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Executive Summary

SARS-CoV-2 EG.5 viruses currently represent more than half (51%) of the SARS-CoV-2 variants in global circulation. The EG.5 sublineages HK.3 and HV.1 have a high growth advantage relative to co-circulating variants, but their associated public health risks are classified low at the global level. Based on the current evidence, their phenotype remains comparable to other XBB variants with which they have been co-circulating for the last 10 months.

Updated Risk Evaluation for EG.5 and its sublineages, 21 November 2023

EG.5 is a descendent lineage of XBB.1.9.2 and carries an additional F456L amino acid mutation in the spike protein. EG.5 was first reported on 17 February 2023 and designated as a variant under monitoring (VUM) on 19 July 2023. On 9 August 2023, WHO published its first risk evaluation of EG.5 and designated EG.5 and its sub-lineages as a variant of interest (VOI). The updated risk evaluation of EG.5 was published on 21 September 2023. This updated risk evaluation replaces previously published risk evaluations of EG.5 and its descent lineage.

As of 20 November 2023, 108 911 sequences of Omicron EG.5 and descendent lineages have been submitted to GISAID from 93 countries. Globally, there has been a steady increase in the proportion of EG.5 reported, with its global prevalence at 51.6% in epidemiological week 44 (30 October to 5 November 2023), Table 1. This is a rise from the data reported four weeks prior (week 40, 2 to 8 October 2023), when the global prevalence of EG.5 was 47.0%.

Table 1: Global proportions of SARS-CoV-2 Variants, week 40 to week 44 of 2023

Lineage	Countries[§]	Sequences[§]	2023-40	2023-41	2023-42	2023-43	2023-44
VOIs							
XBB.1.5*	128	308 614	8.5	8.2	8.3	7.2	8.3
XBB.1.16*	117	94 914	15.9	14.0	12.4	9.8	8.2
EG.5*	89	104 423	47.0	50.2	50.9	51.9	51.6
BA.2.86*	41	3 109	1.8	2.8	4.1	6.4	8.9
VUMs							
DV.7*	38	3 887	1.8	1.8	1.7	1.9	1.9
XBB*	142	88 309	3.4	2.9	2.7	2.8	2.3
XBB.1.9.1*	118	80 383	9.5	8.0	8.0	7.0	6.4
XBB.1.9.2*	95	36 685	2.4	2.3	1.8	2.1	1.9
XBB.2.3*	104	31 394	6.0	5.6	5.2	4.9	3.7
Unassigned	95	152 256	0.5	1.4	2.5	3.6	4.5
Other+	211	6 785 691	3.0	2.6	2.3	2.2	2.2

The largest portion of EG.5 sequences are from the United States of America (24.8%, 27 044 sequences), Canada (12.6%, 13 678 sequences), and China (10.6%, 11 489 sequences). Other countries with at least 1000 sequences are Japan (7.0%, 7571 sequences), South Korea (6.3%, 6880 sequences), United Kingdom (6.3%, 6803 sequences), France (5.5%, 5950 sequences), Spain (4.0%, 4363 sequences), Singapore (2.7%, 2946 sequences), Sweden (2.4%, 2605 sequences), Australia (2.0%, 2207 sequences), Italy (1.9%, 2037 sequences), Denmark (1.4%, 1530 sequences), Belgium (1.2%, 1289 sequences), Germany (1.2%, 1272 sequences), Netherlands (1.0%, 1117 sequences), and New Zealand (0.9%, 1028 sequences).

Within the EG.5 descendent lineages, the subvariants HV.1, HK.3, EG.5.1.1 and JG.3 represent 33.2% of the global proportion of SARS-CoV-2 sequences at epidemiological week 44 (1). The majority of the HV.1 sequences are from the United States of America (5550 sequences; 48.0%) whereas HK.3 and EG.5.1.1 sequences are mainly from China (3049 sequences; 23.7% and 6544 sequences; 21.1% respectively). Most of the JG.3

sequences are Canada (371 sequences, 14.9%). Between epidemiological weeks 40 and 44, the prevalence of HV.1, HK.3 and JG.3 increased from 7.9% to 15.1%, 8.5% to 12.0%, and 1.4% to 5.2%, respectively, whereas the prevalence of EG.5.1.1 decreased from 10.0% to 6.0%. Table 2 below shows the HV.1, HK.3, EG.5.1.1 and JG.3 additional mutations relative to EG.5 in the spike and other proteins.

