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Improving SARS-CoV-2 surveillance, mitigation and control measures in low- and middle-income countries using mobility data and rapid diagnostic tests

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IMPROVING SARS-COV-2 SURVEILLANCE, MITIGATION AND CONTROL MEASURES IN LOW- AND MIDDLE-INCOME COUNTRIES USING MOBILITY DATA AND RAPID DIAGNOSTIC TESTS

by

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ABSTRACT

The SARS-CoV-2 pandemic has infected millions of people globally and continues to spread rapidly in many countries. As global vaccine access remains limited, SARS-CoV-2 transmission can be reduced through non-pharmaceutical interventions (NPIs), such as social distancing and lockdown measures that limiting human contact by restricting human mobility, and diagnostic testing strategies that rapidly identify and isolate infectious individuals. In this dissertation, I conducted three studies that inform SARS-CoV-2 surveillance and control policies in low- and middle-income countries (LMICs). The first study focuses in South Africa, where there have been multiple lockdowns and COVID-19 resurgences since the start of the pandemic.[1] I assessed the association between mobility, as measured by smartphone data, and SARS-CoV-2 case positivity in South African provinces and districts at the ecological-level using regression, cross-correlation and interrupted time series analysis. I found that increases in mobility were positively associated with future COVID-19 incidence aggregated at both the province and district-level, and the association of mobility and COVID-19 incidence remained even when adjusted for district-level confounders.

The second and third studies focus on rapid antigen testing (Ag-RDTs) in general LMIC settings. The main outcomes for these two studies include impact, defined as the percentage of infections averted compared to the base case scenario for each use case, and efficiency, defined as the number of tests needed to avert one infection compared to the base case scenario across use cases. In the second study, I quantified impact and efficiency of Ag-RDTs for population-level community testing using a compartmental model in a general population of 10 million people. This study adds to the literature that Ag-RDTs can be a valuable tool for population-level SARS-CoV-2 surveillance and case detection when testing is frequent and widespread, and diagnosis must be accompanied by corresponding reduction in post-diagnosis contacts in order for testing to be effective. I also identified that community testing is most useful when an epidemic is waning or before an epidemic wave, which is when SARS-CoV-2 prevalence and *Rt* are low.

Finally, the third study assessed efficiency and impact of SARS-CoV-2 Ag-RDT testing strategies by comparing eight mathematical models across several scenarios, hereafter referred to as "use cases". There was a clear trade-off between impact and efficiency; increasing test frequency (and/or more widespread testing of a community) increased impact, but consequently decreased efficiency. Additionally, testing strategies across most scenarios had the greatest impact when *Rt* and/or infection prevalence were low, but were least efficient.

The findings from this dissertation provide further evidence of the importance of public health mitigation and control measures that reduce SARS-CoV-2 spread, such as NPIs and diagnostic testing, particularly in LMICs that have limited access to COVID-19

vaccines. The evidence generated from these studies can be used for future SARS-CoV-2 resurgences, whether from currently circulating variants, emergence of new SARS-CoV-2 variant strains or adaptation for use in future infectious disease outbreaks.

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LIST OF ABBREVIATIONS

ACT-A	Access to COVID-19 Tools-Accelerator
Ag-RDT	Antigen-detecting rapid diagnostic tests
CI	Confidence interval
COVID-19	Coronavirus disease 2019
DoH	Department of Health
FIND	Foundation for Innovative Diagnostics
HIV	Human immunodeficiency virus
ICU	Intensive care unit
IRRs	incidence rate ratios
IVIR-AC	Immunization and Vaccines-related Implementation Research Advisory Committee
LMIC	Low-and-middle-income country
NCEM	National COVID-19 Epidemiology Model
NICD	National Institute of Communicable Diseases
NPIs	Non-pharmaceutical interventions
PPV	Positive predictive value
Rt	Effective reproductive number
RT-PCR	Reverse transcriptase polymerase chain reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard deviation

SEIR	Susceptible-Exposed-Infectious-Recovered
SI	Simulation interval
TB	Tuberculosis
UK	United Kingdom
US	United States

1 INTRODUCTION

The SARS-CoV-2 pandemic has infected millions of people globally, and continues to spread rapidly in many countries. As vaccination remains limited in many low- and middle-income countries (LMICs), strong public health surveillance and mitigation measures such as non-pharmaceutical interventions (NPIs) and diagnostic testing remain vital for reducing further SARS-CoV-2 transmission globally. Public health surveillance for infectious diseases is essential to identify positive cases, isolate, and interrupt transmission. However, current surveillance methods for COVID-19 rely on substandard methods and technologies, and complementary sources of information, such as mobility data, can provide insights into local spread of disease essential for robust case surveillance. Previous work has demonstrated that mobility data is associated with disease burden,[2-5] which can be used to trigger rapid response measures, and can complement other surveillance approaches. Moreover, disease transmission can be reduced through limiting human contact and restricting human mobility through social distancing and lockdown measures.[2-5]

Another valuable strategy to limit disease spread without imposing widespread lockdowns is rapidly identifying and isolating infectious individuals through diagnostic testing. Reverse transcriptase polymerase chain reaction (RT-PCR) remains the current gold standard for diagnosing and screening COVID-19; however, in many LMICs access to PCR testing has been difficult and are plagued by delays.[6,7] The early reliance on RT-PCR testing severely limited the impact that diagnostic testing could have, particularly in LMICs where RT-PCR capacity is largely confined to tertiary medical facilities. Antigen-

detecting rapid diagnostic tests (Ag-RDTs) may expand access to testing and decrease delays in COVID-19 diagnosis,[8] and most recently implemented community-testing strategies globally now primarily depend on Ag-RDTs.[9-11] Given limited resources, there is a need to assess SARS-CoV-2 diagnostic testing strategies across settings to identify scenarios where Ag-RDTs can best be utilized to create the largest reductions in onward transmission.

