Public Health and Health Systems Impacts of SARS-CoV-2 Variants of Concern

Rapid Scoping Review

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Third-Party Materials

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Definitions & Abbreviations

ABM: Agent-based Model
Alpha: variant of concern originating in the United Kingdom, also known as B.1.1.7, VUI 202012/01 and VOC 202012/01
aIRR: adjusted incidence rate ratios
Beta: variant of concern originating in South Africa, also known as B.1.351 and 20H/501Y.V2
BMI: body mass index
CanCOGen: Canadian COVID Genomics Network
CENTRAL: Central Register of Controlled Trials
CFR: Case Fatality Rates
CI: confidence interval
CIDRAP: Center for Infectious Disease Research and Policy
Ct: cycle threshold, provides a relative measure of viral quantity
COG-UK: COVID-19 Genomics UK
CDSR: Cochrane Database of Systematic Reviews
Delta: variant of concern originating in India, also known as B.1.617.2
dQALY: discounted quality-adjusted life years
E484K: escape mutation in the SARS-CoV-2 virus, present in Alpha
ECDC: European Centres for Disease Control
FDA: Food and Drug Administration
Gamma: variant of concern originating in Brazil, also known as P.1 and B.1.28.1
HCW: healthcare workers
HR: Hazard Ratio
HVAC: heating, ventilation, and air conditioning
ICU: Intensive Care Unit
IQR: interquartile range
IR: incidence rate
LOS: length of stay
mRNA: messenger ribonucleic acid
NGS: next generation sequencing
NOS: Newcastle-Ottawa scale
NPI: Non-Pharmaceutical Interventions
NRW: North-Rhine Westphalia
OR: odds ratio
PCR: polymerase chain reaction, method for DNA replication and genome sequencing
PHU: Public Health Unit
PPE: personal protective equipment
PR: prevalence ratio
R: reproduction
R_0: basic reproduction number, expected number of cases generated by one case in a population when everyone is susceptible to infection
R_t: effective reproduction number
RR: risk ratio

RT-LAMP: reverse transcription loop-mediated and transcription-mediated amplification isothermal amplification
RTD: Rapid Antigen Test
SA: South Africa
SAPSII: severity score at admission
SEIR: model including ‘susceptible, exposed, infectious and recovered’ compartments
SIDARTHE: mathematical model which considers ‘susceptible, infection, diagnosed, ailing, recognized, threatened, healed and extinct’ stages of infection
SIRD: model including ‘susceptible, infectious, recovered and deceased’ compartments
SGTF: spike OR S gene target failure, correlates with the increase of confirmed, sequenced variants
SGTL: spike gene late detection
SD: standard deviation
UK: United Kingdom
US: United States
VE: vaccine efficiency
VOC: variant of concern
WHO: World Health Organization
WGS: whole genome sequencing

Abstract

Background: As of May 31st 2021, four SARS-CoV-2 variants of concern (VOC: Alpha, Beta, Gamma and Delta) have been detected in over 132 countries. Increased transmissibility of VOC has implications for public health measures and health system arrangements. This rapid, scoping review aims to provide a synthesis of current evidence related to public health measures and health system arrangements associated with VOC.

Methods: Rapid scoping review. Seven databases were searched up to May 11th, 2021, for terms related to VOC, transmission, public health, and health systems. A jurisdictional scan was conducted up to May 31st, 2021, and is reported in a separate document. Title, abstracts, and full texts were screened independently by two reviewers. Data were double extracted using a standardized form. Studies were included if they reported on at least one of the VOC and public health or health system outcomes.

Results: Of the 2,518 articles screened, 60 studies were included which used a wide range of designs and methods. Most of the studies reported on Alpha, and 38 studies provided data in relation to public health measures. Public health measures, including lockdowns, physical distancing, testing, and contact tracing, were identified as critical adjuncts to a comprehensive, rapid vaccination campaigns. However, reliable measures to track adherence to strategies were not available. For health system arrangements, 25 studies were identified, all except one reported on capacity planning. Most studies found an increase in hospitalization due to Alpha but mixed findings were found on ICU admission. The majority of studies reporting mortality data found an increased risk of death due to VOC. One study reported on the effectiveness of personal protective equipment in reducing VOC transmission in the hospital. No studies reported on screening staff and visitors, adjusting service provisions, or adjusting patient accommodations and shared spaces, which is a significant gap in the literature.

Conclusion: While the findings should be interpreted with caution as most of the sources identified were preprints, findings suggest a combination of non-pharmaceutical interventions (e.g., masking, physical distancing, lockdowns, testing) should be employed alongside a vaccine strategy to improve population and health system outcomes. Findings are mixed on the impact of VOC on health system arrangements, but evidence is trending towards an increased risk of severe outcomes including hospitalization and death in VOC cases compared to wild type SARS CoV2 cases.

Introduction

The SARS-CoV-2 virus, responsible for COVID-19, was declared a global pandemic by the World Health Organization (WHO) in Mar 2020.[1] By May 24th, 2021, over 166 million cases of COVID-19 had been reported worldwide and 3.5 million people have died as a result of COVID-19 since the start of the pandemic.[2] Increased numbers of COVID-19 cases are causing significant concerns around identifying and enforcing public health measures to control the spread of the virus and ensuring health systems can manage current and new hospital admissions.

As of May 31st, 2021, four variants of the original SARS-CoV-2 lineage have been declared variants of concern (VOC) by the WHO, with other variants under ongoing assessment.[3] VOC are defined by their increased potential for transmission, presence of genomic mutations, and rapid spread across countries or regions leading to possible decreased effectiveness of public health measures.[4] In Dec 2020, the Alpha VOC (B.1.1.7, 201/501.1.V1 or 2020/12/01) was first identified in the United Kingdom (UK)[5] and as of May 9th, 2021, 132 countries had reported cases of the Alpha variant.[2] A second VOC was identified in South Africa (SA), known as Beta (B.1.351 or 20H/501Y.V2) and has since been identified in 82 countries,[2] while the Gamma VOC (P.1 or B.1.28.1) which originated in Brazil, has been identified in 52 countries.[2] Most recently, Delta (previously known as B.1.617.2) has been promoted from a variant of interest to VOC, and has been identified in 44 countries.[2] While evidence is continuing to emerge on the impact of the circulating VOC on population health and health systems arrangements, early data suggests there is an increased risk of transmission associated with all four VOC.[2,6–8] Specifically, Alpha is estimated to be between 43-90% more transmissible than non-VOC,[2,6,7] while Beta is between 1.5[9,10] and 2.5[6] times more transmissible than non-VOC. There is limited evidence on the transmissibility of Gamma and Delta, but early trends suggest it also has transmission advantage over non-VOC.[2,6,8] Clearly, these circulating VOC present a risk to public health and safety.

The increased transmissibility of VOC has led to increases in surges in COVID-19 incidence and consequently, hospitalizations and mortality.[7] The first wave of the pandemic demonstrated the potential for even well-equipped health systems to experience overwhelmed intensive care units (ICUs) and system disruption with wide ranging health consequences.[11] As of May 31st, 2021, cases of COVID-19 are decreasing in Canada as the third wave winds down, yet hospitals and ICUs in some regions continue to experience heavy burden and capacity surge impacting the provision of critical care.[12,13] However, due to the emergent nature of SARS-CoV-2 and the VOC, health systems and public health administrators have been challenged to make pragmatic decisions in the absence of evidence. This leaves many public health officials and healthcare administrators with uncertainty about the priority actions to minimize increased risk of spread of VOC and particularly whether there needs to be any existing modification to public health recommendations.[14] There is also increasing pressure on the health system,[15] despite a lack of evidence to inform measures needed to minimize the burden on the healthcare system related to VOC. Therefore, this rapid scoping review aims to provide a synthesis of current evidence related to VOC in the context of public health and health system impacts. This review is a follow-up to the rapid scoping review on transmission conducted by this team[8] and updates a previous version of this review.[16]

Objective

To identify, appraise and summarize evidence related to the following questions about public health and health system impacts of WHO defined SARS-CoV-2 VOC as known in May 2021 (Alpha, Beta, Gamma, and Delta):

1. What is known about the implications of the WHO defined VOC for public-health measures on:

a) Modifying approach to vaccination (e.g., using vaccines that offer greater protection against variants, using different vaccines for first and second doses and/or re-vaccinating those initially vaccinated with vaccines with limited efficacy for new strains)
b) Modifying infection-prevention (i.e., public-health) measures in the community (e.g., changing duration of hand washing; changing mask type and characteristics, double masking, or other changes to masking; and changes to physical and temporal distancing)
c) Modifying infection-control procedures, such as:
   - Changing duration for quarantining of exposed or potentially exposed individuals
   - Changing duration for isolating suspected or confirmed cases (e.g., for exposed health workers)
   - Changing testing strategy, including approach to testing, frequency of testing, and turn-around time for test results
   - Changing approach to contact tracing
   - Changing approach to outbreak management

2. What is known about the implications of the WHO defined VOC for health system arrangement (particularly for hospitals) on:
   a) Adjusting capacity planning to accommodate changes in the risk of re-infection and the risk of severe disease (e.g., hospitalization, admission to ICU, and death)
   b) Adjusting personal protective equipment (PPE) procedures for health workers
   c) Adjusting restrictions and screening of staff and visitors (e.g., visitor policy changes, approach to and frequency of screening)
   d) Adjusting service provision (e.g., cohorting patients in hospitals based on the VOC they have)
   e) Adjusting patient accommodations, shared spaces, and common spaces (e.g., improvement to HVAC (heating, ventilation, and air conditioning) systems)

Design

Rapid scoping review, following standardized rapid and scoping review guidelines.[17–19] This is an update of a review published on May 3rd, 2021.[16] The most up-to-date version will be listed on the COVID-END website.

Methods

A broad, comprehensive search was designed by an information specialist to retrieve all literature related to VOC. The electronic database search was executed on May 11th, 2021 in MEDLINE (Ovid MEDLINE All), Embase (Elsevier Embase.com), the Cochrane Database of Systematic Reviews (CDSR) and Central Register of Controlled Trials (CENTRAL) (Cochrane Library, Wiley), Epistemonikos' L·OVE on COVID-19, and medRxiv and bioRxiv concurrently. Only English-language searches were conducted, but non-English results were considered for inclusion. Full search details are available in Appendix 1.

The grey literature search was not updated for this review, as a more comprehensive jurisdictional scan of Canadian provincial and territorial COVID-19 guidance is reported in a companion document, *Provincial COVID-19 guidance in Canada: a jurisdictional scan and cross-country comparison, May 19-28, 2021*.[20]

Evidence specific to public health and health system arrangement impacts were identified and tagged during the screening process related to any of the above questions. Studies that reported on immune escape (vaccine/prior infection protection), non-VOC impacts, novel testing methods, transmission, case studies without public health or health system impacts, or animal studies were excluded. Reviews, overviews, and news articles that presented no original data were excluded but checked for references to primary studies. If published versions of previously included preprints were identified, they were retained as the primary record.

Title/abstract and full-text screening was completed by two reviewers in Covidence. The data extraction form was designed in consultation with knowledge user partners; data were extracted by two reviewers and verified by a third. The final report was reviewed by health system and infectious disease experts engaged on our team.

Quality appraisal was conducted using the Newcastle-Ottawa scale (NOS).[21] Case-control or cohort design studies were assessed using the NOS while cross-sectional studies were assessed using the adapted NOS.[22] Two team members independently conducted quality appraisal for all eligible studies. Reviewers met to discuss scores and a third, independent team member was consulted to assist with resolving conflicts. Modeling studies and lab-based studies were not appraised.

Cohort studies were awarded a maximum of nine stars and cross-sectional studies awarded a maximum of 10 stars, based on three scoring categories: selection, comparability, and outcome. Two stars were subtracted from pre-print studies as an added layer of quality assessment due to the emerging nature of studies on this topic. Final scores for observational studies were presented as a percentage, based on an average between the two appraiser scores. An overall quality rating of low, medium, or high was reported for each observational study, which correlated with a score of <50%, 50-80% or >80% respectively.

Results

The search retrieved 3,323 electronic database records. After removal of 805 duplicates, 2,518 studies were screened, of which 60 studies were included (see Appendix 2 for PRISMA Flow Diagram). Of those 60 studies, 27 new studies were included in this update and 5 preprints from the first version (May 3rd) were since published. In total, 42 (19 new) were preprints and 18 (8 new) were published in peer-reviewed journals (see Appendix 3 – Tables 1 and 2 for a summary of included studies). Eight sources reported solely on Gamma, one source reported on Beta, 39 sources reported on Alpha, four reported on Alpha, Beta, and Gamma, seven on Alpha and Beta, and one reported on a non-specific VOC (Figure 1). No studies reported on Delta. There was wide variation in countries, with the majority of studies conducted in the UK (n=19), followed by the United States (US) (n=9), France (n=4), Brazil (n=8), Germany (n=4), Israel (n=2), Italy (n=2), Netherlands (n=2) and one each from Canada, Denmark, Japan, Lebanon, Portugal, Switzerland, and South Africa. Three studies reported on multiple countries (Figure 2).

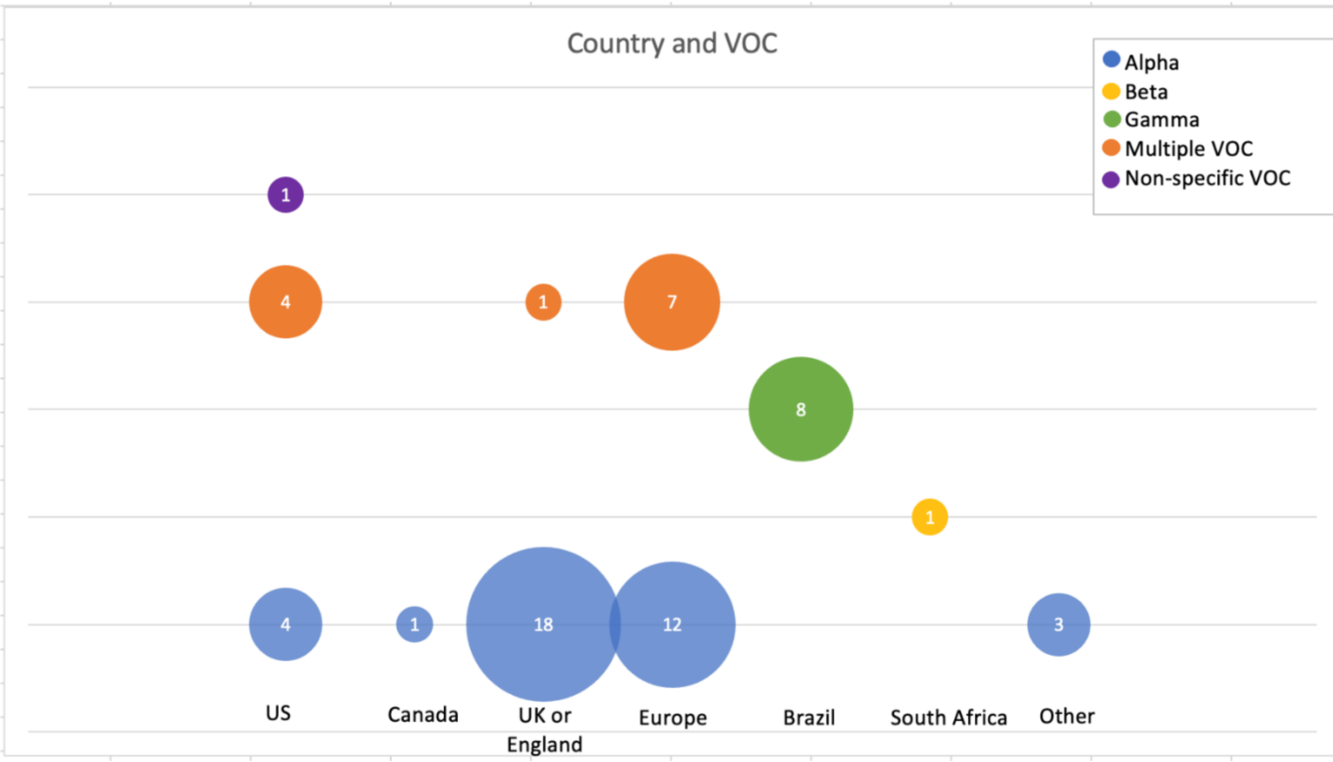

Figure 1. Overview of studies by country or region of data collection and reported VOC up until May 11, 2021

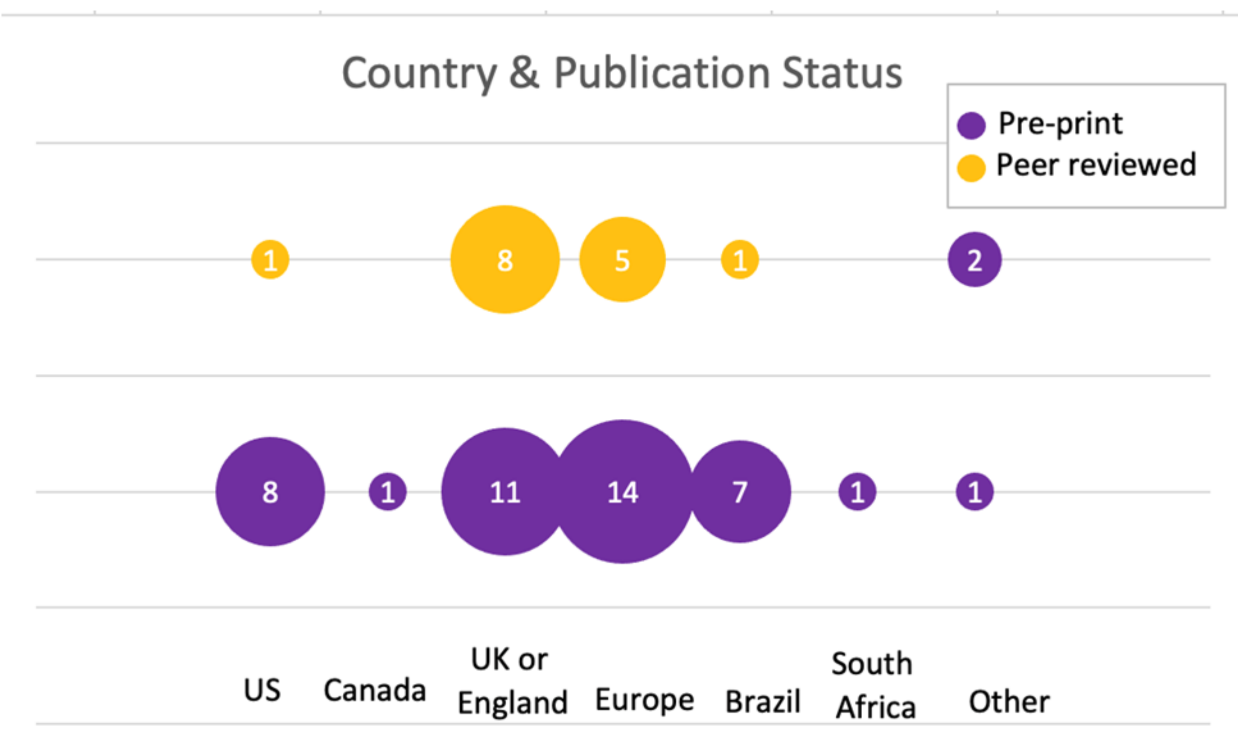

Figure 2. Overview of studies by country or region of data collection and publication status (pre-print or peer reviewed) up until May 11, 2021

Critical Appraisal

Of the 60 preprints and peer-reviewed studies, 12 were cohort studies and 13 used a cross-sectional design, and thus were subject to appraisal using the NOS. Cohort studies scored six to nine stars out of a possible nine, with a range between 67-100% in overall quality. Cross-sectional studies scored one to nine and a half out of a possible 10, with a range of 10-95% overall quality. Nine studies scored 80% or higher,[26–33] indicating high quality. The majority (n=12) scored 50-80%,[34–46] suggesting medium quality, while four studies were considered low quality, scoring 10-44%.[47–50] Forty-two of the 60 included studies were pre-prints, meaning they had not yet been peer reviewed. As the quality of preprints should be interpreted with caution, efforts were made to reflect this in the overall score through the removal of two points. A complete overview of NOS scores by study can be found in Appendix 4. Of note, five studies were laboratory-based and 30 were epidemiological modeling studies and were therefore not included in the quality assessment.

Question 1: Impact of VOC on Public Health Measures

Public health measures in relation to VOC were reported in 38 studies. The following sections report study findings in relation to the three sub-objectives. An overview of public health topic by geographic region of data collection is found in Figure 3. Most public health studies were modeling studies, and therefore were not appraised for quality. Of the seven studies that were eligible for critical appraisal, three were low,[42,47,48] two were medium,[35,46] and two were high quality.[29,30]

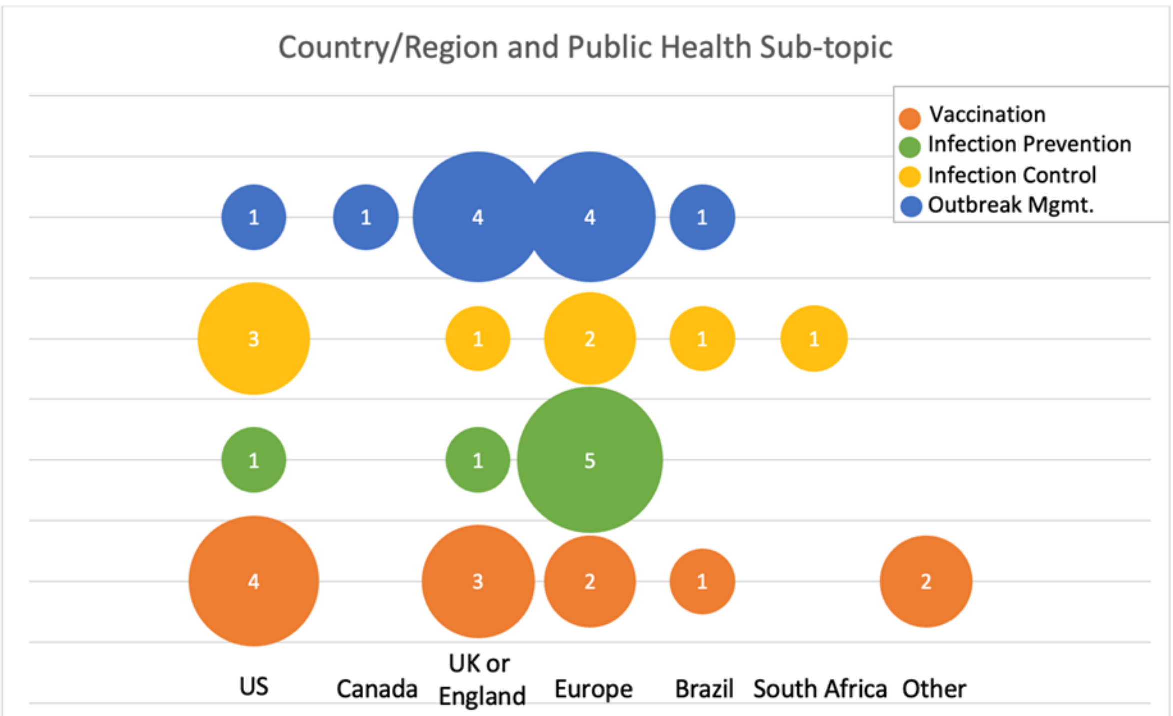

Figure 3. Overview of country or region of data collection and public health sub-topic up until May 11, 2021

Question 1A: **Modifying approach to vaccination (e.g., using vaccines that offer greater protection against variants, using different vaccines for first and second doses and/or re-vaccinating those initially vaccinated with vaccines with limited efficacy for new strains).**

Twelve studies contributed data which may be relevant to modifying the current approach to vaccine scheduling and delivery (see Table 1). Of the 12 studies, 9 were modeling[51–57] or lab-based studies[58,59] which were not critically appraised. Two of the studies that were critically appraised were of low quality[47,48] and one was medium quality.[42]

Key findings for consideration include:

