare-associated infections, community-associated infections, antimicrobial resistance, surveillance, *Clostridioides difficile* infection, methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus*, carbapenemase-producing *Enterobacterales*, *Escherichia coli*, *Candida auris*, Canadian Nosocomial Infection Surveillance Program

Introduction

Healthcare-associated infections (HAI) represent one of the most common adverse events experienced by patients in acute care settings globally (1). In addition to increasing morbidity and mortality, they are associated with longer lengths of stay (LOS) in hospitals and higher costs of care. The prevalence of HAIs has been estimated to be at 3.2% in the United States (US), 6.5% in Europe and 9.9% in Australia, and is likely two-fold greater in developing countries (1–4). In Europe, the cumulative healthcare burden of six HAIs (urinary tract infection, pneumonia, surgical site infection, *Clostridioides difficile* infections [CDIs], bloodstream infections [BSIs], and neonatal sepsis) was greater than the burden of 32 other communicable diseases combined, including influenza and tuberculosis (5). In Canada, a point prevalence survey conducted in 2017 estimated that the prevalence of patients with at least one HAI was 7.9% (6). Importantly, a large proportion of HAIs are preventable and evidence from the US shows that advancements in care and infection prevention and control can decrease HAI rates over time (2).

Many of the microorganisms that cause HAIs have a propensity for antimicrobial resistance (AMR), and growing rates of resistance threaten to undermine efforts to reduce HAI rates (5). Infection with a resistant organism is associated with an 84.4% increased risk of death and in 2019, bacterial AMR was associated with approximately five million deaths globally (7,8). The global economic costs of AMR are also significant (8). Canadian data show that CDI is associated with a longer length of hospital stay, higher all-cause mortality and an average excess cost of $11,056 per patient (9).The rate of AMR is predicted to reach 40% by 2050. In this situation, it is forecasted that 13,700 Canadians could die each year from resistant infections, and the overall annual impact to Canada's GDP would be $21 billion (10). Inappropriate antimicrobial use during the recent COVID-19 pandemic may have contributed towards an increase in AMR (11). Moreover, emerging resistant pathogens such as *Candida auris* (*C. auris*) have necessitated enhanced surveillance and changes to existing infection prevention and control protocols (12). Coordinated global public health action, surveillance, improved antibiotic stewardship, infection prevention and control and public awareness are crucial to identify patterns of antimicrobial resistance and prevent and control emerging infections.

In Canada, the Public Health Agency of Canada collects national data on various HAIs and AMR through the Canadian Nosocomial Infection Surveillance Program (CNISP). Established in 1994, CNISP is a collaboration between the Public Health Agency of Canada, the Association of Medical Microbiology and Infectious Disease Canada and sentinel hospitals from across Canada. The goal of CNISP is to facilitate and inform the prevention, control and reduction of HAIs and antimicrobial resistant organisms in Canadian acute care hospitals through active surveillance and reporting.

In line with the World Health Organization's core components of infection prevention and control (13), CNISP performs consistent, standardized surveillance to reliably estimate HAI burden, establish benchmark rates for national and international comparison, identify potential risk factors and assess and inform specific interventions to improve patient health outcomes. Data provided by CNISP directly support the collaborative goals outlined in the *Pan-Canadian Action Plan on Antimicrobial Resistance* (14).

In this report, we describe the most recent HAI and AMR surveillance data collected from CNISP participating hospitals between 2018 and 2022. Further, we provide a summary of *C. auris* isolates identified from 2012 to 2022 to describe the epidemiology of this pathogen in Canada.

Methods

Design

The CNISP conducts prospective, sentinel surveillance for HAIs (including antimicrobial resistant organisms) (15).

Case definitions

Standardized case definitions for healthcare-associated (HA) and community-associated (CA) infections were used. Refer to **Appendix A** for full-case definitions.

Data sources

Between January 1, 2018, and December 31, 2022, participating hospitals submitted epidemiologic data and isolates for cases meeting the respective case definitions for CDI, methicillin-resistant *Staphylococcus aureus* (MRSA) BSIs, vancomycin-resistant *Enterococcus* (VRE) BSIs and carbapenemase-producing *Enterobacterales* (CPE) infections. Eligible *C. auris* isolates (infections or colonizations) were identified by provincial and territorial laboratories and participating hospital laboratories between January 1, 2012, and December 31, 2022, while CNISP surveillance for clinical characteristics of *C. auris* began on January 1, 2019. In 2022, 88 hospitals in 10 provinces and one territory participated in HAI surveillance and are further described in **Table 1** and **Appendix B**, **Supplemental Figure S1**. Hospital participation varied by surveillance project and year. In 2022, patient admissions captured in CNISP HAI surveillance were distributed across hospitals categorized as either small (1–200 beds, n=39 sites, 44%), medium (201–499 beds, n=34 sites, 39%) or large (500 or more beds, n=15 sites, 17%) (Table 1).

Table 1: Summary of hospitals participating in the Canadian Nosocomial Infection Surveillance Program, by region, 2022

Details of participating hospitals	Western[a]	Central[b]	Eastern[c]	Northern[d]	Total
Total number of hospitals	29	32	26	1	88
Hospital type					
Adult[e]	12	21	16	0	49
Mixed	13	7	9	1	30
Paediatric	4	4	1	0	9
Hospital size					
Small (1–200 beds)	11	7	20	1	39
Medium (201–499 beds)	10	19	5	0	34
Large (500 or more beds)	8	6	1	0	15
Admissions and discharge					
Total number of beds	10,031	11,772	3,258	25	25,086
Total number of admissions	444,247	518,799	107,324	2,313	1,072,683
Total number of patient days	3,653,051	4,048,979	993,560	7,046	8,702,636

[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
[d] Northern refers to Yukon, Northwest Territories and Nunavut
[e] Eleven hospitals classified as "adult" had a neonatal intensive care unit

Epidemiologic (demographic, clinical and outcomes) and denominator data (patient days and patient admissions) were collected and submitted by participating hospitals through the Canadian Network for Public Health Intelligence, a secure online data platform.

Reviews of standardized protocols and case definitions are conducted annually by established infectious disease expert working groups; training for data submission is provided to participating CNISP hospital staff as required. Data quality for surveillance projects is periodically evaluated; additional details on the methodology have been published previously (16,17).

Laboratory data

All patient-linked laboratory isolates (stool samples for CDI cases) were sent to the Public Health Agency of Canada's National Microbiology Laboratory for molecular characterization and antimicrobial susceptibility testing. Isolates for MRSA BSIs, VRE BSIs, CPE infections, *C. auris* (2019–2022) infections and paediatric CDIs were submitted year-round. Adult CDI isolates were submitted annually during a targeted two-month period (March 1 to April 30).

Statistical analysis

Rates of HAI were calculated by dividing the total number of cases identified in patients admitted to CNISP participating hospitals by the total number of patient admissions (multiplied by 1,000) or patient days (multiplied by 10,000). The HAI rates are reported nationally and by region as shown in Table 1. Sites that were unable to provide case data were excluded from rate calculations and missing denominator data were estimated using their previous years reported data, where applicable. Missing epidemiological and molecular data were excluded from analysis. The Mann-Kendall test was used to test trends. Significance testing was two-tailed and differences were considered significant at $p \leq 0.05$.

Where available, attributable and all-cause mortality were reported for HAIs. Attributable mortality rate was defined as the number of deaths per 100 HAI cases where the HAI was the direct cause of death or contributed to death within 30 days of positive culture or histopathology specimen, as determined by physician review. All-cause mortality rate was defined as the number of deaths per 100 HAI cases 30 days following positive culture.

Results

Clostridioides difficile infection

Between 2018 and 2022, overall CDI rates decreased by 7% (5.42 to 5.02 infections per 10,000 patient days); however, this trend was not significant (p=0.327) (**Table 2**). Stratified by source of infection, the incidence of HA-CDI showed a non-significant decrease of 7.3% from 3.95 to 3.66 infections per 10,000 patient days (p=0.327) (Appendix B, **Table S1.1**). Community-associated-CDI rates remained stable when comparing 2018 to 2022 rates per 1,000 patient admissions (Appendix B, Table S1.1).

Table 2: *Clostridioides difficile* infection data, Canada, 2018–2022[a]

C. difficile infection data	Year									
	2018		2019		2020		2021		2022	
Number of infections and incidence rates										
Number of *C. difficile* infection cases	3,850		3,600		3,654		3,643		3,846	
Rate per 1,000 patient admissions	4.19		3.73		4.14		3.99		4.18	
Rate per 10,000 patient days	5.42		4.90		5.35		5.06		5.02	
Number of reporting hospitals	68		73		82		80		72	
Attributable mortality rate per 100 cases (%)[b]	1.3		2.3		2.7		2.4		1.1	
Antimicrobial resistance[c]	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Clindamycin	307	48.7	221	38.9	62	17.1	67	12.4	94	23.6
Moxifloxacin	70	11.1	66	11.6	24	6.6	49	9	29	7.3
Rifampin	10	1.6	6	1.1	3	0.8	9	1.7	4	1.0
Metronidazole	1	0.2	0	0	0	0	0	0	0	0
Total number of isolates tested[d]	630	N/A	568	N/A	363	N/A	542	N/A	399	N/A

Abbreviations: *C. difficile*, *Clostridioides difficile*; N/A, not applicable
[a] All *C. difficile* isolates from 2017 to 2021 submitted to the National Microbiology Laboratory were susceptible to tigecycline and vancomycin
[b] Deaths where *C. difficile* infection was the direct cause of death or contributed to death 30 days after the date of the first positive lab specimen or positive histopathology specimen. Mortality data are collected during the two-month period (March and April of each year) for adults (aged 18 years and older) and year-round for children (aged one year to younger than 18 years old). Among paediatric patients, there was no death attributable to healthcare-associated *C. difficile* infection
[c] *C. difficile* infection isolates are collected for resistance testing during the two-month period (March and April of each year) for adults (aged 18 years and older) and year-round for children (aged one year to younger than 18 years old) from admitted patients only
[d] Total number reflects the number of isolates tested for each of the antibiotics listed above

Regionally, HA-CDI rates have decreased across all regions except the East where rates have increased by 11.7% (p=0.33), but this result is not significant. For CA-CDI, rates remain highest overall in the Central region from 2018 and 2022 (range: 1.39–1.66), followed by West and East. Overall CDI attributable mortality remained low and fluctuated (range: 1.1–2.7 deaths per 100 cases) from 2018 to 2022 (p=1.00) (Appendix B, Table S1.1).

From 2018 to 2022, 35.9% (n=897/2,501) of CDI isolates were resistant to one or more tested antimicrobials. The proportion of *C. difficile* isolates resistant to moxifloxacin decreased by 3.8% between 2018 (11.1%, n=70/630) and 2022 (7.3%, n=29/399) (Table 2). Since 2018, moxifloxacin resistance decreased non-significantly among HA-CDI isolates (4.7%, p=0.142) while a smaller non-significant decrease was observed among CA-CDI (1.0%, p=0.142) (Appendix B, **Table S1.2**). All tested *C. difficile* isolates were susceptible to vancomycin and tigecycline. From 2018 to 2022, the prevalence of ribotype RT027 associated with NAP1 decreased by 4.8% from 8.4% to 3.6% and 1.2% from 3.2% to 2.0%, respectively (Appendix B, **Table S1.3**).

Methicillin-resistant *Staphylococcus aureus* bloodstream infections

Between 2018 and 2022, overall MRSA BSI rates decreased by 2.9% (1.04 to 1.01 infections per 10,000 patient days), with a peak rate observed in 2020 (1.16 infections per 10,000 patient days) (**Table 3**). Stratified by case type, a continued steady increase of 12% (0.5 to 0.56 infections per 10,000 patient days, p=0.05) was observed from 2018 to 2022 in CA-MRSA BSI rates. The HA-MRSA BSI rates remained stable over time (range: 0.42–0.50 infections per 10,000 patient days) (Appendix B, **Table S2.1**).

In 2022, HA and CA-MRSA BSI rates were highest in Western Canada (0.48 and 0.71 infections per 10,000 patient days, respectively) (Appendix B, Table S2.1). Among hospital types, HA and CA-MRSA BSI rates have generally remained highest among adult and mixed hospitals. Stratified by hospital size, rates of HA-MRSA BSI were highest among medium (201–499 beds) and large size hospitals (500 or more beds) while CA-MRSA BSI rates have been highest in medium size hospitals since 2019 (Appendix B, Table S2.1). All-cause mortality remained relatively stable from 2018 to 2022 (range: 16.3%–19.8%) (Table 3). In 2022, 30-day all-cause mortality was higher among those with HA-MRSA (23.6%) compared to those with CA-MRSA (17.5%) (p=0.034).

Clindamycin resistance among MRSA isolates decreased significantly by 16.4% between 2018 and 2022 (2018: 41.1%, n=287/699; 2022: 24.7%, n=147/595) (p=0.0143) (Table 3). Since 2018, the proportion of MRSA isolates with erythromycin and ciprofloxacin resistance decreased, yet remained high (67.7%, n=403/595 and 65.4%, n=389/595 in 2022, respectively) in relation to other antibiotics tested. All submitted MRSA BSI isolates from 2018 to 2022 were susceptible to linezolid, nitrofurantoin and vancomycin.

Comparing HA-MRSA isolates to CA-MRSA isolates, clindamycin resistance was consistently higher among HA-MRSA isolates each year from 2018 (50.0%, n=166/332 vs. 33.0%, n=110/333) to 2022 (28.8%, n=68/236 vs. 21.9%, n=73/334) (Appendix B, **Table S2.2**). There were no other notable differences in antibiotic resistance patterns by MRSA BSI case type.

Table 3: Methicillin-resistant *Staphylococcus aureus* bloodstream infections data, Canada, 2018–2022

MRSA BSI data	Year									
	2018		2019		2020		2021		2022	
Number of infections and incidence rates										
Number of MRSA BSIs	764		881		868		874		820	
Rate per 1,000 patient admissions	0.77		0.85		0.88		0.86		0.83	
Rate per 10,000 patient days	1.04		1.14		1.16		1.13		1.01	
Number of reporting hospitals	62		69		81		80		78	
All-cause mortality rate[a]										
Number of deaths	144		144		152		165		162	
All-cause mortality rate per 100 cases	18.8		16.3		17.5		18.9		19.8	
Antimicrobial resistance[b]	n	%	n	%	n	%	n	%	n	%
Ciprofloxacin	502	71.8	561	70.5	460	65.6	488	65.9	389	65.4
Clindamycin	287	41.1	297	37.3	234	33.4	221	29.8	147	24.7
Erythromycin	527	75.4	603	75.8	507	72.3	508	68.6	403	67.7
Gentamicin	28	4.0	35	4.4	22	3.1	36	4.9	20	3.4
Rifampin	6	0.9	7	0.9	6	0.9	9	1.2	5	0.8
Trimethoprim/sulfamethoxazole	12	1.7	15	1.9	16	2.3	32	4.3	35	5.9
Tetracycline	49	7.0	62	7.8	46	6.6	64	8.6	49	8.2
Tigecycline	0	0	0	0	1	0.1	6	0.8	5	0.8
Total number of isolates tested[c,d]	699	N/A	796	N/A	701	N/A	741	N/A	595	N/A

Abbreviations: MRSA BSI, methicillin-resistant *Staphylococcus aureus* bloodstream infection; N/A, not applicable
[a] Based on the number of cases with associated 30-day outcome data
[b] All MRSA isolates from 2018 to 2022 submitted to the National Microbiology Laboratory were susceptible to linezolid, nitrofurantoin and vancomycin
[c] In some years, the number of isolates tested for resistance varied by antibiotic
[d] Total number reflects the number of isolates tested for each of the antibiotics listed above

Between 2018 and 2022, the proportion of spa types identified as t002 (CMRSA2) and most commonly associated with HA-MRSA continued to decrease from 25.3% of all HA-MRSA isolates in 2018 to 6.4% in 2022. The proportion of spa types identified as t008 (CMRSA10) and most commonly associated with CA-MRSA continued to increase and account for the largest proportion of CA-MRSA isolates from 45.0% in 2018 to 49.1% in 2022 (Appendix B, **Table S2.3**).

Vancomycin-resistant *Enterococcus* bloodstream infections

From 2018 to 2022, VRE BSI rates increased by 5.9%, from 0.34 to 0.36 infections per 10,000 patient days (**Table 4**). Regionally, VRE BSI rates were highest in Western and Central Canada (0.52 and 0.31 infections per 10,000 patient days in 2022, respectively) with few VRE BSIs reported in Eastern Canada (range: 0–0.02 infections per 10,000 patient days) (Appendix B, **Table S3.1**). Stratified by hospital type, VRE BSI rates remained highest in adult hospitals from 2018 to 2022 (range: 0.38–0.47 infections per 10,000 patient days). From 2018 to 2022, VRE BSI rates in paediatric hospitals were low (range: 0–0.25 infections per 10,000 patient days). In 2022, VRE BSI rates were 0.47 infections per 10,000 patient days in large hospitals (500 or more beds), 0.32 infections per 10,000 patient days in medium hospitals (201–499 beds) and 0.17 infections per 10,000 patient days in small hospitals (1–200 beds).

Vancomycin-resistant *Enterococcus* BSIs were predominantly HA, as 90.1% (n=1,135/1,260) of VRE BSIs reported from 2018 to 2022 were acquired in a healthcare facility. All-cause mortality remained high (34%) from 2018 to 2022. The incidence rates by region, hospital type and hospital size are presented in Appendix B, **Table S3.2**.

Between 2018 to 2022, high-level gentamicin resistance among VRE BSI isolates (*Enterococcus faecium*) decreased from 43.2% to 18.8% (p=0.01) (Table 4). Daptomycin non-susceptibility, first identified in 2016, decreased from 6.0% (n=11 isolates) in 2018 to 2.0% (n=4 isolates) in 2022 (p=0.0143). Since 2018, the majority (99.3%) of VRE BSI isolates were identified as *E. faecium*; however, three *Enterococcus faecalis* (*E. faecalis*) were identified in 2018 and one in each of 2020, 2021 and 2022 (Appendix B, **Table S3.3**). Among *E. faecium* isolates, the proportion identified as sequence type (ST)1478 was highest in 2018 (37.2%, n=67/180) and decreased to 8.7% (n=17/196) in 2022 (p=0.05) (Appendix B, **Table S3.4**). Furthermore, the proportion of ST17 isolates significantly increased from 2018 (5.0% n=9/180) to 2022 (46.9%, n=92/196) (p=0.05) (Appendix B, Table S3.4).

Table 4: Vancomycin-resistant *Enterococcus faecium* bloodstream infections data, 2018–2022

VRE BSI data	Year									
	2018		2019		2020		2021		2022	
Vancomycin-resistant *Enterococcus* bloodstream infections data										
Number of VRE BSIs	242		241		224		251		302	
Rate per 1,000 patient admissions	0.25		0.23		0.23		0.25		0.29	
Rate per 10,000 patient days	0.34		0.30		0.30		0.32		0.36	
Number of reporting hospitals	61		70		81		80		80	
Antimicrobial resistance of *Enterococcus faecium* isolates	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Ampicillin	181	98.9	173	100	130	97.0	164	98.8	193	98.0
Chloramphenicol	5	2.7	30	17.3	28	20.9	52	31.3	32	16.2
Ciprofloxacin	183	100	173	100	131	97.8	164	98.8	196	99.5
Daptomycin[a]	11	6.0	7	4.0	4	3.0	4	2.4	4	2.0
Erythromycin	175	95.6	166	96.0	127	94.8	157	94.6	192	97.5
High-level gentamicin	79	43.2	57	32.9	35	26.1	32	19.3	37	18.8
Levofloxacin	181	98.9	173	100	130	97.0	164	98.8	195	99.0
Linezolid	2	1.1	3	1.7	1	0.7	3	1.8	6	3.0
Nitrofurantoin	54	29.5	66	38.2	54	40.3	129	77.7	138	70.1
Penicillin	181	98.9	173	100	131	97.8	164	98.8	194	98.5
Quinupristin/dalfopristin	21	11.5	18	10.4	8	6.0	8	4.8	15	7.6
Rifampicin	163	89.1	160	92.5	114	85.1	153	92.2	182	92.4
High-level streptomycin	62	33.9	42	24.3	29	21.6	48	28.9	48	24.4
Tetracycline	110	60.1	119	68.8	88	65.7	132	79.5	175	88.8
Tigecycline	1	0.5	0	0.0	0	0.0	0	0.0	1	0.5
Vancomycin	178	97.3	170	98.3	129	96.3	161	97.0	196	99.5
Total number of isolates tested[b]	183	N/A	173	N/A	134	N/A	166	N/A	197	N/A

Abbreviations: N/A, not applicable; VRE BSI, vancomycin-resistant *Enterococcus* bloodstream infection
[a] Clinical and Laboratory Standards Institute (CLSI) resistance breakpoints came into effect in 2019 and was applied to all years
[b] Total number reflects the number of isolates tested for each of the antibiotics listed above
Note: Aggregate mortality data reported in-text due to fluctuations in the small numbers of VRE BSI deaths reported each year

Carbapenemase-producing *Enterobacterales*

From 2018 to 2022, CPE infection rates have remained low, although there has been a non-significant increase of 133% in the rates over this period (0.06 to 0.14 infections per 10,000 patient days, p=0.07) (**Table 5**).