Findings from these studies would inform optimal and effective control and mitigation measures that can prevent COVID-19 morbidity and mortality, specifically in limited resource settings. My results provide a stronger evidence base to inform resource allocation and decision making for the current SARS-CoV-2 pandemic, plan for future SARS-CoV-2 resurgences from currently circulating variants or emergence of new variants, or prepare for future infectious disease outbreaks and pandemics.

2 THE EFFECT OF POPULATION MOBILITY ON COVID-19 INCIDENCE IN SOUTH AFRICAN DISTRICTS AND PROVINCES: A LONGITUDINAL ECOLOGICAL STUDY WITH MOBILE PHONE LOCATION DATA

2.1 Introduction

SARS-CoV-2 has infected millions of people globally during the pandemic and continues to spread rapidly in many countries. During the initial COVID-19 outbreaks in March 2020, South Africa was able to prevent large waves of infections with the early implementation of containment measures; however, since then cases in South Africa have steadily increased even with the scale up of national and provincial responses, such as numerous alert levels with associated lockdowns and restrictions.[12] Vaccination is increasingly used to mitigate the impact of the SARS-CoV-2 pandemic in high income settings. However, in low-and-middle-income countries (LMICs) with limited vaccines, such as South Africa, diagnostic testing and non-pharmaceutical interventions (NPIs) remain vital for reducing SARS-CoV-2 transmission. One fundamental element of NPI's ability to reduce disease transmission is limiting human contact by restricting movement through social distancing and lockdown measures.

Several studies have shown that human movement is a vital component of COVID-19 transmission and disease burden,[2-5] and mobility has the potential to predict geographic disease incidence which can then be used to trigger rapid response measures. Human movement may facilitate transmission because it reflects greater opportunity for close contacts, and contact networks formed by individuals support chains of sustained disease

transmission.[13-16] If surveillance systems could incorporate non-traditional sources of information, such as mobility data, they could provide predictions of local spread of disease.

However, evidence of an association between population mobility and COVID-19 incidence in LMICs is lacking, and to date no research has been done on the relationship between mobility and SARS-CoV-2 incidence in South Africa. This study aims to estimate the association between mobility as measured by smartphone data, and SARS-CoV-2 incidence in South African districts and provinces, as well as to examine the effect of government-mandated lockdowns on population mobility. I hypothesize that increases in mobility will be positively associated with COVID-19 incidence.

2.2 Methods

Data source and study population

2.2.1.1 Mobility data

I obtained mobility data from persons who owned a smartphone in South Africa, activated the location on their devices, and used the Moya app[17] between August 30, 2020 and January 3, 2021. The Moya app is a free messaging system paid for by advertising.[17] As of 2021, there were approximately 5 million active users in South Africa (8% of total population), of which 2 million (3% of total population) are daily users.[18] Province-level and district-level smartphone data between August 30, 2020 to January 3, 2021 were used to determine mobility. The mobility data can pinpoint locations transmitted from devices, and were aggregated at the weekly level and stratified

by province. Since the data are aggregated and not obtained at the individual level, I were unable to link device unique IDs and infer sociodemographic characteristics of the users.

2.2.1.2 COVID-19 data

At the district-level, I used the Coronavirus COVID-19 Data Repository for South Africa, which collates COVID-19 reporting data from the South African National Institute of Communicable Diseases (NICD) and Department of Health (DoH).[19] I extracted the incidence of reported province-level COVID-19 cases from the weekly reports of the South African NICD between August 30, 2020 and January 3, 2021.[20] The study period occurs after SARS-CoV-2 scale up of testing in South Africa, and thus any potential biases due to differential testing across time and geographic areas are limited. The data sets were compiled using data from state and local governments and health departments, ensuring its accuracy.

Exposure

The main exposure was *weekly mobility***,** which was measured using smartphone data from Strive, aggregated at the weekly level and stratified by province and district. Weekly mobility was a continuous variable normalized to the minimum and maximum number of mobility movements within each province (for province-level analysis) and each district (for district-level analysis). Normalizing mobility by area accounts for the baseline number of mobility movements for the area, and allows me to compare relative

changes in mobility in each area.[21]

A mobility movement for an individual was recorded when there was >10km movement, which was a predetermined movement threshold that represented substantial mobility essential for disease transmission. The number of weekly mobility movements was defined as the number of unique visits per week; regardless of the number of visits made, multiple trips per week for one individual between the same two provinces were counted as one unique mobility movement. Unique visits may be a more conservative estimate (underestimate) of human movement; however, since a mobility point is not recorded when a phone or location is turned off, using unique visits aggregated at the weekly level may mitigate any potential biases due to differential percentage of phones being turned off daily.

$$\text{Weekly mobility} = \frac{\#\ of\ weekly\ mobility\ movement\ -\ min\ \#\ of\ mobility\ movement\ for\ area}{max\ \#\ of\ mobility\ movement\ for\ area\ -\ min\ \#\ of\ mobility\ movement\ for\ area}$$

Outcome

The main outcome was weekly SARS-CoV-2 incidence, defined as the weekly number of COVID-19 incident cases divided by the population in the area of interest (province or district). The National DoH defined a COVID-19 case as laboratory confirmation of COVID-19 disease by RT-PCR or a rapid antigen test. Confirmed COVID-19 case counts were reported from all provinces and districts in South Africa on a weekly basis.

