Early season co-circulation of influenza A(H3N2) and B(Yamagata): interim estimates of 2017/18 vaccine effectiveness, Canada, January 2018

Danuta M Skowronski¹,², Catharine Chambers¹, Gaston De Serres³,⁴, James A Dickinson⁵, Anne-Luise Winter⁶, Rebecca Hickman⁷, Tracy Chan⁴, Agatha N Jassem²,⁵, Steven J Drews⁸,⁹, Hugues Charest³,⁴, Jonathan B Gubbay⁷,¹⁰, Nathalie Bastien¹¹, Yan Li¹¹, Mel Krajden¹,²

1. British Columbia Centre for Disease Control, Vancouver, Canada
2. University of British Columbia, Vancouver, Canada
3. Institut National de Santé Publique du Québec, Québec, Canada
4. Laval University, Quebec, Canada
5. Centre Hospitalier Universitaire de Québec, Québec, Canada
6. University of Calgary, Calgary, Canada
7. Public Health Ontario, Toronto, Canada
8. Alberta Provincial Laboratory, Edmonton, Canada
9. University of Alberta, Edmonton, Canada
10. University of Toronto, Toronto, Canada
11. National Microbiology Laboratory, Public Health Agency of Canada, Winnipeg, Canada

Correspondence: Danuta M Skowronski (danuta.skowronski@bccdc.ca)

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Using a test-negative design, we assessed interim vaccine effectiveness (VE) for the 2017/18 epidemic of co-circulating influenza A(H3N2) and B(Yamagata) viruses. Adjusted VE for influenza A(H3N2), driven by a predominant subgroup of clade 3C.2a viruses with T131K + R142K + R261Q substitutions, was low at 17% (95% confidence interval (CI): −14 to 40). Adjusted VE for influenza B was higher at 55% (95% CI: 38 to 68) despite prominent use of trivalent vaccine containing lineage-mismatched influenza B(Victoria) antigen, suggesting cross-lineage protection.

The 2017/18 influenza season in Canada has been characterised by co-circulation of influenza A(H3N2) and B(Yamagata) viruses, the latter unusual so early in the season [1]. Most European countries are also experiencing simultaneous influenza A and B epidemics, with B(Yamagata) predominating [2], whereas the United States (US) has experienced a substantial epidemic due predominantly to influenza A(H3N2) [3]. The 2017/18 trivalent influenza vaccine (TIV) includes influenza A/Hong Kong/4801/2014(H3N2)-like (clade 3C.2a) and B/Brisbane/60/2008(Victoria-lineage)-like (clade 1A) antigens. The quadrivalent influenza vaccine (QIV) contains an additional influenza B/Phuket/3073/2013(Yamagata-lineage)-like (clade 3) antigen. The same components were included in the 2016/17 northern and 2017 southern hemisphere vaccines [4].

Low vaccine effectiveness (VE) for the 2017/18 season has been anticipated following the interim report from Australia indicating VE of just 10% during its 2017 influenza A(H3N2) epidemic [5]. In the context of exclusive QIV use, Australia reported higher VE of 57% against co-circulating influenza B viruses [5]. Here we report interim 2017/18 VE estimates for influenza A(H3N2) and influenza B from participating provinces of the Canadian Sentinel Practitioner Surveillance Network (SPSN), where QIV comprised less than one third of vaccine doses distributed overall through the publicly funded campaign.

Vaccine effectiveness evaluation
VE was derived using a test-negative design [6-9]. Nasal/nasopharyngeal specimens and epidemiological data were collected from patients presenting within 7 days of onset of influenza-like illness (ILI) to community-based sentinel practitioners in Alberta, British Columbia, Ontario and Quebec. ILI was defined as acute onset of fever and cough and at least one other symptom including sore throat, myalgia, arthralgia or prostration. Fever was not a requirement for elderly adults 65 years of age and older. Vaccination status was based on patient and/or practitioner reporting of 2017/18 vaccination at least 2 weeks before symptom onset; patients vaccinated less than 2 weeks before onset or with unknown vaccination status/timing were...
excluded. Institutional review boards in each province provided ethical approval for the study.