From 2018 to 2022, the majority of CPE infections (98.0%) were identified in Central (52.1%, n=162/311) and Western Canada (46.0%, n=143/311) while few infections were identified in the East (1.9%, n=6/311) (Appendix B, **Table S4.1**). From 2018 to 2022, large hospitals (500 or more beds) generally reported the highest rates of CPE infections (0.07–0.17 infections per 10,000 patient days). Thirty days all-cause mortality was 16.3% (n=46/282). During this period, 22.8% (n=68/298) of CPE-infected patients reported travel outside of Canada and of those, 67.6% (n=46/68) received medical care while abroad.

The predominant carbapenemases identified in Canada were *Klebsiella pneumoniae* (*K. pneumoniae*) carbapenemase, New Delhi metallo-β-lactamase and Oxacillinase-48 (OXA-48), accounting for 86.0% to 96.0% of identified carbapenemases from 2018 to 2022. Among submitted isolates, *Escherichia coli* remains the most commonly identified carbapenemase-producing pathogen from 2018 to 2022 (range: 23.0%–34.1%) (Appendix B, **Table S4.2**). From 2018 to 2022, carbapenemase-producing pathogens identified as *K. pneumoniae* decreased by 7.0% while *Citrobacter freundii* increased by 6.2%. (Appendix B, Table S4.2). Among the predominant cabapenemases, from 2019 to 2022, the prevalence of meropenem resistance among *K. pneumoniae* carbapenemase isolates decreased by 13.3%. Among New Delhi metallo-β-lactamase isolates, the prevalence of aztreonam resistance decreased by 13%, while amikacin resistance increased by 10.8%. Among OXA-48 isolates, the largest decreases in resistance were seen in ceftriaxone, tobramycin and trimethorpim/sulfamethoxazole (26.6%, 22.5% and 22.3%, respectively) (Appendix B, **Table S4.3 to S4.5**).

Candida auris

A total of 43 isolates (colonizations and infections) have been reported to National Microbiology Laboratory from 2012 to 2022, of which eight had detailed CNISP patient questionnaires completed. Twenty-one cases were from Western Canada,

Table 5: Carbapenemase-producing *Enterobacterales* data, Canada, 2018–2022[a,b]

CPE data	Year									
	2018		2019		2020		2021		2022	
Number of infections and incidence rates										
Number of CPE infections	36		54		41		73		107	
Infection rate per 1,000 patient admissions	0.05		0.06		0.05		0.08		0.11	
Infection rate per 10,000 patient days	0.06		0.08		0.06		0.11		0.14	
Number of reporting hospitals	50		60		72		73		77	
Carbapenemases identified	n	%	n	%	n	%	n	%	n	%
KPC	115	52.3	131	45.3	98	40.0	142	47.4	143	51.4
NDM	55	25.0	104	32.1	80	32.7	80	26.3	60	21.6
OXA-48	30	13.6	46	14.1	48	19.6	47	15.5	64	23.0
SME[c]	4	1.8	1	0.3	2	0.8	1	0.3	0	0.0
NDM/OXA-48	6	2.7	16	4.9	9	3.7	12	3.9	5	1.8
GES	1	0.5	1	0.3	0	0.0	1	0.3	0	0.0
IMP	3	1.4	1	0.3	1	0.4	1	0.3	2	0.7
NMC	2	0.9	4	1.2	7	2.9	15	4.9	2	0.7
VIM	2	0.9	3	0.9	0	0.0	1	0.3	2	0.7
Other	2	0.9	2	0.6	0	0.0	2	0.7	0	0.0
Total number of isolates tested[d]	220	N/A	327	N/A	245	N/A	304	N/A	278	N/A

Abbreviations: CPE, carbapenemase-producing *Enterobacterales*; GES, Guiana extended-spectrum β-lactamase; IMP, active-on-imipenem; KPC, *Klebsiella pneumoniae* carbapenemase; NDM, New Delhi metallo-β-lactamase; NMC, not metalloenzyme carbapenemase; N/A, not applicable; OXA-48, Oxacillinase-48; SME, *Serratia marcescens* enzymes; VIM, Verona integron-encoded metallo-β-lactamase

[a] Includes data for all CPE isolates submitted

[b] *Enterobacter cloacae* complex includes *Enterobacter cloacae* and other *Enterobacter* spp.

[c] Only found in *Serratia marcescens*

[d] Some isolates contain multiple carbapenemases therefore the total number of isolates tested and the number of carbapenemases indicated may not match. *Acinetobacter baumanii* were not included in this table

Note: Aggregate mortality data reported in-text due to fluctuations in the small numbers of CPE deaths reported each year

21 cases were from Central Canada and one case was reported from Eastern Canada. Approximately, one third of isolates were resistant to amphotericin B (34.9%, n=15/43) and two thirds were resistant to fluconazole (67.4%, n=29/43). One third of isolates were multidrug-resistant (resistant to two classes of antifungals) (34.9%, n=15/43). Of the 13 patients with travel information, four reported no travel (31%) while nine reported international travel (69%). Of the nine patients with reported history of travel, eight had received health care abroad (89%). Of the eight patients who received travel abroad, six had known carbapenemase-producing organism status and three tested positive.

Discussion

Canadian Nosocomial Infection Surveillance Program surveillance data have shown that between 2018 and 2022, infection rates in Canada have decreased for CDI and MRSA BSI (7.0% and 2.9%, respectively). Rates have increased for VRE BSI and CPE infection (5.9% and 133%, respectively). A total of 43 *C. auris* isolates were identified from 2012 to 2022.

Declining CDI rate trends observed in the CNISP network follow a parallel trend observed globally; however, rates have been reported to be higher in North America (18,19). German hospitals have seen an approximate 50% decrease in CDI cases from 2015 to 2021 (20). Enhanced infection control practices, antimicrobial stewardship measures and improved surveillance and detection methods may have contributed to the overall decline seen in CDI rates (19). Additionally, CA-CDI patients with mild to moderate symptoms might not have any interactions with the healthcare system, resulting in underestimation of the true burden of CA-CDI (19).

In a representative sample of Canadian acute care hospitals, from 2018 to 2022, a 3.8% decrease in moxifloxacin resistance in both HA and CA-CDI populations is concordant with an overall decrease in the prevalence of RT027. Furthermore, moxifloxacin resistance remained lower (7.3% in 2022) than previously published weighted pooled resistance data for North America (44.0%) and Asia (33.0%) (21,22). The decline in RT027 prevalence from 2018 to 2022 may also have influenced the decline in CDI rates among CNISP hospitals as this ribotype has been associated with increased virulence and fluoroquinolone resistance (23). Additionally, the emergence of RT106 found worldwide and most predominantly in the US presents more fluoroquinolone resistance and higher recurrence rates. The potential emergence of resistant ribotypes warrants further surveillance, monitoring and investigation (24,25).

From 2018 to 2022, MRSA BSI rates decreased overall by 2.9% in the CNISP network. Although for three years, from 2019 to 2021, rates peaked at 1.13–1.16 infections per 10,000 patient days. Methicillin-resistant *Staphylococcus aureus* BSI is associated with increased morbidity and mortality, increased length of hospital stays and increased costs among admitted patients (26–29). The 16.4% decrease in clindamycin resistance among MRSA BSI isolates from 2018 to 2022 was likely associated with the decrease in the proportion of spa type t002 (CMRSA2 epidemic type) identified among tested isolates (30). The HA-MRSA BSI rates observed in the CNISP network from 2018 to 2022 (range: 0.42–0.50 infections per 10,000 patient days) were lower compared to those reported in Australian public hospitals from 2017 to 2020 (range: 0.71–0.76 infections per 10,000 patient days) (31).

The continued increase in the rate of patients hospitalized with CA-MRSA BSI observed in CNISP data from 2018 to 2022 suggests a growing CA-MRSA reservoir, both in Canada and globally (32,33). However, it is promising to see that over the last three years, from 2020 to 2022, CA-MRSA rates have been declining. Nonetheless, strategies to reduce or prevent MRSA infections in the community are still needed, especially in populations with increased risk of contracting CA-MRSA, such as children, athletes, incarcerated populations, seniors with comorbidities and people who inject drugs (34,35). Increasing injection drug use may indicate an emerging at-risk population for CA-MRSA, and as such, screening and eradication of the carriage of MRSA, may be effective in reducing the burden of MRSA BSI overall (34–36).

Vancomycin resistance related to VRE BSI has been shown to be a principal predictor of mortality and is associated with increased hospital burden (37–39). The VRE BSI rate observed in the CNISP network was highest in 2022 (0.36 infections per 10,000 patient days). The ST17 sequence type has contributed to the increased burden of VRE BSI in CNISP-participating hospitals by emerging as the predominant clone, overtaking ST1478. An increase in ST80 has also been seen in CNISP data, increasing from 11.7% in 2018 to 30.6% in 2022. The increase in ST80 seen in Canada is consistent with what has been observed in Sweden over the last three years, resulting in vanA-type and vanB-type outbreaks (40). The VRE BSI trends are further impacted by the number of high-risk patients admitted to hospital (e.g., bone marrow transplants, solid organ transplants, cancer patients, etc.) (41). Although there is a lack of recent data on VRE BSI rates in comparable jurisdictions, there have been increasing trends noted in Europe (42–45), which may be associated, in part, with the introduction and spread of new clones and gaps in infection prevention practices (44–46).

Carbapenemase-producing *Enterobacterales* infections are a significant threat to public health as they are becoming increasingly prevalent in healthcare environments worldwide (47). Active infection with CPE carries a high mortality rate, with the bacteria being resistant to many antibiotics, limiting treatment options for these patients (5,48–52). The Centers for Disease Control and Prevention and the World Health Organization have classified CPE as one of the most urgent antimicrobial-resistance threats (52,53). While the number of CPE infections increased from 2018 to 2022 in the CNISP network, incidence remained low (54). Data on the incidence of CPE infections in other countries, such as the United Kingdom, have also shown an increasing incidence of CPE infections (54,55). Similarly, the number of CPE isolates identified through laboratory surveillance associated with CPE infections has increased in Switzerland from 2013 to 2018 (56). More recently, a shift in the acquisition source of CPE has been observed within the CNISP network. Previously, CPE infections were mostly associated with international travel, but have recently become acquired domestically (85.3%) from 2020 to 2022. As a result, strict implementation of infection control measures, including screening in patients with a previous hospital admission domestically and abroad, are useful to reduce the transmission of CPE in Canadian acute care hospitals.

Candida auris is an emerging multi-drug resistant fungus that can cause HA invasive infections and outbreaks (57). It has been detected across multiple countries and continents including Canada, since its first detection in 2009 (58–61). *Candida auris* has been associated with outbreaks in healthcare settings in many countries, including Canada and the US, although outbreaks in Canada to date have been limited with few cases (57). Reported crude mortality for *C. auris* ranges widely from 15%–60% but is generally similar to other *Candida* species (57–63). Though still relatively rare in Canada, the US reported over 2,000 clinical cases and over 5,000 screening cases in 2022 (64). A survey examining *C. auris* preparedness within CNISP hospitals in 2018 found that most hospitals did not yet have laboratory protocols or infection prevention and control policies in place for detecting and controlling *C. auris* (65). The identification of *C. auris* in routine microbiology laboratories requires identification of *Candida* to the species level, which may not be routinely performed for isolates from non-sterile sites. Treatment options are limited for patients as one third of identified *C. auris* isolates in Canada were multidrug-resistant and additional resistance can develop during antifungal therapy (66). Therefore, rapid identification, screening for colonization in at-risk patients and strict implementation of infection prevention and control measures are required to reduce the transmission of *C. auris* in Canadian healthcare settings. Continued reporting on *C. auris* in Canada is important to assess and monitor the risk of this pathogen, in addition to identifying epidemiological and microbiological trends (66).

The COVID-19 pandemic has had a varied effect on the rates of HAIs in Canada and in the US (67,68). When looking at HAI rates before and during the COVID-19 pandemic, the data showed an immediate increase in HA rates of CDI while MRSA BSI, CPE infection and VRE BSI rates immediately decreased; however, COVID-19 pandemic status was not associated with lasting impacts on monthly rate trends in these infections (69).

Pandemic-related improvements in hand hygiene, personal protective equipment practices, environmental cleaning, screening and infection control practices may have contributed to the decreases in rates observed over the reporting period (70).

Strengths and limitations

The main strength of CNISP is the collection of standardized and detailed epidemiological and laboratory-linked data from 88 sentinel hospitals across Canada for the purpose of providing national HAI and AMR trends for benchmarking and to inform hospital infection prevention and control practices. It is important to note that data in this report include those from the early years of the COVID-19 pandemic; therefore, rates of HAIs and AMR in 2020 and 2021 may be impacted by changes in national, regional and municipal hospital-based infection prevention and control measures.

Epidemiological data collected by CNISP were limited to information available in patient charts. Hospital staff turnover may affect the consistent application of CNISP definitions when reviewing medical charts; however, these data were collected by experienced and trained infection prevention and control staff who receive periodic training with respect to CNISP methods and definitions. Furthermore, data quality assessments were conducted to maintain and improve data quality. These data may be subject to potential selection bias due to the exclusion of sites with missing or incomplete data throughout the study period. A limitation of *C. auris* surveillance is that detailed epidemiologic data are only available on patients identified at CNISP participating hospitals. From 2018 to 2022, CNISP coverage of Canadian acute care beds has increased from 32% to 35%, including increased representativeness in northern, community, rural and Indigenous populations.

Next steps

Recruitment of rural and remote Canadian acute care hospitals to the CNISP network is an ongoing effort to improve the quality and representativeness of Canadian HAI surveillance data. Furthermore, the enhanced hospital screening practices survey is conducted annually to better understand and contextualize changes in HAI rates in the CNISP network. In recent years, CNISP has implemented surveillance for new and emerging pathogens, including *C. auris* and COVID-19. Studies are ongoing to assess the impact of the COVID-19 pandemic on HAI rates and AMR. The CNISP has recently made HAI and antibiotic-resistant organism rates publicly available in a dashboard format using Canada's Health Infobase (71). Lastly, CNISP is also looking to study the feasibility of collecting data in the long-term care sector in Canada to examine status and scope of HAI/antibiotic-resistant organism surveillance, to better understand the burden of HAIs among this at-risk population. To further improve representativeness and generalizability of national HAI benchmark rates, CNISP has launched a simplified dataset accessible to all acute care hospitals across Canada to collect and visualize annual HAI rate data.

Conclusion

Surveillance findings from a national sentinel network of Canadian acute care hospitals indicate that rates of MRSA BSI and CDI have decreased from 2018 to 2022, while rates of VRE BSI and CPE infections have increased. Few cases of *C. auris* were detected in Canada from 2012 to 2022. Consistent and standardized surveillance of epidemiologic and laboratory HAI data are essential to providing hospital practitioners with benchmark rates and informing infection prevention and control and antimicrobial stewardship policies to help reduce the burden of HAI and the impact of AMR in Canadian acute care hospitals.

Authors' statement

Canadian Nosocomial Infection Surveillance Program hospitals provided expertise in the development of protocols in addition to the collection and submission of epidemiological data and lab isolates. The National Microbiology Laboratory completed the laboratory analyses and contributed to the interpretation and revision of the paper. Epidemiologists from Public Health Agency of Canada were responsible for the conception, analysis, interpretation, drafting and revision of the article.

Competing interests

None.

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Appendix A: Surveillance case definitions and eligibility criteria, 2022

Clostridioides difficile infection

A "primary" episode of *Clostridioides difficile* infection (CDI) is defined either as the first episode of CDI ever experienced by the patient or a new episode of CDI that occurs greater than eight weeks after the diagnosis of a previous episode in the same patient.

A patient is identified as having CDI if:

- The patient has diarrhea or fever, abdominal pain and/or ileus AND a laboratory confirmation of a positive toxin assay or positive polymerase chain reaction (PCR) test for *C. difficile* (without reasonable evidence of another cause of diarrhea)

OR

- The patient has a diagnosis of pseudomembranes on sigmoidoscopy or colonoscopy (or after colectomy) or histological/pathological diagnosis of CDI

OR

- The patient is diagnosed with toxic megacolon (in adult patients only)

Diarrhea is defined as one of the following:

- More watery/unformed stools in a 36-hour period

OR

- More watery/unformed stools in a 24-hour period and this is new or unusual for the patient (in adult patients only)

Exclusion:

- Any patients younger than one year
- Any pediatric patients (aged one year to younger than 18 years) with alternate cause of diarrhea found (i.e., rotavirus, norovirus, enema or medication, etc.) are excluded even if *C. difficile* diagnostic test result is positive

***Clostridioides difficile* infection case classification:**

Once a patient has been identified with CDI, the infection will be classified further based on the following criteria and the best clinical judgment of the healthcare and/or infection prevention and control practitioner.

Healthcare-associated (acquired in your facility) CDI case definition:

- Related to the current hospitalization:
  - The patient's CDI symptoms occur in your healthcare facility three or more days (or 72 hours or longer) after admission
- Related to a previous hospitalization:
  - Inpatient: the patient's CDI symptoms occur less than three days after the current admission (or fewer than 72 hours) AND the patient had been previously hospitalized at your healthcare facility and discharged within the previous four weeks
  - Outpatient: the patient presents with CDI symptoms at your emergency room (ER) or outpatient location AND the patient had been previously hospitalized at your healthcare facility and discharged within the previous four weeks
- Related to a previous healthcare exposure at your facility:
  - Inpatient: the patient's CDI symptoms occur less than three days after the current admission (or fewer than 72 hours) AND the patient had a previous healthcare exposure at your facility within the previous four weeks
  - Outpatient: the patient presents with CDI symptoms at your ER or outpatient location AND the patient had a previous healthcare exposure at your facility within the previous four weeks

Healthcare-associated (acquired in any other healthcare facility) CDI case definition:

- Related to a previous hospitalization at any other healthcare facility:
  - Inpatient: the patient's CDI symptoms occur less than three days after the current admission (or fewer than 72 hours) AND the patient is known to have been previously hospitalized at any other healthcare facility and discharged/transferred within the previous four weeks
  - Outpatient: the patient presents with of CDI symptoms at your ER or outpatient location AND the patient is known to have been previously hospitalized at any other healthcare facility and discharged/transferred within the previous four weeks
- Related to a previous healthcare exposure at any other healthcare facility
  - Inpatient: the patient's CDI symptoms occur less than three days after the current admission (or fewer than 72 hours) AND the patient is known to have had a previous healthcare exposure at any other healthcare facility within the previous four weeks
  - Outpatient: the patient presents with CDI symptoms at your ER or outpatient location AND the patient is known to have had a previous healthcare exposure at any other healthcare facility within the previous four weeks

Healthcare-associated CDI but unable to determine which facility:

The patient with CDI DOES meet both definitions of healthcare-associated (acquired in your facility) and healthcare-associated (acquired in any other healthcare facility) CDI, but unable to determine to which facility the case is primarily attributable to.

Community-associated CDI case definition:

- Inpatient: the patient's CDI symptoms occur less than three days (or fewer than 72 hours) after admission, with no history of hospitalization or any other healthcare exposure within the previous 12 weeks
- Outpatient: the patient presents with CDI symptoms at your ER or outpatient location with no history of hospitalization or any other healthcare exposure within the previous 12 weeks

Indeterminate CDI case definition:

The patient with CDI does NOT meet any of the definitions listed above for healthcare-associated or community-associated CDI. The symptom onset was more than four weeks but fewer than 12 weeks after the patient was discharged from any healthcare facility or after the patient had any other healthcare exposure.

