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

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Evidence up to November 15, 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 December 2, 2021, over 262 million cases of COVID-19 have been reported worldwide and over 5.2 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 November 26, 2021, five 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]

Of note, the literature search was conducted prior to the WHO labeling Omicron as a VOC; thus, this update does not include any information related to Omicron.

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
Omicron	B.1.1.529	N/A	Multiple countries	November 2021

Emerging Points of Interest

- **While evidence continues to show that boosters and/or additional doses of vaccine provide good protection against VOC, prioritizing primary dose series completion (1 or 2 doses as required) on a global scale should remain a focus.**
- **Evidence continues to show that combined NPIs are more effective than single NPIs at containing outbreaks and should remain in place until very high vaccination rates (primary dose series) are achieved.**
- **Further evidence shows that interval delay between doses in a primary series (up to 16 weeks) demonstrates vaccine effectiveness (VE) at 5-8 months against VOC.**
- **Further evidence supports the effectiveness of following 1 or 2 doses of non-mRNA vaccine with a second or booster dose of mRNA vaccine.**
- **Further evidence supports that COVID-19 is airborne, with studies showing increased risk of transmission the closer individuals are to an infected individual.**
- **Frequent testing remains an important strategy for containing outbreaks, but modelled and observed approaches vary widely, with little consensus on optimal frequency or administration.**
- **Likewise, recommendations for the ideal length of quarantine and isolation remain varied.**

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.
- A third (booster) vaccine is likely going to be required to stay ahead of Delta variant. Be prepared when your times 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.

NEW Booster Doses, Third Doses and Additional Doses

The following definitions and terminology are used by the WHO throughout its policy recommendations on COVID-19 vaccination.[8]

> **Booster doses** are administered to a vaccinated population that has completed a primary vaccination series (currently one or two doses of COVID-19 vaccine depending on the product) when, with time, the immunity and clinical protection has fallen below a rate deemed sufficient in that population. The objective of a booster dose is to restore vaccine effectiveness from that deemed no longer sufficient.
>
> **Additional doses** of a vaccine may be needed as part of an extended primary series for target populations where the immune response rate following the standard primary series is deemed insufficient. The objective of an additional dose in the primary series is to optimize or enhance the immune response to establish a sufficient level of effectiveness against disease. In particular, immunocompromised individuals often fail to mount a protective immune response after a standard primary series, but also older adults may respond poorly to a standard primary series.

In this report, we use the terms *booster* and *additional doses* as defined by the WHO, which may differ from study author usage.

Results Tables

The following tables present a summary of evidence in relation to each of the categories described above. **44 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*	• **Increasing primary vaccination coverage (2 doses) should be prioritised over additional doses in the design of allocation strategies of COVID-19 vaccines**[9] • Mixing vaccine types may be effective against SARS-CoV-2[10] • Global death toll would increase by 20% if vaccine-rich countries achieve full vaccination status before exporting vaccines to countries in-need[11] • Speed of vaccine rollout is key factor preventing additional VOC-driven waves and associated outcomes[12–22] • While some research suggests change in inter-dose vaccine period from 21 to 42 days is preferrable,[21] postponing second vaccine dose is not recommended in other research to avoid VOC-driven waves[23]	• 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+[25] • **Increasing primary vaccination coverage (2 doses) should be prioritised over additional doses in the design of allocation strategies of COVID-19 vaccines**[9]	• Speed of vaccine rollout is key factor in achieving low IAR and disease burden[16,18] and preventing additional VOC-driven waves[23,27] • Postponing second vaccine dose is not recommended to avoid VOC-driven waves[23] • Herd immunity could be reached in China by Sept 2021 if vaccines extended to age 3+[25]	• **Increasing primary vaccination coverage (2 doses) should be prioritised over third dose in the design of allocation strategies of COVID-19 vaccines**[9] • Targeted vaccine rollout focusing on children[25,28] or adolescents[29–31] needed to mitigate spread and reach herd immunity • **Prioritizing vaccine distribution for children and adults over seniors is needed to minimize death and infection**[32] • **Prioritizing staff vaccination with at least two doses can lead to a large reduction of transmission in nursing homes**[33] • Mixing vaccine types may be effective against SARS-CoV-2[10] • Unvaccinated individuals about 10x more likely to experience symptomatic

