

AT A GLANCE

Companion Guide to Variants of Concern (VOCs)

Background

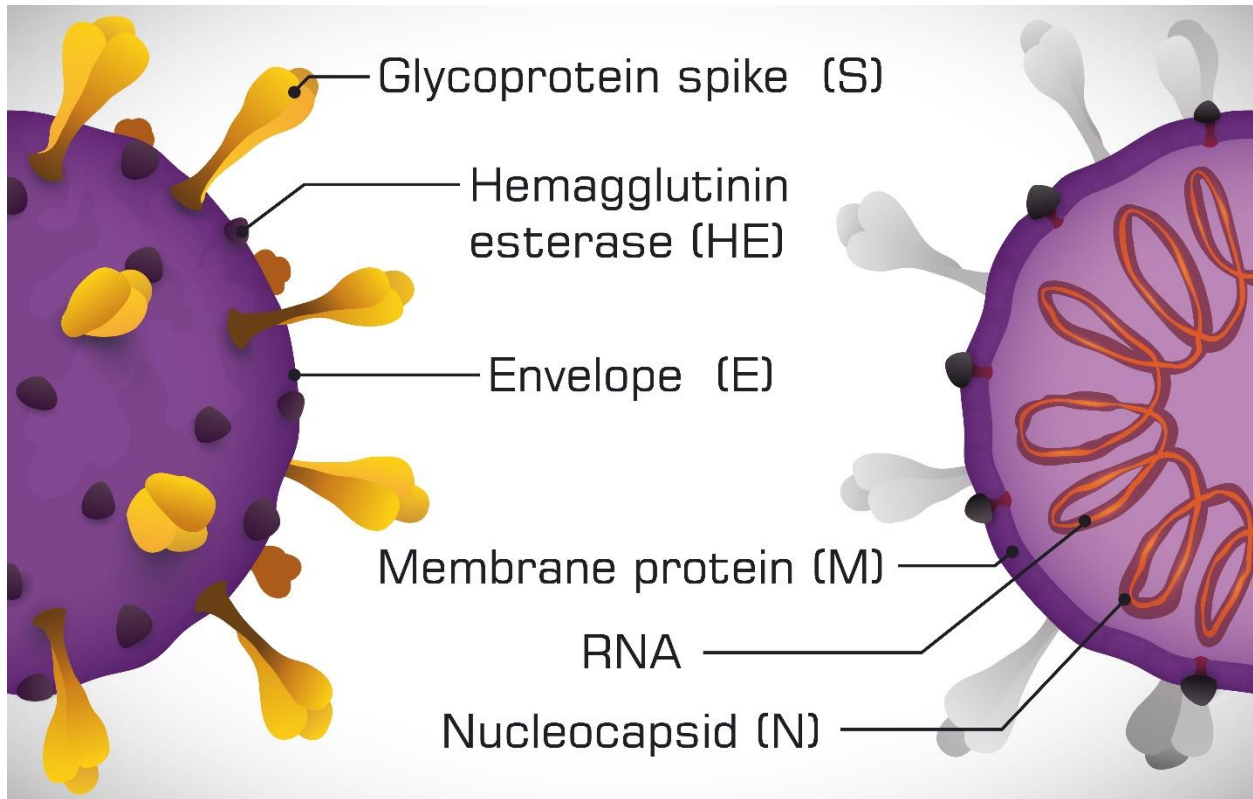
The material in this document is provided to support the understanding of Public Health Ontario's (PHO) *Comparison of SARS-CoV-2 Variants of Concern (VOCs)* table. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mutations occur regularly and most mutations (referred to as "synonymous") do not result in a change in viral proteins (see Figure 1). Non-synonymous mutations change the amino acid sequence and may result in changes in viral proteins. These changes can occur anywhere in the genome, including the receptor-binding domain (RBD) of the spike (S) protein (see Figure 2).¹⁻⁴ The spike protein (also called glycoprotein spike or spike glycoprotein), encoded by the S gene, is the key protein on the viral surface that is involved in binding to the angiotensin-converting enzyme 2 (ACE2) receptor on the surface of host cells, and initiating cell entry during infection. The S protein is also a major target of the immune system. As a result, S protein mutations may alter virus infectivity, replication and pathogenicity, and may result in an altered host immune response.

Mutations in SARS-CoV-2 arise naturally through evolution, with selection of phenotypes increasing viral fitness (replication, transmissibility, immune escape). The emergence of variants has been attributed to within-host evolution during prolonged SARS-CoV-2 infection in persons with immune system compromise, with mutations accumulating over the course of infection.^{5,6} Tegally et al. (2021) hypothesized that a population with high seroprevalence and immunity led to a strong selection pressure for the evolution of mutations.⁷

For the purposes of this document, we will follow the definitions of VOCs as proposed by the Canadian SARS-CoV-2 Variant Surveillance Group.⁸ A variant is a VOC if, through a comparative assessment, it has been demonstrated to be associated with one or more of the following:

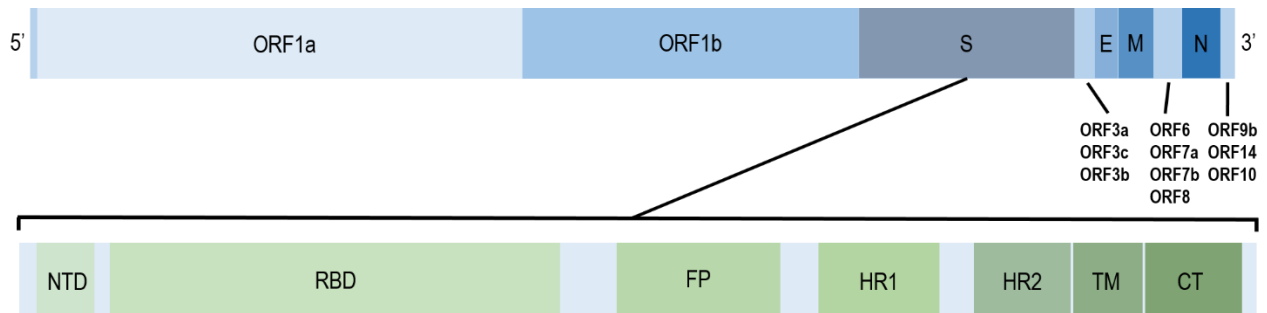
- increased transmissibility or detrimental change in COVID-19 epidemiology; increased virulence or change in clinical disease presentation; decreased effectiveness of available diagnostics, vaccines, therapeutics or public health measures; OR
- is otherwise assessed to be a VOC by WHO; OR
- is otherwise assessed to be a VOC by the Canadian SARS-CoV-2 Variant Surveillance Group.

Figure 1. Diagram of SARS-CoV-2



Source: Getty Images

Figure 2. SARS-CoV-2 Genome, Focusing on the Spike Protein



Legend:

- | | |
|--------------------------------------|-------------------------------|
| CT = cytoplasm domain | N = nucleocapsid |
| E = envelope | NTD = N-terminal domain |
| FP = fusion peptide | ORF = open reading frame |
| HR1 = heptapeptide repeat sequence 1 | RBD = receptor-binding domain |
| HR2 = heptapeptide repeat sequence 2 | S = spike |
| M = membrane | TM = TM domain |

Characteristics and Relevant Terms Used in Ontario to Describe VOCs

PANGO lineage: Phylogenetic Assignment of Named Global Outbreak LINEages ([pangolin](#)) is a software tool used to assign lineages to SARS-CoV-2 genome sequences.^{9,10} Using a dynamic nomenclature of SARS-CoV-2 lineages, sequences are assigned an alphanumeric designation.

Public Health England name: Public Health England has developed a naming system for variants.¹¹ If a variant has “concerning epidemiological, immunological or pathogenic properties”, then it is investigated formally and designated Variant Under Investigation (VUI). The numbers represent year and month it was first detected, followed by a chronological number based on detection timing if first detected in same month and year. Following an investigation of a VUI, Public Health England performs a risk assessment with the relevant expert committee, where the VUI may be designated a VOC.

Nextstrain clade: [Nextstrain](#) is an interactive visualization platform that can be used to analyze and display SARS-CoV-2 genome sequences.¹² Nextstrain clades have a prefix for the year of emergence, followed by the next letter of the alphabet available.

Location first detected: The location first detected is where the first sample (that was positive for the VOC) was collected from an individual.⁹⁻¹³ This is not necessarily the location where the VOC originated or where most prevalent. For the case of P.1, the variant was detected in Japan, from a sample collected from a traveller from Brazil.

Detected in multiple countries: We report if the VOC has been reported beyond the location where it was first detected, based on the information collected from [outbreak.info](#).¹³

Detected in Ontario: Here we report if the VOC is detected or not in Ontario. Presence is based on genome sequences deposited in global repositories and reported by [pangolin](#) and [outbreak.info](#) (a web site that aggregates SARS-COV-2 VOC data).^{9,13} Detection of a VOC in Ontario does not necessarily mean local transmission is occurring. Currently, all SARS-CoV-2–positive specimens in Ontario are tested for the presence of VOCs. A subset of VOC and non-VOC SARS-CoV-2-positive specimens are tested by whole genome sequencing for additional surveillance of VOCs and other emerging variants. Current strategies can detect known VOCs circulating at a prevalence of ~1%, which may then trigger active detection.

Gene mutations (general comment): For comparisons, we limited mutations to those shared at least twice among VOCs. Some mutations are associated with increased transmissibility, disease severity or immune escape; however, this association may be altered when multiple mutations are considered together. For a complete list of mutations for each VOC, please refer to [outbreak.info](#) or [pangolin](#).^{9,13} Mutations are designated by: 1) a letter corresponding to the amino acid in the SARS-CoV-2 reference genome; 2) number corresponding to the amino acid position; and 3) a letter corresponding to the substituted amino acid.

