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Public Health Implications of SARS-CoV-2 Variants of Concern

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Evidence up to October 4, 2021

Introduction
The SARS-CoV-2 virus, responsible for COVID-19, was declared a global pandemic by the World Health Organization (WHO) in March 2020.[1] As of October 22, 2021, over 241 million cases of COVID-19 have been reported worldwide and over 4.9 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 optimal vaccination strategies and enforcing appropriate public health measures to manage the spread of the SARS-CoV-2 virus.

As of September 10, 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 (see Table 1).[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] The increased transmissibility of VOC has led to surges in COVID-19 incidence and consequently, hospitalizations and mortality.[5] Therefore, this living systematic review aims to provide a synthesis of current evidence related to VOC in the context of public health measures. This living synthesis builds on a previous rapid scoping review examining the impacts of VOC on public health and health systems conducted by this team.[6]

Table 1. Current variants of concern (VOC)[3,7]

WHO Name	PANGO LINEAGE	Alternate name	Country first detected in	Earliest samples
Alpha	B.1.1.7	VOC 202012/01	United Kingdom	September 2020
Beta	B.1.351	VOC 202012/02	South Africa	August 2020
Gamma	P.1	VOC 202101/02	Brazil	December 2020
Delta	B.1.617.2	N/A	India	October 2020

Emerging Points of Interest
- **There is evolving evidence regarding changes in vaccine scheduling related to the need for a third dose of vaccine.**
- **Multiple studies show that frequent PCR or rapid antigen testing (ideally, 1-3 times per week) is one of the most effective strategies for preventing and containing outbreaks, especially in schools and post-secondary settings.**

- **Public health measures in the community help mitigate cases in schools, as transmission is more likely to occur in the community than in schools.**
- **Evidence related to public health measures and Delta is emerging rapidly.**
- **An increasing number of modelling studies indicate that by vaccinating children and/or adolescents, the impact of VOC, particularly Delta, could be mitigated, along with the continued vaccination of adults.**
- **Increasing evidence shows that combined NPIs are more effective than single NPIs at containing outbreaks.**
- **Some evidence showing that mixing vaccine types and booster vaccines (i.e., third doses) provides good protection against VOCs.**
- **Increasing evidence suggests that a third dose of vaccine would be beneficial, particularly against Delta, due to waning immunity among early vaccinated populations.**
- **In light of Delta, continued evidence suggests that a combination of vaccine rollout and NPIs is needed to reduce infection.**
- **Universal mask-wearing continues to show importance in reducing the spread of COVID-19, particularly indoors (e.g., workplaces and schools), regardless of vaccination status.**
- **Minimizing social contacts among adults may be required to reduce spread and keep children in school, and hybrid learning may further reduce the spread of COVID-19, hospitalization, and death.**

Patient-Identified Key Messages

- There is a need to continue with masking and other NPIs as indicated by Public Health, even if you are double vaccinated. The public should be reminded that they are not only protecting themselves but more importantly our children and others who are not able to get vaccinated.
- A third (booster) vaccine is likely needed to stay ahead of the Delta variant. Be prepared when your time comes.
- Frequent PCR and rapid testing, including asymptomatic testing, is needed to monitor and manage transmission of VOCs.

Categories of evidence included in this report are as follows:

Modifying approach to vaccines: Any studies that reported on changing approaches to vaccinations such as modelling the rollout schedules or impact of NPIs in relation to vaccine schedules. Four sub-categories fell under this category:

a) Modelling potential vaccination rollout schedules
b) Evaluating past vaccination rollout schedules
c) Modelling potential vaccination rollout schedules in the presence of NPIs
d) Evaluating past vaccination rollout schedules in the presence of NPIs

Infection prevention measures: Any studies that reported on public health measures aimed at preventing the spread of VOC such as mask wearing, hand washing or physical distancing.