	• Proactive surveillance and prioritized vaccination can reduce severe illness and mortality in vulnerable groups[22] with vaccinating children enhancing these benefits[24,25] • Minimal impact of vaccinating youth (10-19yr) in reducing transmission, unless 80% of adult population is vaccinated[26]			infections vs vaccinated people[34] • Speed of vaccine rollout is key factor in achieving low IAR and disease burden[16] , preventing additional VOC-driven waves[16,23,35] • Prioritizing first dose is recommended, as higher protection associated with extended schedules[36] • Postponing second vaccine dose is not recommended to avoid VOC-driven waves[23]
Modelling potential vaccination rollout schedules *for additional doses/boosters*	• Third dose of vaccine is required to eliminate developing mutations and reduce transmission rates[37,38]	• Third dose of vaccine is required to eliminate developing mutations and reduce transmission rates[37]	• Third dose of vaccine is required to eliminate developing mutations and reduce transmission rates[37]	• Third dose of vaccine provides good protection against VOC[39] and may be necessary to mitigate the waning immunity of vaccines and increased infectivity of Delta[29,40,41] • Third dose of vaccine is required to eliminate developing mutations, reduce transmission rates[37,38] • **Boosters can lead to a large reduction of transmission in nursing homes; however, symptomatic infections are likely to continue when community transmission is high[33]**

Evaluating vaccination rollout schedules *for first and second doses*	• Prioritizing first dose is recommended, as higher protection is associated with extended vaccine schedules[36,42,43], but impact on previously infected vs naïve individuals is mixed[42,43] • Mixing vaccine types provides superior protection compared to homologous vaccine (either AstraZeneca or Pfizer)[44] • **Vaccination recommended early in pregnancy to maximize maternal protection, without compromising neonatal antibody protection**[45]	• Prioritizing first dose is recommended, as higher protection associated with extended vaccine schedules[42–44,46,47] but impact on previously infected vs naïve individuals is mixed[42,43] • Mixing vaccine types provides superior protection compared to homologous vaccine (either AstraZeneca or Pfizer)[44] • Second dose can be delayed in situations of limited supply and high incidence[48] • **Vaccination recommended early in pregnancy to maximize maternal protection, without compromising neonatal antibody protection**[45]	• Targeted vaccination of 80+ age group associated with decreased mortality compared with younger group[49] • Prioritizing first dose is recommended, as higher protection is associated with extended vaccine schedules[36,42,43], but impact on previously infected vs naïve individuals is mixed[42,43] • **Vaccination recommended early in pregnancy to maximize maternal protection, without compromising neonatal antibody protection**[45]	• Prioritizing first dose is recommended, as higher protection associated with extended vaccine schedules[36,42,43,46,47], but impact on previously infected vs naïve individuals is mixed[42,43] • Transmission reduction declines 3 months post 2-dose regime of Pfizer and AZ[43,50] • **Targeted vaccine rollout focusing on children**[51] **needed to mitigate spread and reach herd immunity** • **Mixing 1st dose AZ vaccine with 2nd dose mRNA vaccine provides superior protection compared to 2 doses of AZ vaccine** [52] • **Vaccination recommended early in pregnancy to maximize maternal protection, without compromising neonatal antibody protection**[45]

	Appraised studies were of high quality	*Appraised studies were of high quality*	*Appraised study was of medium to high quality*	*Appraised studies were of medium to high quality*
Evaluating vaccination rollout schedules *for additional doses/boosters*	• Third dose of vaccine provides good protection against VOC[49,53–57] • **Previously infected (PI) individuals had higher immune response post-vaccination suggesting PI should be taken into consideration with third dose recommendations**[58] ***Appraised studies were of medium to high quality***	• Third dose of vaccine provides good protection against VOC[53–57,59] • **mRNA vaccine recommended as booster for people who responded poorly to 2 primary doses of inactivated virus vaccine**[60] • **Previously infected individuals had higher immune response post-vaccination suggesting PI should be taken into consideration with third dose recommendations**[58] ***Appraised studies were of low to high quality***	• Third dose of vaccine provides good protection against VOC[53–55] • **mRNA vaccine recommended as booster for people who responded poorly to 2 primary doses of inactivated virus vaccine** [60] • **Previously infected individuals had higher immune response post-vaccination suggesting PI should be taken into consideration with third dose recommendations**[58] ***Appraised studies were of low to high quality***	• Third dose of vaccine provides good protection against VOC[53–57,59,61–63 64,65] including among immunocompromised individuals[66,67] • Third dose of vaccine provides good protection against VOC[53–57,59,61–63] • **mRNA vaccine recommended as booster for people who responded poorly to 2 primary doses of inactivated virus vaccine** [60] • **Previously infected individuals had higher immune response post-vaccination suggesting PI should be taken into consideration with third dose recommendations**[58] ***Appraised studies were of medium to high 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[26,68–76] • NPIs alongside accelerated vaccine roll out is needed	• Advocate for NPIs to remain in place during vaccine roll out until sufficient population immunity[68,69,75]	• Advocate for NPIs to remain in place during vaccine roll out until sufficient population immunity[75]	• Advocate for NPIs to remain in place during vaccine roll out until sufficient population immunity[75,82,85] • Combination of accelerated vaccine rollout, **including among children**[86], and NPIs