- **Age appears to be a factor in immune response after the first dose of mRNA-based vaccines, which may guide second dose prioritization planning**
- **Speed of vaccine rollout is a key factor in lowering infection attack rates given the increased transmissibility of the VOC, with models suggesting a vaccination rate of 60-90 doses per day per 10,000 population required to mitigate VOC risk**
- **Optimal vaccine schedules combined with non-pharmaceutical interventions (NPIs) (i.e., restrictions, masks, physical distancing) would be expected to limit the number of COVID-19 related deaths and preserve ICU capacity**
- **A range of modeling strategies have been employed to understand the impact of the VOC with limited evidence of replication research**

- **Although high vaccine uptake is crucial to limit VOC transmission, age and gender may influence response to public health messages regarding vaccine uptake**
- **Clear messaging about the risk of VOC is an important element of a vaccine information campaign**

Table 1. *Study summary on findings related to modifying approach to vaccination, categorized by study topic*

Author, year (country)	**Study Objective**	**Data Collection**	**Sample**	**Outcome Measures**	**Key Findings**	**Quality Appraisal**
Use of vaccines or vaccine schedules that offer greater protection						
Exploring vaccine protection using a correlate of laboratory neutralization in consideration of variants						
Collier et al., 2021 (UK)	Assess age related immune response following 1st and 2nd dose BNT162b2 vaccination	Dec 9, 2020-Feb 3, 2021	51 adults (n=24, <80 years; n=26, > 80 years)	Serum antibody neutralization 3 weeks after 1st dose	Age was significantly correlated with serum neutralization in both wild type and Alpha after 1st dose of BNT162b2 vaccine. OR 9.5 (2.3-40.2, p=0.002) for participants > 80 years achieving inadequate neutralization against wild type and OR 12.2 (3.1-48.9, p<0.001) for Alpha. No age-related difference in neutralization following 2nd dose	N/A
Jangra et al., 2021 (US)	Assess impact of E484K mutation in neutralizing activity of specific antisera	N/A	34 sera from SARS-CoV-2 positive individuals & 5 from individuals fully vaccinated with Pfizer	Serum neutralization efficiency	In an in vitro microneutralization assay comparing serum neutralization of vaccinated and convalescent individuals against E484K and the USA-WA1/2020 virus, the neutralizing activity was lower against E484K for both human convalescent (low IgG: 2.4-fold, moderate IgG: 4.2-fold, high IgG: 2.6-fold in geometric mean) and post-vaccinated (3.4 fold) individuals	N/A
Luo et al., 2021 (US)	Estimate the durability of mRNA-1273 vaccine against SARS-CoV-2 variants	N/A	33 individuals who received 100ug of mRNA-1273 vaccine on day 1 and 29	Level of binding antibodies and virus neutralization after 1st dose	Based on a regression model of pseudovirus neutralization after 1 dose of mRNA-1273, Beta took 100 days to fall below lower limit of detection (20GMT), Gamma took 202 days to fall below 20GMT and Alpha took 309 days to fall below 20GMT	N/A
Exploring different vaccination schedules						
Pageaud et al., 2021	Model the expected dynamics of	N/A	Santé publique France data	# of individuals recovered, # of in hospital	While rapid vaccination of the whole population within 6 months provides the best outcome, a one-year vaccination campaign with extended non-pharmaceutical interventions (i.e., public health	N/A

Author, year (country)	Study Objective	Data Collection	Sample	Outcome Measures	Key Findings	Quality Appraisal
(France)	COVID-19 with variant strains applying protective measures and several vaccine strategies		from Jan 8th, 2021, Jan 27th, 2021 and Feb 18th, 2021	deaths, ICU resource use	measures) would limit the number of deaths and avoid ICU resource saturation	
Giordano et al., 2021 (Italy)	Model to compare different vaccines campaign scenarios, varying SARS-CoV-2 profiles and NPI restrictions	Italy's epidemic data from Feb 24th-March 26th	Data on new positive case provided by SIDARTHE	Health care costs, death	Findings strongly advocate for NPI to remain in place during vaccine roll out until sufficient population immunity is reached. Pre-emptive NPI actions (close then open at low case #s) could drastically reduce hospitalizations and deaths	N/A
Munitz, 2021 (Israel)	Explore transmission dynamics of Alpha to estimate effectiveness of public health measures on elderly and general population	Dec 6th, 2020-Feb 10th, 2021	>300,000 RT-PCR samples	SGTF data, reproduction number Rt and cycle threshold	Israel's national vaccine program which initially targeted the elderly (60+ years) resulted in containment of Alpha in that population. By Jan 14th, 2021 when 50% of the 60+ were 2 weeks beyond their first dose of Pfizer vaccine, a striking decline was observed in the incidence of Alpha in the 60+ age group compared with 0-19 or 20-59 years of age (r=0.075, p=0.74; r=-0.005, p=0.98, respectively)	N/A
Kim et al., 2021 (US)	Model the impact of using different	N/A	US Population (~330 million)	Infection attack rate (IAR)	Model suggests that speed of vaccine rollout is a key factor in achieving low IAR even after variants emerge. If delivered more	N/A

Author, year (country)	Study Objective	Data Collection	Sample	Outcome Measures	Key Findings	Quality Appraisal
	vaccines with varying efficacies				quickly, low efficacy levels can achieve lower IAR than vaccine with high efficacy levels	
Sah et al., 2021 (US)	Model an accelerated vaccine rollout to curb the spread of SARS-CoV-2 variants	N/A	US population	Hospitalization and death rate	The current pace of vaccine rollout (1 million doses per day or 30 doses per day per 10,000 population) will not prevent exacerbation of the pandemic. Accelerated vaccine (2 million daily doses or 60 doses per day per 10,000 population) delivery would substantially reduce severe health outcomes from emergent SGTF variants with higher transmissibility.	N/A
Tokuda and Kuniya, 2021 (Japan)	Model the impact of various vaccination schedules on infection rate and need for public health measures	Jan 14th, 2020 to Apr 20th, 2021	N/A	Number of daily infections	Based on three possible vaccination schedules (1/1000, 1/500 or 1/250 vaccinations per person per day), and using an increased transmission rate of 1.3 for Alpha, it was estimated that the current vaccination pace of 1/1000 would need to be quadrupled to control the spread of VOC	N/A
Victora et al., 2021 (Brazil)	Assess the effectiveness of Brazil's vaccination campaign on mortality rates	Jan 3rd, 2021 to Apr 22nd, 2021	>370,000 registered deaths	Mortality rate among adults aged 0-79, 80+ and 90+ years	Increased vaccination among Brazilians aged 80+ years was associated with a decline in relative mortality compared to individuals aged 0-79 years during the same time period, when Gamma was prevalent	60% (medium quality)
Attitudes towards vaccines related to VOC						
Bachtiger et al., 2021 (UK)	Assess impact of new variants on COVID-19 vaccine hesitancy and attitude	Nov 13 & Dec 31, 2020	9617 respondents from Imperial College Healthcare NHS Foundation Trust	Attitude toward vaccine prioritization, vaccine behavior	Intention to vaccinate increased from 71.5% (6521/9122) in the first questionnaire to 85% (8,187/9617) in second questionnaire after Alpha emergence. Age and gender influence vaccine behaviours	10% (low quality)

Author, year (country)	Study Objective	Data Collection	Sample	Outcome Measures	Key Findings	Quality Appraisal
Comparing natural or vaccine protection against COVID-19						
Lumley et al., 2021 (UK)	Compare protection conferred by vaccine and Alpha	Apr 2020-Feb 28, 2021	HCW in Oxford University Hospitals	PCR-positive test, antibody status	Natural immunity with detectable anti-spike antibodies & two doses of vaccine (Pfizer or Oxford-AstraZeneca) provides similar protection against SARS-CoV-2 infection and the Alpha variant	44% (low quality)

Use of vaccines or vaccine schedules that offer greater protection

A total of ten studies provide data which may be useful to consider when designing how vaccines are rolled out with the emergence of the variant strains.

Exploring vaccine protection using a correlate of laboratory neutralization in consideration of variants

Three studies contributed data on mRNA vaccines. Two small studies provided data related to serum neutralization protection against VOC. Collier et al. conducted a prospective cohort study in the UK including 51 participants (median age 81 years; n=24, <80 years; n=27 > 80 years), to assess immune response following the first and second dose of mRNA-based vaccines.[58] Vaccine elicited serum antibody neutralization was measured as a dilution of serum required to inhibit infection by 50% in an *in vitro* neutralization assay at least three weeks after the first dose of vaccine. Age was found to be statistically correlated with serum neutralization in both the wild type and Alpha after the first dose. The adjusted odds ratio (OR) for participants aged >80 years versus <80 years for achieving inadequate neutralization against wild type was 9.5 (2.3-40.2, p=0.002) and against the Alpha variant was 12.2 (3.1 – 48.9, p<0.001). Re-testing three weeks after the second dose showed no age-related differences in neutralization activity. Consequently, for individuals >80 years of age the second vaccine dose was important in generating a comparable neutralizing antibody response to younger people.

Jangra et al. examined the impact of the E484K mutation, which is a concern for immune evasion in Beta and Gamma, on the neutralization activity of SARS-CoV-2 specific antisera using a sample of 34 sera from SARS-CoV-2 positive individuals and sera from 5 individuals who were fully vaccinated with the Pfizer vaccine.[59] *In vitro* microneutralization was performed in a blinded manner with both the USA-WA1-2020 virus (similar to strains in the early phase of the COVID-19 pandemic) and an identical recombinant SARS-CoV-2 except for the E484K mutation on the spike receptor binding domain. Serum neutralizing activity of human convalescent and post-vaccinated donors was significantly lower against E484K (convalescent low IgG: 2.4-fold, moderate IgG: 4.2-fold, high IgG: 2.6-fold; vaccinated samples: 3.4-fold based on geometric means) when compared with USA-WA1-2020. These findings suggest that booster vaccines will be required in a Beta and Gamma VOC context.

Luo et al. used a regression model to estimate the long-term durability of mRNA-1273 vaccine (brand name Moderna), based on binding antibodies and virus neutralization levels.[54] Using 92.1% as an estimate of the effectiveness after one dose of vaccine, the model predicted that it would take approximately 411 days for binding antibodies to fall below levels seen on day 15. The model also estimated that it would take 327 days for pseudovirus neutralization and 461 days for live virus neutralization to fall below the lower detection threshold of 20 GMT (geometric mean end-point titers). When considering three VOC (Alpha, Beta and Gamma), the model estimated that pseudovirus neutralization would fall below 20 GMT on day 100 for Beta, day 202 for Gamma, and day 309 for Alpha. In summary, the model estimates that a 2-dose mRNA-1273 vaccine will provide protection against the Alpha, Beta and Gamma VOC for approximately one year, with estimated lower protection for Beta and Gamma. Therefore, booster vaccines may be needed to ensure prolonged protection against VOC.

Exploring different vaccination schedules

Six modeling studies and one observational study examined the impact that changes in the vaccine scheduling would have on VOC. Pageaud et al. used a stochastic agent-based model (ABM), stratified by age, which considered the influence of the variant strains, three different NPI protocols (relaxed, intensive, extended), and four different vaccine schedules (6,12, 18, 24 months) to examine impact on number of cases, deaths, hospitalizations and ICU resource use.[52] A 6-month vaccination campaign with an intensive-NPI resulted in the least number of deaths (~18,000) and avoided ICU resource saturation. With a 12-month vaccine schedule, the number of deaths were 3 times higher and extended-NPI was needed to avoid ICU resource saturation. Vaccine campaigns up to 18 and 24 months would lead to 81 and 93 thousand deaths respectively and saturation of the ICU resources, even with intensive-NPI. In all models with vaccine schedules longer than 6 months, extended-NPI was needed to avoid ICU resource saturation.

Kim et al. used a modified SIRD (susceptible, infectious, recovered, deceased) compartmental model to examine the speed of vaccine distribution and different mutation times or the times when emerging variants cause a decrease in vaccine efficacy levels in the US.[55] The model suggests the speed of vaccine distribution is a key factor to achieve low infection attack rates (IAR) against variants and vaccines with low efficacy levels (<70%) can achieve a lower IAR than a vaccine with high efficacy (>90%) if delivered more quickly. Using an agent-based model of a COVID-19 outbreak, Sah et al. compared scenarios with increased vaccination of 1.5, 2, 2.5, and 3 million doses per day from the current baseline of 1 million per day.[56] Findings suggest that the emergence of a SARS-CoV-2 variant with 30% more transmissibility than wildtype would result in 10.9 (95% Crl:10.0-11.7) hospitalizations and 3.1 (95% Crl:2.8 to 3.3) deaths per 10,000 population over 300 days. Doubling the vaccine rate to 2 million doses per day (60 doses per day per 10,000 or approximately 0.6% population/day) would result in a mean reduction of hospitalizations and deaths by 29.4% and 35.5%, respectively. Further, expanding the rate to 90 vaccine doses per day per 10,000 population would avert 152,048 (95% CrL:134,772-168,696) hospitalizations and 48,448 (95% CrL:42,042-54,285) deaths over 300 days.

Tokuda and Kuniya used an SEIR (Susceptible, Exposed, Infectious, Recovered) compartmental model based on data from Jan 14th, 2020 to Apr 20th, 2021 to determine which pace of vaccination would effectively control the spread of SARS-CoV-2.[57] The model used three possible vaccination scenarios: 1/1000, 1/500 or 1/250 vaccinations per unvaccinated person per day. Based on each scenario, various levels of restrictions were estimated as being necessary to assist in controlling the spread. Using an increased transmission rate of 1.3 for Alpha, authors reported that the current vaccination pace of 1/1000 would need to be quadrupled (to 0.4% of the population/day) to meet containment goals. If a vaccination pace of 1/500 (0.2% population/day) were rolled out in the presence of Alpha, a series of restrictions (i.e., lockdowns) would need to be employed to control the spread.

Giordano et al. employed a SIDARTHE (susceptible, infected, diagnosed, ailing, recognized, threatened, healed and extinct) compartmental model using Italian field data to predict the impact of VOC based on various vaccination campaigns in Italy.[53] Authors reported 20 unique scenarios associated with differing speeds of vaccine rollout, transmissibility profiles and public health measure strategies. Containment strategies (i.e., lockdowns, physical distancing) had a 5-fold impact on reducing human losses in the period of Feb 2021 to Jan 2022 in slow, medium, and fast vaccine schedules indicating NPIs have a larger effect than vaccination speed. The model demonstrates with highly transmissible VOC, NPIs are crucial for controlling the epidemic. Pre-emptive restrictive containment strategies (close first then open at low case numbers) would reduce the peak number of new daily cases (from 38,000 to 14,000) and deaths (peak daily deaths from 600 to 400) at no socio-economic costs when compared with delayed interventions (keep open then close when case numbers start to rise to prevent ICU saturation). This suggests use of proximal indicators would result in fewer severe outcomes than lagging health system-based indicators.

Munitz et al. provided real-world evidence of the effectiveness of mRNA vaccine roll-out through reporting a correlation of Israel's vaccination campaign with rates of variant Alpha using data from >300,000 RT-PCR samples collected between Dec 6th, 2020, and Feb 10th, 2021.[60] Alpha had become the dominant variant (92%) up to Jan 14th, 2021 among all age groups (r>0.99). After Jan 14th (with 50% of 60+ age group receiving first dose of Pfizer vaccine), there was a decline in the 60+ age group compared with individuals 0-19 years old (r=0.075, p=0.74) and 20-59 years old (r=0.0005, p=0.98). A national lockdown implemented in Jan 2021 and a surveillance testing program in nursing homes and the community enabled early detection and helped to contain viral spread in at risk populations.

Victora et al. investigated the impact of the vaccination roll out in Brazil by comparing documented mortality rates due to COVID-19 (n=171,517) from Jan 3rd until Apr 22nd, 2021, with vaccine coverage data.[46] The authors compared changes in mortality rate for two-week intervals among the 80+ and 90+ age groups to younger individuals, aged 0-79 years. Between January and April 2021, the mortality rate of adults aged 90+ years decreased from being 20 times higher to 7.7 times higher than individuals aged 0-79 years. During the same period, the mortality rate of adults aged 80+ years decreased from 13.3 times higher to 6.9 times higher than the 0-79 age group. This decline in mortality rate ratio may be associated with the rapid scale up of vaccinations among the elderly population in early 2021, during a time when the Gamma VOC was the dominant strain and overall mortality rate was accelerating across Brazil. This pre-print study was critically appraised as medium quality so the findings should be interpreted with caution.

Different vaccines for first and second dose (heterologous vaccination schedules)

No published studies to date have reported on this outcome.

Attitudes towards vaccination related to VOC

Changes in COVID-19 vaccine hesitancy related to VOC emergence were assessed in the UK by Bachtiger et al. as part of an ongoing cross-sectional longitudinal study involving 18,581 participants examining the effects on well-being of the COVID-19 pandemic.[48] Study participants were invited to complete weekly surveys through their personal electronic health record, Care Information Exchange. Questionnaires related to vaccine behaviour were sent on Nov 13th, 2020 (following Pfizer vaccine reported efficacy of >90%) and on Dec 31st, 2020 (after first reports of Alpha). Intention to receive the vaccine increased from 71.5% (n=6521 of 9122 participants) in the first questionnaire to 85.1% (n= 8187 of 9617 participants) in the second questionnaire. Three hundred seventy-five participants (3.8%) in the second questionnaire indicated they changed their minds to wanting vaccination considering news of the new VOC, Alpha. Yearly increase in age (adjusted-OR: 1.045 [95% confidence interval (CI):1.039-1.050]) and female gender (adjusted-OR: 0.540 [95%CI:0.461-0.632]) increased and decreased vaccine acceptance, respectively. This study was critically appraised as low quality, so these findings should be interpreted with caution.

Comparing post COVID-19 infection and vaccine protection against Alpha COVID-19

Lumley et al. followed a sample of 13,109 health care workers (HCW) from Oxford University Hospitals to determine the protection conferred following infection from Alpha and one and two doses of Pfizer or AstraZeneca vaccines.[47] The results suggested seropositivity post infection conferred significant protection, similar to vaccination. HCW were offered asymptomatic nasal and oropharyngeal swab PCR testing every two weeks and serological testing every two months from Apr 2020 continuing after the vaccination program start on Dec 8th, 2020. Data is reported up to Feb 28th, 2021. Anti-trimeric spike IgG ELISA was used to determine antibody status. The rates of PCR-positive tests were highest in the unvaccinated seronegative HCWs and 85% lower in unvaccinated seropositive HCWs (aIRR=0.10 [0.08-0.26, p<0.001]). The incidence of any PCR-positive result was reduced by 64% after first dose vaccination in seronegative HCWs (aIRR=0.36 [0.26-0.50; p<0.001]) and 90% following second vaccination (aIRR=0.10 [0.02-0.38; p<0.001]). Alpha did not significantly alter the extent of protection for PCR positive infection in those who were seropositive (aIRR =0.40

[95%CI 0.10-1.64; p=0.20]) or following a first vaccine dose (aIRR=1.84 [0.75-4.49; p=0.18]). Overall, findings suggest immunity induced by natural infection with detectable anti-spike antibodies, including Alpha, and vaccine is robust. This study was critically appraised as low quality, so these findings should be interpreted with caution.

Question 1B: What is known about the implications of the WHO defined VOC for Modifying infection-prevention (i.e., public-health) measures in the community (e.g., changing duration of hand washing; changing mask type and characteristics, double masking or other changes to masking; and changes to physical and temporal distancing)

Nine sources reported on infection-prevention measures in the community, particularly around physical distancing (see Table 2). Eight of these were modeling or lab-based studies[51,53,61–65] thus no quality appraisal was completed. The one cross-sectional study that reported on infection-prevention measures was appraised as medium quality.[42]

Key findings for consideration include:

- **Evidence supporting modification to infection-prevention measures in different community settings (e.g., daycares, schools, workplaces) in response to VOC is sparse, particularly related to hand washing and masking protocols, suggesting jurisdictions have maintained current measures.**
- **Physical distancing and other NPIs are important in reducing the spread of VOC in the community.**
- **Ongoing communication strategies promoting maintenance of physical distancing is an important element in a vaccine campaign**

Table 2. *Study summary on public health infection-prevention measures in the community*

Author, year (country)	**Objective**	**Data collection period**	**Sample**	**Outcome measures**	**Relevant key findings**	**Quality apprais al**
Mask Wearing						
Gurbaxani et al., 2021 (US)	Model face mask efficacy parameters for a variety of specific types of masks and for efficacy estimates, including increased R_0 of VOC	N/A	N/A	Effectiveness of mask wearing	Masks have significant potential for reducing SARS-CoV-2 transmission, even with moderately effective masks, when they are worn consistently correctly (over the chin and covering nose and mouth) and/or per manufacturers' specifications by a large portion of the population	N/A
Handwashing						
Meister et al., 2021 (Germany)	Compare the surface stability of wild type SARS-CoV-2 and Alpha and Beta VOC on different surfaces and their sensitivity to heat, soap and ethanol	N/A	N/A	Viral stability and viral infectivity	There were no differences between wild-type and VOC in their disinfection profiles, indicating that current hygiene measures are sufficient and appropriate	N/A
Physical Distancing						
Borges et al., 2021 (Portugal)	Investigate the proportion of SGTF cases to gain insight on Alpha frequency and spread in Portugal	Week 49, 2020 to week 3, 2021	Data set from Portuguese National Institute of Health Dr. Ricardo Jorge Dec 2020-Feb 5th, 2021	SGTF & SGTL test	Physical distancing measures (general lockdown) implemented in weeks 2 & 3 of 2021 decelerated the growth rate of SGTF positive cases	N/A
Domenico et al., 2021 (France)	Assess the impact of social distancing on historical and variant strain through modeling	N/A	Flash1 survey data from Santé publique France on Jan 28th, 2021	Alpha prevalence	Strong social distancing measures (e.g., curfews, lockdowns, work from home) including mild lockdown were needed to decelerate the surge of Alpha in the third wave	N/A
Vazquez et al., 2021 (Germany)	Estimate SARS-CoV-2 rate of transmission per proximity contact and generate a model	Not reported	605 individuals from one workplace	Proximity data between two coworkers tracked for 44	Using single case workplace proximity data and reproductive numbers for SARS-CoV-2 and Alpha, the transmission rate per contact was determined to be 3 times	N/A

	to simulate infectious disease outbreaks in workplaces			days through Bluetooth wearable devices	higher for Alpha (0.041) vs SARS-CoV-2 (0.014). Workplaces can use proximity data to simulate disease outbreaks and management strategies	
Aiano et al., 2021 (England)	Investigate COVID-19 outbreaks in nurseries reported to Public Health England between Nov 2020 and Jan 2021	Feb 9th-Feb 23rd, 2021	173 nurseries (congregate care setting for < 5-year-old) reporting COVID-19 outbreak in England	Outbreak and facility characteristics	1% of nurseries (324/32,852) reported COVID-19 outbreaks during the study period. There was some evidence of larger outbreak sizes and higher attack rates among staff and students in Jan 2021 when Alpha was predominant.	50% (medium quality)
Lasser et al., 2021 (Austria)	Develop a model calibrated to Austrian school-cluster data to evaluate effectiveness of NPI in preventing transmission in different school types	NA	Austrian school-cluster data	Transmission probability	Overall, the model suggests combination of 2 and 3 preventative strategies for primary and secondary schools respectively to keep transmission low. Under the Alpha scenario with 2 preventative strategies, secondary schools show as much as 3.0-fold increase in clusters with student sources	N/A
Linka et al., 2021 (US)	Model the effects of VOC on disease dynamics with reopening Stanford University in 2020-2021	N/A	Undergraduate students at Stanford University	# of students infected	The outbreak dynamics in the model with the introduction of Alpha and Beta are significantly different from wildtype dynamics. The most affected quarter would be Fall 2020 with 203 cases for wildtype and 4727 and 4256 for Alpha and Beta	N/A
Teslya et al., 2021 (Netherlands)	Investigate the effects of waning compliance to physical distancing measures on COVID-19 vaccine roll-out	N/A	Used vaccination rollout data from Jan 7th-Feb 7th, 2021 from the Netherlands and UK	# of people infected, vaccinated, and compliancy over the vaccine rollout and up to 1-2 years	For Alpha, when vaccine rollout is slow, focusing on improving compliance to physical distancing among the non-vaccinated is best for reducing the number of infections. However, when vaccination is fast, targeting vaccinated people is better.	N/A

Hand washing

Meister et al. compared the surface stability of the wild-type variant and Alpha and Beta VOC on different surfaces and their sensitivity to heat, soap, and ethanol.[64] In terms of ethanol, a common ingredient of several disinfectants, both wild-type and VOC were efficiently inactivated upon treatment with at least 30% ethanol for 30 seconds and hand soap for 1-5 minutes. Thus, current measures of hand hygiene would be effective against Alpha and Beta.

