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EVIDENCE BRIEF

(ARCHIVED) COVID-19 Delta sublineage AY.4.2: Risk Analysis and Implications for Practice

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Key Messages

- As of October 25, 2021, over 26,000 sequences of AY.4.2 have been reported from 42 countries, with a slowly increasing trend since July 2021. Approximately 93% of these sequences were from the United Kingdom (UK).[1]
- 12 cases of AY.4.2 have been detected in Canada as of November 2, 2021,[2] with at least 2 from Alberta as of October 29, 2021,[3] and 5 cases from Ontario as of October 16, 2021.[4]
- Data from England reported a slightly higher growth rate and a higher secondary attack rate of AY.4.2 than Delta. However, preliminary data did not reveal a significant reduction in vaccine effectiveness against asymptomatic and symptomatic infection by AY.4.2 compared to Delta.[5]
- The risk of Delta sublineage AY.4.2 transmission in Ontario is low. The prevalence of AY.4.2 can rise with outbreaks of high case numbers due to pockets of the population with suboptimal vaccine coverage. The overall risk assessment may change as new evidence emerges.

Issue and Research Question

While accounting for only 1.5% of COVID-19 infections in England, the proportion of cases with the AY.4.2 sublineage of the Delta (B.1.617.2) variant has been slowly increasing since its first report in mid-June, 2021.[5] It is still uncertain if the additional mutations in AY.4.2 render the sublineage more transmissible or more resistant to protection by vaccination and/or infection. Given evidence that suggests decreasing protection against COVID-19 as time since completion of the primary vaccine series increases,[6] it is prudent to consider the potential impact of AY.4.2 in Ontario, particularly as Ontario proceeds to gradually lift public health and workplace safety measures against COVID-19.[7]

Methods

From January 17 to November 2, 2021, Public Health Ontario (PHO) Library Services conducted daily searches of primary and preprint literature using the MEDLINE database (search strategies available upon request). In addition, PHO performed grey literature searches daily using news feeds in the Shared Library Services Partnership. English-language peer-reviewed and non-peer-reviewed (preprint) records that described COVID-19 variants.

Genomic Features

- As a newly designated Pango lineage within the Delta Variant of Concern, AY.4.2 contains 3 additional mutations to the Delta genome: A222V and Y145H in the spike protein[1] and A2529V in orf1ab.[5]

Epidemiology (United Kingdom)

- AY.4.2 was designed as a variant under investigation (VUI-21OCT-01) in the UK on October 20, 2021.[8]
- From its first detection in England the week of June 20, 2021, 23,830 AY.4.2 sequences have been identified in the UK as of October 25, linking to 16,876 cases in England.[5]
    - Surveillance data came from hospitalized cases, hospital staff, international travellers, a sample of community-based testing, and national core priority studies.
    - Cases are counted as AY.4.2 sublineage if they carry the existing Delta genome plus any two of the three additional mutations (A222V, Y145H, A2529V), where none of the positions are wild-type (sensitivity = 95.2%; specificity = 97.5% compared to sequencing data).
- The proportion of AY.4.2 sequences among Delta cases has been slowly increasing in the UK:[5]
    - 8.5% in the week of October 4, 2021 (the most recent week with complete sequencing data).
    - 10.3% and 11.3% in the weeks of October 11 and 18, 2021, respectively (incomplete sequencing data).

Transmissibility

- Compared to non-AY.4.2 variants circulating in the same geographic region in the UK, AY.4.2 has a weekly growth rate of 19% from the beginning of August to mid-October, 2021.[5]
- In the period of August 1 to October 5, 2021, higher secondary attack rates (95% confidence interval [CI]) were observed for AY.4.2 compared to other Delta cases in England (significantly in household settings and non-significantly in non-household settings) in contacts of non-travel cases or cases with unknown travel history.[5]
    - In the household setting:
        - AY.4.2: 12.2% (11.8%–12.7%) (2,593 cases/21,218 contacts)

- Delta: 11.2% (11.1%–11.3%) (76,911 cases/686,204 contacts)

- In the non-household setting:[5]
  - AY.4.2: 4.5% (3.9%–5.0%) (257 cases/5,775 contacts)
  - Delta: 4.0% (3.9%–4.1%) (8,076 cases/201,171 contacts)

