Summary

1. On Thursday, 21st January, NERVTAG presented evidence to SAGE of increased disease severity in people infected with variant of concern (VOC) B.1.1.7 compared to people infected with non-VOC virus variants. In that report it was stated that '*data will accrue in coming weeks, at which time the analyses will become more definitive*'.

2. Here we report updated and additional analyses, which together strengthen the earlier finding of increased disease severity in people infected with VOC B.1.1.7 compared to other virus variants.

3. Independent analyses of the risk of hospitalisation and death for S-gene target failure (SGTF; a proxy for VOC B.1.1.7 in the UK) cases and non-SGTF (non-VOC) cases are (also see data table in annex):

    a. LSHTM: reported that the relative hazard of death within 28 days of test for VOC-infected individuals compared to non-VOC was 1.58 (95%CI 1.40–1.79), or 1.71 (95% CI 1.48- 1.97) if adjustment is made for misclassification of SGTF and missingness of data.

    b. Imperial College London: mean ratio of case fatality ratio (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: an updated analysis estimated the mortality hazard ratio for VOC-infected individuals compared to non-VOC was 1.7 (95% CI 1.3 – 2.2) in a matched cohort study.

    d. Public Health England: an updated 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).

    e. Public Health Scotland: the REACT-SCOT study found that the hazard ratio was 1.08 (95% CI 0.78-1.49) for death and 1.40 (95% CI 1.28-1.53) for death or hospital admission in SGTF compared to non-SGTF cases.

    f. Public Health Scotland: the EAVE-II study found the risk of being admitted to hospital is higher for cases with SGTF than for those who are S Gene positive - risk Ratio 1.63 (95% CI 1.48, 1.80). The relative risk of death within 28 days of a positive test was 1.37 (95% CI 1.02, 1.84) for SGTF compared to S Gene positive.

    g. The Hospital Onset Covid Infection (HOCI) study: found the overall HR for in-hospital mortality of B.1.1.7 was 1.09 (95% CI 0.86-1.36, P=0.48). Increased mortality was only observed with the VOC in women over 65 years. The overall HR for ITU admission for B.1.1.7 was 1.15 (95% CI 0.86-1.53, P=0.35).

    h. ICNARC and QRESEARCH: found a higher risk of ICU admission for VOC-patients (HR: 1.44; 95% CI: 1.25, 1.67) compared to non-VOC patients and

no significant difference in the hazard of ICU mortality between the two groups (HR: 0.94; 95% CI: 0.82, 1.09).

    i.   ONS analysis: found that whilst the hazard ratio suggests that the B.1.1.7 variant is associated with higher risk of all-cause mortality, the number of deaths are too low for reliable inference.

    j.   CO-CIN (hospitalised patients only): found no statistically significant change in in-hospital CFR comparing proven B.1.1.7 (n=32) with non-VOC (n=184) (OR 0.63, 95%CI 0.20 – 1.69).

    k.   CO-CIN (hospitalised patients only): a repeat analysis with an updated dataset did not provide evidence to suggest that the variant of concern is linked to a higher risk of in-hospital case fatality (OR 0.67, 95%CI 0.32, 1.40).

    l.   LSHTM: a population-level analysis at the level of upper-tier local authorities resulted in estimates of a 1.4 (1.3-1.5) times higher number of hospitalisations per case and 1.4 (1.2-1.5) times higher number of fatalities per hospitalisation associated with VOC.

4. There are inevitable limitations to these datasets, including representativeness, power, potential biases in case ascertainment, unmeasured confounders, and secular trends.

5. Whilst studies limited to in-patients did not identify evidence of increased disease severity, this is not incompatible with an overall increase in disease severity.

6. Whilst earlier analyses using linked community testing and mortality data showed comparable increases in case fatality ratios, these were all based on the same datasets, and therefore subject to similar biases reducing the level of certainty in the findings. More recent analyses have added a wider range of data sets and been able to control for additional confounders, increasing confidence in the association of the VOC with increased disease severity.

7. **Based on these analyses, it is likely that infection with VOC B.1.1.7 is associated with an increased risk of hospitalisation and death compared to infection with non-VOC viruses**.

8. It should be noted that the absolute risk of death per infection remains low.

Full text

9. 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]

10. 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 of concern B.1.1.7).