	to control outbreak[18,29,31,34,72,75,77–82], with a focus on targeting vulnerable populations[11] **and prisons**[83] • In OECD, countries fully vaccinating 40% of the population would allow for easing of containment policies[84]	• NPIs alongside accelerated vaccine roll out is needed to control outbreak[81]	• NPIs alongside accelerated vaccine rollout is needed to control outbreak[18,81] • Herd immunity is achieved through a combination of natural immunity, the use of different vaccines and social distancing[27]	are required to reduce transmission rate[23,74,77,81,87–95], hospitalizations and deaths[96] • Stringent NPIs and third booster may be needed to stop spread of Delta[40,97–99]
Modelling different vaccine schedules in relation to NPIs *in children or 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[100] • NPI and intense vaccine strategy targeting **children/**students [30,101,102] and/or teachers[103] is needed to substantially reduce the risk of infection • Increasing vaccine coverage in adolescents and regular testing essential to keep schools open[104] • **Including children and adolescents in the vaccination program coupled with moderate NPIs appears necessary to contain Delta transmission**[29]

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[105] ***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[106] ***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[107] • Vaccinated individuals may do less handwashing than non-vaccinated individuals[108] ***Appraised study was of medium quality***	• VOC responds similarly to ethanol and soap as non-VOC[107] • Vaccinated individuals may do less handwashing than non-vaccinated individuals[108] ***Appraised study was of medium quality***	• Vaccinated individuals may do less handwashing than non-vaccinated individuals[108] ***Appraised study was of medium quality***	• Vaccinated individuals may do less handwashing than non-vaccinated individuals[108] • **Use of hand sanitizer on flights may offer protection against of COVID-19 transmission**[109] ***Appraised studies were of medium quality***
Hand washing—*Modelling studies*	N/A	N/A	N/A	N/A
Masking	• Tight fitting masks[110] or double mask combination of surgical/two-layer cloth l + N-95[111] offer better protection • Vaccination status did not change mask wearing in China[108] ***Appraised studies were of medium quality***	• Double mask combination of surgical/two-layer cloth + N-95 improved fit and protection[111] • Vaccination status did not change mask wearing in China[108] ***Appraised study was of medium quality***	• Double mask combination of surgical/two-layer cloth + N-95 improved fit and protection[111] • Vaccination status did not change mask wearing in China[108] ***Appraised study was of medium quality***	• Vaccination status did not change mask wearing in China[108] ***Appraised study was of medium quality***

Masking in the general population—*Modelling studies*	• Moderately effective masks, when worn consistently correctly by a large portion of the population, are effective at preventing transmission[112]	N/A	N/A	• Regardless of vaccination status, masks can reduce the spread of COVID-19[92,113–115]
Masking in school settings—*Modelling studies*	N/A	N/A	N/A	• Universal masking in schools is recommended to reduce in-school transmission[97,103,116–118]
Physical distancing	• Settings where physical distancing is unlikely (e.g., hair salons, visiting with friends inside the home) present the highest risk of transmission[119] • In daycares, strict contact restrictions like group assignments among children and staff assignments to groups prevent infections[120] • Vaccinated individuals may engage in less physical distancing than non-vaccinated individuals[108] ***Appraised studies were of medium to high quality***	• Vaccinated individuals may engage in less physical distancing than non-vaccinated individuals[108] ***Appraised study was of medium quality***	• Vaccinated individuals may engage in less physical distancing than non-vaccinated individuals[108] ***Appraised study was of medium quality***	• Vaccinated individuals may engage in less physical distancing than non-vaccinated individuals[108] • **For flights, passengers within 3 rows of a positive individual are at a greater risk of catching COVID than those sitting 3+ rows away**[109] ***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	• Strong physical distancing measures are critical even with a mass	• Strong physical distancing measures are critical even with a mass vaccination campaign[125]	• Strong physical distancing measures and high compliance are critical even with a

	distancing may need to be strengthened by 33.7%[124]	vaccination campaign[68,125]		mass vaccination campaign[23,122,123] • **Maintaining 1.5 m of separation during conversation is recommended to reduce transmission**[114]
Physical distancing in school settings—*Modelling studies*	• Adult physical distancing may need to be reduced by 30%[89] 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%[89] 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[118]