Specimens collected from week 45 (starting 5 November 2017) to week 3 (ending 20 January 2018) were tested for influenza type/subtype by real-time RT-PCR at provincial public health reference laboratories. Sanger sequencing of the viral haemagglutinin gene was undertaken on a subset of original patient specimens collected up to 13 January 2018 to assess the contribution of genetic clades to VE estimates.

Odds ratios (OR) comparing test-positivity for influenza A(H3N2) or B between vaccinated and unvaccinated participants who were at least 1-year-old were calculated using logistic regression, adjusted for relevant covariates. VE was derived as $(1 − OR) \times 100\%$.

Virological findings
Among 1,408 eligible specimens, 689 (49%) tested positive for influenza, including 338 (49%) influenza A and 351 (51%) influenza B (Figure 1). Among the 330 (98%) subtyped influenza A viruses, 302 (92%) were A(H3N2) and 28 (8%) were A(H1N1)pdm09. Most sequenced influenza A(H3N2) viruses belonged to genetic clade 3C.2a (213/229; 93%) and of these most (204/213; 96%) belonged to a single genetic subgroup of 3C.2a (denoted subgroup 3 by nextflu.org [10]), bearing antigenic site A substitutions T131K and R142K and antigenic site E substitution R261Q (Table 1). Overall 89% of influenza A(H3N2) viruses belonged to clade 3C.2a subgroup 3, which is similar to other surveillance observations from Canada (83%) (Figure 2) and to recent reports from Europe [11]. However, this profile for the 2017/18 season is different from that found by the Canadian SPSN during 2016/17 or by Australia during its 2017 epidemic, when a greater mix of genetic variants contributed to interim analyses and only 14% and 7%, respectively, of influenza A(H3N2) viruses belonged to subgroup 3 (Figure 2).

Virtually all sequenced influenza B viruses were B(Yamagata) clade 3 (227/233; 97%) and all but one had L172Q + M251V non-antigenic site substitutions, the dominant genetic variant circulating globally since 2015 [11]; one virus had M251V without L172Q. Six viruses were influenza B(Victoria) clade 1A (five with a deletion at position 162–163) [11].

Epidemiological findings
Most (64%) participants were adults 20–64-years-old. More influenza B cases (20%) than controls (11%) were children 9–19-years-old ($p<0.01$) (Table 2). More cases of influenza A(H3N2) (25%; $p=0.07$) and influenza B (27%; $p<0.01$) were 50–64-years-old compared with controls (18%).

Adjusted VE against influenza A(H3N2) was 17% (95% confidence interval (CI): −14 to 40) overall and 10%
Sequencing of the haemagglutinin gene was attempted on a subset of available influenza-positive original patient specimens from the Canadian SPSN contributing to interim 2017/18 vaccine effectiveness evaluation (collection dates: 1 November 2017 to 10 January 2018). Sequences were publicly available from the Global Initiative on Sharing All Influenza Data (GISAID) as acknowledged in Supplement 1. Of these 228 A(H3N2) viruses, 199 (87%) belonged to clade 3C.2a, and 189 (83%) overall belonged to the clade 3C.2a subgroup bearing T131K + R142K + R261Q substitutions (nextflu subgroup 3). Furthermore, a single subgroup of clade 3C.2a with T131K + R142K + R261Q substitutions (i.e. nextflu subgroup 3 [10]) is currently predominating (89% of influenza A(H3N2) viruses), whereas a more heterogeneous mix of genetic variants contributed in Canada during 2016/17 [9] and in Australia during their 2017 epidemic [5]. Changes in the proportionate contribution and emerging predominance of clade 3C.2a variants among circulating influenza A(H3N2) viruses are important to monitor globally. The World Health Organization will decide in February 2018 whether to update the current clade 3C.2a vaccine antigen for the 2018/19 northern hemisphere vaccine, having already chosen a clade 3C.2a strain for the southern hemisphere’s 2018 vaccine [4].