Mask protocols

One modelling study reported on mask protocols related to VOC. Gurbaxani et al. modeled face mask efficacy parameters for a variety of specific types of masks and for efficacy estimates to be used as benchmarks for evaluating these products.[63] They found that for at least a 50% reduction in cumulative infections, mask wearing would need to be at least 55% efficacious for arbitrary wearer protection efficacy and 45% effective to reduce death. With a higher reproduction number (estimated at R_0=4.0 with Alpha), when masks are 84% effective at reducing an infectious person's chance at transmitting SARS-CoV-2 and 60% effective at preventing a person from becoming infected once exposed, it only reduced the R_0 to 1.6, compared to <1 for non-VOC. However, when cloth masks performance is optimized with multiple layers, filters, or masks are used with a fitter to ensure a tighter fit, greater reduction can be achieved. Overall, masks have potential for significant reduction in SARS-CoV-2 (VOC and non-VOC) transmission, even with moderately effective masks, when they are worn consistently correctly (over the chin and covering nose and mouth) and/or per manufacturers' specifications by a large portion of the population. Additional protection is necessary in consideration of the Alpha VOC. However, the impact of masks in reducing community transmission has been difficult to separate within bundled NPI interventions. Authors in this study used modelling to assess the potential impact of higher transmission VOC on the potential benefit of masking.

Physical distancing

Seven studies contributed data related to physical distancing in consideration of the VOC (Table 2). In a surveillance study evaluating the spread of Alpha in Portugal between Dec 20th, 2020 and Jan 20th, 2021, Borges et al. concluded that the physical distancing measures (i.e., lockdown, school closures) implemented in weeks 2 and 3 of 2021 strongly decelerated the growth of Alpha.[61] While models had forecasted the proportion of SGTF/SGTL cases to reach up to 68% (95% CI:65-71), the proportion of SGTF and SGTL positive cases remained below 50% until week 7 of 2021.

Domenico et al. used a discrete, stochastic model integrating demography, age profile, social contacts, and mobility data over time to model the impact of social distancing measures on two strains of SARS-CoV-2 (historical and Alpha).[51] Strain circulation dynamics for France, Ile-de-France regions and Nouvelle Aquitaine were secured through Santé Publique France on Jan 28th, 2021. The model estimated that the progressive social distancing implemented in Jan 2021 brought the reproductive number of the historical strain below 1 but the Alpha cases increased exponentially with the estimated reproduction (R) about 1 in all three regions. The authors suggest that strengthening social distancing measures with the addition of restrictive measures such as weekend lockdown, will be needed to decelerate the resurgence of Alpha in a third wave.

Vazquez et al. conducted a novel modelling study at the level of a workplace using co-worker proximity data gathered through Bluetooth technology.[62] Proximity data, collected from button devices worn by 605 workers for a period of 44 days, provided a temporal network to model the spread of airborne viruses. These data are combined with an infection transmission model developed by the team to estimate the SARS-CoV-2 transmission rate per proximity contact. Social distancing is modelled by removing different fractions of the proximity contacts. Based on the proximity data from the sample workplace, the model estimated the transmission rate per proximity contact for SARS-CoV-2 cases as 0.014 and Alpha as 0.041 per proximity contact, approximately 3 times higher. While the introduction of infection-prevention measures such as social distancing and mask wearing reduces the infection rate, Alpha transmissibility remained 2 times larger than the wild-type.

Facility structure and difficulty maintaining physical distancing were identified as important factors in COVID-19 outbreaks in nurseries reported to Public Health England between Nov 2nd, 2020 and Jan 31st, 2021.[42] 171 nurseries from across England completed a questionnaire providing details of the outbreak and the degree of contact between staff and children, including the size and structure of bubbles (a group of staff and children who perform all activities together). Of the 171 nurseries reporting outbreaks, 42% (72/171) occurred across three bubbles whereas 25% (43/171) only involved one bubble. Within bubbles, 74% (127/171) reported children were “never” able to maintain physical distancing and 64% of staff were “never” able to maintain physical distancing with children. The majority of sites reporting outbreaks also shared staff rooms (111/171) and bathrooms (131/169) across bubbles.

Lasser et al. used Austrian school-cluster data to model the impact of different NPI (i.e., room ventilation, masking procedures, student cohorting, and antigen testing) on COVID-19 transmission in different school types (i.e., primary, lower-secondary, upper-secondary, secondary with and without daycare) to derive evidence-based policies for keeping schools open.[74] The most effective measure in reducing cluster size is room ventilation followed by class size reduction, mask wearing, and testing. Primary schools require a combination of at least two of these measures to keep transmission low while secondary schools require a combination of at least three measures. With factoring the increased transmissibility of Alpha, preventative strategies that only combine room ventilation and testing show the largest increases in clusters. Student source cases in secondary schools increase 3-fold (testing once per week) and 2.3-fold (testing twice a week) when compared with original variant.

Linka et al. modeled the effects of campus reopening for undergraduate students attending Stanford University for four quarters between Spring 2020 and Winter 2021.[75] Authors use local epidemiological data from across the US to connect the 50 states to Stanford campus and Bayesian analysis to estimate the number of students infected if the campus had fully reopened. Reopening under the Alpha VOC as dominant, reproduction dynamics would lead to 3,329, 2,555 and 4,727 cases 100 days after reopening in Spring, Summer and Fall 2020 and reopening with Beta as dominant would lead to 2,581, 2,117 and 4,756 cases in the same time sequence. In contrast with using wildtype reproduction dynamics, reopening would result in 58, 162 and 203 cases in Spring, Summer and Fall 2020 during the first 100 days.

Teslya et al. conducted a SEIR modelling study to investigate the effects of waning compliance to physical distancing recommendations on the dynamics of the COVID-19 vaccination roll-out in the Netherlands.[65] In the presence of an Alpha-type variant and considering slow and fast vaccine roll-out regimes, messages to maintain physical distance and limit contacts that target both non-vaccinated and vaccinated individuals are needed to reduce cumulative number of infections over two years. The impact on infection rate of messaging interventions targeting non-vaccinated individuals is similar in both slow and fast vaccination roll-out (13,310 per 100,000 population versus 13,950 per 100,000 population) after two years. Targeting improved compliance among both vaccinated and unvaccinated individuals with fast vaccination rates resulted in the fewest infections past one year (3,740 infections per 100,000 compared to 6,529 per 100,00 for slow vaccination schedule). Ongoing public health messaging regarding adherence to physical distancing measures is an important part of a vaccine campaign.

Question 1C: What is the impact of VOC on modifying infection-control procedures? This question was addressed through the following sub-sections: i) changing testing strategy; ii) quarantine and physical distancing measures; iii) contact tracing; and iv) outbreak management.

We identified 17 studies which contributed data relevant to modifying infection-control procedures which are summarized in Table 4. Of these, 14 were modeling [61,66–78] or lab-based[79,80] and thus not critically appraised. Of the three that were appraised, two were high quality,[29,30] and one was medium quality.[35]

Key findings for consideration include:

- **Non-pharmaceutical interventions (e.g., lockdowns, distancing, mask wearing) appear required to limit transmission during vaccine rollout particularly if rapid mass vaccination is not feasible**
- **Access to data on VOC prevalence and incidence within and between countries is required to guide travel quarantine and testing strategies**
- **High VOC transmission among individuals living in the same household, particularly among pre-symptomatic and asymptomatic cases, is concerning and warrants significant public health measures (i.e., rapid testing, contact tracing, masking, rigorous quarantining, support for sick leave and out of household quarantine)**

Table 4. *Summary of studies presenting findings on testing, duration of quarantine, and infection-control procedures related to VOC*

Author, year (country)	**Objective**	**Data Collection Period**	**Sample**	**Outcome measure**	**Relevant key finding**	**Quality appraisal**
Testing						
Abdel-Sater et al., 2021 (Lebanon)	Evaluate a primer to confirm deletion mutations Δ69/ Δ70 and Δ106/ Δ107	Dec 9th, 2020-Jan 10th, 2021	20 samples from SARS-CoV-2-positive patients confirmed through TaqPath kit	SYBR Green-Based RT-PCR	This primer could be used as a second step test in RT-PCR to confirm Alpha in COVID positive S-Gene negative patients.	N/A
Akingba, 2021 (South Africa)	Evaluate the field performance of the PanBio assay to detect Beta	Nov 17th-20th, 2020	677 patients from 6 mobile clinics	N/A	The assay reliably detected Beta virus infection in ambulatory ill patients. Sensitivity was >90% in patients with high viral loads CTs<30.	N/A
Quarantine						
Yang et al, 2021 (Brazil)	Develop a deterministic model to evaluate the partial quarantine and further relaxation in Sao Paulo State, Brazil	Feb 26th, 2020-Apr 5th, 2021	N/A	COVID-19 cases and fatality curves	The model fit the COVID-19 data (considering VOC and transmission among isolated individuals) and provided a useful means for describing the impact of quarantine, relaxation, and virulence of the epidemic in Sao Paulo State, Brazil. Specifically, in the presence of VOC, the model predicts increased fatality. Additionally, cases of COVID-19 would rise upon relaxation of public health measures, and this is predicted to be a result of VOC rather than lifting of measures.	N/A
Wells et al, 2021 (US)	Model travel between pairs of European countries to identify travel quarantine and testing strategies that will not increase infections in the destination country compared to a strategy	N/A	N/A	Length of quarantine for origin-destination pairs of European countries	Quarantines for European destinations that are specific to travel origin can be informed by country-specific prevalence, daily incidence, vaccine coverage, age-demographics, and travel flow. For Alpha, in countries with similar prevalence, quarantine and testing strategies are similar for wild-type transmission. In contrast there is much greater variance between countries in prevalence of Beta VOC. Consequently, more extreme quarantine and testing measures would be needed to mitigate its impact.	N/A

Author, year (country)	Objective	Data Collection Period	Sample	Outcome measure	Relevant key finding	Quality appraisal
	of complete border closure					
Outbreak management						
Managing outbreaks through lockdowns						
Graham et al., 2021 (Scotland, Wales & England)	Examine the association between regional proportion of Alpha and reported symptoms, disease course, rates of infection and transmissibility	Sep 8th-Dec 31st, 2020	Data from 36920 participants in the COVID Symptom Study who tested positive for COVID-19	Self-reported symptom data	Regional and then national lockdown Dec 19th-Jan 5th led to reduced Rt: 0.8 among regions with high proportion of Alpha cases	80% (high quality)
Scherbina, 2021 (US)	Estimate the benefits of a lockdown in the US similar to those imposed in Europe	N/A	N/A	Estimated future monetary cost of the pandemic	Modeling suggests strict lockdown could reduce R by 76%, or R_0: 0.933. A less restrictive lockdown would lead to R_0:1.66. Optimal lockdown time of 6-7 weeks is needed to achieve high-dQALY outcomes, or 4-5 weeks to meet low-dQALY outcomes	N/A
Ahn et al., 2021 (US)	Examine a multi-model optimization (MMO) framework to optimize COVID-19 containment policies	N/A	A range of forecasting models, multiple cost models for NPI and health outcomes and a 4-level containment strategy	Economic and health costs of policy	The MMO significantly outperforms policies optimized with a single model and continues to be robust with the introduction of Alpha data (50% increase in contact rate and 43-90% higher reproductive number). Findings indicate the importance of tracking and containing VOC before they become widespread.	N/A
Kühn et al., 2021 (Germany)	Model different lockdown and restriction strategies to avoid spread of SARS-CoV-2 VOC between neighboring regions	N/A	Population in Germany	SARS-CoV-2 Incidence levels	A combined strategy of local lockdowns and systematic testing can contain isolated local outbreaks in a general low incidence setting. Unrestricted travel between high and low incidence regions is problematic and strict local measures in combination with frequent testing of commuters proves highly effective in preventing spread of localized infection hot spots.	N/A
Managing outbreaks through physical distancing						

Author, year (country)	Objective	Data Collection Period	Sample	Outcome measure	Relevant key finding	Quality appraisal
Borges et al., 2021 (Portugal)	Investigate the proportion of SGTF cases to gain insight on Alpha frequency and spread in Portugal	Dec 2020-Feb 5th, 2021	3367 positive SGTF tests (proxy for Alpha) from Portuguese National Institute of Health	SGTF & SGTL test	After implementing public health measures, a decelerating trend was observed in proportion of SGTF/SGTL remaining below 50% in week 7 of 2021	N/A
Buchan et al., 2021 (Canada)	Compare household secondary attack rates in those with VOC versus non-VOC index cases in Ontario	Feb 7th-27th, 2021	5617 index cases and 3397 secondary cases	Household secondary attack rate 1-14 days after index case	Secondary attack rate 1.31 higher in VOC vs non-VOC in same household, further accentuated in asymptomatic (RR=1.91) and pre-symptomatic (RR=3.41) cases. Findings suggest need for aggressive public health measures physical distancing, masking, testing and contact tracing	67% (medium quality)
Chudasama et al., 2021 (England)	Conduct comparative analysis of household clustering of COVID-19 infections	Oct 1st-Dec 15th, 2020	57,382 positive sequenced cases	# and proportion of variant and wildtype cases	Alpha variant cases were almost twice as likely to give rise to household clusters than wild-type	89% (high quality)
Zimerman et al., 2021 (Brazil)	Assess whether social isolation into small families or groups is associated with the emergence of new variants	Jun 1st, 2020-Jan 10th, 2021	773 genomic sequence samples	Social isolation index (SII), which is based on percentage of individuals who stayed within 450m of their home	In the state of Amazonas, where household sizes are large, there was a positive correlation between SII and the prevalence of Gamma when SII was above 40%. Authors hypothesize that forced prolonged cohabitation may boost viral mutation and increased infectivity.	N/A
Managing through other public health measures						
Moore et al., 2021 (UK)	Model consequences of relaxing NPI and influence of vaccination on individual risk	UK data for 7 NHS regions of England and the 3 devolved nations from Feb 2020-Jan 2021	N/A	Daily hospital admissions, deaths until Jan 1st, 2024	Although vaccine substantially reduces total COVID-19 related deaths, the model, assuming 60-85% vaccine efficacy, 75-95% age-dependent vaccine coverage and R of 3.15, indicates continuance of NPIs is necessary once the vaccine program is complete to limit the number of deaths	N/A

Author, year (country)	Objective	Data Collection Period	Sample	Outcome measure	Relevant key finding	Quality appraisal
Shattock et al., 2021 (Switzerland)	Model the impact of different vaccine scenarios and NPI strategies on the COVID-19 pandemic	OpenCOVID epidemiologic data up to Mar 5th, 2021	Population in Switzerland	COVID-19 cases, hospitalizations, ICU admissions, deaths up to Sep 2021	Rigorous monitoring of vaccine uptake and the emergence of new variants is required to safeguard against a significant third wave. The combination of both vaccine uptake and ongoing NPIs will dictate the size of the third wave.	N/A
Bosetti et al., 2021 (France)	Develop a mathematical model to better understand the interplay between the variants, the vaccines, and the control measures	N/A	Metropolitan France	Hospitalizations and deaths	Quick rollout of vaccines to at-risk individuals and NPIs are needed to mitigate the impact of emerging variants	N/A
Piantham and Ito, 2021 (UK)	Propose a method to estimate selective advantage of mutant strain over previous strains	Sep 1st, 2020-Feb 19th, 2021	71692 Alpha strains and 65850 non-Alpha strains	Time from illness onset in a primary case to illness onset in secondary case (using serial interval distribution)	Alpha has an estimated reproduction advantage of 33.7% over non-VOC, suggesting control measures need to be strengthened by 33.7%	N/A
Smith et al., 2021 (UK)	Assess the impact of environment (e.g., temperature) on VOC transmission	Oct 19th-Dec 7th, 2020	N/A	Global population density, temperature, and R	Warmer temperatures are associated with decreased VOC transmission. However, impact of temperature is only secondary to public health measures, with UK observing effect of temperature on VOC only after lockdown measures lifted	N/A

**high-dQALY: discounted quality-adjusted life years based on $431,000 being the higher end; low-dQALY: discounted quality-adjusted life years based on $150,000 being the lower end; NA = not appraised

Duration of quarantine and/or isolation

Yang et al. developed a deterministic model to evaluate the partial quarantine and relaxation in San Paulo State, Brazil.[72] The epidemic in Sao Paulo State is characterized by four phases; phase 1 is the natural epidemic, just before introducing partial quarantine; phase 2 is the epidemic under isolation; phase 3 is the epidemic under relaxation; and phase 4 is the epidemic with more virulent variant SARS-CoV-2. Model parameters are estimated against observed data from Feb 26th, 2020 to Apr 5th, 2021. The model of deaths and cases during these phases produce two sigmoid-shaped curves, the first from Feb 26th to Nov 10th, 2020 and the second from Nov 11th, 2020 to Apr 5th, 2021. During the first curve, the peaks of the daily death (Jul 2nd, 2020) and cases (Jul 1st, 2020) are 277 and 4,808 respectively. The peak deaths and cases in the second curve occur on Apr 1st, 2021 and are 463 and 8,015 respectively. The numbers in the second peak reflect the relaxation, transmission in isolated individuals, and transmission of more virulent variant. The model described 75,700 deaths which is 98.1% of the 77,165 observed fatalities. Further estimation of deaths from Apr 5th to Oct 2021 using the model parameters estimate the number of deaths at 49,910.

Wells et al. developed an analytical approach to evaluate quarantine and testing strategies to reduce importation of VOC, compared with border closure in 31 pairs of European countries.[71] Extending the duration of post travel quarantine was suggested, along with travel restrictions. The impact of Alpha and Beta was evaluated using current estimates of their frequencies of circulation within pairs of destination-origin countries and quantified the sufficient duration of travel quarantine with the goal of no net increase in the incidence of VOCs or wild-type. At the time of analysis, Alpha was widespread across Europe, therefore sufficient quarantine and testing is similar to general COVID-19 transmission. In contrast, Beta prevalence is lower with greater variation across European countries. Consequently, sufficient quarantine and testing would need to be more extreme than general wild-type transmission. Extending the duration of post travel quarantine is suggested, along with travel restrictions when substantial asymmetry exists in the number of travelers and prevalence of cases between countries. Preventing both increased general transmission and increased transmission of VOCs within-country due to international travel would require lengthier quarantines and more travel restrictions compared to preventing general transmission alone. The sufficient duration of travel quarantine increased substantially (median of six days vs median of zero days).

Frequency or change of testing for VOC

We identified a wide range of studies evaluating different VOC genome sequencing strategies, antigen tests or assays and primers for use in rapid PCR tests in our search. However, studies regarding testing were only included in this report if they explicitly identified implications for potentially modifying existing public health testing measures. Two studies were deemed relevant for this sub-question.

Abdel-Sater et al. describe a primer set that could be used in a rapid, low-cost screening protocol to confirm deletion of mutations Δ69/ Δ70 in the spike gene and Δ106/ Δ107 in the NSP6 gene to detect VOCs.[79] The method was tested using 20 clinical samples from previously tested SARS-CoV-2 positive patients, 16 of which were S-negative and four were S-positive. The primer set successfully identified the presence and absence of S deletions Δ69/ Δ70 in 100% of both the S-negative and S-positive profiles. This protocol may be of particular benefit in areas where access to laboratories to conduct genome sequencing is limited.

A rapid test widely available in Canada, the PanBio SARS-CoV-2 Rapid Antigen Test (RTD), was evaluated between Nov 17th-20th, 2020, by Akingba et al. in 677 patients attending one of 6 mobile clinics in Nelson Mandela Bay, South Africa.[80] At this time, South Africa was experiencing their second wave of the pandemic and Beta was responsible for 84% of infections in Nelson Mandela Bay. The same nasopharyngeal swab used in the RTD was also sent for PCR for direct comparison. The antigen test had an overall sensitivity of 69.17% (95%CI:61.44,75.80) and specificity of 99.02% (95%CI:98.78,99.26) across both VOC and wildtype. However, sensitivity improved in clinical samples with a high viral load (CT), with 100% detection when CT was <20, 95.5% when CT was 20-25 and 89.3% when CT was between 26-30.

Contact tracing

No studies were identified related to impact of VOC on contact tracing.

Changing approach to outbreak management

Thirteen studies reported on different approaches to outbreak management across a range of settings and outcomes. Four studies discussed managing outbreaks through stricter lockdowns. Four studies reported on the impact of physical distancing in different settings on outbreak management. Five studies reported on outbreak management through various public health measures in different community settings.

Managing outbreaks through lockdown measures

Graham et al. conducted an ecological study to explore the rate of infection and transmissibility of Alpha in the UK.[29] Between Sep 28th-Dec 27th, 2020, Alpha was found to increase R_t (effective reproduction number) to 1.35 compared with historical SARS-CoV-2 variants. However, following a strict lockdown between Dec 19th, 2020 and Jan 5th, 2021 the estimated R_t of Alpha had decreased to 0.8 in three regions in England where 80% of infections were related to the variant.

A modeling study conducted by Scherbina et al. identified the impact of different lockdown measures on community infection rates of Alpha with assessment of future monetary costs, in the form of missed work days, direct medical costs and the value of lost lives.[67] The authors suggested that a strict lockdown could reduce the transmission rate to below one (R_0=0.933), while a less strict lockdown would see the reproductive number exceed one (R_0=1.66) and worsen the impact across all measures.

Ahn et al. evaluated a multi-model optimization (MMO) policy framework which included a range of forecasting models, multiple cost models of NPIs and health outcomes, and a 4-level pandemic containment strategy to determine the optimal pandemic response policy for all 50 states in the US.[72] The MMO outperformed the single model in terms of policy optimization and the performance remained robust when challenged with Alpha. With the introduction of Alpha as the dominant strain in Mar 2021, the MMO policy response indicates most states would stay longer in level 3 and 4 containment (higher levels of restriction) and the total 12-month cost would increase by 37% if Alpha becomes the predominant strain across all 50 states, highlighting the importance of tracking and containment.

Kühn et al. modeled the effect of regionally differentiated restrictions and systematic testing of commuters on the overall incidence and the frequency of necessary lockdowns. In low incidence settings, a combination of locally imposed lockdowns and systematic testing would contain isolated local outbreaks.[73] Local lockdown plus frequent commuter testing (2-5 times per week) and quick implementation of outbreak management in response to local outbreaks within one week were suggested as most effective means for reducing incidence of COVID-19, based on transmission characteristics of the Alpha VOC.

Managing outbreaks through physical distancing

Borges et al. associated the implementation of public health measures, namely physical distancing, in Portugal with a decrease in proportion of SGTF/SGTL (i.e. an indicator of Alpha).[61] The proportion of Alpha was forecasted to reach 65% (95% CI: 62-68) of circulating SARS-CoV-2 cases by mid Feb 2021. Following implementation of public health measures in mid Jan 2021, the country observed a declining trend with proportions remaining below 50% in early Mar 2021.

A study by Buchan et al. conducted in Ontario, Canada compared the number of secondary attack rates among households with reported VOC cases versus households with non-VOC index cases.[35] VOC household secondary attack rates were 1.28 times higher versus non-VOC. Further, the secondary attack rates were observed to be higher for asymptomatic index cases (RR=1.91, 95%CI:0.96,3.80) and pre-symptomatic cases (RR=3.41, 95%CI:1.13,10.26). The increased transmission of VOC in households particularly for asymptomatic and pre-symptomatic cases suggests a need to support strict household quarantine guidance for exposed persons and isolation on development of any symptoms, and provision of supports for isolation, testing, outside the home quarantine support and monitoring of cases. Similarly, Chudasama et al. examined household clustering among 57,382 SARS-CoV-2 cases reported in England between Oct 1st and Dec 15th, 2020, identifying increased odds of household clustering with Alpha (OR=2.13, 95% CI 1.98-2.31) compared with wild-type variant.[30] This was reduced slightly (OR=1.88, 95% CI 1.67-2.08) when adjusted for region, time, age, sex, race and ethnicity of the index cases.

