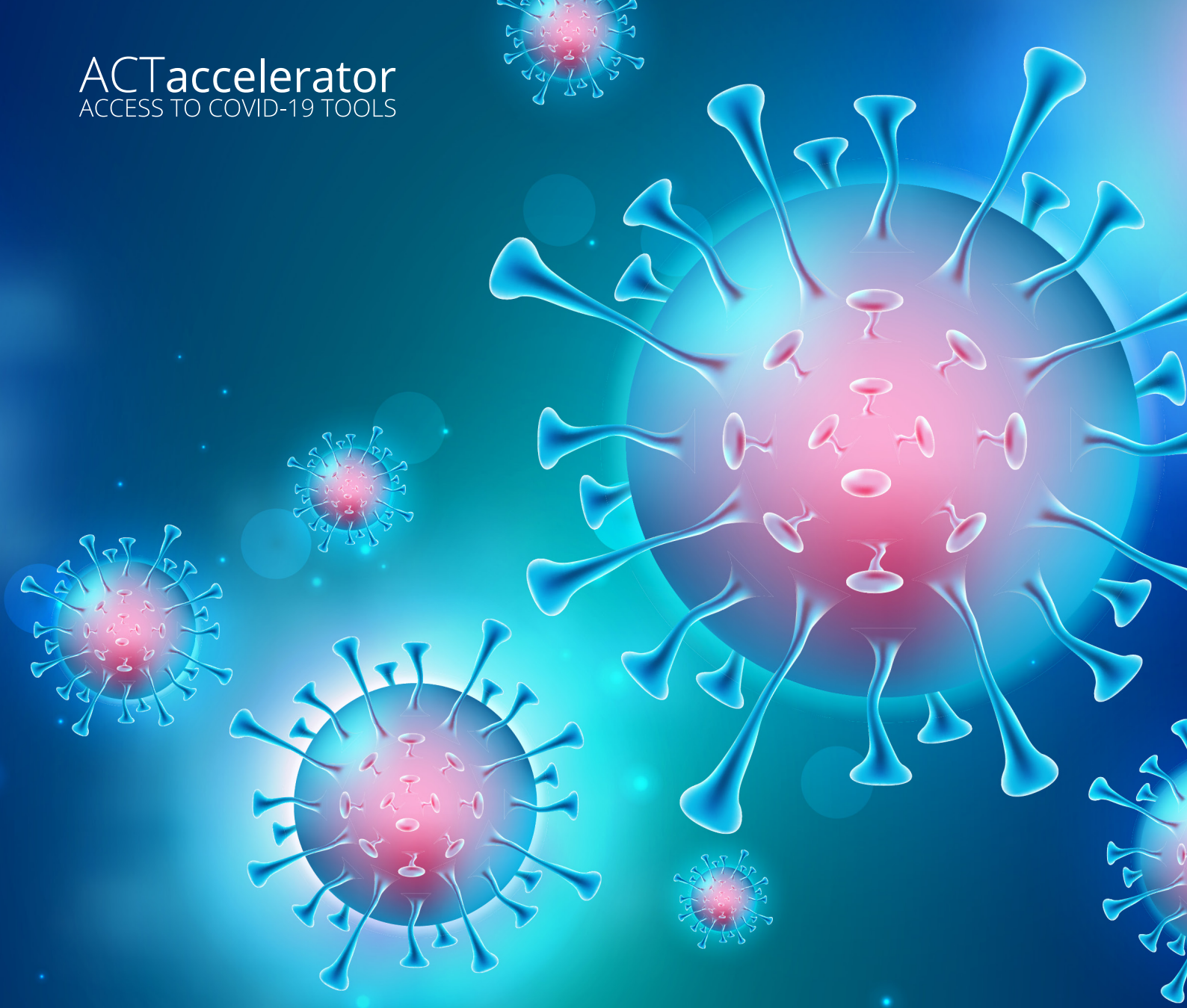
ACTaccelerator
ACCESS TO COVID-19 TOOLS



Expanded use case analysis for

Rapid antigen diagnostics for SARS-CoV-2 mitigation

PHASE 1 RESULTS FROM THE ACT-ACCELERATOR
SARS-COV-2 RAPID ANTIGEN TESTING MODELING CONSORTIUM

ACKNOWLEDGEMENTS

This report has been prepared by the secretariat of the ACT-Accelerator (ACT-A) rapid antigen diagnostic modelling consortium. The consortium was co-led by Dr Brooke Nichols, BU, and Prof. Colin Russell, AUMC. The secretariat included Karla Therese L Sy, Joshua Chevalier, Megan Hansen, and Dr Mariet Benade, all from BU; Sarah J Girdwood from HE2RO; Dr Alvin X Han from AUMC; and Dr Amy Toporowski and Naushin Huq from FIND.

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CONTENTS

EXECUTIVE SUMMARY

The COVID-19 pandemic has led to nearly 220 million recorded cases and 4.5 million recorded deaths worldwide as of September 2021. While vaccination is increasingly used to mitigate the impact of the pandemic in high-income settings, **diagnostic testing and non-pharmaceutical interventions remain vital for reducing SARS-CoV-2 transmission, particularly in low- and middle-income countries (LMICs).** Antigen-detecting rapid diagnostic tests (Ag-RDT) are inexpensive, with quick time to results, making them useful for detecting infectious cases. When used in conjunction with coherent policies for isolating infectious individuals, Ag-RDTs can help to reduce the spread of SARS-CoV-2.

UNDERSTANDING WHEN AND IN WHAT SETTINGS AG-RDTS CAN BEST BE UTILIZED TO MOST EFFECTIVELY REDUCE ONWARD TRANSMISSION IS CRITICAL FOR DECISION MAKING AND RESOURCE ALLOCATION EFFORTS.

The work described in this report aims to quantify the impact of SARS-CoV-2 Ag-RDT testing strategies on COVID-19 outcomes in a variety of subnational use cases and settings by combining outcome measures from different mathematical models. In doing so, **we sought to provide a robust evidence-base for the use of Ag-RDTs in various settings and to quantify the value of expanded access to Ag-RDTs.** The models used in this work evaluated different use cases, including (a) community testing, (b) mass gatherings, (c) K-12 schools, (d) universities, (e) border crossings, and (f) testing to exit quarantine.

THE RESULTS PRESENTED IN THIS REPORT CAN HELP TO GUIDE USE CASE-SPECIFIC IMPLEMENTATION OF AG-RDT TESTING AND CAN HELP SET EXPECTATIONS FOR THE USE CASE-SPECIFIC IMPACT OF DIFFERENT TESTING STRATEGIES.

Importantly, the results presented here do not quantify the potential impact of different testing strategies on community transmission outside of the specific use cases considered here and, because of differences in modelling frameworks among use cases, it is not possible to directly compare the utility of testing strategies among use cases. The next phase of this project will focus on using an agent-based modelling framework to directly investigate the impact of each use case on community transmission and the potential effectiveness of each of these use cases, alone and in combination, in different LMIC archetypes.

The three main findings from this collected work are:

1. Across use cases, increasing test frequency (or more testing of a community) was associated with greater numbers of infections averted;
2. In general, testing strategies across most use cases were highly effective when the effective reproductive number at time *t* (Rt) and/or infection prevalence was low, in large part because testing and isolation help to keep prevalence low;
3. Most use case testing strategies require more tests to avert infections when Rt and/or prevalence are low; this is due to the low probability of any individual testing positive in these situations.

BACKGROUND

DIAGNOSTIC TESTING FOR SARS-COV-2 REMAINS AN EFFECTIVE PANDEMIC RESPONSE TOOL BY ALLOWING FOR THE TIMELY DETECTION AND ISOLATION OF INFECTIOUS CASES, THUS REDUCING THE POTENTIAL FOR FURTHER TRANSMISSION.

Real-time reverse transcription polymerase chain reaction (RT-PCR) tests and antigen-detecting rapid diagnostic tests (Ag-RDT) are the two key diagnostic modalities in the 'test, trace, isolate and treat' strategy of our pandemic response. **RT-PCR tests remain the gold standard for COVID-19 diagnostic testing, with higher test sensitivity and specificity than Ag-RDTs,** but they require laboratory infrastructure, sample transport, skilled personnel and can be plagued by long turnaround times. RT-PCR tests capture a large proportion of COVID-19 positive cases, making it the diagnostic most widely used to confirm COVID-19 infection. Ag-RDTs have lower test sensitivity (>80% in symptomatic individuals in the first 5-7 days of illness), but can be performed at point of care and provide results within 10–30 minutes. In many circumstances, speed and frequency of testing outweigh the benefits of higher test sensitivity and specificity provided by RT-PCR, making Ag-RDTs a valuable tool for triaging, case detection, outbreak investigation, and contact tracing.

AS A SURVEILLANCE AND CONTROL STRATEGY, REDUCING POPULATION-LEVEL SPREAD REQUIRES GREATER ACCESSIBILITY AND FASTER RESULT TURNAROUND TIME TO IDENTIFY CASES WHILE THEY ARE STILL INFECTIOUS.

Ag-RDTs are low-cost and can be utilized for the scale-up of diagnostic testing in limited resource settings – where RT-PCR testing capacity is somewhat circumscribed – and to support surveillance or response efforts where RT-PCR testing is readily accessible. Ag-RDTs can be deployed in outbreak investigations to quickly identify positive cases and break the chain of transmission, and to understand the extent of the outbreak in intra-community settings, such as health care facilities, schools or the workplace. This is beneficial in settings where access to RT-PCR testing is limited, but also in cases where the turnaround time of available tests is not rapid enough to support outbreak response decisions. Ag-RDTs can also be useful for contact tracing, where positive symptomatic and asymptomatic contacts can be identified and isolated; however, a negative Ag-RDT result is not currently recommended to rule out infection in this population, as they may be in the incubation stage. Beyond outbreak investigations, Ag-RDTs may be suitable for the identification of positive cases through widespread and routine community testing, especially at testing centers or care facilities where infection may be suspected.

As with all diagnostic tests, the utility of Ag-RDTs is largely dependent upon the positive and negative predictive value (PPV and NPV) of these tests in different settings. These metrics are heavily influenced by SARS-CoV-2 prevalence in the tested cohort. When SARS-CoV-2 prevalence is high and Ag-RDTs have a high PPV, testing can identify positive cases to be moved to isolation and reduce the further epidemic transmission of the virus within the community, especially if there is an adequate number of contact tracing teams and associated personnel to implement testing campaigns. Conversely, under conditions of low SARS-CoV-2 prevalence and thus a higher NPV, it may be reasonable to implement Ag-RDT testing to rule out active infection in some settings.[1] **Importantly, Ag-RDTs show best testing performance in individuals in the infective stage of illness (within 5–7 days of symptom onset).** In asymptomatic individuals, whose duration of illness cannot be measured, frequent testing has been proposed,[2,3] although the risk of false positive test results in such low prevalence populations is higher. Taken together, Ag-RDTs, when accompanied by isolation following a positive test, have the potential of being especially useful for the control and mitigation of the COVID-19 pandemic, especially in limited resource settings. However, further evidence is needed to identify and clearly define the use cases where Ag-RDTs might have the greatest impact, and why, for these settings.

Different use settings are likely to require different diagnostic testing strategies to most efficiently reduce transmission. Identifying the use cases where Ag-RDTs can best be utilized to create the largest reductions in onward transmission is important for decision making and resource allocation efforts, particularly during heightened demand, when epidemic transmission is high.

THIS STUDY AIMS TO QUANTIFY THE IMPACT OF SARS-COV-2 AG-RDT TESTING STRATEGIES ON COVID-19 OUTCOMES IN VARIABLE SUBNATIONAL USE CASES AND SETTINGS, BY COMBINING OUTCOME MEASURES FROM MULTIPLE MODELS. IN DOING SO, WE SEEK TO PROVIDE A ROBUST EVIDENCE BASE FOR THE USE OF AG-RDTS IN VARIOUS LMIC SETTINGS AND TO QUANTIFY THE VALUE OF EXPANDED ACCESS TO AG-RDTS.

METHODS: APPROACH TO THE MODELING CONSORTIUM

This report draws on the input of seven research groups who each developed mathematical models to assess the potential impact of Ag-RDT testing for SARS-CoV-2 infection: Boston University, London School of Hygiene and Tropical Medicine, Institute for Disease Modeling, Harvard T.H. Chan School of Public Health, New York University Grossman School of Medicine, Amsterdam University Medical Center, Agency for Science, Technology, and Research (A*STAR Singapore), and the South African COVID Modeling Consortium (South African Centre for Epidemiological Modelling and Analysis (SACEMA), University of Cape Town, Health Economics and Epidemiology Research Office, and the South African Institute for Communicable Diseases). All collaborators agreed to provide output from their models and make adjustments where relevant or required.

Initially, we set out to conduct a multi-model comparison from each of the groups across various use cases: (a) community testing, (b) mass gatherings, (c) K-12 schools, (d) universities, (e) border crossings, and (f) testing to exit quarantine. Given the limited number of modeling groups that could effectively adapt their models to assess a given use case, all but one (border crossings) showed the results from a single modeling group.

Each modeling group was asked to run a set of scenarios. For models with longitudinal output, output was requested over a 90-day simulation period (K-12 schools (kindergarden to 12th grade/high school, or primary and secondary education), and universities). The remainder of the use cases provided output for between 1–365 days depending on the use case (community testing, mass gatherings, border crossings, testing to exit quarantine). The parameters that were varied were use-case dependent, but most generally included varying the epidemic conditions (the effective reproductive number at time *t* (Rt), and the current prevalence of COVID-19 in the target population), and the frequency of testing for asymptomatic infections (testing in the community, K-12 schools, and universities). Rt and prevalence was varied to assess the impact and efficiency of testing depending on the specific local stage of the epidemic; for example, high Rt and low prevalence would suggest the start of a new epidemic wave.

Test specificity, or the ability of the test to correctly identify those without the disease (true negative rate), affects the true positive rate (also known as the positive predictive value [PPV]). Prevalence also affects PPV; in general, greater specificity and greater prevalence increases PPV (fewer false positives). Thus, **the utility of the Ag-RDT depends on SARS-CoV-2 prevalence and test specificity.** Where SARS-CoV-2 prevalence is greater and Ag-RDTs have a high PPV, testing can identify positive cases that can be moved to isolation and reduce the further transmission of the virus. Whereas under conditions of low SARS-CoV-2 prevalence and a lower PPV, there will be increased false positive results, which increase the number of days spent unnecessarily isolating, with possible economic consequences. **Across use cases, mean sensitivity ranged from 80% to 85%, or was conditional on intra-host viral load dynamics.** Specific assumptions about sensitivity and specify are outlined in the **Appendix**. Future work will consider the use cases at very low SARS-CoV-2 prevalence to determine tradeoffs between further epidemic control (reduction in cases) and economic costs (isolation of false positive individuals).

Across all use cases, we calculated two outcomes relative to the status quo in each use case:

1. **the percent and number of infections averted** (or percent of infectious days averted or the number of infectious imports averted per 100,000 travelers, depending on respective use case), and

2. **the number of tests required to avert one infection** (or avert one infectious day or infectious import per 100,000 travelers, depending on respective use case).

To calculate these outcomes, we determined the number of Ag-RDT COVID-19 tests conducted, and the number of COVID-19 infections for each scenario, where COVID-19 infections were defined as all diagnosed and undiagnosed asymptomatic, pre-symptomatic, mild, and severe infections, and the number of COVID-19 infections for the base case scenarios. The *exiting quarantine* use case used a modified version of these outcomes (infection days instead of infections).

The original ambition of the modeling consortium was to examine the impact of each of the use cases on community transmission more broadly. It is important to note that the only use case and model that could assess community impact was the community testing use case. Direct comparisons on the utility of each use case were difficult to assess through this report alone. The next phase of this work will involve the further development and refinement of an agent-based model parameterized to multiple LMIC archetypes to integrate all use cases simultaneously in differing proportionalities.

Therefore, within this report, each of the use cases is accompanied by a description of the methods of the modeling approach (with additional details in the **Appendix**) followed by the modeling results. The full synthesis of all results, as well as uncertainty estimates across all use cases, can be found in **sections 4 and 5** of the report. A **glossary** of commonly used modeling terms are is found at the end of this report.

USE CASES

1. COMMUNITY TESTING

BACKGROUND

Community-level testing of COVID-19, defined as random mass testing of the population, has mostly relied on RT-PCR testing, which is expensive, time consuming and requires a robust laboratory infrastructure. In settings where testing capacity is limited, Ag-RDTs can be used to increase testing capacity. There has been incomplete guidance on the use of Ag-RDTs for widespread community testing in the general population, as current WHO guidance focuses on symptomatic testing of individuals meeting COVID-19 case definition,[4] and Ag-RDTs in low prevalence populations have greater risk of giving false positive results. Even so, for routine surveillance purposes, **the speed and frequency of Ag-RDT testing may still potentially outweigh the benefits of higher test sensitivity and specificity provided by RT-PCR.**

APPROACH

The National COVID-19 Epi Model (NCEM), a stochastic compartmental transmission model of COVID-19 transmission dynamics in **nine provinces in South Africa,** was modified to quantify the likely impact of different COVID-19 Ag-RDT strategies on disease transmission in the general population and communities. The model structure, parameters, and assumptions can be found in greater detail online.[5] To adapt this model, additional transitions were added, defined as the flow between compartments, where individuals can move when diagnosed with COVID-19 and subsequently isolated, reducing disease transmission in the general population. **Figure 1** shows the original NCEM versus the adapted NCEM. The model assumes that diagnosed COVID-19 infections will be isolated with differential isolation adherence and a consequent reduction in number of contacts (isolation effectiveness). Additionally, the model assumes that all COVID-19 hospitalizations are isolated, and thus do not contribute to the force of infection. **The total modeled population size of South Africa was 58.8 million, and the simulation was run for 365 days.** More information on assumptions and parameters can be found in the **Appendix**.

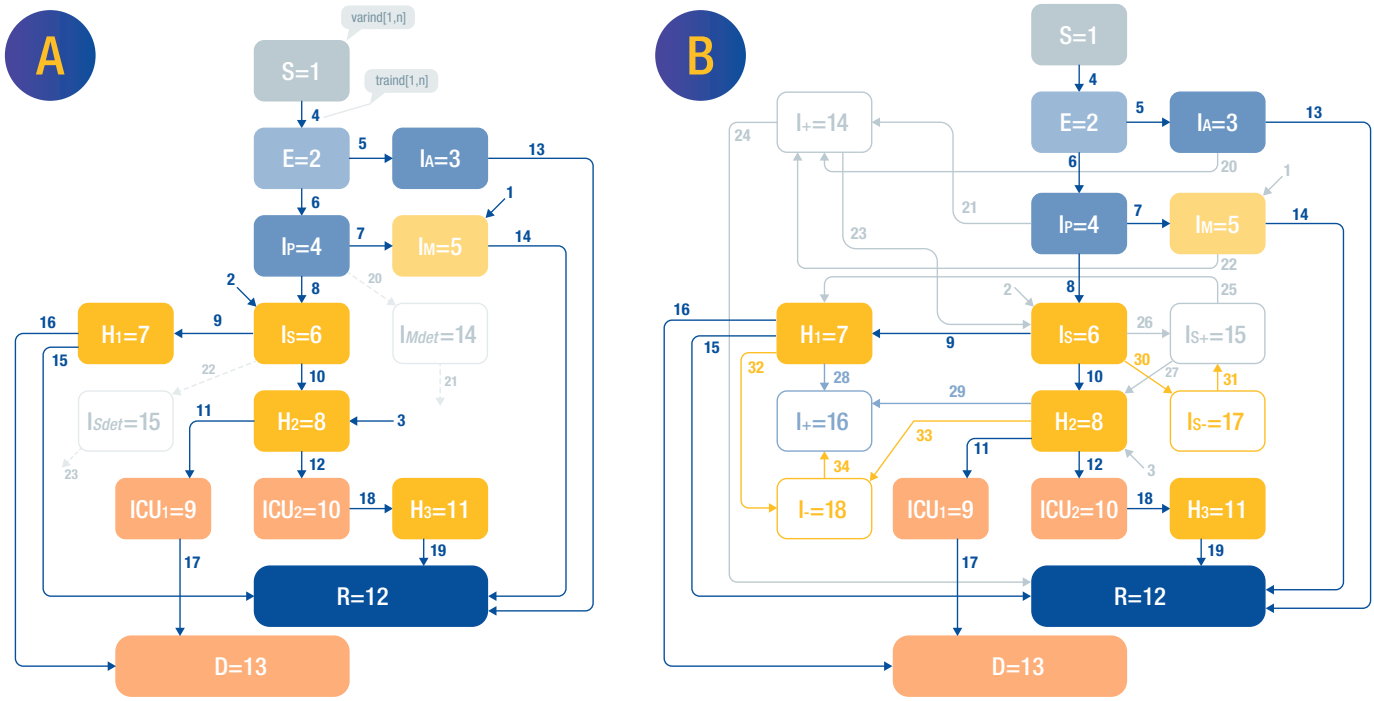

Figure 1. **(A)** The original NCEM model
(B) Adapted NCEM model incorporating additional compartments for diagnosed mild infection, severe infection, and hospitalization.