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 in the general population	• 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[126] • Employees more likely to get tested using saliva samples than nasal swabs[126] • Testing and routine surveillance of populations at risk are critical[127] • Self-collection and pooling approaches to testing of travellers allows large-scale screening using less human, material and financial resources[128] ***Appraised studies were of high quality***	• **Mass testing (with whole genome sequencing) as soon as an index case was identified quelled community transmission**[129] • 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[126] • Employees more likely to get tested using saliva samples than nasal swabs[126] ***Appraised studies were of high quality***	• Mass saliva analysis is a cheap, easy to collect, and feasible asymptomatic testing strategy to potentially slow variant outbreaks[130] ***Appraised study was of low quality***	N/A
Testing in school settings	• In one university setting, compulsory weekly testing of students living in dormitories successfully detected an outbreak[131]; in	N/A	N/A	N/A

	another, asymptomatic mass testing needed to be very frequent (~every 3 days) to be effective at containing outbreaks[132] ***Appraised study was of medium quality***			
Testing <u>in the general population</u>—*Modelling studies*	• **When Alpha is dominant, testing is most effective when the vaccination rate is low to moderate, and less effective when the vaccination rate is high**[133] • Expanding testing capacity and reducing testing delays (e.g., time from testing to results) both have an effect on epidemic growth[134] • Offering targeted rapid testing and beginning quarantine procedures sooner can prevent workplace outbreaks[135] • Testing and routine surveillance of populations at risk are critical[136] • Surveillance of travellers remains important[70] • Daily testing for 5 days could circumvent the need for quarantine of travellers[137]	• Expanding testing capacity and reducing testing delays (e.g., time from testing to results) both have an effect on epidemic growth[134] • Testing and routine surveillance of populations at risk are critical even with a mass vaccination campaign[68]	• Expanding testing capacity and reducing testing delays (e.g., time from testing to results) both have an effect on epidemic growth[134]	• More frequent testing (PCR or rapid antigen) is an effective NPI against Delta[103,113,138–140] • Optimal testing strategies vary, ranging from **as frequently as every other day (vs. twice a week for wild type)**[140] to weekly mass testing[141,142] • **When Delta is dominant, testing alone is not enough to contain outbreaks, but must be combined with widespread vaccination; testing targeted at unvaccinated population has the greatest impact**[133] • Rapid antigen tests perform best in low prevalence settings; when prevalence increases, they perform poorly due to high numbers of false negatives[138] • Rapid antigen test performance improves with

	• Pre-flight tests may prevent the majority of transmission from travellers[137]			repeat testing (in **two** models, 2 tests 36 hours apart[115,138]; in another, 3 times/week[113]) • Expanding testing capacity and reducing testing delays (e.g., time from testing to results) both have an effect on epidemic growth[134,140]
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[103] • In schools, regular testing is a more effective strategy than bubble quarantining[139] • In partially vaccinated K-12 schools, regular testing may effectively prevent outbreaks; effect correlates with frequency (i.e., testing 1-2 times/week is better than biweekly)[104] • In K-12 schools with mandatory masking, testing 50% of students reduced infections to 22%[116]
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[126]	• Some studies found that mandatory quarantine and contact tracing are required[77]	• Mandatory quarantine may be an effective way to contain Gamma[147]	• **Passengers sharing rooms during quarantine after traveling have a greater risk transmission risk than those isolating alone**[109]