Discussion

In most other interim analyses by the Canadian SPSN, type B viruses comprised less than 10% of influenza detections, whereas in 2017/18, they were identified in an equal proportion with influenza A(H3N2) [7-9]. Although the reasons for an earlier influenza B onset are unclear, Canada experienced a substantial influenza A(H3N2) epidemic in 2016/17 that may have altered population immunity and the overall 2017/18 influenza A(H3N2) contribution [9].

Nearly all (93%) characterised influenza A(H3N2) viruses were clade 3C.2a, a change from 2016/17 when most (80%) of the A(H3N2) viruses instead belonged to clade 3C.2a1 [9]. Furthermore, a single subgroup of clade 3C.2a with T131K + R142K + R261Q substitutions (nextflu subgroup 3) is currently predominating (89% of influenza A(H3N2) viruses), whereas a more heterogeneous mix of genetic variants contributed in Canada during 2016/17 [9] and in Australia during their 2017 epidemic [5]. Changes in the proportionate contribution and emerging predominance of clade 3C.2a variants among circulating influenza A(H3N2) viruses are important to monitor globally. The World Health Organization will decide in February 2018 whether to update the current clade 3C.2a vaccine antigen for the 2018/19 northern hemisphere vaccine, having already chosen a clade 3C.2a strain for the southern hemisphere’s 2018 vaccine [4].

Our 2017/18 interim VE estimate of 17% (95% CI: −14 to 40) is less than half that reported for the same A(H3N2) vaccine in 2016/17, including interim analyses by the Canadian SPSN (42%; 95% CI: 18 to 59) [9], the US Flu VE Network (43%; 95% CI: 29 to 54) [12] and the European I-MOVE Network (38%; 95% CI: 21 to 51) [13]. Our estimate is also lower than end-of-season estimates from Canada (37%; 95% CI: 20 to 51) [14] and the US (34%; 95% CI: 24 to 42) for 2016/17 [15], and lower than is expected generally for influenza A(H3N2) vaccines (33%; 95% CI: 26 to 39) [16].

Our 2017/18 interim VE for influenza A(H3N2) is more comparable to the 2017 southern hemisphere interim VE of 10% (95% CI: −16 to 31) reported from Australia [5]. Differences in virological and participant profiles, as well as the stage of the epidemic, have to be taken into account when comparing VE estimates across studies. Working-age adults comprised the majority of

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**Figure 2**

Clade distribution of influenza A(H3N2) variants, Canada, 2017/18 interim vaccine effectiveness evaluation vs other sources of data

| Clade | Description | Proportion |
|-------|-------------|------------|
| 3C.2a | with T131K + R142K + R261Q (nextflu subgroup 3) | 60% |
| 3C.2a | with N35 + D53N + R142G + S144R + N171K + I192T + Q197H (nextflu subgroup 4) | 30% |
| 3C.2a | with N123K + K90R + H311Q (nextflu subgroup 5) | 10% |
| 3C.2a | with T131K + R142K + R261Q (nextflu subgroup 3) | 40% |
| 3C.2a | with T131K + R142K + R261Q (nextflu subgroup 3) | 20% |
| 3C.2a | with T131K + R142K + R261Q (nextflu subgroup 3) | 10% |

NML: National Microbiology Laboratory; SPSN: Sentinel Practitioner Surveillance Network.
participants in both studies and the 2017/18 interim VE against influenza A(H3N2) among Canadian SPSN participants 20–64-years-old (10%; 95% CI: −31 to 39) is also comparable to the 2017 estimate reported from Australia for 15–64-year-olds (16%; 95% CI: −11 to 36). Sample size for other age groups (e.g. children, elderly adults) was too limited to derive reliable interim estimates or to inform protection in specific high-risk groups.