Compartments: S–Susceptibles, **E**–Exposed, **I_A**–Asymptomatic infections, **I_P**–Presymptomatic infections, **I_M**–Mild infections, **I_S**–Severe infections, **H_1**–non-ICU hospitalizations, **H_2**–ICU hospitalizations, **ICU_1**–ICU deaths, **ICU_2**–ICU recovereds, **H_3**–post-ICU hospitalizations, **R**–recovered, **D**–deaths, **I_+**–Asymptomatic/presymptomatic/mild infections diagnosed, **I_{S+}**–Severe infections diagnosed, **H_+**–Hospitalizations diagnosed

We focused our analyses on two model outputs: 1) the percentage of infections averted, and 2) the number of tests required to avert one infection. We also assessed two secondary outcomes, total infections averted and total infections. In this use case, we assume a base case Ag-RDT testing scenario in which there is no large-scale asymptomatic community testing, and we only test 15% of symptomatic mild cases, 50% of severe cases, and 100% of hospitalized cases. We assessed the effect of additional percentages of Ag-RDT testing in the whole population, on top of the base case testing proportions.

We also varied several epidemic parameters and SARS-CoV-2 diagnostic testing factors to assess the utility of Ag-RDT in various epidemic scenarios. These include: frequency of testing, Rt, COVID-19 prevalence, and isolation effectiveness (reduction in the force of infection when diagnosed) (**Table 1**). To be realistic, the model does not assume a contact tracing infrastructure, given the substantial human resource burden.

Additionally, we have assumed three different levels of adherence to isolation (isolation effectiveness) given the fact that it may be difficult for some people to isolate (20% reduction in community contacts, 50%, and 80%). The sensitivity of the diagnostic tests for both symptomatic and asymptomatic COVID-19 cases was assumed to be 85% (80% to 90%), and the relative transmissibility of asymptomatic and pre-symptomatic cases compared to symptomatic cases was 0.75 (0.70 to 0.80).

RESULTS

Greater percent of infections averted was generally associated with higher proportion tested and increased frequency of Ag-RDT testing for most scenarios (**Figure 2**). There is also a greater percentage of infections averted when the effective reproductive number is lower and prevalence of disease is lower.

Greater frequency of testing and greater proportion of individuals tested lead to more tests per averted infection (**Figure 3**). Fewer tests per averted infection are needed when there is greater isolation effectiveness (defined as a reduction in number of contacts when diagnosed positive).

In addition, there were more tests per averted infection when Rt and prevalence were high. The model assumed no contact tracing in this use case. However, the implementation of contact tracing in addition to widespread community testing would have further improved the effectiveness of asymptomatic community testing, if human resources were available and trained to conduct this type of large-scale public health program.

The number of infections averted followed the same trend as percentage infections avert (**Figure 4**), where greater proportion of infection averted was generally associated with more widespread and greater frequency of Ag-RDT testing, and greater isolation effectiveness substantially increasing the total infections averted. The base case total number of infections (if we only tested 15% of symptomatic infections, 50% of severe cases, and all hospitalized cases) ranged from 39.9 to 53.1 million, or 68% to 90% of the population depending on the epidemic parameters.

Figure 5 5 shows the total infections in millions for each scenario, as well as the base case scenarios, where we see **widespread, frequent, and effective testing to be related to a lower number of total infections across all levels of Rt and prevalence.** It is important to note, that to enable comparison to other use-cases, we have had to make non-dynamic assumptions about each scenario (e.g. artificially setting Rt and prevalence). In reality, these processes are dynamic, and a dynamic evaluation of each strategy across varying epidemic trajectories will be required in the next phase of the modeling consortium work.

Parameter	Values
Effective reproductive number	0.8, 1.2, 2.0
Prevalence of COVID-19	0.1%, 1%
Proportion of community tested	2.5%, 5%, 20%, 50%, 90%
Frequency of community testing	Once/two weeks, once/week, twice/week
Reduction in number of contacts post positive test	20%, 50%, 80%

Table 1. Parameters varied for each community testing use case scenario

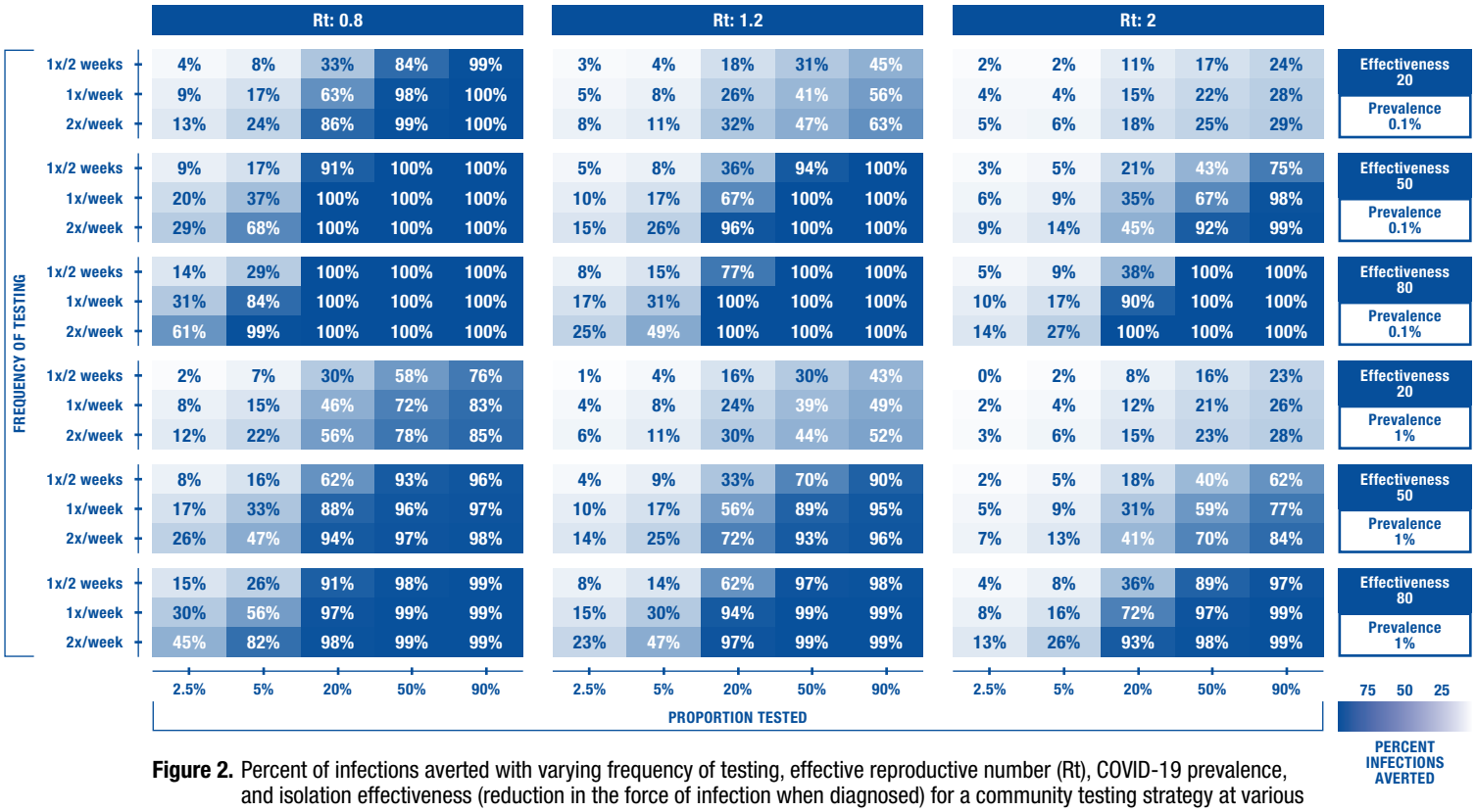

Figure 2. Percent of infections averted with varying frequency of testing, effective reproductive number (Rt), COVID-19 prevalence, and isolation effectiveness (reduction in the force of infection when diagnosed) for a community testing strategy at various proportions of the community tested.

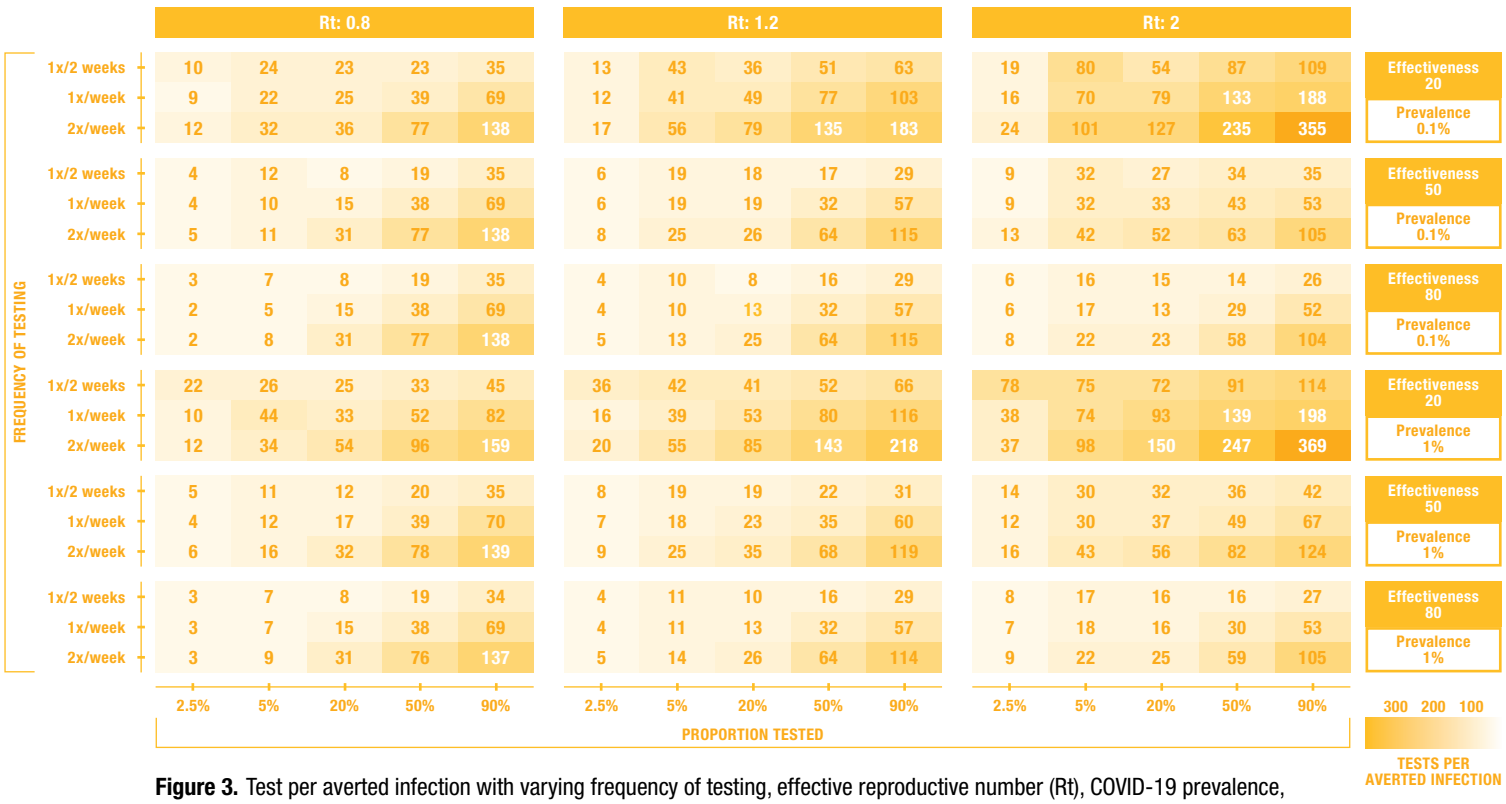

Figure 3. Test per averted infection with varying frequency of testing, effective reproductive number (Rt), COVID-19 prevalence, and isolation effectiveness (reduction in the force of infection when diagnosed) for a community testing strategy at various proportions of the community tested.

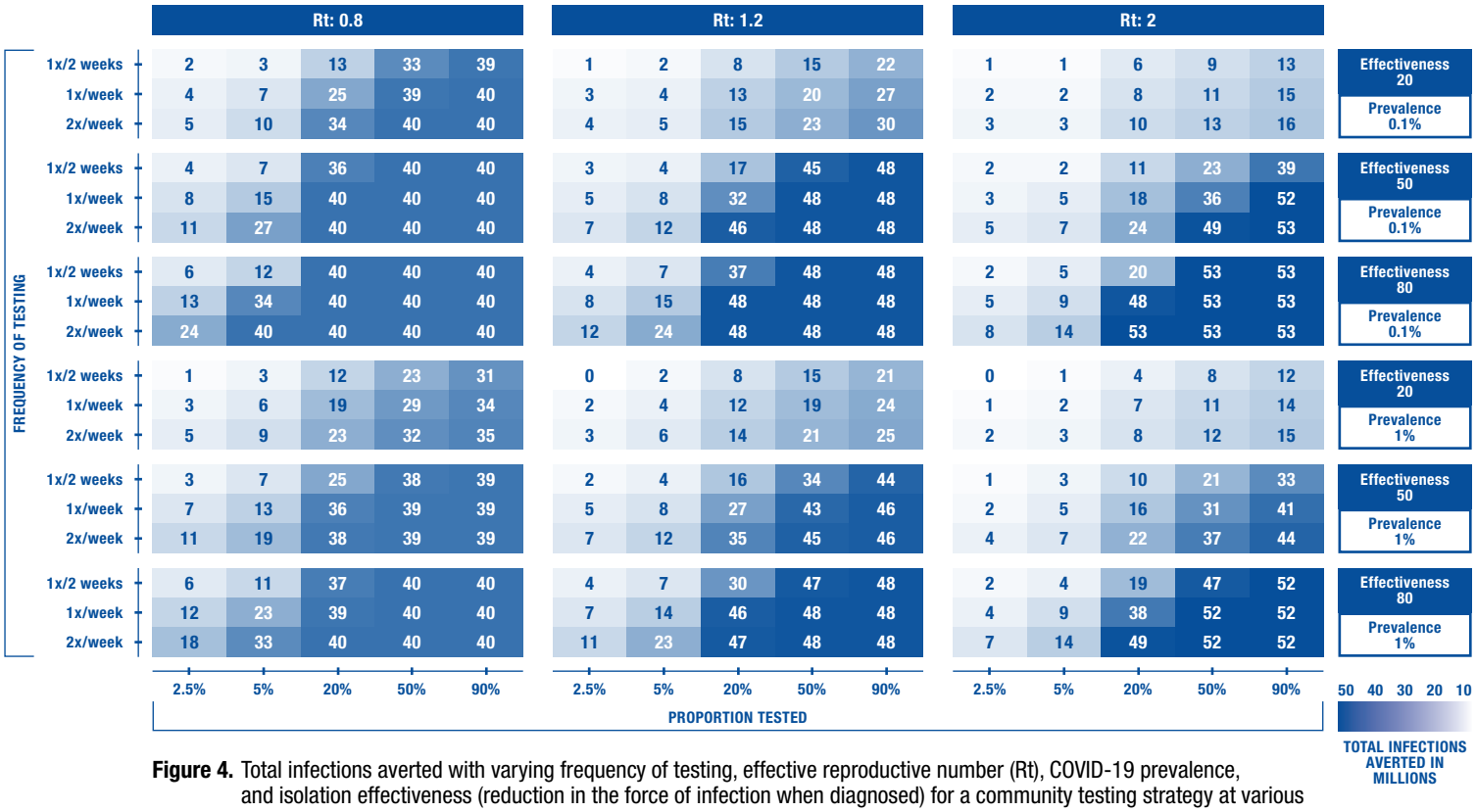

Figure 4. Total infections averted with varying frequency of testing, effective reproductive number (Rt), COVID-19 prevalence, and isolation effectiveness (reduction in the force of infection when diagnosed) for a community testing strategy at various proportions of the community tested.

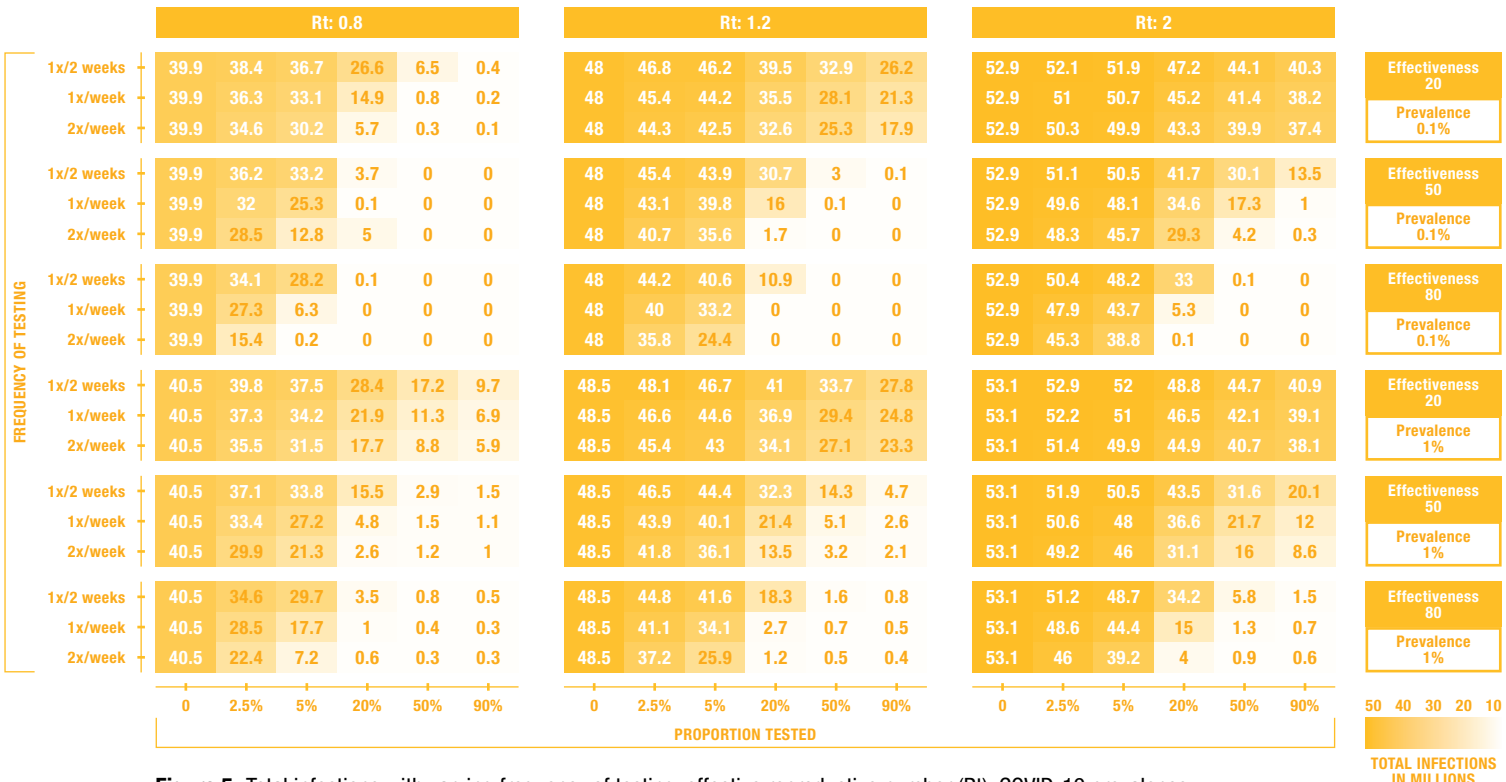

Figure 5. Total infections with varying frequency of testing, effective reproductive number (Rt), COVID-19 prevalence, and isolation effectiveness (reduction in the force of infection when diagnosed) for a community testing strategy at various proportions of the community tested (total modeled population size of South Africa = 58.8million).

IN SUMMARY, A GREATER PERCENTAGE OF INFECTIONS ARE AVERTED WITH MORE FREQUENT AND MORE WIDESPREAD COMMUNITY-WIDE AG-RDT COVID-19 TESTING ACROSS ALL EPIDEMIC SCENARIOS.

