

RESEARCH ARTICLE

Miscarriage after SARS-CoV-2 vaccination: A population-based cohort study

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Abstract

Objective: To evaluate the risk of miscarriage following SARS-CoV-2 vaccination, while accounting for the competing risk of induced abortion.

Design: Population-based cohort study.

Setting: Ontario, Canada.

Participants: Women aged 15–50 years with a confirmed pregnancy at ≤19 completed weeks' gestation.

Methods: Exposure to first SARS-CoV-2 vaccination, handled in a time-varying manner, was defined as (i) unvaccinated, (ii) remotely vaccinated >28 days before the estimated conception date or (iii) recently vaccinated ≤28 days before conception and up to 120 days after conception.

Main outcome measures: The outcome was miscarriage, occurring between the estimated date of conception and up to 19 completed weeks of pregnancy. Fine-Gray hazard models, accounting for the competing risk of induced abortion, generated hazard ratios (aHR), adjusted for socio-demographic factors, comorbidities, and biweekly periods.

Results: Included were 246 259 pregnant women, of whom 34% received a first SARS-CoV-2 vaccination. Miscarriage occurred at a rate of 3.6 per 10 000 person-days among remotely vaccinated women and 3.2 per 10 000 person-days among those recently vaccinated, in contrast to a rate of 1.9 per 10 000 person-days among unvaccinated women, with corresponding aHR of 0.98 (95% confidence interval [CI] 0.91–1.07) and 1.00 (95% CI 0.93–1.08).

Conclusions: SARS-CoV-2 vaccination was not associated with miscarriage while accounting for the competing risk of induced abortion. This study reiterates the importance of including pregnant women in new vaccine clinical trials and registries, and the rapid dissemination of vaccine safety data.

KEY WORDS

induced abortion, miscarriage, pregnancy, safety, SARS-CoV-2 vaccination

1 | INTRODUCTION

Assessment of potential risks is an important part of vaccine evaluation in pregnant populations.¹ Prior studies reported no associated risk between SARS-CoV-2 vaccination and either miscarriage^{2–5} or congenital anomalies.^{6,7} However, pregnant people, and those trying to get pregnant, were

among those identified as having lower SARS-CoV-2 vaccine uptake.⁸ Prior studies on SARS-CoV-2 vaccination and miscarriage lacked information about the timing of vaccination in relation to the estimated date of conception, potentially resulting in exposure misclassification bias.⁹ Furthermore, some individuals exposed to certain innocuous agents during early pregnancy perceive there to be a higher risk of

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potential teratogenic effects, to such an extent that they may seek induced abortion.¹⁰ Accordingly, induced abortion may be a competing event with miscarriage (as a woman who has an induced abortion can no longer experience a miscarriage), which can then influence the causal interpretation of the risk of miscarriage following SARS-CoV-2 vaccination.⁹

To overcome some of the aforementioned limitations, this population-based study was completed within a universal health system, with a high uptake of SARS-CoV-2 vaccination, and the systematic collection of vaccination and induced abortion data. Competing risks of both miscarriage and induced abortion were evaluated in relation to SARS-CoV-2 vaccination before or during pregnancy, using a potentially more accurate method to estimate the timing of conception.

2 | METHODS

2.1 | Study population

A population-based cohort study was conducted using linked patient-level administrative datasets in Ontario, Canada, where there is universal access to SARS-CoV-2 vaccination, and induced abortion data are complete.^{11,12} Linked datasets include the capture of all SARS-CoV-2 vaccinations (<https://data.ontario.ca/dataset/covid-19-vaccine-data-in-ontario>), laboratory testing (Ontario Laboratories Information System [OLIS]), hospitalisations, emergency department visits, outpatient visits, hospital births, and both procedural and pharmaceutical induced abortion, as detailed in Table S1. Data were linked and analysed at ICES (www.ices.on.ca), an independent, non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyse healthcare and demographic data, without consent, for health system evaluation and improvement.

Included were females aged 15–50 years who either had a first positive serum or urine human chorionic gonadotropin (HCG) test recorded in OLIS and/or who had a first-trimester ultrasound – either of which was completed between 14 December 2020 (the date when SARS-CoV-2 vaccines became available in Canada) and 1 December 2021 (to enable all eligible women to be assessed for the outcomes up to 19 completed weeks' gestation).