Statistical analysis

2.2.1.3 Province-level analysis

I conducted descriptive analyses to examine the change over time in weekly mobility and SARS-CoV-2 incidence provincially, and whether weekly mobility changed when the country was placed on alert with mandated lockdowns. I then conducted a time series cross-correlation analysis in order to assess the unadjusted time-varying association between weekly mobility and current or future SARS-CoV-2 incidence. A time series cross-correlation quantifies the synchrony, defined as how strongly two time series at various points in time are associated with each other.[22] When two time series demonstrate synchrony, the observations rise or fall simultaneously or with a measurable shift in time called a lag time. I also assessed potential lag times between mobility and COVID-19 incidence, to assess the lag at which the maximum cross-correlation occurs (i.e., mobility is associated with SARS-CoV-2 incidence after *x* weeks). The cross-correlation coefficient was used to quantify the level of cross-correlation, which ranges from -1 (negative correlation) to +1 (positive correlation). A value of 0 would indicate no cross-correlation.[23]

The cross-correlation coefficient $\rho_{x,y}(h)$ of time series X_t and Y_t with lag time h is

$$\rho_{XY}(h) = \frac{\gamma_{XY}(h)}{\sqrt{\gamma_{XX}(0) * \gamma_{YY}(0)}}, h = 0, \pm 1, \pm 2..$$

Where $\gamma_{XX}(0)$ and $\gamma_{YY}(0)$ are variances of X_t and Y_t, respectively.

Next, I conducted an interrupted time series analysis, a method that has been previously used to evaluate the impact of population-level changes, such as a public health interventions or policy changes, at any defined point in time using segmented regression.[24,25] Segmented regressions assessed whether there was any "mobility breakpoint",[2] defined as an abrupt longitudinal change in mobility, and at what date; when there is a significant mobility breakpoint, I also assessed whether there was any change in COVID-19 incidence, or "COVID-19 breakpoint", before and after the mobility breakpoint. I also examined whether mobility breakpoints corresponded with changes in lockdown alerts, and I hypothesize that mobility breakpoints would occur during government-mandated lockdowns.

(1) $\text{Mobility}_t = \beta_0 + \beta_1 time + \beta_2 mobilitybreakpoint_t + \beta_3 time \cdot mobilitybreakpoint_t$

(2) $\text{COVID}_t = \beta_0 + \beta_1 time + \beta_2 mobilitybreakpoint_t + \beta_3 time \cdot mobilitybreakpoint_t$

where *time* is in weeks, and $mobilitybreakpoint$ is a dummy variable indicating whether the current time is before or after the mobility breakpoint. For (1) the outcome is Weekly mobility at time *t*, and for (2) the outcome $is\ \text{COVID}_t$ is COVID incidence at time *t*. β_3 indicates the slope change in the outcome following the mobility breakpoint. The effect size indicates whether there was a change in slope before and after the mobility breakpoint. For large β_3 slope would suggest that COVID incidence changed substantially during the COVID-19 pandemic due to a change in mobility. Data analysis was conducted in R version 4.0.2.[26]

2.2.1.4 District-level analysis

I first conducted descriptive analyses to examine weekly mobility and SARS-CoV-2 incidence stratified by district. Then, I used mixed-effects negative binomial regression for a time-series analysis, to examine longitudinal associations between weekly mobility and subsequent COVID-19 incidence in South African districts. I used random intercepts for districts and provinces, with district area population as an offset. Coefficients and 95% confidence intervals (Cis) from the negative binomial model were exponentiated and are interpretable as incidence rate ratios (IRRs). The lag at which the maximum cross-correlation occurs at the province-level was used in the district area regressions.

I adjusted for additional independent variables of time-invariant ecological-level TB incidence, HIV prevalence, population density (all at the district level) and province, as potential confounders. Relevant covariates were *a priori* selected as confounders based on existing knowledge of the association between exposure and outcome. Population density was calculated from data from Statistics South Africa mid-year population estimates,[27] calculated as the population divided by total square kilometer per geographic area district. HIV prevalence and TB incidence were calculated using most recent 2016 estimates collated by the African COVID-19 vulnerability index.[28]

I report univariable associations between each independent variable (excluding province) and the outcome (COVID-19 incidence) and full results from the adjusted model. All analyses were done in R version 4.0.2[26] and modelling was done with the glmmTMB package.

Ethical approval

Since the study uses de-identified ecological data, institutional review board ethical approval was not needed.

2.3 Results

Descriptive analysis

Between August 30, 2020, and January 3, 2021, the total COVID-19 incidence in South Africa was 1070.4 cases per 100,000 population (Table 2.1). Among the nine South African provinces, Western Cape had the highest COVID-19 incidence (1931.4 cases per 100,000 people), as well as the highest mean weekly mobility at 0.608 (Table 2.2). Correspondingly, Limpopo had the lowest reported COVID-19 incidence (380.7 cases per 100,000 people) and the lowest mean weekly mobility at 0.517 (Table 2.2). Figure 2.1 shows weekly mobility and COVID-19 incidence per 100k population for each of the nine districts.

In the districts, tertiles of COVID-19 incidence corresponded to an increase in weekly mobility; the tertile with the lowest COVID-19 incidence had a mean weekly mobility of 0.461, the tertile with the middle COVID-19 incidence had a mean weekly mobility of 0.468, and the tertile with the highest COVID-19 incidence had a mean weekly mobility of 0.501 (Table 2.1). Table 2.1 outlines the district area characteristics and stratified by cumulative COVID-19 incidence tertiles.

Time series cross-correlation among provinces

The lag time with the maximum cross-correlation between the longitudinal time series of weekly mobility and current/future COVID-19 incidence was 2 weeks ($\rho = 0.423$), indicating that mobility most greatly affects subsequent COVID-19 incidence after two weeks. The cross-correlation coefficient of weekly mobility and COVID-19 incidence on the same week (lag = 0) was 0.398, and the cross-correlation with lag=1 was 0.401.