	• Alpha cases almost twice as likely to give rise to household clusters compared with wild type cases, highlighting importance of quarantining household contacts[143,144] • Mandatory quarantine and contact tracing are required[105,127,137,145–147] ***Appraised studies were of low to high quality***	• Conversely, in a workplace with mandatory daily testing and other NPIs for close contacts, quarantine was not required to contain outbreaks[126] ***Appraised studies were of high quality***	***Appraised study was of low quality***	***Appraised study was of medium quality***
Quarantine (close contacts and travellers) <u>in the general population</u>—*Modelling studies*	• **Quarantine periods of 0-10 days with a PCR test exit requirement can be as effective as a total travel ban at maintaining the current level of Alpha circulation within most European countries**[145] • At least 40% (ideally 50%) of close contacts must be traced and quarantined to achieve containment of strain-specific outbreaks[134] • Mandatory quarantine and contact tracing are required[69,75] and may need to be extended to indirect contacts in workplace settings[135]	• At least 40% (ideally 50%) of close contacts must be traced and quarantined to achieve containment of strain-specific outbreaks[134] • 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[145]	• At least 40% (ideally 50%) of close contacts must be traced and quarantined to achieve containment of strain-specific outbreaks[134] • Forced prolonged cohabiting may boost viral ability to generate Gamma mutation[149]	• **Quarantine periods of 0-3 days with a PCR test exit requirement can be as effective as a total travel ban at maintaining the current level of Delta circulation within most European countries**[145] • At least 40% (ideally 50%) of close contacts must be traced and quarantined to achieve containment of strain-specific outbreaks[134]

	• A 10-day quarantine period may be as effective as a 14-day quarantine period[137]			
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[132]	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[139] • 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[104]
Isolation (confirmed COVID-19/VOC cases)	N/A	N/A	N/A	• **Based on Delta's duration of virologic shedding, the ideal isolation period is at least 10 days from a positive test or onset of symptoms, or until the resolution of symptoms, whichever is longer[150]** ***Appraised study was of medium quality***
Isolation (confirmed COVID-19/VOC cases) <u>in the general population</u>—	• **60-75% of cases would need to be traced and isolated in order to control an Alpha outbreak in Ontario[151]** • Complete isolation of Alpha cases is required to	N/A	N/A	• **Isolating cases rapidly by communicating test results as soon as possible is integral to containing Delta[140]** • A 10-day isolation requirement for positive

Modelling studies	prevent outbreaks; even a small number of infected people dramatically increases the probability of sustained community transmission[12]			cases and their households is ideal for containing outbreaks[141]
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[132]	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[152]	• Lockdowns can exacerbate outbreaks when transient workers are forced to return home from cities to smaller villages[152]	N/A	• Lockdown was one of the most effective strategies to address India's Delta wave[153], **and is integral to China's Delta response**[154] ***Appraised study was of medium quality***
Lockdowns <u>in the general population</u>—*Modelling studies*	• Decreased retail and recreational mobility contributed the most to a reduction in community transmission[155] • Alpha requires stronger lockdown measures than wild type[38,79,95,156,157] including increased length,[158,159] earlier implementation[156] and stricter regional travel restrictions[38,136]	N/A	N/A	• Delta requires stronger lockdown measures than wild type [38,95] • In an Australian model, the strength of lockdown had a bigger impact on hospitalizations and deaths than vaccination strategies[161] • Early public interventions—lockdowns imposed during an 'optimal time window'—

	• Shorter, stricter lockdowns may be more effective than longer, moderate lockdowns due to waning adherence[160]			lead to reduced death counts from Delta[162]
Lockdowns <u>in school settings</u>—*Modelling studies*	• Keeping schools partially open while keeping most of society closed brought R below 1 in a UK model[88]	N/A	N/A	N/A
Other/combined NPIs <u>in the general population</u>	• 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[163] • In daycares, NPIs like closures in the event of an outbreak can help contain Alpha[164] ***Appraised study is of high quality***	• **Implementing a combination of contact tracing, mass testing, and whole genome sequencing effectively controlled community transmission**[129] • NPIs should be implemented until herd immunity is reached[25] ***Appraised study was of high quality***	N/A	• Combined NPIs were required to address India's Delta wave[153] • NPIs should be implemented until herd immunity is reached[25]
Other/combined NPIs <u>in school settings</u>	• Opening schools is associated with increased infection rates in the community, but	N/A	N/A	• In schools, combined NPIs such as masking, routine testing, ventilation, social distancing, and isolation

	transmission is more likely to occur outside of school and be related to community prevalence[165] • Public health measures in the community decreased school-related growth 2-6 times[165] • In a university setting, isolation of students with COVID-19, contact tracing, and institution-wide prevention measures contributed to reductions in transmission[131] ***Appraised study is of medium quality***			when symptomatic are very important[106,139] ***Appraised study is of medium quality***
Other/combined NPIs <u>in the general population</u>—*Modelling studies*	• **With an 80% vaccination rate, transmission of Alpha after reopening Australia's international borders continued even with multiple NPIs in place, but hospitalizations remained low**[85] • Multiple NPIs are more effective than single NPIs,[17,25,166] and reactive NPIs (e.g., quarantine of close contacts) must be deployed quickly • Strong test-trace-isolate programs can be sufficient	N/A	• Strict NPIs are required to contain Gamma[25,87]	• **With an 80% vaccination rate and limited NPIs, reopening Australia's international borders led to a major surge in Delta infections and hospitalizations**[85] • **A combination of strict NPIs (including testing) can control Delta outbreaks**[166] • Combined NPIs in the community have an immediate impact on case levels vs. the delayed impact of vaccines[97]