Methicillin-resistant *Staphylococcus aureus* (MRSA) infection

MRSA bloodstream infection (BSI) case definition:

- Isolation of *Staphylococcus aureus* from blood

AND

- Patient must be admitted to the hospital

AND

- Is a "newly identified *S. aureus* infection" at a Canadian Nosocomial Infection Surveillance Program (CNISP) hospital at the time of hospital admission or identified during hospitalization

Infection inclusion criteria:

- Methicillin-susceptible *Staphylococcus aureus* (MSSA) or MRSA BSIs identified for the first time during this current hospital admission
- MSSA or MRSA BSIs that have already been identified at your site or another CNISP site but are **new** infections

Criteria to determine NEW MSSA or MRSA BSI:

- Once the patient has been identified with a MSSA or MRSA BSI, they will be classified as a new MSSA or MRSA if they meet the following criteria: more than 14 days since previously treated MSSA or MRSA BSI and, in the judgment of infection control physicians and practitioners, represents a new infection

Infection exclusion criteria:

- Emergency, clinic, or other outpatient cases who are **NOT admitted** to the hospital

Healthcare-associated (HA) case definition:

Healthcare-associated is defined as an inpatient who meets the following criteria and in accordance with the best clinical judgment of the healthcare and/or infection prevention and control practitioner:

- Patient is on or beyond calendar day 3 of their hospitalization (calendar day 1 is the day of hospital admission)

OR

- Has been hospitalized in your facility in the last 7 days or up to 90 days depending on the source of the infection

OR

- Has had a healthcare exposure at your facility that would have resulted in this bacteremia (using best clinical judgment)

OR

- Any patient who has a bacteremia not acquired at your facility that is thought to be associated with any other healthcare exposure (e.g., another acute-care facility, long-term care, rehabilitation facility, clinic or exposure to a medical device)

Healthcare-associated (HA) case definition (newborn):

- The newborn is on or beyond calendar day 3 of their hospitalization (calendar day 1 is the day of hospital admission)
- The mother was **NOT** known to have MRSA on admission and there is no epidemiological reason to suspect that the mother was colonized prior to admission, even if the newborn is fewer than 48 hours of age

- In the case of a newborn transferred from another institution, MSSA or MRSA BSI may be classified as HA your acute-care facility if the organism was **NOT** known to be present and there is no epidemiological reason to suspect that acquisition occurred prior to transfer

Community-associated case definition:

- No exposure to healthcare that would have resulted in this bacteremia (using best clinical judgment) and does not meet the criteria for a healthcare-associated BSI

Vancomycin-resistant *Enterococcus* (VRE) infection

VRE BSI case definition:

- Isolation of *Enterococcus faecalis* or *faecium* from blood

AND

- Vancomycin minimum inhibitory concentration (MIC) of **at least** 8 µg/ml

AND

- Patient must be admitted to the hospital

AND

- Is a "newly" identified VRE BSI at a CNISP facility at the time of hospital admission or identified during hospitalization

A newly identified VRE BSI is defined as a positive VRE blood isolate more than 14 days after completion of therapy for a previous infection and felt to be unrelated to previous infection in accordance with best clinical judgment by infection control physicians and practitioners.

Exclusion criteria:

- Emergency, clinic, or other outpatient cases who are **not admitted** to the hospital

Healthcare-associated (HA) case definition:

Healthcare-associated is defined as an inpatient who meets the following criteria and in accordance with the best clinical judgment of the healthcare and/or infection prevention and control practitioner:

- Patient is on or beyond calendar day 3 of their hospitalization (calendar day 1 is the day of hospital admission)

OR

- Has been hospitalized in your facility in the last 7 days or up to 90 days depending on the source of the infection

OR

- Has had a healthcare exposure at your facility that would have resulted in this bacteremia (using best clinical judgment)

OR

- Any patient who has a bacteremia not acquired at your facility that is thought to be associated with any other healthcare exposure (e.g., another acute-care facility, long-term care, rehabilitation facility, clinic or exposure to a medical device)

Carbapenemase-producing *Enterobacterales* (CPE) infection

Case eligibility:

- Patient is admitted to a CNISP hospital or presents to a CNISP hospital emergency department or a CNISP hospital-based outpatient clinic
- Laboratory confirmation of carbapenem resistance or carbapenemase production in *Enterobacterales* spp.

Following molecular testing, only isolates determined to be harbouring a carbapenemase are included in surveillance. If multiple isolates are submitted for the same patient in the same surveillance year, only the isolate from the most invasive site is included in epidemiological results (e.g., rates and outcome data). However, antimicrobial susceptibility testing results represent all CPE isolates (including clinical and screening isolates from inpatients and outpatients) submitted between 2018 and 2022; duplicates (i.e., isolates from the same patient where the organism and the carbapenemase were the same) were excluded.

Candida auris

Patients admitted to a participating hospital or presenting to a hospital emergency department or a hospital-based outpatient clinic with laboratory confirmation of *C. auris* from any specimen.

Included in this surveillance project are all clinical or screening samples that were positive for *C. auris* by any method. Currently, *C. auris* can be identified by rRNA sequencing, Vitek MS MALDI-TOF (with either the clinical database v3.2 or later or the RUO database), or Bruker MALDI-TOF (with either the clinical database v6903 or later or the RUO database). The project also includes potential *C. auris* misidentifications or "No identification" as outlined in the **Table A1** below.

Table A1: Laboratory identification of *Candida auris*

Identification method	Identification of suspect isolates
Vitek MS MALDI Clinical database older than v3.2	*C. haemulonii* No ID/low discrimination *C. rugosa* (not a problem for v3.0 or later) *C. pulcherrima* (not a problem for v3.0 or later)
Bruker MALDI Clinical database older than v6903	No ID
Vitek 2 version 8.01	*C. haemulonii* *C. duobushaemulonii* No ID/low discrimination
Vitek 2 version before 8.01	*C. haemulonii* *C. duobushaemulonii* *C. lusitaniae* *C. famata* No ID/low discrimination
API 20C AUX	*Rhodotorula glutinis* (characteristic red colour not present) *C. sake* No ID/low discrimination
API Candida	*C. famata*
BD Phoenix yeast identification system	*C. haemulonii* *C. catenulata* No ID

Abbreviations: *C., Candida*; MALDI, Matrix-Assisted Laser Desorption Ionization; MS, mass spectrometry

Appendix B

Supplemental figures and tables are available upon request to the author: cnisp-pcsin@phac-aspc.gc.ca

Figure S1: Number and proportion of patient admissions included in the Canadian Nosocomial Infection Surveillance Program by hospital type and size, 2022
Table S1.1: Cases and incidence rates of healthcare-associated and community-associated *Clostridioides difficile* infection by region, hospital type and hospital size, Canada, 2018–2022
Table S1.2: Antimicrobial resistance of healthcare-associated and community-associated *Clostridioides difficile* infection isolates, Canada, 2018–2022
Table S1.3: Number and proportion of common ribotypes of healthcare-associated and community-associated *Clostridioides difficile* infection cases, Canada, 2018–2022
Table S2.1: Cases and incidence rates of healthcare-associated and community-associated methicillin-resistant *Staphylococcus aureus* bloodstream infections by region, hospital type and hospital size, 2018–2022
Table S2.2: Antimicrobial resistance of healthcare-associated and community-associated methicillin-resistant *Staphylococcus aureus* bloodstream infection isolates, Canada, 2018–2022
Table S2.3: Number and proportion of select methicillin-resistant *Staphylococcus aureus* spa types (with corresponding epidemic types) identified
Table S3.1: Number of vancomycin-resistant *Enterococcus* bloodstream infections incidence rates by region, hospital type and hospital size, 2018–2022
Table S3.2: Number of healthcare-associated vancomycin-resistant *Enterococcus* bloodstream infections and incidence rates by region, hospital type and hospital size, 2018–2022
Table S3.3: Number and proportion of vancomycin-resistant *Enterococcus* bloodstream infections isolate types identified, 2018–2022
Table S3.4: Distribution of vancomycin-resistant *Enterococcus faecium* bloodstream sequence types, 2018–2022
Table S4.1: Number of carbapenemase-producing *Enterobacterales* infections and incidence rates by region, hospital type and hospital size, 2018–2022
Table S4.2: Number and proportion of main carbapenemase-producing pathogens identified
Table S4.3: Antimicrobial susceptibility testing for *Klebsiella pneumoniae* carbapenemase, 2019−2022
Table S4.4 Antimicrobial susceptibility testing for New Delhi metallo-β-lactamase, 2019−2022
Table S4.5: Antimicrobial susceptibility testing for OXA-48, Oxacillinase-48, 2019−2022

Device and surgical procedure-related infections in Canadian acute care hospitals, 2018–2022

Canadian Nosocomial Infection Surveillance Program[1]*

Abstract

Background: Healthcare-associated infections (HAIs) are a significant healthcare burden in Canada. National surveillance of HAIs at sentinel acute care hospitals is conducted by the Canadian Nosocomial Infection Surveillance Program.

Objective: This article describes device and surgical procedure-related HAI epidemiology in Canada from 2018 to 2022.

Methods: Data were collected from over 60 Canadian sentinel acute care hospitals between January 1, 2018, and December 31, 2022, for central line-associated bloodstream infections (CLABSIs), hip and knee surgical site infections (SSIs), cerebrospinal fluid shunt (CSF) SSIs and paediatric cardiac SSIs. Case counts, rates, patient and hospital characteristics, pathogen distributions and antimicrobial resistance data are presented.

Results: Between 2018 and 2022, 2,258 device-related infections and 987 surgical procedure-related infections were reported. A significant rate increase was observed in adult mixed intensive care unit CLABSIs (1.07–1.93 infections per 1,000 line days, p=0.05) and a non-significant rate increase was observed in SSIs following knee arthroplasty (0.31–0.42 infections per 100 surgeries, p=0.45). A fluctuating rate trend was observed in CSF shunt SSIs over the time period and a significant rate decrease in paediatric cardiac SSIs was observed (68%, from 7.5–2.4 infections per 100 surgeries, p=0.01). The most commonly identified pathogens were coagulase-negative staphylococci (22.8%) among CLABSIs and *Staphylococcus aureus* (42%) among SSIs.

Conclusion: Epidemiological and microbiological trends among selected device and surgical procedure-related HAIs are essential for benchmarking infection rates nationally and internationally, identifying any changes in infection rates or antimicrobial resistance patterns and helping inform hospital infection prevention and control and antimicrobial stewardship policies and programs.

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Keywords: hospital-associated infection, acute care, surveillance, antimicrobial resistance, device-associated infection, surgical procedure-related infection, surgical site infection, CLABSI, central line-associated bloodstream infection, hip and knee arthroplasty surgical site infection, cerebrospinal fluid shunt surgical site infection, paediatric cardiac surgical site infection, Canada

Introduction

Healthcare-associated infections (HAIs) contribute to excess patient morbidity and mortality, leading to increased healthcare costs, longer hospital stays and increased antimicrobial resistance (1). Healthcare-associated infections may occur during the use of invasive devices and following surgical procedures (2). More specifically, surgical procedure-related infections are among the most prevalent HAIs and are responsible for a longer hospitalization of approximately seven to 11 days (3). Device and surgical procedure-related infections are also associated with a high-cost burden, accounting for almost $50,000 per central

line-associated bloodstream infections (CLABSIs) case and $28,000 per surgical site infection (SSI) case (4).

A 2017 point prevalence study in Canadian sentinel acute care hospitals found that device and surgical procedure-related infections accounted for 35.6% of all reported HAIs (5). Central line-associated bloodstream infections accounted for 21.2% of device and surgical procedure-related infections while prosthetic implants accounted for 19.4% (5). The risk of device and surgical procedure-related infections is associated with patient demographics and comorbidities, in addition to the type of hospital in which the patient received care (6–8).

Understanding the epidemiology of device and surgical procedure-related HAIs is essential to provide benchmark rates over time, which help to inform effective antimicrobial stewardship and infection prevention and control measures. In addition, the collection and analysis of antimicrobial susceptibility data are important to inform the appropriate use of antimicrobials and help reduce antimicrobial resistance (9). This report provides an epidemiological overview of select device and surgical procedure-related HAIs from 2018 to 2022 in over 60 hospitals participating in the Canadian Nosocomial Infection Surveillance Program (CNISP).

Methods

Design

Since its establishment in 1994, CNISP has conducted national HAI surveillance at sentinel acute care hospitals across Canada, in collaboration with the Public Health Agency of Canada and the Association of Medical Microbiology and Infectious Disease Canada (AMMI Canada). Data are presented for the following device and surgical procedure-related HAIs: CLABSIs; hip and knee arthroplasty SSIs; cerebrospinal fluid (CSF) shunt SSIs; and paediatric cardiac SSIs.

Case definitions

Device and surgical procedure-related HAIs were defined according to standardized protocols and case definitions (see **Appendix**). Complex infections, defined as deep incisional and organ/space, were included in hip and knee SSI surveillance, while CLABSIs identified in intensive care unit (ICU) settings were included in CLABSI surveillance. The adult mixed ICU, adult cardiovascular surgery intensive care unit (CVICU), paediatric intensive care unit (PICU) and neonatal intensive care unit (NICU) were included as eligible ICU settings. Adult mixed intensive care units included any adult ICU with a mix of patient types as part of the ICU patient mix (i.e., medical/surgical, surgical/trauma, burn/trauma, medical/neurosurgical).

Data source

Epidemiological data for device and surgical procedure-related infections identified between January 1, 2018, and December 31, 2022 (using surgery date for surgical site infections and date of positive blood culture for CLABSIs) were submitted by participating hospitals using standardized data collection forms. Hospital participation varied by surveillance project and year. Data submission and case identification were supported by training sessions and periodic evaluations of data quality.

Statistical analysis

To calculate hip and knee SSI, CSF shunt SSI and paediatric cardiac SSI rates, the number of cases were divided by the number of surgical procedures performed (multiplied by 100). To calculate CLABSI rates, the number of cases was divided by line day denominators (multiplied by 1,000). Neonatal intensive care unit CLABSI rates stratified by birth weight category were not included in this report. To calculate proportions of pathogens, the number of pathogens were divided by the total number of identified pathogens. Denominators may vary, as missing and incomplete data were excluded from analyses. Median and interquartile ranges (IQR) were calculated for continuous variables. Trends over time were tested using the Mann-Kendall test. Significance testing was two-tailed and differences were considered significant at a *p*-value of ≤ 0.05. Analyses were conducted using R version 4.1.2 and SAS 9.4.

Results

Over 60 hospitals contributed device and surgical procedure-related infection data to CNISP between 2018 and 2022 (**Table 1**), with medium-sized (n=201–499 beds) adult hospitals (n=16 sites, 25%) being the most common (data not shown). Overall, 2,258 device-related infections and 987 surgical procedure-related infections were reported. Among all SSIs reported (n=987), hip and knee infections represented 68% (n=667) of these types of infections.

A total of 2,496 pathogens were identified from device-related infections and 1,056 pathogens from surgical procedure-related cases between 2018 and 2022. Of the identified pathogens for CLABSIs, 61% were gram-positive, 24% were gram-negative and 15% were fungal. Of the identified pathogens for SSIs, 79% were gram-positive, 19% were gram-negative and 1.5% were fungal. Coagulase-negative staphylococci (CoNS) and *Staphylococcus aureus* were the most frequently reported pathogens for CLABSIs and SSIs, respectively (**Table 2**). From 2018 to 2022, the proportion of methicillin-resistant *S. aureus* (MRSA) was 16% for CLABSIs and 11% for SSIs (data not shown).

Table 1: Characteristics of acute care hospitals participating in device and surgical procedure-related healthcare-associated infection surveillance, 2022

Characteristic of hospitals	CLABSI-adult mixed ICU	CLABSI-adult CVICU	CLABSI-PICU	CLABSI-NICU	CSF shunt SSI	Paediatric cardiac SSI	Hip and knee SSI	Total unique hospitals
Total number of participating hospitals	36	8	12	18	16	6	32	64
Hospital type								
Adult	27	6	N/A	4[a]	4	N/A	15	33
Mixed	9	2	4	6	2	N/A	17	22
Paediatric	N/A	N/A	8	8	10	6	N/A	9
Hospital size								
Small (1–200 beds)	2	1	7	8	8	3	6	18
Medium (201–499 beds)	22	3	4	7	5	3	15	31
Large (500 or more beds)	12	4	1	3	3	N/A	11	15

Abbreviations: CLABSI, central line-associated bloodstream infection; CSF shunt SSI, cerebrospinal fluid shunt surgical site infection; CVICU, cardiovascular surgery intensive care unit; ICU, intensive care unit; N/A, not applicable; NICU, neonatal intensive care unit; PICU, paediatric intensive care unit; SSI, surgical site infection
[a] Four hospitals classified as "adult" also had a NICU

Table 2: Distribution and rank of the five most frequently reported gram-negative, gram-positive and fungal pathogens, 2018–2022[a]

Pathogen category	Rank	Pathogen	CLABSI N=2,258		Hip and knee N=667		CSF shunt N=151		Paediatric cardiac N=169	
			n	%	n	%	n	%	n	%
Gram-positive	1	Coagulase-negative staphylococci[b]	568	22.8	143	18.9	58	35.6	22	16.3
	2	*Staphylococcus aureus*[c]	257	10.3	288	38.0	49	30.1	77	57.0
	3	*Enterococcus* spp.	536	21.5	33	4.4	6	3.7	1	0.7
	4	*Streptococcus* spp.	58	2.3	69	9.1	4	2.5	9	6.7
	Other gram-positive[d]		94	3.8	64	8.4	13	8.0	0	0.0
	Total gram-positive		1,513	60.6	597	78.8	130	79.8	109	80.7
Gram-negative	1	*Klebsiella* spp.	139	5.6	18	2.4	8	4.9	3	2.2
	2	*Escherichia coli*	126	5.0	26	3.4	8	4.9	1	0.7
	3	*Enterobacter* spp.	99	4.0	34	4.5	3	1.8	5	3.7
	4	*Pseudomonas* spp.	67	2.7	29	3.8	4	2.5	3	2.2
	5	*Serratia* spp.	46	1.8	11	1.5	2	1.2	2	1.5
	Other gram-negative[e]		133	5.3	40	5.3	5	3.1	2	1.5
	Total gram-negative		610	24.4	158	20.8	30	18.4	16	11.9
Fungi	1	*Candida albicans*	189	7.6	2	0.3	1	0.6	3	2.2
	2	Other *Candida* spp.[f]	175	7.0	1	0.1	2	1.2	6	4.4
	Other fungi[g]		9	0.4	0	0.0	0	0.0	1	0.7
	Total fungal		373	14.9	3	0.4	3	1.8	10	7.4
Total			2,496	N/A	758	N/A	163	N/A	135	N/A

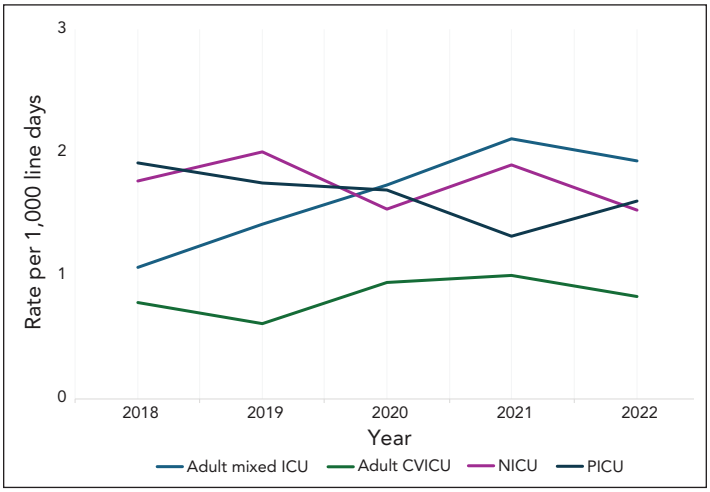
Abbreviations: CLABSI, central line-associated bloodstream infections; CSF shunt, cerebrospinal fluid shunt; N/A, not applicable
[a] Frequency distribution percentage rounded to the nearest tenth decimal
[b] Coagulase-negative staphylococci included *S. lugdunensis*, *S. haemolyticus*, *S. epidermidis*, *S. capitis*, *S. hominis* and *S. warneri*
[c] *Staphylococcus aureus* includes methicillin-resistant *S. aureus*, methicillin-susceptible *S. aureus* and unspecified *S. aureus*
[d] Other gram-positive pathogens included anaerobic gram-positive cocci, *Finegoldia magna*, *Clostridioides* spp., *Lactobacillus* spp. and others
[e] Other gram-negative pathogens included *Stenotrophomonas* spp., *Morganella morganii*, *Proteus mirabilis*, *Pantoea spp.*, *Prevotella* spp., *Bacteroides fragilis* and others
[f] Other *Candida* spp. included *C. dubliniensis*, *C. glabrata*, *C. krusei*, *C. lusitaniae*, *C. parapsilosis* and *C. tropicalis*
[g] Other fungi included *Aspergillus* spp., *Trichophyton tonsurans* and unspecified fungi

Central line-associated bloodstream infections

A total of 2,258 CLABSIs were reported between 2018 and 2022, with the majority occurring in adult mixed ICUs (n=1,411, 62.5%) and NICUs (n=456, 20.2%). Overall, NICUs had the highest rates of CLABSIs between 2018 and 2022 (1.75 infections per 1,000 line days), followed by adult mixed ICUs (1.66 infections per 1,000 line days), PICUs (1.65 infections per 1,000 line days) and adult CVICUs (0.82 infections per 1,000 line days) (**Table A1**).