Infection control measures: Any studies that reported on public health measures aimed at controlling the spread of VOC such as quarantines, lockdowns, screening or testing strategies.

Results Tables

The following tables present a summary of evidence in relation to each of the categories described above. **42 studies were added to this update, and the most recent content is in bold, blue font.**

Table 2. Evidence related to modifying approach to vaccination, divided by VOC
*Note: Only observational studies were appraised for quality

Category	Alpha (B.1.1.7)	Beta (B.1.351)	Gamma (P.1)	Delta (B.1.617.2)
Modifying approach to vaccination				
Modelling potential vaccination rollout schedules *for first and second doses*	• **Mixing vaccine types may be effective against SARS-CoV-2**[8] • **Global death toll would increase by 20% if vaccine-rich countries achieve full vaccination status before exporting vaccines to countries in-need**[9] • Accelerated vaccine rollout (60 doses/day/10,000 pop) would reduce severe health outcomes[10] • Estimated current vaccine schedule of 1/1000 doses/person/day would need to be quadrupled to control the spread of VOC[11] • Speed of vaccine rollout is key factor in achieving low IAR, burden of disease[12–18], preventing additional VOC-driven waves[19], and mitigating the effect of decreased vaccine effectiveness[20] • Change in inter-dose vaccine period from 21 to 42 days is preferrable for vaccine mode of action at the end of infection course, severe	• Speed of vaccine rollout is key factor in achieving low IAR and disease burden[13] • Herd immunity could be reached in China by Sept 2021 if vaccines extended to age 3+[24]	• Speed of vaccine rollout is key factor in achieving low IAR and disease burden[16,18] and preventing additional VOC-driven waves[19,26] • Postponing second vaccine dose is not recommended to avoid VOC-driven waves[19] • Herd immunity could be reached in China by Sept 2021 if vaccines extended to age 3+[24]	• **Targeted vaccine roll out focusing on children**[27] **or adolescents**[28–30] **needed to mitigate spread and reach herd immunity** • **Mixing vaccine types may be effective against SARS-CoV-2**[8] • **Unvaccinated individuals about 10x more likely to experience symptomatic infections vs vaccinated people**[31] • Speed of vaccine rollout is key factor in achieving low IAR and disease burden[16], preventing additional VOC-driven waves [19], and mitigating the effect of decreased vaccine effectiveness[20] • Prioritizing first dose is recommended, as higher protection

	epidemic and low vaccine supply rate[21] • Postponing second vaccine dose is not recommended to avoid VOC-driven waves[19] • Proactive surveillance and prioritized vaccination can reduce severe illness and mortality in vulnerable groups[22] with vaccinating children enhancing these benefits[23,24] • Minimal impact of vaccinating youth (10-19yr) in reducing transmission, unless 80% of adult population is vaccinated[25]			associated with extended schedules[32] • Postponing second vaccine dose is not recommended to avoid VOC-driven waves[19] • Herd immunity could be reached in China by Sept 2021 if vaccines extended to age 3+; however, 87.5% of entire population would need to be vaccinated with a 95% efficacious vaccine using Delta's transmission properties[24]
Modelling potential vaccination rollout schedules *for third doses*	• Third dose of vaccine is required to eliminate developing mutations and reduce transmission rates[33,34]	• Third dose of vaccine is required to eliminate developing mutations and reduce transmission rates[33]	• Third dose of vaccine is required to eliminate developing mutations and reduce transmission rates[33]	• **Third dose of vaccine provides good protection against VOC[35] and may be necessary to mitigate the expected waning immunity of vaccines and increased infectivity of Delta[28,36]** • Third dose of vaccine is required to eliminate developing mutations, reduce

