

NERVTAG

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Summary

1. The variant of concern (VOC) B.1.1.7 appears to have substantially increased transmissibility compared to other variants and has grown quickly to become the dominant variant in much of the UK.
2. Initial assessment by PHE of disease severity through a matched case-control study reported no significant difference in the risk of hospitalisation or death in people infected with confirmed B.1.1.7 infection versus infection with other variants. [1]
3. Several new analyses are however consistent in reporting increased disease severity in people infected with VOC B.1.1.7 compared to people infected with non-VOC virus variants.
4. There have been several independent analyses of SGTF and non-SGTF cases identified through Pillar 2 testing linked to the PHE COVID-19 deaths line list:
 - a. LSHTM: reported that the relative hazard of death within 28 days of test for VOC-infected individuals compared to non-VOC was 1.35 (95%CI 1.08-1.68).
 - b. Imperial College London: mean ratio of CFR for VOC-infected individuals compared to non-VOC was 1.36 (95%CI 1.18-1.56) by a case-control weighting method, 1.29 (95%CI 1.07-1.54) by a standardised CFR method.
 - c. University of Exeter: mortality hazard ratio for VOC-infected individuals compared to non-VOC was 1.91 (1.35 - 2.71).
 - d. These analyses were all adjusted in various ways for age, location, time and other variables.
5. An updated PHE matched cohort analysis has reported a death risk ratio for VOC-infected individuals compared to non-VOC of 1.65 (95%CI 1.21-2.25).
6. There are several limitations to these datasets including representativeness of death data (<10% of all deaths are included in some datasets), power, potential biases in case ascertainment and transmission setting.
7. **Based on these analyses, there is a realistic possibility that infection with VOC B.1.1.7 is associated with an increased risk of death compared to infection with non-VOC viruses.**
8. It should be noted that the absolute risk of death per infection remains low.
9. An analysis of CO-CIN data has not identified an increased risk of death in hospitalised VOC B.1.1.7 cases. However, increased severity may not necessarily be reflected by increased in-hospital death risk.

10. Since the time lag from infection to hospitalisation and death is relatively long, data will accrue in coming weeks, at which time the analyses will become more definitive.

Full text

11. Previously, preliminary results from a matched-cohort study conducted by PHE reported no statistically significant increased risk of hospitalisation or death in VOC-infected individuals compared to non-VOC [1].
12. On Friday 15th January NERVTAG was presented with two papers that reported an increased case fatality rate in subjects with s-gene target failure (SGTF, a proxy for variant B.1.1.7).
13. Both papers used the same core dataset of SGTF cases identified through Pillar 2 testing linked to the PHE COVID-19 deaths line list: a paper from LSHTM [2] and a paper from Imperial College London [3].
14. The LSHTM paper used a Cox proportional hazards model to estimate change in risk of death within 28 days of test for individuals infected with the VOC [2].
 - a. The study was based on 2,583 deaths among 1.2 million tested individuals. 384 deaths were among SGTF individuals.
 - b. Results were controlled for age, sex, index of multiple deprivation, and Upper Tier Local Authority (UTLA).
 - c. The relative hazard of death within 28 days of test was 1.35 (95%CI 1.08-1.68) for VOC-infected individuals, compared to non-VOC, with adjustment made for misclassification of SGTF.
 - d. Focusing only on individuals with SGTF after 1 November 2020 (no adjustment for SGTF misclassification), the relative hazard of death is 1.28 (95%CI 1.06-1.56).
 - e. Relative increases in CFR appeared to be consistent across age groups
 - f. Sensitivity analyses including further hospital pressure covariates (proportion of beds capable of mechanical ventilation occupied; proportion of beds capable of non-invasive ventilation occupied; number of staff absences per bed among medical staff; and number of staff absences per bed among nursing staff) did not substantially change the measure of effect.
15. The Imperial Paper reported the results of a non-parametric analysis of fatal outcomes associated with B1.1.7 [3].
 - a. Two methods were used to evaluate the differences in mortality between VOC and non-VOC cases: case-control-weighting, and standardised CFR. In each case, the ratio of s-gene positive to s-gene negative case fatality ratios (CFRs) is calculated.
 - b. The study considers data from all of England and includes specimen dates in the epidemiological week range 46-54 (54 being week 1 of 2021) inclusive. Estimates are adjusted for NHS STP area, epidemiological week, ethnicity

code, and age band.

