BRIEF REPORT

The feasibility of targeted test-trace-isolate for the control of SARS-CoV-2 variants [version 1; peer review: 2 approved with reservations]

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Abstract

The SARS-CoV-2 variant B.1.1.7 reportedly exhibits substantially higher transmission than the ancestral strain and may generate a major surge of cases before vaccines become widely available, while the P.1 and B.1.351 variants may be equally transmissible and also resist vaccines. All three variants can be sensitively detected by RT-PCR due to an otherwise rare del11288-11296 mutation in orf1ab; B.1.1.7 can also be detected using the common TaqPath kit. Testing, contact tracing, and isolation programs overwhelmed by SARS-CoV-2 could slow the spread of the new variants, which are still outnumbered by tracers in most countries. However, past failures and high rates of mistrust may lead health agencies to conclude that tracing is futile, dissuading them from redirecting existing tracers to focus on the new variants. Here we apply a branching-process model to estimate the effectiveness of implementing a variant-focused testing, contact tracing, and isolation strategy with realistic levels of performance. Our model indicates that bidirectional contact tracing can substantially slow the spread of SARS-CoV-2 variants even in regions where a large fraction of the population refuses to cooperate with contact tracers or to abide by quarantine and isolation requests.

Keywords

epidemiology, SARS-CoV-2, COVID-19, contact tracing, bidirectional tracing, backward tracing, B.1.1.7, test-trace-isolate

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Introduction

The frequency of the B.1.1.7 variant of SARS-CoV-2 has grown rapidly from its initial detection in October 2020 to become the dominant strain in southeastern England by the start of 2021. Studies have estimated the new strain is between 40% and 80% more contagious^{1,2}. The rapid exponential growth of B.1.1.7, now found in dozens of countries, risks another and potentially higher wave of COVID-19 cases prior to widespread vaccination. Meanwhile, early reports suggest that current vaccines³ and prior SARS-CoV-2 exposure⁴ may be less protective against the B.1.351 and P.1 variants now common in South Africa and Brazil.

All three variants share an otherwise rare del11288–11296 mutation in orf1ab that can be detected using a single RT-PCR reaction⁵; B.1.1.7 can also be distinguished with the TaqPath diagnostic test⁶, twenty million of which are manufactured weekly⁷. As such, existing COVID-19 testing infrastructure can be used to track the transmission of the new variants. Samples testing positive by other kits can be re-screened⁸ without an emergency use authorization.

Test-trace-isolate (TTI) strategies have been widely used to mitigate the spread of SARS-CoV-2⁹. Models by the present authors¹⁰ and others¹¹ have found that incorporating backwards tracing to identify infector individuals could dramatically increase the efficacy of tracing programs. However, testing delays, mistrust, and low compliance have undermined the confidence of health authorities in the benefits of TTI^{12,13}. Moreover, efficacy sharply decreases when caseloads are high¹⁴, as is true for SARS-CoV-2 – but not yet the variants – in many regions.

Given the current low prevalence of the variants in most jurisdictions and the ability to identify cases of the new variant using existing testing infrastructure, we hypothesized that TTI programs dedicated to controlling them could substantially reduce the harm inflicted prior to widespread vaccination of populations later in 2021, especially if vaccine reformulation is needed. Such programs could be enhanced through incorporation of bidirectional tracing¹⁰.

However, the effectiveness of TTI strategies varies widely from region to region due to programmatic and population-level differences in variables such as the proportion of cases who share their contact history with contact tracers; the proportion who comply with quarantine and isolation requests; and the overall rate of tracing success. Given this variation, it is unclear whether tracing programs exhibiting realistic levels of performance could feasibly dampen the spread of the new variants.

To evaluate the potential benefits of applying targeted test-trace-isolate to control variants, we applied a branching-process model of COVID-19 contact tracing¹⁰ to estimate the change in the effective reproduction number achievable across a wide range of parameters.

Methods

In our branching-process model¹⁰, each case generates a number of new cases drawn from a negative binomial distribution according to pre-specified incubation- and generation-time distributions (Table 1). Cases are identified and isolated based on symptoms alone or through contact tracing. Cases either comply with isolation requests or ignore them completely according to some fixed probability of compliance; cases that comply generate no further cases.

Successful tracing depends on the identified case sharing their contact history with tracers, and on the contact in question taking place within the time window (measured in days pre-symptom onset for symptomatic cases, and days pre-identification for asymptomatic cases). Environmental transmission is assumed untraceable. Symptomatic cases require a positive test before initiating contact tracing.