				transmission rates[33,34]
Evaluating vaccination rollout schedules *for first and second doses*	• Prioritizing first dose is recommended, as higher protection is associated with extended schedules[32,37] **particularly in individuals not previously exposed to SARS-CoV-1**[38] • Mixing doses (AstraZeneca + Pfizer) at 10-12 week intervals was well tolerated & improved immunogenicity compared to 2 doses of the same vaccine at the same or shorter intervals[39] ***Appraised studies were of high quality***	• Mixing doses (AstraZeneca + Pfizer) at 10-12 week intervals was well tolerated & improved immunogenicity compared to 2 doses of the same vaccine at the same or shorter intervals[39] • **2 doses of vaccine with 10 week delay increases antibody response in serum samples of both previously infected and naïve individuals**[40] • **Second dose can be delayed in situations of limited supply and high incidence**[41] ***Appraised studies were of high quality***	• Targeted vaccination of 80+ age group associated with decreased mortality compared with younger group[42] ***Appraised study was of medium quality***	• Prioritizing first dose is recommended, as higher protection associated with extended schedules[32] **particularly in individuals not previously exposed to SARS-CoV-1**[38] • **2 doses of vaccine with 10-week delay increases antibody response in serum samples of both previously infected and naïve individuals**[40] • **Transmission reduction declines 3 months post 2-dose regime of Pfizer and AZ**[43] ***Appraised studies were of medium to high quality***
Evaluating vaccination rollout schedules *for third doses*	• **Third dose of vaccine provides good protection against VOC**[44,45]	N/A	• **Third dose of vaccine provides good protection against VOC**[44,45]	• Third doses can increase antibody levels and neutralizing

	Appraised study was of medium quality		*Appraised study was of medium quality*	capability[46] among immunocompromised individuals[47] • **Third dose can result in short term reduction of testing positive for Delta compared with 2-dose regime**[46] • **Third dose of vaccine provides good protection against VOC**[44,45,48,49] *Appraised studies were of medium quality*
Modelling different vaccine schedules in relation to NPIs *in the general population*	• Advocate for NPIs to remain in place during vaccine roll out until sufficient population immunity[25,50–57] • NPIs alongside accelerated vaccine roll out is needed to control outbreak[18,28,30,31,54,57–61], **with a focus on targeting vulnerable populations**[9] • In OECD, countries fully vaccinating 40% of the population would allow for easing of containment policies[62]	• Advocate for NPIs to remain in place during vaccine roll out until sufficient population immunity[50,51,57]	• **Advocate for NPIs to remain in place during vaccine roll out until sufficient population immunity**[57] • **NPIs alongside accelerated vaccine rollout is needed to control outbreak**[18] • **Herd immunity is achieved through a combination of natural immunity, the use of different vaccines and social distancing**[26]	• **Advocate for NPIs to remain in place during vaccine roll out until sufficient population immunity**[57] • Combination vaccine (accelerated) and NPIs are required to reduce transmission rate[19,56,58,63–69], hospitalizations and deaths[70] • Stringent NPIs and third booster may be needed to stop spread of Delta[36,71,72]

Modelling different vaccine schedules in relation to NPIs *in school settings*	N/A	N/A	N/A	• Even with the combination of vaccine and NPIs, infections will hit school aged children the hardest during the Fall 2021[73] • NPI and intense vaccine strategy targeting students [29,74] **and/or teachers**[75] is needed to substantially reduce the risk of infection • Increasing vaccine coverage in adolescents and regular testing essential to keep schools open[76]
Evaluating different vaccine schedules in relation to NPIs *in the general population*	N/A	N/A	N/A	• **High vaccine rates plus multicomponent prevention strategies are important to reduce transmission in congregate settings**[77] ***Appraised study was of high quality***
Evaluating different vaccine schedules in relation to NPIs *in school settings*	N/A	N/A	N/A	• **Staff vaccination and strict NPI are needed in schools to protect younger children**[78]

				Appraised study was of medium quality

Table 3. Evidence related to infection prevention measures, divided by VOC
*Note: Only observational studies were appraised for quality