However, even with frequent and widespread testing, there would be a limited percentage of infections averted when there is no reduction in the number of contacts post-diagnosis, and even becomes harmful, increasing the number of tests needed to avert an infection.

Importantly, LMIC health systems are unlikely to be able to scale up COVID-19 testing to a large percentage of the population. Averting a substantial number of cases through asymptomatic community testing alone in LMICs would require more tests per week than have been purchased through the ACT-A diagnostics pillar to date. To achieve the most substantial reductions in disease burden (**Figure 4**) for Nigeria, for example, would require ~1.4 billion Ag-RDTs per month. Even in the most modest scenario considered in Figure 4 – testing 1% of the population once every two weeks – would require ~4 million Ag-RDTs per month for Nigeria alone, with negligible reductions in infections.

So, while mass asymptomatic community testing (accompanied by viable mechanisms of isolation) can facilitate disease control, the associated costs make it feasible only in small, defined settings. **Additional cost-effectiveness studies on these findings need to be conducted to identify key candidate settings for asymptomatic community testing.**

2. MASS GATHERINGS

BACKGROUND

WHO defines mass gatherings as any gatherings for which the number of people attending are enough to place additional strain on planning and response resources where these events take place. What constitutes a mass gathering is therefore context-specific. During the current pandemic, mass gatherings have been a contentious point in policies aimed at reducing the spread of COVID-19, with restrictions placed on the maximum number of people allowed to attend church services, funerals, concerts, sporting events, graduations, etc. Mass gatherings can either be once-off (e.g. concerts) or recurring (church services) and targeting these events for Ag-RDT testing prior to entry may reduce the likelihood of super-spreader events while being more tolerable to event attendees than other testing strategies aimed at reducing the spread of COVID-19, such as mask-wearing or lockdowns.

APPROACH

The model for this use case was developed at the Harvard University T.H. Chan School of Public Health to estimate the number of individuals who would be expected to attend a mass gathering while infected. To estimate how an individual's detectability and infectiousness change over time, the authors used prospective longitudinal SARS-CoV-2 testing data collected among players, staff, and vendors participating in the US National Basketball Association's (NBA) occupational health programme.[6] They used a Bayesian statistical model to estimate the peak Ct value, the time from first detectability to the peak Ct value, and the time from the peak Ct value to cessation of acute viral shedding for infected individuals. Using this information, they developed a probabilistic model to estimate how many infectious individuals would be missed by a test administered between 1 and 3 days prior to the mass gathering. **The use case presented here made use of an online interactive version of the model created by the researchers.**

The analyses presented here focused on varying two key parameters: 1) the prevalence of COVID-19 in the community at the time of the event, and 2) the duration of the event (**Table 2**). Additional parameter assumptions are outlined in the Appendix. The duration of the event was a key consideration given that the initial rate of viral increase is so rapid that even for events of just a few hours long, a person infected with SARS-CoV-2 could become infectious during the event. Other non-varied parameters included variable "effective sensitivity" based on the time of testing prior to the event, with a 99% sensitivity assumption on Ag-RDT tests used when the infectiousness threshold was Ct value 30, which goes down to 76% when the test is administered 2 days prior to the event.

To explore the relationship between prevalence, event duration and time of testing, we report all scenarios per 10,000 people attending a mass gathering, thereby accounting either for a singular event with 10,000 people or multiple smaller events that add up to 10,000 attendees in total. The model was not intended to estimate transmission events at the occasion itself, but rather the number of infectious individuals who would be successfully screened from attending the event. We then estimated the number of infectious attendees detected prior to the event if attendees were asked to test 3 days prior, 2 days prior, 1 day prior or day of the event.

Parameter	Values
Prevalence of COVID-19	0.1%, 1%
Duration of event	1hrs, 3hrs, 5hrs
Timing of test	3, 2, or 1 day prior to event, day of event

Table 2. Parameters varied for each mass gathering use case scenario

RESULTS

Higher prevalence, longer event duration and more time elapsed between testing and the mass gathering were associated with higher numbers of infectious individuals at mass gatherings (**Figure 6**). While higher prevalence was associated with a higher absolute number of infectious individuals detected and prevented from attending the mass gathering, the percentage of infectious individuals detected through testing remained stable over different prevalence rates (**Figure 7**).

Event duration slightly increased the number of individuals in the population that were or would become infectious during the event if tested 3 days prior to the event from 40.6 to 42.0 per 10,000 population, while decreasing the infectious individuals prevented from attending by testing from 62.8% to 59.3%. Testing closer to the time of the event was associated with a higher number of infectious individuals detected through testing, though testing 3 days prior still averted more than 60% of infections in all scenarios, except for events of 5-hour duration with 1% population prevalence.

There are situations in which testing prior to the event may be considered advantageous as compared to testing at an event itself, such as increased feasibility, preventing people gathering to access testing just prior to the mass gathering. These considerations need to be weighed with the likelihood of reduced efficacy of Ag-RDT testing as a transmission mitigation strategy.

Some limitations should be considered when interpreting these findings. There is a singular input for the prevalence in the population, which could under- or overestimate the number of infectious attendees detected if participants travel from areas with infection prevalence that is substantially different than the assumed community prevalence. It should also be considered that people attending mass gatherings may be different from the general population in a way that affects their risk of exposure to COVID-19 prior to the mass gathering taking place.

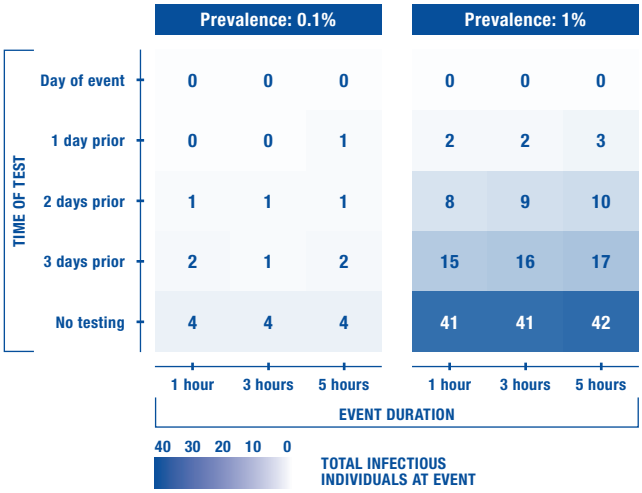

Figure 6. Total infectious individuals at event per 10,000 population attending mass gatherings, after testing, varied by time between testing and time of the event, COVID prevalence, and duration of the event

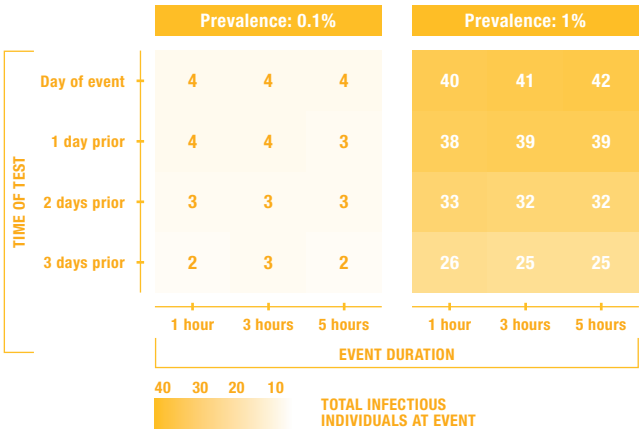

Figure 7. Total infectious individuals detected during testing prior to mass gatherings per 10,000 population, varied by time between testing and time of the event, COVID prevalence, and duration of the event

The results presented here do not include the potentially increased risk of exposure in the time leading up to or immediately after the event. Similarly, these results do not offer guidance on limiting the number of attendees to mass gatherings. Finally, this model does not capture the dynamics of different sized events with different parameters that could modulate transmission (such as ventilation, masks, ability to social distance, etc.). Future work should aim to model different parameters surrounding mass gatherings of different sizes and then calculate the added value of rapid antigen testing as an additional mitigation strategy at one of these events, and compare these results to effectiveness of existing interventions that limit the capacity of the events. Depending on the type of mass gathering considered and the frequency with which they occur, mass gatherings as an intervention touchpoint may overlap with community testing to some extent (e.g. through testing at places of worship).

IN SUMMARY, THE RESULTS SUGGEST THAT USING AG-RDTS TO SCREEN MASS GATHERING ATTENDEES THE DAY BEFORE OR THE DAY OF AN EVENT OFFERS THE GREATEST REDUCTIONS IN DISEASE TRANSMISSION AT MASS GATHERINGS, COMPARED WITH TESTING AT EARLIER TIME POINTS.

Despite the need for substantially more investigation to interrogate the wide variation of potential mass gathering settings, our findings give greater evidence to the value of Ag-RDT in mass gathering situations, as self-test Ag-RDT can return same day testing results, something which is not as feasible with RT-PCR.

3. K-12 SCHOOLS

BACKGROUND

Schools are important points of in-person gathering in most communities. Across the world, primary and secondary schools have been closed in response to the COVID-19 pandemic. During the first wave of global infection, children were less likely to contract, transmit, or show symptoms of COVID-19.[7] School districts that practiced COVID-19 precautions such as mask-wearing, physical distancing, symptom screening, handwashing, and indoor air ventilation were observed to have SARS-CoV-2 prevalence no greater than their surrounding communities.[8]

However, more transmissible SARS-CoV-2 variants have increased the likelihood of transmission in schools.[9] **COVID-19 diagnostic testing could serve as an effective way to reopen schools while preventing SARS-CoV-2 outbreaks.** Testing could be implemented with COVID-19 Ag-RDTs, which provide rapid results and are feasible to implement in a school-age population and do not require additional laboratory infrastructure. Here, an Ag-RDT screening strategy and its corresponding outcome was modeled for teachers with or without the inclusion of primary and secondary pupils, using 2019 school attendance data from Malawi.

APPROACH

A mathematical model was originally developed by researchers at New York University Grossman School of Medicine to evaluate the impact that various mitigation measures, including testing, would have on the transmission of SARS-CoV-2 in New York City Schools. Information about the model was posted on medRxiv, and updated code (programmed in R) for the analysis of this use case has been posted on GitHub.[10,11] This model is a simulation model of classroom dynamics and probability of onward SARS-CoV-2 transmission, parameterized using number of children per classroom and ratio of pupils to teachers.

The model was adapted for the purposes of this use case and re-parameterized to reflect school settings in Malawi. The updated model simulations represent 299 individual schools (representing 1/5th the total number of schools in Malawi), using Malawian school population sizes and student-teacher ratios (**Table 3**). **The entire set of 299 schools was run 50 times for each scenario.** The mean and bootstrapped 95% confidence interval is reported below for each scenario.

Population	Number per school	Total in school simulations
Primary schools (pupils age 5-12)	757	917,955
Secondary schools (pupils age 13-18)	701	196,560
Teachers	11 (Primary), 19 (Secondary)	18,685

Table 3. Total denominator population of each scenario (representative of 1/5th of all schools in Malawi)[12–16]

Given the nature of questions surrounding testing in schools specifically, multiple testing scenarios were evaluated: testing teachers only, testing teachers and secondary school pupils, testing teachers and primary school pupils, and testing teachers and all pupils. All scenarios included symtomatic testing of all teachers and pupils in addition to assigned routine testing. These testing scenarios were then further varied by different testing frequencies and under different epidemic conditions (**Table 4**).

All scenarios were compared to counterfactual base cases with the same epidemic parameters and symtomatic testing for teachers and pupils. We also compared scenarios to a counterfactual base case with no testing in the event that symptomatic testing is not widely available (**Appendix Figures 1 to 4**). Further, there remain concerns at both national and local levels about the need to close a whole school or multiple classrooms following a positive test, causing hesitancy to implement testing within schools, as well as concerns about cost. We have therefore assumed no classroom or school quarantine following a positive test. Only the person who tested positive is assumed to stay home until no longer infectious.

In these simulations, primary school pupils were 43% as susceptible as adults and 63% as infectious as adults.[17] No difference in susceptibility/infectiousness for secondary school pupils and adults was assumed. The sensitivity of the AgRDT was assumed to be 85%.

RESULTS

Amongst the four testing scenarios evaluated, the most effective strategy at reducing the number of SARS-CoV-2 infections among pupils and teachers was testing all teachers plus all pupils, followed by testing all teachers plus secondary school pupils, testing all teachers plus primary school pupils, and finally only testing all teachers (**Figure 8**).

Parameter	Values evaluated
Effective reproductive number	0.8; 1.2; 2.0
Prevalence of COVID-19	0.1%; 1%
Testing scenario	Testing only teachers; testing teachers and 5-12 year olds; testing teachers and 13-18 year olds; testing all teachers and all pupils
Testing frequency	Once/two weeks; once/week; twice/week

Table 4. Parameters varied for each K-12 use case scenario

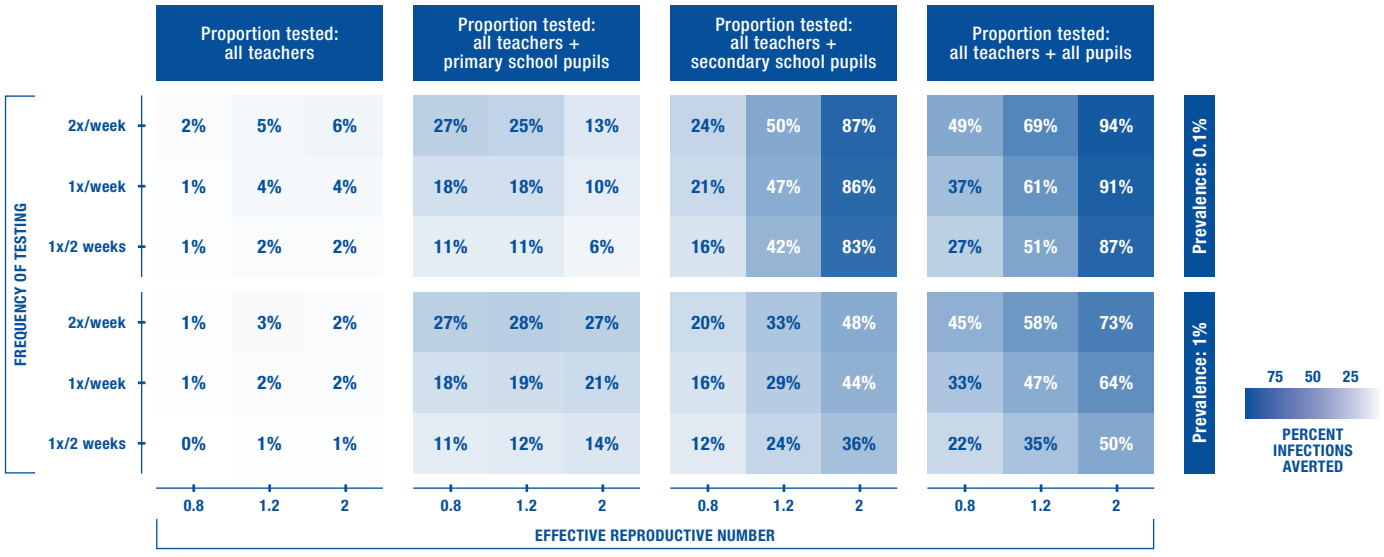

Figure 8. Percent of infections (amongst all teachers and pupils) averted compared to the same epidemic scenario with only symptomatic testing in schools; varied by targeted testing population, COVID prevalence, effective reproductive number and frequency of testing.

Maximum impact of the school testing strategies (particularly for the testing of all teachers and all pupils, and testing of all teachers and secondary school pupils) is achieved when SARS-CoV-2 prevalence is low and Rt is high- such as at the start of a new wave (83%-94% infections averted). This illustrates the utility of surveillance for being able to understand the current prevalence and Rt of SARS-CoV-2 to be able to rapidly deploy effective mitigation measures, such as routine testing in schools.

Unsurprisingly, an increasing frequency of testing also results in an increased proportion of infections averted. However, this comes at the price of efficiency – the greater the frequency of testing the greater the number of tests required to prevent one infection (**Figure 9**).

While testing all pupils plus all teachers is the most effective scenario in reducing the number of new infections, testing all teachers and all pupils ages 13-18 was the most efficient strategy in terms of the number of tests required to prevent a new infection across the majority of epidemic conditions and testing frequencies. This is, however, likely due to the underlying assumption that young children are less likely to be infectious as compared to older children and adults – an assumption that has evolved with new currently circulating variants.

Figures 10 and 11 represent the total number of infections during the 90-day time period **(Figure 10**, with a total denominator reported in **Table 3**), and total number of infections averted (**Figure 11**). When the scenarios were compared to the base case scenario of no testing, all trends were generally the same, but with a lower percent and fewer total infections averted, and more tests per averted infection (**Appendix Figures 1 to 4**).

FURTHER CONSIDERATIONS

Feasibility of such a scenario and resources required to implement depends on country-level guidance and policy. Having such a program effective at scale requires some degree of self-testing or lay-person administered Ag-RDT. Furthermore, the total size of the school-going population would dictate the total resources required of such a program, plus the potential community-level benefit (which was not modeled here).

The modeling presented here reflects the school system and age distribution and student-teacher ratio of Malawi. Approximately 31% of people living in Malawi are of school-going age, exemplifying both the potential impact that testing in schools could have more generally, but also the level of financial/resource investment required to execute an effective school testing strategy. Moreover, we assumed that no additional non-pharmaceutical interventions are conducted in the base case (no intervention) scenario, which may not be accurate given the extent of the COVID-19 pandemic.

Future work should assess further impact of K-12 school-based testing on community transmission and cost-effectiveness of investing in school-based testing as a primary mechanism for the prevention of SARS-CoV-2 transmission in the broader community across a number of country archetypes, and compared with other testing strategies.

Also, the assumptions made here about reduced transmissibility of SARS-CoV-2 might not hold true for emerging variants of concern and further analyses are required to evaluate the impact of differences in virus transmissibility among K-12 school populations. Finally, to enable some level of comparison to other use-cases, we have had to make non-dynamic assumptions about each scenario (e.g. artificially setting Rt and prevalence). In reality, these processes are dynamic, and a dynamic evaluation of each strategy across varying epidemic trajectories will be required.

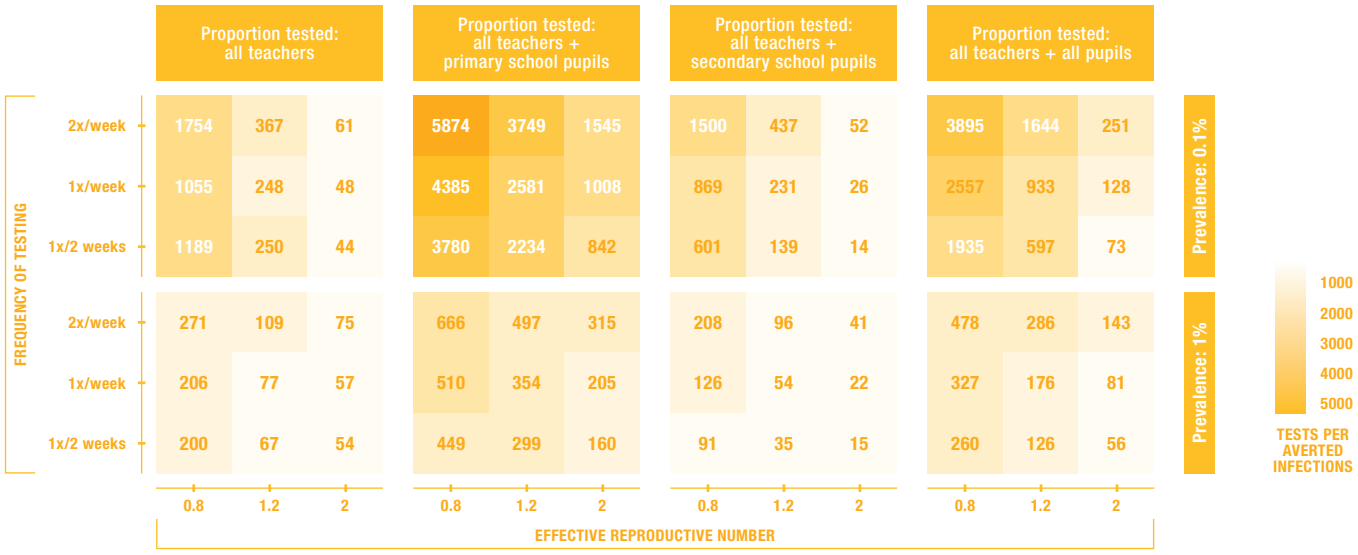

Figure 9. Number of tests required per infection averted compared to the same epidemic scenario with only symptomatic testing in schools; varied by targeted testing population, COVID prevalence, effective reproductive number and frequency of testing.