Outbreaks were initialized with 20 index cases to minimize stochastic extinction and designated as “controlled” if reaching extinction before reaching 10,000 cumulative cases. Effective reproduction numbers (R_{eff}) were computed as the mean number of child cases produced per case¹⁰.

Results

To investigate the potential for TTI to mitigate the spread of variants, we investigated the effective reproduction number achieved across a range of data-sharing and trace-success rates (Figure 1). To account for uncertainty in variant transmissibility, we explored outcomes for reproduction numbers between 1.2 and 2.0; these values assume that non-tracing interventions are already in place.

In the absence of contact tracing, identification and isolation of symptomatic cases alone reduced R_{eff} by 0.2 to 0.3 even when quarantine and isolation compliance was low (Figure 1, top rows). When identification and isolation left R_{eff} substantially greater than 1 (when base $R \geq 1.4$), moderate levels of tracing could have substantial effects.

When contacts were traced up to two days prior to symptom onset, roughly 60–70% data sharing and trace success rates were required to achieve an R_{eff} reduction of at least 0.1, relative to isolation alone. If the window was extended to six days pre-onset to enable more effective bidirectional tracing, roughly 45–55% data sharing and trace success was sufficient. Higher levels of data sharing and trace success could achieve substantially larger reductions: in many scenarios, 85% data sharing and trace success reduced R_{eff} by >0.2 in the two-day case and >0.35 in the six-day case.

Due to the exponential growth of uncontrolled epidemics, small reductions in R_{eff} can have a large impact on the total number of downstream cases arising from a given index case over a given timespan. For example, under a simple geometric series approach, reducing R_{eff} by 0.1 from a starting value between 1.2 and 2.0 reduces the total number of child cases

Table 1. Parameters of the branching-process model.

Parameter	Value	Sources and Notes
% asymptomatic carriers	40%	15–19
Relative infectiousness of asymptomatic carriers	45%	Informed by viral loads and tracing results described in 15,19–23
% environmental transmission	5%	24,25
Proportion pre-symptomatic transmission	38%	Informed by 19,20,22,23,26–31
Generation time skew parameter (α)	0.397	Corresponds to pre-symptomatic transmission rate specified above.
% of symptomatic cases identified without tracing	50%	32
% of cases who comply with isolation	50%, 70%, 90%	Assumed
Test sensitivity	70%	33,34
R_{base} (before test/trace/isolate)	1.0 to 2.0	Assumes a pre-B.1.1.7 R of $\sim 1.0^{1,2}$.
Overdispersion	0.11	35
Number of initial cases	20	Assumed
Incubation period	6.0 $\pm$ 2.1 days (lognormal distribution)	1,36,37
Delay from onset to isolation	3.8 $\pm$ 2.4 days (Weibull distribution)	38
Delay for testing	1 $\pm$ 0.3 days (gamma distribution)	Assumed
Delay for manual tracing	1.5 $\pm$ 4.8 days (lognormal distribution); median 0.5 days	Previous reports suggest most contacts can be traced within one day, but some take longer ³⁹

after 10 generations by 37–43%; an R_{eff} reduction of 0.2 results in a reduction in child cases of 61–66%. Given an average generation time of six days, 10 generations equates to roughly two months – enough time, given sufficient delay in the spread of the new variant, to vaccinate a substantial fraction of the population.

Discussion

Our results suggest that regions with even moderately functional contact tracing programs focused on the new variants could substantially slow their spread. Given a two-day window for bidirectionally tracing contacts pre-symptom onset, our model predicts that a program with 70% trace success, 70% data sharing, and 70% compliance with isolation could achieve an R_{eff} reduction of at least 0.1 relative to the no-tracing case. Given a six-day window for efficient bidirectional tracing, regions with just 50% data-sharing, trace success, and isolation compliance could achieve a reduction of 0.1.

Under simple assumptions, such a reduction would reduce the number of child cases produced in two months by roughly

40%, buying time for vaccination to immunize many more people. More effective tracing programs can achieve larger reductions. Higher rates of cooperation might be achieved through home visits by contact tracers; exoneration for anything discovered in the course of contact tracing¹³; and financial and other support of people in quarantine and isolation⁴⁰. In principle, concentrating vaccination in communities experiencing out-of-control variant transmission could further impair viral spread and increase the sustainability of TTI for COVID-19 control.

These results assume a high availability of suitable diagnostic tests and a rapid and consistent testing turnaround. They also take no account of any medical, demographic, geospatial or behavioral variation between cases that could influence the spread of the new variants.