Table 2: EG.5 descendent lineages and mutations

Variant	Parent Lineage	Additional Spike Mutations relative to EG.5	Additional Mutations in other proteins relative to EG.5
EG.5	XBB.1.9.2	NA	NA
HV.1	EG.5.1.6	S:Q52H, S:F157L, S:L452R	ORF1a:S1857L
HK.3	EG.5.1.1	S:Q52H, S:L455F	ORF1b:D54N
EG.5.1.1	EG.5.1	S:Q52H	ORF1b:D54N
JG.3	EG.5.1.3	S:Q52H, S:L455F, S:S704L	ORF1a:R542C, ORF1a:T2274I

Based on the available evidence, the public health risk posed by EG.5 is evaluated as low at the global level. While EG.5 has shown increased prevalence, growth advantage, and immune escape properties compared to other currently circulating variants, there have been no reported changes in disease severity to date. While concurrent increases in the proportion of EG.5 and COVID-19 hospitalizations have been observed in some countries, no direct associations have been made between these hospitalizations and EG.5, and current hospitalizations are lower when compared to previous waves. However, due to its growth advantage and immune escape characteristics, EG.5 has caused a rise in case incidence and has become the most prevalent variant globally.

WHO and its Technical Advisory Group on SARS-CoV-2 Evolution (TAG-VE) continue to recommend that Member States prioritize specific studies to better address uncertainties relating to antibody escape and severity of EG.5. The suggested timelines are estimates and will vary from one country to another based on national capacities:

- Conduct neutralization assays using human sera, representative of the affected community(ies), and live virus isolates of EG.5 and its sublineages with the fastest growth such as HV.1 and HK.3 (from two to four weeks, see table below for the results from previously conducted studies)
- Perform a comparative evaluation to detect changes in rolling or ad-hoc indicators of severity (from four to 12 weeks, see table below for the results from previously conducted studies).

The WHO and its Technical Advisory Group on COVID-19 Vaccine Composition (TAG-CO-VAC) continue to regularly assess the impact of variants on the performance of COVID-19 vaccines to inform decisions on updates to vaccine composition (2).

The risk evaluation below is based on currently available evidence and will be revised regularly as more evidence and data from additional countries become available.

Overall risk evaluation: Low	EG.5 and its sublineages has spread globally and several countries with rising EG.5 prevalence have seen increases in cases and hospitalizations. However, at present, there is no evidence of an increase in disease severity directly associated with EG.5 compared with other Omicron sublineages and therefore available evidence does not suggest that EG.5 has additional public health risks. However, additional data outlined in this risk evaluation are needed for a more comprehensive evaluation of the risk posed by the emerging EG.5 subvariants such as HK.3 and HV.1.		
Indicator	Evidence	Level of risk	Level of confidence
Growth advantage	Comparing epidemiological week 40 (2 to 8 October 2023) to week 44 (30 October to 5 November 2023), the global proportion of EG.5 relative to other circulating variants showed a notable increase, rising from 47.0% to 51.6%. Similarly, for countries with the highest proportion of EG.5 sequences, the prevalence of EG.5 in these countries rose from 40.1% to 48.1% for the United States of America, from 50.5% to 60.9% for Canada, and from 92.2% to 98.2% for China. Based on WHO's internal variant growth rate analysis, whose methodology is similar to the methods used by the United Kingdom Health Security Agency (UK HSA), EG.5 and its descendent lineages have the fastest growth among variants currently circulating globally, and in the European and Western Pacific regions (3,4). The UK HSA has estimated EG.5.1.1 to have the highest growth rate in the country, with an estimated prevalence of 7.4% (95% confidence interval [CI]: 5.5-9.9) as of 27 October 2023 (5). The United States Centers for Disease Control and Prevention (US CDC)	High	High