All influenza vaccine manufacturing in Canada is egg-based. Mutations that arise from egg adaptation of the vaccine strain may affect VE, an issue also identified for the current season’s A(H3N2) vaccine component [17,18]. In Canada this season, antigenic characterisation of influenza A(H3N2) viruses has only been presented in relation to a cell-propagated version of the vaccine reference strain; characterisation against an egg-based version has not been reported [1]. Among the small subset of Canadian viruses that could be successfully characterised, all were considered antigenically similar to the cell-propagated vaccine strain [1]. Conversely, where relatedness to the egg-propagated version of the vaccine strain has been specifically explored elsewhere, more variability has been identified, with a greater proportion of viruses considered antigenically distinct from the egg-propagated version [5,11,19].

We found higher VE of 55% (95% CI: 38 to 68) against influenza B despite prominent use of TIV containing a B(Victoria) antigen that was lineage-mismatched to almost exclusively B(Yamagata) viruses. Approximately 70% of vaccine doses distributed in SPSN provinces during the 2017/18 season were TIV, albeit with regional variation that will be explored in end-of-season analyses. Substantial cross-lineage VE for influenza B has been observed previously [20], including during the prior 2016/17 season in Canada when VE against lineage-mismatched influenza B using the same B(Victoria) TIV component was 73% (95% CI: 52 to 84) [14] and QIV comprised an even smaller proportion (< 25%) of vaccine doses distributed. Our estimate for the current season is comparable to the interim VE of 57% (95% CI: 41 to 69) for influenza B reported from Australia, despite exclusive use of QIV in that country [5].

Other agent–host and immuno–epidemiological interactions, including birth cohort effects induced by differential prime–boost exposures, may also play a role in VE [21]. The effect of prior vaccination history was

| TABLE 1 Virological profile of influenza specimens contributing to interim 2017/18 vaccine effectiveness evaluation based on Sanger sequencing, Canadian Sentinel Practitioner Surveillance Network, 5 November 2017–13 January 2018 (n = 462) |