In a post-hoc analysis assessing the time series cross-correlation of COVID-19 incidence and future mobility, I assessed whether SARS-CoV-2 incidence was also associated with subsequent mobility, as suggested by the interrupted time series analysis in Section 1.3.3. There was no cross-correlation with COVID-19 incidence and weekly mobility after 1 ($\rho = 0.086$) and 2 weeks ($\rho = -0.086$), but there was negative cross-correlation with a lag time of 3 weeks ($\rho = -0.213$). This result is consistent with the interrupted time series analysis that suggests that not only is greater mobility associated with greater future SARS-CoV-2 incidence, but subsequently greater SARS-CoV-2 incidence is associated with future lower human movement.

Interrupted time series analysis among provinces

Eastern Cape, Free State, KwaZulu-Natal, Mpumalanga, Northern Cape, and the Western had mobility breakpoints (Table 2.3) Overall, mobility breakpoints mostly occurred between December 10, 2020 to December 20, 2020, approximately 1 to 2 weeks before the December 29, 2020 alert level 3. The only exception was the November 24, 2020

mobility breakpoint in the Western Cape.

Of these provinces with statistically significant mobility breakpoints, Gauteng, KwaZulu Natal, Mpumalanga, and Northern Cape also had significant COVID-19 breakpoints (Table 2.3). Aside from Mpumalanga where the mobility and COVID-19 breakpoint occurred on the same day (12/17/2020), mobility breakpoints generally occurred after COVID-19 breakpoints (mean: 8 days, 95% CI: 8 to 9 days). The slope for COVID-19 after the COVID-19 breakpoint were all positive (indicating a sharp increase in COVID cases), while the slope for mobility after the mobility endpoint were all negative (indicating a subsequent sharp reduction in human movement) or close to null (Table 2.3). This demonstrates that in addition to the mobility associated with future COVID-19 incidence (as evidenced in the time series cross-correlation in Section 1.3.2), there is also an inverse association with SARS-CoV-2 incidence and subsequent mobility (i.e. sharp decreases in mobility occur two weeks after an uptick in COVID-19 incidence).

Longitudinal associations between weekly mobility and subsequent COVID-19 incidence at the district-level

I used 2 weeks as the lag time for the district-level analysis since the maximum cross-correlation between weekly mobility and COVID-19 incidence among the provinces was two weeks apart. Unadjusted analysis demonstrated that weekly mobility, population density, and TB incidence were independently positively associated with weekly COVID-19 incidence, while HIV prevalence was negatively associated with COVID-19

incidence. A 10% increase in weekly mobility increases the COVID-19 incidence by 22% (IRR=1.22, 95% CI: 1.19 to 1.25) (Table 2.4) while an increase of 1,000 population per km^2 increases COVID-19 incidence rate by 52% (IRR=1.22, 95% CI: 1.19 to 1.25). An increase in TB incidence of one TB case per 100k results in a 3% increase in the rate of COVID-19 incidence (IRR=1.03, 95% CI: 1.01 to 1.04), but an increase in 1% of HIV prevalence decreases COVID-19 incidence by 8% (IRR=0.92, 95% CI: 0.89 to 0.97) (Table 2.4). Regression models adjusting for all independent variables did not change effect estimates; a 10% increase in weekly mobility adjusting for population density, HIV prevalence, and TB incidence, increases the incidence of COVID-19 by 21% (IRR=1.21, 95% CI: 1.19 to 1.24) (Table 2.4).

2.4 Discussion

My findings demonstrate that increases in mobility were positively associated with future COVID-19 incidence aggregated at both the province and district-level, and the association of mobility and COVID-19 incidence remained even when adjusted for district-level confounders. My results also showed that not only is greater mobility associated with increased future SARS-CoV-2 incidence, but subsequently greater SARS-CoV-2 incidence is associated with future decreased human movement, albeit to a lesser extent. Human movement also started declining approximately a week or two before the alert level 3 lockdown was issued, suggesting that people socially distanced on their own accord in response to reports of greater SARS-CoV-2 transmission, which was consistent across all South African provinces.

This study is important for several reasons. First, there is a paucity of studies demonstrating the evidence of the association between population mobility and COVID-19 in LMICs, particularly in South Africa. My findings are consistent with a number of other studies in various settings showing the positive association between human mobility and COVID-19 outcomes.[2-5,29,30] These findings add to the body of evidence that restricting human movement is a valuable mitigation tool to the SARS-CoV-2 pandemic, as SARS-CoV-2 continues to spread and resurge and variants continue to emerge globally. Second, I note that mobility generally decreased prior to alert lockdowns, which these findings suggest are likely due to people's response to increases in COVID-19 incidence, and that lockdowns do not necessarily correspond to a subsequent change in population movement. Lastly, this work demonstrates the potential for digital health tools such as smartphones to provide a valuable source of mobility data. The use of mobility data in modelling infectious diseases such as COVID-19 and other future outbreaks is essential to capture disease transmission; however current sources of population-level mobility data in South Africa, such as Facebook and mobile phone data, have inherent biases.[31] Smartphone mobile phone location data could potentially be more generally representative of the source population of interest, especially as smartphone use has been increasing through the years,[32] and because the Moya app does not require data in order to be used and is not attached to a mobile phone carrier.

This study has a number of limitations. This is an ecological study using population-level data, and group-level risk factors examined in this study must be interpreted carefully and as such these associations are not necessarily informative regarding the true mechanisms

of SARS-CoV-2 transmission at an individual level. Moreover, mobility data may have inherent biases due to differential access of people to smartphones. A recent report estimated that approximately a 23.3% of South African population had access to a smartphone in 2020.[32] Previous research has shown that there is decreased mobility and lower COVID-19 outcomes in areas of greater SES.[2] If areas with higher socioeconomic status have greater access to smartphones and use the Moya app, and the study population included in this study include areas with both decreased mobility and lower COVID-19 outcomes than areas not included in this study, then the association between mobility and COVID-19 may be potentially biased upward and an overestimate. Even if the study population included in this study that use the free Moya app are areas with lower socioeconomic status, and have increased mobility and worse COVID-19 outcomes, the effect estimate would still be biased upward. However, the Moya app is a free messaging system that is paid for by advertising, and thus I expect that the study population would be representative of the source population. Since the data are aggregated and not obtained at the individual level, I am unable to link device unique IDs and infer sociodemographic characteristics of the individual users. However, given the paucity of data and research of mobility and COVID-19 in South Africa and other LMICs, these findings only give greater impetus to conduct research at the individual level to fully examine and disentangle these associations. Finally, the association could still potentially be confounded by other covariates that were not adjusted for in the regression analysis, due to lack of available data. I attempted to account for possible confounding from potential differential testing across provinces by including a random intercept term in the