	Nowcast model-based projections continue to forecast national increases in EG.5 and its descendent lineages; with the predicted prevalence of HV.1 to be at 29.0% and that of EG.5 to be at 21.7% between 29 October and 11 November 2023 (6). With regards to transmissibility, the same study revealed some differences in transmissibility and virus tropism between EG.5.1 and XBB.1.5; a slightly higher transmission efficacy was found for EG.5.1 (five of six pairs of hamsters: 83%) compared with that of XBB.1.5 (56% transmission), and most of the EG.5.1-exposed animals (four of six exposed animals: 67%) had detectable virus in the lungs (as well as in nasal samples) as opposed to XBB.1.5-exposed animals that only had detectable virus in nasal samples (7). * see footnote for more explanations		
Antibody escape	EG.5 has the mutation F456L, which is located within epitopes of many class-1 mABs directed at the receptor-binding domain and predicts antibody evasion. EG.5.1 showed a small but significant (1.3 to 2-fold) increase in resistance to serum neutralization from individuals with BQ.1 or XBB breakthrough infections, compared with XBB.1.5 (8-11). However, in live virus neutralization, this difference was not visible and neutralization titers were comparable to those for XBB.1. (12). Using pseudoviruses, the 50% neutralization titer (NT50) of all BTI sera tested against HK.3 (i.e. XBB.1.5 + S:L455F) was lower than those against the parental XBB.1.5, and the NT50 of EG.5.1 BTI sera against HK.3 was again lower than that against EG.5.1. This suggest that the increased in HK.3 prevalence may be	Moderate	Moderate

	attributable to its immune evasion properties (7). ** see footnote for more explanations		
Severity and clinical considerations	There are currently no reports of increased disease severity due to EG.5 compared to other Omicron sublineages. A laboratory-based study using Syrian hamsters reported no obvious differences in growth ability and pathogenicity between XBB.1.5 and EG.5.1 (7). An update to a study from Singapore reported no differences in the severity of EG.5 infections, as compared to that of other XBB descendent lineages (13). Another recent study aiming to phenotype the virulence of SARS-CoV-2 variants in hamsters observed the virulence of EG.5.1 to be comparable to that of BA.2.75 but significantly higher than that of BA.1 (14). It remains to be known how this result translates into infection in humans, and there is currently no epidemiological data pointing at this direction. Further evaluation is required to confirm these differences and determine the factors contribute to them. In some countries where EG.5 was the most reported variant, they observed increases in hospitalizations following increases in cases. However, all observed trends should be interpreted cautiously due to the reduction in surveillance activities for human cases, including a decreased volume of testing, a shift in testing strategies and delays in reporting. *** see footnote for more explanations	Low	Low

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Annex:

*** Growth advantage**
Level of risk: High, as the variant is the fastest growing variant in several WHO regions as well as rapidly increasing in prevalence globally. Since the first risk evaluation of EG.5 was published on 9 August 2023, the variant has maintained steady growth rates over time, becoming the dominant variant globally.

Confidence: High, as the growth advantage has been estimated by several groups of experts and in several countries and WHO regions. EG.5 and its sublineages currently account for >50% of the sequences submitted to GISAD globally.

**** Antibody escape**
Level of risk: Moderate, due to immune evasion of XBB.1.5 neutralizing antibodies, the previous globally dominant variant that peaked at >50% prevalence.

Confidence: Moderate, as immune escape results are based on work from multiple laboratories, including some that have used live viruses.

***** Severity and clinical considerations**
Level of risk: Low, as currently there are no reports of elevated disease severity associated with this variant.

Confidence: Low. Although, there is regular co-ordination and data sharing between all WHO Regional colleagues, countries and partners, reporting of new hospitalizations and ICU data with the WHO has decreased substantially, therefore caution should be taken when interpreting severe cases due to this decrease in reporting. Further work on characterizing virus tropism in the laboratory is needed, as only one study reported subtle differences (as compared to XBB.1.5) in Syrian hamsters, and the significance of those findings are unclear. Additional studies in humans would be needed to further assess the impact of this variant on clinical outcomes.

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