From 2018 to 2022, CLABSI rates fluctuated in NICUs and PICUs, while CLABSI rates in adult mixed ICUs increased significantly by 80% (1.07–1.93 infections per 1,000 line days, p=0.05) (**Figure 1**). Though rates of CLABSI in adult CVICUs were low overall, adult CVICU CLABSI rates increased 28% from 2018 to 2021 (0.78–1.0 infections per 1,000 line days) before decreasing 20% to 0.83 infections per 1,000 line days in 2022.

Figure 1: Rate of central line-associated bloodstream infection per 1,000 line days by intensive care unit type, 2018–2022



Abbreviations: CVICU, cardiovascular intensive care unit; ICU, intensive care unit; NICU, neonatal intensive care unit; PICU, paediatric intensive care unit

Among CLABSIs identified in adult mixed ICUs, the median age was 60 years (IQR=47–69 years), with males representing the majority of cases (66%). All-cause mortality within 30 days following the first positive culture, for adult mixed ICU CLABSI patients was 32% (n=452/1,411). Among CLABSIs identified in adult CVICUs, the median age was 65 years (IQR=51–72 years), with males representing 72% of cases. Within 30 days following the first positive culture, all-cause mortality for adult CVICU CLABSI patients was 29.1% (n=39/134). Among CLABSIs identified in PICUs, the median age was seven months (IQR=3–36 months), with males representing 58% of cases. Within 30 days following the first positive culture, all-cause mortality for PICU CLABSI patients was 8.9% (n=23/257). Among CLABSIs identified in NICUs, the median age at first positive culture was 19 days (IQR=9–41 days). Males represented 59% of NICU cases and all-cause mortality within 30 days of positive culture was 12% (n=53/456).

The most commonly identified pathogens among CLABSIs overall were CoNS and *Enterococcus* spp. (22.8% and 21.5%, respectively), which aligned with the most commonly identified pathogens among adult mixed ICUs and adult CVICUs. Among PICU and NICU CLABSIs, CoNS and *S. aureus* were the most commonly identified pathogens (data not shown). Among CLABSIs identified with *Serratia* spp., most were in the adult mixed ICU (54.3%, n=25/46), followed by NICU (17.4%, n=8/46), PICU (17.4%, n=8/46) and adult CVICUs (10.9%, n=5/46).

Hip and knee surgical site infections

A total of 667 complex hip and knee SSIs were reported between 2018 and 2022, of which the majority were hip arthroplasties (n=440, 66%). Among hip and knee SSIs, 55% (n=242) were organ/space infections and 45% (n=198) were deep incisional infections (**Table 3**). From 2018 to 2022, knee SSI rates increased non-significantly by 35.5% (0.31–0.42 infections per 100 surgeries, p=0.45) while hip SSI rates fluctuated between 0.75 and 0.88 infections per 100 surgeries (p=0.33) (**Figure 2**). During the COVID-19 pandemic in 2020, knee SSI rates remained stable while hip SSI rates decreased by 40%, compared to 2019. In 2022, both hip and knee SSI rates increased to 0.72 and 0.42 infections per 100 surgeries respectively, returning to rates observed in the pre-pandemic period (Figure 2 and **Table A2**).

Table 3: Frequency of hip and knee surgical site infections by year and infection type, 2018–2022

Year	Deep incisional SSI		Organ/space SSI		All cases
	n	%	n	%	n
Hip arthroplasty					
2018	34	34.7	64	65.3	98
2019	52	50.0	52	50.0	104
2020	22	44.9	27	55.1	49
2021	44	49.4	45	50.6	89
2022	46	46.0	54	54.0	100
Overall	198	45.0	242	55.0	440
Knee arthroplasty					
2018	22	55.0	18	45.0	40
2019	27	50.9	26	49.1	53
2020	14	37.8	23	62.2	37
2021	23	62.2	14	37.8	37
2022	33	55.0	27	45.0	60
Overall	119	52.4	108	47.6	227

Abbreviation: SSI, surgical site infection

The median patient age was 68 years (IQR=59–75 years) for hip SSIs and 66 years (IQR=59–74 years) for knee SSIs. The median time from procedure to hip and knee infections was 22 days (IQR=15–34 days) and 24 days (IQR=16–39 days), respectively. For data collected between 2018 and 2022, the median length of stay was three days (IQR=1–7 days) for hip SSIs and two days (IQR=1–4 days) for knee SSIs. Most patients (84%, n=552/661)

Figure 2: Rate of hip and knee surgical site infections per 100 surgeries, 2018–2022

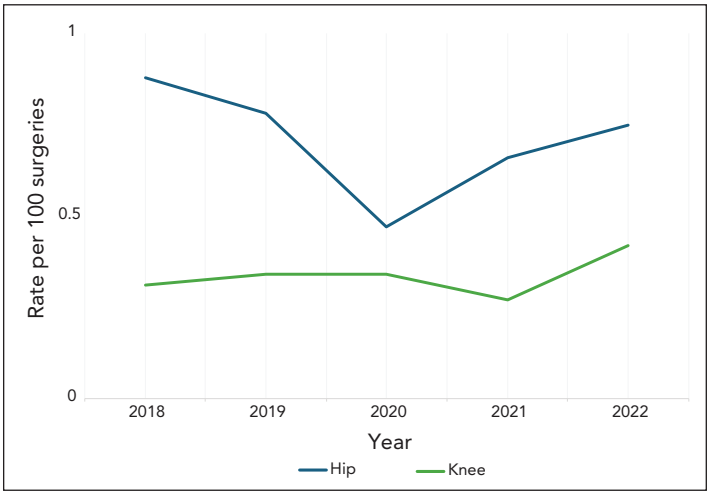
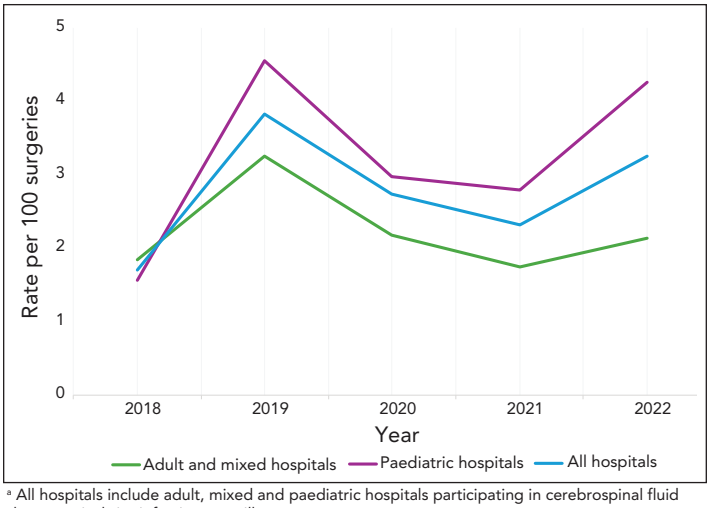


Figure 3: Cerebrospinal fluid shunt surgical site infection rates per 100 surgeries by hospital type[a], 2018–2022



[a] All hospitals include adult, mixed and paediatric hospitals participating in cerebrospinal fluid shunt surgical site infection surveillance

with an SSI following hip or knee arthroplasty were readmitted and 66% (n=431/652) required revision surgery. Within 30 days after first positive culture, five all-cause deaths (2.1%, n=9/427) were reported among patients with a complex SSI following a hip arthroplasty while zero all-cause deaths were reported among patients with a knee arthroplasty SSI. Among hip and knee SSI cases, *S. aureus* and CoNS were the most commonly identified pathogens at 38% and 19%, respectively, and did not differ by deep or organ/space infection type (data not shown).

Cerebrospinal fluid shunt surgical site infections

Between 2018 and 2022, 151 CSF shunt SSIs were reported, with an overall rate of 2.9 infections per 100 surgeries (range: 1.7–3.82 infections per 100 surgeries, **Table A3**). Paediatric and adult/mixed hospitals infection rates were not significantly different at 3.2 and 2.5 infections per 100 surgeries, respectively (p=0.17). Cerebrospinal fluid shunt SSI rates in all hospitals decreased throughout the COVID-19 pandemic in 2020 and 2021 (**Figure 3**), then increased by 41% in 2022 (2.3 infections per 100 surgeries in 2021 to 3.3 infections per 100 surgeries in 2022). Paediatric hospital CSF shunt SSI rates decreased by 39% from 2019 to 2021, before increasing again to 4.3 infections per 100 surgeries in 2022, in keeping with the fluctuating rate trend observed since 2011 (data not shown).

More than half of CSF shunt SSIs (53.6%, n=81/151) were identified from new surgeries while 46.4% (n=70/151) were identified from revision surgeries. The median age was 47 years (IQR=36–62 years) for adult patients and three years (IQR=0.4–9 years) for paediatric patients. Females represented 54% (n=82/151) of cases and median time from surgery to infection was 19 days (IQR=10–40 days). The most commonly identified pathogens from CSF shunt SSIs were CoNS and *S. aureus* (36% and 30% of identified pathogens, respectively). Outcome data were not collected for CSF shunt SSI surveillance.

Paediatric cardiac surgical site infections

A total of 169 paediatric cardiac SSIs were reported between 2018 and 2022 (**Table 4**). Most of these SSIs were superficial infections (62%), followed by organ/space infections (30%). Overall, the average paediatric cardiac SSI rate was 3.9 infections per 100 surgeries (**Table A4**). From 2018 to 2022, rates decreased significantly by 68% and consistently, from 7.5 to 2.4 infections per 100 surgeries (p=0.01) (**Figure 4**). The high rate in 2018 was caused by outlier cases attributable to two hospitals.

The median age of patients with a paediatric cardiac SSI was 40 days (IQR=6–246 days) and the median time from surgery to onset date of infection was 16 days (IQR=8–24 days). Among the three deaths reported within 30 days of infection onset (1.8% of cases), one death was unrelated to the paediatric cardiac SSI, while two deaths were attributable to the paediatric cardiac SSI. *Staphylococcus aureus* and CoNS were the most commonly identified pathogens from paediatric cardiac SSIs (57% and 16% of identified pathogens, respectively) and did not differ by superficial, organ/space or deep infection type (data not shown).

Antibiogram

Results of antimicrobial susceptibility testing for the most frequently identified gram-positive, gram-negative and fungal pathogens from device and surgical procedure-related HAIs are listed in **Figure 5** and **Figure 6**. The *S. aureus* isolates were resistant to cloxacillin/oxacillin (MRSA) in 15% (n=28/189) of CLABSIs and 12% (n=40/337) of SSIs. Meropenem resistance ranged from 3% to 38% in gram-negative pathogens identified from CLABSIs. No meropenem resistance was observed among pathogens isolated from SSIs. Seventy-six vancomycin-resistant *Enterococci* were identified among CLABSIs (23%).

Table 4: Paediatric cardiac surgical site infection rates by year and infection type, 2018–2022

Year	Superficial incisional SSI cases		Organ/space SSI cases		Deep incisional SSI cases		All cases[a]
	n	%	n	%	n	%	
2018	18	46.2	15	38.5	6	15.4	39
2019	19	54.3	14	40.0	2	5.7	35
2020	29	78.4	6	16.2	2	5.4	37
2021	23	65.7	9	25.7	3	8.6	35
2022	15	65.2	6	26.1	2	8.7	23
Overall	104	61.5	50	29.6	15	8.9	169

Abbreviation: SSI, surgical site infection
[a] Excludes cases with missing infection type information

Figure 4: Paediatric cardiac surgical site infection rates per 100 surgeries, 2018–2022

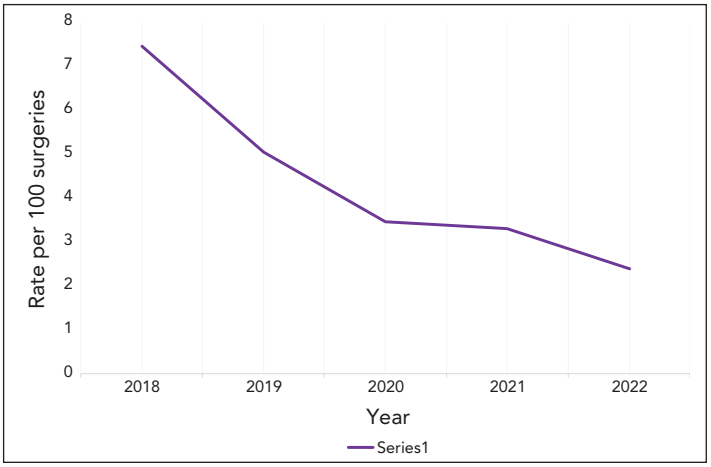
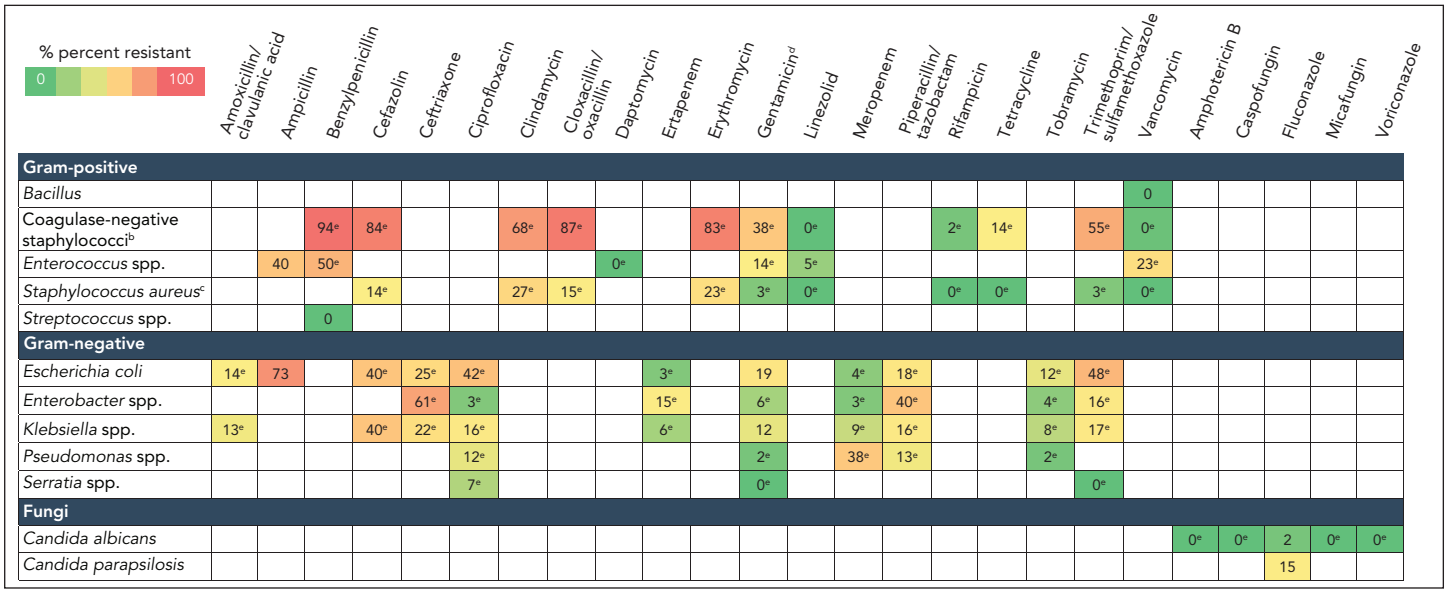
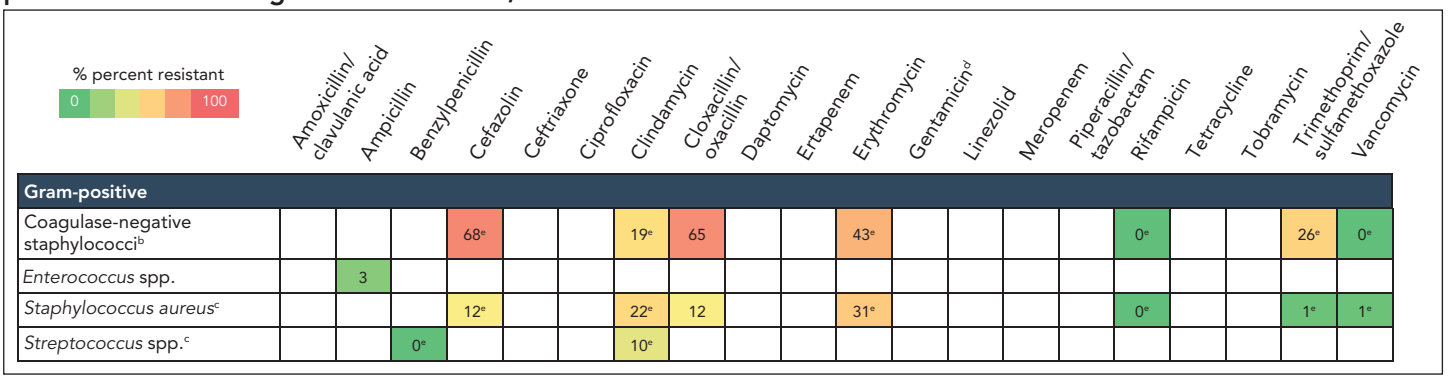


Figure 5: Antibiogram results[a] from pathogens identified from central line-associated bloodstream infections, 2018–2022[b,c,d,e]



[a] Antibiotic/organism combinations with fewer than 30 tests were excluded
[b] Coagulase-negative staphylococci included *S. lugdunensis, S. haemolyticus, S. epidermidis, S. capitis, S. hominis* and *S. warneri*
[c] Included methicillin-susceptible *S. aureus* and methicillin-resistant *S. aureus* (MRSA)
[d] Gentamicin synergy for gram-positive organisms
[e] Less than 90% of isolates were tested

Figure 6: Antibiogram results[a] from pathogens identified from hip and knee, cerebrospinal fluid shunt and paediatric cardiac surgical site infections, 2018–2022[b,c,d,e]



[a] Antibiotic/organism combinations with fewer than 30 tests were excluded
[b] Coagulase-negative staphylococci included *S. lugdunensis, S. haemolyticus, S. epidermidis, S. capitis, S. hominis* and *S. warneri*
[c] Included methicillin-susceptible *S. aureus* and methicillin-resistant *S. aureus* (MRSA)
[d] Gentamicin synergy for gram-positive organisms
[e] Less than 90% of isolates were tested

Discussion

This report summarizes 2,258 device-related infections and 987 surgical procedure-related infections identified over five years of surveillance (2018–2022) from 64 hospitals across Canada. During this time, rates of device and surgical procedure-related HAIs have increased significantly by 80% for adult mixed ICU CLABSIs and non-significantly by 36% for knee SSIs. The COVID-19 pandemic has had a varied impact on the rates of device and surgical procedure-related HAIs (10). In Canada, preliminary investigations suggest that the COVID-19 pandemic had an immediate but unsustained impact on HAI rate trends (11). Rates of SSIs in the CNISP network initially decreased in 2020 during the COVID-19 pandemic, when elective surgeries were postponed, before increasing towards pre-pandemic levels in 2021. Ongoing investigations continue to assess the influence of pandemic-related factors such as changes in infection control practices, screening, laboratory testing and antimicrobial stewardship on the observed rates of HAIs.