Category	Alpha (B.1.1.7)	Beta (B.1.351)	Gamma (P.1)	Delta (B.1.617.2)
Infection prevention measures				
Hand washing	• VOC responds similarly to ethanol and soap as non-VOC[79] • Vaccinated individuals may do less handwashing than non-vaccinated individuals[80] ***Appraised study was of medium quality***	• VOC responds similarly to ethanol and soap as non-VOC[79] • Vaccinated individuals may do less handwashing than non-vaccinated individuals[80] ***Appraised study was of medium quality***	• Vaccinated individuals may do less handwashing than non-vaccinated individuals[80] ***Appraised study was of medium quality***	• Vaccinated individuals may do less handwashing than non-vaccinated individuals[80] ***Appraised study was of medium quality***
Hand washing—*Modelling studies*	N/A	N/A	N/A	N/A
Masking	• No difference was found between surgical and cloth masks, but tighter fitting masks recommended indoors[81] • Double mask combination of surgical/two-layer cloth l + N-95 improved fit and protection[82] • Vaccination status did not change mask wearing in China[80] ***Appraised studies were of medium quality***	• Double mask combination of surgical/two-layer cloth + N-95 improved fit and protection[82] • Vaccination status did not change mask wearing in China[80] ***Appraised study was of medium quality***	• Double mask combination of surgical/two-layer cloth + N-95 improved fit and protection[82] • Vaccination status did not change mask wearing in China[80] ***Appraised study was of medium quality***	• Vaccination status did not change mask wearing in China[80] ***Appraised study was of medium quality***

Masking <u>in the general population</u>—*Modelling studies*	• Moderately effective masks, when worn consistently correctly by a large portion of the population, are effective at preventing transmission[83]	N/A	N/A	• **Regardless of vaccination status, masks can reduce the spread of COVID-19**[69] • **Masks are recommended in the workplace unless 100% vaccination with 95% effectiveness and community infection rate is <150 per 100,000**[84]
Masking <u>in school settings</u>—*Modelling studies*	N/A	N/A	N/A	• Universal masking in schools is recommended to reduce in-school transmission[71,75,85–87]
Physical distancing	• Settings where physical distancing is unlikely (e.g., hair salons, visiting with friends inside the home) present the highest risk of transmission[88] • In daycares, strict contact restrictions like group assignments among children and staff assignments to groups prevent infections[89] • Vaccinated individuals may engage in less physical distancing than non-vaccinated individuals[80]	• Vaccinated individuals may engage in less physical distancing than non-vaccinated individuals[80]	• Vaccinated individuals may engage in less physical distancing than non-vaccinated individuals[80]	• Vaccinated individuals may engage in less physical distancing than non-vaccinated individuals[80]

	Appraised studies were of medium to high quality	***Appraised study was of medium quality***	***Appraised study was of medium quality***	***Appraised study was of medium quality***
Physical distancing in the general population— ***Modelling studies***	• Strong physical distancing measures are critical, even with a mass vaccination campaign[19,91] and physical distancing may need to be strengthened by 33.7%[93]	• Strong physical distancing measures are critical even with a mass vaccination campaign[50,94]	• Strong physical distancing measures are critical even with a mass vaccination campaign[94]	• Strong physical distancing measures and high compliance are critical even with a mass vaccination campaign[19,91,92]
Physical distancing in school settings— ***Modelling studies***	• **Adult physical distancing may need to be reduced by 30%[66] to minimize high case counts and allow children to return to school**	N/A	N/A	• **Adult physical distancing may need to be reduced by 30%[66] to minimize high case counts and allow children to return to school** • **Increasing social distance (e.g., hybrid schooling) can reduce peak hospitalization and death, although it is more disruptive to learning[87]**

Table 4. Evidence related to infection control measures, divided by VOC
*Note: Only observational studies were appraised for quality