2.2 | Exposure

The main exposure of interest was the first SARS-CoV-2 vaccination, handled in a time-varying manner. Accordingly, a woman could contribute observation time as being unvaccinated, and then subsequently as vaccinated. Initial assessment of vaccination was either as *remotely vaccinated* (anytime between 14 December 2020, up to 29 days before the estimated date of conception) or *recently vaccinated* (from within 28 days before conception up to 120 days after conception, to allow at least 20 days of follow-up). *Remotely* and *recently vaccinated* groups were compared with those

unvaccinated any time before conception and up to 120 days after conception (the referent). For example, a woman vaccinated on 1 February 2021 would be designated as exposed from that date onward, but unexposed before that date.

The study outcome was miscarriage, occurring between the estimated date of conception and up to 19 completed weeks of pregnancy, based on diagnostic and fee codes (Table S1). The gestational age at which a miscarriage or induced abortion occurred was determined from the estimated date of conception. For livebirths and stillbirths, the estimated date of conception was back-calculated from the gestational age at the corresponding date of birth, as recorded in the MOMBABY dataset for all hospital births. For miscarriage or induced abortion, given that the last menstrual period was not available in the study datasets, the estimated date of conception was calculated using a published algorithm with moderate accuracy.¹³ Briefly, the algorithm included 273 584 singleton live-birth pregnancies that had a first-trimester ultrasound and measured serum HCG at 4–12 weeks' gestation in Ontario, from 2012 to 2018. HCG accuracy was estimated compared with known gestational age, within a boundary of ± 1 week. At all gestational ages, the positive predictive value was consistently under 42% and the negative predictive values were over 96%.¹³ In the current study, for those who had a quantitative serum HCG, the algorithm subtracts the predicted gestational age at the date of the serum HCG test from the test date. For those without a serum HCG but who had a first-trimester ultrasound (33.8% of miscarriages and 38.1% of induced abortions), multiple imputation was used to impute the estimated gestational age using chained equations (i.e. the fully conditional specimen method).

The competing risk of induced abortion comprised either a procedural or a pharmaceutical induced abortion, including a mifepristone-misoprostol prescription for pharmaceutical induced abortion^{12,14} (Table S1).

2.3 | Statistical analysis

Participant characteristics were presented by vaccination status, as proportions or means. Recently and remotely vaccinated groups were each contrasted to unvaccinated women using standardised differences, with a value >0.10 denoting an important difference.

Crude incidence rates for miscarriage were calculated and expressed per 10 000 person-years. Two modelling strategies were then used: (1) a Cox proportional hazard model and (2) a Fine-Grey hazard model, accounting for the competing risks of induced abortion. For both models, the time scale used was in gestational days. Censoring occurred on the earliest of maternal death, loss of OHIP eligibility (typically due to outmigration from Ontario), reaching the end of the study period of 31 March 2022, or reaching 140 days post-conception without an outcome event. To be clear, once a woman experienced a miscarriage (or induced abortion) she was no longer followed in the study cohort for either vaccination exposure or a future outcome event. A Fine-Grey

model is comparable to a Cox proportional hazard model that considers any individual experiencing a competing risk to be permanently cured of the outcome of interest. In both models, recently and remotely vaccinated women were respectively compared with unvaccinated individuals, and hazard ratios (HR) were adjusted for age, rurality, neighbourhood income quintile, immigration status, comorbidity using collapsed ambulatory diagnostic groups from the Johns Hopkins Adjusted Clinical Group (ACG) system,¹⁵ diagnosed obesity, parity, diagnosed infertility and biweekly calendar period for the estimated date of conception of a given pregnancy. Models were then re-run by vaccine type (messenger ribonucleic acid [mRNA], adenovirus-vectored [Ad-V] or other/unspecified, each versus no vaccination).

Given the low to moderate positive predictive value of the aforementioned algorithm for estimating date of conception,¹³ two additional analyses were performed, in which the estimated conception date was shifted by 2 weeks earlier (Additional analysis 1), and then by 2 weeks later (Additional analysis 2).