11. 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]

12. Since then, drawing on analyses of multiple datasets, further evidence of an increase in disease severity in people infected with VOC B.1.1.7 has emerged. A summary of their findings is presented below.

13. 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 3,382 deaths among 1 million tested individuals. 1,722 deaths were among SGTF individuals.

    b. Results were controlled for age, sex, index of multiple deprivation, ethnicity, residence type (care home versus residential versus other), specimen date, and Lower Tier Local Authority (LTLA).

    c. The relative hazard of death within 28 days of test was 1.71 (95% CI 1.48-1.97) for VOC-infected individuals, compared to non-VOC, with adjustment made for misclassification of SGTF and missingness of data.

    d. Focusing only on individuals with SGTF after 1 November 2020 (no adjustment for SGTF misclassification or missingness), the relative hazard of death is 1.58 (95%CI 1.40–1.79).

    e. Relative increases in CFR appeared to be consistent across age groups, when comparison was done for the age groups 1-54, 55-69, 70-84, 85+ (due to the limited number of deaths below the age of 55), however absolute risk of CFR is not increased substantially below the age of 55.

    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.

    g. There is a statistically significant interaction of SGTF with residence type suggesting a potential interaction with frailty: the hazard ratio for care home residents was 2.43 (1.72–3.35), compared to the hazard ratio for the general population of 1.53 (1.35–1.74).

14. 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 when comparison was done for the age groups 1-54, 55-69, 70-84, 85+ (due to the limited number of deaths below the age of 55), however absolute risk of CFR is not increased substantially below the age of 55.

    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.

15. 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).

16. A subsequent independent case control analysis of Pillar 2 data linked to the death line list by University of Exeter, reported a mortality hazard ratio for VOC-infected individuals compared to non-VOC was 1.7 (95% CI 1.3 – 2.2) in a sample size of 54,773 pairs, (n=109,546).

a. Study period: 1st October 2020 to 29th Jan 2021. Paired S-gene positive "controls" to S-gene negative "cases" by matching on gender, ethnicity, index of multiple deprivation, location (as lower tier local authority region), age (within a tolerance of ±5 years), and date of positive specimen (within a tolerance of ±1 day).

b. Because the data is from Pillar 2, cases were in general younger than typical COVID-19 cohorts (mean age 46.3) and under-represent elderly (only 0.5% of the cohort were >80 years old). The South West, East of England and to a lesser extent the South East are under-represented as the lighthouse labs in those areas do not always report S-gene status.

c. There were 272 deaths following a first positive SARS-CoV-2 test, 101 occurring in S-gene positive controls and 171 occurring in S-gene negative cases. A Cox proportional hazards model was used to account for censoring, although this is also controlled for by the close match on specimen date

17. Public Health Scotland presented two studies:

    a. A case control study (REACT-SCOT) used a Cox Regression model to estimate hazard of death and hospital admission in SGTF compared to non-SGTF cases. [5]

        i. All Pillar 2 (Lighthouse lab) test-positive cases up to 6 Jan with SGTF status scored were linked to deaths and hospital admissions up to 22 Jan 21.

        ii. Hazard ratios were estimated by Cox regression stratifying by calendar time and adjusting for age, sex, recent hospital exposure and mean Ct of the ORF and N gene.

        iii. The hazard ratio was 1.08 (95% CI 0.78-1.49) for death (292 events, 74 in SGTF cases) and 1.40 (95% CI 1.28-1.53) for death or hospital admission (3765 events, 1220 in SGTF cases).

    b. A cohort study (EAVE-II), which included all of the Scottish population – data linkage of primary care, secondary care, laboratory and death data. [6]

        i. A cox survival model was used to estimate the risk of hospitalisation following a positive test result for SGTF v SG positive. This model was fitted to all the data using all follow up available. The model included p spline terms for age and calendar time as well as demographic and risk group data.

        ii. The risk of being admitted to hospital is higher for cases with S Gene deletion than for those who are S Gene positive. Risk Ratio 1.63 (95% CI 1.48, 1.80).

        iii. The relative risk of death within 28 days of a positive test was 1.37 (95% CI 1.02, 1.84) for S Gene deletion compared to S Gene positive.