Our results suggest that TTI programs could help slow the spread of more transmissible and vaccine-resistant variants in regions where they are currently rare, providing vital time for widespread vaccination. As TTI efficacy is limited at high

Figure 1. Evaluating the efficacy of bidirectional contact tracing for controlling rare SARS-CoV-2 variants. Neighbor-averaged contour plots, showing R_{eff} achieved by bidirectional manual contact tracing with a tracing window of (a) two or (b) six days pre-symptom onset, under different combinations of trace success probability (x-axis), rate of data sharing with manual contact tracers (y-axis), rate of compliance with isolation and quarantine (row) and base reproduction number (columns). Other disease parameters are specified in Table 1. Isolation of symptomatic cases is sufficient to reduce R even when no traces succeed and/or no cases share their data with contact tracers. “Trace success probability” refers to trace attempts that are not otherwise blocked by environmental transmission or refusal to share data.

caseloads¹⁴, these findings indicate that tracing programs should immediately prioritize controlling the new variants rather than less transmissible – but currently more widespread – ancestral strains.

Data availability

All data underlying the results are available as part of the article and no additional source data are required.

Software availability

Source code available from: <https://github.com/willbradshaw/covid-bidirectional-tracing>.

Archived source code as at time of publication: <http://doi.org/10.5281/zenodo.4279557>⁴¹

License: MIT License

Author contributions

K.M.E. conceived the study. J.H.H. and A.L.L. identified a suitable model framework. W.J.B. designed and programmed the adapted model, advised by the other authors. W.J.B. ran all simulations and generated figures. All authors jointly wrote and edited the manuscript.

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Tim C. D. Lucas

Imperial College London, London, UK

In this study the authors use established and previously published models of contact tracing to examine whether targeted test and trace systems could suppress novel variants. The premise is sound; contact tracing scales poorly, so while it is not necessarily effective at control SARS-CoV-2 at large once national prevalence is high, the numbers of certain variants are still low in a number of countries and therefore contact tracing might be able to control those new variants as they are seeded into a country. Whether this approach would work or not is not trivially obvious and so this study is asking an important question with policy implications globally.

The analytical approach taken is quite simple in that the authors assume (and back up with some literature) that the variants can be identified easily and that therefore contact tracing of a new variant can continue without any reference to the dominant variant.

Comments:

- Most of my comments relate to this assumption that contact tracing of new variants can be modelled by simply ignoring the dominant variant.
- First, I would like to see this assumption explicitly stated in the methods just to make it completely clear to the reader.
- There are a number of further considerations with this assumption that I think should be discussed.
- Given the high rate of vaccination and previous infection with the original SARS-CoV-2 strain, many countries are now in a state where immunity cannot be ignored. This is all handled by Reff, but I think it needs to be mentioned that Reff is combining NPIs, immunity or partial immunity from vaccination (depending on whether there's vaccine escape in the variant) and partial immunity from previous infection with other strains.

- The authors state that new variants can be detected with RT-PCR and TaqPath. However, does this extra step create no extra delay in the process? I imagine this would depend on the specific organisation but might be worth considering and mentioning.
- Furthermore, is this identification of variants 100% accurate? The false negative rate (someone is infected with a new variant but the test says they are infected with the original variant) can be just included as part of the test sensitivity and I wouldn't be surprised if the difference is fairly small. More worrying for me is the false positive rate (someone is infected with the original variant but the tests says they are infected with a new variant). This is important because the rationale for the study relies entirely on the fact that there are not many cases with the new variant in a country but if, say, the false positive rate (as defined above) is even 1% then the large number of original variant cases in a country will quickly lead to the targeted test-trace-isolate system being swamped. This effect will obviously vary with the prevalence of original variant SARS-CoV-2.
- I only know the literature for the UK, but even the lowest compliance rates used here are much higher than those measured (I wouldn't be surprised if some countries have much high compliance rates though). I am taking my values from the reference below (Smith *et al.*, 2020¹), but there might be more up-to-date surveys in the UK and I don't know at all about other countries.
- From self-reported behaviour (past behaviour, not intentions) in the UK, about 12% of people with symptoms requested a test. This relates to the 50% of symptomatic cases identified without tracing parameter. Some details of how you selected 50% from ref 32 would be useful, as the values in that paper range from 5% to 100% depending on the country and time. In the UK, of those contacted by track and trace, 11% of people fully complied with 2 weeks self isolation (this relates to the 50%-90% comply with isolation parameter). So at the very least I think it might be useful to state that these values might be quite optimistic in some settings.
- Finally, a minor and subjective point, but it might be useful to present Figure 1 with a diverging colour palette that clearly distinguishes $R_{eff} < 1$ and $R_{eff} > 1$.