Category	Alpha (B.1.1.7)	Beta (B.1.351)	Gamma (P.1)	Delta (B.1.617.2)
Infection control measures				
Testing <u>in the general population</u>	• Offering voluntary testing 1-2 times/week to all employees and daily to close contacts of cases for 10 days allowed employees to continue working rather than quarantine[95] • Employees more likely to get tested using saliva samples than nasal swabs[95] • Testing and routine surveillance of populations at risk are critical[96] • Self-collection and pooling approaches to testing of travellers allows large-scale screening using less human, material and financial resources[97] ***Appraised studies were of high quality***	• Offering voluntary testing 1-2 times/week to all employees and daily to close contacts of cases for 10 days allowed employees to continue working rather than quarantine • Employees more likely to get tested using saliva samples than nasal swabs[95] ***Appraised study was of high quality***	• Mass saliva analysis is a cheap, easy to collect, and feasible asymptomatic testing strategy to potentially slow variant outbreaks[98] ***Appraised study was of low quality***	N/A
Testing <u>in school settings</u>	• **In one university setting, compulsory weekly testing of students living in dormitories successfully detected an outbreak**[99]; in another, asymptomatic mass testing needed to be	N/A	N/A	N/A

	very frequent (~every 3 days) to be effective at containing outbreaks[100] ***Appraised study was of medium quality***			
Testing in the general population—*Modelling studies*	• **Expanding testing capacity and reducing testing delays (e.g., time from testing to results) both have an effect on epidemic growth**[101] • Another strategy to prevent outbreaks in the workplace is to offer targeted rapid testing (rather than mass testing) and begin quarantine procedures sooner for direct and indirect contacts[102] • Testing and routine surveillance of populations at risk are critical[103] • Surveillance of travellers remains important[52] • Daily testing for 5 days could circumvent the need for quarantine of travellers[104] • Pre-flight tests may prevent the majority of transmission from travellers[104]	• **Expanding testing capacity and reducing testing delays (e.g., time from testing to results) both have an effect on epidemic growth**[101] • Testing and routine surveillance of populations at risk are critical even with a mass vaccination campaign[50]	• **Expanding testing capacity and reducing testing delays (e.g., time from testing to results) both have an effect on epidemic growth**[101]	• **More frequent testing (PCR or rapid antigen) is an effective NPI against Delta**[75,84,105,106] • **Rapid antigen tests perform best in low prevalence settings; when prevalence increases, they perform poorly due to high numbers of false negatives**[105] • **Rapid antigen test performance improves with repeat testing (in one model, 2 tests 36 hours apart**[105]**; in another, 3 times/week**[84] • **Expanding testing capacity and reducing testing delays (e.g., time from testing to results) both have an effect on epidemic growth**[101] • The optimal testing strategy is weekly testing of the entire unvaccinated population, plus a 10-day isolation requirement for positive cases and their households[107,108]

Testing <u>in school settings</u>—*Modelling studies*	N/A	N/A	N/A	• **In schools, the only single NPI (vs. combined NPIs) that is effective is antigen testing students twice weekly**[75] • **In schools, regular testing is a more effective strategy than bubble quarantining**[106] • In a model of partially vaccinated K-12 schools, regular testing effectively prevented outbreaks; effect correlated with frequency (i.e., testing 1-2 times/week was better than biweekly)[76] • In another model of K-12 schools with mandatory masking, testing 50% of students reduced infections to 22%[85]
Quarantine (close contacts and travellers) <u>in the general population</u>	• In a workplace with mandatory daily testing and other NPIs for close contacts, quarantine was not required to contain outbreaks[95] • Alpha cases almost twice as likely to give rise to household clusters compared with wild type cases, highlighting importance of quarantining household contacts[109,110]	• Some studies found that mandatory quarantine and contact tracing are required[77] • Conversely, in a workplace with mandatory daily testing and other NPIs for close contacts, quarantine was not required to contain outbreaks[95]	• Mandatory quarantine may be an effective way to contain Gamma[113]	N/A