Statistical analyses were carried out using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

3 | RESULTS

A total of 246 257 pregnant women met the study inclusion criteria (Figure 1). Of these, 43 981 (17.9%) had been recently vaccinated (median [IQR] 6 [0–12] weeks' gestation), and 39 494 (16.0%) were remotely vaccinated. In contrast to unvaccinated women, those vaccinated were more likely to be older, reside in a higher-income area and have higher rates of diagnosed infertility (Table 1). Of those vaccinated, 99% received the mRNA vaccine, and 1% received an Ad-V vaccine or some other/unspecified type.

After a median duration of follow-up in pregnancy of 139 days (IQR 139–139), miscarriage occurred at a rate of 3.6 per 10 000 person-days among remotely first-time vaccinated women and 3.2 per 10 000 person-days among those recently vaccinated, in contrast to a rate of 1.9 per 10 000 person-days among unvaccinated women (Table 2). The median (IQR) gestational age at miscarriage was 9 (7–12) weeks among recently vaccinated women, 9 (6–11) weeks among remotely vaccinated and 8 (6–11) weeks among unvaccinated individuals.

In the first Cox-adjusted model, relative to unvaccinated women, the adjusted Hazard ratios (aHRs) for miscarriage were 0.97 (95% confidence interval [CI] 0.89–1.05) among those remotely vaccinated and 0.98 (95% CI 0.91–1.06) in women recently vaccinated (Table 2). Modelling induced abortion as a competing risk, the aHR for miscarriage was 0.98 (95% CI 0.91–1.07) comparing remotely vaccinated with unvaccinated women, and 1.00 (95% CI 0.93–1.08) comparing recently vaccinated with unvaccinated individuals (Table 2). Analyses showed no higher risk of miscarriage with either mRNA or other/unspecified vaccine types (Table 3).

Induced abortion occurred at a rate of 7.7 per 10 000 person-days among remotely vaccinated women, 7.4 per 10 000 person-days among those recently vaccinated, and 4.2 per 10 000 person-days in unvaccinated individuals (Table S2). The respective median (IQR) gestational age at induced abortion was 8 (6–9), 7 (5–8) and 7 (6–9) weeks. In the first Cox-adjusted model, relative to unvaccinated women, the aHRs for induced abortion were 0.94 (95% CI 0.89–0.99) among those remotely vaccinated and 1.10 (95% CI 1.05–1.16) in those recently vaccinated (Table S2). After modelling miscarriage as a competing risk, the respective aHR for induced abortion were 0.94 (95% CI 0.89–0.99) and 1.11 (95% CI 1.06–1.16) (Table S2). Results were similar for mRNA and other/unspecified vaccine types (Table S3).

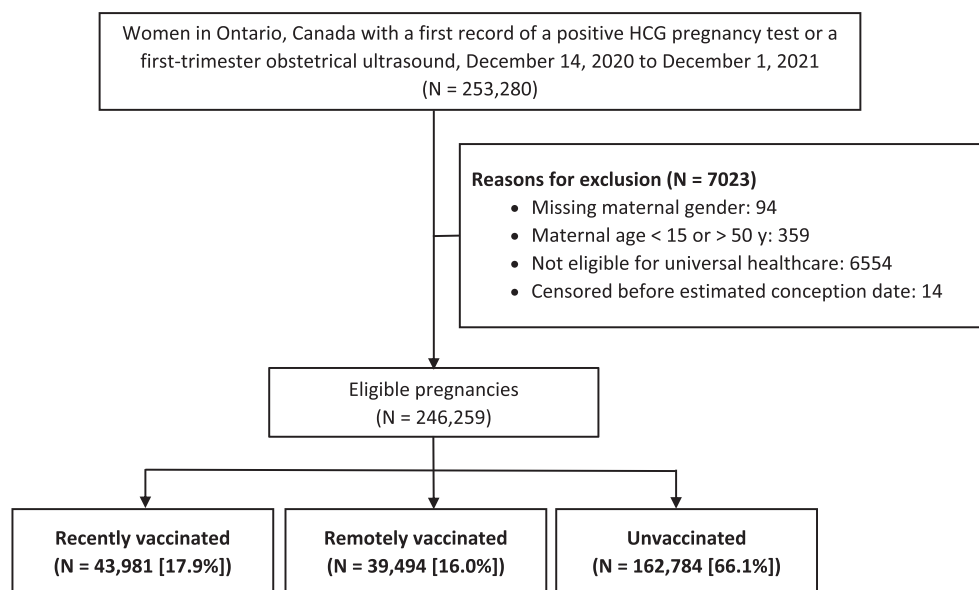


FIGURE 1 Cohort creation.