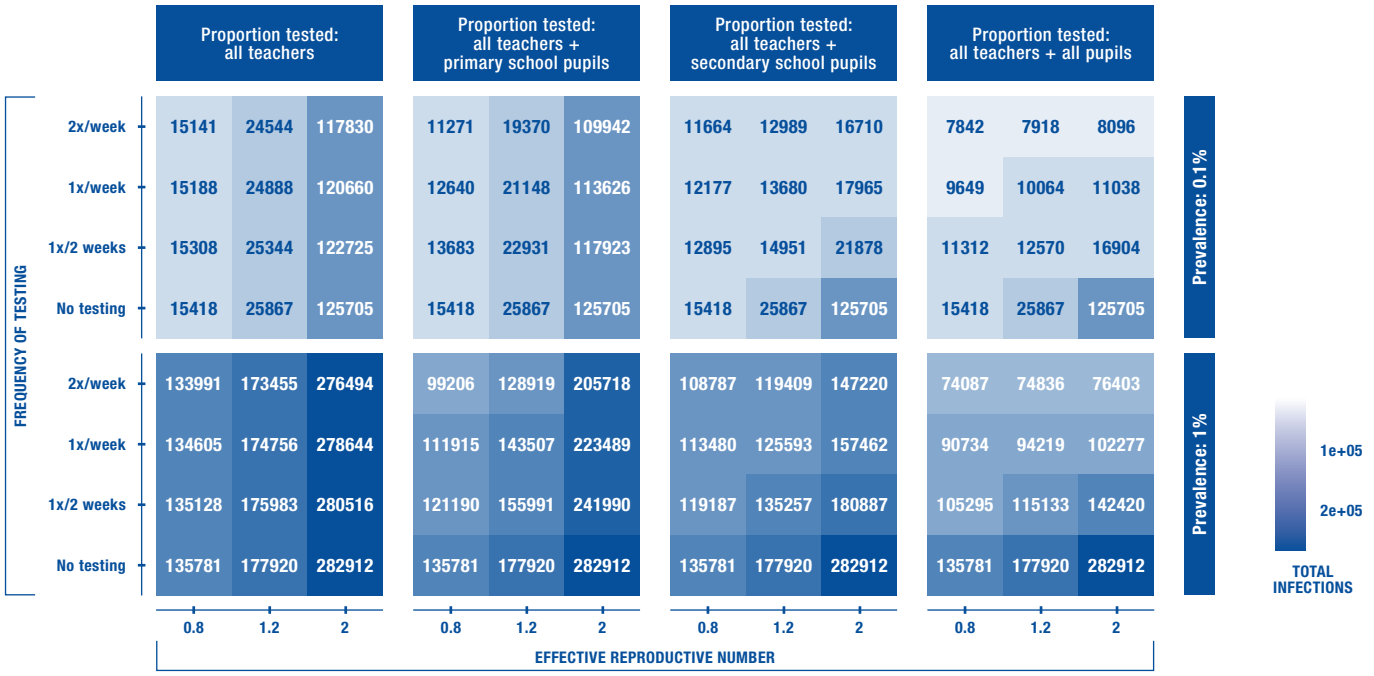

Figure 10. Total number of infections amongst pupils and teachers (no testing = only symptomatic testing), varied by targeted testing population, COVID prevalence, effective reproductive number and frequency of testing.

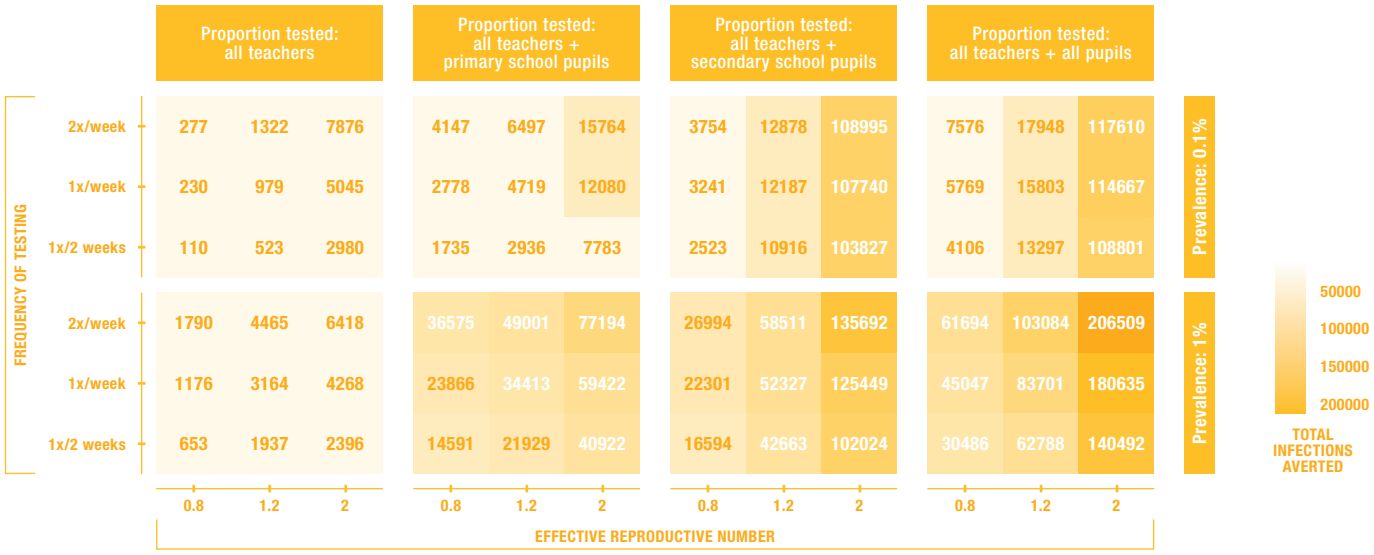

Figure 11. Total number of infections averted amongst pupils and teachers compared to the same epidemic scenario with only symptomatic testing in schools, varied by targeted testing population, COVID prevalence, effective reproductive number and frequency of testing.

4. UNIVERSITIES

BACKGROUND

The COVID-19 pandemic led to the closure of schools and universities across the globe for in-person learning. **University campuses are potential hotpots for COVID-19 transmission,** as students spend long periods of time in classrooms, may reside in dormitories or shared housing and maintain a range of social contacts.[18] This puts both the university population and the surrounding community at greater risk of COVID-19 infection. However, the closing of universities had negative consequences on both a student's ability to learn and on universities' financial stability. In the Fall of 2020 in the United States, many universities attempted to reopen with regular COVID-19 reverse transcriptase PCR (RT-PCR) surveillance of students, faculty, and staff to mitigate on-campus transmission.[19]

An RT-PCR testing strategy can be costly and therefore not feasible at universities with limited financial resources or lack of laboratory capacity, or be hindered by long turn-around-times in a setting where the timely identification of cases is important for success. Up to this point there has been little data or guidance on the use of COVID-19 rapid antigen diagnostic tests (Ag-RDTs) in the university setting. **A successful Ag-RDT screening strategy could allow universities to safely resume in-person operations, especially in limited resource settings.** An Ag-RDT screening strategy was modelled in a university setting under varying epidemic conditions by applying a previously developed agent-based network model to a sample university population.

APPROACH

The university model was originally developed by a team of researchers from Boston University to inform COVID-19 interventions necessary for their Fall 2020 reopening strategy.[20] The model utilizes Covasim, a stochastic agent-based simulator developed by the Institute for Disease Modeling (IDM). The model used predefined classroom and household network structures from a sample university population of 3,681 faculty, staff, and students to project COVID-19 cases and outcomes within the population. The model was adapted for an Ag-RDT screening strategy by adjusting test sensitivity to 85% and turn-around-time for test results to 0 days. Several model parameters were varied to observe the performance of Ag-RDTs in the university setting under differing epidemic conditions and testing frequencies. Daily case incidence and tests used were model outputs of interest in this analysis.

Model simulations were run using the variables shown in **Table 5**, representing a total of **18 distinct scenarios**. Daily imported infections represented the level of COVID-19 community prevalence at either 0.1% or 1.0%. To calculate the number of daily imported infections the university population was multiplied by prevalence level and divided by the average infectious period of SARS-CoV-2.[21] Effective reproductive numbers (Rt) were reflected in the model by incorporating a series of intervention methods, including – classroom level interventions (masks, social distancing, and class cohorts), reduced housing density or contact tracing. Rapid antigen testing was implemented for every member of the population either twice weekly, once weekly or every other week. Simulations were run with Python 3.8.3 through the Boston University Shared Computing Cluster. **Each simulation was run for 90 days, 1000 times.** Means and 95% confidence intervals for daily incident infections and daily tests were computed using SAS 9.4.

RESULTS

Ag-RDT screening in the university setting was most effective under low levels of Rt and low community prevalence. At an Rt of 0.8 and community prevalence of 0.1%, any Ag-RDT testing frequency prevented most infections (>90%), represented as a percentage of infections averted as compared to a baseline scenario with no testing (**Figure 12**). Under these conditions, testing once every two weeks of students, faculty, and staff required the fewest number of Ag-RDT tests to prevent one infection while preventing a comparable number of infections to weekly or twice weekly testing (**Figure 13**). The absolute number of infections and infections averted that correspond to the percentages in **Figure 12** are illustrated in **Figures 14 and 15**. As the Rt and community prevalence increase, there is a significant reduction in the percentage of infections averted. This is seen most markedly at an Rt of 1.2 and community prevalence level of 1%, with the percent of infections averted decreasing from 87% to 42% under twice weekly testing, as compared to a prevalence level of 0.1%.

Parameter	Values evaluated
Effective Reproductive Number (Rt)	0.8; 1.2; 2.0
Daily Imported Infections into the university	0.1% or 1%
Test Frequency	Once/two weeks; once/week; twice/week

Table 5. Parameters varied for each university use case scenario

When the Rt is 2 or higher, an increase in community prevalence is unlikely to make a significant difference in a population this small. When the Rt and prevalence are high, twice weekly testing prevents the greatest number of infections, but with significantly more tests necessary per averted infection.

This university modelling analysis comes with important assumptions and limitations. First, the sample university population, while it was meant to imitate a real university population, was small in comparison to that of most universities, composed of only 3,681 people. In scenarios with a high Rt, the epidemic began to burn itself out within the 90-day simulation period. Simulations run with a larger population could lead to slightly different results. However, simulations were run 1000 times, providing narrow 95% confidence intervals (**Section 4**). Second, the university model assumed perfect compliance with isolation of confirmed positive cases, tracing, and quarantine of known contacts of the positive cases. In practice, compliance with these interventions will likely be less than 100%, which could lead to more onward transmission. Finally, this modelling analysis only observed the effectiveness of three different testing frequencies, while these are the most likely scenarios in a university setting, testing a student every time they came to campus, and therefore catching potential infections before onward transmission, could be a successful strategy.

An Ag-RDT strategy at a university would be most effective and prevent the largest percentage of infections under any scenario when testing is conducted twice weekly. However, this frequency of testing also uses the greatest number of tests to prevent one infection. When the Rt is low, testing once weekly or biweekly would also be sufficient at preventing a comparable number of infections. In this analysis, Rt was represented in the model by implementing various mitigation measures, such as mask wearing, social distancing and contact tracing. The greatest number of infections can be prevented with the least number of tests when these additional measures are in place. In order for an Ag-RDT screening strategy to be successful and resource efficient at universities, additional intervention methods should be utilized as well.

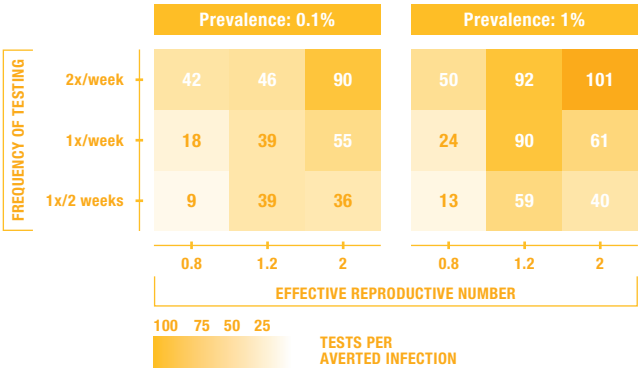

Figure 13. Number of Ag-RDTs used per COVID-19 infection averted over a 90-day period in the university setting, varied by COVID prevalence, effective reproductive number and frequency of testing.

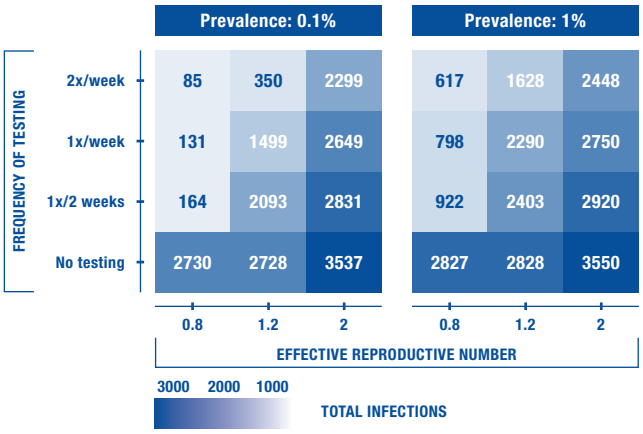

Figure 14. Total number of COVID-19 infections under each testing scenario compared to baseline with no testing, varied by COVID-19 prevalence, effective reproductive number and frequency of testing.

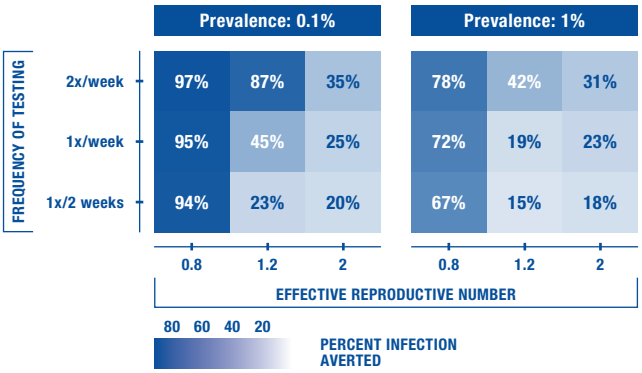

Figure 12. Percent of COVID-19 infections averted over a 90-day period in the university setting when routinely testing with Ag-RDTs, varied by COVID prevalence, effective reproductive number and frequency of testing.

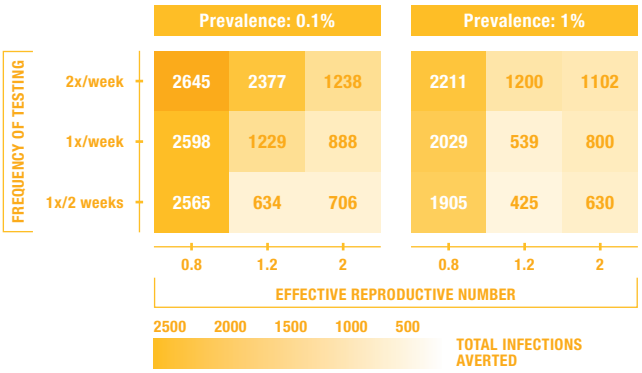

Figure 15. Total number of COVID-19 infections averted under each testing scenario compared to a baseline scenario with no testing, varied by COVID-19 prevalence, effective reproductive number and frequency of testing.

5. BORDER CROSSINGS

BACKGROUND

Throughout the COVID-19 pandemic, countries have had varying success containing community transmission of SARS-CoV-2 within their borders.[22] **Containing community transmission and preventing the importation of new infectious cases of SARS-CoV-2 into a country remains crucial in areas without widespread access to vaccines, especially as more infectious variants of SARS-CoV-2 emerge.** Effective travel related control measures are still needed to prevent the spread of these variants. Some countries have implemented entry requirements that international travelers provide proof of a negative COVID-19 reverse transcription polymerase chain reaction (RT-PCR) test within 72-hours of arrival.

While this is possible to implement in many high-income countries and for air travel, this is frequently not possible at land-border crossings, particularly in low- and middle-income countries (LMICs), due to frequent cross-border travel and resource constraints. However, antigen rapid diagnostic tests (Ag-RDTs) are less costly than RT-PCR tests, do not require laboratory-based infrastructure, can be performed on-site by appropriately trained non-laboratory staff, and provide results within minutes, enabling decentralization of diagnostic testing.[23] **This use case investigates the use of Ag-RDTs for screening at border crossings, with or without the need for a prior RT-PCR test.**

APPROACH

Three different models were used to predict the effectiveness of an Ag-RDT screening strategy at border crossings with or without prior negative RT-PCR test results in a hypothetical daily travel population of 100,000 individuals. The Boston University School of Public Health (BUSPH) model is an algebraic algorithm with input derived from a compartmental transmission model, the Agency for Science Technology and Research (A*STAR) model is agent-based, while the London School of Hygiene and Tropical Medicine (LSHTM) model used an individual-based simulation. Model parameters used can be seen in **Table 6**, and further model details can be found in the appendix or related publications or pre-prints.

For 72-hour pre-PCR test sensitivity, the A*STAR model used a sensitivity distribution based on day of symptom onset at time of testing. The LSHTM model used viral load trajectories and corresponding probabilities based on the day of SARS-CoV-2 exposure for both Ag-RDT sensitivity and 72-hour pre-PCR sensitivity. COVID-19 prevalence among cross-border travelers was varied from 0.1%–2.0%. **Eight distinct scenarios were run with each model.** The key model output was undetected daily infections crossing the border per 100,000 travelers, which was used to compute the number of infectious imports averted per 100,000 travelers and the number of tests per infectious import averted. Scenarios that included a 72-hour pre-PCR test were considered to use two tests per traveler. These outputs were in comparison to baseline scenarios without testing.

RESULTS

The LSHTM model predicted the most conservative outcome with the largest number of daily undetected infections crossing the border per 100,000 travelers under both testing strategies (**Figure 16**). The A*STAR model predicted the smallest difference with the addition of a 72-hour pre-PCR test, finding that most infections detected through pre-PCR testing would have been detected at the border with an Ag-RDT. The BUSPH and LSHTM models found a marked difference in the number of undetected infections with the addition of a 72-hour pre-travel RT-PCR requirement. The difference between the models may arise from A*STAR model's assumption that the incubation period being largely undetectable by either Ag-RDT

Parameter	BUSPH Model	A*STAR Model	LSHTM Model
COVID-19 Prevalence (%)	0.1, 0.5, 1.0, 2.0		
Daily Travel Volume	100,000		
Ag-RDT Sensitivity	85%	80%	85%
72-hour pre-PCR Sensitivity	88%[24]	*	*
Testing scenario	Ag-RDT on arrival alone; Ag-RDT on arrival plus a negative PCR test within 72 hours of travel		

Table 6. Key parameters varied for each border crossings use case scenario

or PCR and a different approach to test sensitivity based on thresholding a log normal distribution on each day of infection. In this scenario, the 80% sensitivity value is the relative cumulative sensitivity of Ag-RDT compare to PCR's 100%.

Among all three models, undetected infections increased as COVID-19 prevalence increased among cross-border travelers. The number of tests per averted infectious import had the opposite trend, requiring far more tests to capture one infection at low prevalence levels (**Figure 17**). The similarity between models can be more readily visualized in **Figure 18**, which shows the number of infectious imports averted per 100,000 travelers under the given testing strategy.

The effectiveness of a border screening strategy for COVID-19 is highly dependent on the prevalence of infection among travelers and the sensitivity of the tests. From a resource allocation perspective, a border screening strategy may be more beneficial when COVID-19 prevalence is high among travelers or at borders where the prevalence amongst travelers is greater.

In addition, such a strategy will also be influenced by the volume of travel at a given border. Furthermore, the public health impact will be dependent on the status of the epidemic within a given country, as infectious imports will have a more consequential impact when community transmission is largely under control.[25] This aspect remains to be investigated with the results presented here.