Central line-associated bloodstream infections

Where comparable data were available, the rates of CLABSI in adult ICUs (overall rate: 0.82 and 1.66 infections per 1,000 line days for CVICUs and mixed ICUs, respectively) were lower than those in the United Kingdom but higher than those in Western Australia (12–14). In the United Kingdom, 2021 and 2022 rates of CLABSI in the adult and cardiac ICU were 2.5 and 1.6 infections per 1,000 line days, respectively (14). In Western Australia, CLABSI rates in adult ICU settings ranged from 0.0 to 0.8 infections per 1,000 line days between 2018 and 2022 and may be lower than levels in Canada due to differences in surveillance methodologies including the number and type of hospitals under surveillance (12). Compared to CNISP adult mixed ICU CLABSI rates, a European Centre for Disease Prevention and Control report noted similar or higher 2019 rates in France and Italy (1.4–3.8 infections per 1,000 line days), while Austrian and Lithuanian CLABSI rates were lower (0.1–0.2 infections per 1,000 line days) (15).

Rates of CLABSIs in the NICU and PICU fluctuated from 2018 to 2022 but were higher overall (1.75 and 1.65 infections per 1,000 line days, respectively) compared to CLABSI rates in adult mixed ICUs and adult CVICUs (1.66 and 0.82 infections per 1,000 line days, respectively). Data available from the United States from 2018 to 2022 indicate the standardized incidence ratios (defined as the ratio of observed number of infections compared to the 2015 baseline) have reported similar fluctuating trends and have experienced a 9% decrease in CLABSI rates between 2021 and 2022 (16–20). Higher rates of CLABSIs have been seen in other limited resource settings compared to those observed in the CNISP network; a large surveillance study of ICUs in 45 countries from Latin America, Europe, Eastern Mediterranean, Southeast Asia and Western Pacific World Health Organization regions reported pooled mean CLABSI rates of 5.37 per 1,000 line days in PICUs (57 participating ICUs) and 4.66 in medical/surgical adult ICUs (182 participating ICUs) between January 2015 and December 2020 (21).

Surgical site infections

Among SSIs included in this surveillance report, hip and knee SSIs were the most prevalent. Hip SSI rates fluctuated across reporting years, while knee SSI rates increased non-significantly. Surveillance from the United Kingdom indicates hip and knee SSI rates slightly increased for 2021 and 2022, after remaining stable for 10 years (22). Compared to CNISP data, hip and knee SSI rates reported in Southern Australia were higher overall and have also seen increases in recent years; hip SSI rates increased from 2018 to 2020 (1.80–1.91 infections per 100 procedures), while knee SSI rates increased from 0.79 to 0.88 infections per 100 procedures, during the same time period (23). In accordance with results from other regions, the most common pathogens among hip and knee SSIs were *S. aureus* and CoNS, likely attributed to the contamination of implant devices by the patient's endogenous skin flora (24,25). Higher median age of patients with hip and knee SSIs relate to the older age of patients requiring joint replacements and the increased likelihood of surgical complications (26). Our data indicate that frequent readmission and revision surgeries are required for SSIs, both of which place high economic and resource burdens on the Canadian healthcare system, consistent with other studies from the United States, Australia and the United Kingdom (27–30).

The overall rate of SSIs from CSF shunts was 2.85 per 100 surgeries from 2018 to 2022. Stratification of CSF shunt SSI data by paediatric and adult/mixed hospitals showed that from 2018 to 2022, adult rates (2.5 infections per 100 surgeries) and paediatric rates (3.2 infections per 100 surgeries) were not significantly different. Data from historical CNISP surveillance shows a fluctuating trend in CSF shunt SSI rates from 2011 to 2020 (31). Compared to historical data, CSF shunt SSI rates among paediatric patients from 2018 to 2022 (3.2%) were lower than those from 2000 to 2002 (4.9%), signifying a decrease in SSI rates among paediatric populations (32). The rate of CSF shunt SSI among adult patients from 2018 to 2022 (2.5%) was also lower compared to that of 2000 to 2002 (3.2%) (32). A national survey from 2017 conducted in England showed a mean brain shunt infection rate of 1.9% (range: 0–4.4%), which is lower than what we observed, although there may be variations in the definitions and methodologies of rate calculation (33).

The overall rate of paediatric cardiac SSI between 2018 and 2022 was 3.93 per 100 surgeries. The relatively high rate of paediatric cardiac SSI in 2018 should be interpreted with caution, as rates may fluctuate due to the limited number of annual cases. Literature regarding paediatric cardiac SSI rates is limited; however, a pre-post intervention study from 2013 to 2017 has reported successful reduction in paediatric cardiac SSI rates from 3.4 to 0.9 per 100 surgeries in a quaternary, paediatric academic center in California following the implementation of a postoperative SSI reduction care bundle (34).

Antibiogram

The percentage of *S. aureus* isolates that were MRSA among CLABSIs (15%) and SSIs (12%) was lower in the CNISP network compared to data reported by Centers for Disease Control and Prevention where 44% and 38% of *S. aureus* isolates were MRSA for CLABSIs and SSIs, respectively (35).

Of the identified *Enterococcus* spp. in CLABSIs, 23% were vancomycin-resistant *Enterococci* (VRE). From National Healthcare Safety Network surveillance in the United States, 73% of *Enterococcus faecium* and 4% of *Enterococcus faecalis* pathogens identified from CLABSIs in ICUs were VRE in 2021 (36). Meropenem resistance was low in most gram-negative pathogens identified among CLABSIs and SSIs (0%–8%) in the CNISP network, and similar to carbapenem resistance levels reported in the United States in 2021 (5% among *Klebsiella* spp.; 6% among *Enterobacter* spp.; and 0.8% among tested *E. coli* isolates) (37).

However, among *Pseudomonas* spp. identified in CLABSIs, meropenem resistance was 38%, which is higher than levels reported in the United States (21% carbapenem-resistant *Pseudomonas aeruginosa* among CLABSIs in 2021) (38,39). Overall, antibiogram patterns observed in the CNISP network may differ compared to other countries due to differences in surveillance methodologies, antimicrobial stewardship practices, types of hospitals or patient populations under surveillance and differences in circulating molecular strain types.

Strengths and limitations

The main strength of CNISP surveillance is the standardized collection of detailed epidemiological and molecular linked data from a large representative network of sentinel hospitals across Canada. From 2018 to 2022, CNISP coverage of Canadian acute care beds has increased from 32% to 35%, including increased representativeness in northern, community, rural, and Indigenous populations. To further improve representativeness, CNISP has launched a simplified dataset accessible to all acute care hospitals across Canada to collect and visualize annual HAI rate data. The number of hospitals participating in each HAI surveillance project differed and epidemiologic data collected were limited to the information available in the patient charts. For CLABSI surveillance, data were limited to infections occurring in the ICU settings, and as such may only represent a subset of CLABSIs occurring in the hospital. Further, differences in surveillance protocols and case definitions limit comparison with data from other countries. Studies are ongoing to assess the impact of the COVID-19 pandemic on device and surgical procedure-related HAIs and antimicrobial resistance.

Conclusion

This report provides an updated summary of rates, pathogen distributions and antimicrobial resistance patterns among select device and surgical procedure-related HAIs and relevant pathogens. The collection and analysis of national surveillance data are important to understanding and reducing the burden of device and surgical procedure-related HAIs. These data provide benchmark rates for national and international comparison and inform antimicrobial stewardship and infection prevention and control programs and policies.

Authors' statement

Canadian Nosocomial Infection Surveillance Program hospitals provided expertise in the development of protocols in addition to the collection and submission of epidemiological and microbiological data. Epidemiologists from Public Health Agency of Canada were responsible for the conception, analysis, interpretation, drafting and revision of the article.

Competing interests

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Appendix: Case definitions

Central line-associated bloodstream infection

Only central line-associated bloodstream infections (CLABSIs) related to an intensive care unit (ICU) admission were included in surveillance.

Bloodstream infections case definition:

Bloodstream infection is **NOT** related to an infection at another site and it meets one of the following criteria:

Criterion 1: Recognized pathogen cultured from at least one blood culture, unrelated to infection at another site.

OR

Criterion 2: At least one of: fever (higher than 38°C core), chills, hypotension; if aged younger than 1 year, fever (higher than 38°C core), hypothermia (lower than 36°C core), apnea or bradycardia **AND** common skin contaminant (see list below) cultured from at least two blood cultures drawn on separate occasions or at different sites, unrelated to infection at another site. Different sites may include peripheral veins, central venous catheters or separate lumens of a multilumen catheter. Different times include two blood cultures collected on the same or consecutive calendar days via separate venipunctures or catheter entries. The collection date of the first positive blood culture is the date used to identify the date of positive culture. Two positive blood culture bottles filled at the same venipuncture or catheter entry constitute only one positive blood culture.

Central line-associated bloodstream infection case definition:

A CLABSI must meet one of the following criteria:

Criterion 1: A laboratory-confirmed bloodstream infection (LCBSI) where a central line catheter (CL) or umbilical catheter (UC) was in place for more than two calendar days on the date of the positive blood culture, with day of device placement being Day 1.

OR

Criterion 2: A LCBSI where a CL or UC was in place more than two calendar days and then removed on the day or one day before positive blood culture was drawn.

Intensive care unit-related central line-associated bloodstream infection case definition:

A CLABSI related to an ICU if it meets one of the following criteria:

Criterion 1: CLABSI onset after two days of ICU stay.

OR

Criterion 2: If the patient is discharged or transferred out of the ICU, the CLABSI would be attributable to the ICU if it occurred on the day of transfer or the next calendar day after transfer out of the ICU.

Note: If the patient is transferred into the ICU with the CL and the blood culture was positive on the day of transfer or the next calendar day, then the CLABSI would be attributed to the unit where the line was inserted.

Common skin contaminants:

Diphtheroids, *Corynebacterium* spp., *Bacillus* spp., *Propionibacterium* spp., coagulase-negative staphylococci (including *S. epidermidis*), viridans group streptococci, *Aerococcus* spp., *Micrococcus* spp. and *Rhodococcus* spp.

Hip and knee surgical site infection

Only complex surgical site infections (SSIs) (deep incisional or organ/space) following hip and knee arthroplasty were included in surveillance.

A deep incisional surgical site infection must meet the following criterion:

Infection occurs within 90 days after the operative procedure and the infection appears to be related to the operative procedure and involves deep soft tissues (e.g., facial and muscle layers) of the incision and the patient has at least **ONE** of the following:

- Purulent drainage from the deep incision but not from the organ/space component of the surgical site
- Deep incision that spontaneously dehisces or is deliberately opened by the surgeon and is culture-positive or not cultured when the patient has at least one of the following signs or symptoms: fever (higher than 38°C) or localized pain or tenderness (a culture-negative finding does not meet this criterion)
- An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation or by histopathologic or radiologic examination
- Diagnosis of a deep incisional SSI by a surgeon or attending physician

An organ/space surgical site infection must meet the following criterion:

Infection occurs within 90 days after the operative procedure and the infection appears to be related to the operative procedure and infection involves any part of the body, excluding the skin incision, fascia or muscle layers, that is opened or manipulated during the operative procedure and patient has at least **ONE** of the following:

- Purulent drainage from a drain that is placed through a stab wound into the organ/space
- Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space
- An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation or by histopathologic or radiologic examination
- Diagnosis of an organ/space SSI by a surgeon or attending physician

Cerebrospinal fluid shunt surgical site infection

Only patients who underwent a placement or revision of a cerebrospinal fluid (CSF) shunting device and the infection occurred within one year of surgery were included in surveillance.

Cerebrospinal fluid shunt-associated surgical site infection case definition:

An internalized CSF shunting device is in place **AND** a bacterial or fungal pathogen(s) is identified from the cerebrospinal fluid **AND** is associated with at least **ONE** of the following:

- Fever (temperature 38°C or higher)
- Neurological signs or symptoms
- Abdominal signs or symptoms
- Signs or symptoms of shunt malfunction or obstruction

Paediatric cardiac surgery surgical site infection

Only surgical site infections following open-heart surgery with cardiopulmonary bypass among paediatric patients (younger than 18 years of age) were included in surveillance.

A **superficial incisional SSI** must meet the following criterion: Infection occurs within 30 days after the operative procedure and involves only skin and subcutaneous tissue of the incision and meets at least **ONE** of the following criteria:

- Purulent drainage from the superficial incision
- Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision
- At least **ONE** of the following signs or symptoms of infection:
  - Pain or tenderness, localized swelling, redness or heat, and the superficial incision is deliberately opened by a surgeon, and is culture-positive or not cultured (a culture-negative finding does not meet this criterion)
  - Diagnosis of superficial incisional SSI by the surgeon or attending physician

A **deep incisional SSI** must meet the following criterion:

Infection occurs within 90 days after the operative procedure and the infection appears to be related to the operative procedure **AND** involves deep soft tissues (e.g., facial and muscle layers) of the incision **AND** the patient has at least **ONE** of the following:

- Purulent drainage from the deep incision but not from the organ/space component of the surgical site
- Deep incision spontaneously dehisces or is deliberately opened by the surgeon and is culture-positive or not cultured when the patient has at least one of the following signs or symptoms: fever (higher than 38°C) or localized pain or tenderness (a culture-negative finding does not meet this criterion)
- An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation or by histopathologic or radiologic examination
- Diagnosis of a deep incisional SSI by a surgeon or attending physician

An **organ/space SSI** must meet the following criterion:

Infection occurs within 90 days after the operative procedure and the infection appears to be related to the operative procedure **AND** infection involves any part of the body, excluding the skin incision, fascia or muscle layers, that is opened or manipulated during the operative procedure **AND** the patient has at least **ONE** of the following:

- Purulent drainage from a drain that is placed through a stab wound into the organ/space
- Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space
- An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation or by histopathologic or radiologic examination

Table A1: Rate of central line-associated bloodstream infection per 1,000 line days by intensive care unit type, 2018–2022

Year	Adult mixed ICU	Adult CVICU	NICU	PICU
2018	1.07	0.78	1.77	1.92
2019	1.42	0.61	2.01	1.75
2020	1.74	0.95	1.54	1.70
2021	2.11	1.00	1.90	1.32
2022	1.93	0.83	1.53	1.61
Overall	1.66	0.82	1.75	1.65

Abbreviations: CVICU, cardiovascular intensive care unit; ICU, intensive care unit; NICU, neonatal intensive care unit; PICU, paediatric intensive care unit

Table A2: Rate of hip and knee surgical site infections per 100 surgeries, 2018–2022

Year	Hip	Knee
2018	0.88	0.31
2019	0.78	0.34
2020	0.47	0.34
2021	0.66	0.27
2022	0.75	0.42
Overall	0.71	0.34

Table A3: Cerebrospinal fluid shunt surgical site infection rates per 100 surgeries by hospital type, 2018–2022

Year	Adult and mixed hospitals	Paediatric hospitals	All hospitals[a]
2018	1.84	1.56	1.70
2019	3.25	4.55	3.82
2020	2.17	2.97	2.73
2021	1.75	2.79	2.31
2022	2.14	4.26	3.25
Overall	2.50	3.15	2.85

[a] All hospitals include adult, mixed, and paediatric hospitals participating in cerebrospinal fluid shunt surgical site infection surveillance

Table A4: Paediatric cardiac surgical site infection rates per 100 surgeries, 2018–2022

Year	Rate
2018	7.46
2019	5.04
2020	3.46
2021	3.31
2022	2.38
Overall	3.93

SCOPING REVIEW

Thematic description of factors linked with extended-spectrum beta-lactamase-producing Enterobacteriaceae in humans

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Abstract

Background: Extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae are associated with serious antimicrobial-resistant infections in Canadians. Humans are exposed to ESBL-producing Enterobacteriaceae through many interconnected pathways. To better protect Canadians, it is important to generate an understanding of which sources and activities contribute most to ESBL exposure and infection pathways in Canada.

Objective: The aims of this scoping review were to thematically describe factors potentially associated with ESBL-producing Enterobacteriaceae colonization, carriage and/or infection in humans from countries with a very high human development index and describe the study characteristics.

Methods: Four databases (PubMed, CAB Direct, Web of Science, EBSCOhost) were searched to retrieve potentially relevant studies. Articles were screened for inclusion, and factors were identified, grouped thematically and described.

Results: The review identified 381 relevant articles. Factors were grouped into 13 themes: antimicrobial use, animals, comorbidities and symptoms, community, demographics, diet and substance use, health care, household, occupation, prior ESBL colonization/carriage/infection, residential care, travel, and other. The most common themes reported were demographics, health care, antibiotic use and comorbidities and symptoms. Most articles reported factors in hospital settings (86%) and evaluated factors for ESBL-producing Enterobacteriaceae infections (52%).

Conclusion: This scoping review provided valuable information about which factor themes have been well described (e.g., health care) and which have been explored less frequently (e.g., diet or animal contact). Themes identified spanned human, animal and environmental contexts and settings, supporting the need for a diversity of perspectives and a multisectoral approach to mitigating exposure to antimicrobial resistance.

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Keywords: ESBL, Enterobacteriaceae, risk factors, humans, knowledge synthesis

Introduction

Antimicrobial resistance (AMR) is a real and growing public health threat (1). Infections caused by extended-spectrum beta-lactamase (ESBL)-producing bacteria are a major concern because beta-lactam antibiotics are commonly used to treat a variety of infections, and some classes, such as third-generation cephalosporins and monobactams are listed as critically important for use in human medicine by the World Health Organization (2,3). Further, infections with ESBL-producing

bacteria are associated with increased likelihood of severe illness and mortality and can result in treatment failures, which can lead to increased hospital-stay duration and hospital costs (4,5).

In 2018, it was reported that approximately one in four bacterial infections in Canada were resistant to first-line antibiotics, which led directly to approximately 14,000 deaths (5). Additionally, AMR has been reported to lead to negative socio-economic outcomes, including increased healthcare costs, loss of productivity, increased inequality and decreased trust in the government and public health agencies (5,6). Therefore, AMR consequences are far-reaching and have widespread implications to humans, animals and society.

The primary producers of ESBLs are Enterobacteriaceae, notably *Escherichia coli* and *Klebsiella pneumoniae*, and these bacteria are being increasingly identified in Canada, and worldwide (7–9). Extended-spectrum beta-lactamase-producing Enterobacteriaceae are widely dispersed among populations (9–11), including carriage or colonization within healthy individuals, and those with serious infections (e.g., urinary tract, bloodstream, pneumonia) (5,12,13).

Extended-spectrum beta-lactamase-producing Enterobacteriaceae have also been detected in companion animals, livestock, wildlife, water, soil, vegetables, meat and seafood, all of which can be possible sources of exposure for humans (11,14,15). Because of the variety of exposure pathways, a One Health approach that considers the interconnections between humans, animals, and their shared environments is required to cover the full scope of this growing public health threat (16,17).

Past systematic reviews have explored factors associated with ESBL-producing Enterobacteriaceae colonization and infections (13,18–27); however, systematic reviews are intentionally narrow in scope, providing knowledge on specific research questions. This project aimed to describe the breadth of factors previously reported to be associated with ESBL-producing Enterobacteriaceae in Canada or similar countries. This information could be used to inform various parallel projects within the Public Health Agency of Canada, such as the Integrated Assessment Model of Antimicrobial Resistance (iAM.AMR) project (15,28), and to help better understand Canadians' exposure to antimicrobial-resistant bacteria. Therefore, the objectives of this scoping review were 1) to thematically describe factors potentially associated with ESBL-producing Enterobacteriaceae colonization, carriage and/or infection in humans from countries with a very high human development index, and 2) to describe the study characteristics.

Methods

Below the methods are described in brief. For a full description of the methodology, refer to Goltz *et al.* (29).

Protocol registration

An *a priori* protocol of this scoping review is available online. This review followed the methodological framework described by Arksey and O'Malley (30), and the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension for Scoping Reviews (31).

Search strategy

Search terms and databases searched are described in the protocol document. Four databases (PubMed, CAB Direct, Web of Science and EBSCOhost) were searched through the University of Guelph McLaughlin Library to retrieve potentially relevant articles. The search string for this review was adapted from Murphy *et al.* (32), with consultation from co-authors, in addition to a University of Guelph librarian. All databases were filtered to only include articles published in English. The initial search was completed in August 2020 and updated in August 2021.

Search results were uploaded into the EndNote X9.3.3 (Clarivate Analytics, Philadelphia, United States), deduplicated, and then uploaded to DistillerSR (Evidence Partners, Ottawa, Canada), for additional deduplication, eligibility screening and data extraction.