18. The COG-UK Hospital Onset COVID-19 Infection (HOCI) study reported on mortality and intensive therapy unit (ITU) admissions according to presence of the VOC on viral sequencing. [7]

   a. Study sites are sequencing all positive SARS-CoV-2 samples from hospitalised patients and healthcare workers. Data were collected from nine participating hospitals on mortality and ITU admissions for 2386 inpatients with sample date between 16th November 2020 and 10th January 2021.

   b. VOC 202012/01 was identified in 1090 (45.5%) of the samples. Mixed effects Cox models were used to estimate the overall association between the VOC and each outcome, with adjustment for sex and age and exploratory analysis of interactions with these variables.

   c. 533 (22.3%) patients died during the study period. The overall HR for mortality of the VOC was 1.09 (95% CI 0.86-1.36, P=0.48). Evaluation of an interaction between VOC status and sex found an association of the VOC with mortality in females (HR 1.41, 95% CI 1.04-1.90) but not in males (0.89, 95% CI 0.67-1.17), with a further interaction with age suggesting that increased mortality was only observed with the VOC in women over 65 years.

   d. 320 (13.4%) patients were admitted to ITU. The overall HR for ITU admission for the VOC was 1.15 (95% CI 0.86-1.53, P=0.35). On evaluation of an interaction between VOC status and sex, the HR for ITU admission for the VOC in males was 0.85 (95% CI 0.61-1.18) and that for females was 1.94 (1.25-2.99). There was no evidence of an interaction between VOC and age.

19. ICNARC and QRESEARCH reported two studies which used flexible parametric survival models to estimate the relative risk of ICU admission and ICU mortality for VOC compared to non-VOC patients. [8]

   a. Both studies were restricted to Pillar 2 patients tested between the 1st of November and 27th of January 2021.

   b. Both studies used flexible parametric survival models (Royston-Parmar model) adjusted for patient demographics (age, sex, deprivation index, geographical region) and medical characteristics. An indicator of the week in which the positive test was taken (ICU admission analysis) and the week when the patient was admitted to ICU (ICU mortality analysis) was included in the models, to account for time dependent biases.

   c. The hazard of ICU admission was estimated using used the QResearch dataset linked with pillar 2 testing data from PHE and the ICNARC Case Mix Programme (CMP) dataset. Only patients with at least 12 days of follow up from the date of the positive test were included. The data contained 331,321 patients, of which 99,444 (30.0%) had the VOC. There were 1,171 patients admitted to ICU, of which 428 (36.5%) had the VOC.

   d. The hazard of ICU mortality was estimated using the ICNARC CMP dataset linked with testing data from PHE. There were 6,038 patients admitted to ICU with a positive test in the study period, of which 2088 had the VOC. The

analysis was restricted to patients who had a minimum of 28 days follow-up after ITU admission, as the proportion who had not completed their ICU care was larger in the VOC group (42%) than in the non-VOC group (27%).

   e. There was a higher risk of ICU admission for VOC-patients (HR: 1.44; 95% CI: 1.25, 1.67) compared to non-VOC patients and a non significant difference in the hazard of ICU mortality between the two groups (HR: 0.94; 95% CI: 0.82, 1.09).

20. An analysis from the ONS Coronavirus Infection Survey. CIS respondents who first tested positive on or after 15th November 2020 (N=8,811) were linked to the mortality registration data for deaths occurring up to 17th January 2021.

   a. Out of 4217 positive cases compatible with the new UK variant, 11 deaths were identified. 7 deaths were observed among the 2745 positive cases that were not were compatible with the new UK variant, and 1 among the 1840 cases with unknown variant.

   b. Hazard ratios for death were estimated using a Cox proportional hazard regression model, adjusted for age and gender.

   c. Whilst the hazard ratio suggests that the new UK variant is associated with higher risk of all-cause mortality, the number of deaths are too low for reliable inference.

   d. This analysis will be repeated weekly, as more recent deaths are made available, and the linkage between CIS and PDS (used to retrieve NHS numbers) is improved.