regression to adjust for province-level effects. Differential testing by local governments within provinces are less likely to strongly impact these findings, as most funding for SARS-CoV-2 in South Africa is distributed at the province-level.[33] Moreover, the study period occurred before the vaccination roll-out across South Africa, and thus the association was not confounded by vaccination rates.

Our findings are consistent with previous research across geographic settings demonstrating that increases in mobility are positive associated with COVID-19 outcomes.[2-5,29,30] To my knowledge, this is one of the first studies to systematically assess the interrelationship among mobility, COVID-19, and subsequent mobility in South Africa aggregated at both the district and province-level. I show a 2-week lag time between human movement and COVID-19 incidence, and a 3-week lag time between the reduction in human movement after an increase in COVID-19 increase. Moreover, mobility also started declining approximately a week or two before the alert level 3 lockdown was issued on December 29, 2020. Coronavirus disease is still a health crisis; to effectively fight this pandemic, sociodemographic and health disparities must be addressed. As SARS-CoV-2 continues to resurge and new variants continue to emerge globally, restricting and monitoring human movement will be a valuable mitigation tool for reducing SARS-CoV-2 disease transmission.

2.5 Tables and Figures

Table 2.1 District area characteristics overall and stratified by tertiles of cumulative COVID-19 incidence, August 30 2020 to Jan 3 2021

District charactertistics (median, IQR)	Total	Tertiles of cumulative COVID-19 incidence, per 100,000 population		
		Lowest: 0–718.1	Middle: 784.5–1521.1	Highest: 1698.0–4126.5
Cumulative COVID-19 incidence (per 100k population)	1070.4 (546.0, 1806.2)	494.0 (365.3, 546.0)	1123.7 (939.4, 1290.0)	2414.9 (1876.3, 3026.1)
Weekly mobility movements per person	540.5 (378.3, 703.1)	346.7 (288.9, 472.6)	543.3 (400.4, 579.2)	719.3 (643.5, 809.4)
Mean weekly mobility	0.480 (0.439, 0.526)	0.461 (0.432, 0.523)	0.468 (0.434, 0.505)	0.501 (0.457, 0.553)
Population density (population/km^2)	55.6 (23.3, 118.0)	60.8 (38.6, 79.4)	53.9 (23.3, 117.4)	40.1 (16.5, 520.0)
HIV prevalence (% of population ages 15 to 49)	17.9 (12.9, 21.6)	21.1 (17.6, 24.1)	18.7 (14.5, 21.6)	13.7 (10.2, 16.4)
TB incidence (per 100k popu)	26.5 (13.8, 39.2)	21.5 (14.8, 30.8)	24.0 (9.0, 37.0)	39.0 (23.0, 45.0)

Abbreviations: COVID-19 = Coronavirus disease 2019; HIV= human immunodeficiency virus; TB = tuberculosis.

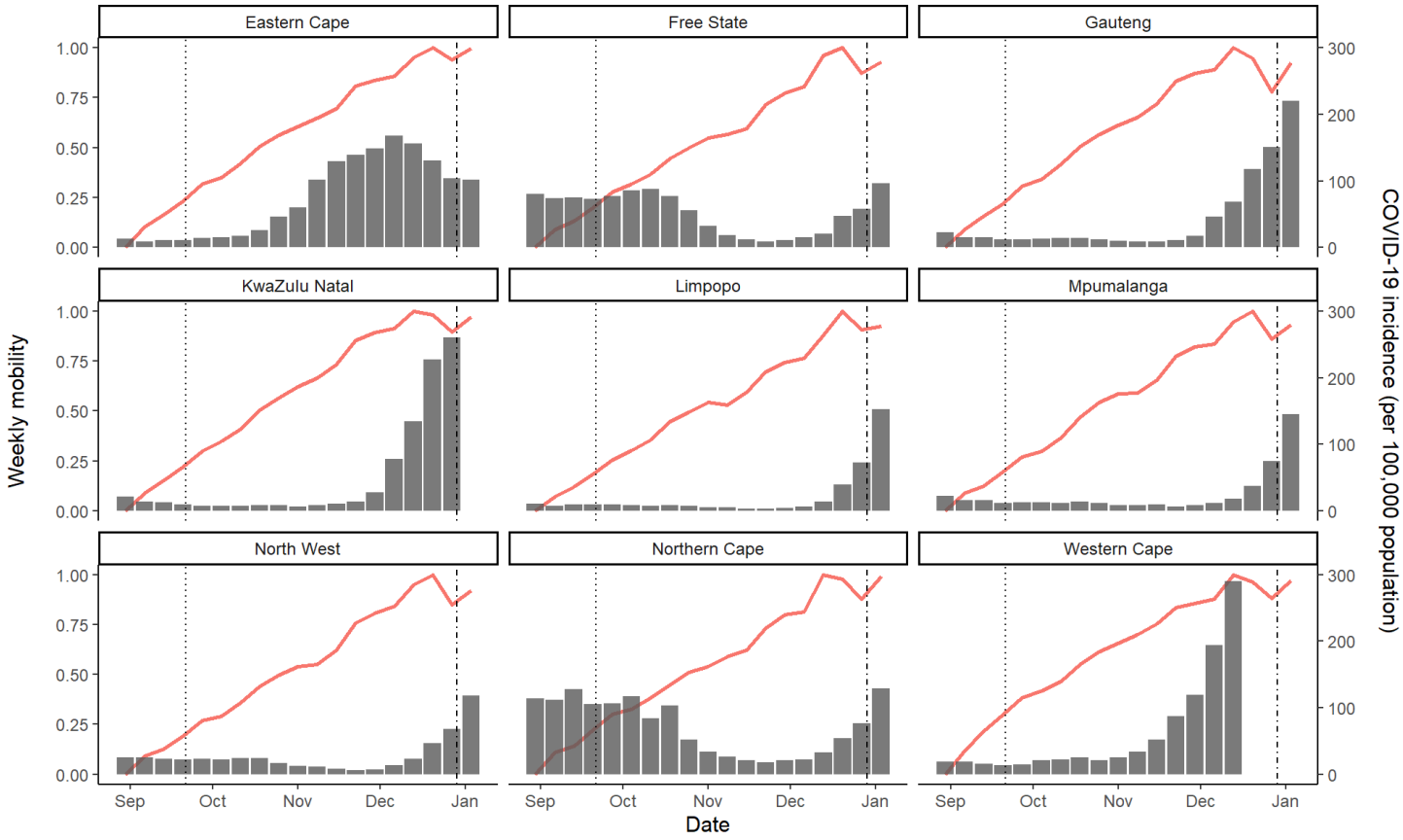
Table 2.2 Weekly mobility per person and cumulative COVID-19 incidence, August 30 2020 to Jan 3 2021