- c. Across all specimens, the mean ratio of CFRs is 1.36 (95%CI 1.18-1.56) by the case-control weighting method, and 1.29 (95%CI 1.07-1.54) by the standardised CFR method. This estimate includes a correction for the probability over time that a specimen with SGTF is the VOC.
 - d. Relative increases in CFR appeared to be consistent across age groups.
 - e. Subsequent correction for possible differences in PCR cycle threshold values (ct) between VOC and non-VOC cases was included by restricting both groups only to those samples with ct <30. This adjustment made no meaningful difference.
16. A PHE retrospective matched cohort study was also reported [4]:
 - a. 23 November 2020 – 4 January 2021 study period (period when >90% of sequenced SGTF samples confirmed to be VOC202012/01). Matching based on 10-year age bands, sex, week of test and lower-tier local authority.
 - b. 92,207 SGTF cases and corresponding comparators were included in the matched cohort (n = 184,414), although routine hospitalisation data is subject to reporting delays and this should be considered preliminary.
 - c. The odds of SGTF cases being admitted was not significantly different to non-SGTF cases (OR = 1.07, 95% CI 0.86 – 1.33).
 - d. Initial analysis identified 152 deaths following a first positive SARS-CoV-2 test, n = 86 (0.09%) SGTF cases and n = 66 (0.07%) comparator cases. It was noted that 0.07% to 0.09% represents a 28% relative increase in the risk of death, which is compatible with the results from LSHTM and Imperial.
 - e. Initial analysis of 14,939 SGTF cases and 15,555 comparators who had at least 28 days between specimen date and the study period end date. There were 25 deaths (0.17%) in SGTF cases and 26 deaths (0.17%) in comparators (RR 1.00, 95% CI 0.58 – 1.73).
 - f. Updated linkage of deaths data to the same matched cohort on 19/01/2021 identified there were 65 deaths among non-SGTF cases (0.1%) and 104 deaths among SGTF cases (0.2%), within 28 days of specimen date. With this increased time for follow-up and ascertainment of deaths, the risk ratio increased to 1.65 (95%CI 1.21-2.25).
17. There are potential limitations in these datasets:
 - a. The dataset used in the LSHTM, Imperial, Exeter and PHE analyses is based on a limited subset of the total deaths. This includes approximately 8% of the total deaths occurring during the study period. Of all coronavirus deaths, approximately 26% occur in individuals who have had a Pillar 2 test, and only 30% of these have S-gene data. The results of all studies may therefore not be representative of the total population.
 - b. Restriction of analysis in the PHE matched cohort to people with a full 28 days follow up at the first analysis reduced statistical power and removed the

excess death signal. However, the LSHTM analysis show an increasing divergence in CFR between VOC and non-COV with time since diagnosis. A later update of the PHE analysis with additional follow-up time identified an increased risk ratio for 28-day case fatality.

- c. Some laboratories only report SGTF if the PCR cycle threshold (ct) value is <30, since target gene failure can occur with low viral loads. For the LSHTM paper, no such ct threshold was applied to non-SGTF positive samples.
 - i. A sensitivity analysis of the Imperial study produced a CFR ratio estimate where the cycle threshold was limited to <30 for both SGTF and non-SGTF samples. The estimate was 1.37 (95%CI 1.19-1.56) by the case-control weighting method, and 1.30 (95%CI 1.08-1.57) by the standardised CFR method. These results were similar to those obtained without this restriction.
 - d. The increased transmissibility of VOC B.1.1.7 compared to non-VOC variants might lead to differences in the context in which cases are occurring. For example, if institutional outbreaks are more likely with B1.1.7 compared to non-VOC, then an age matched analysis might be comparing frail elderly people in nursing home outbreaks of B.1.1.7 with healthier elderly people infected with the non-VOC virus in the community. However, both the Imperial and the LSHTM analyses showed increased CFRs across all age groups. This potential bias could therefore not explain the increased CFR in younger age groups.
 - e. If there is an increase in the severity of infection with VOC B1.1.7, we would also expect to see an increase in the risk of hospitalisation. Currently, we do not have evidence of an increased risk of hospitalisation in individuals with VOC B1.1.7 but data are limited due to lags in the availability of hospitalisation data.
18. A rapid analysis of CO-CIN data during the period in which VOC B1.1.7 emerged was reported [5]:
- a. Across the whole CO-CIN cohort, there is no observed increase in hospital case fatality in the period during which VOC emerged in England, after adjusting for period of admission, age, sex, deprivation, and ethnicity.
 - b. Compared to March 2020, hospital CFR continues to be lower and has been stable in September through December.
 - c. Data return from CO-CIN is currently reduced and unevenly distributed, which will impact on the representativeness of findings. Importantly there are a substantial number of outcomes missing from cases admitted in late December, when the impact of VOC emergence would start to be apparent in hospital data.
 - d. A sub-analysis included linked data from 21,882 cases (21,596 non-VOC and 286 VOC) from across the whole CO-CIN cohort. VOC in this sub-study was robustly determined by COG sequence lineage, rather than assumed by

SGTF. Outcome data was available for only 143 VOC cases. However; 32 VOC cases were identified at one trust with good data quality returns throughout the period of study.