| Genetic clade with substitutions (nextflu subgroup) | Alberta | British Columbia | Ontario | Quebec | Overall |
|---------------------------------------------------|---------|------------------|---------|--------|---------|
|                                                   | n  | %  | n  | %  | n  | %  | n  | %  | n  | %  |
| Influenza A(H3N2)                                 |    |     |    |     |      |     |     |     |      |     |
| Clade 3C.2a                                       | 114 | 100 | 38 | 100 | 50 | 100 | 27 | 100 | 229 | 100 |
| + N31S+D53N+R142G+S144R+L142T+Q197H (subgroup 1)  | 2  | 2   | 0  | 0   | 0  | 1   | 4  | 3   | 1   | 3   |
| + N121K+S144K (subgroup 2)                        | 1  | 1   | 1  | 1   | 3  | 6   | 1  | 4   | 6   | 3   |
| + T131K+R142K+R261Q (subgroup 3)                  | 102 | 89  | 35 | 92  | 45 | 90  | 22 | 82  | 204 | 89  |
| Clade 3C.3a                                       | 9  | 8   | 2  | 5   | 1  | 2   | 3  | 11  | 15  | 7   |
| + N121K+T135K (subgroup 4)                        | 2  | 2   | 1  | 3   | 0  | 0   | 0  | 3   | 3   | 1   |
| + N121K+K92R+H311Q (subgroup 5)                   | 7  | 6   | 1  | 3   | 1  | 2   | 3  | 11  | 12  | 5   |
| Clade 3C.3a1                                      | 0  | 0   | 0  | 0   | 0  | 1   | 2  | 0   | 0   | 1   |
| Influenza B                                       | 76 | 100 | 83 | 100 | 63 | 100 | 11 | 100 | 233 | 100 |
| Yamagata lineage clade 3                          | 76 | 100 | 82 | 99  | 62 | 98  | 7  | 64  | 227 | 97  |
| Victoria lineage clade 1A                         | 0  | 0   | 1  | 1   | 1  | 2   | 4  | 36  | 6   | 33  |
| Characteristic                        | All participants (column %) | % vaccinateda (row %) | Overall | na | % | na | % | Negative controls | Overall | na | % | Negative controls | Overall | na | % | Negative controls | Overall | na | % | Negative controls | Overall | na | % | Negative controls |
|--------------------------------------|----------------------------|-----------------------|---------|----|----|----|----|------------------|---------|----|----|------------------|---------|----|----|------------------|---------|----|----|------------------|---------|----|----|------------------|
| Overall                              | 302 100                   | NA                    | 351 100 | 719 | 100 | 33 | NA | 80 23            | 253 35  | NA | NA | NA |
| Age group (years)                    |                           |                       |         |     |     |    |    |                  |         |     |     |                  |         |     |     |                  |         |     |     |                  |
| 1–8                                  | 18 6                      |                       | 21 6    | 64 9 | 2   | 11 | 0 0 | 0 0              | 0 0     | 1 1 | 1 1 | 15 18            |
| 9–19                                 | 31 10                     | 0.07                  | 70 20   | 82 11 | 7 23 | 1 1 | 1 1 | 15 18            |
| 20–49                                | 126 42                    | < 0.01                | 117 33  | 325 45 | 34 27 | 21 18 | 21 18 | 91 28            |
| 50–64                                | 77 25                     | 0.53                  | 95 27   | 131 18 | 26 34 | 30 32 | 30 32 | 48 37            |
| ≥ 65                                 | 50 17                     |                       | 48 14   | 117 16 | 31 62 | 28 58 | 28 58 | 89 76            |
| Median (range)                       | 43 (2–87)                 | 0.17                  | 43 (9–15)| 39 (1–96) | 53.5 (3–87) | 61.5 (12–91) | 52 (1–96) | < 0.01 |
| Sex                                  |                           |                       |         |     |     |    |    |                  |         |     |     |                  |         |     |     |                  |         |     |     |                  |
| Female                               | 185 62                    | 0.45                  | 205 59  | 421 59 | 71 38 | 0.02 | 55 27 | 0.03 | 162 38 |
| Male                                 | 115 38                    |                       | 143 41  | 291 41 | 29 25 | 0.02 | 24 17 | 0.02 | 90 31 |
| Unknown                              | 2 NA                      |                       | NA 0    | NA 0 | NA 0 | NA 0 | NA 0 | NA 0 | NA 0 |
| Co-morbiditya                        |                           |                       |         |     |     |    |    |                  |         |     |     |                  |         |     |     |                  |         |     |     |                  |
| No                                   | 226 77                    | 0.57                  | 262 80  | 524 76 | 63 28 | < 0.01 | 46 18 | < 0.01 | 155 30 |
| Yes                                  | 66 23                     | 0.12                  | 65 20   | 168 24 | 33 50 | < 0.01 | 31 48 | < 0.01 | 92 55 |
| Unknown                              | 10 NA                     |                       | NA 0    | NA 0 | NA 0 | NA 0 | NA 0 | NA 0 | NA 0 |
| Province                             |                           |                       |         |     |     |    |    |                  |         |     |     |                  |         |     |     |                  |         |     |     |                  |
| Alberta                              | 127 42                    | < 0.01                | 91 26   | 201 28 | 40 31 | 0.10 | 14 15 | < 0.01 | 75 37 |
| British Columbia                     | 48 16                     |                       | 107 30  | 200 28 | 16 33 | 0.10 | 31 29 | < 0.01 | 70 35 |
| Ontario                              | 77 25                     | < 0.01                | 114 32  | 203 28 | 33 43 | < 0.01 | 33 29 | < 0.01 | 84 41 |
| Quebec                               | 50 17                     |                       | 39 11   | 115 16 | 11 22 | 0.02 | 2 5 | 0.02 | 24 21 |
| Specimen collection interval from ILI onset (days)f |                           |                       |         |     |     |    |    |                  |         |     |     |                  |         |     |     |                  |         |     |     |                  |
| ≤ 4                                  | 239 79                    | < 0.01                | 252 72  | 499 69 | 78 33 | 0.73 | 58 23 | 0.87 | 170 34 |
| 5–7                                  | 63 21                     | 0.42                  | 220 31  | 22 22 | 0.34 | 83 38 |
| Median (range)                       | 3 (0–7)                   | < 0.01                | 3 (0–7) | 3 (0–7) | 3 (0–7) | 0.18 | 3 (1–7) | 0.96 | 3 (0–7) | 0.88 |
| Specimen collection month           |                           |                       |         |     |     |    |    |                  |         |     |     |                  |         |     |     |                  |         |     |     |                  |
| November                             | 38 13                     | 0.10                  | 23 7    | 129 18 | 6 16 | 0.04 | 1 4 | 0.03 | 27 21 |
| December                             | 124 41                    | < 0.01                | 117 33  | 259 37 | 47 38 | 0.04 | 23 20 | 0.03 | 99 37 |
| January                              | 140 46                    |                       | 211 60  | 321 45 | 47 34 | 0.04 | 23 20 | 0.03 | 127 40 |
| 2017/18 vaccination status           |                           |                       |         |     |     |    |    |                  |         |     |     |                  |         |     |     |                  |         |     |     |                  |
| Vaccination without regard to timingg | 112/314                   | 0.48                  | 87/398  | 285/751 | 38 NA | NA 0 | NA 0 | NA 0 | NA 0 | NA 0 | NA 0 | NA 0 | NA 0 | NA 0 | NA 0 | NA 0 | NA 0 | NA 0 | NA 0 | NA 0 | NA 0 | NA 0 |
| ≥ 2 weeks before ILI onset           | 100 33                    | 0.52                  | 80 23   | 253 35 | NA 0 | NA 0 | NA 0 | NA 0 | NA 0 | NA 0 | NA 0 | NA 0 | NA 0 | NA 0 | NA 0 | NA 0 | NA 0 | NA 0 | NA 0 | NA 0 | NA 0 | NA 0 | NA 0 |