The understanding of the importance of household transmission in VOC is evolving, with a study conducted by Zimerman et al. in Brazil, reporting contrasting findings based on mobility data.[69] In their study comparing prevalence of the Gamma variant with mobility based social isolation data, authors found that prevalence of Gamma actually increased when individuals remained within 450m of their home. Policies and practices around in home isolation and adherence to in home isolation was not assessed. This study therefore highlights the need to tailor public health measures to specific populations and that vigilance regarding household transmission is warranted.

Managing outbreaks through other public health measures

Moore et al. extended a model of SARS-CoV-2 dynamics that matched UK data from seven National Health Services regions in England and Scotland, Wales and Northern Ireland to include the consequences of changing NPIs, the Alpha variant, and vaccination patterns.[76] When vaccine protection is high (85%), with all second doses administered, there is a substantial decrease in R, although it does not fall below 1. If NPIs are completely lifted in Jan 2022, with 85% protection, an infection wave is predicted which will result in 21,400 deaths (95% CI 1,480-57,600).

Shattock et al. used an individual-based transmission model of SARS-CoV-2 infection to represent the impact of different vaccine schedules and NPI strategies on the COVID-19 pandemic in Switzerland.[77] Analysis suggests that maintaining NPIs in place in early Mar-Sep 2021 will still result in an increase in daily cases, hospitalizations, and deaths leading to the third wave. The size of the third wave is dependent on both vaccination rates and NPI schedules. With larger steps or quick relaxations, the ICU occupancy will increase above 25% capacity. Increasing vaccination rates from 50,00 to 100,000 doses per day results in a halved and slightly earlier third wave peak and coupled with a gradual relaxation scenario, this rate results in substantial reduction in ICU occupancy and deaths until Sep 2021.

Bosetti et al. used a mathematical model to understand how the emergence of more transmissible variants such as Alpha, implementation of NPIs, and vaccine roll-out schedules could influence the direction of the pandemic in the coming months in Metropolitan France.[78] As Alpha becomes the dominant variant, a strengthening of control measures to strong intensity for 6 weeks starting on Mar 22nd, may shift the pandemic rebound to a later time when a larger portion of the population has been vaccinated. Increasing mRNA vaccine rate from 200,000 to 400,000 doses per day and AstraZeneca from 100,000 to 125,000 doses per day and better vaccine coverage (90%) in those >75 years of age after Apr 1st, 2021 would decrease hospital burden by 9-33%.

In a modeling study conducted by Piantham and Ito, it was estimated that Alpha has a reproductive advantage of 33.7% over non-VOC.[66] Authors reported that public health measures should therefore be strengthened by 33.7% to account for the increased transmissibility of Alpha.

Smith et al. assessed the impact of temperature on VOC prevalence in the UK.[68] Warmer temperatures were found to be associated with lower VOC transmission, but this was only secondary to the impact of public health measures.

Question 2: Health System Arrangements

Health system impacts due to VOC were reported in 25 studies. The sections below are divided by sub-objectives and are discussed in relation to the relevant objective. Overall, 19 studies related to health system impacts were eligible for critical appraisal. Two were appraised as low quality,[49,50] 10 as medium,[34,36,37,39–41,43–45] and seven as high.[26–29,31–33,38] Figure 4 provides an overview of studies which explored various aspects of capacity planning (i.e., sub-question 2A) in relation to country or region. Due to non-existent or insufficient studies in the other sub-objectives, they were not visualized.

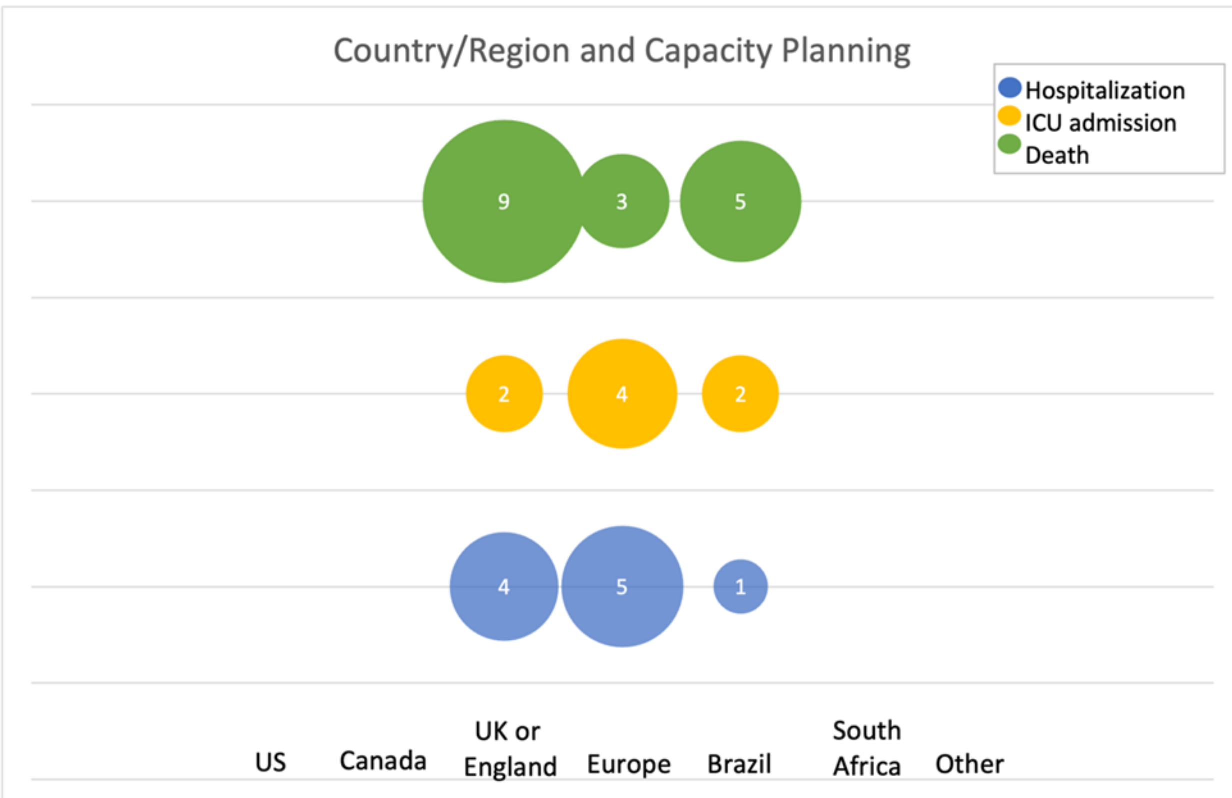

Figure 4. Overview of country or region of data collection and capacity planning sub-topics up to May 11, 2021

Question 2A: Adjusting capacity planning to accommodate changes in the risk of re-infection and the risk of severe disease (e.g., hospitalization, admission to ICU, and death).

Key findings for consideration include:

- **NPI (e.g., curfew, lockdown) may minimize risk of exceeding optimal hospital capacity due to VOC infections**
- **Emerging data is somewhat conflicting but overall suggests there is an increase in hospitalization and severity of illness due to VOC. Vaccination patterns, the populations in which VOC are transmitting (eg.., VOC transmission by age as an independent predictor of severity), and health system strain may influence these parameters.**
- **Findings are mixed on the impact of VOC on intensive care unit admissions**
- **More studies (n=12) found an increased risk of mortality compared to studies that found no change (n=6). In studies that reported an increase in mortality, Alpha was found to increase the risk between 15% to 67% compared to non-VOC. The**

impact of rationed critical care and health system capacity strain on mortality may be difficult to separate in some of these studies

While most studies related to this sub-question reported on the impact of VOC on hospitalization, admission to ICU and death (see Table 6), Haas et al. also discussed it in light of the impact of vaccine efficiency (VE).[38] Haas et al. conducted the first nationwide estimates on the effectiveness of two doses of the Pfizer vaccine against a range of SARS-CoV-2 outcomes, including hospitalization and deaths, in Israel. The Haas study was appraised as high quality in the critical appraisal. Between Dec 2020 and Apr 2021, there were 232,268 COVID-19 infections, 154,648 (66.6%) in people over 16 years, in Israel. There were 7,694 hospitalizations, of which 4,481 were severe and critical, and 1,113 deaths in people over 16 years. The prevalence of Alpha of tested cases was 94.5%. During the study period, 72.1% of people over 16 years and 90.0% of people over 65 years received two doses of Pfizer. Among COVID-19 related hospitalizations, most were in people unvaccinated (5,526, 71.8%) with a small number of admissions who had received two doses in the prior seven days (596, 7.7%). The incidence rate (IR) (per 100 000 person-days) of COVID-19 among people over 16 years was 91.5 in unvaccinated and 3.1 in vaccinated at least seven days after the second dose. The adjusted VE was 95.3% (95% CI 94.9-95.7) against COVID-19 infection. Adjusted VE against COVID-19 hospitalization was 97.2% (95% CI 96.8-97.5) and VE against severe and critical hospitalization was 97.5% (95% CI 97.1-97.8). In relation to deaths, 715 (64.2%) were in unvaccinated individuals and 138 (12.4%) in individuals who had received the second dose at least seven days ago. Adjusted VE against death was 96.7% (95% CI 96.0-97.3). Vaccine efficiency estimates against all outcomes were slightly higher when measured 14 days after the second dose than VE estimates after seven days. However, overall, this study suggested there is high VE seven days after the second dose of Pfizer against hospitalizations, severe and critical hospitalizations, and deaths. Hass et al. also report that vaccine effectiveness against death was 96.7% at 7+ days and 98.1% at 14+ days after the second dose, compared to 77.0% 14-21 days after the first dose.[38]

Domenico et al. provided a mathematical model to estimate the role that curfew measures could have on hospitalization in France.[51] They found that if the epidemic progressed under curfew conditions (6pm nightly, implemented nationwide Jan 16th) before school holidays and vaccination is accelerated, hospital capacity would be reached around week 13 in France (which had 2.2% Alpha penetration), week 12 in Île-de-France (which had the highest Alpha penetration, 6.9%), and week 14 in Nouvelle Aquitaine (which had the lowest Alpha penetration, 1.7%). The partial relaxation of social distancing (estimated at 15% increase in effective reproduction number) would shorten these estimates by at least 1 week. Stronger social distancing, equivalent to the efficacy measured during the second lockdown (estimated 15% reduction in effective reproduction number), would maintain hospitalizations below the peak of the second wave in Île-de-France and Nouvelle Aquitaine but would not be enough to avoid a third wave in France, even under accelerated vaccination (100k-200k doses/day). Accelerated (200,000 first doses/day) and optimistic vaccination rollouts (300,000 first doses/day) would reduce weekly hospitalizations by about 20% and 35% in week 16 (i.e., Apr 19th-25th, 2021) compared to a stable vaccination campaign without acceleration (100,000 first doses/day). It is important to use proximal indicators under different community conditions to inform health system planning.

Table 6. *Summary of findings for capacity planning and health systems arrangements*

	Hospitalization/Severity	Admission to ICU	Death
Increased due to VOC	• After adjusting for sex, age, region and comorbidities, individuals with Alpha were 1.6x more likely to be hospitalized vs wild type (adjusted OR of 1.64, 95%CI, 1.32-2.04). Individuals with Alpha had a 64% increased risk of hospitalization. (Bager et al., Denmark, Jan-Feb 2021, medium quality)[34] • There was a statistically significant increase in the hospitalization rate for regions in the top 10% percentile of reported VOC cases. Regarding time dynamic effects, the hospitalization rate was ~38% higher in high VOC regions (9+ VOC cases) compared to their pre-VOC observation (Mitze and Rode, Germany, Jan-Feb 2021, no appraisal)[81] • In wave two (high Alpha prevalence), the number of admissions increased (35.1% v 54.8%) vs. with wave one (non-Alpha). Patients with non-Alpha and Alpha were not significantly different in terms of age or ethnicity, but where more likely to be female, obese but less frail. On admission, Alpha patients were more likely to be hypoxic. (Snell et al., UK, Mar 2020-Feb 2021, medium quality)[41] • There was a significant association between infection with Alpha and hospitalization in UK within 14 days of positive test (OR: 1.39, 95%CI 0.98-1.98, p=0.07), however, the length of hospital stay was similar. After adjusting for sex, age, ethnicity, residential property classification and week of specimen date, the risk of hospitalization was higher in Alpha cases compared to wild type cases (HR 1.34, 95% CI:1.07-1.66, p=0.01). (Dabrera et al., UK, Oct-Dec 2020, medium quality)[37]	• There was an estimated increase of 1.29 [CI: 0.5, 2.1] additional COVID-19 patients in intensive care per 100,000 population, which is a 42% increase compared to the hospitalization rate pre-VOC (combined). (Mitze and Rode, Germany, Jan-Feb 2021, no appraisal)[81] • In both the adjusted and unadjusted analysis, the primary care group had a higher risk of admission to critical care for Alpha patients compared with the non-Alpha patients (adjusted HR: 1.99; 95% CI: 1.59 - 2.49). In the critical care cohort, a lower risk of admission for critical care in the Alpha group was mainly accounted for after adjustment for date of admission to critical care (HR: 0.84, 95% CI: 0.64 - 0.99). (Patone et al., England, Nov 2020-Jan 2021, medium quality)[40] • VOC cases were more likely to be admitted to the ICU than non-VOC cases (Alpha: 1.4%, p=.002; Beta: 2.3%, p=0.001; Gamma: 2.1%, p=0.005 vs. non-VOC: 0.6%). In an unmatched analysis, VOC were 2.2-3.3 times more likely to be admitted to ICU than non-VOC. (Funk et al., 7 Europe, Sep 2020-Mar 2021, high quality)[31]	• An increase of 0.1 in the proportion of Alpha was related with a 15.3% increase in the total number of deaths (Jabłońska et al., Europe, Jan-Feb 2021, medium quality)[39] • The mortality hazard ratio for people with Alpha compared to those with previous variants was 1.64 (95% CI 1.32 to 2.04). In this community-based, relatively low-risk group, there was a 32% to 104% increased risk of death. (Challen et al., UK, Oct 2020-Feb 2021, high quality)[26] • The estimated hazard ratio for Alpha was 1.55 (95% CI 1.39–1.72), indicating that the hazard of death in the 28 days following a positive test was 55% (39– 72%) higher for Alpha than non- Alpha. Correcting for misclassification and missing SGTF status, this increased to 61% (42–82%). (Davies et al., UK, Nov 2020-Feb 2021, no appraisal)[82] • Alpha was associated with 67% increased risk of death at 28 days after a positive COVID-19 test (HR: 1.67, 95%CI, 1.34-2.09). (Grint et al., England, Nov 2020-Jan 2021, high quality)[28] • There is an 18% increase in fatality risk for Alpha compared to non-Alpha with a Case Failure Rate (CFR) at 1.18 (95% CI: 0.40, 3.28). (Zhao et al., UK, Sep 2020-Jan 2021, no appraisal)[83] • There was an 8.2% increase in CFR (15.6% for Gamma from 7.5% original) in maternal deaths out of maternal cases, with the first three months of 2021 accounting for 46.2% of death thus far. (Takemoto et al., Brazil, Mar 2020-Apr 2021, medium quality)[45] • There was a 33% increase in mortality when considering the effect of Alpha in England. (Ackland et al., UK, Sep 21st-Nov 5th, 2020, no appraisal)[84] • While there were no changes in CFR in children or adolescent, all other groups above 20 years of age had statistically significant increases in CFR when diagnosed in Feb 2021

	Hospitalization/Severity	Admission to ICU	Death
	• Individuals with Alpha (SGFT-positive) were more likely to be hospitalized (OR 3.44, 95%CI 1.76-6.75) than non- Alpha (SGFT-negative) cases (Loconsole et al., Italy, Dec 2020-Mar 2021, high quality)[33] • These was an increase in proportion of patients with severe COVID-19, from 5% in the first wave to 10% in the second wave (associated with Gamma). There was no difference between sex but the proportion of patients with pre-existing conditions among severe cases was higher in the second wave (33%) compared to the first (25%). (Freitas et al., Brazil, Nov 2020-Feb 2021, medium quality)[43] • Significantly higher proportion of VOC cases were admitted to the hospital compared to non-VOC (Alpha 11.0%, Beta: 19.3%, Gamma: 20.0% vs. non-VOC: 7.5%, p<0.001). In an adjusted OR in matched multivariable analysis found that VOC cases had higher chance of hospitalization than non-VOC cases (aOR: 1.6-4.2) (Funk et al., 7 European countries, Sep 2020-Mar 2021, high quality)[31]		(Gamma) as opposed to Jan 2021 (non-Gamma) (De Oliveira et al., Brazil, Jan-Feb 2021, low quality)[50] • Each geographical region of Brazil varied in terms of their mortality over the three periods, with the North region being the hardest hit, experiencing a collapse in the provision of healthcare in the first wave and last periods (Gamma) with high mortality in all age groups. (De Andrade et al., Brazil, Feb 2020-Feb 2021, low quality)[49] • The proportion of women who died from COVID-19 increased from 34% in the first wave (non-VOC) to 47% in the second wave (Gamma). Additionally, there was an increase in proportion of deaths for individuals in all age groups (20-59 years) in both sexes. (Freitas et al., Brazil, Apr 2020-Jan 2021, medium quality)[43] • The CFR was higher across all groups after the emergence of Gamma, with ages groups of 20-39 and 40-59 having a higher proportional increase in the second wave than the first wave because of Gamma prevalence. Additionally, people without pre-existing conditions experienced a higher proportional increase in death in the second wave (22%) than the first (13%) (Freitas et al., Brazil, Nov 2020-Feb 2021, medium quality)[44]
No change between VOC and wild-type	• After correcting for mean age, sex, ambient temperature, and humidity, there was no association between Alpha and the number of symptoms reported over a 4-week period after a positive test, the number of hospitalizations, length of symptom duration or proportion of asymptomatic cases (Graham et al., Scotland, Wales and England, Sep-Dec 2020, high quality)[29] • There was no significant difference in time to hospital admission from symptom onset for patients with Alpha than for patients without Alpha. (Frampton et al., UK, Nov-Dec 2020, high quality)[27]	• In terms of intensive care, the numbers were too small to be conclusive on the association with Alpha (13 ICU among 128 Alpha admissions (10.2%) versus 115 ICU among 1090 admissions (10.6%) after infection with other lineages. (Bager et al., Denmark, Jan-Feb 2021, medium quality)[34] • There was no significant difference between those admitted to the ICU before Alpha was dominate (23%) compared to after, (26% and 35%, p=0.374). For ICU patients, neither the severity score at	• There was no difference in the percentage of patients with and without Alpha who died within 28 days (16% Alpha vs. 17% non-Alpha, p=0·74). There was no excess mortality risk associated with Alpha compared with non- Alpha in unadjusted analyses (PR 0·85 [95% CI 0·52–1.41] for Alpha vs non-Alpha) or adjusted analysis (PR 1·12 [95% CI 0·71–1·78]). (Frampton et al., UK, Nov-Dec 2020, high quality)[27] • In the unadjusted analysis, there was no difference in 28-day mortality risk for Alpha compared to non-Alpha patients, but after adjusting for confounders, there was a higher risk of 28-day mortality in Alpha patients (adjusted HR: 1.59; 95% CI: 1.25- 2.03), mainly explained by age (HR: 1.53, 95% CI: 1.28-

	Hospitalization/Severity	Admission to ICU	Death
	• Pairing 29 Alpha cases to 58 controls (non-Alpha) on age and gender, there was no significant difference on time from first symptoms to ED admission or severity or need for immediately ICU management. (Courjon et al., France, Dec 2020-Feb 2021, medium quality)[36]	admission (SAPSII) nor the depth of the respiratory distress seemed to increase by the variant (Courjon et al., France, Dec 2020-Feb 2021, medium quality)[36] • While there was variation in the age profile of hospitalized patients between Feb 2020-Feb 2021, but there was no evidence of an increase in hospitalization in the last period (related to high Gamma) for adults between 18 and 50 years (De Andrade et al., Brazil, Feb 2020-Feb 2021, low quality)[49] • There was no difference in ICU admissions or length of admission for maternal patient before or after the emergence of Gamma (Takemoto et al., Brazil, Mar 2020-Apr 12th, 2021, medium quality)[45] • There was no significant difference in length of critical care stay or proportion of patients admitted to critical care with Alpha & Beta compared to non-VOC (Garvey et al., England, Dec 15th-31st, 2021, high quality)[32]	1.82 with adjustment for age alone). In the critical care cohort, after adjusting for confounders, critical care mortality did not differ significantly between Alpha and non-VOC Alpha groups (adjusted HR: 0.93, 95% CI 0.76-1.15). (Patone et al., England, Nov 2020-Jan 2021, medium quality)[40] • In a matched cohort analysis, there was no evidence of an association between Alpha and non-Alpha on death within 28 days of COVID-19 positive test (OR: 0.90, 95%CI 0.57-1.41, p=0.64), with similar median time between positive test and death (8 days for Alpha and 9 days for non-Alpha (Dabrera et al., UK, Oct-Dec 2020, medium quality)[37] • There was no difference found in the death rate between Alpha (0.6%) and non-Alpha individuals (0.9%), p=0.64 (Loconsole et al., Italy, Dec 2020-Mar 2021, high quality)[33] • There was no difference in mortality between individuals with Alpha & Beta compared to non-VOC (Garvey et al., England, Dec 15th-31st, 2021, high quality)[32] • There was no increased risk of death for any of the VOC (Alpha, Beta or Gamma) compared to non-VOC. (Funk et al., Europe, Sep 2020-Mar 2021, high quality)[31]

Hospitalization/Severity

Ten studies reported on health system impacts related to hospitalization and severity of illness, including three new studies identified in this update. Seven studies across Europe and Brazil reported increases in hospitalization and/or severity of illness associated with VOC compared to the wild type. All three new studies report an increase in risk of hospitalization and severity, resulting in seven studies finding an increased risk of hospitalization due to VOC. Three studies found no difference. Among the ten studies that reported on hospitalization, five were appraised as medium quality studies[34,36,37,41,43] and four as high-quality studies[27,29,31,33] (one not appropriate for appraisal). Table 6 provides a summary of findings with additional detail provided in text below.

Increases in risk of hospitalization/severity

Bager et al. conducted an observational cohort study of 35,887 SARS-CoV-2 positive individuals in Denmark from Jan 1st to Feb 9th, 2021.[34] While Denmark was in a lockdown after Dec 16th and it was effective in reducing case numbers and hospital burden, Alpha increased during this time and was found to have a reproduction number of 1.25 on Feb 16th. 11.6% of their sample had Alpha and the proportion of individuals with Alpha increased from 1.9% to 45.1% during their data collection period. They found no significant difference in hospitalization between Alpha vs non-Alpha in their crude analysis (OR 0.87; 95%CI, 0.72-1.05), but after adjusting for sex, age, region and comorbidities, Alpha was 1.6 times more likely to be associated with hospitalized than wild type (adjusted OR of 1.64, 95%CI, 1.32-2.04). They concluded that individuals infected with Alpha had a 64% increased risk of hospitalizations compared to individuals infected with other lineages.

An epidemiological and modeling study was conducted in Germany on the 7-day incidence rate (per 100,000 population), and the hospitalization rate (per 100,000 population).[81] All three VOC were combined for power due to the low spread in Germany at the time of the study – by Feb 4th, 2021, 204 out of 401 (50.1%) of the HUT-3 regions had at least one VOC case. Hard-hit cities included Flensburg where the 7-day incidence rate drastically increased in Jan 2021 relative to the average development in Germany due to illegal parties and NRW cities (Cologne, Leverkusen, and Duren). The hospitalization rate for Flensburg shows a significant increase ~16 days after treatment start (considered one week before the first VOC case). However, this should be interpreted with caution as it was calculated on a relatively small number of hospitalized patients per 100,000 population at the local area level (i.e., 2 patients before VOC vs. 8 cases after VOC). Interestingly, the treatment effects estimate, for the NRW cluster, indicated an increase in the 7-day incidence rate by ~40% but no significant increase in hospitalization rates. Difference-in-difference analysis point to positive but insignificant correlations for all regions but in regions with an early VOC reporting before Jan 22nd, they found a statistically significant increase in the hospitalization rate for regions in the top 10% percentile of reported VOC cases. Regarding time dynamic effects for the hospitalization rate, significant effects were found ~15 days after treatment start for regions with 9+ VOC cases. After 20 days, the hospitalization rate was ~38% higher in high VOC regions compared to their pre-VOC observation. This corresponds with two additional patients in intensive care per 100,000 in high VOC regions, suggesting that hospitalization tends to grow over time with Alpha cases.