21. A rapid analysis of CO-CIN data during the period in which VOC B1.1.7 emerged was reported: [9]

   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.

g. An updated analysis of CO-CIN data (study period 1st October 2020 to 12th January 2021) did not provide evidence to suggest that the variant of concern is linked to a higher risk of in-hospital case fatality. [10]

   i. A mixed-effects multivariable logistic regression model including 202 VOC cases from 91 hospitals (of which 108 had a 28-day mortality outcome ascertained), with 1:1 matching by age, sex, and admission date to non-VOC cases, did not provide evidence of a difference in the 28-day fatality rate in patients admitted to hospital (OR 0.67, 95%CI 0.32-1.40).

   ii. A Cox proportional hazards survival regression model where VOC cases were matched to non-VOC cases (1:3, n=103 matchable VOC cases) also did not provide evidence of a difference in the 28-day fatality rate in patients admitted to hospital (HR 0.81, 95%CI 0.50-1.32).

   iii. This analysis is limited by small numbers and the instability of a dynamic dataset.

22. LSHTM undertook a population-level (ecological) analysis of the relationship between cases (Pillar 1 and Pillar 2), hospitalisations, and deaths as a function of local prevalence of SGTF. [11]

   a. This analysis suggests that VOC has increased the number of hospitalisations per case, and deaths per hospitalisation, which, in turn, is compatible with an increase in the case-hospitalisation rate and the hospitalisation-fatality rate.

   b. Allowing baseline ratios to vary at the level of upper-tier local authorities resulted in estimates of a 1.4 (1.3-1.5) times higher number of hospitalisations per case and 1.4 (1.2-1.5) times higher number of fatalities per hospitalisation associated with VOC.

   c. These estimates need to be interpreted with caution as they are likely to be confounded by other factors that varied over time and that could have affected changes in the rate of hospitalisations or deaths.

23. Limitations:

   a. The majority of these analyses are limited to community testing data, except the HOCI and LSHTM ecological studies.

b. Less than 10% of all deaths are included in some datasets and the number of deaths are too low for reliable inference.

c. There are several confounding factors which may not be adequately adjusted, for example, in these datasets nursing home status may be poorly identified, there may be confounding by setting of infection acquisition, confounded by comorbidities or goals of care (e.g. no transfer to acute care hospitals/advanced measures.)

d. While these analyses are adjusted for age, sex, deprivation, LTLA etc., given increased transmission potential of VOC, this may not be sufficient adjustment if not a) stratified by LTCF and b) adjusted for comorbidities and c) secular trends.

Conclusion

24. There is evidence from analysis of multiple different datasets that infection with VOC B1.1.7 is associated with an increased risk of hospitalisation and death compared to infection with non-VOC viruses.

25. There are potential limitations in all datasets used but together these analyses indicate that it is likely that VOC B.1.1.7 is associated with an increased risk of hospitalisation and death compared to infection with non-VOC viruses.

Recommendations

26. ONS are assessing hospitalisation and deaths linked to ONS survey participants. This dataset will suffer from less ascertainment bias than other datasets since participants are a random selection and ascertainment of cases is not dependent on symptoms of on seeking a test from the Test and Trace. However, it may have limited power.

27. While the majority of analyses tried to control for confounding by nursing home, poor recording of LTCF residents in hospital data will not allow this to be adequately addressed, therefore residual confounding through unidentified nursing home residence could occur. Detailed documentation of nursing home cases and deaths is needed. Further analysis could be done through specific stratified analyses of pillar 2 among only the care-home residents and adjust for comorbidities.

28. Increased transmission per contact by setting could shift from a null effect to signal (increased CFR with a variant that leads to more transmission) if confounded by comorbidities in the network/cluster/setting. This could be ameliorated by controlling for comorbidities but this will likely require linkage with Co-Cin (which is diminished in coverage now) or primary care analysis.

References

[1] Public Health England, "Investigation of novel SARS-CoV-2 Variant of Concern 202012/01: Technical briefing 2," 2020.

[2] N. Davies, K. Diaz-Ordaz and R. Keogh, "Relative fatality hazard in Pillar 2 testing individuals with VOC," *LSHTM - Unpublished Analysis,* 2021.

[3] N. Ferguson, "Non-parametric analysis of fatal outcomes associated with B1.1.7," *Imperial College London, Unpublished Analysis,* 2021.

[4] Public Health England, *Unpublished analysis,* 2021.

[5] P. M. McKeigue, D. McAllister, J. Bishop, S. Hutchinson, N. Lone, J. McMenamin, D. Goldberg, C. Robertson and H. M. Colhoun, "Relation of SARS-CoV-2 variant 2020-12/01 to transmission-related factors and to severity of COVID-19 in Scotland: REACT-SCOT case-only linkage study [preliminary results]," *Unpublished analysis - Preliminary results,* 2021.