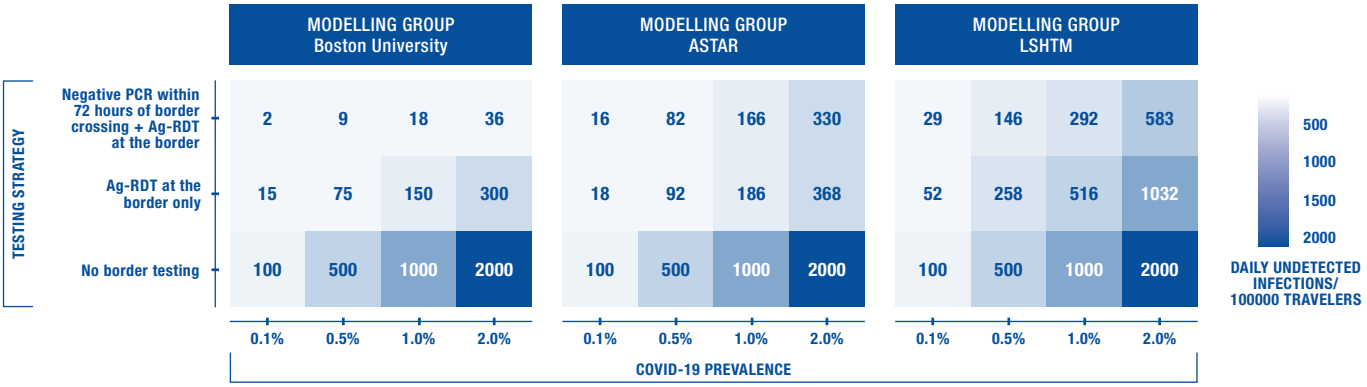

Figure 16. Daily undetected COVID-19 infections per 100,000 cross-border travelers under the given testing regimen compared to a baseline scenario with no testing, by COVID prevalence and modeling group.

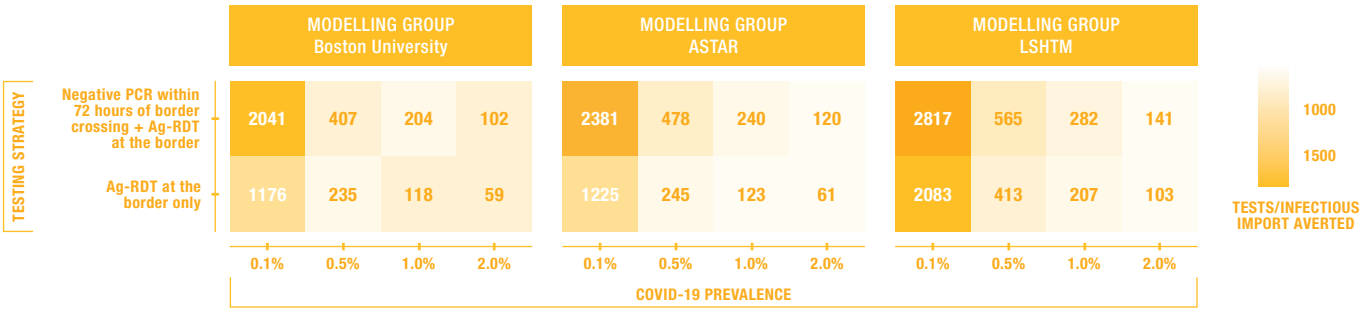

Figure 17. Ag-RDT and/or RT-PCR tests administered per infectious import averted, by COVID prevalence and modeling group.

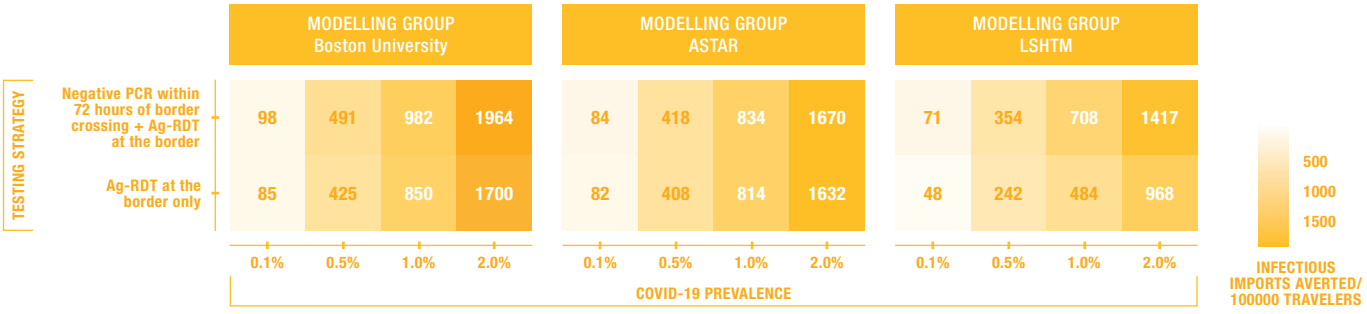

Figure 18. Infectious imports averted per 100,000 cross-border travelers (compared to no testing), by COVID prevalence and modeling group.

6. TESTING TO EXIT QUARANTINE AND ISOLATION FOLLOWING CONTACT TRACING

BACKGROUND

Quarantine and isolation are non-pharmaceutical interventions that can reduce the transmission of SARS-CoV-2. Most jurisdictions recommend a 14-day quarantine period following exposure to a known test-positive case, or following (international) travel, and a 10-day isolation period following a positive test.[26,27] However, quarantine and isolation can cause considerable economic and social costs at the individual and society level and recent evidence suggests that adherence to quarantine and isolation is poor, reducing its efficacy.[28] Strategic testing, to allow for exit from quarantine or isolation early or daily testing in the absence of quarantine, can be used to reduce the economic and social costs as well as potentially improve quarantine and isolation adherence. Testing for this purpose using a RT-PCR testing strategy is costly and may not be a feasible option for low resource settings. **The increasing availability of Ag-RDTs opens up this strategy to low resource settings.** There is little data or guidance on the use of Ag-RDTs to shorten quarantine and isolation. This use case seeks to determine the optimal use of Ag-RDT testing strategies to reduce the burden of long quarantine or isolation post the infectious period.

APPROACH

A quarantine and contact tracing model was originally developed by a team of researchers at the Centre of Mathematical Modelling of Infectious Diseases at the London School of Hygiene and Tropical Medicine. The model and all assumptions are published in a Lancet Public Health article.[29] This model is an individual-based simulation of viral load trajectories. The probability of detection by Ag-RDT, as well as infectivity, is determined by the viral load at the time of testing. The model was adapted for the purposes of this use case to include (1) test-to-release from isolation *n* days after developing symptoms or a positive test and, (2) updated adherence values to take into account assumed enhanced adherence for less time spent in quarantine or isolation due to testing.

There are five main scenarios that differ depending on whether there was quarantine or no quarantine, no testing or test on release from quarantine or isolation, or, as an alternative to quarantine, daily testing on being traced as a contact (**Table 7**).

Scenario	Description
1	Status quo quarantine (14 days) and isolation (10 days)
2	Test to release quarantine, status quo isolation
3	Test to release quarantine, test to release isolation
4	Daily testing quarantine, status quo isolation
5	Daily testing quarantine, test to release isolation

Table 7. Main scenarios

A hypothetical cohort of 10,000 exposed contacts that should enter quarantine was modelled. Outputs included the number of infectious person days – total, spent in quarantine/isolation, or in the community, as well as the total number of Ag RDT tests used. Based on these outputs, the number of Ag RDT tests required to avert an infectious person-day in the community was calculated relative to a status quo of 14 days in quarantine and 10 days in isolation. The number of tests used in daily testing was calculated as the number of tests used up to and including the first positive test, at which point an individual begins isolation and ceases testing if completing the full 10 days, or has a test to release from isolation.

Model outputs were informed by adherence parameters which vary depending on the duration of quarantine without symptoms or the duration of isolation following a positive test or symptom onset. Results were adjusted linearly by day to take into account assumed enhanced adherence from a reduction in the quarantine/isolation requirement (**Table 8**).

Days	3	5	7	10	14
Adherence in quarantine without symptoms	50%	46%	41%	37%	28%
Adherence in isolation following a positive test result	100%	97%	93%	86%	/
Adherence in 'isolation' following development of symptoms	100%	93%	86%	71%	/

Table 8. Adherence adjustments

Notes: End points for adherence in quarantine without symptoms, and isolation following development of symptoms taken from Steens et al. 2020.[30] Adherence end point for adherence following a positive test result from ONS 2021.[31] Adherence at day 3 assumed and adherence at days between start and end point calculated linearly.[32]

Scenario	Exposed prevalence (%)	Delay to contact tracing (days)	Quarantine?	Days in quarantine	Quarantine exit testing	Daily testing in quarantine (days)	Days in isolation	Isolation exit testing
1	1,10,50	0,3	Y	14	None	NA	NA (10)	NA (None)
2	1,10,50	0,3	Y	3,5,7,10	Test to release	NA	10	None
3	1,10,50	0,3	Y	3,5,7,10	Test to release	NA	3,5,7	Test to release
4	1,10,50	0,3	N	0	Daily	1,3,5,7,10	10	None
5	1,10,50	0,3	N	0	Daily	1,3,5,7,10	3,5,7	Test to release

Table 9. Key parameters. Within each scenario row, all combinations of the comma-separated values are considered.

Model simulations were run in R using the parameters shown in **Table 9**, representing a total of **222 distinct scenarios.** These sub-scenarios differ by the assumption on underlying 'prevalence' of the exposed contacts (1%, 10%, or 50%), the delay to contact tracing (0 or 3 days), the number of days spent in quarantine prior to an exit test (0, 3, 5, 7 or 10 days), the number of days of daily Ag-RDT testing if no quarantine is required (for 3, 5, 7 or 10 days), and the number of days spent in isolation prior to an exit test (3, 5, 7, or 10 days) or not. If the delay from an index case tracing exceeds or equals that of the quarantine duration, then quarantine does not occur, e.g. in the case of a 3-day delay and 3-day quarantine. Confidence intervals were calculated by bootstrapping for 10 secondary cases per index case (500 index cases per scenario) then up-scaling to the assumed prevalence/attack rate for 10,000 contacts.

RESULTS

Any Ag-RDT testing strategy to exit quarantine or isolation early is very effective at reducing the number of infectious days in the community relative to the status quo due to the improvement in adherence to quarantine/isolation that we estimated (assuming the rates of adherence were similar to or better than those derived for the UK and Norway) (**Figures 19A and 19B**).[30,31] Daily testing in the absence of quarantine for 5,7 or 10 days, and a test to release strategy for isolation from day 3 or 5 averted the most infectious person-days. With daily testing, the added benefit of 7 or 10 days of testing was negligible and largely negligible after 3 days when the delay to contact tracing was 3 days.

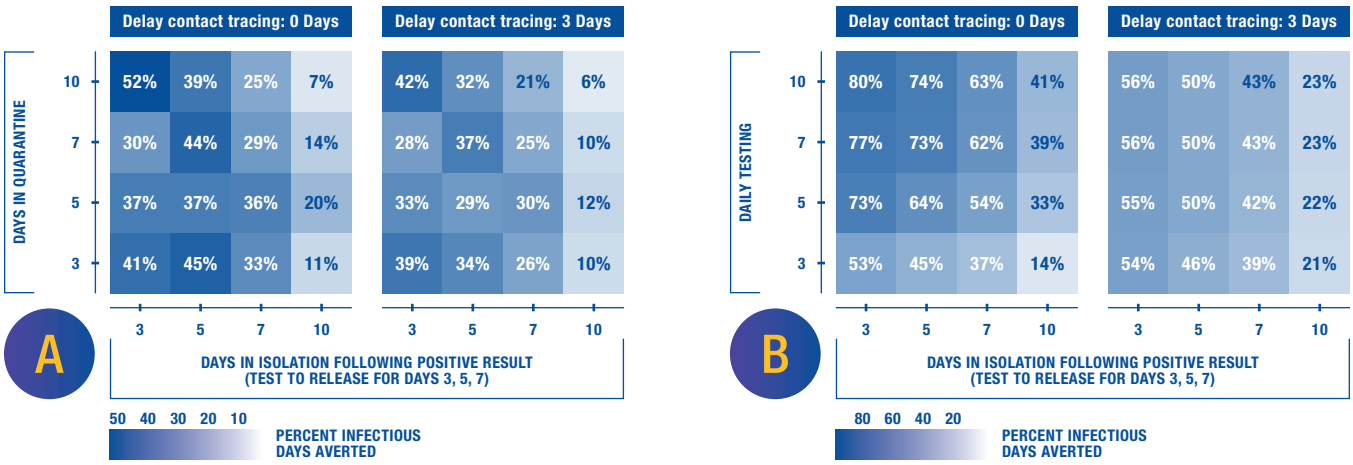

Figure 19. **(A)** Proportion infectious days averted (test to exit); **(B)** proportion infectious days averted (daily testing).

Notes: These figures are shown for a 10% prevalence. There was a < 1% difference with a 1% and 50% prevalence.

Figures 20A and 20B reiterate the results from **Figure 19**. Daily testing in lieu of quarantine averts more infectious days than a test to release strategy. More infectious days are averted if there is zero delay to contact tracing. Daily testing in the absence of quarantine for 5,7 or 10 days, and a test to release strategy for isolation from day 3 or 5 averted the most infectious person-days. In addition, unsurprisingly, more infectious days are averted the higher the prevalence.

Across all scenarios, low exposed contact prevalence was associated with more tests required to avert an infectious person-day in the community (**Figure 21 A and B**). This is because an Ag-RDT testing strategy for low versus high prevalence 'captures' less infectious days in the community for the same number of tests. **Regardless of prevalence, test to release strategies for both quarantine and isolation were the most efficient at averting infectious person-days** (**Figure 21 A**). In general, the longer the required time period in isolation, the more tests required to avert one infectious person-day relative to the status quo. Similarly, in general the longer the required time period for either testing daily in the absence of quarantine, or the number of required quarantine days prior to a test to release, was associated with more tests per infectious person-day averted. Longer delays in contact tracing were also associated with more tests required to avert an infectious person-day, except in the first 3 days of daily testing following a 3-day delay.

Daily testing, whilst the most resource intensive in terms of tests, produces the largest benefit in terms of a reduction in required quarantine days, potentially reducing economic and social costs (**Table 10**).

There are a number of limitations with this model, as discussed in detail in the original article, for example: index cases seek out and take a test within 1 day after the onset of symptoms; only a single generation of infection is examined; and the use of a simplifying assumption that the Ct curve is a reasonable proxy for both the infectivity and probability of detection by testing[4].

In addition, we used assumptions of enhanced adherence following shorter periods of isolation or quarantine. In general, the testing strategy results in shorter quarantine or isolation periods with higher assumed rates of adherence reducing the number of infectious person-days in the community to a greater degree than that of longer quarantine or isolation periods which have lower assumed rates of adherence, and hence may overestimate the effectiveness of our testing strategies. In particular, for those whose test to release from isolation is positive, the model assumed the same adherence level would remain for the continuation of the isolation period, overestimating the adherence for those individuals. Furthermore, we have used linearly adjusted adherence values by day. These estimates as well as a functional form for adherence need to be verified by additional research.

The model has not quantified the cost associated with false positive results which, in the absence of a test to release from quarantine, or daily testing in the absence of quarantine, would have been incorrectly placed into isolation. In low prevalence settings there are likely to be a greater proportion of false positives. However, the number of false positives who are forced to undergo a period in isolation will never offset the total reduction in quarantine or isolation days as a result of Ag RDT testing strategies. Lastly, **no estimate of the economic or social costs has been included in this analysis.** Future research needs to quantify the reduction in economic and social costs from the reduction in quarantine/isolation days associated with daily testing and test to release strategies relative to the costs of increased Ag RDT testing.

Quarantine and isolation could be shortened by testing to exit, or replaced by daily contact testing, which may avert more infectious person-days in the community if testing induces individuals to adhere better than they do to a longer 14-day quarantine or 10-day isolation periods. Reducing contact tracing delays and boosting adherence is key to reducing the number of infectious person-days in the community. Whether the costs of additional Ag RDT tests are offset by reduced economic costs due to reduced days spent in quarantine or isolation, remains to be investigated.

	Days in quarantine	Reduction in quarantine days per 10,000 cohort
Status quo	14	-
Test to release	10	40,000
	7	70,000
	5	90,000
	3	110,000
Daily testing	0	140,000

Table 10. Reduction in quarantine days per 10,000 cohort

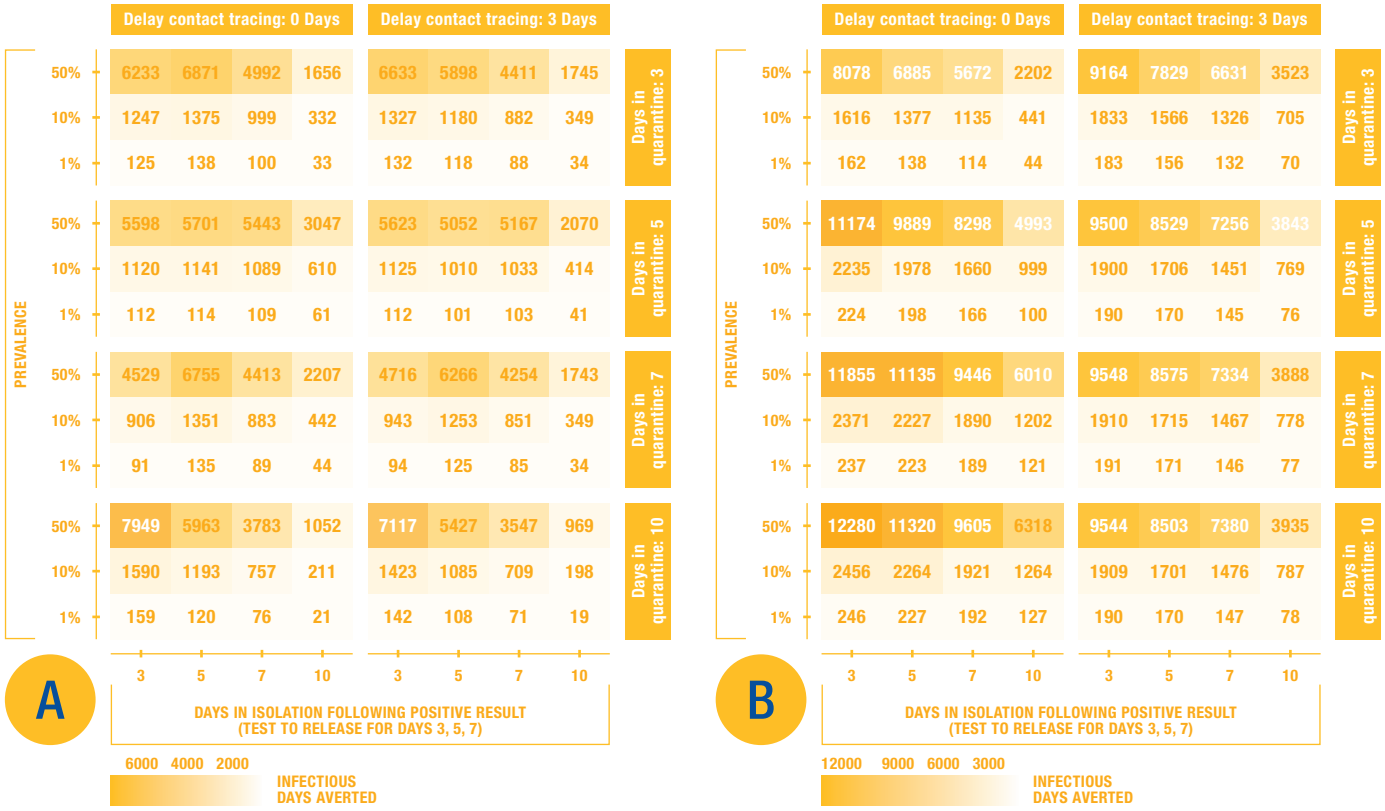

Figure 20. **(A)** Number of Infectious Person-day averted: Test to Release Quarantine;
(B) Number of Infectious Person-day Averted: Daily testing – no quarantine.