Province	Cumulative COVID-19 incidence (per 100k persons)	Weekly mobility movements per person	Mean weekly mobility*
Eastern Cape	1397.6	275.9	0.579
Free State	1003.5	445.7	0.532
Gauteng	789.4	503.9	0.570
KwaZulu Natal	1199.0	351.2	0.585
Limpopo	380.7	377.8	0.517
Mpumalanga	454.5	377.1	0.546
North West	516.3	365.3	0.531
Northern Cape	1352.9	381.2	0.547
Western Cape	1931.4	568.1	0.608

Abbreviations: COVID-19 = Coronavirus disease 2019;

*****Normalizing mobility by accounting for the minimum and maximum number of mobility movements for each province.

Figure 2.1 Weekly mobility and COVID-19 incidence (per 100,000 population) of the nine South African provinces.



Abbreviations: COVID-19 = Coronavirus disease 2019

Red lines represent the weekly mobility (normalized within each province), and histograms denote the COVID-19 incidence (per 100,000 population). Vertical lines indicate timing of alert level implemented in South Africa; the dotted line indicates change from alert level 2 to alert level 1 (in effect from 21 September to 28 December 2020), and dashed line represents change from alert level 1 to alert level 3 (in place from 29 December 2020 until 28 February 2021).[34] Higher alert levels denote greater levels of non-pharmaceutical interventions.

Table 2.3 Weekly mobility breakpoints and COVID-19 breakpoints for the nine districts of South Africa.

	Weekly mobility			COVID-19		
Province	Date of breakpoint	Slope before breakpoint (95% CI)	Slope after breakpoint (95% CI)	Date of breakpoint	Slope before breakpoint (95% CI)	Slope after breakpoint (95% CI)
Eastern Cape	12/15/2020 (12/14 to 12/16)*	0.009 (0.008 to 0.009)	0.004 (0.001 to 0.006)	12/11/2020 (12/10 to 12/13)	1.745 (1.335 to 2.155)	-2.76 (-5.826 to 0.306)
Free State	12/20/2020 (12/19 to 12/20)*	0.008 (0.008 to 0.009)	-0.004 (-0.011 to 0.004)	12/09/2020 (12/7 to 12/10)	-0.877 (-1.154 to -0.601)	3.411 (1.342 to 5.479)
Gauteng	12/11/2020 (12/10 to 12/11)*	0.009 (0.008 to 0.01)	-0.006 (-0.011 to 0)	12/02/2020 (12/1 to 12/2)*	-0.063 (-0.202 to 0.075)*	6.158 (5.496 to 6.82)*
KwaZulu Natal	12/10/2020 (12/10 to 12/11)*	0.009 (0.009 to 0.01)	-0.003 (-0.006 to 0.001)	11/27/2020 (11/27 to 11/27)*	-0.063 (-0.231 to 0.106)*	8.929 (8.384 to 9.474)*
Limpopo	10/17/2020 (10/10 to 10/25)	0.008 (0.008 to 0.009)	-0.001 (-0.015 to 0.013)	12/16/2020 (12/16 to 12/17)*	-0.028 (-0.122 to 0.065)*	8.051 (6.833 to 9.268)*
Mpumalanga	12/17/2020 (12/17 to 12/18)*	0.009 (0.008 to 0.009)	-0.005 (-0.012 to 0.002)	12/17/2020 (12/16 to 12/17)*	-0.066 (-0.147 to 0.016)*	7.748 (6.681 to 8.814)*
Northern Cape	12/19/2020 (12/18 to 12/20)*	0.009 (0.008 to 0.009)	-0.006 (-0.013 to 0.002)	12/10/2020 (12/9 to 12/10)*	-0.204 (-0.301 to -0.108)*	4.358 (3.638 to 5.079)*
North West	12/15/2020 (12/13 to 12/17)	0.008 (0.008 to 0.009)	0.001 (-0.007 to 0.01)	12/08/2020 (12/7 to 12/9)	-1.281 (-1.586 to -0.975)	4.449 (2.163 to 6.735)
Western Cape	11/24/2020 (11/23 to 11/26)*	0.009 (0.008 to 0.01)	0.002 (-0.001 to 0.005)	11/10/2020 (11/9 to 11/11)	0.185 (-0.493 to 0.864)	6.38 (5.281 to 7.478)

Abbreviations: COVID-19 = Coronavirus disease 2019

* Significant

Table 2.4 Associations between weekly mobility, district weekly COVID-19 incidence, and district area characteristics from mixed-effects negative binomial models

	Unadjusted*		Adjusted†	
	IRR	95% CI	IRR	95% CI
Weekly mobility (10% increase)	1.22	1.19 to 1.25	1.21	1.19 to 1.24
Population density (1,000 population/km^2)	1.52	1.12 to 2.08	1.38	1.04 to 1.82
HIV prevalence (% of population ages 15 to 49)	0.92	0.89 to 0.97	0.93	0.89 to 0.99
TB incidence (per 100k population)	1.03	1.01 to 1.04	1.02	1.01 to 1.04

Abbreviations: COVID-19 = Coronavirus disease 2019; IRR=incidence rate ratio.