Snell et al. conducted a retrospective cohort study in the United Kingdom on 2,341 individuals admitted to the Guy's Hospital and St. Thomas Hospital within 14 days following a positive test during first wave (Mar 13th-May 12th, 2020, n=838, considered non-Alpha) and second wave (Oct 2020-Feb 2021, n=1,503, predominantly Alpha).[41] In wave two, the number of admissions increased compared with wave one (54.8% vs. 35.1%). In the second wave, Alpha made up 83% of all sequenced isolates and 85% of sequenced isolates from admitted cases. Snell et al. examined differences between the two waves in terms of patient composition. Comparing admitted patients with Alpha (n=400) or non-Alpha (n=910), the groups were not significantly different in age (62 years vs 64 years, p=0.22) or ethnicity. However, patients with Alpha were more likely to be female (48.0% vs 41.8%, p=0.01), less likely to be frail (14.5% vs 22.4% p=0.001), more likely to be obese (30.2% v 24.8%, p=0.048), and more likely to be hypoxic on admission (70.0% vs 62.5%, p=0.029), the main indicator of severe disease, than non-Alpha patients.

Dabrera et al. conducted a matched cohort study in the UK to explore whether Alpha was associated with more severe clinical outcomes compared to wild type COVID-19.[37] In 5,642 cases, 131 individuals had a hospital admission within 14 days of their positive test: 76 (2.7%) VOC and 55 (1.9%) wild-type cases (p=0.006). There was a non-significant association between infection with Alpha and hospitalization within 14 days of positive test (OR: 1.39, 95%CI 0.98-1.98, p=0.07) and the length of hospital stay was comparable (Alpha median length of stay (LOS) 5 days (IQR 3-10, range 0-37) vs wild type LOS 8 days (IQR 4-13.5 days, range 0-31), p=0.07). In univariable analysis, Alpha infection and risk of hospitalization within 14 days were not associated (HR: 1.07, 95%CI: 0.89-1.29, p=0.48); however, adjusting for potential confounders (sex, age, ethnicity, residential property classification and week of specimen date) resulted in the risk of hospitalization being higher for Alpha cases compared to wild type cases (HR 1.34, 95% CI:1.07-1.66, p=0.01).

Loconsole et al. conducted a cross-sectional study to evaluate the spread of Alpha in southern Italy from Dec 2020 to Mar 2021, using SGTF as proxy.[33] They found that Alpha increased in prevalence from 0% in the last week of Dec 2020 to 69.2% in

Mar 2021. Individuals with Alpha were more likely to be symptomatic ($p<0.0001$) and were more likely to be hospitalized ($p<0.0001$) than non-Alpha individuals. Using multivariate logistic regression, the OR was 3.44 (95% CI-1.76-6.75) for hospitalization, with the authors suggesting that Alpha results in a worse evolution of infection.

Freitas et al. conducted an epidemiological analysis describing the severity and mortality profile of COVID-19 cases in southern Brazil, considering two periods before (Nov-Dec 2020) and after the emergence of variant Gamma (Feb 2021).[44] They found that there was an increase in the proportion of patients with severe COVID-19, which increased from 5% in the first wave to 10% in the second wave, which was associated with Gamma. The authors found no difference in mortality between sex of patients, but they did find that proportion of patients with pre-existing conditions among severe cases was higher in the second wave (33%) compared to the first (25%). Additionally, the proportion of people under 60 with severe COVID-19 was higher in the second wave (47%) than the first wave (39%). The increase in severity of COVID-19 outcomes occurred in people aged 20 to 59 years, ranging from 5.5 times higher for 20–39-year-olds to 7.7 times higher in 40–59-year-olds.

Funk et al. explored differences in VOC cases (Alpha, Beta and Gamma) to non-VOC cases in Cyprus, Estonia, Finland, Ireland, Italy, Luxembourg and Portugal between Sep 20th, 2020 to Mar 14th, 2021.[31] They found that a significantly higher proportion of VOC cases were admitted to the hospital compared to non-VOC (Alpha: 11.0%, Beta: 19.3%, Gamma: 20.0% vs. non-VOC: 7.5%, $p<0.001$). In an adjusted OR in matched and unmatched multivariable analysis found that VOC cases had higher chances of hospitalization than non-VOC cases (aOR: 1.6-4.2 matched and 1.7-3.6 unmatched). There was variation in the risk of hospitalization based on age and VOC. People aged 20–59 years had 2.3 to 3.0 times greater odds of hospitalization with Alpha compared with non-VOC cases. The highest odds for hospitalization for Beta was 3.5 to 3.6 times higher for age groups 40-79 years compared to non-VOC cases. Finally, for individuals aged 20-79, the risk of hospitalization was 3.0 to 13.1 times higher.

<u>No changes in risk to hospitalization/severity</u>

Graham et al. conducted a longitudinal cohort study on 36,920 users of the COVID symptom study mobile app in Scotland, Wales and seven regions in England who tested positive for COVID-19 between Sep 28th-Dec 27th, 2020 while the proportion of Alpha was exploding, along with surveillance data from 98,170 sequences from the COVID-19 UK Genetics Consortium (COG-UK), 16% of which were Alpha.[29] Therefore this study took place before health system strain was excessive. They compared the proportion of Alpha in each region and the proportion of reports per week for each symptom, disease burden and self-reported hospitalization. After adjusting for mean age, sex, ambient temperature, and humidity, there was no association between Alpha and the number of symptoms reported over a 4-week period after a positive test, the number of hospitalizations, long symptom duration or proportion of asymptomatic cases.

Frampton et al. conducted a cohort study in the UK to describe emergence of Alpha in two North Central London hospitals including clinical outcomes in patients with and without the VOC.[27] Of the 341 samples sequenced and positive for SARS-CoV-2, 198 (58%) were Alpha and 143 (42%) were non-Alpha. Eighty-eight (44%) of Alpha patients received oxygen by mask or nasal prongs compared with 42 (30%) of non-Alpha patients. While risk of hospitalization within 14 days of a test and time to hospital admission from symptom onset were similar, Alpha patients were younger, had fewer comorbidities and more likely to be from an ethnic minority compared to non-Alpha patients.

Courjon et al. conducted an observational study in France (Nice) with 1,247 patients admitted to the emergency department to analyze changes in clinical profile and outcomes.[36] Of those admitted by Feb 22nd, 29 had Alpha (12.5%). This reflects the prevalence of Alpha in the area, which increased from 2.6% in Dec 2020 to 79.1% in Feb. In hospitalized patients, the mean age of admission was significantly lower in the period between Feb 8th-22nd (considered high Alpha) at 59.2 years (SD=14.0) compared to Dec 7th-21st (no/low Alpha) at 70.7 years (SD=13.6), $p < 0.001$. Patients were also more likely to have no comorbidity (42% vs. 16%, $p = 0.04$). When pairing 29 cases to 58 controls on age and gender, there was no significant difference between Alpha patients and non-Alpha on time from first symptoms to emergency department admission or severity or need for immediate ICU management.

VOC impact on Admission to ICU

Eight studies reported on health system impacts related to admission to ICU. Three studies across Europe reported increases in admission to ICU with VOC compared to the wild type; however, another five studies found no difference. Among the three new studies, one found an increase in ICU admissions and two found no difference. Among the eight studies that reported on admission to ICU, two were appraised as high quality,[31,32] four were medium quality,[34,36,40,45] and one as low quality[49] (one not appropriate for appraisal). Table 6 provides a summary of findings with additional detail provided in text below.

Increases in ICU Admission

Mitze and Rode conducted an epidemiological and modeling study in Germany on the hospitalization rate per 100,000 population.[81] All three VOC were combined for power due to the low spread in Germany at the time of the study. Mitze and Rode found an increase of 1.29 [CI: 0.5, 2.1, $p<0.05$] additional COVID-19 patients in intensive care per 100,000 population, which is a 42% rise in hospitalization in VOC regions compared to pre-VOC regions (3.08 patients in intensive care per 100,000 population).

Patone et al. conducted a retrospective cohort study in England to explore the risk of critical care admission for patients with Alpha compared with wild type.[40] They compared two cohorts: a ‘primary care cohort’ which included patients in primary care with a positive community COVID-19 test reported between Nov 1st, 2020-Jan 26th, 2021 (n=381,887, 52.0% Alpha, and 712 were admitted to critical care, 63.1% Alpha). The ‘critical care cohort’ were patients admitted for critical care with a positive community COVID-19 test reported with an identified SGTF status between Nov 1st, 2020 and Jan 27th, 2021 (n=3432, 58.8% Alpha). In both the adjusted and unadjusted analysis, the primary care group had a higher risk of admission to critical care for Alpha patients compared with the non-Alpha patients (adjusted HR: 1.99; 95% CI: 1.59 - 2.49). Considering time varying HR, it increased from 1.20 (95% CI: 0.58 - 2.48) at one day to 3.29 (95% CI: 1.17 - 6.29) at fifteen days after a positive test. There was no significant interaction between Alpha and sex, ethnic group, or age group. Adjusting only for the date of positive test did not account for the increased risk of admission for critical care (adjusted HR 1.28 95% CI: 1.05 - 1.56). In the critical care cohort, Alpha ICU patients tended to be younger (means 57.8 versus 59.3 years) and less obese than non-Alpha patients. Acute severity of illness, as measured by the APACHE II score, tended to be lower in Alpha patients, but the proportion receiving invasive mechanical ventilation within the first 24 hours of critical care and organ support was similar between the two groups. After adjusting for date of admission to critical care, the lower risk of admission for critical care in the Alpha group was accounted for (adjusted HR: 0.84, 95% CI: 0.64 - 0.99).

Funk et al. found that VOC cases were more likely to be admitted to the ICU than non-VOC cases (Alpha: 1.4%, p=.002; Beta: 2.3%, p=0.001; Gamma: 2.1%, p=0.005 vs. non-VOC: 0.6%).[31] In an unmatched analysis, VOC were 2.2 to 3.3 times more likely to be admitted to ICU than non-VOC. Interestingly, ICU admission did not differ for Alpha but increased for Beta (aOR: 8; 95% CI: 3.7–17.3) only for those aged 40–59 years. For individuals aged 40 or older, there was a 2.9 to 13.9 times higher odds of ICU admission with Gamma than non-VOC.

No Changes in ICU Admission

Bager et al. found an increased risk of general hospitalization due to Alpha, yet the numbers were inconclusive on the impact of Alpha on intensive care admission due to small sample sizes.[34] They reported only 13/128 ICU among Alpha admissions (10.2%) compared to 115/1090 ICU admissions after infection with wild type (10.6%).

Courjon et al. found no significant difference between percentage of COVID-19 hospitalized patients admitted to the ICU before Alpha was dominate (23% [Dec 7th-21st, 2021]) compared to after (26% [Jan 24th-Feb 7th, 2021] and 35% [Feb 8th-22nd, 2021]), p=0.374.[36] For ICU patients, neither the severity score at admission (SAPSII) nor the depth of the respiratory distress seemed to increase with Alpha.

De Andrade et al. conducted an epidemiological study during the first year of the pandemic to compare the age profile of patients hospitalized with COVID-19 as well as hospital mortality and ICU use by age group in large geographic regions of Brazil.[49] They compared across three time periods: (1) Feb 16th-Jun 20th, 2020; (2) Jun 21st-Oct 24th, 2020; (3) Oct 25th, 2020-Feb 20th, 2021. The third timepoint corresponds with the increasing prevalence of Gamma in Brazil. Of the 620,363 completed records of patients hospitalized, 244,611 (34.0%) had indication for use of ICU. While there was variation in the age profile of hospitalized patients between the three periods, there was no evidence of an increase in hospitalization during the last period for adults between 18 and 50 years. Geographically, they report that in the North and Northeast regions, the proportion of 18 to 50-year-olds in the last period was similar to the first period during which they were also substantially affected by the pandemic. In the Southeast and South of Brazil, there was a consistent reduction in these age groups over the periods. In the Central West region, which experienced the pandemic more during the second period, hospitalization for adults between 18 and 50 years old was higher in the first period, decreasing and maintaining during the second and third period. They conclude that the rise in the North aligns with a collapse of the health care system in some areas, which was likely associated with disease severity due to Gamma.

Takemoto et al. completed a cross-sectional analysis to examine the impact of Gamma on obstetric populations in Brazil.[45] They found no significant difference in the ICU admission risk for maternal patients between 2020 and 2021 (p=0.769) and there was no difference in length of ICU admission (p=0.269).

Garvey et al. report on 152 patients (79 Alpha, 1 Beta) who were admitted to University Hospitals Birmingham (England) between Dec 15th-31st, 2020.[32] They found no significant differences between VOC and non-VOC on mean length of stay (11.51 vs. 9.56 days), mean critical care length of stay (15.25 vs. 18.93 days), or proportion of patients admitted to critical care (0.111 vs. 0.19). The only significant difference they reported is that patients with VOC were more likely to have a cough (0.59) than patients with non-VOC (0.38), $p<0.05$.

VOC impact on mortality

Seventeen studies reported on health system impacts related to risk of death. Six studies in Europe and six in Brazil reported increased risk of death for individuals with Alpha and Gamma, respectively, compared to the wild type; however, another six studies found no difference among VOC broadly across Europe. Among the 17 studies, six were apprised as high quality,[26–28,31–33] six were medium quality,[37,39,40,43–45] and two were low quality[49,50] (three not appropriate for appraisal). Table 6 provides a summary of findings with additional detail provided in text below.

Increases in Death

Jabłońska et al. conducted a correlational study across 38 European countries to detect the association between COVID-19 mortality and proportion of VOC through the second wave in Europe using multivariate regression models.[39] A higher proportion of Alpha across countries was associated with higher COVID-19 mortality peak and total mortality during the second wave of the pandemic in Europe. Between Jan 1st to Feb 25th, 2021, "an increase of 0.1 in the proportion of Alpha was related to a 15.3% increase in the cumulative number of deaths during that period" (p.5).

Challen et al. conducted a matched cohort study in the UK to explore whether there is change in mortality at 28 days from infection with Alpha compared with wild type.[26] The study consisted of 54,906 matched pairs who tested positive for COVID-19 between Oct 1st, 2020 and Jan 29th, 2021 (followed until Feb 12th, 2021). In 54,902 matched cohort pairs, there were 227 deaths in Alpha individuals vs. 141 non-Alpha individuals. The mortality hazard ratio for people with Alpha compared to those with non-Alpha was 1.64 (95% CI 1.32 to 2.04). As a community-based study, this suggests that even in a relatively low-risk group, there was an increased risk of death from 32% to 104%.

Davies et al. conducted an epidemiological modeling study to describe the association between Alpha and hazard of death and disease severity within 28 days of positive test in the UK.[82] Of the 2,245,263 individuals with a positive community test between Nov 1st, 2020 and Feb 2021, half (51.1%) had a conclusive SGTF reading and, of these, 58.8% had SGTF, indicative of Alpha. Among those with known SGTF status, the crude COVID-19 death rate was 1.86 deaths per 10,000 person-days of follow-up in the Alpha group versus 1.42 deaths in the non-Alpha group. The hazard ratio for Alpha was 1.55 (95% CI 1.39– 1.72), meaning that the risk of mortality in the 28 days following a positive test was 55% higher for Alpha than for non-Alpha cases. After correcting for misclassification of SGTF and missing SGTF status, there was a 61% (95% CI: 42–82%) higher hazard of death associated with Alpha; however, this was not consistent across age groups. In females aged 70–84, the estimated risk of death within 28 days of a positive SARS-CoV-2 test increased from 2.9% without Alpha to 4.4% with Alpha (95% CI 4.0–4.9%) and for males 70-84, it increased from 4.7% to 7.2% (95% CI: 6.4–7.9%). Similarly, in females 85 or older, the estimated risk increased from 13% to 19% (95% CI: 17–21%) and for males 85 or older, it increased from 17% to 25% (95% CI: 23-27%). These estimates reflect a substantial increase in absolute risk in older age groups, but the risk of COVID-19 death following a positive test in the community remains below 1% in most individuals younger than 70 years old.

Grint et al. conducted a cohort study to estimate the risk of death following COVID-19 infection in England by comparing Alpha to non- Alpha.[28] They found that Alpha was consistently associated with increased risk of death within 28 days compared to non-Alpha cases with the hazard ratio at 1.67 (95%CI, 1.34-2.09, p<0.0001). The risk of death was low for those under 65 years of age without comorbidities, though higher for males than females (Alpha: Males 0.14%; Females: 0.07% vs. non-Alpha: Males: 0.09%; Females: 0.05%). The risk of death was consistently higher for males and increased with age and with comorbidities. The highest risk was seen among those aged 85 years or older with 2+ comorbidities (Alpha: Males 24.3%; Females: 14.7% vs. non-Alpha: Males: 16.7%; Females: 9.7%).

Zhao et al. conducted an observational, retrospective analysis to assess the risk of COVID-19 case fatality in the United Kingdom using data from Sep 1st, 2020, to Jan 31st, 2021.[83] They found that overall, Case Fatality Ratio (CFR) increased from 1% in Sep to 2.2% in Nov, where it stabilized. They estimated that Alpha resulted in an increase of 18% in the CFR compared to the original variant.

Ackland et al. conducted a modeling study to track the statistical CFR in the second wave of the UK COVID-19 outbreak, and to understand its variations over time.[84] They found that when taking Alpha into account, there was a 33% increase in mortality, which the authors link to increased infectivity, making Alpha more dangerous.

De Oliveira et al. conducted an epidemiology study to explore data from the state of Parana, in the south of Brazil, where the Gamma variant was identified on Feb 16th, 2021, to assess trends in mortality data as reported CFRs among different age-groups.[50] Prior to the introduction of Gamma, all age groups had either a decline or stable CFR, however, in Feb 2021, an increase in CFR for almost all age groups was observed. While there were no changes in CFR in children or adolescent, all other groups above 20 years of age had statistically significant increases in CFR when diagnosed in Feb 2021 as opposed to Jan 2021. For individuals between 20 and 29 years of age, there was a 3-fold higher risk of death when diagnosed in Feb 2021 compared to Jan (RR: 3.15 [95%CI: 1.52-6.53], p<0.01). This risk of death was also higher in other age groups, although to a lesser extent – 93% for 30–39-year-old (1.93 [95%CI:1.31-2.85], p<0.01), 11-% for 40-49-year-old (RR: 2.10 [95%CI:1.62-2.72], p<0.01), and 80% for 50-59-year-old (RR: 1.80 [95%CI:1.50-2.16], p<0.01).

De Andrade et al. reported that each region in Brazil varied in terms of their mortality over three periods, with the North region being the hardest hit, experiencing a collapse in the provision of healthcare in the first and last periods with high mortality in all age groups, with a rise in hospital deaths among adults aged 18-60 years.[49] The high mortality in the third wave was among adults aged 18-70 years, reflecting the severity of the pandemic in the region and the impact of Gamma.

Takemoto et al. found that the CFR was higher in 2021 (15.6%) compared to 2020 (7.4%), suggesting that the risk of mortality was higher for maternal patients after the emergence of Gamma.[45] In fact, the authors report that the first three months of 2021 accounted for 46.2% of all maternal deaths thus far. There was no significant difference in terms of age, type of residence, COVID-19 diagnostic criteria, cardiovascular disease, or diabetes but the proportion of white women was higher in 2021. There was also a significant difference between regions, with an increase in the south (which is wealthier), which the authors concluded that healthier, wealthier women were dying due to the collapse of the healthcare system in Brazil related to the growth of Gamma.

Freitas et al. found that the proportion of women who died from COVID-19 increased from 34% in the first wave (Apr-May 2020, non-VOC) to 47% in the second wave (Jan 2021, Gamma).[43] The risk was greatest in the 20-39-year-old group and the 40–59-year-old group (RR= 1.96 (1.4-2.8) and 2.31 (2.0-2.7), respectively). Additionally, there was an increase in proportion of deaths for individuals in all age groups (20-59 years) in both sexes. There were no significant differences for mortality in males, but the risk of death for men aged 20-39 was more than double in the second wave than the first wave 2.1 ([1.6-2.8], p <0.0001) and was higher in men aged 40-59 years 1.42 ([1.3-1.6], p <0.0001).

Freitas et al., reporting on different time periods than the above study, found that the CFR was higher across all groups after the emergence of Gamma, with ages groups of 20-39 and 40-59 having a higher proportional increase in the second wave because of Gamma prevalence (28%, 1370 deaths) compared to the first wave of Nov/Dec 2020 (18%, 670 deaths).[44] Additionally, people without pre-existing conditions experienced a higher proportional increase in death in the second wave (22%) than the first (13%).

<u>No Changes in Death</u>

Frampton et al. conducted a cohort study in the UK to describe emergence of Alpha in two North Central London hospitals including clinical outcomes in patients with and without the VOC.[27] Of the included 399 patients, the proportion of patients who had severe disease (i.e., WHO level of ≥6) or death were similar: 38% in the non-Alpha group vs. 36% in the Alpha. The proportion of patients at level 6 or levels 7–9 on the WHO ordinal scale or who died were not statistically different: 18% in the non-Alpha group were at level 6 and 2% were at levels 7–9; 15% in the Alpha group were at level 6 and 6% were at levels 7-9. Similar rates of mortality were found, with 16% patients with Alpha dying within 28 days versus 17% with non-Alpha. In both the unadjusted and adjusted analysis (controlling for hospital, sex, age, comorbidities, and ethnicity), there was no increased risk of mortality or severe disease with Alpha compared to non-Alpha.

Patone et al. found no difference in death within 28 days between the Alpha group and non-Alpha group (0.3% both).[40] In the unadjusted analysis, there was no difference in 28-day mortality risk for Alpha compared to non-Alpha patients, but after adjusting for confounders, there was a higher risk of 28-day mortality in Alpha patients, (adjusted HR: 1.59; 95% CI: 1.25- 2.03), mainly explained by age (HR: 1.53, 95% CI: 1.28-1.82 with adjustment for age alone). In the critical care cohort, after adjusting for confounders, critical care mortality did not differ significantly between Alpha and non-VOC Alpha groups (adjusted HR: 0.93, 95% CI 0.76-1.15). Both cohorts had no evidence of an interaction between Alpha and ethnic group, age group, or sex.

In the matched cohort study of 5,642 individuals, Dabrera et al. found that 76 died within 28 days of a positive test; of which, 36 (1.3%) were infected with Alpha and 40 (1.4%) were infected with wild-type SARS-CoV-2.[37] There was no association between Alpha and non-Alpha groups and death within 28 days of COVID-19 positive test (OR: 0.90, 95%CI 0.57-1.41, p=0.64), with similar median time between positive test and death (8 days for Alpha and 9 days for non-Alpha (Kruskal Wallis p=0.79). In the unadjusted analysis, there was a negative relationship between risk of death and Alpha infection (HR: 0.54, 95%CI:0.42-0.69, p=0.00); however, after adjusting for confounders (sex, age, ethnicity, residential property classification, week of specimen date and testing Pillar), there was no difference in risk of death among Alpha cases compared to non-Alpha (HR: 1.06, 95%CI:0.82-1.38, p=0.65).

Loconsole et al. found no significant difference in death between those with Alpha (0.6%) and non-Alpha (0.9%), p=0.64.[33] Garvey et al. report on 152 patients (79 Alpha, Beta) who were admitted to University Hospitals Birmingham (England) between Dec 15th-31st, 2020.[32] There was no difference in the proportion of patients who died with Alpha (0.18) compared to non-VOC (0.21).

Funk et al. found no significant increase risk of death in either the matched or unmatched multivariate analysis when comparing VOC to non-VOC cases.[31] Interestingly, the percentage of patients who died with Alpha (2.0%) was significantly lower than non-VOC cases (4.0%), p<0.05. The authors attribute this to potentially misidentified/misclassification of samples and time of data collection.