	• Mandatory quarantine and contact tracing are required[77,96,104,111–113] ***Appraised studies were of low to high quality***	***Appraised studies were of high quality***	***Appraised study was of low quality***	
Quarantine (close contacts and travellers) <u>in the general population</u>—*Modelling studies*	• **At least 40% (ideally 50%) of close contacts must be traced and quarantined to achieve containment of strain-specific outbreaks**[101] • Mandatory quarantine and contact tracing are required[69,75] and may need to be extended to indirect contacts in workplace settings[102] • A 10-day quarantine period may be as effective as a 14-day quarantine period[104]	• **At least 40% (ideally 50%) of close contacts must be traced and quarantined to achieve containment of strain-specific outbreaks**[101] • Some studies found that mandatory quarantine and contact tracing are required[76], and Beta may require more extreme quarantine and testing measures than other variants[111]	• **At least 40% (ideally 50%) of close contacts must be traced and quarantined to achieve containment of strain-specific outbreaks**[101] • Forced prolonged cohabiting may boost viral ability to generate Gamma mutation[114]	• **At least 40% (ideally 50%) of close contacts must be traced and quarantined to achieve containment of strain-specific outbreaks**[101]
Quarantine (close contacts and travellers) <u>in school settings</u>—*Modelling studies*	• In a university setting, quarantine of close contacts is important in preventing transmission during the term [100]	N/A	N/A	• **In schools, bubble quarantine (i.e., sending classroom contacts home) results in large numbers of pupils absent from school, with only modest impact on classroom infection rates**[106] • In K-12 schools, reactive quarantining of classes with

				a confirmed case do not have a high benefit, but do have a high cost in terms of student-days lost[76]
Isolation (confirmed COVID-19/VOC cases)	N/A	N/A	N/A	N/A
Isolation (confirmed COVID-19/VOC cases) <u>in the general population</u>—*Modelling studies*	• Complete isolation of Alpha cases is required to prevent outbreaks; even a small number of infected people dramatically increases the probability of sustained community transmission[12]	N/A	N/A	• To control outbreaks, the optimal testing strategy is weekly testing of the entire unvaccinated population, plus a 10-day isolation requirement for positive cases and their households[107]
Isolation (confirmed COVID-19/VOC cases) <u>in school settings</u>—*Modelling studies*	• In a university setting, isolation of confirmed cases is important in preventing transmission during the term[100]	N/A	N/A	N/A
Lockdowns <u>in the general population</u>	• **Lockdowns can exacerbate outbreaks when transient workers are forced to return home from cities to smaller villages[115]**	• **Lockdowns can exacerbate outbreaks when transient workers are forced to return home from cities to smaller villages[115]**	N/A	• **Lockdown was one of the most effective strategies to address India's Delta wave[116]**
Lockdowns <u>in the general population</u>—	• **Decreased retail and recreational mobility contributed the most to a**	N/A	N/A	• Delta requires stronger lockdown measures than wild type[34,64]

Modelling studies	**reduction in community transmission**[117] • Alpha requires stronger lockdown measures than wild type[34,60,64,118,119] including increased length,[120,121] earlier implementation[118] and stricter regional travel restrictions[34,103] • Shorter, stricter lockdowns may be more effective than longer, moderate lockdowns due to waning adherence[122]			• In an Australian model, the strength of lockdown had a bigger impact on hospitalizations and deaths than vaccination strategies[70] • Early public interventions—lockdowns imposed during an 'optimal time window'—lead to reduced death counts from Delta[123]
Lockdowns in school settings—*Modelling studies*	• Keeping schools partially open while keeping most of society closed brought R below 1 in a UK model[65]	N/A	N/A	N/A
Other/combined NPIs in the general population	• In June 2021, when Alpha was still prevalent, VOC were highest in Canadian provinces with moderate vaccine uptake and strict NPIs, and lowest in provinces with low vaccine uptake and moderate NPIs; this may suggest that the *timing* of NPI implementation (reactive vs. proactive) may have more of an impact than stringency[124]	• NPIs should be implemented until herd immunity is reached[24]	N/A	• **Combined NPIs were required to address India's Delta wave**[116] • NPIs should be implemented until herd immunity is reached[24]