*Unadjusted models include weekly COVID-19 incidence (outcome) and each single variable (exposure)

†Adjusted models include weekly COVID-19 incidence (outcome), weekly mobility (primary exposure), population density, HIV prevalence, TB incidence (all at the district level), and province.

3 REDUCING SARS-COV-2 TRANSMISSION THROUGH ROUTINE COMMUNITY TESTING: A MODELLING ANALYSIS

3.1 Introduction

While vaccination is increasingly used to mitigate the impact of the COVID-19 pandemic, the use of diagnostic testing remains vital for case identification and reducing SARS-CoV-2 transmission, particularly as new variants arise that partially escape immunity induced by prior infections and vaccination. In the first year of the pandemic, diagnostic testing for COVID-19 primarily relied on reverse transcriptase polymerase chain reaction (RT-PCR) testing.[35,36] RT-PCR remains the gold standard for diagnosing and screening COVID-19, is highly sensitive and specific, and has been the most widely used method to diagnose COVID-19 infections throughout the pandemic.[35] However, RT-PCR testing is expensive, can have long turnaround times,[7] and is limited by a global shortage of test kits and the availability of instruments.[6] For routine community-based testing, the speed, frequency, and feasibility of testing using rapid antigen diagnostic tests (Ag-RDTs) may potentially outweigh the benefits of higher test sensitivity and specificity provided by RT-PCR. Importantly, the use of Ag-RDTs may enable broader public-health testing campaigns targeted at mitigating the COVID-19 pandemic, particularly in countries with limited or strained PCR capacity. Ag-RDTs, when accompanied by isolation following a positive result, have the potential to be of substantial utility for the control and mitigation of the COVID-19 pandemic. With the greater testing capacity that Ag-RDTs provide, most recently implemented community-testing strategies depend on Ag-RDTs.[9-11]

Despite the potential utility of Ag-RDTs, questions remain as to how effective community-based testing campaigns – defined as random mass testing of the population, which include screening at healthcare facilities or home self-testing – for SARS-CoV-2 have been to date, what factors (such as frequency, proportion tested, and epidemic parameters) have driven their relative success, and how their effectiveness can be improved moving forward. Countries such as the United Kingdom (UK), Slovakia, and Denmark have complemented their broad symptomatic testing programs with widespread community-level testing to varying levels of success.[9-11,37] With the rise of the Omicron variant,[38] the COVID-19 response in the United States (US) has now shifted to providing expanded and more accessible at-home Ag-RDTs.[31] Since limited financial and human resources need to be dedicated to community-based testing, understanding when and where testing can be most impactful is paramount.

To that end, I developed a mathematical model to quantify the impact and efficiency of Ag-RDTs for population-level community testing, and to identify the testing and epidemic parameters where use of Ag-RDTs would be expected to result in the largest reduction in SARS-CoV-2 transmission.

3.2 Methods

Overview of the compartmental model

The National COVID-19 Epidemiology Model (NCEM) is a stochastic compartmental transmission model initially developed to reflect the SARS-CoV-2 pandemic in South

Africa. I then modified this model to quantify the likely impact of different SARS-CoV-2 Ag-RDT strategies on population-level disease transmission in a general population of 10 million people. The compartmental model has a Susceptible-Exposed-Infectious-Recovered (SEIR) structure, that accounts for varying levels of infection and disease severity (asymptomatic, mild, severe, and critical cases) and includes several treatment pathways (outpatient severe cases, non-intensive care unit (ICU) hospitalizations, and ICU beds). The original model structure, parameters, and assumptions have been previously described in greater detail,[39] and relevant key assumptions for this model are outlined below.

To adapt the NCEM, additional transitions between compartments were added, where COVID-19-tested individuals can isolate upon a positive test result, thus reducing disease transmission in the general population. Specifically, when tested positive, groups in each infected health state transition to a mirrored diagnosed composite health state (e.g. from asymptomatically, pre-symptomatically or mildly infected to a "non-severe COVID and diagnosed" health state). The diagnosed health states then have a variable reduction in their contact rate set within each scenario.

Figure 3.1 shows the structure of the adapted NCEM, where the additional compartments and transitions for diagnosed non-severe infections, severe infections, and hospitalizations are in blue. The simulation was run for 365 days to assess the medium-term relative impact of testing strategies on the epidemic. Appendix 6.1 outlines the differential equations used in the adapted compartmental model, and the original equations have been outlined previously.[39,40]

Outcomes

I assessed the total number of SARS-CoV-2 tests conducted, and the cumulative number of COVID-19 infections for each scenario in 365 days, where COVID-19 infections are defined as all asymptomatic, pre-symptomatic, mild, and severe infections, as well as hospitalized cases. I focused the analyses on two model outcomes relative to the status quo base case scenario:

(a) Impact - the percentage of infections averted,

$$= \frac{I_{bc} - I_s}{I_{bc}}$$

(b) Efficiency - the number of tests required to avert one infection

$$= \frac{T_s}{I_{bc} - I_s}$$

Where I_{bc} is the cumulative number of COVID-19 infections in the base case scenario, I_s is the cumulative number of COVID-19 infections in the scenario of interest, and T_S is the total number of Ag-RDT tests conducted in scenario of interest.