	to maintain low case numbers[77,167] • Regional mobility networks and spatial connectivity drive patterns of transmission throughout the United States[122] • Strict NPIs may lead to overdispersion of highly transmissible variants, leading to their eventual dominance[168]; evolution of highly transmissible variants may actually be a sign that NPI policies are effective[169]			• In a model of France, the only way to contain Delta was to keep combined NPIs in place until 100% vaccination coverage was reached[75] • Regional mobility networks and spatial connectivity drive patterns of transmission throughout the United States[122] • Even modest improvements in a find, test, trace, isolate and support program would control transmission[170] • **On a cruise ship simulation model, a combined approach of rapid testing, vaccination rates, and masking when possible reduced the likelihood of outbreaks**[115]
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[132]	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[103] • In schools, continued use of multiple NPIs (e.g., universal

				masking and distancing or cohorting) is recommended[30,101,171], combined with high vaccination coverage[117]

Overview of the Evidence

As of December 3, 2021, 166 studies have reported on VOC and public health measures. We include 122 studies from earlier reports (including 20 studies from an earlier rapid review[6], 31 from the first iteration of this report[172], 30 from the updated search on August 25, and 41 from the updated search on October 4). 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 Delta (n=101 studies) or Alpha (n=106), with fewer studies reporting on Beta (n=39 studies) and Gamma (n=32 studies).

Modifying Approach to Vaccine Delivery

- 103[9–29,29–38,40–79,81–106,117,119,131,142,173,174] 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.[22,24,42,46,48]
- Evidence is emerging about the value of third dose or booster vaccines[37], particularly in the context of Delta[50,53,54,61,64,98,119] and immunocompromised patients.[66]
- Several modelling studies[100,101,104]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.[28–31]
- **Evidence suggests following 1 or 2 doses of non-mRNA vaccine with a dose of mRNA vaccine as second or booster dose provides superior protection against VOC**[10,44,52,60]

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.[107]
- One study found that vaccinated individuals may engage in less handwashing and physical distancing than non-vaccinated individuals but not mask wearing.[108]
- **Use of hand sanitizer on flights may offer protection against of COVID-19 transmission**[109]
- Modelling studies suggest that when worn correctly, masks are effective against Alpha[112 110] and Delta, regardless of vaccination status[92,114,115], unless 100% vaccination with 95% effectiveness and community infection rate are <150 per 100,000.[113] Double masking may offer better for protection against all VOCs.[111]
- Universal masking in schools is recommended to reduce in-school transmission.[97,103,116–118]
- **Eleven** studies reported on VOC and physical distancing measures.[23,68,89,109,114,118–121,124,125] 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.[89,118] **Two studies show that when you are in close proximity to an infected individuals (e.g., on planes, having conversations), there is an increased likelihood of transmission.**[109,114]

Infection Control Measures

- Twenty-four [68,70,103,104,113,115,116,126–142] 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.
- Fifteen[109,125–127,132,134,135,137,139,143–147,149] 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. **The ideal length of quarantine, and whether quarantine and testing are enough to circumvent travel bans, vary across studies.**
- Six[12,132,140,141,150,151] 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, **but one observational study has defined the ideal period of isolation for Delta cases as at least 10 days, based on the duration of virologic shedding.**
- Fifteen[79,88,95,136,151–159,161,162] 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[138,162] studies suggested earlier implementation of lockdown measures to limit virus spread.
- Twenty-eight[17,25,43,75,77,85,87,97,101,103,106,115,117,122,129,131,132,135,139,153,164–171] 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. Three[17,25,166] studies found that deploying a combination of NPIs is more effective than single NPIs, and multiple studies recommended employing NPIs in conjunction with vaccine rollout to mitigate the spread of Alpha or Delta. **NPIs remain important until very high vaccination rates are achieved.**

Methods

This living synthesis is building on previous evidence gathered up to May 11, 2021. Searches for this update were run on November 15, 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] while the appropriate Joanna Briggs critical appraisal tools were used for studies included in the living syntheses. Critical appraisal was not conducted for modelling or laboratory studies.

List of Abbreviations

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

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