- e. Restricting the analysis to a trust with high proportion of proven VOC which has maintained good quality data returns, and after adjusting for age and sex, found no statistically significant change in hospital CFR comparing proven VOC (n=32) with non-VOC (n=184) (OR 0.63, 95%CI 0.20 – 1.69).
 - f. An increase in case fatality rates would not necessarily manifest as an increase in case fatality rates amongst those hospitalised. Rather, it may increase the proportion of cases who are ill enough to meet the severity threshold for hospitalisation, but not affect the likelihood of death amongst those who are sick enough to be admitted.
19. A subsequent independent case control analysis of Pillar 2 data linked to the death line list by Exeter University, matched on age, specimen time, location, ethnicity, gender and index of multiple deprivation, reported a mortality hazard ratio for VOC-infected individuals compared to non-VOC was 1.91 (1.35 - 2.71).

Summary

- 20. There is evidence from analysis of Pillar 2 testing data linked to COVID-19 deaths that infection with VOC B.1.1.7 is associated with an increased case fatality rate compared to infection with non-VOC viruses. The relative increase in CFR appears to be apparent across age groups.
- 21. An initial retrospective matched cohort study from PHE (also based on linked testing and mortality data) found no evidence of a significant difference in risk of hospitalisation or death between individuals with VOC and individuals with non-VOC when analysis was restricted to those with completed 28 days follow up, but had insufficient statistical power to assess this accurately. A later update of the analysis with additional follow-up time, has now also identified an increased risk ratio for 28-day case fatality.
- 22. CO-CIN has not found evidence of an increase in hospital case fatality rate associated with VOC B.1.1.7, both across the whole cohort and in a single trust with a high rate of good quality data using sequence determined lineage. However, increased severity may not necessarily be reflected by increased in-hospital death risk.
- 23. There are limitations in all datasets that it may not be possible to resolve but as more data accrue the analyses will become more definitive.

Conclusion

- 24. **There is a realistic possibility that VOC B.1.1.7 is associated with an increased risk of death compared to non-VOC viruses.**

Recommendations

25. PHE to review if cases associated with care homes can be flagged in Pillar 2 data for an analysis adjusted for care home status.
26. ONS should assess if it is possible to link ONS survey participants to SUS data on hospitalisations and to deaths. This dataset would suffer from less ascertainment bias since participants are a random selection and ascertainment of cases is not dependent on symptoms or on seeking a test from the Test and Trace. This analysis will be limited in power, so analyses comparing ONS estimates of the proportion of the population infected over time, with the number of hospitalisations and deaths over time, stratified by age and region, could also provide insight as to whether case fatality rates have changed during the period of emergence of the virus.
27. Co-CIN to stratify analyses by region to assess whether in hospital mortality time trends differ in those regions affected by the VOC earliest.
28. ISARIC CCP-UK / CO-CIN to be re-prioritised as Tier 1 UPH study.

References

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3. Davies, N., Diaz-Ordaz, K., Keogh, R. 2021. Relative fatality hazard in Pillar 2 tested individuals with VOC. LSHTM – unpublished analysis.
4. PHE, 2021. Unpublished analysis.
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Annex.

Data table – preliminary results

Paper	Method	Sample	Outcome	Estimate of Effect	95%CI
Imperial	Non-parametric analysis: case-control weighting	All samples, corrected for probability that S-gene negative samples are the VOC	Ratio of S-negative to S-positive case fatality ratios	1.36	1.18-1.56
Imperial	Non-parametric analysis: standardised CFR	All samples, corrected for probability that S-gene negative samples are the VOC	Ratio of S-negative to S-positive case fatality ratios	1.29	1.07-1.54
LSHTM	Cox proportional hazards model	All samples, adjusted for misclassification of SGTF	Hazard ratio for death VOC-infected individuals to non-VOC infected individuals	1.35	1.08-1.68
LSHTM	Cox proportional hazards model	All samples, after 01.11.20 (not adjusted for misclassification of SGTF)	Hazard ratio death for VOC-infected individuals to non-VOC infected individuals	1.28	1.06-1.56
Exeter	Matched case control study	Samples since 01 October, various adjustments	Hazard ratio death for VOC-infected individuals to non-VOC infected individuals	1.91	1.35-2.71
CO-CIN	Multinomial model	CO-CIN data from a single trust	Odds ratio of death in hospitalised VOC-infected individuals to non-VOC infected individuals	0.63	0.20-1.69
PHE	Retrospective matched cohort study (initial analysis)	Cases and comparators <u>with at least 28 days</u> between specimen date and study end date	Odds ratio of hospital admission in SGTF cases vs non-SGTF cases	1.07	0.86-1.33
PHE	Retrospective matched cohort study (initial analysis)	Whole cohort	Relative risk of death in SGTF cases vs non-SGTF cases within 28 days of a +ve result	1.3	0.95-1.79
PHE	Retrospective matched cohort study (initial analysis)	Cases and comparators <u>with at least 28 days</u> between specimen date and study end date	Relative risk of death in SGTF cases vs non-SGTF cases within 28 days of a +ve result	1.00	0.58-1.73
PHE	Retrospective matched cohort study (updated analysis 19/01)	Whole cohort	Relative risk of death in SGTF cases vs non-SGTF cases within 28 days of a +ve result	1.65	1.21-2.25