TABLE 1 Characteristics of 246 259 women in Ontario with an identified pregnancy between 14 December 2020 and 1 December 2021, by receipt of first SARS-CoV-2 vaccination.

Characteristic	Exposure groups			Standardized difference	
	Recently vaccinated ^a (<i>n</i> = 43 981)	Remotely vaccinated ^b (<i>n</i> = 39 494)	Unvaccinated (<i>n</i> = 162 784)	Recently vaccinated vs. unvaccinated	Remotely vaccinated vs. unvaccinated
Mean (SD) age, years	31.2 (5.4)	31.0 (5.1)	30.6 (5.5)	0.10	0.07
Income quintile					
1 (lowest)	8884 (20.2)	7688 (19.5)	37 658 (23.1)	0.07	0.09
2	9088 (20.6)	8187 (20.7)	34 044 (20.9)	0.01	0.005
3	9349 (21.3)	8571 (21.7)	34 615 (21.3)	0	0.01
4	9100 (20.7)	8146 (20.6)	31 743 (19.5)	0.03	0.03
5 (highest)	7560 (17.2)	6902 (17.5)	24 724 (15.2)	0.05	0.06
Urban residence	40 514 (92.1)	36 440 (92.3)	146 924 (90.3)	0.07	0.07
Immigrant	12 775 (29.0)	11 521 (29.2)	46 153 (28.4)	0.01	0.02
Comorbidity score ^c					
≤2	17 208 (39.1)	15 304 (38.8)	63 568 (39.1)	0.002	0.01
3 to 4	12 448 (28.3)	11 175 (28.2)	44 363 (27.3)	0.02	0.02
≥5	14 325 (32.6)	13 015 (33.0)	54 853 (33.6)	0.02	0.02
Nulliparous	23 257 (52.9)	21 666 (54.9)	81 325 (50.1)	0.05	0.09
Diagnosed obesity	1526 (3.5)	1518 (3.8)	4724 (2.9)	0.03	0.05
Diagnosed infertility	8833 (20.1)	8507 (21.5)	24 662 (15.2)	0.13	0.17
SARS-CoV-2 vaccine					
mRNA	43 610 (99.2)	39 003 (98.8)	NA	15.3	12.6
Other/unspecified	371 (0.8)	491 (1.2)	NA	0.13	0.16
Median (IQR) person-days of follow-up in pregnancy, days	139 (139–139)	139 (139–139)	139 (139–139)	0.00	0.00

Note: All data are presented as *n* (%) unless otherwise indicated.

Abbreviation: NA, not applicable.

^aVaccinated ≤28 days before the estimated date of conception.

^bVaccinated >28 days before the estimated date of conception.

^cJohns Hopkins Adjusted Clinical Groups (ACGs).

TABLE 2 SARS-CoV-2 vaccination timing and associated risk of miscarriage, accounting for the competing risk of induced abortion.

Exposure ^a	No. with outcome	No. person-days of follow-up	Rate per 10 000 person-days (95% CI)	Adjusted hazard ratio without competing risk of induced abortion (95% CI) ^b	Adjusted hazard ratio with competing risk of induced abortion (95% CI) ^b
Unvaccinated (<i>n</i> = 162 784)	4536	2 381 9847	1.9 (1.8–2.0)	1.00 (Referent)	1.00 (Referent)
Remotely vaccinated (<i>n</i> = 39 494)	1820	5 103 520	3.6 (3.4–3.7)	0.97 (0.89–1.05)	0.98 (0.91–1.07)
Recently vaccinated (<i>n</i> = 43 981)	1164	3 635 796	3.2 (3.0–3.4)	0.98 (0.91–1.06)	1.00 (0.93–1.08)

Note: Data are presented by time-varying exposure to first SARS-CoV-2 vaccination.

^aExposure is time-varying. Thus, some individuals may have contributed time as being unvaccinated, and then subsequently as being vaccinated. Remotely vaccinated individuals were vaccinated >28 days before the estimated date of conception. Recently vaccinated individuals were vaccinated ≤28 days before the estimated date of conception.