Eligibility criteria

To meet the inclusion criteria, articles needed to be primary research, be from countries similar to Canada with a very high human development index (33), be written in English, and contain quantifying associations between factors and ESBL-producing Enterobacteriaceae colonization, carriage and/or infection in humans. No articles were excluded based on publication year, study population characteristics (e.g., age, sex or health status) or study setting (e.g., household or hospital). These inclusion criteria were selected because of the Canadian focus of this article, and therefore aimed to identify articles with Canadian and similar populations. Further, only English articles were included due to available language resources. Relevant systematic reviews and meta-analyses were excluded but their reference lists were used to identify additional articles that were not captured by the search.

Selection of articles

The DistillerAI tool feature was used to screen titles/abstracts. The DistillerAI tool was trained by two reviewers using 226 articles. Once trained, all titles/abstracts were screened by the DistillerAI tool and a human reviewer. Title/abstract screening conflicts were resolved by a third human reviewer. Articles included based on title/abstract had the full text screened by two

reviewers and conflicts were resolved through discussion by the two reviewers.

Data charting

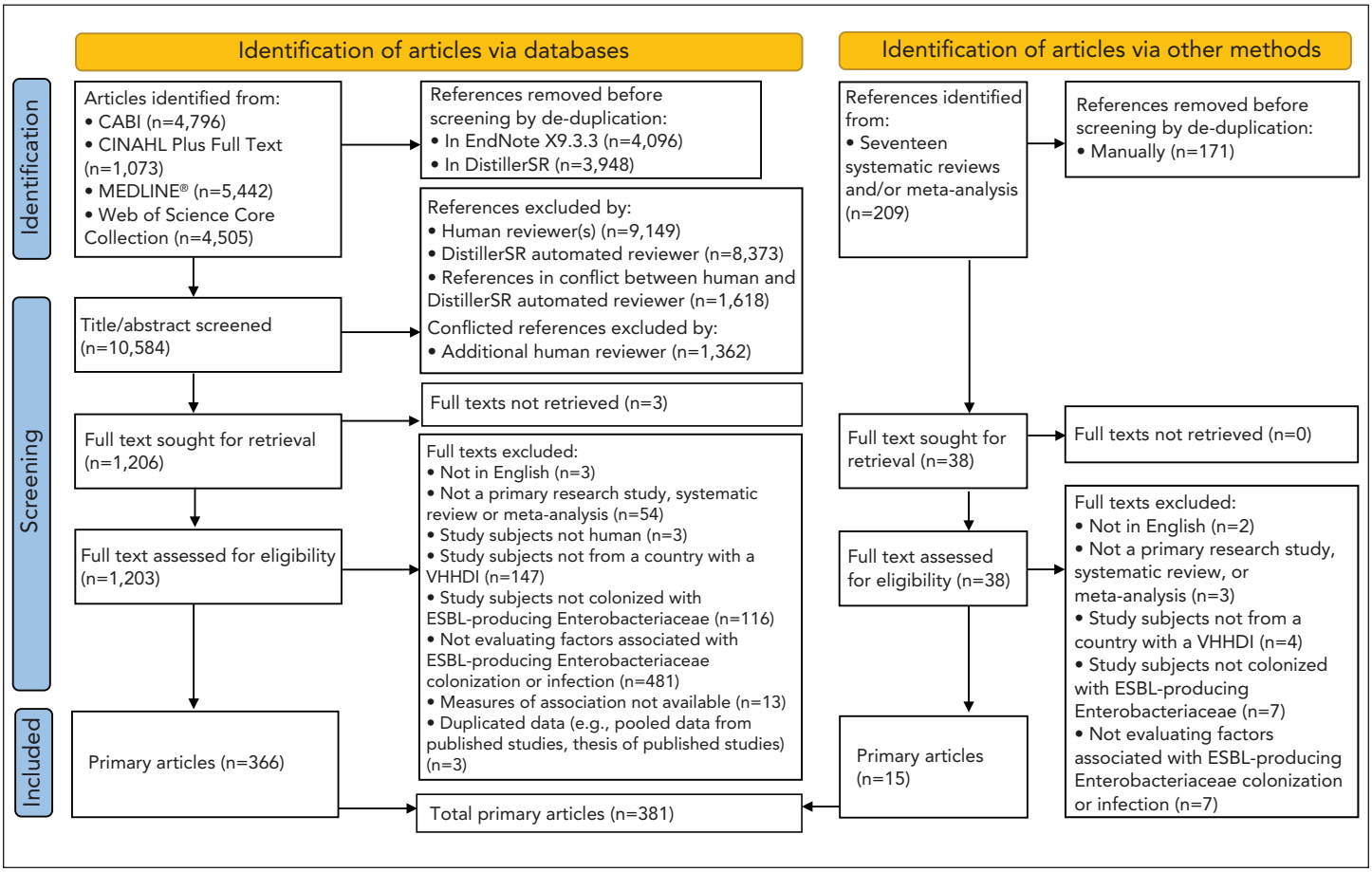
Following full text review, relevant data were charted using DistillerSR by a single reviewer. Data extracted included: publication year, study design, country region (based on World Health Organization regions) (34), data collection method (primary, e.g., questionnaire or interview; secondary, e.g., database or medical charts), sample setting (e.g., hospital), outbreak episode, age of participants, microorganisms evaluated, type of colonization, carriage, or infection evaluated and factor themes (n=13). A factor was defined as a measured observation (e.g., penicillin use) that was investigated for its relationship with ESBL-producing Enterobacteriaceae (32,35). Individual factors were grouped into 13 themes created through an iterative process informed by previous work (15). Themes were 1) antimicrobial use (i.e., antibacterial, antiviral, antifungal), 2) animals (i.e., contact with animals), 3) comorbidities and symptoms (i.e., conditions or presenting symptoms), 4) community (i.e., factors that occur in the community), 5) demographics, 6) food and consumption, 7) health care (i.e., factors that occur in a hospital setting or are related to receiving health care), 8) household (i.e., factors that occur at the home), 9) occupation (i.e., factors related to employment), 10) prior ESBL colonization/carriage/infection, 11) residential care (i.e., factors that occur in a residential setting such as a nursing home), 12) travel (i.e., factors related to international travel) and 13) other factors (i.e., factors that did not fall into a previously defined theme). If a factor belonged to more than one theme (e.g., patient took antibiotics while on vacation), it was recorded in all relevant themes (e.g., antimicrobial use and travel).

Results

Study screening and inclusion

After deduplication, 10,584 eligible records were identified. Following screening (abstract/title, full text), 366 articles were included. Screening also identified 17 systematic reviews and/or meta-analyses and 15 additional articles were identified through review of their reference lists. Therefore, 381 articles were included in this review, published between 1991 and August 5, 2021 (**Figure 1**).

Figure 1: Flow diagram of the interface search, screening process and included articles to identify articles reporting risk factors for extended-spectrum beta-lactamase-producing Enterobacteriaceae in humans[a]



Abbreviations: ESBL, extended-spectrum beta-lactamase; VHHDI, very high human development index
[a] Adapted from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram factor themes (36)

Across the 381 included articles, factors were grouped into 13 themes: health care (n=325 articles), antimicrobial use (n=325), demographics (n=319), comorbidities and symptoms (n=307), residential care (n=76), travel (n=76), prior ESBL colonization/carriage/infection (n=44), food and consumption (n=44), household (n=29), occupation (n=29), animal (n=25), community (n=11) and other (n=146) (additional details available upon request). Each theme covered a wide range of risk factors associated with ESBL-producing Enterobacteriaceae (**Table 1**).

Table 1: Description of factors represented by the factor themes for colonization, carriage and/or infection with extended-spectrum beta-lactamase-producing Enterobacteriaceae reported by the articles included in this review

Factor theme	Factor categories	Factor examples
Antimicrobial use	Antibiotic, antiparasitic, antiviral, antifungal use	Penicillin use Amoxicillin-clavulanate use Fluconazole use
	Status of antimicrobials	Mother given antibiotics before delivery Admitted on antibiotics Inadequate empirical antibiotic treatment
Animal	Animal contact	Cat owner Living with dogs Farm animal contact
	Animal lifestyle	Pet given antibiotics ESBL in pigs Companion animal eats raw meat
Community	Community activities	Public swimming/bathing in freshwater or seawater Playing on a sports team Daycare attendance
Comorbidities and symptoms	History of a medical condition	AIDS Cancer Diabetes
	Comorbidity scores	Charlson comorbidity index ICU chronic disease score Sequential organ failure assessment score
	Symptoms	Blood pressure Fever Septic shock
Demographics	Demographic information	Age Ethnicity Language spoken
Health care	Healthcare setting	Admitted from home Admission to emergency department Prior ICU
	Healthcare setting risks	ESBL-positive prior room occupant Hospital length of stay Hand disinfectant in the patient's room
	Procedures or treatments	Chemotherapy Surgery Acid suppressor use
Household	Household members	Family member is a carrier (mother, father, sister) Children younger than 12 years old in the household Household member took antibiotics
	Household setting risks	Shared use of towels Distance to nearest broiler farm
Residential care	Residential care stay	Nursing home residence Long-term care facility stay
	Residential care setting risks	Use of shared bathroom Staff training in hand hygiene Existence of a preferential list of antibiotics
Food and consumption	Food and water type	Chicken consumption Seafood consumption Bottled water
	Food and water source	Purchased from market/shop Own produce/local farmer Central water supply
	Food and water handling	Sterilized feeding bottles Regular/sometimes hand washing before food preparation Dishcloth use longer than one day
	Substance consumption	Alcohol Smoking Illicit drugs
Prior ESBL colonization/ carriage/ infection	Prior ESBL-producing organism	Prior ESBL colonization Prior ESBL infection
Occupation	Occupation type	Veterinarian Farmer Caregiver
	Occupation setting risks	Average number of hours working on the pig farm per week Contact with patient's excretions Assistance in patient's wound care
Travel	Travel risks	Visited other country Health care abroad Accommodation type (e.g., camping, house, hotel, with locals)
Other	Acquisition/ onset location	Community acquisition Acquired prior to admission Nosocomial onset
	Time of acquisition	Season Year of sample
	Details about bacteria	Resistant genes Polymicrobial information

Abbreviations: ESBL, extended-spectrum beta-lactamase; ICU, intensive care unit

Study characteristics

A summary description of the articles is reported in **Table 2**. Of the 381 articles included, 378 were observational study designs, and three were experimental. Most of the studies (n=235) were conducted in European Region countries, including six multinational studies (Table 2). Seven studies were conducted in Canada.

Over half (56%) of all articles reported data for specific age groups with the most common being adults/young adults (33%). Eighteen articles (5%) reported factors as part of an ESBL-producing Enterobacteriaceae outbreak (all in hospital settings). For most studies (53%), data were reported from secondary data sources (e.g., databases, medical charts), with 20% from primary data sources (e.g., questionnaires, interviews) and 7% from both primary and secondary data sources. For 20% of the studies, it was unclear how the data were obtained (Table 2).

Articles often reported factors for Enterobacteriaceae (40%), but many reported specific microorganisms including *E. coli* (20%), *K. pneumoniae* (11%), *Enterobacter cloacae* (1%), *Klebsiella* spp. (1%), *Proteus mirabilis* (1%), and *Providencia stuartii* (1%). Other articles sought to report different combinations of Enterobacteriaceae species (e.g., *Klebsiella* spp. and *E. coli*) (Table 2).

Most articles were performed in hospital settings (86%), followed by non-hospital healthcare settings (7%), community settings (6%), and residential care facilities (4%). Eleven of these articles were sampled from multiple of these different sample settings (Table 2). Overall, the highest number of articles identified for each factor theme were those that had performed their study in hospital settings, except for the community theme (**Figure 2**).

Articles reported factors for 1) infection (52%), 2) colonization/carriage (33%), and 3) colonization/carriage/infection (13%) (**Table 3**). Factors potentially associated with ESBL-producing Enterobacteriaceae infections were reported in over half of the articles (52%) (mostly bloodstream infections or urinary tract infections). More articles identified factors for infection than colonization/carriage (**Figure 3**), especially for the factor themes antimicrobial use, demographics, comorbidities/symptoms and health care. Colonization/carriage was reported in a third of the articles (33%), with most focused on gastrointestinal carriage. Animal, community, food and consumption, household, occupation and travel themes were more frequently reported for colonization/carriage (Figure 3). For eight articles (2%) it was unclear whether the study was reporting colonization/carriage or infection.

Table 2: Study characteristics of the included articles

Study characteristics	Number of articles	
	n	%
Study design		
Observational	378	99
Experimental	3	1
Country region		
European Region[a]	235	62
Western Pacific Region	78	20
Region of the Americas	60	16
Eastern Mediterranean Region	8	2
Age group		
Adults/young adults	125	33
Children	40	11
Neonates/newborns/infants	19	5
Multiple defined age groups (e.g., children and adults)	15	4
Elderly	14	4
Undefined	168	44
Setting where samples were obtained[b]		
Hospital	328	86
Non-hospital health care	27	7
Community	22	6
Residential care facilities	16	4
Outbreak		
No	363	95
Yes	18	5
Factor data collection method		
Secondary data (e.g., databases, medical charts)	201	53
Primary data (e.g., questionnaire, interview)	76	20
Multiple data collection methods (i.e., primary and secondary data)	27	7
Unclear	77	20
Microorganisms evaluated		
Enterobacteriaceae[c]	154	40
Escherichia coli	78	20
Klebsiella pneumoniae	42	11
Enterobacter cloacae	4	1
Klebsiella spp.	2	1
Proteus mirabilis	2	1
Providencia stuartii	1	1
Other[d]	98	26

[a] Six multinational articles within the European Region
[b] Eleven articles sampled from multiple of these different sample settings
[c] Studies evaluating Enterobacteriaceae, Enterobacterales or Enterobacteria
[d] Different combinations of bacteria species not described broadly as Enterobacteriaceae (e.g., *K. pneumoniae* and *E. coli*, bacterial isolates/cultures, gram-negative bacteria)

Table 3: Description of reported extended-spectrum beta-lactamase-producing Enterobacteriaceae outcomes reported in the included articles

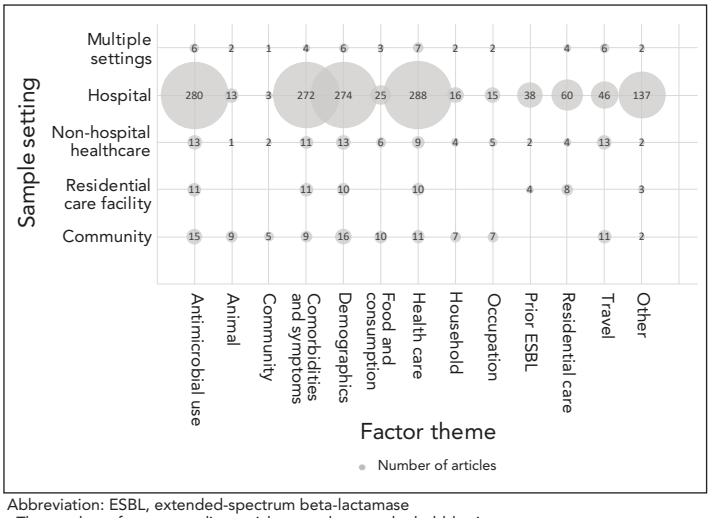
Colonization/carriage and/or infection details	Number of articles[a]	
	n	%
Infection	**198**	**52**
Bacteremia/bloodstream infection	75	20
Urinary tract infection	52	14
Non-specific cultures (e.g., general surveillance or database records)	49	13
Acute pyelonephritis	5	1
Acute bacterial prostatitis	2	1
Bacteremia/bloodstream infection and urinary tract infection	1	1
Bacteremia/bloodstream infection, urinary tract infection and catheter-associated infection	1	1
Bacteremic spontaneous bacterial peritonitis	1	1
Catheter-associated urinary tract infection	1	1
Complicated cystitis	1	1
Foot infection	1	1
Genital tract infections	1	1
Peritonitis	1	1
Pneumonia	1	1
Sepsis	1	1
Spontaneous bacterial peritonitis	1	1
Sternal wound infection	1	1
Urinary tract infection/acute pyelonephritis	1	1
Urosepsis	1	1
Ventilator-associated pneumonia	1	1
Colonization/carriage	**125**	**33**
Gastrointestinal (e.g., fecal, stool, rectal, peri-rectal)	110	29
Non-specific cultures (e.g., general surveillance or database records)	5	1
Gastrointestinal and nasal	2	1
Gastrointestinal and vaginal	2	1
Gastrointestinal, vaginal and nasopharyngeal	1	1
Gastrointestinal, nasal and navel	1	1
Gastrointestinal, nasal, oropharyngeal and urine	1	1
Gastrointestinal, nasal and throat	1	1
Skin	1	1
Urinary	1	1
Colonization/carriage and/or infection	**51**	**13**
Non-specific colonization/carriage and/or non-specific infection	38	10
Urinary colonization/carriage and/or urinary tract infection	6	1
Gastrointestinal colonization/carriage and/or non-specific infection	5	1
Respiratory colonization/carriage and/or infection	1	1
Urinary colonization/carriage and/or urinary tract infection, cystitis and pyelonephritis	1	1

Table 3: Description of reported extended-spectrum beta-lactamase-producing Enterobacteriaceae outcomes reported in the included articles (*continued*)

Colonization/carriage and/or infection details	Number of articles[a]	
	n	%
Unclear	**8**	**2**
Non-specific isolation	7	2
Urinary isolation	1	1

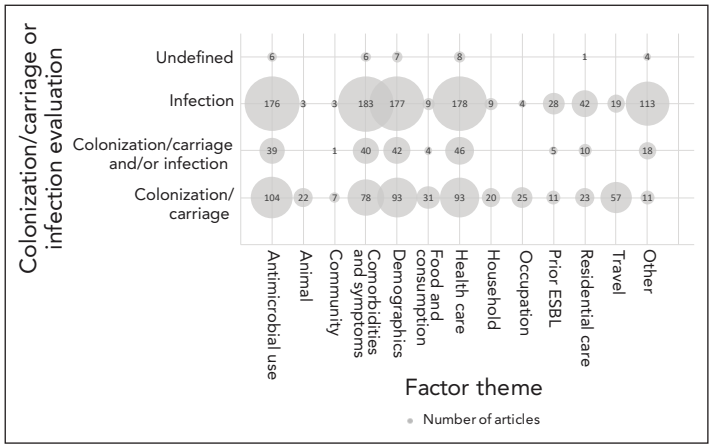
[a] Four articles had two extended-spectrum beta-lactamase-producing Enterobacteriaceae outcome evaluations

Figure 2: Factor themes reported in the articles by study sample setting for colonization/carriage and/or infection with extended-spectrum beta-lactamase-producing Enterobacteriaceae[a]



Abbreviation: ESBL, extended-spectrum beta-lactamase
[a] The number of corresponding articles correlates to the bubble size

Figure 3: Factor themes reported in the articles by the study evaluation of colonization/carriage or infection for colonization/carriage and/or infection with extended-spectrum beta-lactamase-producing Enterobacteriaceae[a]



Abbreviation: ESBL, extended-spectrum beta-lactamase
[a] The number of corresponding articles correlates to the bubble size

Many comparison groups were reported (**Table 4**). The most common was an ESBL-positive Enterobacteriaceae culture compared with an ESBL-negative Enterobacteriaceae culture (n=171). Twenty articles reported two comparator groups (e.g., case-case-control studies).