Question 2B: Adjusting personal protective equipment (PPE) procedures for health workers

One modeling study, which was not critically appraised, reported on this outcome. Pham et al. evaluated the impact of different PPE interventions on transmission, HCW absenteeism and test positivity as a marker of intervention efficiency against Alpha transmission through modeling.[85] In the baseline scenario, it was assumed that HCWs were using PPE while in COVID wards when seeing patients but not during breaks or when in other parts of the hospital, assuming 95% of HCW worked in same wards over time. While specific PPE was not defined, PPE efficiency was defined as percentage reduction of droplet transfer. Assuming 90% effective PPE use in COVID wards, they found that extending PPE use to non-COVID wards (all HCW used PPE with 90% effectiveness when on ward) would prevent 93.7% of all transmissions and would also prevent outbreaks among patients and HCWs. Even if PPE effectiveness was reduced to 70%, findings did not change significantly, however, if was reduced to 50% or below, screening HCWs every 3 days was more effective than PPE use in all wards. Overall, PPE use in all wards was model to be more effective than all other interventions.

Question 2C: Adjusting restrictions to and screening staff and visitors (e.g., visitor policy changes, approach to and frequency of screening)

No studies to date have reported on this outcome.

Question 2D: Adjusting service provision based on VOC status (e.g., cohorting patients in hospitals based on the SARS-CoV-2 variants they have)

No studies to date have reported on this outcome.

Question 2E: Adjusting patient accommodations, shared spaces and common spaces (e.g., improvement to HVAC systems)

No studies to date have reported on this outcome.

Discussion

This rapid scoping review sought to identify, appraise, and summarize evidence related to the impact of VOC known in May 2021 (Alpha, Beta, Gamma, and Delta) on public health measures and health system arrangements. Our search identified 38 articles on public health measures and 25 articles related to health system arrangements.

Critical Appraisal

A total of 25 original research studies were assessed for quality (excluding 35 lab or modeling studies), indicating a strength of this review. While observational studies ranged in quality from low to high, the majority were preprints that have not yet been peer reviewed. Therefore, findings should be interpreted with caution to inform health system and public health recommendations. The studies which scored higher on the NOS were those which selected participants from large, representative samples and controlled for most confounders. Studies which tended to score lower on the NOS were those where self-reported data were used or when limited description of the non-respondent group was provided for cross-sectional studies. It is important to note that the NOS was originally developed for cohort and case-control studies, rather than studies of cross-sectional design. Although an adapted version of NOS was used to score cross-sectional studies,[22] there may be some limitations in applying this adapted version. The NOS tool favours studies with large sample sizes with a particular emphasis on secure record linkage. The studies appraised in this rapid review tended to be based on large national databases, most often in countries where COVID-19 is reported on a mandatory basis. This resulted in studies receiving high scores even before consideration of the methodology or results of the paper. In this updated review, we appraised a larger proportion of cross-sectional and ecological studies. These studies often scored low in the area of comparability. Cross-sectional and ecological studies tended to report only descriptive statistics. Limited multivariate analysis or uses of controls were performed. Therefore, any inference of causality or association must be taken with caution.

We applied an additional quality control measure to observational studies by decreasing preprint study scores by two points. While this approach of downgrading preprints provides further appraisal of study quality, it is not considered in the standard NOS scoring instructions. For the purpose of presenting the most recent evidence on this topic, it was important to include preprint studies, which are typically excluded from systematic reviews, but are an essential consideration in COVID-19 reviews.

Interestingly, the majority of observational studies were related to health systems. Of the seven observational studies which reported on public health measures, only two were considered to be high quality. This is important to highlight as our jurisdictional scan of provincial public health measures[20] may be based on limited evidence, or on low quality evidence at best.

Public Health Measures

Thirty-eight studies contributed data relevant to modifying existing public health measures in consideration of VOC. Modeling studies were the most common design (28/38) followed by observational studies (7/38) and laboratory studies (3/38). Of note, most studies (25/38) are preprints and have not undergone peer-review. We identified limited evidence focused on modification to handwashing or masking related to the emergence of variant strains. In general, although available evidence is varied and scarce, findings from the included studies overwhelmingly support the implementation of strong public health measures (i.e., lockdowns, distancing, testing, contact tracing), running in parallel with an accelerated vaccine schedule. Of note, most studies contributing data to this question reported on mRNA vaccines. The increased transmissibility of the VOC signals the need for more pre-emptive restrictions (close phase first and then open at low case numbers) versus reactive (open first, then close to prevent ICU saturation) strategies. Studies relevant to this question focused broadly on social distancing as a strategy, with no specific recommendation regarding objective metrics such as proximity time or distance or type of social distancing strategy. Included studies identified the need for attention to managing contacts in specific environments such as households, educational and early care centres, and workplace settings. Few recommendations were provided to address these needs. Age and gender may be an important target to consider when developing a population vaccine promotion campaign.

Health Systems Arrangements

Overall, there were 25 studies that reported on health system impacts, with almost all reporting on impact on hospitalization, ICU admissions and deaths. Among the studies that reported on the impact of VOC on hospitalization, trends suggest there is an increase in hospitalization due to VOC, with most reporting on Alpha. There seems to be less agreement on the impact of Alpha on intensive care admissions, with three studies reporting increased admission to ICU with Alpha compared to the wild type, and three studies reporting no difference. There are limited studies to date on ICU admissions for Beta and Gamma, but the two studies that reported on these VOC did not find any difference on ICU admission. While we did not conduct any meta-analysis for this review, there were double the number of studies that found an increased risk of mortality due to VOC (12 studies) compared to those that found no change (6 studies). For studies that reported an increase in mortality risk, Alpha was found to increase the risk from 15% to 67% compared to non-VOC, suggesting that Alpha could be linked with higher mortality than non-Alpha strains. One study reported on the effectiveness of PPE in reducing VOC transmission in the hospital. No studies reported on screening staff and visitors, adjusting service provisions (e.g., cohorting), or adjusting patient accommodations and shared spaces, which is a significant gap in the literature. Of note, almost all studies on health system arrangements were on Alpha, with limited studies on Beta and Gamma and none on Delta, thus it is unclear whether all VOC hold the same risk of increased mortality. Finally, all studies on health system arrangements come from three areas – United Kingdom, Europe, and Brazil, thus, the impact of VOCs on other health systems around the world are predominantly unreported in the literature to date.

Limitations

While this rapid scoping review has several strengths, there are limitations that must be acknowledged. First, due to the rapid production of the literature on COVID-19 and VOC, most of the studies included in this review were preprints and have thus not yet undergone peer review. As mentioned above, this must be considered when interpreting the findings. However, in this update, five previously included preprints were found to be published after peer review, indicating that the peer reviewed literature is rapidly changing.

Additionally, our search strategy was limited to articles that specified reporting on one of the recognized VOC (Alpha, Beta, Gamma or Delta). Given the growing trend that VOC are replacing the wild type as the dominant strain as well as the continued emergence of other variants of interest, future consideration of expanding the search strategy may be warranted.

A third limitation is that our review is limited to studies that reported specifically on VOC, which makes it difficult to interpret some of the findings without taking into consideration the wider literature on SARS-CoV-2. For example, we report on attitudes towards vaccines only in context of VOC, without wider acknowledgement of the extensive body of literature on vaccine hesitancy.

Research Gaps

As evident in this rapid review, the nature of and findings on the impact of VOC on public health measures and health systems arrangements are quickly changing and emerging. In the month between our searches, our team identified 27 new articles to add in this update and five articles that had previously been preprint which are now published in a peer reviewed journal. We have identified several specific research gaps that need to be addressed to provide more robust evidence around public health measures and health system arrangement decisions.

1. Evidence is needed related to best practices for screening staff and visitors in health service organizations and adjusting service provisions
2. Evidence is needed to support/refute adjusting patient accommodations (cohorting) and shared spaces in a hospital setting with the presence of different strains
3. Information to support changes in guidance related to masking in light of more transmissible strains is needed
4. Evidence to guide best practice standards for screening and testing for VOC under different conditions is needed
5. Standardized approaches and tools are needed to track adherence to different public health measures
6. Methods for appraising modeling studies need to be developed
7. Novel methods to collect and analyze data are needed to inform infection-prevention strategies for safer workplace environments with the emergence of highly transmissible strains
8. Standards for sharing surveillance data nationally to rapidly inform health policy and health system guidance documents are recommended worldwide
9. Additional data is needed on Beta, Gamma and Delta VOC to determine whether the risks to health system arrangements are similar for all VOC
10. Evidence from other countries currently not reported on but are experiencing significant impact of VOC (e.g., India) is important to add to the existing literature

Lessons Learned

The authors share the following lessons learned throughout this rapid review process:

- Active and ongoing engagement with knowledge users is essential to ensure end products address the main questions. Regular communication assists with addressing uncertainty about scope, particularly when examining rapidly changing, complex, and heterogeneous literature. Ready access to content experts and knowledge users as well as an experienced review team is important for the consistency of the data extraction and analysis when addressing complex review questions.
- Answering multiple questions in one rapid scoping review was a challenge; the team recommends careful consideration of the scope of single reviews in future work
- The complexity of the review question and the timing expectation of outputs made patient engagement in all stages of the review challenging. The team is engaging patient partners in the development of the knowledge translation plan

- The large volume of guidance documents, variation in indexing strategies and rapid rate of change in this subject area made a traditional systematic approach to collecting grey literature challenging. A separate jurisdictional scan, using targeted, iterative methods, was a more appropriate method to identify current COVID-19 guidance in Canada.

Conclusion

This rapid scoping review provides synthesized evidence related to the public health and health system impacts of the four SARS-CoV-2 VOC (Alpha, Beta, Gamma, and Delta). While the findings should be interpreted with caution as most of the sources identified were preprints, findings suggest a combination of non-pharmaceutical interventions (e.g., masking, physical distancing, lockdowns, testing, contact tracing) should be employed alongside a vaccine strategy to improve population and health system outcomes. Additionally, while the findings are mixed on the impact of VOC on health systems arrangements, the evidence is trending towards increased hospitalization and mortality.

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Appendix 1: *Literature Search Strategy*

MEDLINE

COVID-19 search filter: CADTH https://covid.cadth.ca/literature-searching-tools/cadth-covid-19-search-strings/

1	(coronavirus/ or Betacoronavirus/ or coronavirus infections/) and (disease outbreaks/ or epidemics/ or pandemics/)
2	(ncov* or 2019ncov or 19ncov or covid19* or covid or sars-cov-2 or sarscov-2 or sarscov2 or severe acute respiratory syndrome coronavirus 2 or severe acute respiratory syndrome corona virus 2).ti,ab,kf,nm,ot,ox,rx,px.
3	((new or novel or "19" or "2019" or wuhan or hubei or china or chinese) adj3 (coronavirus* or corona virus* or Betacoronavirus* or CoV or HCoV)).ti,ab,kf,ot.
4	((coronavirus* or corona virus* or Betacoronavirus*) adj3 (pandemic* or epidemic* or outbreak* or crisis)).ti,ab,kf,ot.
5	((wuhan or hubei) adj5 pneumonia).ti,ab,kf,ot.
6	or/1-5 [CADTH COVID-19 filter, no date limit]
7	(((uk or united kingdom or england or english or britain or british or kent) adj3 (variant* or voc or vui)) or "b117" or "20i 501yv1" or "variant of concern 202012 01" or "voc 202012 01" or "variant under investigation in december 2020" or "variant under investigation 202012 01" or "vui 202012 01").ti,ab,kw,kf.
8	(((south africa* or sa) adj3 (variant* or voc or vui)) or "b1351" or "501v2" or "501yv2" or "20h 501yv2" or "20c 501yv2").ti,ab,kw,kf.
9	((brazil* adj3 (variant* or voc or vui)) or "p1" or "b11281" or ((mutation* or spike*) adj3 (k417t or e484k or n501y))).ti,ab,kw,kf.
10	((mutation* or spike*) adj3 d614g).ti,ab,kw,kf.
11	((india* adj3 (variant* or voc or vui)) or "b1617*" or "g 452v3" or "voc 21apr" or "vui 21apr" or double mutation or double mutant or double variant or ((mutation* or spike*) adj3 (e484q or l452r or p681r))).ti,ab,kw,kf.
12	or/7-11
13	6 and 12
	551 results 2021-05-11

Embase

COVID-19 search filter: CADTH adapted to Embase.com format; line 1 exploded

1	'SARS-related coronavirus'/exp
2	('coronavirinae'/de OR 'Betacoronavirus'/de OR 'coronavirus infection'/de) AND ('epidemic'/de OR 'pandemic'/de)

3	(ncov* OR 2019ncov OR 19ncov OR covid19* OR covid OR 'sars-cov-2' OR 'sarscov-2' OR 'sars-cov2' OR sarscov2 OR 'severe acute respiratory syndrome coronavirus 2' OR 'severe acute respiratory syndrome corona virus 2'):ti,ab,kw,de,tt,oa,ok
4	((new OR novel OR '19' OR '2019' OR wuhan OR hubei OR china OR chinese) NEAR/3 (coronavirus* OR 'corona virus*' OR Betacoronavirus* OR cov OR hcov)):ti,ab,kw,de,tt,oa,ok
5	((coronavirus* OR 'corona virus*' OR Betacoronavirus*) NEAR/3 (pandemic* OR epidemic* OR outbreak* OR crisis)):ti,ab,kw,tt,oa,ok
6	((wuhan OR hubei) NEAR/5 pneumonia):ti,ab,kw,tt,oa,ok
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
8	(((uk OR 'united kingdom' OR england OR english OR britain OR british OR kent) NEAR/3 (variant* OR voc OR vui)) OR 'b.1.1.7' OR b117 OR '20i 501y.v1' OR 'variant of concern 202012 01' OR 'voc 202012 01' OR 'variant under investigation in december 2020' OR 'variant under investigation 202012 01' OR 'vui 202012 01'):ti,ab,kw
9	((('south africa*' OR sa) NEAR/3 (variant* OR voc OR vui)) OR 'b.1.351' OR b1351 OR '501.v2' OR '501y.v2' OR '20h 501y.v2' OR '20c 501y.v2'):ti,ab,kw
10	((brazil* NEAR/3 (variant* OR voc OR vui)) OR 'p.1' OR p1 OR 'b.1.1.28.1' OR b11281 OR ((mutation* OR spike*) NEAR/3 (k417t OR e484k OR n501y))):ti,ab,kw
11	((mutation* OR spike*) NEAR/3 d614g):ti,ab,kw
12	((india* NEAR/3 (variant* OR voc OR vui)) OR 'b.1.617*' OR b1617* OR 'g 452.v3' OR 'voc 21apr' OR 'vui 21apr' OR 'double mutation' OR 'double mutant' OR 'double variant' OR ((mutation* OR spike*) NEAR/3 (e484q OR l452r OR p681r))):ti,ab,kw
13	#8 OR #9 OR #10 OR #11 OR #12
14	#7 AND #13
	460 results 2021-05-11

Cochrane

1	MeSH descriptor: [Coronavirus] this term only
2	MeSH descriptor: [Betacoronavirus] this term only
3	MeSH descriptor: [Coronavirus Infections] this term only
4	{or #1-#3}
5	MeSH descriptor: [Disease Outbreaks] this term only
6	MeSH descriptor: [Epidemics] this term only
7	MeSH descriptor: [Pandemics] this term only
8	{or #5-#7}

9	#4 and #8
10	(ncov* or 2019ncov or 19ncov or covid19* or covid or "sars-cov-2" or "sarscov-2" or sarscov2 or "severe acute respiratory syndrome coronavirus 2" or "severe acute respiratory syndrome corona virus 2"):ti,ab,kw
11	((new or novel or "19" or "2019" or wuhan or hubei or china or chinese) near/3 (coronavirus* or "corona virus*" or Betacoronavirus* or cov or hcov)):ti,ab,kw
12	((coronavirus* or "corona virus*" or Betacoronavirus*) near/3 (pandemic* or epidemic* or outbreak* or crisis)):ti,ab,kw
13	((wuhan or hubei) near/5 pneumonia):ti,ab,kw
14	{or #9-#13}
15	(variant* or voc or vui or mutation* or spike):ti,ab
16	#14 and #15
	121 results in CENTRAL 2021-05-11 **2 results in CDSR 2021-05-11**

Epistemonikos

Basic search of the following terms within the LOVE:
variant* OR voc OR vui OR "B.1.1.7" OR "20I/501Y.V1" OR "202012/01" OR "B.1.351" OR "501.V2" OR "501Y.V2" OR "20H/501Y.V2" OR "20C/501Y.V2" OR "P.1" OR "B.1.1.28.1" OR "K417T" OR "E484K" OR "N501Y" OR "D614G" OR "B.1.617" OR "B.1.617.1" OR "B.1.617.2" OR "B.1.617.3" OR "G/452.V3" OR "VOC-21APR" OR "VUI-21APR" OR "double mutation" OR "double mutant" OR "double variant" OR "E484Q" OR "L452R" OR "P681R"
1766 results 2021-05-11

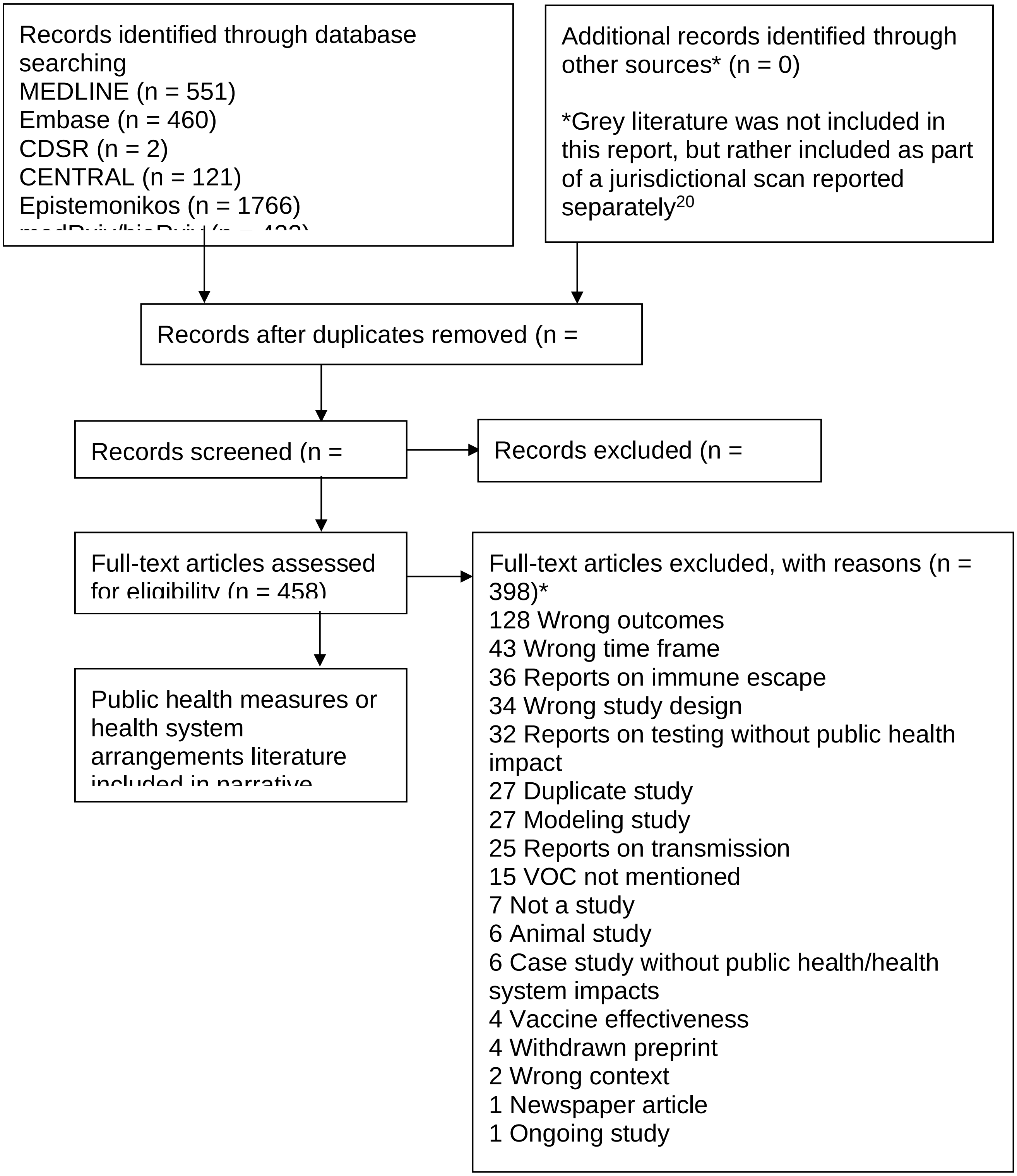
medRxiv / bioRxiv

medRxiv and bioRxiv simultaneous search; Date limit: October 1 2020 – present; Title and Abstract search; All words (unless otherwise specified); 50 per page; Best Match; **update date limit for each update (February 1 2021 – present, March 2021 – present, April 7 2021 – present)**
Searches:

uk variant united kingdom variant england variant english variant britain variant british variant kent variant south africa variant brazil variant variant of concern *(phrase search)* variants of concern *(phrase search)*

B.1.1.7 20I/501Y.V1 202012/01 B.1.351 501.V2 501Y.V2 20H/501Y.V2 20C/501Y.V2 P.1 B.1.1.28.1 K417T E484K N501Y D614G india variant B.1.617 B.1.617.1 B.1.617.2 B.1.617.3 G/452.V3 VOC-21APR VUI-21APR double mutation *(phrase search)* double mutant *(phrase search)* double variant *(phrase search)* E484Q L452R P681R

Appendix 2: *PRISMA Diagram*



Appendix 3: *Summary of Findings Tables for Public Health Sources*

Legend:

Study Design	Low Quality	Medium Quality	High Quality
Observational study			
Guidance documents			
Laboratory study			
Modelling study			

Table 1: *Summary of Public Health Sources*

Author, date	**Date of data collection**	**Source**	**Objective**	**Study design**	**Setting**	**Sample size**	**Outcome measures**	**Variant**	**Country**	**Main finding**
Graham, 2021	Sep 8th- Dec 31st, 2020	Lancet Public Health	To examine the association between the regional proportion of Alpha and reported symptoms, disease course, rates of reinfection, and transmissibility.	Cross-sectional study	Community	36,920 COVID-19 positive users of the COVID symptom app. Surveillance data from the (COG-UK) and a SGTF correlate in community testing data.	Regional proportion of Alpha and symptoms, disease course, rates of reinfection and transmissibility. Disease burden was also examined by assessing self-reported hospital visits and reported long symptom duration	Alpha	UK	No evidence of changes in reported symptoms, disease severity and disease duration associated with Alpha.
Chudasama, 2021	Oct 1st- Dec 15th, 2020	Journal of Infection	A comparative analysis of household clustering to	Cross-sectional study	Community	57,382	Household outbreak	Alpha	UK	Analysis of national data has shown that Alpha cases were almost twice as likely to give rise to household clusters compared with

Author, date	Date of data collection	Source	Objective	Study design	Setting	Sample size	Outcome measures	Variant	Country	Main finding
			provide a rapid assessment of transmissibility of this variant against other sequenced cases.							wild type cases. Household exposures are high risk with passive surveillance demonstrating high attack rates, providing an important indicator of transmissibility as household exposures are unlikely to differ between cases infected with different variants and their contacts.
Buchan, 2021	Feb 7th-27th, 2021	medRxiv	To compare secondary attack rates in households with VOC versus non-VOC index cases in Ontario	Retrospective cohort study	Community	We identified 5,617 index cases and 3,397 secondary cases across the study period. Amongst index cases, 1,318 were classified as VOC (151 Alpha and 1,167 N501Y) and 4,299 were classified as non-VOC	Household secondary attack rate, defined as the number of household secondary cases that occurred 1-14 days after the index case divided by the total number of household secondary contacts.	Alpha	Canada	This study provides strong evidence of increased transmissibility in households due to VOC and suggests that asymptomatic and pre-symptomatic transmission may be of particular importance for VOC. Our study suggests that more aggressive public health measures will be needed to control VOC and that ongoing research is needed to understand mechanisms of VOC transmissibility to curb their associated morbidity and mortality.
Victora, 2021	Week 1-14, 2021	medRxiv	Evaluate the real-life effectiveness of the vaccination campaign	Observational, retrospective epidemi	Community	370,000 registered deaths in Brazil	Mortality rate ratios over two-weekly periods in between Jan 3rd, 2021 and Apr 22nd, 2021 for individuals	Gamma	Brazil	Rapid scale up of vaccination among elderly Brazilians in early 2021 was associated with a decline in relative mortality compared to younger individuals

Author, date	Date of data collection	Source	Objective	Study design	Setting	Sample size	Outcome measures	Variant	Country	Main finding
			among the elderly in Brazil	ological study			aged 80+ and 90+ years			
Aiano, 2021	Nov 2nd, 2020-Jan 31st, 2021; contacted up to Feb 23rd, 2021	SSRN	To assess the risk of SARS-CoV-2 infection and attack rates in staff and children attending nurseries over a three-month period when community SARS-CoV-2 infections rates were high and the Alpha variant was spreading rapidly across England	Cross-sectional	Nurseries/daycares	324 nurseries had an outbreak; 173 agreed to take part, reporting 1657 cases	Outbreak sizes and attack rates	Alpha	UK, England	In nurseries reporting an outbreak, one in three staff were affected compared to one in thirty children. We found some evidence of increased transmissibility and higher attack rates associated with the Alpha variant
Lumley 2021	Sep 1st, 2020-Feb 28th, 2021	MedRxiv	1) Investigate & compare protection from SARS-CoV-2 infection through vaccination and prior infection (using anti-spike antibody status). 2)	Observational cohort	Oxford University Hospitals (OUH)	13, 109 individual HCWs contributed 2,835,260 person-days follow-up. 74% female, 27% nurses, 14% physicians,	PCR-confirmed symptomatic SARS-CoV-2 infection. Also considered any PCR-positive result (i.e., either symptomatic or asymptomatic) Antibody status was determined using an anti-trimeric spike IgG ELISA using an 8	Alpha	Oxfordshire, UK	Pooling data from unvaccinated and Pfizer-BioNTech and AstraZeneca vaccinated HCWs showed that natural infection resulting in detectable anti-spike antibodies and two doses of vaccine both provide robust protection against SARS-CoV-2 infection, including against the Alpha variant of concern.