^bAdjusted for age; rurality; income quintile; immigration status; comorbidity, using collapsed ambulatory diagnostic groups from the Johns Hopkins Adjusted Clinical Groups (ACG) system; diagnosed obesity; parity; diagnosed infertility; and biweekly time period of the estimated date of conception.

TABLE 3 SARS-CoV-2 vaccination type and associated risk of miscarriage, accounting for the competing risk of induced abortion.

Exposure ^a	No. with outcome	No. person-days of follow-up	Rate per 10 000 person-days (95% CI)	Adjusted hazard ratio without competing risk of induced abortion (95% CI) ^b	Adjusted hazard ratio with competing risk of induced abortion (95% CI) ^b
Unvaccinated (<i>n</i> = 162 784)	4536	2 381 9847	1.9 (1.8–2.0)	1.00 (Referent)	1.00 (Referent)
mRNA (<i>n</i> = 43 610)	1146	3 602 518	3.2 (3.0–3.4)	0.97 (0.91–1.04)	0.99 (0.93–1.06)
Other/unspecified (<i>n</i> = 371)	18	33 277	5.4 (2.9–7.9)	1.11 (0.84–1.45)	1.09 (0.83–1.42)

Note: Data are presented by time-varying exposure after first SARS-CoV-2 vaccine type.

^aExposure is time-varying.

^bAdjusted for age; rurality; income quintile; immigration status; comorbidity, using collapsed ambulatory diagnostic groups from the Johns Hopkins Adjusted Clinical Groups (ACG) system; diagnosed obesity; parity; diagnosed infertility; and biweekly time period of the estimated date of conception.

Shifting the estimated conception date by either 2 weeks earlier or 2 weeks later did not materially alter the results (Tables S4 and S5).

4 | DISCUSSION

4.1 | Main findings

This population-based cohort study observed no relation between first SARS-CoV-2 vaccination and miscarriage, specifically while accounting for the competing risk of induced abortion.

4.2 | Strengths and limitations

Electronic medical databases may be prone to selection bias, such as only including pregnancies past a certain gestational age,¹⁶ which can introduce immortal time bias by limiting study participants to only those who can be assessed for the exposure of interest.¹⁷ The potential for immortal time bias – the influence of misclassified follow-up time for individuals who were vaccinated – was mitigated by treating vaccine exposure as time-varying¹⁸ and by commencing cohort accrual on 14 December 2020 (when SARS-CoV-2 vaccination became available in Canada). A vaccinated woman may have been more inclined to seek medical attention in the event of a miscarriage; however, such differential ascertainment of the outcome would have likely inflated the risk of miscarriage in vaccinated individuals. Even so, not all women who experience miscarriage seek healthcare, and they, too, would not be captured in this study. Vaccination status and study outcomes, including both procedural and pharmaceutical-induced abortion, are fully ascertained within Ontario's universal healthcare databases, however.

Precise determination of the day of embryo death is largely not possible, even within prospective cohort studies,¹⁹ especially when using administrative health data. In the study of certain medications, such as non-steroidal anti-inflammatory drugs (NSAIDs), the drug is often used to manage the discomfort or pain of miscarriage, and thus indication bias is introduced.²⁰ In the study of SARS-CoV-2 vaccination, however, such indication bias would not be expected, although a woman experiencing the onset of miscarriage, or who has recently miscarried, might delay getting vaccinated. This study comprised women whose pregnancy was confirmed by HCG testing or a first-trimester ultrasound. We could not account for those who may have been pregnant but had yet to have a confirmatory pregnancy test, including those who may have experienced a miscarriage (or induced abortion) before that time. Take, for example, a woman who had a fetal demise at 8 weeks' gestation without any symptoms – a 'missed miscarriage' – and who then received a SARS-CoV-2 vaccination at 9 weeks' gestation. If she was subsequently diagnosed with

a miscarriage at 10 weeks, she would have been classified as experiencing a miscarriage 'at 10 weeks' gestation'. By inflating the event-free follow-up time among the unvaccinated exposure group, and misclassifying some mothers who had a miscarriage as recently "vaccinated", this would tend to inflate the HR. For induced abortions, in which the procedural or prescription date is accurately captured, exposure-outcome misclassification is much less likely. Further, misclassification of exposure by the estimated date of conception was partly mitigated by applying a validated algorithm for estimating gestational age within the first trimester of pregnancy,¹³ and by the additional analyses shifting the date of conception by 2 weeks. Lastly, the current study identified a miscarriage or induced abortion as that occurring up to 19 completed weeks' gestation, a convention used by others in the study of SARS-CoV-2 vaccination early in pregnancy.²¹ While this same time-point is used in Canada²² and in major clinical reviews,²³ other jurisdictions, such as the UK, consider miscarriage as that occurring up to 23 completed weeks' gestation.²⁴