	• In daycares, NPIs like closures in the event of an outbreak can help contain Alpha[125] ***Appraised study is of high quality***			
Other/combined NPIs <u>in school settings</u>	• **Opening schools is associated with increased infection rates in the community, but transmission is more likely to occur outside of school and be related to community prevalence**[126] • **Public health measures in the community decreased school-related growth 2-6 times**[126] • **In a university setting, isolation of students with COVID-19, contact tracing, and institution-wide prevention measures contributed to reductions in transmission**[99] ***Appraised study is of medium quality***	N/A	N/A	• **In schools, combined NPIs such as masking, routine testing, ventilation, social distancing, and isolation when symptomatic are very important**[78,106] ***Appraised study is of medium quality***
Other/combined NPIs <u>in the general population</u>—	• Multiple NPIs are more effective than single NPIs,[17,24] and reactive NPIs (e.g., quarantine of close	N/A	• Strict NPIs are required to contain Gamma[24,63]	• **Combined NPIs in the community have an immediate impact on case levels vs. the delayed impact of vaccines**[71]

Modelling studies	contacts) must be deployed quickly • Strong test-trace-isolate programs can be sufficient to maintain low case numbers[58,127] • Regional mobility networks and spatial connectivity drive patterns of transmission throughout the United States[91] • Strict NPIs may lead to overdispersion of highly transmissible variants, leading to their eventual dominance[128]; evolution of highly transmissible variants may actually be a sign that NPI policies are effective[129]			• **In a model of France, the only way to contain Delta was to keep combined NPIs in place until 100% vaccination coverage was reached**[57] • Regional mobility networks and spatial connectivity drive patterns of transmission throughout the United States[91] • Even modest improvements in a find, test, trace, isolate and support program would control transmission[130]
Other/combined NPIs <u>in school settings</u>—*Modelling studies*	• In a university setting, staggering the return of students to residences is not significantly effective in preventing transmission[100]	N/A	N/A	• **The most effective NPI combination to prevent outbreaks in schools is improved ventilation and weekly antigen testing of teachers and students if a student is the source of infection; if a teacher is the source, mask usage is also required**[75] • In schools, continued use of multiple NPIs (e.g., universal masking and distancing or cohorting) is

				recommended[29,74,131], combined with high vaccination coverage[86]

Overview of the Evidence

As of October 22, 2021, 126 studies have reported on VOC and public health measures. We include 84 studies from earlier reports (including 21 studies from an earlier rapid review[6], 31 from the first iteration of this report[132], and 32 from the updated search on August 25, 2021). The key findings of included studies can be found in tables 2-4 above, while a more detailed summary of each study can be found in the supplementary material tables. The majority of reported evidence was related to Alpha (n=88), with fewer studies reporting on Beta (n=28 studies), Gamma (n=25 studies) and a rapidly growing volume of evidence related to Delta (n=60 studies).

Modifying Approach to Vaccine Delivery

- 76[8–34,36–39,39–60,62–69,71–78,86,88,99,108,133] studies reported on vaccine delivery. The majority of modelling studies explored potential vaccine rollout schedules and made recommendations for accelerated vaccination campaigns. This included studies that modelled vaccine rollout in both the presence and absence of NPIs, such as lockdown measures.
- **There is evidence to support delay of the second dose under certain conditions, such as limited supply and high incidence.**[22,23,38,40,41]
- Evidence is emerging about the value of third dose or booster vaccines[33], particularly in the context of Delta[43–46,48,72,88] and immunocompromised patients.[47]
- Several modelling studies[73,74,76]suggest infections will likely hit school-aged children the hardest and recommend different targeted vaccine schedules with continued NPIs including testing.
- NPIs are recommended to continue in tandem with a vaccine rollout schedule.
- **Modelling studies suggest that extending vaccine rollout to children and/or adolescents would help mitigate the spread of VOC, particularly Delta.**[27–30]

