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XBB.1.5 Updated Rapid Risk Assessment, 25 January 2023

Following a TAG-VE meeting on 23 January 2023, the WHO has revised the confidence level of the risk assessment for XBB.1.5 from “Low” (assessed on 11 January 2023) to “Moderate” (25 January 2023), using additional reports from countries on prevalence and growth advantage, and laboratory-based studies.

XBB.1.5 is descendent lineage of XBB, which is a recombinant of two BA.2 descendent lineages. From 22 October 2022 to 23 January 2023, 8931 sequences of the Omicron XBB.1.5 variant have been reported from 54 countries (excluding low coverage sequences). Most of these sequences are from the United States of America (75.0%). The other countries include the United Kingdom (9.9%), Canada (3.0%), Denmark (2.0%), Germany (1.5%), Ireland (1.3%) and Austria (1.3%).

Based on its genetic characteristics and growth rate estimates, XBB.1.5 is likely to contribute to increases in case incidence globally. There is moderate-strength evidence for increased risk of transmission and immune escape. From reports by several countries, no early signals of increases in severity have been observed. The number of cases associated with XBB.1.5 is still low and thus severity cannot yet be confidently assessed. Taken together, available information does not suggest that XBB.1.5 has additional public health risk relative to the other currently circulating Omicron descendent lineages.

WHO and the TAG-VE recommend Member States prioritize the following studies to better address uncertainties relating to the growth advantage, antibody escape, and severity of XBB.1.5. The suggested timelines are estimates and will vary from one country to another based on national capacities:

- Neutralization assays using human sera representative of the affected community(ies) and XBB.1.5 live virus isolates (2-4 weeks)
- Comparative assessment to detect changes in rolling or ad hoc indicators of severity (see table below, 4-12 weeks)

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

	Indicator	Confidence in the assessment
Growth advantage	In the United States of America, XBB1.5 is increasing in many regions (the prevalence of XBB.1.5 in some regions is predicted to be 80%, while in others, 20-50%). In the United Kingdom, growth advantage relative to BQ.1.1 was estimated to 38.9%, with high uncertainty due to the small number of sequenced XBB.1.5 cases.[1,2] Further, the ECDC has reported growth of XBB.1.5 in several countries, including Iceland where it has increased to 8.7% in week 2 of 2023.[3] In addition, *in silico* analysis reported that the mutation S:F486S (present in XBB.1) abrogated the local hydrophobic interaction with ACE-2 while 486P (present in XBB.1.5) restored it. The amino acid change to 486P contributes to higher ACE-2 binding affinity, and suggests a mechanism for XBB.1.5 to have a higher growth advantage as compared to its parent lineage XBB.1.[4]	Moderate
Antibody escape	Using pseudotyped virus neutralization assays, XBB.1.5 is shown to be as immune evasive as XBB.1, one of the Omicron subvariants with the highest immune escape to date.[4-8] Antibody titers against XBB.1 were mostly absent in individuals with a history of vaccination with the index vaccine (2-4 doses), were higher in those who recently received a bivalent (BA.5) vaccine booster, and highest in individuals with hybrid immunity.[5,6] There are currently no data on real world vaccine effectiveness against severe disease or death.	Moderate
Severity and clinical considerations	Severity assessments in human populations are ongoing. The number of cases associated with XBB.1.5 is still low and thus clinical severity cannot yet be confidently assessed. XBB.1.5 does not carry any known mutation(s) associated with potential changes in severity (such as S:P681R).[9,10]	Low
Risk assessment	Based on its genetic characteristics and growth rate estimates, XBB.1.5 is likely to contribute to increases in case incidence globally. There is moderate-strength evidence for increased risk of transmission and immune escape. From reports by several countries, no early signals of increases in severity have been observed. The number of cases associated with XBB.1.5 is still low and thus severity cannot yet be confidently assessed. Taken together, available information does not suggest that XBB.1.5 has additional public health risks relative to the other currently circulating Omicron descendent lineages.	

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Risk assessment framework and indicators used to assess risk and confidence given available evidence

	Rapid indicators: 0-4 weeks	Confidence in the assessment		
		LOW	**MODERATE**	**HIGH**
Growth advantage	Evidence of a growth advantage likely to lead to global predominance A. An increase in variant specific Rt B. Logistic growth (compared to currently circulating variant) (Nb variants with subnational-limited growth are not assessed).	All data derived from one country	At least two models; data from two countries not linked by close travel	At least two models and at least three countries in three regions, over more than two weeks
Immune escape	• Genomic (predictive) and structural biology assessment • Pseudovirus neutralization using vaccinee sera **or** pre-banked population serosurveys • Reinfection rate through a cohort study or surveillance system • Signals from outbreak investigations (Rapid VE is unlikely by 28 days so the rapid RA cannot reach high confidence).	One indicator (reinfection, neutralization or structural model)	Two indicators including neutralization data	[rapid VE]
Severity and clinical considerations	• Change in a rolling surveillance metric for severity synchronized with increase in variant e.g. ○ Infection hospitalization ratio ○ Indicators from sentinel hospital network (e.g. surveillance of severe acute respiratory infections) ○ Comparison of admission trends with previous variants • Change in the demographic profile of who is admitted to hospital • Change in clinical phenotype • Major tests/therapeutics issues	One metric, one country	Multiple metrics, one country OR same method in multiple countries	Multiple metrics, multiple countries in multiple regions
Risk assessment	Including overall view of threat in the wider context, confidence level in the assessment, and identification of urgent priority work.			

References

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