Details on Mutations

Spike Mutations

The spike protein is responsible for the ability of SARS-CoV-2 to bind to and invade host cells. SARS-CoV-2 S-proteins bind to host cell receptors expressing ACE2 and transmembrane protease serine 2 (TMPRSS2).^{8,14}

- **A701V (alanine to valine at amino acid 701):** The A701V mutation is located near S1 subunit cleavage site; however, the biological significance of this mutation is not well understood.¹⁵
- **D614G (aspartic acid to glycine at amino acid 614):** The D614G mutation is located in the RBD and linked to increased transmissibility, infectivity and viral loads.^{14,16-18}
- **E484K/Q (glutamic acid to lysine/glutamine at amino acid 484):** The E484K mutation is linked to immune escape and potentially decreased vaccine effectiveness. The mutation has led to decreased effectiveness of monoclonal antibodies, convalescent plasma and vaccine sera.^{15,19,20} The E484Q mutation has not been associated with any change in receptor-binding avidity,²¹ but clinical effectiveness of some monoclonal antibodies may be compromised.²²
- **K417N/T (lysine to asparagine/threonine at amino acid 417):** K417N/T mutations are located in the RBD and linked to increased binding affinity, transmissibility and immune escape.²³
- **L18F (leucine to phenylalanine at amino acid 18):** The L18F mutation is located in the N-terminal domain and linked to immune escape and increased replication.²⁴
- **L452R (leucine to arginine at amino acid 452):** The L452R mutation is located in the RBD of the S protein and has been associated with immune escape from therapeutically relevant monoclonal antibodies and convalescent sera,^{21,25,26} and enhanced receptor binding affinity and transmissibility.²⁷
- **N501Y (asparagine to tyrosine at amino acid 501):** The N501Y mutation is located in the RBD of the S protein and linked to increased ability to invade host cells via ACE2 receptors.^{15,19}
- **P681H/R (proline to histidine/arginine at amino acid 681):** P681H/R mutations are located near the S1/S2 subunit linkage site and potentially linked to increased infectivity and replication.²⁸
- **Δ69/70 ([deletion] of amino acids 69 and 70):** Amino acids 69 and 70 are located in the N-terminal domain of the S protein, potentially leading to changes in the S1 subunit.²⁹ This mutation has been linked to potential evasion of the human immune response. The Δ69-70 mutation has led to negative results in polymerase chain reaction (PCR) assays that target the S gene (i.e., S-Gene Target Failure [SGTF]). The impact on the performance of molecular diagnostic tests overall is minimal as most assays use multiple gene targets.

Impact of VOCs on Epidemiology

Increased transmissibility: The increased transmissibility of a VOC within populations is inferred from increases in incidence, higher secondary attack rates, increases in reproductive number (R_t), increased binding affinity to ACE2 receptors, and viral loads.^{14,16,17,24,30-34} The magnitude of the increase in transmissibility is not fully understood and varies by the proxy used, the geographic region, the modelling approach, the scope and practice of pandemic control measures, and the relative transmissibility of concurrent circulating strains.

Increased disease severity: Increased disease severity is typically inferred from hospitalization, symptomology, illness duration and death data reported by jurisdictions in which the variant is circulating.^{19,31-34} The exact magnitude of disease severity is not fully understood.

Impact on molecular tests: To assess the impact of a VOC on molecular diagnostic tests authorized for use in Ontario, we focus on rRT-PCR-based tests of non-S-gene targets (i.e., E, N, ORF1a/b, RdRp genes; [Figure 2](#)).³¹⁻³⁵

Impact on antigen tests: The rapid antigen tests currently licensed by Health Canada and in use in Ontario detect the N protein; therefore, they are unlikely to be affected ([Figure 2](#)). Preliminary laboratory analysis indicates that rapid antigen tests that target the N protein are able to detect B.1.1.7.^{33,35,36}

Impact on serological tests: The impact of mutations on serological assays has not been investigated; however, there is potential for decreased detection if S and/or N proteins are targeted in a specific assay ([Figure 2](#)).³⁵

Immune escape: Variants or sets of mutations are known to confer partial or complete escape from therapeutically relevant monoclonal antibodies and neutralizing antibodies in COVID-19 convalescent plasma.^{18-20,23,24,30-35} The exact magnitude of the immune escape is not fully understood.

Impact on vaccine effectiveness: For vaccine effectiveness, we concentrate on vaccines approved for use in Canada, namely the Moderna mRNA-1273, Pfizer-BioNTech BNT162b2 mRNA, Oxford/AstraZeneca AZD1222 and Janssen Ad26.COVS.2 vaccines.^{20,29,31-34,37} The exact magnitude VOCs have on vaccine effectiveness is not fully understood.

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At a Glance

An *At a Glance* is a brief document offering an overview of a topic or steps in a process, in a concise manner.

Public Health Ontario

Public Health Ontario is an agency of the Government of Ontario dedicated to protecting and promoting the health of all Ontarians and reducing inequities in health. Public Health Ontario links public health practitioners, front-line health workers and researchers to the best scientific intelligence and knowledge from around the world.

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