Author, date	Date of data collection	Source	Objective	Study design	Setting	Sample size	Outcome measures	Variant	Country	Main finding
			Estimate the protection from different vaccines, after one versus two doses and from infections with the Alpha variant			median age 39(30-50)	million units threshold to determine antibody-positivity. To assess the impact of the Alpha variant on (re)infection risk, PCR-positive results with and without SGTF, and those confirmed as Alpha on sequencing.			
Bachtiger, 2021	Nov 13th and Dec 31st, 2020	medRxiv	To inform public health messaging by determining how changes in COVID-19 vaccine hesitancy, attitudes towards administration, emergence of new variants & vaccine availability may affect herd immunity	Cross-sectional	Community	9617 (2nd questionnaire relevant to outcome measures)	Willingness to receive COVID-19 vaccine, attitudes towards prioritization, plans to change behaviour following vaccination	Alpha	UK	Slight increase in vaccine acceptance after learning of circulating VOC but vaccine acceptance is still below levels that would enable progress towards herd immunity. Overall majority (85.1%) of people want vaccine, and few people (12.5%) plan on drastically changing behavior following vaccination. Participatory community engagement should be part of a strategy to improve uptake by considering the public's preferences, such as those expressed here that teachers and BAME groups should be prioritized.
Abdel-Sater, 2021	Dec 9th, 2020-Jan 10th, 2021	medRxiv	To evaluate a Primer for use with SYBR RT-PCR test as a second step	Laboratory study	N/A	20 samples from COVID positive patients with Ct<30	Quantitative SYBR Green Based RT-PCR	Alpha	Lebanon	The SYBR RT-PCR test could be used as a second step test for early confirmation of VOC Alpha in COVID Positive S-Gene negative patients in case of shortage in

Author, date	Date of data collection	Source	Objective	Study design	Setting	Sample size	Outcome measures	Variant	Country	Main finding
			means for confirming Alpha or similar variant in COVID positive patients							sequencing tests. Our efforts will be helpful and can contribute to the early detection of the new variant (VUI 202012/01), for the prevention of transmission and early intervention
Akingba, 2021	Nov 17th-20th, 2020	medRxiv	Evaluate the field performance of the PanBio assay and provide evidence of performance on patients infected with 501Y.V2	Laboratory study	Community Testing, Mobile Clinics	A total of 677 patients from 6 mobile clinics were tested by both antigen and PCR	Used nasopharyngeal swabs to determine the accuracy of Abbott PanBio COVID-19 antigen RTD. RT-PCR was done using the Seegene nCoV assay with amplification on BioRad CFX realTime PCR machine	Beta	South Africa	The assay had an overall sensitivity of 69.2% and specificity of 99% in this clinical context. However, sensitivity was highly dependent on viral load. The assay reliably detected 501Y.v2 virus infection in ambulatory ill patients in this high prevalence community setting. Sensitivity was >90% in patients with high viral loads CTs<30. To optimize the use of antigen RDTs in different and changing circumstances, clinical predictors and the epidemiological context should be considered when deciding how to deploy these assays.
Collier and Ferreira, 2021	Dec 9th, 2020-Feb 3rd, 2021	medRxiv	Assess age correlated immune response following 1st & 2nd dose with mRNA-based vaccine in unselected	Laboratory study	Community	51 participants; N=24, <80 years; N=27, >80 years; median age 81	Inadequate vaccine-elicited serum antibody neutralization activity at least 3 weeks after the first dose of vaccine measured as a dilution of serum required to inhibit infection by 50%	Alpha	UK	Age was statistically correlated with serum neutralization. There was a significantly higher risk of a suboptimal neutralizing antibody response following first dose vaccination with BNT162b2 in those above the age of 80, cautioning against extending the

Author, date	Date of data collection	Source	Objective	Study design	Setting	Sample size	Outcome measures	Variant	Country	Main finding
			elderly participants from the community & younger health care workers				in an in vitro neutralization assay			dosing interval in this high risk population.
Jangra, 2021	Not Reported	MedRxiv	To investigate the impact of the E484K mutation in the neutralizing activity of SARS-CoV-2 specific antisera	laboratory study	N/A	A total of 34 sera were selected from study participants based on their SARS-CoV-2 S enzyme linked immunosorbent assay antibody titer (negative [N=4] versus weak [N=8], moderate [N=11] or strong positive [N=11]). Sera from five individuals who received two doses of the Pfizer SARS-CoV-2 vaccine was included.	Serum neutralization efficiency	Non-specific, similar to Beta and Gamma	US	These data indicate that the E484K mutation present in circulating SARS-CoV-2 strains that belong to the Beta and Gamma lineages reduces the neutralizing activity of human polyclonal sera induced in convalescent (infected with previous strains) and vaccinated individuals. It is important to aim for the highest titers possible induced by vaccination, as this should enhance the chances for protection even in the case of antigenic drift of circulating SARS-CoV-2 strains

Author, date	Date of data collection	Source	Objective	Study design	Setting	Sample size	Outcome measures	Variant	Country	Main finding
Meister, 2021	N/A	Journal of Infectious Diseases	To compare the surface stability of 3 SARS-CoV-2 strains, the preexisting variant (wild type) and the currently emerging Alpha and Beta variants on different surfaces and their sensitivity to heat, soap and ethanol	Laboratory study	Community/general public	N/A	Viral stability over 48hr (for testing different surfaces); viral infectivity (for testing effect of soap/ethanol); reduction of viral titers by end point dilution to calculate TCID50 values (to test susceptibility to heat)	Alpha, Beta	Germany	The currently circulating VOC did not exhibit enhanced surface stability or differences in disinfection profiles indicating that current hygiene measures are sufficient and appropriate...Overall, our data support the application of currently recommended hygiene concepts to minimize the risk of Alpha and Beta transmission
Borges, 2021	Week 49 2020 to week 3 2021	Eurosurveillance	To investigate the proportion of SGTF cases to gain insight on Alpha frequency and geographical spread in Portugal	Modeling study	Community	Of the 36,651 positive results, 3,367 (9.2%) corresponded to SGTF tests (i.e., proxy for Alpha); Equivalent to 9.5% of COVID-19 positive tests in the same time frame	Proportion of COVID-19 cases likely classified as Alpha, based on SGTF, from RT-PCR tests with TaqPath COVID-19 assay; and impact on number of cases due to lockdown measures in week 2/3	Alpha	Portugal	Physical distancing measures implemented in weeks 2 and 3 strongly decelerated the growth rate with the proportion of SGTF and SGTL remaining below 50% until week 7 2021. This reinforces the need to implement robust public health measures adapted to this new variant to mitigate the impact of COVID-19 in terms of hospitalizations and deaths.
Domenico, 2021	Jan 2021 start date used for	medRxiv	To assess the impact of implemented measures on	Modelling study	Community	N/A	Estimated # cases of historical strain and VOC based on various social distancing	Alpha	France	Social distancing and nightly curfews would bring down the R of historical strain, however VOC would continue to increase. It is

Author, date	Date of data collection	Source	Objective	Study design	Setting	Sample size	Outcome measures	Variant	Country	Main finding
	projected modelling		two COVID strains (Alpha & wild type) through modeling				measures using data from a large-scale genome sequencing initiative conducted in France			important to continue strong social distancing measures while increasing vaccination to reduce hospitalization.
Giordano, 2021	model estimated using data collected within a 110-day window ending on Feb 7th, 2021	Nature Medicine	Model impact of mass vaccination campaigns, different transmission rates due to new variants and different enforced countermeasures and assess associated healthcare costs	Modeling study	N/A	NR	fraction of successfully immunized people within one year.	Alpha, Beta	Italy	Non-pharm interventions (Physical distancing, testing and contact tracing) are critical throughout a mass vaccination campaign to keep the reproduction numbers low until a sufficient population immunity is achieved.
Munitz, 2021	Dec 6th, 2020-Feb 10th, 2021	Cell Reports Medicine	To explore the transmission dynamics of Alpha & estimate the success of screening, surveillance & vaccination on mitigating risk in the general public & elderly	Modeling study	Community & nursing homes	primary data of >300,000 RT-PCR samples	SGTF data from RT PCR tests, effective reproduction number (Rt) and cycle threshold values (ct)	Alpha	Israel	Our data confirmed that pro-active surveillance programs of populations at risk such as those found in nursing homes were capable of early detection, which likely enabled containment of further viral spread within this housing community. This is observed by the significant difference in Ct threshold levels, which were higher in nursing homes in comparison with the

Author, date	Date of data collection	Source	Objective	Study design	Setting	Sample size	Outcome measures	Variant	Country	Main finding
										general population. Thus, proactive protection programs such as routine surveillance and monitoring of populations at risk combined with prioritized vaccination, is achievable and will result in a reduction of severe illness and subsequent death.
Scherbina, 2021	Not Reported	SSRN	Whether the US would benefit from a COVID lockdown similar to the lockdowns imposed in a number of European countries using the most recent data.	Modeling study	Community	N/A	Future monetary cost of the pandemic based on: 1) loss of productivity due to missed work of the symptomatically ill, 2) the cost of medical interventions that could have been used elsewhere, 3) the value of lives of the projected fatalities. Measured based on value of statistical life (VSL) and discounted QALY	Alpha	US	In a hypothetical scenario in which the more contagious U.K. variant of the virus becomes predominant in the U.S. one month from now, a lockdown would be substantially more valuable than for the currently prevailing variant; its optimal duration will lengthen, and the associated net savings will nearly triple. Even with vaccinations, a lockdown will generate significant net benefits and that it should optimally last four weeks under the baseline assumptions.
Smith, 2021	Oct 19th-Dec 7th, 2020	medRxiv	To assess the impact of environment on VOC transmission	Modelling study	Community	N/A	Transmission intensity estimates (R)	Alpha	UK	Like other SARS-CoV-2 strains, Alpha spread with greater transmission in colder and more densely populated parts of England. However, there is evidence of Alpha having a transmission advantage at warmer temperatures compared to other strains. This implies that spring and

Author, date	Date of data collection	Source	Objective	Study design	Setting	Sample size	Outcome measures	Variant	Country	Main finding
										summer conditions are unlikely to slow Alpha's invasion in Europe and across the Northern hemisphere - an important consideration for public health interventions.
Vazquez, 2021	Not reported	medRxiv	To estimate the rate of transmission per proximity contact, a generative model to simulate infectious disease outbreaks within workplaces, estimates of the rate of super-spreading events per imported case and an evaluation of mask use as an example of non-pharmaceutical interventions within the workplace.	Modeling study	Modeling of workplace transmission	605 Individuals in a workplace	Using Bluetooth button devices, they tracked when the distance between two coworkers was less than 1.5m for 15 seconds. This data was used to model the spread of virus. They estimated disease transmission rates and examined super-spreading events (where # of secondary cases equals or exceeds 10). A procedure was developed to simulate the disease transmission given the proximity contact data, the disease infectious period and the probability of disease transmission after repeated contacts	Alpha	Germany	Workplace proximity contact data can be used to develop a tailored model to simulate the spread of Alpha and the impact of containment strategies

Author, date	**Date of data collection**	**Source**	**Objective**	**Study design**	**Setting**	**Sample size**	**Outcome measures**	**Variant**	**Country**	**Main finding**
Zimerman, 2021	Jun 1st, 2020, and Jan 10th, 2021	Cureus	To assess if social isolation into small family or groups is associated with the emergence of new severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) variants, particularly the Gamma lineage and E484K mutants, in Brazil and in the state of Amazonas	Modelling study	Community	A total of 773 samples were obtained throughout the period encompassed by the present analysis in Brazil	For the evaluation of the prevailing SARS-CoV-2 genomes present in Brazil and in the state of Amazonas, all human related sequences available on the GISAID collected between Jun 1st, 2020, and Jan 31st, 2021. Social isolation was measured by the daily values of the Social Isolation Index (SII), which shows the percentage of individuals who stayed within a distance of 450 meters from their homes on a given day. Daily SII was collected from the In Loco© website between Feb 1st, 2020, and Jan 24th, 2021, for Brazil and the state of Amazonas. Number of daily COVID-19 deaths was noted between Mar 12th, 2020, and Jan 24th, 2021, through the official database of the	Gamma	Brazil	In the present study, SII was found to be positively associated with a substantial rise in the prevalence of these new variants. However, this correlation could only be observed when SII was above 40% (Nov 2020-Jan 2021), suggesting that the SARS-CoV-2 ability to mutate was dependent on high levels of SII in the state of Amazonas, Brazil. Findings reinforce the hypothesis that forced prolonged cohabiting may boost viral ability to generate mutation.

Author, date	Date of data collection	Source	Objective	Study design	Setting	Sample size	Outcome measures	Variant	Country	Main finding
							Brazilian Ministry of Health.			
Pageaud, 2021	N/A	medRxiv	To analyze the expected dynamics of COVDI-19 epidemic after applying protective measures and considering the increasing proportion of more infectious variants and several vaccination strategies	Modeling study	Community	N/A	Cumulative # of individuals removed, cumulative # of deaths in hospital, daily prevalence in ICU beds and its saturation indicator. Saturation of ICU beds was calculated as the cumulative # of new cases requiring ICU when all beds were already occupied.	Alpha, Beta, Gamma	France	This race against the COVID-19 historical strain and its variant strains is an issue of vaccination strategy. It is mandatory to vaccinate most of the population within a year, and preferably within 6 months. Should a 6-month vaccination campaign not be feasible, then reinforced NPI should be considered.
Piantham and Ito, 2021	Sep 1st, 2020-Feb 19th, 2021	medRxiv	To propose a method to estimate the selective advantage of a mutant strain over previously circulating strains using the time course of Alpha strain frequencies and the distribution	Modelling study	Community	71,692 of Alpha strains vs. 65,850 non-Alpha strains	The serial interval is the time from illness onset in a primary case to illness onset in a secondary case	Alpha	UK	The result indicated that the control measures against Alpha strain needs to be strengthened by 33.7% from that against previously circulating strains. To get the same control effect as before, contact rates between individuals needed to be restricted to 0.748 of the contact rates that had been achieved by the control measures taken for previously circulating strains.

Author, date	Date of data collection	Source	Objective	Study design	Setting	Sample size	Outcome measures	Variant	Country	Main finding
			of serial intervals.							
Luo, 2021	N/A	medRxiv	To estimate the long-term durability of mRNA-1273 vaccine and to integrate studies about differences in antibody neutralization to SARS-CoV-2 variants to understand how variants can affect the durability of the vaccine	Modelling study	Community	N/A	Antibody level and neutralization	Alpha, Beta, Gamma	US	That mRNA1273 two dose vaccine can provide over a year of protection against COVID-19 from the initial D614G variant. It is likely by the second year, protection against COVID-19 will fall below single dose efficacy. Therefore, there should be consideration for a booster shot a year after the first set of vaccines. If there is an observed increase in variants with higher resistance such as Beta and Gamma, a booster vaccine against the newer variants should be considered to increase protection against resistant variants.
Kim, 2021	Dec 14th, 2020-Mar 2nd, 2021	medRxiv	To evaluate the trade-offs between speed of distribution vs. efficacy of multiple vaccines when variants emerge	Modelling Study	Community	N/A	Evaluate the impact of each vaccine type using infection attack rate (IAR) as the main health outcome	Alpha, Beta	US	That the speed of the vaccine distribution is a key factor to achieve low IAR levels, even though the vaccine may have high efficacy both before and after the variants emerge.
Sah, 2021	N/A	Eclinical Medicine	To evaluate the impact of accelerated vaccine distribution on	Modelling study	Community	N/A	Transmission probability; Hospitalization (non-ICU and ICU)	Alpha	US	That the current pace of vaccine rollout is insufficient to prevent the exacerbation of the pandemic that will be attributable to the novel, more contagious SARS-CoV-2

Author, date	Date of data collection	Source	Objective	Study design	Setting	Sample size	Outcome measures	Variant	Country	Main finding
			curbing the disease burden of novel SARS-CoV-2 variants							variants. Accelerating the vaccination rate should be a public health priority for averting the expected surge in COVID-19 hospitalizations and deaths that would be associated with widespread dissemination of the SGTF variants.
Tokuda and Kuniya, 2021	Jan 14th-Apr 20th, 2021	medRxiv	To construct the COVID-19 epidemic curve to examine effect of vaccination schedules and need for restrictions (lockdown)	Modelling study	Community	N/A	Number of new infections per day	Alpha	Japan	If the vaccination pace could not be quadrupled from the current pace, Japan could not achieve Zero Covid status, which is reflected by a low COVID-19 death rate and less economic damage.
Gurbaxani, 2021	N/A	medRxiv	To extend the model of Worby and Chang to use age-stratified social contact patterns for the general U.S. population, and we analyzed the model both employing the measured face mask efficacy	Modelling study	Community	N/A	Effectiveness of mask wearing	Alpha	US	Showed the potential for substantial reduction in SARS-CoV-2 transmission, even with moderately effective masks, when they are worn consistently correctly (over the chin and covering nose and mouth) and/or per manufacturers' specifications by a large portion of the population.

Author, date	Date of data collection	Source	Objective	Study design	Setting	Sample size	Outcome measures	Variant	Country	Main finding
			parameters for a variety of specific types of masks and for efficacy estimates that can act as benchmarks for evaluating these products							
Teslya, 2021	N/A	Research square	Use of a socio-epidemiological model to investigate the effects of waning of compliance to physical distancing measures on the dynamics of COVDI-19 as vaccine is rolled out in the population	Moedlling study	Community	N/A	Numbers of infected, vaccinated and compliant individuals over the course of the vaccination rollout, cumulative numbers of infected individuals after 1 and 2 years into vaccine program	Alpha	Netherlands	For Alpha, when vaccine rollout is slow, targeting the non-vaccinated population with interventions aimed at improving compliance to physical distancing measures is best for reducing the # of infections and targeting vaccinated people is better when vaccination is fast. Fast vaccination and better compliance with physical distancing of vaccinated people is the only way excessive infections can be avoided. If vaccine rollout is slow, the positive effects on the incidence with be counteracted by fading compliance and increasing contact rates in the population.
Yang, 2021	Feb 26th, 2020-Apr 5th, 2021	medRxiv	Develop a deterministic modeling to evaluate the partial	Modelling study	Community	N/A	COVID-19 cases and fatalities curves	Gamma	Brazil	The model fitted the CoViD-19 data (considering VOCs and transmission among isolated individuals) and provided a useful means for describing the impact of

Author, date	Date of data collection	Source	Objective	Study design	Setting	Sample size	Outcome measures	Variant	Country	Main finding
			quarantine and further relaxation in Sao Paulo State.							quarantine, relaxation and virulence of the epidemic in Sao Paulo State, Brazil.
Wells, 2021	N/A	medRxiv	Use modeling travel between pairs of European countries to identify travel quarantine and testing strategies that will not increase infections in the destination country compared to a strategy of complete border closure	Modelling study	Community	N/A	Length of quarantine for origin-destination pairs of European countries	Alpha, Beta	US	Quarantines for European destinations that are specific to travel origin can be informed by country-specific prevalence, daily incidence, vaccine coverage, age-demographics and travel flow. Among countries with surveillance enabling estimation of Alpha frequency, sufficient quarantine and testing is similar for this variant to that determined for general transmission. In contrast, the Beta VOC was at relatively low frequency in most European countries, with much greater variance in prevalence. Consequently, sufficient quarantine and testing would be more extreme and more distinct for this variant than that determined in a general analysis of COVID-19 transmission.
Ahn, 2021	N/A	SSRN	To propose a multi-model optimization (MMO) framework that identifies	Modelling study	Community	NR	Policies	Alpha	US	Considering the heterogeneity across states, we have determined the MMO policies for all 50 US states over a one-year period and estimated the associated outcomes. Under our optimal

Author, date	Date of data collection	Source	Objective	Study design	Setting	Sample size	Outcome measures	Variant	Country	Main finding
			policies that perform well across structurally distinct models, and we apply this to design 12-month COVID-19 containment strategies							policy, we show that some states can be on the trajectory to the halfway normal or minimal response policies for most 2021, while we recommend a few states to spend a significant portion of the year in more restrictive interventions. We also find that the prevalence of highly infectious variants (e.g., Alpha) can significantly increase the 12- month cost, which strongly supports the case for aggressive work to contain variants.
Kühn, 2021	N/A	medRxiv	To provide viable strategies of careful opening of facilities in low-incidence regions without being affected by neighboring regions of substantially higher incidence.	Modelling study	Community	N/A	Effectiveness of lockdowns, measured by number of new cases	Alpha	Germany	In order to keep the spread of the virus under control, strict regional lockdowns with minimum delay and commuter testing of at least twice a week are advisable.
Moore, 2021	various time points between Jan	Lancet Infectious Diseases	To use epidemiological data from the UK together with estimates	Modelling study	Community	N/A	Used a two-dose model to simulate the effect of vaccination in both reducing infection (and hence onward	Alpha	UK	For all vaccination scenarios they investigated, their predictions highlight the risks associated with early or rapid relaxation of NPIs. Although novel vaccines against

Author, date	Date of data collection	Source	Objective	Study design	Setting	Sample size	Outcome measures	Variant	Country	Main finding
	2021-Jan 2022		of vaccine efficacy to predict the possible long-term dynamics of SARS-CoV-2 under the planned vaccine rollout.				transmission) and reducing symptomatic disease.			SARS-CoV-2 offer a potential exit strategy for the pandemic, success is highly contingent on the precise vaccine properties and population uptake, both of which need to be carefully monitored.
Shattock, 2021	Feb 18th, 2020-May 3rd, 2021	medRxiv	Model multiple vaccine rollout scenarios with several phased NPI relaxation strategies and examine impact on the epidemic in Switzerland	Modelling study	Community	N/A	Number of confirmed cases, hospitalizations, ICU Admissions, and deaths	Alpha, B.1351	Switzerland	Based on their model, strong increases in vaccination rates from 0.6% to 1.2% of the population results in halved and slightly earlier third wave peak. Furthermore, gradual phased relaxation of NPI can substantially reduce ICU occupancy and deaths until Sep 2021.
Bosetti, 2021	N/A	HAL Archives	To develop mathematical models and explore scenarios that help understand how the interplay of the key drivers of the pandemic (the variants, the vaccines and the control measures) will	Modelling study	Community	N/A	Hospitalization	Alpha	France	The current curfew and conditions appear sufficient to control the spread of the historical virus but not that of Alpha. With vaccination targeting those at higher risk of hospitalization, the burden on hospitals could quickly be alleviated. However, our assessment suggests that this effect may not be sufficient to compensate for the increased transmissibility of Alpha.