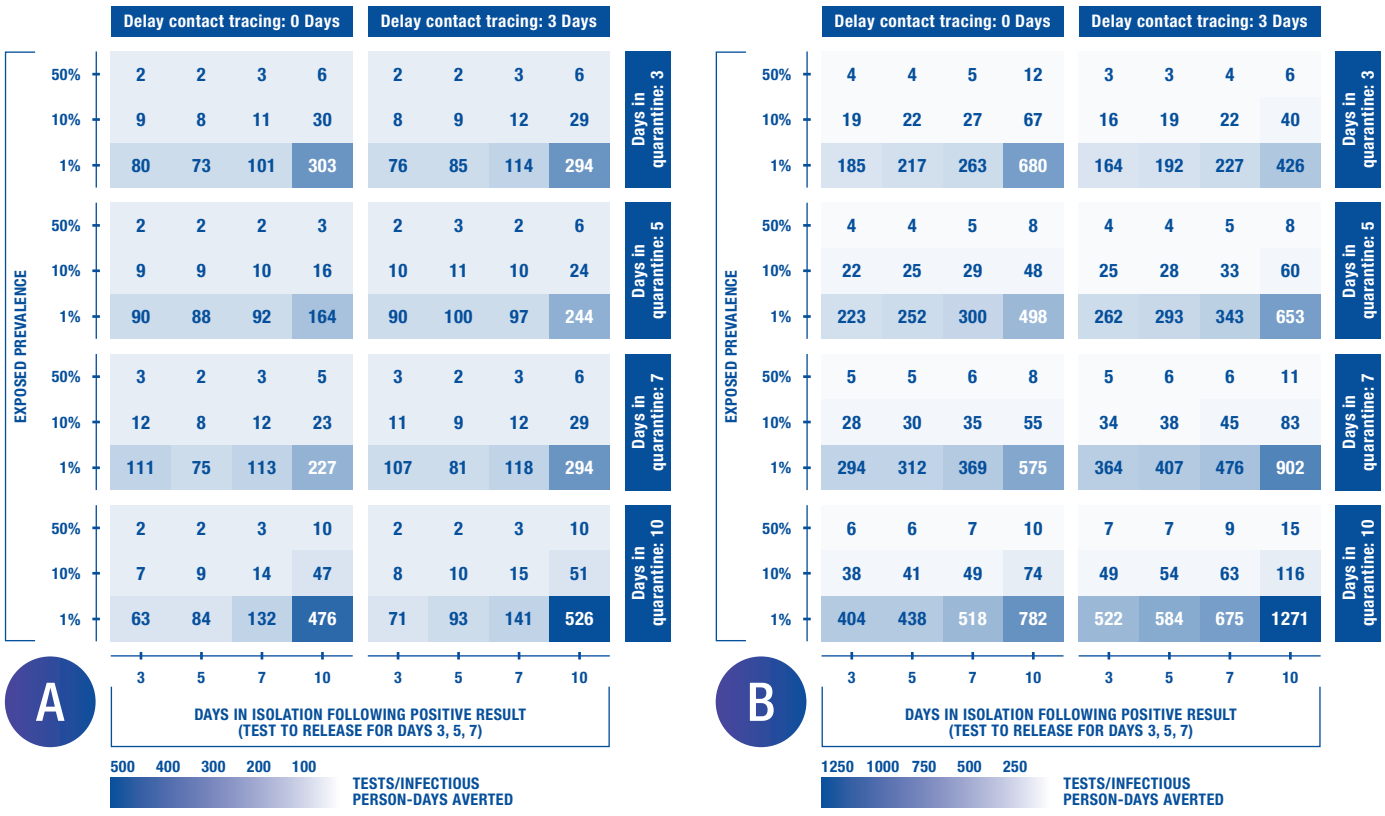

Figure 21. **(A)** Tests per Infectious Person-day averted: Test to Release Quarantine;
(B) Tests per Infectious Person-day Averted: Daily testing – no quarantine.

USE CASE UNCERTAINTY

In an effort to compare uncertainty estimates (95% simulation intervals) across use cases, scenarios were selected that had similar parameters. The three consistent parameters were (1) prevalence of COVID-19 (2) effective reproductive number (Rt) and (3) frequency or timing of tests. Some models have additional testing strategies, which we also kept constant. **Table 11** describes the use case scenarios used to compare the uncertainty estimates in the figure.

In **Figure 22** we compare the point estimates across the two main outcomes (percent infections averted and test per averted infection) for community testing, K-12 schools, Universities, Mass gatherings, Border crossings, and Exiting quarantine use cases. Some use cases do not model certain epidemic parameters, and thus were excluded from the figure. Instead of the number of infections, the outcome for the Exiting quarantine use case was the number of infectious days. **Figure 22A** assesses the percent infections averted and the number test per averted infection when Rt = 1.2 or not applicable and prevalence is 1%, **Figure 22B** when Rt = 1.2 or not applicable and prevalence is 0.1%, **Figure 22C** when Rt = 0.8 and prevalence is 1%, and **Figure 22D** when Rt = 0.8 and prevalence 0.1%.

The outcomes for percent infections averted ranged from 19% (universities; Rt=1.2, prevalence=1%) **to 99%** (community testing; Rt=0.8, prevalence=0.1%), and the simulation intervals varied slightly. The test per averted infection ranged from 18 tests (universities; Rt=0.8, prevalence=0.1%) to 2557 tests (K-12 schools; Rt=0.8, prevalence=0.1%), with a similar trend in the width of simulation intervals across use cases. Use cases that targeted a certain group of people (Mass gatherings, Border crossings, exiting quarantine) had greater uncertainty than use cases that focused on a larger subpopulation (community testing, K-12 schools, and universities).

OVERALL, HIGH COVID-19 PREVALENCE IN THE POPULATION MAKES AG RDT TESTING MORE EFFICIENT, WHERE THE TEST PER AVERTED INFECTION IS LOWER WHEN PREVALENCE IS 1%.

The trend for impact (percent infections averted) and efficiency (test per averted infection) are similar for both prevalence = 1% (**Figure 22C**) and prevalence 0.1% (**Figure 22D**) when Rt is 0.8, but test per averted infection is generally higher when prevalence is 0.1%. Ag RDT use in universities is more impactful (greater percentage of infections averted) when Rt is low, while use in K-12 schools when Rt is high.

Among total infections averted and total infections, the width of the simulation intervals were generally small, except for border crossings. The width of the border crossing interval may be due to the model structure of the LSHTM model, which used viral load trajectories to calculate the corresponding probability of infection. Overall, the simulation intervals were narrow across use cases and outcomes, demonstrating that the estimates did not vary greatly due to stochasticity.

Use case	Prevalence	Rt	Test frequency	Additional testing strategy/ additional information
Community testing	1%, 0.1%	0.8, 1.2	Once a week	Tested 50% of the population with testing effectiveness of 50%
K-12 schools	1%, 0.1%	0.8, 1.2	Once a week	Tested all teachers and students
Universities	1%, 0.1%	0.8, 1.2	Once a week	N/A
Mass gatherings	1%	1.2	Once	Event duration of 5 hours, and a test 2 days prior to the event.
Border crossings	1%	N/A	Once	Ag-RDT at the border only
Exiting quarantine	1%	N/A	One test to release from quarantine and one test to release from isolation	Delay to contract tracing is 3 days, 5 days in quarantine, and 5 days in isolation

Table 11. Description of the use case scenarios to compare uncertainty estimates.

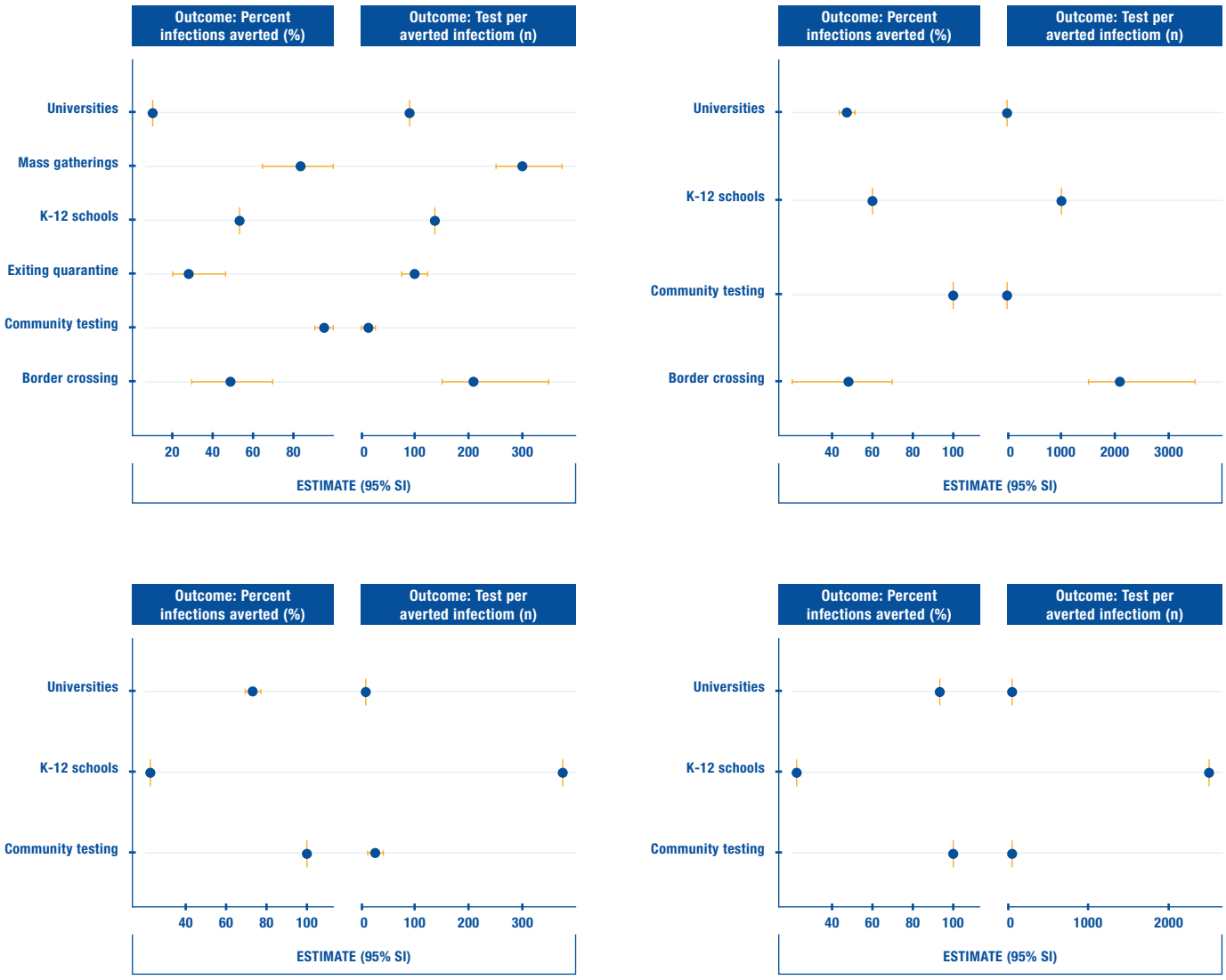

Figure 22. Point estimate and 95% simulation intervals for percent infections averted and test per averted infection when
(A) Rt = 1.2 or not applicable and prevalence is 1%,
(B) Rt = 1.2 or not applicable and prevalence is 0.1%,
(C) Rt = 0.8 and prevalence is 1%,
(D) Rt = 0.8 and prevalence 0.1%.

SYNTHESIS AND NEXT STEPS

THE AIM OF THE USE CASE ANALYSIS WAS TO IDENTIFY A RANGE OF SCENARIOS ACROSS THE VARIOUS SECTORS OF SOCIETY WHERE AG-RDT SCREENING FOR COVID-19 WOULD BE APPROPRIATE FOR USE.

It can then be determined how to allocate and optimize Ag-RDTs to reduce COVID-19 transmission and re-open societies safely: allowing schools and universities to re-open, sporting events, concerts and places of worship to open, reduce quarantine periods, halt outbreaks and resume travel. The different use case settings presented above require different testing strategies to most efficiently and effectively reduce infections across a range of epidemic conditions.

WE SYNTHESIZE SOME OF THE MAIN FINDINGS ACROSS USE CASES BELOW:

ACROSS USE CASES, A HIGHER FREQUENCY OF TESTING (OR MORE WIDESPREAD TESTING) WAS ASSOCIATED WITH A GREATER IMPACT IN TERMS OF INFECTIONS AVERTED.

In the community testing use case, across all the epidemic scenarios, a greater percentage of infections are averted with more frequent and more widespread community-wide Ag-RDT testing, given that positive cases comply with isolation (isolation effectiveness). Similarly, for the K-12 use case, an increased frequency of testing also resulted in a larger proportion of infections averted and, more widespread testing – testing all students plus all teachers – was the most effective scenario in reducing the number of new infections. An Ag-RDT strategy in a university setting was most effective and prevented the largest percentage of infections under any scenario when testing was conducted twice weekly.

Any Ag-RDT testing strategy to exit quarantine or isolation early was very effective at reducing the number of infectious days in the community relative to the status quo of no testing due to the estimated improvement in adherence to quarantine/isolation. High frequency testing, or daily testing in the absence of quarantine for at least 5 days and a test to release strategy for isolation averted the most infectious person-days if testing induced individuals to adhere better than they would to a longer 14-day quarantine or 10-day isolation period.

In the case of mass gatherings, the timing, rather than the frequency of the test was most important. Using Ag-RDT tests to screen mass gathering attendees the day before or the day of an event offered the greatest reduction in infectious individuals at mass gatherings. While the testing strategy modeled at border crossings was slightly different from that of other use cases, an additional negative COVID-19 RT-PCR test result prior to Ag-RDT screening at the border offered a greater reduction in the number of undetected infections entering a country.

IN GENERAL, TESTING STRATEGIES ACROSS MOST USE CASES WERE MOST EFFECTIVE WHEN RT AND/OR PREVALENCE IS LOW.

The effective reproductive number of SARS-CoV-2 (Rt) and the prevalence of COVID-19 within the community are two influential factors in the success of a testing strategy. Under widespread community testing, a high Rt and high prevalence necessitated a larger proportion of individuals be tested more frequently to maximize a reduction in transmission. On the other hand, K-12 schools and universities had somewhat contrasting results. While both models agreed that a greater proportion of infections could be prevented under low COVID-19 prevalence, they present opposite results in the context of Rt. K-12 schools saw a greater reduction in cases under a high Rt, while universities saw a greater reduction in cases when the Rt was low. These differences could be reflective of both the transmission dynamics within networks among the use cases and the way Rt was represented in the model. For example, the university model expressed Rt within the university community (a closed community) and was not reflective of the broader community, indicating that testing works best in concert with other interventions that bring the Rt below 1. For both use cases, it remains to be determined what effect their respective testing strategies will have on the broader community.

The effect of COVID-19 prevalence on Ag-RDT screening at border crossings is less apparent as it is largely restricted by the performance of the tests used. As COVID-19 prevalence increases, more infectious imports are both averted and enter undetected. So, while fewer cases of COVID-19 will enter a country when the prevalence is low, the impact these undetected infections have on the recipient community remains to be analyzed.

BUT, IN GENERAL, MOST USE CASE TESTING STRATEGIES REQUIRE MORE TESTS TO AVERT INFECTIONS WHEN RT AND/OR PREVALENCE ARE LOW.

Across all scenarios in the quarantine and isolation use case, low exposed contact prevalence was associated with more tests required to avert an infectious person-day in the community. This is because an Ag-RDT testing strategy for low versus high prevalence 'captures' less infectious days in the community for the same number of tests. Similarly, with border crossings, the number of tests per infectious import averted required far more tests to capture one infection at low prevalence levels. At mass gatherings, more tests are required to detect one infectious person if prevalence is low. In both the community testing and K-12 schools use cases more tests are also required per infection averted when the prevalence is low.

Notably this was not the case in the University use case. In the university setting, when the Rt is low, testing once weekly or bi-monthly would be sufficient at preventing a comparable number of infections (to higher frequency of testing). When the Rt and prevalence are high, twice weekly testing prevented the greatest number of infections, but with significantly more tests necessary per averted infection. This is largely because the marginal gain in number of cases prevented decreases as the Rt and prevalence increase, while the number of tests administered remains the same under the given frequency. These contrasting outcomes (in comparison to the other use cases) speak to the limitations of the university model as a closed community with a small population.

IN GENERAL, LOWER FREQUENCY TESTING STRATEGIES ARE MORE EFFICIENT.

In the K-12 use case, the greater the frequency of testing, the greater the number of tests required to prevent one infection and subsequently the less efficient the strategy. Testing all teachers and all students ages 13-18 was the most efficient strategy in terms of the number of tests required to prevent a new infection across the majority of epidemic conditions and testing frequencies. In terms of the community testing use case, the lower the frequency of testing in the community consequently decreased the number of tests per infection averted in most scenarios. The trade-off between impact and efficiency was less stark in the University setting when the Rt was low, where bi-monthly testing of students, faculty, and staff required the least number of Ag-RDT tests to prevent one infection while preventing a comparable number of infections to weekly or twice weekly testing. However, as the Rt increases more frequent testing averts a larger percentage of infections while requiring more tests and reducing efficiency.

When testing to exit quarantine and/or isolation, test to release strategies were generally more efficient and utilized less Ag-RDT tests compared to an intensive daily testing strategy. However, this efficiency comes at the expense of a smaller reduction in the number of infectious days.

Efficiency is perhaps most clear in the mass gatherings use case, which is largely dictated by the time of testing. Testing the day of the event detects the greatest number of infectious individuals while utilizing the same number of tests as compared to testing in the days prior to the event, as attendees are more likely to become infectious the longer the time between testing and the event.

The efficiency of border crossing testing remains to be determined in the next phase of our analysis.

The models for the different use cases utilize a number of simplifying assumptions in order to reduce complexity, which introduces several limitations in the interpretation of our findings. For example, the models are unconstrained by healthcare worker capacity or total number of tests. Furthermore, we have not validated models based on ongoing pilot projects, such as testing at mass gatherings or routine asymptomatic testing. Moreover, across use cases, we have modeled the most likely scenarios that would provide greater insight into interventions that would provide robust epidemic control and surveillance. As a tradeoff between complexity and parsimony of our models, we weren't able to model all possible testing scenarios.

NEXT STEPS

THE RESULTS PRESENTED FOR THE USE CASES IN THIS REPORT ONLY QUANTIFY THE EFFECTIVENESS OF TESTING STRATEGIES WITHIN EACH USE CASE.

The results presented here do not offer any information on the impact of each use case on the broader community or the effects these testing strategies could have on onward community transmission. Importantly, the results of each use case can not be directly compared with one another because of differences in the underlying modelling frameworks and the lack of explicit consideration of the proportion of any population that might be captured within any particular use case.

THE NEXT PHASE OF THIS PROJECT WILL FOCUS ON USING AN AGENT BASED MODELLING FRAMEWORK TO INVESTIGATE THE RELATIVE POTENTIAL EFFECTIVENESS OF EACH OF THESE USE CASES IN DIFFERENT LMIC COUNTRY ARCHETYPES (DIFFERENT DEMOGRAPHIES, URBAN/RURAL GEOGRAPHIES, MIXING PATTERNS, AND LEVELS OF PUBLIC HEALTH RESOURCES).

This will include explicit evaluation of when and in what settings different combinations of use cases are likely to be most efficient for monitoring levels of epidemic activity and reducing transmission. The results from this phase of the project will be used to draft recommendations for both the most efficient and most impactful use of Ag-RDT resources in different country archetypes. This phase will include a cost-effectiveness component, where we intend to incorporate costs, as well as explicitly modeling the expected impact of false positives as well as false negatives. Some costs that may be incorporated into the model include costs of testing, contact tracing, and isolation of both true and false positive AgRDT individuals (and their contacts).

In addition, we will conduct additional quantitative analyses related to the specificity of the AgRDT tests. We aim to estimate sensitivity of AgRDTs by day post-infection, and incorporate this into the model. We also intend to assess optimal allocation of a given number of tests, or potentially healthcare worker capacity, across use cases. Additional scenarios may also be modeled, such as implementation of self-testing and relying on individuals to self-isolate.

THE FINAL PHASE OF THE PROJECT WILL FOCUS ON DIAGNOSTIC NETWORK OPTIMIZATION BASED ON THE AGENT-BASED MODELLING FRAMEWORK ABOVE AND SPECIFIC INFORMATION ABOUT DIAGNOSTIC RESOURCE ACCESSIBILITY AND LOCATIONS.

The primary goal of this phase of the project will be to determine optimal testing strategies that balance trade-offs between feasibility, costs, and infections. The secondary goal will be to evaluate the trade-off between impact and efficiency of different testing strategies.

CONCLUSION

Speed and frequency of testing to provide real-time SARS-CoV-2 case data outweigh the benefit of higher test sensitivity, making Ag-RDTs a valuable tool for case detection, outbreak investigation and contact tracing. These findings emphasize the value of widespread, high frequency Ag-RDT COVID-19 testing. However, health systems in limited resource settings may have difficulty scaling up testing to the levels evaluated in this report; thus, it is imperative to determine the optimal testing strategy that balances trade-offs between feasibility, costs, and infections. Additional cost-effectiveness studies that extend these findings need to be conducted to evaluate the trade-off between impact and efficiency. The results from these use cases provide an evidence base for the use of Ag-RDTs in various settings and provide an estimate of the impact of expanding access to Ag-RDTs.

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APPENDIX: FURTHER MODEL DESCRIPTIONS AND SECONDARY ANALYSES

ACT-A DX MODELLING CONSORTIUM PARAMETER AND ASSUMPTIONS TABLES

The below tables summarize the parameters and assumptions of the different models that informed the different use cases.