ILI: influenza-like illness; NA: not applicable.

The number of participants with unknown sex or comorbidity are shown in table but excluded from the denominator for calculating percentages.

a Vaccination status based on patient and/or practitioner report; defined as receipt of 2017/18 seasonal influenza vaccine ≥ 2 weeks before symptom onset. Patients vaccinated ≤ 2 weeks before onset or with unknown vaccination status/timing were excluded.

b p value for comparison of influenza A(H3N2) cases to negative controls. Differences were compared using the chi-squared test or Wilcoxon rank-sum test.

c p value for comparison of influenza B cases to negative controls. Differences were compared using the chi-squared test or Wilcoxon rank-sum test.

d p value for comparison of vaccinated participants to unvaccinated participants. Differences were compared using the chi-squared test or Wilcoxon rank-sum test.

e Includes chronic co-morbidities that place individuals at higher risk of serious complications from influenza as defined by Canada’s National Advisory Committee on Immunization (NACI), including: heart, pulmonary (including asthma), renal, metabolic (such as diabetes), blood, cancer or immunocompromising conditions, conditions that compromise management of respiratory secretions and increase risk of aspiration, or morbid obesity (body mass index ≥ 40).

f Missing specimen collection dates were imputed as the laboratory accession date minus 2 days, the average time between specimen collection and accession dates among specimens with complete information for both values.

g Participants who received seasonal 2017/18 influenza vaccine ≤ 2 weeks before ILI onset or for whom vaccination timing was unknown were excluded from the primary analysis. They are included here for assessing vaccination regardless of timing for comparison to other sources of vaccination coverage.
not assessed here owing to sample size limitations, but will be explored as part of the end-of-season analyses.