Author, date	Date of data collection	Source	Objective	Study design	Setting	Sample size	Outcome measures	Variant	Country	Main finding
			shape its dynamics for the coming months							
Lasser, 2021	N/A	medRxiv	To quantify how many transmissions can be expected for the different scenarios in the different school types, in a way that is appropriate to derive evidence-based policies for keeping schools open at a controllable infection transmission risk	Modelling study	Schools	Model estimates based on data from 616 clusters involving 2,822 student-cases and 676 teacher cases	Transmission probability	Alpha	Austria	Different types of schools require different combinations of preventive measures. The ideal mix of mitigation measures needs to be more stringent in secondary schools than in primary schools and needs to preferentially focus on teachers as sources of infection. Even under strict prevention measures, larger clusters in schools will still occur at regular intervals when the incidence in the general population is high enough. However, in this work we have shown that keeping schools open during the COVID-19 pandemic a calculable risk can be achieved by a combination of stringently enforced measures.
Linka, 2021	N/A	medRxiv	The objectives of this study are twofold: First, we perform a retrospective study to evaluate the risks that would	Modelling study	University campus (Stanford)	N/A	Effective reproduction number	Alpha, Beta	US	With no additional countermeasures, during the most affected quarter, the fall of 2020, there would have been 203 cases under baseline reproduction, compared to 4727 and 4256 cases for the Alpha and Beta variants. The results suggest that population

Author, date	**Date of data collection**	**Source**	**Objective**	**Study design**	**Setting**	**Sample size**	**Outcome measures**	**Variant**	**Country**	**Main finding**
			have been associated with the reopening of Stanford University in the spring, summer, and fall of 2020, and winter of 2021. Second, we complement our analysis by exploring the possible effect of variants on the overall disease dynamics.							mixing presents an increased risk for local outbreaks, especially with new and more infectious variants emerging across the globe. Tight outbreak control through mandatory quarantine and test-trace-isolate strategies will be critical in successfully managing these local outbreak dynamics.

Table 2: *Summary of Health Systems Sources*

Author, date	**Date of data collection**	**Source**	**Objective**	**Study design**	**Setting**	**Sample size**	**Outcome measures**	**Variant**	**Country**	**Main finding**
Challen, 2021	Oct 1st, 2021-Feb 12th, 2021	BMJ	To establish whether there is any change in mortality from infection with Alpha compared with circulating SARS-CoV-2 variants	Matched cohort study	Community - genomic surveillance data and death records	54,906 matched cohort pairs (on age, sex and ethnicity) of participants who tested positive for SARS-CoV-2	Death within 28 days of the first positive SARS-CoV-2 test result	Alpha	UK	Probability that the risk of mortality is increased by infection with Alpha is high; infection with Alpha has the potential to cause substantial additional mortality compared with previously circulating variants.
Graham, 2021	Sep 8th-Dec 31st, 2020	medRxiv	To examine the association between the regional proportion of Alpha and reported symptoms, disease course, rates of reinfection, and transmissibility.	Cross-sectional study	Community	36,920 COVID-19 positive users of the COVID symptom app. Surveillance data from the (COG-UK) and a SGTF correlate in community testing data.	Regional proportion of Alpha and symptoms, disease course, rates of reinfection and transmissibility. Disease burden was also examined by assessing self-reported hospital visits and long reported symptom duration	Alpha	UK	No evidence of changes in reported symptoms, disease severity and disease duration associated with Alpha.
Grint, 2021	Nov 16th, 2020-Jan 11th, 2021	medRxiv	To estimate the risk of death following SARS-CoV-2 infection in England, comparing	Cross-sectional observational cohort study, chart review	Community - health admin database	SGTF status was known for 184,786 people (n=91,775 non-VOC and n=93,011 VOC)	All-cause mortality based on relative hazard of death ratio and absolute risk of death by 28 days, comparing VOC to non-VOC	Alpha	England	Alpha was associated higher mortality than the wild type, which increases with age and comorbidities, and males have a higher risk than females.

Author, date	**Date of data collection**	**Source**	**Objective**	**Study design**	**Setting**	**Sample size**	**Outcome measures**	**Variant**	**Country**	**Main finding**
			VOC to non-VOC							
Frampton, 2021	Nov 9th Dec 20th, 2020	Lancet	To describe emergence of Alpha in two North Central London hospitals including comparing virological characteristics and clinical outcomes.	Cohort study	Hospital	Of 496 patients with samples positive for SARS-CoV-2 on PCR and who met inclusion criteria, 341 had samples that could be sequenced. 58% had Alpha	Severe disease (defined as point 6 or higher on the WHO ordinal scale within 14 days of symptoms or positive test) and death within 28 days of a positive test,	Alpha	UK	While length of stay, risk of hospitalization within 14 days of a test, and time to hospital admission from symptom onset were similar, Alpha patients were younger, had fewer comorbidities and more likely to be from an ethnic minority compared to non-Alpha patients. There was no increased risk of mortality or severe disease with Alpha compared to non-Alpha.
Courjon, 2021	Dec 2020-Feb 2021	Research Square	To analyze modification in clinical profile and outcome traits.	Cohort study	Hospital	ED (n=1247) & Infectious disease ward or ICU (n=232)	Timeline of UK-variant spreading; Profile of COVID-19 patients admitted in ED; Assessment comparison of hospitalized patients in Infectious Diseases and ICU departments	Alpha	France	There was no significant difference on time from first symptoms to ED admission, severity, need for immediate ICU management, ICU admission, or severity score on admission between Alpha and non-Alpha.
Funk, 2021	weeks 38/2020-10/2021	Euro Servillence	To analyze COVID-19 cases infected with any of the three VOC: Alpha/S gene target failure (SGTF), Beta or Gamma.	Retrospective cross-sectional study	Community	23,343 had information on SARS-CoV-2 variants, of which 19,995 were VOC and 3,348 non-VOC cases included in this analysis.	Data included information on sex, age, clinical symptoms, pre-existing conditions, hospital and intensive care unit (ICU) admission and outcome (i.e., survived or died).	Alpha, Beta, Gamma	Cyprus, Estonia, Finland, Ireland, Italy, Luxembourg and Portugal	Showed an increased risk for hospitalizations and ICU admission associated with the SARS-CoV-2 variants Alpha/SGTF, Beta and Gamma, also in middle-aged individuals, which underlines the necessity to rapidly reach high levels of vaccine coverage and adhere to public health measures

Author, date	Date of data collection	Source	Objective	Study design	Setting	Sample size	Outcome measures	Variant	Country	Main finding
			Then compare them with cases reported as infected with non-VOC virus with a focus on disease severity.							to reduce SARS-CoV-2 incidence and prevent severe cases.
Loconsole, 2021	Dec 22nd, 2020-Mar 9th, 2021	Environmental Research and Public Health	The aim of this study was to evaluate the spread of Alpha in southern Italy from Dec 2020-Mar 2021 through detection of the SGTF which could be considered a robust proxy of VOC Alpha	Cross-sectional study	Community	3075	Positive SGTF detection, symptomology (i.e., Hospitalization)	Alpha	Italy	SGTF-positive cases were more likely to be symptomatic and to result in hospitalization ($p<0.0001$). Strengthened NPIs and rapid vaccine deployment are crucial to contain the spread of Alpha and flatten the curve of the third wave.
Garvey, 2021	Dec 15th-31st, 2020	Journal of Infection	Whole genome sequencing on a substantial proportion of our SARS-CoV-2 positive samples. Here, we report our observations and outcomes	Cross-sectional study	Hospital	152 - 79 were Alpha and 1 was Beta	Clinical outcomes: hospital length of stay, ethnicity, age, sex, critical care admission, critical care length of stay, treatment given for COVID-19 (dexamethasone or Remdesivir), oxygen and ventilatory support,	Alpha, Beta	UK	Alpha was associated with younger age; an increased proportion of patients being admitted to critical care for longer periods but the association wasn't statistically significant. Whilst numbers of patients were relatively low, no increase in mortality was observed.

Author, date	Date of data collection	Source	Objective	Study design	Setting	Sample size	Outcome measures	Variant	Country	Main finding
			of Alpha infected patients admitted to UHB during Dec 2020				death, co- morbidities and presenting symptoms			
Haas, 2021	Jan 24th- Mar 6th, 2021	Lancet	To provide nationwide estimates of the effectiveness of two doses of Pfizer against SARS-CoV-2 outcomes, including deaths, and document the first evidence of nationwide public-health impact following the widespread introduction of the vaccine at the population level	Observational study	Community	There were 202 684 SARS-CoV-2 infections in Israel, of which 93.9% was Alpha. There were 6,040 hospitalizations, 3,470 severe and critical hospitalizations, and 754 deaths among persons aged >15 years.	Range of SARS-CoV-2 outcomes, including all SARS-CoV-2 infections (symptomatic and asymptomatic), hospitalizations (severe and critical) and deaths	Alpha	Israel	Two doses of Pfizer >7 days after admission were highly effective in preventing initial COVID-19 infection, hospitalizations, severe and critical hospitalizations, and deaths at a time when Alpha was the dominant strain.
Bager, 2021	Jan 1st- Feb 9th, 2021	Lancet – preprint	To link SARS-CoV-2 genomic data with Danish health	Observational cohort study	Community & hospital (linked	A total of 35,887 test-positive individuals were	Hospital admission within 14 days after a positive SARS-cov-2	Alpha	Denmark	Infection with Alpha was associated with a 64% increased risk of hospitalization compared with

Author, date	Date of data collection	Source	Objective	Study design	Setting	Sample size	Outcome measures	Variant	Country	Main finding
			registers and estimate the risk of hospitalization among cases with Alpha compared with cases detected with other SARS-cov-2 lineages		national surveillance data to hospital admission data)	identified, 11.6% with Alpha.	PCR test or 48hr before a positive test			individuals infected with wild type SARS-CoV-2.
Patone, 2021	Nov 1st, 2020-Jan 27th, 2021	medRxiv	To estimate the risk of critical care admission, mortality in critically ill patients, and overall mortality associated with Alpha compared with the original variant. We also compare clinical outcomes between these variants' groups.	Retrospective cohort design, using mathematical modeling in analysis	Community & Hospital - critical care	The 'primary care cohort' was patients in primary care with a positive community COVID-19 test reported between Nov 1st, 2020-Jan 26th, 2021. The first cohort included 198,420 patients. Of these, 80,494 had VOC Alpha	The outcomes of interest for the primary care cohort were receipt of critical care and 28-day mortality. The outcomes of interest for the critical care cohort were duration of organ support (respiratory, cardiovascular, renal, neurological and liver) in critical care, duration of critical care and mortality at the end of critical care.	Alpha	England	There was an increased risk of COVID-19 28-day mortality and admission for critical care associated with Alpha in the primary care cohort. In the critical care cohort, after adjusting for confounders, critical care mortality did not differ significantly between Alpha and non-VOC Alpha groups.
Snell, 2021	Mar 13th, 2020 and	medRxiv	To compare admission characteristics	Retrospective	Hospital	2341 total; n=838 in wave	Comparison of the demographic, physiological and	Alpha	UK	While there was double the admissions in Wave 2 (Alpha), patients with Alpha were similar in

Author, date	Date of data collection	Source	Objective	Study design	Setting	Sample size	Outcome measures	Variant	Country	Main finding
	Feb 17th, 2021		of hospitalized cases during the two dominant waves of infection for local healthcare planning	cohort study		1 and 1503 in wave two	laboratory parameters of hospitalized SARS-CoV-2 positive cases during Wave 1/non-Alpha and Wave2/primarily Alpha extracted from hospital electronic health record.			age and ethnicity compared to non-Alpha. Significant differences were Alpha patients were less likely to be frail but more likely to be obese hypoxic on admission, the main indicator of severe disease, than non-Alpha patients.
Jabłońska, 2021	Mid-Jun and mid-Aug 2020 to Feb 25th, 2021	medRxiv	To detect potential association between COVID-19 mortality and proportion of Alpha through the second wave of the pandemic in Europe with the use of multivariate regression models.	Cohort study, involving multiple cross-sections	Community	A dataset of 3971 SARS-CoV-2 virus strains identified between Dec 2019 and Mar 2021	COVID-19 deaths during the second wave of COVID-19 pandemic	Alpha and 11 other variants	38 European countries	Findings suggest that the development and spread of Alpha had a significant impact on the mortality during the second wave of COVID-19 pandemic in Europe.
Dabrera, 2021	Oct 2020-Jan 2021	SSRN	To assess whether infection with Alpha was associated with more severe clinical	Matched cohort study	Community	63,609 genomically sequenced COVID-19 cases	Risk in hospitalization and risk of mortality within 28 days of test	Alpha	UK	There was a 34% increased risk in hospitalization associated with Alpha compared to wild-type cases, however, no significant difference in the risk of mortality was found after adjusting for confounders.

Author, date	Date of data collection	Source	Objective	Study design	Setting	Sample size	Outcome measures	Variant	Country	Main finding
			outcomes compared to wild-type infection							
Takemoto, 2021	Mar 2020-Apr 12th, 2021	medRxiv	Examine impact of Gamma variant on obstetric population in Brazil	Cross-sectional study	Community	8,248 COVID-19 maternal SARS cases	Confirmed maternal deaths in women 10-50 years old	Gamma	Brazil	The number of COVID-19 maternal deaths increased significantly (7.4% vs 15.6%) from 2020 to 2021 in Brazil.
Freitas, 2021	Apr 2020-Mar 1st, 2021	SciELO - PrePrints	In order to describe and identify potential changes in the mortality profile associated temporally with the emergence of the Gamma strain in the state of Amazonas, we used the data of the national epidemiological surveillance system, publicly available to analyze the epidemiological	Cross-sectional study	Community	In the first wave of the COVID-19 pandemic in Amazonas, 46,342 cases were recorded and, in the second wave, 61,273 cases	Demographic data, self-reported ethnicity, clinical data, comorbidities, hospitalization, admission to the ICU, need ventilatory support and symptom onset dates, hospital admission and outcome	Gamma	Brazil	Findings suggest that simultaneously with the emergence of the Gamma strain in the state of Amazonas, there was an increase in the proportion of deaths in the group of women and in the populations between 20 and 59 years of both sexes. There were also relative increases in the different age groups and genders in the mortality, lethality and hospital lethality rates.

Author, date	Date of data collection	Source	Objective	Study design	Setting	Sample size	Outcome measures	Variant	Country	Main finding
			profile of COVID-19 cases that occurred in that state at two distinct epidemiological moments: during the peak of the first wave, between April and May 2020, and in January 2021, month in that the new variant came to dominate.							
Freitas, 2021	Apr 19th, 2020-Mar 20th, 2021	medRxiv	An epidemiological analysis describing and comparing the severity and mortality profile of covid-19 cases in the RS state, considering two periods before and after the emergence of	Cross-sectional study	Community	230,986 cases of covid-19 were confirmed in the first wave and 150,942 cases in the second wave	Demographic data, self-reported ethnicity, presence of pre-existing risk conditions (supplements), data on the onset of symptoms, hospitalization and hospital outcome, as well as data on the occupation of ward beds and intensive care unit (ICU) beds	Gamma	Brazil	Findings showed an increase in the proportion of young people and people without previous illnesses among severe cases and deaths in the state of RS after the identification of the local transmission of variant Gamma in the state. There was also an increase in the proportion of severe cases and in the CFR, in almost all subgroups analyzed, this increase was heterogeneous in different age groups and sex.

Author, date	Date of data collection	Source	Objective	Study design	Setting	Sample size	Outcome measures	Variant	Country	Main finding
			variant Gamma.							
de Oliveira et al., 2021	Sep 1st, 2020 and Mar 17th, 2021	medRxiv	To assess recent trends in mortality data among different age-grouped populations in Brazil.	Cross-sectional study	Community	553,518 individuals infected with SARS- CoV-2 in Parana between Sep 2020 and Mar 2021	Case fatality rates (CFRs)	Gamma	Brazil	There was an 80-215% increased risk of mortality for adults in different age categories between 20-59 years between Feb 2020 and Jan 2021, when Gamma was prominent.
de Andrade et al., 2021	Feb 16th 2020 - Feb 20, 2021	medRxiv	To compare, during the first year of the pandemic the age profile of patients hospitalized by COVID-19, as well as hospital mortality and use of ICUs, by age group, in large geographic regions of Brazil.	Cross-sectional	Hospital	720,36 completed records of patients hospitalized by Covid-19	Hospital mortality and use of ICUs	Gamma	Brazil	Each geographical region of Brazil varied in terms of their mortality over the three periods, with the North region being the hardest hit, experiencing a collapse in the provision of healthcare in the first wave and last periods (associated with Gamma) with high mortality in all age groups.
Davies, 2021	Sep 1st, 2020-Feb 14th, 2021	medRxiv	Describe association between SGTF and hazard of death/disease severity	Modeling study	Community	2,245,263 individuals with a positive community test, 51.1% of which had a	COVID-19 death occurring within 28 days of an individual's first positive COVID test	Alpha	UK	The hazard of death in the 28 days following a positive test is 55% (39– 72%) higher for Alpha than for non- Alpha cases. Correcting for misclassification of SGTF and missingness in SGTF status, this

Author, date	Date of data collection	Source	Objective	Study design	Setting	Sample size	Outcome measures	Variant	Country	Main finding
						conclusive SGTF reading and, of these, 58.8% had SGTF (suggesting Alpha).				increases to 61% (42–82%). Alpha is not only more transmissible than pre-existing SARS-CoV-2 variants but may also cause more mortality.
Domenico, 2021	Jan 7-8 2021	medRxiv	To assess the impact of implemented measures on two COVID strains (i.e., Alpha and wild type) through modeling	Modelling study	Community	N/A	Estimated # cases of historical strain and VOC based on various social distancing measures using data from a large-scale genome sequencing initiative conducted in France	Alpha	France	Social distancing implemented in Jan 2021 would bring down the R of historical strain, however VOC would continue to increase. School holidays also slowed down dynamics. Accelerating vaccinations will help but won't be sufficient to stop the spread of the VOC, even with optimistic vaccination rates
Mitze and Rode, 2021	Dec 15th, 2020-Feb 4th, 2021.	MedRxiv	To provide estimates of the epidemiological trends associated with the reporting of Alpha and non-Alpha for two key indicators: i) the 7-day incidence rate, and ii) the hospitalization rate.	Modelling study	Community, hospital	Data on daily SARS-CoV-2 infection data for each of the health regions from the COVID-19 dashboard of the Robert Koch Institute. The number of hospitalized patients in intensive care was taken from	Comparing the development in epidemiological outcome variables of two groups (non-Alpha and Alpha). Outcomes of interest were i) the 7-day incidence rate (SARS-CoV-2 infections per 100,000 population over the last seven days) and ii) the hospitalization rate (hospitalized patients in	Pooled information on VOC	Germany	There was a significant increase in the hospitalization rate in regions in the top 10% percentile of reported VOC cases with an estimated increase of 1.29 [CI: 0.5, 2.1] additional COVID-19 patients in intensive care per 100,000 population.

Author, date	Date of data collection	Source	Objective	Study design	Setting	Sample size	Outcome measures	Variant	Country	Main finding
						the INFAS corona database.	intensive care per 100,000 population).			
Pham, 2021	Feb-Aug 2020	medRxiv	To explore the effectiveness of different infection prevention strategies for HCWs in hospitals in the absence of vaccination using an agent-based model of nosocomial SARS-CoV-2 transmission.	Modeling study	Hospital	N/A	We computed the effective reproduction number for patients and HCWs to evaluate an intervention's effectiveness. Also measured HCW absenteeism and numbers of nosocomial infections	Alpha	Netherlands	In response to the emergence of more transmissible SARS-CoV-2 variants, universal PPE use in all hospital wards is the most effective in preventing nosocomial transmission and is the most effective intervention to reduce the reproduction number and absenteeism. Regular screening and contact tracing of HCWs are also effective interventions, but critically depend on the sensitivity of the diagnostic test used.
Zhao, 2021	Sep 1st, 2020-Jan 31st, 2021	Viruses	Use a statistical inference framework to assess the risk of COVID-19 case fatality using the disease surveillance data on a real-time basis. We reconstruct the real-time and variant-specific	Modelling study	Community	149,789 complete human SARS-CoV-2 strains from the GISAID	Case fatality ratio (CRF)	Alpha	UK	Overall CRF increased from 1% in September 2020 to 2.2% in November 2020 and stabilized at this level. The variant-specific change in CRF may increase by 18% of fatality risk compared with the original 501N variant.

Author, date	**Date of data collection**	**Source**	**Objective**	**Study design**	**Setting**	**Sample size**	**Outcome measures**	**Variant**	**Country**	**Main finding**
			CFR of COVID-19 empirically and infer the change in fatality risk associated with N501Y substitution in SARS-CoV-2.							
Ackland, 2021	Apr 22nd, 2021	medRxiv	To track the statistical CFR in the second wave of the UK coronavirus outbreak, and to understand its variations over time.	Modelling study	Community	NR	Estimates of case fatality rates and their variations over time	Alpha	UK	The relationship between cases and deaths, even when controlling for age, is not static through the second wave of coronavirus in England. The rapid growth in CFR in December can be understood in part in terms of a deadlier new variant Alpha, while a decline in January correlates with vaccine roll-out, suggesting that vaccine reduce the severity of infection, as well as the risk.

Appendix 3: *Quality Appraisal*

Table 1. *Quality Appraisal of research articles using the Newcastle-Ottawa scale (NOS) tool (*High quality: 80-100%; Medium quality: 50-80%; Low quality: <50%)

Author, year	**Pre-print (PP)/ Peer Review (PR)**	**Source**	**Average score per category**			**Adjust for PP**	**Total Score (%) out of 9 (cohort) or 10 (cross-sectional)**	**Overall Quality**
			Selection	Comparability	Outcome			
Cohort Study Design								
Bager, 2021	PP	SSRN	3.5	2	2.5	-2	6 (67)	Medium
Buchan, 2021	PP	MedRxiv	3.5	2	2.5	-2	6 (67)	Medium
Challen, 2021	PR	BMJ	4	2	3	N/A	9 (100)	High
Courjon, 2021	PP	Research Square	4	0.5	2.5	-2	5 (56)	Medium
Chudasama, 2021	PR	Journal of Infection	3.5	2	2.5	N/A	8 (89)	High
Dabrera, 2021	PP	SSRN	4	2	2	-2	6 (67)	Medium
Frampton, 2021	PR	Lancet	4	2	3	N/A	9 (100)	High
Grint, 2021	PR	Eurosurveillance	4	2	3	N/A	9 (100)	High
Haas, 2021	PR	Lancet	4	2	2	N/A	8 (80)	High
Jabłońska, 2021	PP	MedRxiv	4	1	2	-2	5 (56)	Medium
Lumley, 2021	PP	MedRxiv	3	2	1	-2	4 (44)	Low
Patone, 2021	PP	MedRxiv	4	2	2	-2	6 (67)	Medium
Cross-sectional Study Design								
Aiano, 2021	PP	SSRN	4	1	2	-2	5 (50)	Medium
Bachtiger, 2021	PP	MedRxiv	2	1	0	-2	1 (10)	Low
de Andrade, 2021	PP	MedRxiv	2.5	1	2.5	-2	4 (40)	Low
de Oliveira, 2021	PP	MedRxiv	2	0	2	-2	2 (20)	Low
Freitas, 2021	PP	SciELO pre-prints	4	1.5	2.5	-2	6 (60)	Medium
Freitas, 2021	PP	MedRxiv	4	1.5	3	-2	6.5 (65)	Medium
Funk, 2021	PR	Eurosurveillance	4.5	2	3	N/A	9.5 (95)	High
Garvey, 2021	PR	Journal of Infection	4	2	3	N/A	9 (90)	High
Graham, 2021	PR	Lancet	3	2	3	N/A	8 (80)	High
Loconsole, 2021	PR	Environmental Research and Public Health	4	1.5		N/A	8.5 (85)	High
Snell, 2021	PP	MedRxiv	3	1	3	-2	5 (50)	Medium
Takemoto, 2021	PP	MedRxiv	4	1.5	2.5	-2	6 (60)	Medium
Victora, 2021	PP	MedRxiv	4	1.5	2.5	-2	6 (60)	Medium