Table 4: Reporting of outcome comparisons among articles for colonization/carriage and/or infection with extended-spectrum beta-lactamase-producing Enterobacteriaceae in the included articles

Positive outcome (e.g., cases)	Negative outcome (e.g., controls)	Number of articles[a]	
		n	%
ESBL-positive for Enterobacteriaceae culture (e.g., ESBL-producing *E. coli* urine culture)	ESBL-negative for the same explicitly defined Enterobacteriaceae culture (e.g., non-ESBL-producing *E. coli* urine culture)[b]	171	45
ESBL-producing Enterobacteriaceae colonization/carriage positive (e.g., ESBL-producing *E. coli* fecal sample)	Negative for same explicitly defined ESBL-producing Enterobacteriaceae colonization/carriage (e.g., negative for ESBL-producing *E. coli* fecal sample)[c]	119	31
ESBL-producing Enterobacteriaceae infection positive (e.g., ESBL-producing *E. coli* UTI)	Negative for same explicitly defined ESBL-producing Enterobacteriaceae infection (e.g., negative for ESBL-producing *E. coli* UTI)[d]	34	9
ESBL-producing Enterobacteriaceae colonization/carriage and/or infection (e.g., ESBL-producing Enterobacteriaceae colonization/carriage or infection)	Negative for same explicitly defined ESBL-producing Enterobacteriaceae colonization/carriage and/or infection (e.g., negative for ESBL-producing Enterobacteriaceae colonization/carriage or infection)[e]	32	8
ESBL positive for Enterobacteriaceae culture (e.g., ESBL-producing Enterobacteriaceae urine culture)	ESBL negative for a combination of explicitly defined Enterobacteriaceae and non-Enterobacteriaceae of the same culture (e.g., non-ESBL-producing Enterobacteriaceae and non-ESBL-producing non-Enterobacteriaceae urine culture)[f]	16	4
ESBL positive for Enterobacteriaceae culture (e.g., ESBL-producing *E. coli* urine culture)	ESBL negative for bacteria that was not explicitly defined of the same culture (e.g., non-ESBL-producing bacterial urine culture)[g]	7	2
Developed an ESBL-producing Enterobacteriaceae infection	Positive for ESBL-producing Enterobacteriaceae colonization/carriage	6	2
CTX-M-producing Enterobacteriaceae	Different genotype producing Enterobacteriaceae (e.g., TEM or SHV-producing Enterobacteriaceae)	5	1
Positive for ESBL-producing Enterobacteriaceae culture (e.g., ESBL-producing *E. coli* blood culture)	ESBL-negative with a different explicitly defined Enterobacteriaceae or non-Enterobacteriaceae bacteria culture (e.g., non-ESBL-producing *K. pneumoniae* or *Pseudomonas* spp. blood culture)	5	1
Positive for ESBL-producing Enterobacteriaceae culture acquired in a specified setting (e.g., community-acquired *E. coli* UTI)	Positive for ESBL-producing Enterobacteriaceae culture acquired in a different specified setting (e.g., hospital-acquired *E. coli* UTI)	2	1
Positive for ESBL-producing Enterobacteriaceae colonization/carriage in combination with an ESBL-producing Enterobacteriaceae infection	Positive for ESBL-producing Enterobacteriaceae colonization/carriage in combination with an infection not caused by ESBL-producing Enterobacteriaceae	2	1
ESBL-positive for Enterobacteriaceae culture (e.g., ESBL-producing *E. coli* urine)	ESBL-positive for Enterobacteriaceae from a different culture (e.g., ESBL-producing *E. coli* blood)	1	1
ESBL-positive Enterobacteriaceae culture (e.g., ESBL-producing *E. coli* blood culture)	The same culture with any other bacteria than the compared ESBL-positive Enterobacteriaceae strain (i.e., cultures could be negative or positive for any bacteria blood culture except ESBL-producing *E. coli*)	1	1

Abbreviations: *E. coli*, *Escherichia coli*; ESBL, extended-spectrum beta-lactamase; UTI, urinary tract infection

[a] Twenty articles provided two comparisons

[b] Control groups were non-ESBL producers but may have other resistance-susceptibility profiles

[c] Control groups were negative for the same ESBL-producing Enterobacteriaceae colonization/carriage; however, the controls were positive or negative for the presence of other Enterobacteriaceae or non-Enterobacteriaceae cultures

[d] Control groups were negative for the same ESBL-producing Enterobacteriaceae infection; however, the controls were positive or negative for the presence of other Enterobacteriaceae or non-Enterobacteriaceae cultures

[e] Control groups were negative for the same ESBL-producing Enterobacteriaceae colonization/carriage and/or infection. However, the presence of other Enterobacteriaceae or non-Enterobacteriaceae cultures were not explicitly reported

[f] Control group explicitly reported Enterobacteriaceae in combination with non-Enterobacteriaceae families (e.g., *E. coli*, *Klebsiella* spp., and *Pseudomonas* spp.)

[g] Control group did not explicitly report bacterial species within the study; therefore, it was unclear whether the control group included only Enterobacteriaceae cultures or whether non-Enterobacteriaceae species cultures were included

Discussion

In this scoping review, we identified 381 articles reporting factors for ESBL-producing Enterobacteriaceae. Most of the included articles were published in the last 10 years, likely corresponding to the urgency to understand the growing rates of human acquisition of ESBL-producing Enterobacteriaceae and the exponential growth of scientific publications generally (8,37–39). It is noteworthy that most articles focused on factors related to antimicrobial use, comorbidities/symptoms, demographics and health care, and that only a small proportion of identified articles reported factors associated with animal contact, community, and food and consumption; mainly related to colonization/carriage of ESBL-producing Enterobacteriaceae. Although there were fewer articles that reported these themes, they may provide important information as previous articles have suggested that animal contact, food consumption and household or community transmission may play a role in ESBL-producing Enterobacteriaceae exposure (11,17,40–42). It is unclear whether the individual factors that were most frequently reported in these articles were in fact more often associated with ESBL-producing Enterobacteriaceae (i.e., had larger measures of association), whether they had been evaluated and reported more frequently than others, or whether studies evaluating these factors were better funded.

Study setting may be an explanation for the larger number of articles on antimicrobial use, comorbidities/symptoms, demographics and health care factors reported. Most articles were conducted in hospital settings and over half of the articles used secondary sources of information (e.g., medical records or databases). This setting and source combination may have been selected on account of the relative ease of accessibility to the data. Factors associated with resistant infections in hospitals are major concerns, and therefore are an important area of research. Although some factors reported from hospital settings may be connected to those in the community settings (e.g., taking medication), factors reported from hospital settings may not be representative of factors from community settings (e.g., populations, comorbidities, varying activities). Thus, the results from studies conducted in hospital settings are not generalizable to other settings.

This review identified studies where the subjects were sampled from countries with a very high human development index (33) as we were interested in factors relevant to the Canadian context. Most studies were conducted in the European Region (n=235), followed by the Western Pacific (n=78), the Americas (n=60) and the Eastern Mediterranean (n=8). Only seven studies were performed in Canada; however, a large body of literature was collected that can be used to understand the existing knowledge of factors associated with acquiring ESBL-producing Enterobacteriaceae in similar populations. Although these countries have similarities, differences in policies and practices may limit the generalizability of the data specifically to Canada.

Several articles reported similar factors for Enterobacteriaceae infection, regardless of their AMR status, including comorbidities, demographics and health care (43–45). Factors associated with ESBL-producing Enterobacteriaceae colonization or infection may be related to bacterial traits rather than distinguishing between susceptible and resistant bacteria, which is important because interventions that target the pathogen, regardless of the resistance, are likely effective at reducing both resistant and susceptible strains. This highlights the importance of selecting the appropriate comparator (control group) for the intended research question and interpretation of findings. Many different outcome comparators were identified in our review. Each comparison combination provides different information that contributes to a better overall understanding of factors associated with ESBL-producing Enterobacteriaceae.

This article reports the breadth of factors associated with ESBL-producing Enterobacteriaceae reported in the literature. Many references frequently reported demographic factors (e.g., age and ethnicity) and groups that may be particularly vulnerable. While these factors cannot be modified, they can be used to identify particularly vulnerable groups for which interventions can be targeted. Other articles reported modifiable factors (e.g., food, travel, antimicrobial use), which can be targeted as interventions and potentially implemented immediately (e.g., food-related interventions), noting dependencies on feasibility and cost, whereas others may require more gradual, multi-pronged solutions (e.g., reducing comorbidities). A multidisciplinary approach to address feasible health-promoting strategies and the complex nature of AMR with multiple drivers is necessary.

Work is currently underway to better describe the factors identified in these articles. This will provide the number of factors reported per study and quantitative data reported for these factors (i.e., the strength and direction of association between the factor and ESBL-producing Enterobacteriaceae). Further, factors from this review will be used to populate models within the iAM.AMR project (15,28) to improve our understanding of the pathways of human exposure to ESBL-producing Enterobacteriaceae. This information will help to inform which human characteristics, behaviours and actions impact the probability of becoming colonized or infected with ESBL-producing Enterobacteriaceae and to identify which factors to prioritize for interventions. This information will be valuable for understanding how to advise Canadians about mitigating their probability of acquiring resistant bacteria and reducing the negative health impacts associated with infection.

Limitations

Articles were identified from select online databases, omitting research from grey literature. This may have introduced a publishing bias, as findings that were not disseminated through peer-reviewed publications were not reviewed for inclusion (e.g., theses and dissertations, government reports) and articles

with null, negative or inconclusive findings are less likely to be published (46). Language bias was a consideration as the review was constrained to English-language articles; however, the impact of this bias was likely negligible as approximately 98% of science publications are written in English (47,48).

Another limitation included single reviewer data extraction on account of resource limitations. Multiple individuals extracting study data reduces errors and misclassification bias (49). To mitigate these types of errors and to identify errors in data extraction, the authors were involved in both data collection development and analysis.

Lastly, the grouping of factors into themes evolved during data extraction. Grouping factors into themes was challenging because of differences in terminology used, the populations studied, and definitions applied. Combining data from different studies was onerous due to heterogeneity of the study data (e.g., same variable measured on different scales, missing data) (50). Terms, including carriage and colonization, were not standardized across studies and were used interchangeably; therefore, some data had to be combined (e.g., colonization and/or carriage) or captured as "unclear."

Conclusion

This review synthesized evidence from a large collection of articles reporting factors associated with ESBL-producing Enterobacteriaceae colonization, carriage and/or infections in humans within very high human development index countries. Factors were reported in many different settings, age groups and organisms, and using different outcome comparison groups. This variability between studies highlighted the need for transparent or, where possible, harmonized reporting of methods to allow for appropriate interpretations and comparisons between the factors reported. Overall, studies conducted in hospital settings predominated and the most common factor themes reported were antimicrobial use, comorbidities/symptoms, demographics and health care. Articles reporting animal contact, food consumption/practices and activities in the community were not as numerous and thus limited information about these factors were identified. There is a need for more studies examining factors associated with ESBL-producing Enterobacteriaceae in the community, which have been identified as being of concern (6,8).

This scoping review synthesized knowledge about potential sources and activities that affect the risk of human exposure to ESBL-producing Enterobacteriaceae. Factor themes identified spanned human, animal and environmental contexts and settings support the need for a diversity of perspectives and a multisectoral approach to AMR. The results of this article will help guide recommendations to reduce the risk of acquiring ESBL-producing Enterobacteriaceae for Canadians, as well as other similar countries, while considering numerous sources of exposure in various settings. These results will also guide future research for activities and in settings that are understudied.

Authors' statement

JG — Conceptualization, methodology, formal analysis, writing–review & editing
CU — Formal analysis, writing–review & editing
SP — Formal analysis, review & editing
CM — Conceptualization, methodology, review & editing
CAC — Conceptualization, methodology, review & editing
EJP — Conceptualization, methodology, formal analysis, review & editing

Competing interests

JG, CU, SP, CM and CAC have no conflicts of interest to declare. EJP is (or has been in the last five years) engaged in research grants/contracts funded by the Canadian Institutes of Health Research, the Natural Sciences and Engineering Research Council, the Ontario Ministry of Agriculture, Food and Rural Affairs, the Public Health Agency of Canada, and the Canadian Safety and Security Program. She is currently President of the Board of Directors of the Centre for Coastal Health, member of the Board of Directors of the McEachran Institute, member of the Advisory Council for Research Directions: One Health, and a member of the Royal Society of Canada One Health Working Group. Prior to February 2019, she was employed by the Public Health Agency of Canada.

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EPIDEMIOLOGIC STUDY

Characteristics associated with SARS-CoV-2 testing, infection and vaccine uptake among essential non-healthcare workers in Montréal, 2021

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Abstract

Background: Essential non-healthcare workers experienced higher rates of SARS-CoV-2 infection compared to non-essential workers.

Objective: Identify characteristics associated with SARS-CoV-2 testing, infection and vaccine uptake among essential non-healthcare workers in Montréal, Québec.

Methods: Secondary, cross-sectional analysis of data collected from participants prospectively recruited in two observational studies (first study, Onsite Testing Study, January–March 2021; second study, Self-Testing Study, July–October 2021) of essential non-healthcare workers in 2021. Logistic regression with generalized linear mixed models was used to explore characteristics associated with our outcomes (previous SARS-CoV-2 testing, exposure and vaccination).

Results: Overall, 2,755 participants were included (first study, Onsite Testing Study, n=2,128; and second study, Self-Testing Study, n=627). A higher proportion of participants identified as male (n=1,601; 58%), non-White (n=1,527; 55%) and worked in the manufacturing/supplier sector (n=1,706; 62%). Relative to the first study, Onsite Testing Study, participants in the second study, Self-Testing Study, had higher odds (78% vs. 46%; aOR 4.1, 95% CI: 3.2–5.2) of previous SARS-CoV-2 testing and of testing positive prior to study enrolment (6.2% vs. 4.3%; aOR 1.7, 95% CI: 1.1–2.6). Individuals reporting recent SARS-CoV-2 exposure had higher odds of previous SARS-CoV-2 testing (aOR 4.0, 95% CI: 3.0–5.4), while older age (aOR 0.98, 95% CI: 0.98–0.99 per one-year increase) and being male (aOR 0.6, 95% CI: 0.5–0.7) were associated with lower odds of previous testing. Results were similar in stratified analyses. Participants from businesses with more than 50 employees had higher odds of having received a SARS-CoV-2 vaccine (91% vs. 80%; aOR 2.6, 95% CI: 1.4–4.8).

Conclusion: Consideration of individual and business characteristics associated with testing and vaccination programs for SARS-CoV-2 could improve equity, uptake and impact.

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Introduction

The SARS-CoV-2 transmission continues globally (1). Certain populations have been differentially impacted by SARS-CoV-2, such as visible minorities and those with jobs considered "high risk" (2). Notably, essential non-healthcare workers working in-person have experienced higher rates of SARS-CoV-2 infection compared to non-essential workers and those who were able to work from home (3–6). In Montréal, Canada, essential non-healthcare workplaces were most commonly implicated in large outbreaks (7).

In 2021, we conducted two studies among non-healthcare essential workers in Montréal, Canada. In the first study, we visited businesses to assess onsite sampling for SARS-CoV-2 testing from January to March 2021 (8); a period with substantial public health measures to curb SARS-CoV-2 transmission and prior to the wide availability of SARS-CoV-2 vaccines. In the second study, we evaluated self-testing for SARS-CoV-2 with rapid diagnostic tests in similar businesses, from July to October 2021 (9); a period with minimal public health measures in effect and after all adults were eligible for SARS-CoV-2 vaccination (10). These studies, conducted among similar populations during periods with differential public health measures and vaccine availability, provide an opportunity to better understand characteristics associated with SARS-CoV-2 testing and infection, vaccine uptake and population behaviours.

The aim of this study was to leverage data collected during two prospective studies among individuals from non-healthcare businesses in Montréal in 2021, to conduct descriptive, exploratory analyses to identify characteristics associated with SARS-CoV-2 testing and infection, vaccine uptake, and population behaviours (e.g., travel outside Montréal and the province of Québec).

Methods

Study designs, participants and procedures

We conducted a secondary analysis of data collected from participants prospectively recruited in two studies. The first (hereafter, the "Onsite Testing Study") was a prospective, cross-sectional study taking place from January 27 to March 12, 2021, and the second (hereafter, the "Self-Testing Study") was a prospective, cross-sectional study from July 7 to October 8, 2021. Identical questionnaires were used in both studies except for additional questions related to vaccination in the Self-Testing Study, **Appendix 1**, **Supplemental material**. Detailed descriptions of the individual studies are available elsewhere (8,9).

Onsite Testing Study

In this study, non-healthcare essential businesses primarily within the borough of Montréal-Nord were contacted. Businesses could be of any size and eligible employees were those 18 years of age and older who were asymptomatic and who had not tested positive for SARS-CoV-2 in the previous four weeks. Our study team visited participating businesses to collect saline gargle samples for SARS-CoV-2 testing from consenting employees present on the day of our visit.

Self-Testing Study

In this study, non-healthcare businesses in the Greater Montréal Area identified by Montréal Public Health as having at least two cases of SARS-CoV-2 within the last 14 days were contacted. Participant eligibility was identical to the Onsite Testing Study. However we preferentially visited businesses with more than 50 employees. At participating businesses, consenting employees present on the day of our visit performed a SARS-CoV-2 rapid antigen detection test (Panbio™ COVID-19 Ag Rapid Test Device; Abbott Laboratories) under the supervision of the study team.

Public health measures and vaccine availability in Montréal during 2021

Public health measures and vaccine availability differed between included studies, with extensive public health measures and travel restrictions within Québec and Canada in place during the Onsite Testing Study period, and comparatively fewer measures and interprovincial travel restrictions in effect during the Self-Testing Study period.

Throughout Québec, a province-wide curfew from 8:00 p.m. to 5:00 a.m. was instituted on January 9, 2021, ending on May 28, 2021 (11,12), encompassing the entirety of the Onsite Testing Study period. With respect to travel limitations, non-essential travel was discouraged until May 28, 2021, while the border between Ontario and Québec was closed for non-essential travel from April 19 to June 16, 2021 (13,14). Public health measures also included the closing of all non-essential businesses in Montréal from December 25, 2020, until February 8, 2021 (15,16). Gradually and up to June 28, 2021, most public health measures were relaxed. Gathering and capacity limits, however, remained in place (17) and were increased on August 1, 2021. No additional public health measures were imposed until December 16, 2021, due to the Omicron variant (18,19).

The rollout of SARS-CoV-2 vaccines in Montréal began on March 1 and by May 14, 2021, all adults in Québec were eligible to receive a SARS-CoV-2 vaccine, approximately 10 weeks prior to the start of the Self-Testing Study (10,20).

Statistical analyses

We performed descriptive analyses using medians and interquartile ranges (IQR) for continuous data and proportions for categorical data for individual and business characteristics of the total population, as well as for each study population separately. Characteristics between the two study populations were compared using appropriate statistical tests (i.e., Kruskal-Wallis tests for continuous variables, and chi-squared or Fisher's exact tests for categorical variables).

Individual characteristics evaluated included age (continuous), sex (male, female), self-reported ethnicity (White, non-White), household income based on forward sortation area (top 60% income quintile, bottom 40%), self-reported presence of a health condition (yes, no) and self-reported smoking history (never, current/previous smoker). Business characteristics included sector (manufacturer/supplier, retail/consumer facing, office, childcare) and business size (50 employees or fewer, more than 50 employees). Questionnaires and data harmonization between studies are described in **Appendix 2**, **Supplemental material**, **Tables S1 to S2**, respectively.

We evaluated five outcomes: 1) receipt of a SARS-CoV-2 test prior to study enrolment; 2) positive SARS-CoV-2 test result more than four weeks prior to study enrolment; 3) self-reported travel outside the Montréal area or Québec in the previous 14 days; 4) known SARS-CoV-2 exposure, excluding exposure at workplaces, in the previous 14 days; and 5) receipt of at least one dose of a SARS-CoV-2 vaccine. Each outcome was evaluated in the pooled study population, except for SARS-CoV-2 vaccination, which was only available in the Self-Testing Study.

We performed logistic regression with generalized linear mixed models to estimate the adjusted odds ratio (aOR) and 95% confidence interval (CI) for each outcome, with the business sector treated as a random intercept. Models included weakly informative priors to deal with quasi-complete separation of some fixed effects observed in previous studies (8). Models were adjusted for individual and business characteristics as well as the study (to determine differences in risk between studies), as appropriate. Confounders considered included age, sex, smoking, other health factors, ethnicity, income based on forward sortation area, recent travel outside Québec, exposure to someone with SARS-CoV-2 and business size. We repeated all analyses stratified by study, sex, ethnicity, income and business sector. If directions of effect for characteristics assessed differed significantly, we assessed effect modification using likelihood ratio tests of models with versus without interaction terms. Data were analyzed using R (version 4.2.2) using base packages or the blme (version 1.0–5) and BhGLM (version 1.1.0) packages.