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Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Epidemiology. Previous research on contact tracing for SARS-CoV-2.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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Akira Endo

Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK

This study considers the effectiveness of contact tracing focused on variants in reducing the reproduction number. Focusing contact tracing efforts on variants is an interesting approach and may be relevant to the current situation of variant circulations worldwide. The model and the analysis themselves seem well constructed and implemented. However, the authors' analysis only focuses on a single variant essentially, and does not account for some important aspects that need to be considered to estimate the effect of real-world contact tracing in the presence of multiple variants. As a result, I am not sure if this study provides new insights that are distinct from existing studies on contact tracing for a single-pathogen outbreak. In addition, it should be noted that given a fixed capacity for contact tracing, the reduction in the reproduction number would not be permanent if the outbreak continues to grow. I believe these issues, along with other comments detailed below, need to be addressed for this study to be truly of epidemiological and public health interest.

Major comments:

- Please clarify how this study is distinct from existing studies on contact tracing considering a single-pathogen outbreak (including the authors' own study cited here).

- There seems to be a mismatch between the study motivation/context and the modelling approach. One of the points the authors are trying to make is that the contact tracing efforts should be focused on variants because they are of more epidemiological importance (due to potentially higher transmission or immunoescape). I do not disagree with this point, but there are several major issues regarding how it was handled in the manuscript.
 - The reproduction number R is used as an objective variable to measure the effect of contact tracing. This is useful to connect interventions and the dynamic evolution of the epidemic, but essentially assumes that the same level of tracing can continue everywhere long-term, regardless of the epidemic size. This is obviously not true as the authors also state in the manuscript. In conditions where R is above 1, transmission of variants would continue and overwhelms the tracing capacity at some point, pushing R back to the original value eventually. Focusing on R may be useful in identifying conditions required to control the outbreak (i.e. $R < 1$), but it is unrealistic to consider that the tracing can keep R lower than the original value in a long term if the resulting value exceeds 1.
 - Variants are no longer minor in many places now (see for example: <https://covid.cdc.gov/covid-data-tracker/#variant-proportions>), and I am not sure how much this assumption of 'minor variants' is relevant to the actual situation. Moreover, even in places where the variants are still minor, if the (effective) transmissibility of the variants is higher than the existing virus, they would rapidly replace the existing viruses, potentially in a few weeks/months.
 - Exclusion of existing strains. The main argument regarding the tracing capacity is that the variants account for a small proportion of cases and thus can be handled if tracing focuses on these variants. However, even if such focused intervention is possible by tests that can distinguish variants, existing non-variant viruses may continue spreading if their R is above 1. Although such a situation may still have some benefit, e.g. if preventing the spread of immunoescaping variants would ensure the success of the vaccination program, such contexts should be clarified and discussed.
 - Cost and capacity. As discussed above, contact tracing would work as estimated here only until the capacity is reached. However, I feel efforts associated with tracing is not seriously considered in the analysis. For example, if all contacts of cases within the tracing period are traced, extending the tracing period from 2 days to 6 days would incur substantial additional effort for tracing. I believe it is important to discuss to what extent contact tracing might be sustainable for each setting because the presented results become invalid once the capacity is reached.

Given the points above, I would recommend the authors reconsider what outcome measure to use and how to present them; e.g. consideration of the growth of "non-targeted" viruses, conditions required to keep R below 1, whether tracing can "buy time" until achieving a sufficient level of vaccination before reaching the capacity, optimising the intensity of other NPIs (e.g. lockdowns) in the presence of contact tracing, etc., such that the results are relevant to what may actually happen.

- The Introduction looks lightweight and lacking necessary details or contexts. There are a lot of concepts that may not be familiar enough to every reader but are not sufficiently explained (e.g. TTI, backward contact tracing, bidirectional tracing, why TaqPath test can distinguish B.1.1.7... etc.) and thus may require a succinct clarification. Please also note that

this paper may be read in 20 years from now, when the reader may not have the same level of recognition of the current situation. In this light, for example, I feel the first paragraph of Introduction may sound a bit abrupt to the reader who is less aware of the overall timeline of the pandemic. Also see some of the specific comments in the Minor comments section.