1. COMMUNITY TESTING MODEL

Boston University: Karla Therese L Sy, Dr Brooke Nichols

Model information		Description
Model type	Describe model structure (compartmental, agent-based, etc)	Compartmental model
Age structure	Age structure or distribution assumed in model	None
Network structure	Explicit or implicit network assumptions?	No network assumptions
Spatial structure	Is a spatial structure assumed?	Yes
	If yes, what level of granularity?	Province level
	How is the spatial structure parameterized?	Varying levels of proportion of cases
	Is there a varying force of infection in each geographic area?	Yes
	What is the connectivity between use case and the population (i.e. fully integrated, semi-closed), and how is this parameterized?	Use case is same as the community

MODEL PARAMETERIZATION			
Parameter type	**Description**	**Value/ description**	**Range**
Infectiousness/ duration	Time from point of infection to onset of symptoms (days)	2	1 to 3
	Duration of infectiousness for asymptomatic cases	7	6 to 8
	Duration of infectiousness for mild cases	5	4 to 6
	Duration of infectiousness for severe cases	5	4 to 6
	Duration of pre-symptomatic infectiousness	4	2 to 6
	Relative infectiousness of asymptomatic & pre-symptomatic cases compared to symptomatic cases	0.75	0.70 to 0.80
Serial interval	Time from onset of symptoms in primary case to onset of symptoms in secondary case		

MODEL PARAMETERIZATION				
Parameter type	**Description**	**Value/description**	**Range**	**Notes**
Severity	Proportion of cases that are asymptomatic	0.75	0.7-0.8	Different for each province
	Proportion of cases that are mild	0.2375	0.23-0.24	
	Proportion of cases that are severe	0.0125	0.01-0.07	
Treatment	Proportion of mild cases that seek treatment (outpatient)	N/A		
	Proportion of severe cases that seek treatment (hospitalised)	0.6	0.4-0.7	
	Average days from symptom onset to treatment seeking for mild cases	N/A		
	Average days from symptom onset to hospitalisation for severe cases	5	4 to 6	
Intervention assumption	Are there any interventions in place in the community (i.e. lockdown, social distancing, masks, vaccinations)?	Isolation with COVID-19 positive diagnosis		
	How are you representing these interventions (reduction in Rt, reduced proportion of susceptible, reduction in network connectivity?)	Reduction in force of infection through reduction in effective number of contacts		
	Are there any interventions in place in the use case (i.e. lockdown, social distancing, masks, vaccinations)?	Use case is same as the community		
	How are you representing these interventions (reduction in Rt, reduced proportion of susceptible, reduction in network connectivity?)	Use case is same as the community		
Contact rates	R0	2.5		
Testing	Time from test to result (minutes/hours/days/ or assumed 'immediate')	Immediate		
	Proportion of people in the use case that get tested	1%, 5%, 20%, 50%, and 90%		
	Frequency of testing	1x/week, 2x/week, and 1x/2 weeks		
	Criteria for accessing a test (e.g. in widespread community testing, is it age targeted, or sympomatic only?)	Widespread community testing		
	Time to return to testing pool after testing positive	Immunity assumed for the rest of the time period		
Use case specific parameter	Population size (community)	58775021		
	Population size (use case)	Same as above		
	Percent of the total population in the use case	100%		
	Additional measures in the use case, in addition to testing, assumed	None		
	Efficacy of measures in reducing Rt	20%, 50%, 80%		
Additional relevant/ key parameters not yet described	Sensitivity of AgRDT (both symptomatic and asymptomatic cases)	0.85	0.75-0.9	

2. K-12 SCHOOLS MODEL

New York University, Dr Anna Berhsteyn

Model information		Description	Notes
Model type	Describe model structure (compartmental, agent-based, etc.)	Simulation	Simulated outbreaks w/in school

MODEL PARAMETERIZATION			
Parameter type	**Description**	**Value/description**	**Range**
Infectiousness/ duration	Time from point of infection to onset of symptoms (days)	5 days	
	Duration of infectiousness for asymptomatic cases		
	Duration of pre-symptomatic infectiousness	Days infectious	1-4 days, before symptoms are detected then isolation
	Relative infectiousness of asymptomatic & pre-symptomatic cases compared to symptomatic cases	Not specified	
Severity	Proportion of cases that are asymptomatic	26 - 39%	
Intervention assumption	Are there any interventions in place in the use case (i.e. lockdown, social distancing, masks, vaccinations)?	Masks, 6-foot social distancing, ventilation, hand-hygiene, class cohorts/rotation, daily symptom screening	
	How are you representing these interventions (reduction in Rt, reduced proportion of susceptible, reduction in network connectivity?)	Reduced secondary attack rate (SAR)	
Contact rates	Average daily contacts	9 -13	(Student cohort size) for days in-person
	Probability of infection given an infectious contact	18.10%	Secondary attack rate
	OR		
	Transmission rate (beta)	$f(t) = (1/\Gamma(k)\Theta k) * tk-1e-t/\Theta$	Distributed transmission from index case over 2 weeks, gamma distribution, k=2.25, Θ=2.80

Parameter type	Description	Value/description	Range	Notes
Testing	Time from test to result (minutes/hours/days/ or assumed 'immediate')	1 day		
	Proportion of people in the use case that get tested	Monthly / Weekly	10, 20% / 10%, 20%, 100%	Randomly tested
	Frequency of testing	Monthly / Weekly		
	Criteria for accessing a test (e.g. in widespread community testing, is it age targeted, or symptomatic only?)	Randomly allocated surveillance testing		
	Time to return to testing pool after testing positive	2 weeks		
Use case specific parameter	Population size (use case)	339 in-person (475 total)		Median Students per school

3. UNIVERSITIES MODEL

Boston University, Dr Laura White and Dr Eric Kolaczyk
This model utilizes Covasim developed by the Institute for Disease Modeling (IDM), Dr Cliff Kerr.

Model information		Description	Notes
Model type	Describe model structure (compartmental, agent-based, etc.)	Agent-based	
Age structure	Age structure or distribution assumed in model	Yes, continuous variable in the model	Age-specific contact matrices are used to generate individuals and their expected contacts. There is age-specific disease susceptibility, progression, and mortality probabilities.
Network structure	Explicit or implicit network assumptions?	Three different kinds of explicit networks: random network, SynthPop, and hybrid network	Random networks, SynthPops network - Census or survey data such as those from Demographic and Health Surveys are used to inform demographic characteristics (e.g., age, household size, school enrollment, and employment rates). Age-specific contact matrices are then used to generate individuals and their expected contacts. SynthPops generates household, school, and work contact networks; Hybrid network - each person in the population has contacts in their household, school, workplace, and community. A population of individuals is generated according to a location-specific age distribution, and each individual is randomly a signed to a household using location-specific data on household sizes.
	How were the networks generated?	Census or survey data - DHS, school enrollment data, data on workplace sizes	
Spatial structure	Is a spatial structure assumed?	No	While typical simulations do not have their own internal spatial structure, we do often model larger spatial areas as the combination of smaller ones. For example, we've modeled individual districts within Uttar Pradesh. We don't typically consider mixing between regions, but simply because we haven't yet had good enough data to inform it – the functionality for it is in the model.
	Is there a varying force of infection in each geographic area?	No, but there is varying FOI for each contact type	When using the explicitly network structure, default transmission probabilities are roughly 0.050 per contact per day for households, 0.010 for workplaces and schools, and 0.005 for the community. The weighted mean end up being close to the default β value of 0.016 for a well-mixed population.
	What is the connectivity between use case and the population (i.e. fully integrated, semi-closed), and how is this parameterized?	Fully integrated	We draw random contacts for each individual from other individuals in the population, where n is drawn from a Poisson distribution with rate parameter λc equal to the expected number of contacts in the general community (with λc = 20 as a default).

MODEL PARAMETERIZATION

Parameter type	Description	Value/description	Range	Notes
Infectiousness/ duration	Time from point of infection to onset of symptoms (days)	1.1 days	τ_{sym} ~ lognormal (1.1, 0.9)	
	Duration of infectiousness for asymptomatic cases	8 days	τ_{ra} ~ lognormal (8.0, 2.0)	
	Duration of infectiousness for mild cases	8 days	τ_{rm} ~ lognormal (8.0, 2.0)	Time from symptom onset to recovery
	Duration of infectiousness for severe cases	18.1 days	τ_{rs} ~ lognormal (18.1, 6.3)	
	Duration of pre-symptomatic infectiousness	1 day	τ_{sym} ~ lognormal (1.1, 0.9)	
	Relative infectiousness of asymptomatic & pre-symptomatic cases compared to symptomatic cases	1		Default assumption that transmissibility is the same whether or not an individual has symptoms. There is a parameter that can be modified as needed depending on the modeling application or context.

MODEL PARAMETERIZATION				
Parameter type	**Description**	**Value/description**	**Range**	**Notes**
Serial interval	Time from onset of symptoms in primary case to onset of symptoms in secondary case	N/A		
Severity	Proportion of cases that are asymptomatic	Dependent on age (Table 2)		
	Proportion of cases that are mild	Dependent on age (Table 2)		
	Proportion of cases that are severe	Dependent on age (Table 2)		
Treatment	Proportion of mild cases that seek treatment (outpatient)	0		
	Proportion of severe cases that seek treatment (hospitalized)	Dependent on age (Table 2)		
	Average days from symptom onset to hospitalization for severe cases	6.6 days	τ_{sev} ~ lognormal (6.6, 4.9)	
Intervention assumption	Are there any interventions in place in the community (i.e. lockdown, social distancing, masks, vaccinations)?	We can specify		
	How are you representing these interventions (reduction in Rt, reduced proportion of susceptible, reduction in network connectivity?)	Reduction in beta, or reduction in network connectivity		
	Are there any interventions in place in the use case (i.e. lockdown, social distancing, masks, vaccinations)?	We can specify		
	How are you representing these interventions (reduction in Rt, reduced proportion of susceptible, reduction in network connectivity?)	Reduction in beta, or reduction in network connectivity		
Contact rates	Average daily contacts			It can be specified as with contacts based on data for households, schools, and workplaces; an assumption of 20 daily community contacts; an average transmission rate of 0.016 per contact per day, with weights of 3.0: 0.6 : 0.6 : 0.3 for households, schools, workplaces, communities respectively. So the risk of transmission per household contact per day = 0.016*3.0 ≈ 5%, although usually this is calibrated to epidemiological data.
	Transmission rate (beta)	0.16		When using the explicit network structure, default transmission probabilities are roughly 0.050 per contact per day for households, 0.010 for workplaces and schools, and 0.005 for the community. The weighted mean end up being close to the default β value of 0.016 for a well-mixed population. This value is typically calibrated by the user to best match local epidemic data.

MODEL PARAMETERIZATION			
Parameter type	**Description**	**Value/description**	**Notes**
Testing	Time from test to result (minutes/hours/ days/ or assumed 'immediate')	We can specify	
	Proportion of people in the use case that get tested	We can specify	
	Frequency of testing	We can specify	
	Criteria for accessing a test (e.g. in widespread community testing, is it age targeted, or symptomatic only?)	We can specify	We can specify the probabilities that that people with different risk factors and levels of symptoms will receive a test on each day. Separate daily testing probabilities can be entered for t hose with/without symptoms, and those in/out of quarantine.
	Time to return to testing pool after testing positive	None, after testing positive they go on to recover	
Use case specific parameter	Population size (community)	We can specify	
	Population size (use case)	We can specify	
	Percent of the total population in the use case	We can specify	
	Additional measures in the use case, in addition to testing, assumed	Physical distancing, masks, hygiene, contact tracing	Contact tracing is parameterized by the probability that a contact can be traced, and by the time taken to identify and notify contacts.
	Efficacy of measures in reducing Rt	We can specify	
Additional relevant/ key parameters not yet described	Probability that someone doesn't get their test results	We can specify	

4. MASS GATHERINGS MODEL

Harvard T.H. Chan School of Public Health. Dr Stephen Kissler and Dr Yonatan Grad

Model information		Description	Notes
Model type	Describe model structure (compartmental, agent-based, etc)	Simulation	Bayesian statistical model
MODEL PARAMETERIZATION			
Parameter type	**Description**	**Value/description**	**Notes**
Intervention assumption	Are there any interventions in place in the community (i.e. lockdown, social distancing, masks, vaccinations)?	No	
	Are there any interventions in place in the use case (i.e. lockdown, social distancing, masks, vaccinations)?	No	
Testing	Time from test to result (minutes/hours/days/ or assumed 'immediate')	Not specified	Can examine test w/ result 0 to 3 days prior to event
	Proportion of people in the use case that get tested	100%	
	Frequency of testing	Once before event	
	Criteria for accessing a test (e.g. in widespread community testing, is it age targeted, or symptomatic only?)	All event participants	
Use case specific parameter	Population size (use case)	1000 individuals	
	Additional measures in the use case, in addition to testing, assumed	Prevalence	Prevalence set to 2% in analysis
ADDITIONAL RELEVANT/KEY PARAMETERS NOT YET DESCRIBED			**In analysis**
	Asymptomatic individuals shed for 9.7 days	These parameters are variable in modeling tool	
	Symptomatic individuals shed for 13.4 days	These parameters are variable in modeling tool	
	Test limit of detection (Ct)	Can be specified	40 Ct for RT-qPCR, 35 Ct for Ag-RDT
	Sampling sensitivity	Can be specified	1% for RT-qPCR, 5% for Ag-RDT
	Infectiousness threshold (Ct)	Can be specified. Time infectious dependent on proliferation time, clearance time & peak Ct –determines amount of time below 30Ct	Ct <= 30.
	Event duration	Can be specified	N/A
	Proliferation time mean and 95%CI/SD (days)	2.7 days (1.2, 3.8)	
	Clearance time mean and 95%CI/SD (days)	7.4 days (3.9, 9.6)	
	Peak Ct and 95%CI/SD	22.4 (20.6, 24.1)	

5. BORDER CROSSING MODELS
5.1 A*STAR MODEL

Agency for Science, Technology and Research: Dr Yin Xiao Feng, Dr Yiqi Seow

Model information		Description	Notes
Model type	Describe model structure (compartmental, agent-based, etc)	Agent-based	A*STAR model

MODEL PARAMETERIZATION				
Parameter type	**Description**	**Value/description**	**Range**	**Notes**
Infectiousness/ duration	Time from point of infection to onset of symptoms (days)	3-14 days	3 - 14 (median 4.5 days)	same across all types of cases
	Duration of infectiousness for asymptomatic cases		11-12 days	relative infectiousness to be configured
	Duration of infectiousness for mild cases	Not differentiated		
	Duration of infectiousness for severe cases	Not differentiated		
	Duration of pre-symptomatic infectiousness		4 days before symptom onset	
	Relative infectiousness of asymptomatic & pre-symptomatic cases compared to symptomatic cases	0.5	0 to 1 (configurable)	
Severity	Proportion of cases that are asymptomatic	0.5		
Intervention assumption	Are there any interventions in place in the community (i.e. lockdown, social distancing, masks, vaccinations)?	to some extent		
	How are you representing these interventions (reduction in Rt, reduced proportion of susceptible, reduction in network connectivity?)	Reduction in Rt		
	How are you representing these interventions (reduction in Rt, reduced proportion of susceptible, reduction in network connectivity?)	Reduction in Rt		
Contact rates	R0	Varied (0.5-6)		Rt is determined by comfort of policy makers. We don't make pre-assumption on Rt. We just adjust it to suit the expected understanding
Testing	Time from test to result (minutes/hours/days/ or assumed 'immediate')	Variable depending on user request	1 to 12 hours	
	Proportion of people in the use case that get tested	Depends on use case		
	Frequency of testing	Determined by user request	every 24 hours and above	
	Criteria for accessing a test (e.g. in widespread community testing, is it age targeted, or symptomatic only?)	Government-mandated testing at the border		
	Time to return to testing pool after testing positive	Not included in the model		

MODEL PARAMETERIZATION			
Parameter type	**Description**	**Value/description**	**Range**
Use case specific parameter	Population size (community)	Only modeled infected cases	incidence of 100 new infections / day in source country in traveling population
	Population size (use case)	Only modeled infected cases	incidence of 100 new infections / day in source country in traveling population
	Additional measures in the use case, in addition to testing, assumed	Not included in the model	
	Efficacy of measures in reducing Rt	Not included in the model	
Additional relevant/key parameters not yet described		Contact tracing in reducing 'leaked' transmission	

5.2 BOSTON UNIVERSITY MODEL

Boston University. Joshua Chevalier, Dr Brooke Nichols

Model information		Description	Range
Model type	Describe model structure (compartmental, agent-based, etc)	Algebraic Algorithm	
MODEL PARAMETERIZATION			
Parameter type	**Description**	**Value/description**	**Range**
Intervention assumption	Are there any interventions in place in the community (i.e. lockdown, social distancing, masks, vaccinations)?	Lockdowns, social distancing, mask-use	
	How are you representing these interventions (reduction in Rt, reduced proportion of susceptible, reduction in network connectivity?)	Reduction in Rt	
Contact rates	R0	Rt = 0.73 – 1.45	
Testing	Time from test to result (minutes/hours/days/ or assumed 'immediate')	Immediate	
	Proportion of people in the use case that get tested	0% – 100%	
	Frequency of testing	Once at border	
	Criteria for accessing a test (e.g. in widespread community testing, is it age targeted, or symptomatic only?)	Randomly allocated to border crossers	
Use case specific parameter	Population size (community)	Country Dependent	
	Population size (use case)	Country Dependent	Represented as imports/100,000 population
	Percent of the total population in the use case	Country Dependent	
	Additional measures in the use case, in addition to testing, assumed	Variable daily border crossings	
ADDITIONAL RELEVANT/KEY PARAMETERS NOT YET DESCRIBED			
	Prevalence	0.2 – 2%	
	Test Sensitivity	80%	50 – 90%
	Proportions of land or air travelers	0% – 100%	25% increments

5.3 LSHTM MODEL

London School of Hygiene and Tropical Medicine, Dr Billy Quilty and Dr Sam Clifford.