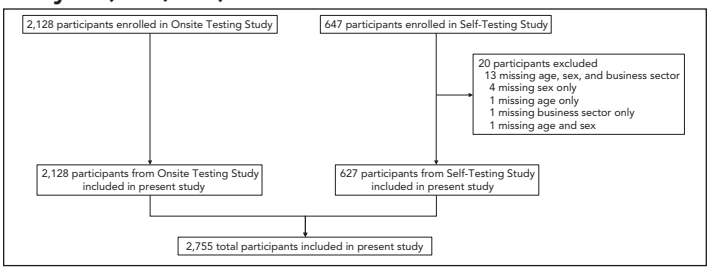
Ethical approval

The original studies were approved by the research ethics board of the Research Institute of the McGill University Health Centre (2021–7057 and MP-37-2022-7762), as was the present study (2023-9046). Given the nature of a secondary analysis of data for the present study, a waiver of informed consent was obtained.

Results

Overall, 2,775 participants completed a questionnaire between the two studies (Onsite Testing Study, n=2,128; Self-Testing Study, n=647), of which 2,755 were ultimately included in this analysis (**Figure 1**). All 20 exclusions pertained to the Self-Testing Study.

Figure 1: Number of participants enrolled in original studies that were ultimately included in the present analysis (n=2,755)



The median age of participants was 48 (IQR: 37–57) years, 1,154 (42%) were female, 1,527 (55%) identified as non-White and many (n=1,704; 62%) lived in areas with household incomes in the two lowest quintiles. Most participants (n=1,706; 62%) worked in the manufacturing/supplier sector and at businesses with more than 50 employees (n=1,755; 64%). Participant characteristics in terms of business sector and size, sex, self-reported ethnicity, and presence of health conditions varied significantly ($p<0.05$) between studies (**Table 1**). Disaggregated participant characteristics regarding ethnicity, income and business sector are in Appendix 2, Table S1.

Compared to participants in the Onsite Testing Study, those in the Self-Testing Study had significantly higher odds (78% vs. 46%; aOR 4.1, 95% CI: 3.2–5.2) of being previously tested for SARS-CoV-2 (**Table 2**). Moreover, participants with recent SARS-CoV-2 exposure had higher odds of previous SARS-CoV-2 testing compared to those without recent exposure (78% vs. 50%; aOR 4.0, 95% CI: 3.0–5.4). Older age (aOR 0.98, 95% CI: 0.98–0.99 per one-year increase) and being male (aOR 0.6, 95% CI: 0.5–0.7) were associated with lower odds. These findings regarding sex being associated with SARS-CoV-2 testing were largely consistent in stratified analysis (Appendix 2, **Tables S2 to S6**); however, we noted significant effect modification of sex by ethnicity, study and sector.

Table 1: Characteristics of included participants in each study and overall

Characteristics	Number and percentage of participants in Onsite Testing Study N=2,128	Number and percentage of participants in Self-Testing Study N=627	Number and percentage of total participants N=2,755	*p*-value
Age, median (IQR), years	48 (IQR: 37–57)	48 (IQR: 34–57)	48 (IQR: 37–57)	0.477
Business sector				
Manufacturing/supplier	1,408 (66.2)	298 (47.5)	1,706 (61.9)	<0.001
Retail/customer facing	426 (20.0)	90 (14.3)	516 (18.7)	
Office	181 (8.5)	239 (38.1)	420 (15.2)	
Childcare	113 (5.3)	0 (0)	113 (4.1)	
Business size				
1–50 employees	895 (42.1)	105 (16.7)	1,000 (36.3)	<0.001
More than 50 employees	1,233 (57.9)	522 (83.2)	1,755 (63.7)	
Sex				
Male	1,320 (62.0)	281 (44.8)	1,601 (58.1)	<0.001
Female	808 (38.0)	346 (55.2)	1,154 (41.9)	
Ethnicity				
White	926 (43.5)	302 (48.2)	1,228 (44.6)	0.0441
Non-White	1,202 (56.5)	325 (51.8)	1,527 (55.4)	
Income				
Highest 60%	797 (37.4)	254 (40.5)	1,051 (38.1)	0.181
Lowest 40%	1,331 (62.5)	373 (59.5)	1,704 (61.8)	
Any health factors				
No	1,681 (79.0)	457 (72.9)	2,138 (77.6)	0.0015
Yes	447 (21.0)	170 (27.1)	617 (22.4)	
Smoking history				
Never smoked	1,668 (78.4)	484 (77.2)	2,152 (78.1)	0.563
Current/previous smoker	460 (21.6)	143 (22.8)	603 (21.9)	
Recent travel outside of Montréal[a]				
Yes	50 (2.3)	111 (17.7)	161 (5.8)	<0.001
No/not reported	2,078 (97.6)	516 (82.3)	2,594 (94.1)	
Recent travel outside of Québec[a]				
Yes	8 (0.4)	15 (2.4)	23 (0.8)	<0.001
No/not reported	2,120 (99.6)	612 (97.6)	2,732 (99.2)	
Any contact with a person with confirmed COVID-19 outside of the workplace?				
No	1,878 (88.2)	555 (88.5)	2,433 (88.3)	<0.001
Yes, previous (more than 14 days ago)	222 (10.4)	38 (6.1)	260 (9.4)	
Yes, casual recent (within 14 days)	28 (1.3)	34 (5.4)	62 (2.2)	
Previous testing for SARS-CoV-2				
No	1,155 (54.3)	138 (22.0)	1,293 (46.9)	<0.001
Yes	973 (45.7)	489 (78.0)	1,462 (53.1)	
Result was negative	882 (41.4)	450 (71.8)	1,332 (48.3)	0.438
Result was positive	91 (4.3)	39 (6.2)	130 (4.7)	
SARS-CoV-2 vaccination[b]				
No	N/A	68 (10.8)	N/A	N/A
Yes	N/A	559 (89.1)	N/A	
One dose	N/A	166 (26.5)	N/A	N/A
Two doses	N/A	393 (62.7)	N/A	

Abbreviations: IQR, interquartile range; N/A, not applicable
[a] Recent travel defined as occurring within the previous 14 days
[b] Information on vaccination only available for participants in the Self-Testing Study
Note: Two-sided *p*-values are calculated using Fisher exact or chi-squared test, as appropriate for categorical data and Wilcoxon rank sum or Kruskal-Wallis test for continuous data

Table 2: Logistic regression results for characteristics associated with being tested for SARS-CoV-2 prior to study enrollment

Characteristics	Number and percentage of participants who received prior testing for SARS-CoV-2 (n/N)	aOR (95% CI)[a]
Age (per 1-year increase)	N/A	0.98 (0.98–0.99)
Sex		
Female	708/1,154 (61.3)	Ref.
Male	754/1,601 (47.1)	0.62 (0.52–0.73)
Ethnicity		
White	632/1,228 (51.5)	Ref.
Non-White	830/1,527 (54.3)	1.13 (0.94–1.36)
Income		
Highest 60%	554/1,051 (52.7)	Ref.
Lowest 40%	908/1,704 (53.3)	1.02 (0.86–1.21)
Health factor		
None reported	1,138/2,138 (53.2)	Ref.
Any reported	324/617 (52.5)	0.98 (0.80–1.21)
Smoking history		
Never smoked	1,146/2,152 (53.2)	Ref.
Current/previous smoker	316/603 (52.4)	1.11 (0.90–1.36)
Any recent travel[b]		
None reported	1,347/2,590 (52.0)	Ref.
Travel reported	115/165 (69.7)	1.15 (0.78–1.69)
Any contact		
None reported	1,209/2,433 (49.7)	Ref.
Contact reported	253/322 (78.6)	4.01 (3.01–5.35)
Business size		
1–50 employees	478/1,000 (47.8)	Ref.
More than 50 employees	984/1,755 (56.1)	1.00 (0.82–1.22)
Study		
Onsite Testing Study (January–March 2021)	973/2,128 (45.7)	Ref.
Self-Testing Study (July–October 2021)	489/627 (78.0)	4.10 (3.24–5.19)

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; N/A, not applicable; Ref., reference category
[a] Business sector included as a random intercept in the model
[b] Recent travel defined as occurring within the previous 14 days

Table 3: Logistic regression for characteristics associated with testing positive for SARS-CoV-2 more than four weeks prior to study enrollment

Characteristics	Number and percentage of participants who tested positive for SARS-CoV-2 more than four weeks prior to study enrollment (n/N)	aOR (95% CI)[a]
Age (per 1-year increase)	N/A	0.98 (0.97–1.00)
Sex		
Female	55/1,154 (4.8)	Ref.
Male	75/1,601 (4.7)	1.14 (0.77–1.70)
Ethnicity		
White	52/1,228 (4.2)	Ref.
Non-White	78/1,527 (5.1)	1.25 (0.82–1.88)
Income		
Highest 60%	46/1,051 (4.4)	Ref.
Lowest 40%	84/1,704 (4.9)	1.11 (0.76–1.62)
Health factor		
None reported	101/2,138 (4.7)	Ref.
Any reported	29/617 (4.7)	1.12 (0.72–1.75)
Smoking history		
Never smoked	107/2,152 (5.0)	Ref.
Current/previous smoker	23/603 (3.8)	0.78 (0.48-1.25)
Any recent travel[b]		
None reported	123/2,590 (4.7)	Ref.
Travel reported	7/165 (4.2)	0.72 (0.32–1.61)
Any contact		
None reported	87/2,433 (3.6)	Ref.
Contact reported	43/322 (13.3)	3.85 (2.60–5.71)
Business size		
1–50 employees	48/1,000 (4.8)	Ref.
More than 50 employees	82/1,755 (4.7)	0.95 (0.61–1.48)
Study		
Onsite Testing Study (January–March 2021)	91/2,128 (4.3)	Ref.
Self-Testing Study (July–October 2021)	39/627 (6.2)	1.65 (1.05–2.57)

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; N/A, not applicable; Ref., reference category
[a] Business sector included as a random intercept in the model
[b] Recent travel defined as occurring within the previous 14 days

Similarly, participants in the Self-Testing Study had higher odds of testing positive for SARS-CoV-2 more than four weeks prior to study enrolment (6.2% vs. 4.3%; aOR 1.7, 95% CI: 1.1–2.6) compared to those in the Onsite Testing Study (**Table 3**); there was no evidence (p=0.75) of effect modification by sector (Appendix 2, Table S6). We found those reporting recent SARS-CoV-2 exposure also had higher odds (aOR 3.9, 95% CI: 2.6–5.7) of testing positive. However, when limiting this analysis only to those who had previously been tested, there was no difference between studies in the odds of previously testing positive for SARS-CoV-2 (Appendix 2, **Table S7**). This was also the case in analyses limited to males (Appendix 2, Table S2) and those stratified on income (Appendix 2, Table S4).

When examining individual behaviours, participants in the Self-Testing Study had substantially higher odds (aOR 8.2, 95% CI: 5.6–12.1) of reporting recent travel outside Montréal or Québec (**Table 4**). Moreover, older participants (aOR 0.98, 95% CI: 0.97–0.99 per one-year increase) and those who identified as non-White (aOR 0.3, 95% CI: 0.2–0.5) had lower odds of reporting any recent travel. This was largely consistent in stratified analyses (Appendix 2, Tables S2 to S6), with evidence of effect modification (p<0.001) by business sector. When limiting this analysis to only those in the Self-Testing Study, vaccination was not associated with travel (Appendix 2, **Table S8**). We did not identify any difference between studies in terms of recent exposure to someone with confirmed SARS-CoV-2 in the total population (Appendix 2, **Table S9**), which was consistent in stratified analyses (Appendix 2, Tables S2 to S6).

Table 4: Logistic regression for characteristics associated with any self-reported travel outside of Montréal or Québec within the 14 days prior to study enrollment

Characteristics	Number and percentage of participants who reported any travel (n/N)	aOR (95% CI)[a]
Age (per 1-year increase)	N/A	0.98 (0.97–0.99)
Sex		
Female	62/1,154 (5.4)	Ref.
Male	103/1,601 (6.4)	1.38 (0.97–1.97)
Ethnicity		
White	127/1,228 (10.3)	Ref.
Non-White	38/1,527 (2.5)	0.30 (0.19–0.46)
Health factor		
None reported	123/2,138 (5.7)	Ref.
Any reported	42/617 (6.8)	1.18 (0.79–1.77)
Income		
Highest 60%	82/1,051 (7.8)	Ref.
Lowest 40%	83/1,704 (4.9)	0.83 (0.59–1.17)
Study		
Onsite Testing Study (January–March 2021)	50/2,128 (2.3)	Ref.
Self-Testing Study (July–October 2021)	115/627 (18.3)	8.24 (5.59–12.13)

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; N/A, not applicable; Ref., reference category
[a] Business sector included as a random intercept in the model

Regarding SARS-CoV-2 vaccination (only available in the Self-Testing Study; **Table 5**) only participants from businesses with more than 50 employees had higher odds of receiving at least one vaccine dose (91% vs. 80%; aOR 2.6, 95% CI: 1.4–4.8).

Table 5: Logistic regression for characteristics associated with receiving at least one dose of a vaccine against SARS-CoV-2 among the Self-Testing Study population after vaccine availability to this group

Characteristics	Number and percentage of participants who received one or more doses of a vaccine against SARS-CoV-2 (n/N)	aOR (95% CI)[a]
Age (per 1-year increase)	N/A	1.01 (0.99–1.03)
Sex		
Female	313/346 (90.5)	Ref.
Male	246/281 (87.5)	0.81 (0.48–1.38)
Ethnicity		
White	275/302 (91.0)	Ref.
Non-White	284/325 (87.4)	0.62 (0.34–1.14)
Income		
Highest 60%	233/254 (91.7)	Ref.
Lowest 40%	326/373 (87.4)	0.65 (0.37–1.13)
Health factor		
None reported	405/457 (88.6)	Ref.
Any reported	154/170 (90.6)	1.13 (0.62–2.06)
Any recent travel[b]		
None reported	453/512 (88.5)	Ref.
Travel reported	106/115 (92.2)	1.63 (0.78–3.44)
Any contact		
None reported	493/555 (88.8)	Ref.
Contact reported	66/72 (91.7)	1.58 (0.66–3.77)
Business size		
1–50 employees	84/105 (80.0)	Ref.
More than 50 employees	475/522 (91.0)	2.57 (1.39–4.75)

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; N/A, not applicable; Ref., reference category
[a] Business sector included as a random intercept in the model
[b] Recent travel defined as occurring within the previous 14 days

Findings were consistent in stratified analyses among males and those self-identifying as White (Appendix 2, Tables S2 to S3). In stratified analysis among those in the three highest income quintiles (Appendix 2, Table S4), participants identifying as non-White had lower odds of vaccination (aOR 0.3, 95% CI: 0.1–0.9), while participants working at businesses in the retail sector with more than 50 employees (Appendix 2, Table S6) had higher odds of vaccination (aOR 14.7, 95% CI: 3.5–61.1). We found significant effect modification on odds of vaccination by previous SARS-CoV-2 exposure and ethnicity, with those having previous exposure and self-identifying as White having significantly higher odds of vaccination compared to those self-identifying as non-White (Appendix 2, Table S3).

Discussion

In this pooled analysis of prospective cross-sectional studies, we found significant increases in the number of non-healthcare essential workers being tested and testing positive for SARS-CoV-2 during 2021 in Montréal, with men the least likely to get tested. Mobility in the form of travel outside the Montréal area increased later in 2021. While the overall SARS-CoV-2 vaccination rate among non-healthcare essential workers was high, it was highest among those working at businesses with more than 50 employees.

Approximately four out of five participants reporting recent SARS-CoV-2 exposure received a PCR test, substantially more than people not reporting previous exposure, suggesting adherence with public health guidance and messaging surrounding SARS-CoV-2 testing. However, we did not find any difference in the proportion of participants reporting recent SARS-CoV-2 exposure between studies. This observation is likely driven by the variable intensity of public health measures and differing levels of virus circulation during each study period. Aggressive public health measures were in place during the Onsite Testing Study period, where approximately 1,000 people tested positive for SARS-CoV-2 daily in Québec (21). However, a subsequent reduction in measures during the Self-Testing Study, and attendant increases in travel outside the Montréal area observed in our analysis, likely did not increase the number of effective contacts, as 400 people tested positive each day during this period.

These data also provide insight into population behaviours. We found a higher likelihood among women than men for being previously tested for SARS-CoV-2, which aligns with literature on the higher frequency of healthcare access and of preventive health actions among women (22–26). Overall vaccine uptake among participants was high (89.1%) and equivalent to the proportion of adults 18 years of age or older who had received at least one COVID-19 vaccine dose in Québec by the end of the Self-Testing Study (27). However, vaccine uptake was highest among people working in businesses with at least 50 employees, which we speculate could be due to factors such as employer encouragement, availability of onsite vaccination efforts, motivation to prevent transmission in larger workplaces stemming from a sense of community (28,29) or business neighbourhood location within the Greater Montréal Area. We did not find any significant difference in SARS-CoV-2 vaccine uptake by self-reported ethnicity and neighbourhood income, though these factors were explored in a large survey of vaccine intent among Canadian adults (26). The survey found those with the lowest household income had higher odds of responding that they were unlikely to get vaccinated; however, racialized populations had lower odds of providing this response. Taken together, our analysis can be used to support decision-making and targeting of future public health programs to encourage preventive health behaviours, such as encouraging testing among men and simplifying access and/or encouraging vaccination among smaller businesses.

Strengths and limitations

Key strengths of this study are the relatively large populations included in the analysis, the diverse nature of participants permitting exploration of various demographic and business-related factors, use of identical questionnaires for data collection, and temporal differences in data collection between studies, which allowed evaluations over time. This study is nonetheless subject to limitations. Some responses may have been impacted by recall biases as participants had to report previous testing history, travel and contact, though for most of these variables, the recall period was only 14 days. Only businesses experiencing a SARS-CoV-2 outbreak were included in the Self-Testing Study and larger businesses were preferentially recruited, which may have led to selection bias. Moreover, studies were conducted over different time periods in a rapidly evolving pandemic, and participant profiles between studies differed on demographic characteristics. We did not collect details on motivations for specific behaviours (e.g., decision to travel) and thus were unable to evaluate these aspects. Participant characteristics and behaviours were self-reported, which may have led some participants to not respond truthfully to some questions due to fear of consequences. We examined several outcomes in this study, and this may increase our risk of type I error.

Conclusion

This pooled analysis of non-healthcare essential workers in Montréal in 2021 found that men were less likely to get tested for SARS-CoV-2 and those working at businesses with 50 or fewer employees were less likely to be vaccinated against SARS-CoV-2, but there were no significant differences in vaccination rates by sex, income or ethnicity. These data may contribute to decision-making regarding the design of testing and vaccination programs, as well as the allocation of resources to improve equity and the uptake and effectiveness of interventions for SARS-CoV-2 and other health threats (30).

Authors' statement

CC — Methodology, formal analysis, writing–original draft, writing–review & editing
DM — Methodology, writing–review & editing
JP — Methodology, writing–review & editing
CPY — Conceptualization, methodology, writing–review & editing
JRC — Conceptualization, methodology, formal analysis, writing–original draft, writing–review & editing, supervision, funding acquisition

All authors had access to the data and contributed to the preparation of this 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

JP has received grants from AbbVie and MedImmune; personal fees from AstraZeneca and grants and personal fees from Merck; and has served as an advisor to the Canadian Federal COVID-19 Immunity Task Force, unrelated to and outside of the submitted work. CPY has provided consulting services to and sat on independent data monitoring committees for Medicago; and has served as scientific advisor for the Canadian Federal COVID-19 Immunity Task Force, unrelated to and outside the submitted work. JRC has provided SARS-CoV-2 consulting services to the Canadian Federal COVID-19 Immunity Task Force and the World Bank, unrelated to and outside the submitted work. The other authors (CC and DM) report no competing interests.

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Appendix

Supplemental figures and tables are available upon request to the author at: jonathon.campbell@mcgill.ca

Appendix 1: Participant questionnaires

Participant questionnaire from the Onsite Testing Study
Participant questionnaire from the Self-Testing Study

Appendix 2: Data harmonization

Table S1: Characteristics of included participants and businesses in each study and overall
Table S2: All analyses stratified on sex
Table S3: All analyses stratified on self-reported ethnicity
Table S4: All analyses stratified on neighborhood income quintiles
Table S5: All analyses stratified on study
Table S6: All analyses stratified on business sector
Table S7: Logistic regression for characteristics associated with testing positive for SARS-CoV-2 more than four weeks prior to study enrollment among those who were tested
Table S8: Logistic regression for characteristics associated with any self-reported travel outside Montréal or Québec within the 14 days prior to study enrollment among those in the Self-Testing Study only
Table S9: Logistic regression for characteristics associated with any self-reported contact with someone with SARS-CoV-2 outside of the workplace within the 14 days prior to study enrollment

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