[6] C. Roberston, A. Sheikh, J. McMenamin and EAVE II Study Group, "Clinical Characteristics of S Gene Dropout Cases," *Unpublished analysis,* 2021.

[7] COG-UK Hospital Onset Covid-19 Infection (HOCI) Study, *Unpublished analysis,* 2021.

[8] ICNARC and QRESEARCH Group, *Unpublished analysis,* 2021.

[9] A. Docherty, E. Harrison and C. Semple, "Hospital case fatality and emergence of variant of concern B117, rapid report to NERVTAG and SAGE," *Unpublished analysis,* 2021.

[10] C. Cheyne, G. Burnside, D. Hughes, L. Turtle, M. Garcia-Finana and C. Semple, "Analysis on recent hospital case fatality and variant of concern VOC2020-01 using CO-CIN data (10th February 2021)," *Unpublished analysis,* 2021.

[11] S. Abbott, S. Funk and CMMID Covid-19 Working Group, "Population-level association between S-gene target failure and the relationship between cases, hospitalisations, and deaths of Covid-19," *Pre-print, available online,* 2021.

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 and missingness of data	Hazard ratio for **death** for VOC-infected individuals to non-VOC infected individuals	1.71	1.48-1.97
LSHTM	Cox proportional hazards model	All samples, after 01.11.20 (not adjusted for misclassification of SGTF and missingness of data)	Hazard ratio **death** for VOC-infected individuals to non-VOC infected individuals	1.58	1.40-1.79
Exeter	Matched case control study	Samples since 01 October, various adjustments	Hazard ratio **death** for VOC-infected individuals to non-VOC infected individuals	1.7	1.3-2.2
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
CO-CIN	Mixed-effects multivariable logistic regression model (updated analysis 10/02)	CO-CIN data from 91 hospitals in England	Odds ratio of **death** for VOC compared to non-VOC <u>in hospitalised patients</u>.	0.67	0.32-1.40
CO-CIN	Cox proportional hazards survival regression model (updated analysis 10/02)	CO-CIN data from 91 hospitals in England	Hazard ratio of **death** for VOC compared to non-VOC <u>in hospitalised patients.</u>	0.81	0.50-1.32

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
PHS	Case-only cohort (cases up to 6/01, follow-up to 22/01)	Whole cohort, survival format allows for censoring	Rate ratio for **death** in SGTF cases vs non-SGTF cases up to 28 days of a +ve result	1.08	0.78-1.49
PHS	Case-only cohort (cases up to 6/01, follow-up to 22/01)	Whole cohort, survival format allows for censoring	Rate ratio for **hospitalisation or death** in SGTF cases vs non-SGTF cases up to 28 days of a +ve result	1.40	1.28-1.53
PHS	Cohort study – Cox survival model	Whole cohort	Risk ratio of **hospitalisation** following a positive test result for SGTF vs SG positive	1.63	1.48, 1.80
PHS	Cohort study – Cox survival model	Whole cohort	Risk ratio of **death** within 28 days of a positive test following a positive test result for SGTF vs SG positive	1.37	1.02, 1.84
HOCI	Mixed effects Cox model	Inpatient cohort from 9 sites	Hazard ratio for **death** in VOC vs non-VOC	1.09	0.86-1.36
HOCI	Mixed effects Cox model	Inpatient cohort from 9 sites	Hazard ratio **for ITU admission** in VOC vs non-VOC	1.15	0.86-1.53
ICNARC/ QRESEARCH	Flexible parametric survival model (Royston-Parmar)	Patients with at least 12 days follow up from the date of positive test	Hazard ratio of **ICU admission** for VOC-infected individuals compared non-VOC infected individuals	1.44	1.25-1.67
ICNARC	Flexible parametric	Patients with a minimum of 28	Hazard ratio of **ICU mortality** for VOC-	0.94	0.82-1.09

	survival model (Royston-Parmar)	days follow up after ICU admission	infected individuals compared non-VOC infected individuals		
LSHTM	Population-level analysis	Upper-tier Local Authority level	Multiplicative increase in **hospitalisations per case** associated with VOC	1.4	1.3-1.5
LSHTM	Population-level analysis	Upper-tier Local Authority level	Multiplicative increase in **fatalities per hospitalisation** associated with VOC	1.4	1.2-1.5