4.3 | Interpretation

These findings on SARS-CoV-2 vaccination and miscarriage are consistent with prior studies. A recent meta-analysis comprising 149 685 women, showed a relative risk for miscarriage of 0.71 (95% CI 0.89–1.28) in women vaccinated compared with controls.²⁵ A case-control study from the US Vaccine Safety Datalink included 13 160 cases with miscarriage and 92 286 controls with ongoing pregnancy and observed an odds ratio of 1.02 (95% CI 0.96–1.08) for miscarriage associated with SARS-CoV-2 vaccination in the preceding 28 days.² These estimates are also in keeping with other population-based registry studies from the Norway and Scotland.^{4,5}

We remained uncertain about the observed association between recent SARS-CoV-2 vaccination and induced abortion. To our knowledge, no other studies have explored the relation between SARS-CoV-2 vaccination and the risk of induced abortion. While there are differences between mRNA and Ad-V vaccines, neither contains a live virus, and pregnancy termination is not recommended after vaccine exposure.^{26,27} The benefits of vaccinating pregnant women outweigh any potential adverse risks, especially when the infection transmission rate is high, the infection poses a risk to the mother and/or fetus, or the vaccine is unlikely to cause harm.²⁷ This was the case for SARS-CoV-2 vaccination in pregnancy.²⁸ Others previously observed a higher risk of induced abortion following inadvertent administration of other vaccine types, including against varicella, as well as measles, mumps and rubella, during pregnancy of up to about 12 weeks' gestation.^{29,30} Although the reasons for induced abortion were not known herein, it is unlikely that a given induced abortion that followed soon after a woman received her SARS-CoV-2 vaccination was explained by a higher rate

of screened congenital anomalies, given that the median gestational age at induced abortion was only 8 weeks and that SARS-CoV-2 vaccination is not associated with birth defects.^{6,7}

Our findings also demonstrate that during the study period, SARS-CoV-2 vaccination rates in pregnant individuals, or those close to pregnancy, were low – about 17% – as compared with a rate of 65% in non-pregnant US women during the same study period.⁸ Given that COVID-19 infection during pregnancy is associated with serious maternal and neonatal morbidity,^{31–33} the current study can inform healthcare providers, pregnant women and those considering a pregnancy about the safety of SARS-CoV-2 vaccination in relation to miscarriage risk.

5 | CONCLUSION

The current findings confirm the lack of association between SARS-CoV-2 vaccination and miscarriage, including after accounting for induced abortion. Accordingly, the current study findings reiterate the importance of including pregnant women in new vaccine clinical trials and registries, followed by rapid dissemination about vaccine safety around the time of conception and across each trimester of pregnancy.

AUTHOR CONTRIBUTIONS

Concept and design: MV, JR. Acquisition, analysis or interpretation of data: MV, DF, JK, JR, JS. Statistical analysis: JS had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drafting of the paper: MV. Critical revision of the paper for important intellectual content: All authors.

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CONFLICT OF INTEREST STATEMENT

MV, JS, JK, JR: None reported. During the conduct of this work, DBF worked for the University of Ottawa and had academic appointments at the Children's Hospital of Eastern Ontario Research Institute and ICES; she is currently employed by Pfizer.

DATA AVAILABILITY STATEMENT

The dataset from this study is held securely in coded form at ICES. Legal data sharing agreements between ICES and data providers (e.g. healthcare organisations and government) prohibit ICES from making the dataset publicly available, however, access may be granted to those who meet prespecified criteria for confidential access, available at <https://www.ices.on.ca/DAS> (email: das@ices.on.ca). The full dataset creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programmes may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

ETHICS STATEMENT

Ethics approval was obtained from the Queen's Health Sciences Research Ethics Board on 3 January 2022 (No. 6035318).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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