- The Methods section is too simple and does not contain sufficient information for the reader to comprehend the overall structure of the analysis. Although it does not need to contain every technical detail of the model and analysis as the supplementary methods can be found in the repository (but please include a link and description in the paper so that the reader can easily find it), I feel more information from the supplementary methods should be extracted and summarised in the main text. For example, from the current Methods section I cannot interpret how the course of transmission was characterised, what is the assumed procedure of tracing (Is it always bidirectional tracing? I feel 2-day window is too short for backward tracing), how environmental transmission was assumed to work, how R was calculated, etc.
- I believe additional sensitivity analysis would be necessary. For example, the overdispersion parameter (0.11 used in the current analysis) is estimated to be slightly higher (0.3-0.5) in some studies where interventions were in place (Adam *et al.*, 2020¹). As the authors assume that interventions may be affecting R during contact tracing, possible changes in overdispersion should also be considered. Delay from secondary transmission to quarantine of contacts (defined as a sum of various delay distribution) would also affect the effectiveness of contact tracing in a nontrivial manner.
- Is the effect of vaccines not considered, although as in Introduction it was one of the major motivation for considering controlling variants? Vaccines may affect different viruses similarly or differently, depending on the type of variants.
- Supplementary Methods, "Identified contacts are quarantined, ...isolated, tested, and traced as described above": what is the difference between quarantining and isolation of traced contacts? Does this mean all traced contacts of a case are put under quarantine regardless of their true infection status, but only tested if they are symptomatic (which changes the label from quarantine to isolation)? If so, it is expected that as the epidemic grows there would be a substantial number of quarantined individuals, and at some point this might be impossible (e.g. due to depletion of essential workers) and the Reff control could collapse.

Minor comments:

- Throughout: please spell out acronyms at their first appearance, including SARS-CoV-2 and COVID-19.
- Introduction, protection against B.1.351 and P.1: now the evidence is not limited to in-vitro studies (e.g. Madhi *et al.*, 2021² and Kustin *et al.*, 2021³). Please update and include clinical findings. Also summarise what we know about protection against B.1.1.7.
- "All three variants share...; B.1.1.7 can also be...": I would suggest that the authors first describe B.1.1.7 that can be detected by TaqPath tests (with some more background context, as this is primarily happening in UK and not necessarily recognized by the wider audience) and then go on to a discussion of potential detectability of other variants

(because this is only a hypothetical scenario so far in my understanding, as opposed to detection of B.1.1.7). Also, would there be any data on the rollout of these variant-distinguishable tests worldwide?

- “Samples testing positive...”: This needs more context. Why is authorisation going to be an issue and why can re-screening bypass it?
- “as is true for SARS-CoV-2 – but not yet the variants – in many regions”: I feel this is unclear. TTI capacity would be overwhelmed when the overall caseloads are high, even if the variants account for a very small fraction of them. It should be made clear if this indicates contact tracing would only target variants distinguished by the (variant-specific) tests.
- Method, “child cases” may be interpreted as cases that are children. Secondary transmissions?
- Results, “In the absence of contact tracing, identification and isolation of symptomatic cases alone reduced Reff by 0.2 to 0.3...”: I couldn’t read this from the top rows of Figure 1. This may correspond to 0% of cases sharing data or 0% trace success probability, but Reff for such a scenario cannot be read from the figure because there is no colour scales or numbers.
- “When identification and isolation...substantial effects.”: I am not sure how “moderate levels” and “substantial effects” are defined.
- “Due to the exponential growth of uncontrolled epidemics...over a given timespan”: As stated above, this is only the case if contact tracing can continue without hitting the capacity. If R goes back to the original level after tracing is overwhelmed, there may be only a marginal difference in the final epidemic size.
- Discussion, “Higher rates of cooperation...quarantine and isolation”: related to the first major comment, these efforts would make tracing more effective but require a substantial amount of effort and cost, and warrant discussion.
- Please update references. Many of the preprints cited here have now been published in peer-reviewed journals, which might include more up-to-date information.

References

1. Adam DC, Wu P, Wong JY, Lau EHY, et al.: Clustering and superspreading potential of SARS-CoV-2 infections in Hong Kong. *Nat Med.* **26** (11): 1714-1719 [PubMed Abstract](#) | [Publisher Full Text](#)
2. Madhi SA, Baillie V, Cutland CL, Voysey M, et al.: Efficacy of the ChAdOx1 nCoV-19 Covid-19 Vaccine against the B.1.351 Variant. *N Engl J Med.* 2021. [PubMed Abstract](#) | [Publisher Full Text](#)
3. Kustin T, Harel N, Finkel U, Perchik S, et al.: Evidence for increased breakthrough rates of SARS-CoV-2 variants of concern in BNT162b2 mRNA vaccinated individuals. *medRxiv.* 2021. [Publisher Full Text](#)

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

Not applicable

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Infectious disease modelling

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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