Disease Severity

- Preliminary data from England between May 15 and October 24, 2021 suggest similar rates of hospitalization and death between AY.4.2 and other Delta sublineages. However, the analysis did not take into consideration vaccination status and age.[5]
  - Percentage (95% CI) of cases attending to emergency care with subsequent admission:
    - AY.4.2: 0.27% (0.18%–0.39%) (27/10,024 cases)
    - Delta: 0.25% (0.23%–0.26%) (1,789/728,088 cases)
  - Percentage (95% CI) of deaths in any setting within 28 days of positive specimen date:
    - AY.4.2: 0.49% (0.49%–0.82%) (64/10,023 cases)
    - Delta: 0.53% (0.53%–0.56%) (3,813/727,986 cases)

Vaccine Effectiveness

- Preliminary analysis found no evidence of significantly altered vaccine effectiveness against symptomatic and asymptomatic COVID-19 in England across the three vaccines used, after adjusting for travel, ethnicity, sex, age, index of multiple deprivation quintile, comorbidities, health and social care worker status, region of England and week of test.[5] Adjusted odds ratio (95% CI) of infections by AY.4.2 vs. Delta at ≥ 14 days after dose 2 are:
  - Against symptomatic and asymptomatic infections in hospitals and community:[5]
    - All vaccines: 1.04 (0.97–1.11)
    - Astra Zeneca: 1.02 (0.95–1.09)
    - Moderna: 0.96 (0.69–1.35)
    - Pfizer BioNTech: 1.08 (1.00–1.16)
  - Against symptomatic infection in community:[5]
    - All vaccines: 1.03 (0.94–1.13)
    - Astra Zeneca: 0.98 (0.89–1.08)
    - Moderna: 1.14 (0.66–1.98)

- Pfizer BioNTech: 1.12 (1.00–1.26); suggesting a minimal reduction in vaccine effectiveness from 83% to 81%.

Ontario Risk Assessment

- The risk of Delta sublineage AY.4.2 transmission in Ontario is low with a high degree of uncertainty. As of October 16, 2021, AY.4.2 had been detected in Ontario in five cases. The prevalence of AY.4.2 can rise with outbreaks of high case numbers due to pockets of the population with suboptimal vaccine coverage. The overall risk assessment may change as new evidence emerges (see Table 1).
- Further epidemiological and laboratory studies are in progress to assess if AY.4.2 confers any additional phenotypic impacts (e.g., a change in transmissibility, disease severity, escape from natural and/or vaccine-induced immunity).[1]

Table 1. Risk Assessment for Delta Sublineage AY.4.2

Issue	Risk Level	Degree of Uncertainty
Increased Transmissibility	**Insufficient information** Based on preliminary data from the UK, researchers have shown slightly higher secondary attack rates with AY.4.2 in household settings, compared to Delta.	**High**
Disease Severity	**Insufficient information** Based on preliminary data from the UK, researchers demonstrate similar rates of hospitalization and death in patients with AY.4.2, compared to Delta.	**High**
Re-infection and Breakthrough Infections	**No information** To date, there are no reports of re-infection or breakthrough infections with AY.4.2.	**High**
Lowered Vaccine Effectiveness	**Limited information** Based on preliminary data from the UK, researchers noted no significant change in in VE against symptomatic and asymptomatic COVID-19 in patients with AY.4.2, compared to Delta.	**High**
Impacts on Testing / Surveillance	**Low** The risk of AY.4.2 cases not being detected in Ontario's surveillance program is low.	**Low**

Practice Implications

- Public Health Agency of Canada is monitoring AY.4.2, and epidemiological and laboratory studies are in progress to assess if AY.4.2 confers any biological significance to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) (e.g., a change in transmissibility, disease severity, escape from natural and/or vaccine-induced immunity).
- Vaccination remains one of the most effective layers of protection against SARS-CoV-2, as each transmission event plays a role in fostering further mutations of the virus. [9]
- Along with vaccination, a multi-layered approach to Coronavirus Disease 2019 (COVID-19) prevention (including cleaning hands, masking, physical distancing, ventilation, staying home when sick) should continue to be promoted in the context of more transmissible emerging variants. [10]

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