Infection Prevention Measures

- The one study that reported on handwashing and VOC found that Alpha and Beta respond similarly to ethanol and soap as wildtype SARS-CoV-2.[79]
- One study found that vaccinated individuals may engage in less handwashing and physical distancing than non-vaccinated individuals but not mask wearing.[80]
- **Modelling studies suggest that when worn correctly, masks are effective against Alpha[83] and Delta, regardless of vaccination status[69], unless 100% vaccination with 95% effectiveness and community infection rate are <150 per 100,000.**[84]
- One study found no difference between cloth and surgical masks against Alpha,[81] but another study found double masking better for protection against all VOCs.[82]
- **Universal masking in schools is recommended to reduce in-school transmission.**[71,75,85–87]
- **Nine** studies reported on VOC and physical distancing measures.[19,50,66,87–90,93,94] All studies recommended imposing strong physical distancing measures in the presence of all VOCs. **Two studies suggest that reducing social contacts by adults may be required**

to minimize spread and keep children in school, yet hybrid learning may further reduce the spread of COVID-19, hospitalization, and death.[66,87]

Infection Control Measures

- Twenty[50,52,75,76,84,85,95–108] studies reported on testing strategies related to VOC. Testing and routine surveillance of populations are critical to containing Alpha, Beta and Delta, even in the presence of mass vaccination campaigns. Cheaper approaches to testing are possible for detecting Alpha and Gamma.
- Fourteen[94–96,100–102,104,106,109–114] studies reported on quarantine and VOC. Mandatory quarantine were reported as necessary to contain Alpha and Beta. Alpha and Gamma were identified as giving rise to more household clusters than wildtype, suggesting a need for adequate household quarantine measures.
- Three[12,100,107] studies reported on isolation and VOC to contain transmission of the virus. One study was related to Alpha and Gamma respectively. Isolation duration varied across studies.
- Thirteen[60,64,65,70,103,115–121,123] studies reported on lockdowns and VOC. All studies reported needing strict lockdown measures to contain Alpha or Delta. Some studies recommended longer lockdowns and more restrictive travel restrictions, while one study recommended short, strict lockdowns to mitigate the waning adherence to longer lockdowns. Two studies suggested earlier implementation of lockdown measures to limit virus spread[105,123].
- Twenty-four[17,24,37,57,58,63,71,74,75,78,86,91,99,100,102,106,116,125–131] studies reported on other NPI infection control measures and VOC. Two studies recommended modest to strong test, trace and isolate strategies as necessary to control the spread of Alpha and Delta. Two studies found that deploying a combination of NPIs is more effective than single NPIs[17,24], and multiple studies recommended employing NPIs in conjunction with vaccine rollout to mitigate the spread of Alpha or Delta.

Methods

This living synthesis is building on previous evidence gathered up to May 11, 2021. Searches for this update were run on October 4, 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. Titles/abstracts and full text 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 measures. Critical appraisal was conducted for case-control, cohort, and cross-sectional studies using the Newcastle-Ottawa Scale for studies included in our previous rapid review[6] and appropriate Joanna Briggs critical appraisal tools for studies included in this living syntheses. Critical appraisal was not conducted for modelling or laboratory studies. Patient partners attended weekly review team meetings, reviewed summary tables for each update and developed important messages for a public audience.

List of Abbreviations

COVID-19: coronavirus disease 2019
IAR: infection attack rate
NPI: non-pharmaceutical intervention/s
R: effective reproduction number
VOC: variant/s of concern
WHO: World Health Organization

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