Conclusions
As reported from Australia for the 2017 southern hemisphere vaccine, interim estimates from Canada for the 2017/18 northern hemisphere vaccine indicate low VE of less than 20% against influenza A(H3N2), notably among working-age adults. While the influenza A(H3N2) epidemic continues, adjunct protective measures should be reinforced to minimise the associated disease burden in high-risk individuals [22]. Interim 2017/18 VE estimates against influenza B are higher at 55% despite prominent TIV use, suggesting cross-lineage protection.

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Conflict of interest
GDS has received grants unrelated to influenza from GSK and Pfizer and travel reimbursement to attend an ad hoc advisory board meeting of GSK also unrelated to influenza; he has provided paid expert testimony in a grievance against a vaccine-or-mask healthcare worker influenza vaccination policy for the Ontario Nurses Association. JBG has received research grants from GlaxoSmithKline Inc. and Hoffman-La Roche Ltd to study antiviral resistance in influenza, and from Pfizer Inc. to conduct microbiological surveillance of Streptococcus pneumoniae. MK has received research grants from Roche, Merck, Siemens, Hologic, and Boehringer Ingelheim for unrelated studies. Other authors have no conflicts of interest to declare.

Table 3
Interim 2017/18 vaccine effectiveness estimates, Canadian Sentinel Practitioner Surveillance Network, 5 November 2017–20 January 2018 (n = 1,408)

| Model | Influenza A(H3N2) | Influenza B | Overall (A and B) |
|-------|-------------------|-------------|------------------|
|       | % vac | n vac / N | % vac | n vac / N | % vac | n vac / N | % vac |
| All participants |       |       |       |       |       |       |       |
| Sample size |       |       |       |       |       |       |       |
| Cases | 100/302 | 33 | 80/351 | 23 | 186/689 | 27 |
| Controls | 253/719 | 35 | 253/719 | 35 | 253/719 | 35 |
| Vaccine effectiveness |       |       |       |       |       |       |       |
| Unadjusted | 9 | −21 to 31 | 46 | 27 to 59 | 32 | 14 to 46 |
| Age group | 15 | −15 to 38 | 49 | 30 to 63 | 36 | 18 to 50 |
| Province | 8 | −23 to 31 | 49 | 31 to 62 | 34 | 16 to 47 |
| Specimen collection interval | 8 | −23 to 31 | 46 | 27 to 59 | 31 | 14 to 45 |
| Calendar time | 13 | −16 to 35 | 52 | 35 to 64 | 38 | 21 to 51 |
| Full covariate adjustment | 17 | −14 to 40 | 55 | 38 to 68 | 42 | 25 to 55 |
| Participants 20–64 years-old |       |       |       |       |       |       |       |
| Sample size |       |       |       |       |       |       |       |
| Cases | 60/203 | 30 | 51/212 | 24 | 113/439 | 26 |
| Controls | 139/456 | 30 | 139/456 | 30 | 139/456 | 30 |
| Vaccine effectiveness |       |       |       |       |       |       |       |
| Unadjusted | 4 | −37 to 33 | 28 | −5 to 50 | 21 | −6 to 41 |
| Full covariate adjustment | 10 | −31 to 39 | 40 | 10 to 60 | 31 | 6 to 49 |

CI: confidence interval; n vac: number vaccinated; N: number total; % vac: percentage vaccinated; VE: vaccine effectiveness.

*Analyses adjusted for age group (categorical: 1–8, 9–19, 20–49, 50–64 or ≥ 65 years), province (categorical: Alberta, British Columbia, Ontario or Quebec), specimen collection interval (categorical: ≤ 4 or 5–7 days) and calendar time (categorical: 2-week intervals based on week of specimen collection).
Authors’ contributions
Principal investigators (epidemiological): DMS (National and British Columbia); JAD (Alberta); ALW (Ontario); and GDS (Québec). Principal investigator (laboratory): ANJ and MK British Columbia; SJD (Alberta); JBG (Ontario); HC (Québec); and NB and YL (National Microbiology Laboratory). Genomic sequencing and analysis: RH and TC. Epidemiological data analysis: CC and DMS. Preparation of first draft: CC and DMS. Draft revision and approval: all.

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