Model information		Description	Notes
Model type	Describe model structure (compartmental, agent-based, etc)	Stochastic, Agent-based	Individual-based simulation of varying viral load trajectories. Not a transmission model
Spatial structure	Is a spatial structure assumed?	Country-level	
	If yes, what level of granularity?	Country-level	
	What is the connectivity between use case and the population (i.e. fully integrated, semi-closed), and how is this parameterized?	No connection between use case and population. Modelled reduction in infectiousness of air-travelers	Do not differentiate between household v non-household transmission

MODEL PARAMETERIZATION				
Parameter type	**Description**	**Value/description**	**Range**	**Notes**
Infectiousness/ duration	Time from point of infection to onset of symptoms (days)	5.1 days	(95%: 2.3, 11.5 days)	Ct peak. Kissler et al. 2020. McAloon et al. 2020
	Duration of infectiousness for symptomatic cases	17 days	SD 0.94 days	Individual infectivity conditional upon culture probability given viral load. Pickering et al. 2021. Days after exposure
	Duration of pre-symptomatic infectiousness	Variable		Individual infectivity conditional upon culture probability given viral load. Pickering et al. 2021.
	Relative infectiousness of asymptomatic & pre-symptomatic cases compared to symptomatic cases	60%		Asymptomatic persons shed virus for 60% of the duration of symptomatic persons.
Severity	Proportion of cases that are asymptomatic	31%	24-38%	Buitrago-Garcia et al. 2020
Intervention assumption	Are there any interventions in place in the use case (i.e. lockdown, social distancing, masks, vaccinations)?	(1) Pre-flight testing: no testing, PCR test, Lateral flow test (LFT) test. (2) Quarantine and/or testing on arrival. Post-flight quarantine 0(baseline),3,4,7,10,14 days. On final day of quarantine, either no test, LFT test, PCR test. A positive test at the end of quarantine leads to an additional 10 days of self-isolation. For those with no quarantine, travelers take LFT tests daily for 3,5,7, or 10 days.		
	How are you representing these interventions (reduction in Rt, reduced proportion of susceptible, reduction in network connectivity?)	Reduction in R of infectious arrivals. A reduction in risk represented by number of imported cases per day as a percentage of domestic incidence in the destination country		
Testing	Time from test to result (minutes/hours/days/ or assumed 'immediate')	Assumed immediate		
	Proportion of people in the use case that get tested	0-100%		
	Frequency of testing	Zero-Multiple, depending on scenario. Pre-arrival test (LFT/PCR); post-arrival tests: once on quarantine exit (PCR/LFT), or daily for 3,5,7,10 days (LFT)		
	Criteria for accessing a test (e.g. in widespread community testing, is it age targeted, or symptomatic only?)	Air-travel and quarantine		

MODEL PARAMETERIZATION				
Parameter type	**Description**	**Value/description**	**Range**	**Notes**
Use case specific parameter	Population size (community)	Country-dependent		
	Population size (use case)	Volume of air-travel who are infected. Varies by country		
	Percent of the total population in the use case	Varies by country		
	Additional measures in the use case, in addition to testing, assumed	Quarantine upon arrival (0-14 days), self-isolation (0-10days).		Not assumed, explicitly modelled
	Efficacy of measures in reducing Rt	Varies depending on scenario		
ADDITIONAL RELEVANT/KEY PARAMETERS NOT YET DESCRIBED				
	Volume of air travelers	Number of flights per route; assumed 142 travelers per flight		OpenSky flight database
	Incidence/prevalence of COVID-19 amongst travelers from origin country	Applying an estimate of under-ascertainment of cases based on reported deaths and infection fatality ratio		
	Test sensitivity	Assumed immediate		
	Proportion of people in the use case that get tested	0-100%		
	Frequency of testing	Test sensitivity is conditional on intra-host viral load dynamics. Use results of Innova test (Pickering et al) and estimate the mean probability of detection for a give Ct value for LFT. PCR tests are assumed to be 100% sensitive for Ct values < 35, and 0% for Ct > 35.		
	Proportion of individuals adhering to quarantine in the absence of symptoms	28%		Individuals are either fully adherent or non-adherent. Steens et al. 2020
	Proportion of individuals adhering to symptomatic self-isolation	71%		Steens et al. 2020
	Proportion of individuals adhering to self-isolation following a positive test	86%		ONS 2021

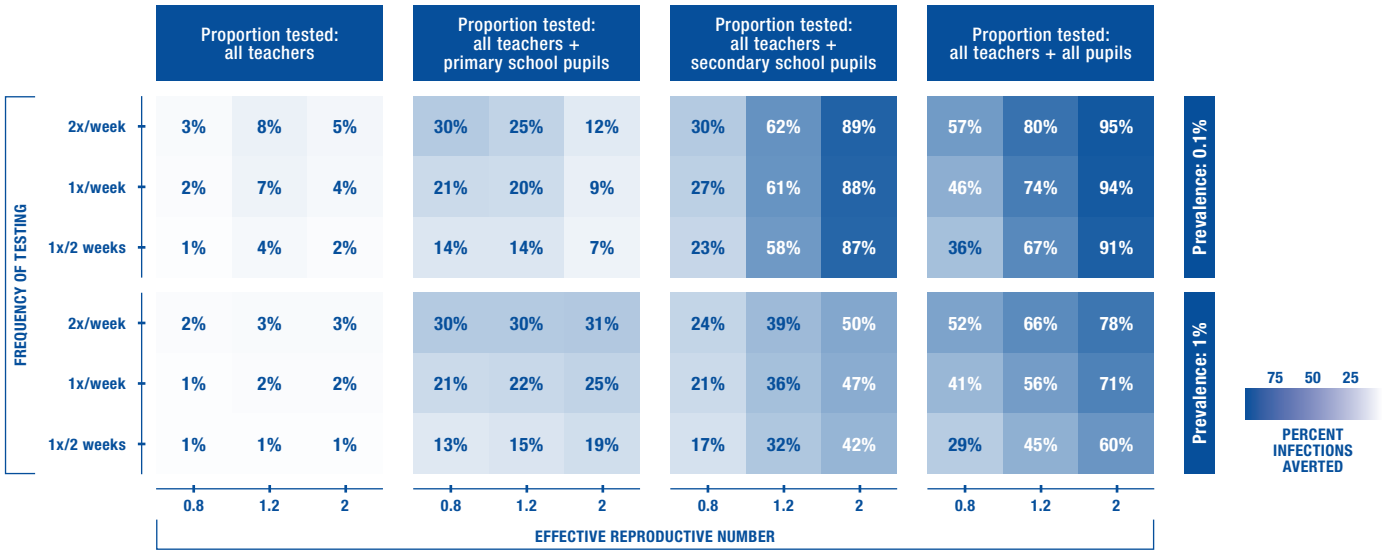
6. QUARANTINE AND CONTACT TRACING MODEL

London School of Hygiene and Tropical Medicine, Dr Billy Quilty and Dr Sam Clifford.

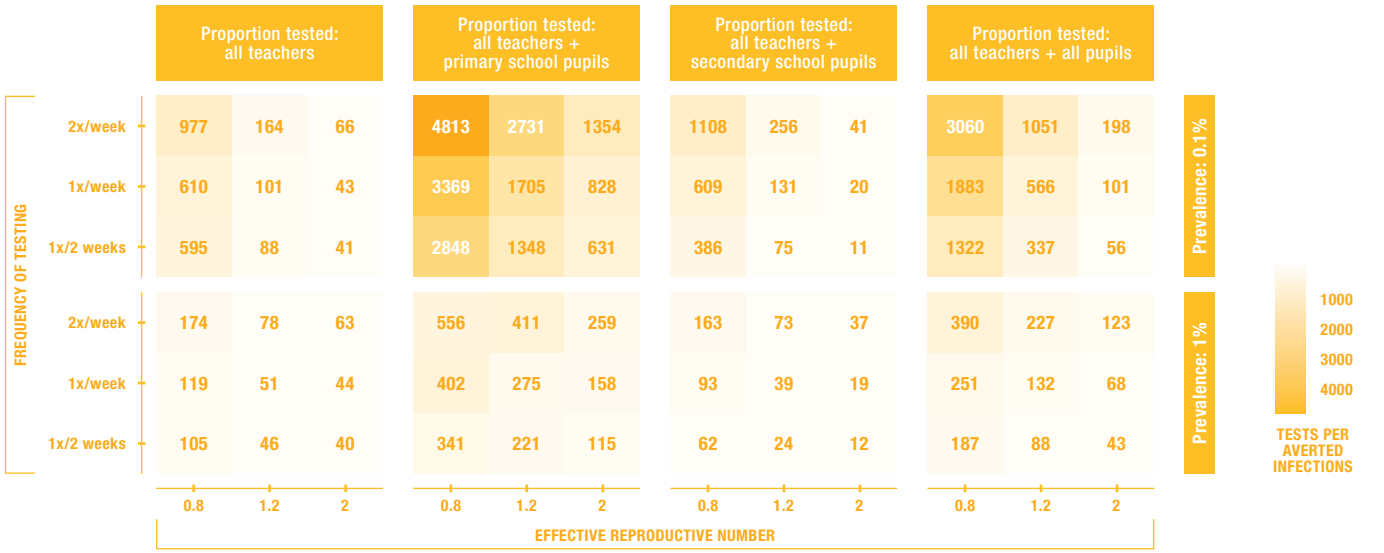
Model information		Description	Notes
Model type	Describe model structure (compartmental, agent-based, etc)	Stochastic, Agent-based	Individual-based simulation of varying viral load trajectories. Not a transmission model
Spatial structure	What is the connectivity between use case and the population (i.e. fully integrated, semi-closed), and how is this parameterized?	No connection between use case and population. Modelled reduction in the infectiousness period of exposed contacts	Do not differentiate between household v non-household transmission

MODEL PARAMETERIZATION				
Parameter type	**Description**	**Value/description**	**Range**	**Notes**
Infectiousness/ duration	Time from point of infection to onset of symptoms (days)	5.1 days	(95%: 2.3, 11.5 days)	Ct peak. Kissler et al. 2020. McAloon et al. 2020
	Duration of infectiousness for symptomatic cases	17 days	SD 0.94 days	Individual infectivity conditional upon culture probability given viral load. Pickering et al. 2021. Days after exposure
	Duration of pre-symptomatic infectiousness	Variable		Individual infectivity conditional upon culture probability given viral load. Pickering et al. 2021.
	Relative infectiousness of asymptomatic & pre-symptomatic cases compared to symptomatic cases	60%		Asymptomatic persons shed virus for 60% of the duration of symptomatic persons.
Severity	Proportion of cases that are asymptomatic	31%	24-38%	Buitrago-Garcia et al. 2020
Intervention assumption	Are there any interventions in place in the use case (i.e. lockdown, social distancing, masks, vaccinations)?	(1) Test to release from quarantine: investigate quarantine durations of 0,3,5,7,10,14 days post exposure to an index case with either no testing, or testing with PCR or Lateral flow test (LFT) test on the last day of quarantine; (2) Daily testing in lieu of quarantine: Take a LFA every day for 1,3,5,7,10 or 14 days. (3) Self-isolation: Secondary cases displaying symptoms at any point post-exposure, or testing positive at any time, will isolate until 10 days have passed since onset of symptoms.		
	How are you representing these interventions (reduction in Rt, reduced proportion of susceptible, reduction in network connectivity?)	Effectiveness determined by the proportion of infectious distribution (from culture) spent in quarantine or isolation (following a positive test or symptoms), i.e transmission potential averted.		
Testing	Time from test to result (minutes/hours/days/ or assumed 'immediate')	Assumed immediate		
	Proportion of people in the use case that get tested	100%		
	Frequency of testing	Scenario dependent		
	Criteria for accessing a test (e.g. in widespread community testing, is it age targeted, or symptomatic only?)	Scenario dependent. Upon symptom onset, or exit from quarantine, or daily in lieu of quarantine		

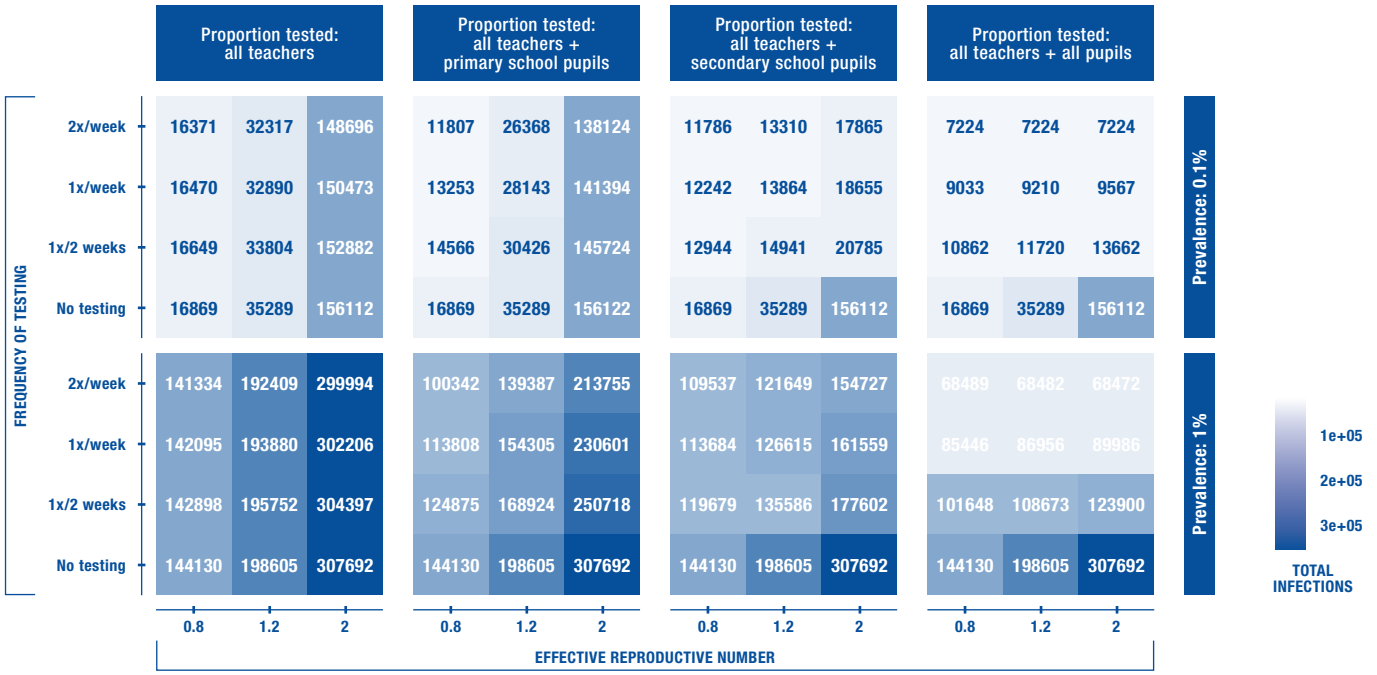
MODEL PARAMETERIZATION				
Parameter type	**Description**	**Value/description**	**Range**	**Notes**
Use case specific parameter	Population size (use case)	Simulated 1000 index cases with 10 secondary cases.		Model infected persons only, do not take in to account false positives. This was adjusted in the use case.
	Additional measures in the use case, in addition to testing, assumed	Quarantine (0-14 days), self-isolation (10days).		Not assumed, explicitly modelled
	Efficacy of measures in reducing Rt	Varies depending on scenario		
ADDITIONAL RELEVANT/KEY PARAMETERS NOT YET DESCRIBED				
	Test sensitivity	Test sensitivity is conditional on intra-host viral load dynamics. Use results of Innova test (Pickering et al) and estimate the mean probability of detection for a give Ct value for LFT. PCR tests are assumed to be 100% sensitive for Ct values < 35, and 0% for Ct > 35.		
	Contact tracing delays	Delay of 3 days from sample being taken to contacts being instructed to quarantine	0, 1.5 and 3 days	
	Proportion of individuals adhering to quarantine in the absence of symptoms	50%	0%, 100%	Individuals are either fully adherent or non-adherent. Sampled from a Bernoulli distribution with the probability given by the proportion adhering
	Proportion of individuals adhering to symptomatic self-isolation or isolation following a positive test	67%	0%, 100%	Individuals are either fully adherent or non-adherent. Sampled from a Bernoulli distribution with the probability given by the proportion adhering



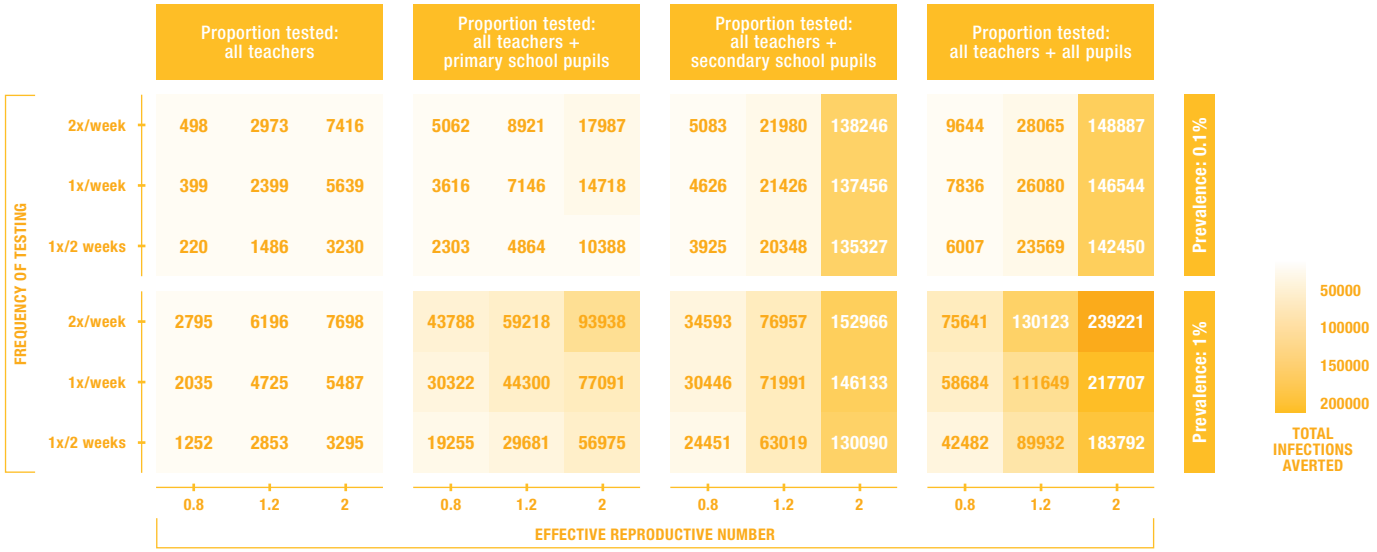
Appendix Figure 1. Percent of infections (amongst all teachers and pupils) averted compared to the same epidemic scenario without testing in schools; varied by targeted testing population, COVID prevalence, effective reproductive number and frequency of testing.



Appendix Figure 2. Number of tests required per infection averted compared to the same epidemic scenario without testing in schools; varied by targeted testing population, COVID prevalence, effective reproductive number and frequency of testing.



Appendix Figure 3. Total number of infections amongst pupils and teachers, varied by targeted testing population, COVID prevalence, effective reproductive number and frequency of testing.



Appendix Figure 4. Total number of infections averted amongst pupils and teachers compared to no testing, varied by targeted testing population, COVID prevalence, effective reproductive number and frequency of testing.

GLOSSARY OF TERMS

ACRONYMS

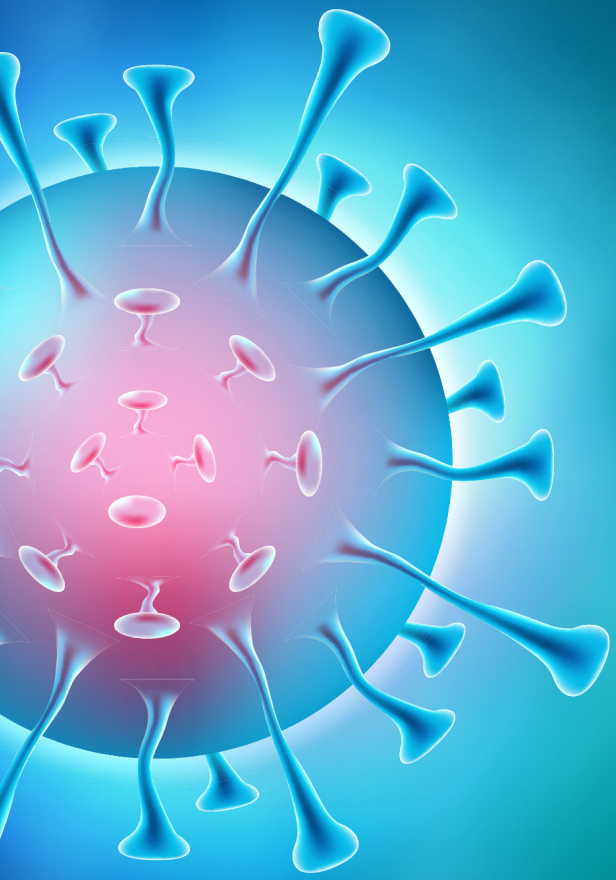
Ag-RDT	Antigen Detecting Rapid Diagnostic Test
Ct (value)	Cycle threshold, in PCR, number of cycles required for the fluorescent signal to cross the threshold.
LFT	Lateral Flow Test, typically given to people who do not have symptoms of COVID-19 which give quick results.
LMIC	Low- and middle-income countries defined by the World Bank Group; low-income economies ($1,005 or less GNI per capita) or as lower-middle-income economies ($1,006 to $3,955 GNI per capita).
NCEM	National COVID-19 Epi Model, a compartmental model of the COVID-19 transmission dynamics of South Africa.
NPV	Negative Predictive Value, the probability a person will not have a disease given they test negative. **[Pr (Disease -I Test -] = true negative tests / total negative tests**
PPV	Positive Predictive Value, the probability a person will have a disease given they test positive. **[Pr (Disease +I Test +] = true positive tests / total positive tests**
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction, the gold standard for COVID-19 testing.
TAT	Turnaround time, the amount of time taken to complete a process or fulfill a request.

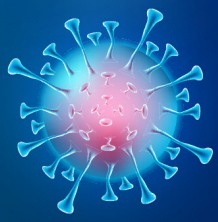
MODELS

Agent-based Model	An agent-based model (ABM) is a computational model for simulating the actions and interactions of autonomous agents (both individual or collective entities such as organizations or groups) in order to understand the behavior of a system and what governs its outcomes.
Bayesian Statistical Model	An approach to statistical modeling that treats all entities (variables, model parameters, missing data, and more) as random variables characterized by distributions.
Compartmental Model	The simplest models in the mathematical study of infectious disease dynamics. The population is divided into categories (compartments) of infectious disease (e.g. susceptible, infected, recovered) and their movement through various compartments of the model.
Simulation	An imitation of a process or scenario.

OTHER TERMS

Effective reproductive number	(R_t) The expected number of subsequent infections directly generated by one case in a population where some individuals are susceptible to infection, and others are not. The effective reproductive number depends on whether individuals have previously been infected or immunized. **$R_t = R_0 * x$**
Incubation period	The time between infection and the onset of clinical symptoms. Incubation period can depend upon infectious dose, replication of the pathogen, susceptibility, and host characteristics.
Isolation Effectiveness	Adherence to isolation following a positive diagnosis of COVID-19 and the subsequent reduction in the number of exposed contacts.
Stochastic	Being defined by a random probability distribution.
Triaging	Assigning degrees of importance or urgency to patients from amongst a large number that require attention.





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