

Severity of COVID-19 sub-lineages XBB/XBB 1.5/XBB1.16, EG.5.1. and JN.1. in England

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The SARS-CoV-2 JN.1 lineage, descendant of BA.2.86 emerged in late 2023 and accounted for around 85% of the sequenced cases in England by the end of January 2024.^{1,2} The difference between BA.2.86 and JN.1 is one substitution in the spike protein and three substitutions in non-spike protein.¹ This substitution can signify change in transmissibility and effectiveness of the current vaccines.³ The aims of the analysis were to estimate the odds of intensive care unit (ICU) admission or death amongst hospitalised cases with XBB/XBB 1.5/XBB1.16 (XBBs) compared to EG.5.1. and JN.1; and to estimate the length of stay amongst hospitalised cases as a measure of variant severity.

The study period was from 4th September 2023 to 21st January 2024. Information on data sources is available in the supplementary material. Data were extracted on 12th February 2024 to allow time for discharge and for data completeness to be high.

To estimate the odds of ICU admission or death by variant amongst sequenced cases admitted to hospital, individuals aged 50 years and older who were hospitalised with a positive polymerase chain reaction test were included as previously described.⁴ Variant status was identified by whole genome sequencing.⁵ Only individuals where sequencing detected XBBs, EG.5.1. and JN.1. variants were included. Multivariable penalized logistic regression was used with ICU admission or death as the outcome, variant as the primary variable of interest and with adjustment for vaccination status, week of test date, sex, age group, and risk group status (identified as being at risk, clinically extremely vulnerable or severely immunosuppressed and identified recently as requiring an autumn booster due to a clinical risk factor by the NHS Cohorting as a Service). Sensitivity analyses were conducted to estimate the odds of ICU admission or death for those with a respiratory ICD-10 code in the primary diagnosis field.

To estimate length of stay amongst hospitalised cases, the median length of stay and interquartile range

(IQR) were reported. A Cox proportional hazards survival regression was used with time to discharge as the outcome and variant was included as an independent variable with confounder adjustment as described above. For this analysis only individuals who had an admission date, discharge date and a length of stay between 0 and 21 days (to ensure all individuals in the study period had time to be discharged and to allow for delays in the SUS hospitalisation data reporting) were included. The analysis was stratified by those who died and those who did not die. Model outputs are reported as the predicted median length of stay.

There was no significant difference in the adjusted odds of admission to ICU or death for those with EG.5.1 (OR 0.48, 95% C.I.; 0.21–1.09) or JN.1 (OR 0.58, 95% C.I.; 0.20–1.65) compared to XBBs (Fig. 1a). After restricting to individuals with a respiratory code in their primary diagnosis field, there was also no significant difference in the adjusted odds of admission to ICU or death for those with EG.5.1 (OR 0.39, 95% C.I.; 0.11–1.31) or JN.1 (OR 0.26, 95% C.I.; 0.03–2.05) compared to XBBs (Supplementary Table S1).

The predicted median length of stay with adjustment for confounders showed no significant difference for those hospitalised with EG.5.1 (median 5.4 days; 95% C.I.; 5.0–5.7 days), JN.1 (median 5.0 days; 95% C.I.; 4.6–5.5 days), or XBBs (median 5.2 days; 95% C.I.; 4.9–5.5 days) (Fig. 1b). Sensitivity analyses restricting to those with a respiratory code in their primary diagnosis field also found no significant difference in the length of stay by variant (Supplementary Table S2).

Overall, these data do not suggest that JN.1 and EG.5.1 causes more severe disease than XBB sub-lineages. We found no statistically significant difference in the odds of ICU admission or death among hospitalised individuals infected with JN.1 or EG.5.1 compared to XBBs. The length of stay following hospitalisation also did not statistically differ by variants. These findings agree with a study from Denmark which also found no difference in severity.⁶



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a

	Total	ICU admission or death (% of total)	Adjusted ORs (95% CI)	P value
XBB - XBB1.5 - XBB1.16	1,654	27 (1.6%)	Baseline	-
EG.5.1	1,005	7 (0.7%)	0.48 (0.21-1.09)	0.08
JN.1	1,158	9 (0.8%)	0.58 (0.20-1.65)	0.31

Adjusted odds ratio (OR) and 95% confidence intervals (CI) comparing risk of ICU admission or death among individuals who were admitted to hospital, and had a length of stay of two or more days, for cases with JN.1, EG.5.1 compared to XBBs.

Adjustment for week of test date, sex, age group, risk group status, and vaccination status.

b

	Person-time (days)	Incidence rate (95% CI)	Total	Hazard Ratio (95% CI)	Predicted median length of stay (95% CI) days	Median length of stay (IQR) days
XBB - XBB1.5 - XBB1.16	11,595	0.13 (0.13-0.14)	1,507	Baseline	5.19 (4.88-5.50)	5 (2-10)
EG.5.1	7,334	0.13 (0.12-0.14)	923	0.95 (0.88-1.03)	5.37 (5.00-5.73)	6 (2-11)
JN.1	8,607	0.14 (0.13-0.14)	1,166	1.06 (0.95-1.19)	5.04 (4.64-5.45)	5 (2-10)

Adjusted hazard ratio (HR) and 95% confidence intervals (CI) comparing length of stay among individuals who were admitted to hospital with JN.1, EG.5.1 compared to XBBs.

Cox proportional hazards model with adjustment for week of test date, sex, age group, risk group status and vaccination status.

Figure 1: Adjusted OR and 95% CI comparing risk of ICU admissions for cases (a) and Adjusted HR and 95% CI comparing length of stay for cases (b) with JN.1, EG.5.1 compared to XBB/XBB1.5/XBB1.16.

To conclude, the results showed that JN.1 and EG.5.1 do not cause more severe disease as compared to the XBB variants.

Contributors

C.Q. and F.C.M.K. wrote the manuscript. J.L.B., N.A. and M.R. conceptualised the study. F.C.M.K. and J.S. curated the data. F.C.M.K. and C.Q. conducted the formal analysis. All co-authors reviewed the manuscript.

Data sharing statement

This work is carried out under Regulation 3 of The Health Service (Control of Patient Information) (Secretary of State for Health, 2002) using patient identification information without individual patient consent. Data cannot be made publicly available for ethical and legal reasons, i.e. public availability would compromise patient confidentiality as data tables list single counts of individuals rather than aggregated data.

Ethics committee approval

UKHSA has legal permission, provided by Regulation 3 of The Health Service (Control of Patient Information) Regulations 2002, to process patient confidential information for national surveillance of communicable diseases and as such, individual patient consent is not required to access records.

Declaration of interests

The Immunisation Department provides vaccine manufacturers (including Pfizer) with post-marketing surveillance reports about pneumococcal and meningococcal disease which the companies are required to submit to the UK Licensing authority in compliance with their Risk Management Strategy. A cost recovery charge is made for

these reports. M.K. received honoraria for speaking at conference on patient-reported outcome measures for people with HIV.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.lanepe.2024.100975>.

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