I also assessed two secondary outcomes, total infections averted and total infections in the population.

Model analysis

3.2.1.1 Model parameters and assumptions

The model was calibrated to empirical COVID-19 data from various sources, including transition parameters, and proportion of cases that are mild, moderate, or severe. All parameter inputs and corresponding sources are outlined in Appendix 6.2. Parameters were randomly drawn from a triangular distribution defined by the lower, upper, and mode values, and simulations were run 50 times for each parameter set. I ran the simulation probabilistically to construct stable 95% simulation intervals (SI) to account for the stochasticity of the model and incorporate uncertainty in the final estimates. The sensitivity of the diagnostic tests for COVID-19 cases was assumed to be 85% (80% to 90%).[8,41] Individuals only test positive once they leave the exposed compartment and are in the presymptomatic phase, which is approximately the 2 days before symptom onset. The relative transmissibility of asymptomatic and presymptomatic cases compared to symptomatic cases was assumed to be 0.75 (0.70 to 0.80).[42] I also assumed that individuals not tested do not change their behavior, those who have false negatives will also not change their behavior.

3.2.1.2 Ag-RDT testing scenarios

The impact of Ag-RDT testing scenarios were quantified to assess the utility of Ag-RDT across different epidemic conditions for all use cases. Table 3.2 outlines the parameters varied for each use case testing scenario. The parameters that were varied were use-case

dependent, but most often the frequency of testing for asymptomatic infections (testing in the community, K-12 schools, and universities) was varied. Select use cases varied the proportion tested (community testing), isolation effectiveness (community testing), duration and timing of testing (mass gathering), groups tested (K-12), and days delay to contact tracing, quarantine, exit testing, and number of days (exit quarantine). All testing scenarios were compared to a counterfactual base case scenario with the same epidemic parameters as the base case (Table 3.1).

3.2.1.3 Threshold analysis under different epidemic conditions

I conducted threshold analysis of the Ag-RDT testing scenarios under different combinations of SARS-CoV-2 epidemic parameters (Table 3.1). Threshold analysis is used to understand the drivers of variability in the impact and efficiency outcomes, as defined in section 3.2.2.[43] In these analyses, I assessed how changes to the effective reproductive number (*Rt*) and SARS-CoV-2 prevalence can affect the utility of testing, and whether results are robust to alternative assumptions about the epidemic characteristics. *Rt* is defined as the number of secondary infections one infectious case will infect in the case's lifetime in a population with both susceptible and immune people, and is a time-varying parameter that reflects the changing levels of immunity in the population and the impact of control measures to limit transmission. I modelled different *Rt* values to account for differing vaccination rates, nonpharmaceutical intervention (NPI) implementation, and/or general phase of the pandemic in a country at a given time. Daily SARS-CoV-2 external importation prevalence at the start of the

epidemic was set to either 0.1% or 1.0% to correspond to low or high prevalence periods. To calculate the number of daily imported infections entering the population with infections acquired elsewhere, the total population was multiplied by the prevalence (0.1% and 1.0%) and divided by the average infectious period of SARS-CoV-2.[21]

Computational work reported was performed on the Shared Computing Cluster which is administered by Boston University's Research Computing Services (www.bu.edu/tech/support/research). All analyses of model output were conducted in R version 4.0.0.[26]

3.3 Results

Impact

Impact was defined as the percentage of infections averted compared to the base case scenario for each use case. As expected, a greater proportion of infections averted (greater impact) was generally associated with higher proportion tested and increased frequency of Ag-RDT testing for most scenarios (Figure 3.2A). In the epidemic scenario with high disease transmission (*Rt*=2) and high COVID-19 prevalence (1%), when the population was tested once every two weeks and test positive individuals isolated at 50% effectiveness, the percent infections averted increased from 11.29% (95% SI: 5.41% to 18.62%) when 2.5% of the population was tested to 49.34% (95% SI: 41.09% to 51.1%) when 20% of the population was tested, and to 90.26% (95% SI: 84.62% to 92.6%) when 90% of the population was tested. Similarly, increased frequency of testing increased the impact of Ag-RDT testing. Keeping everything else constant, when 20% of the

population was tested, increasing frequency of testing from once every 2 weeks to once a week and twice a week increased impact from 49.34% to 63.53% (95% SI: 54.7% to 66.5%) and 73.39% (95% SI: 63.76% to 76.74%) respectively. A greater percent of infections were averted and fewer tests per averted infection were needed when there was greater isolation effectiveness (defined as a reduction in number of contacts when diagnosed positive) (Figure 3.2). Even with frequent and widespread testing, there would be a limited percentage of infections averted when there was no reduction in the number of contacts post-diagnosis (Figure 3.2A).

Efficiency

Efficiency was defined as the number of tests needed to avert one infection compared to the base case scenario across use cases. In contrast, these greater-frequency and higher-proportion tested scenarios required more tests per averted infection - thus less efficient per test used (Figure 3.2B). In the previous epidemic scenario with high disease transmission and high COVID-19 prevalence, and 2.5% of the population was tested once every two weeks and isolated at 50% effectiveness, efficiency was 7.31 (95% SI: 7.00 to 10.08) tests per averted infection. The number of tests per averted infection increased (less efficient) to 12.81 (95% SI: 8.54 to 26.51) and to 31.51 (95% SI: 21.20 to 57.93) when 20% and 90% of the population was tested, respectively. Similarly, more frequent testing decreased efficiency; when 20% of the population was tested, increasing frequency to once a week increased the number of tests per averted infection to 9.23

(95% SI: 9.22 to 12.45), and testing twice a week increased efficiency to 15.21 (95% SI: 13.35 to 20.76) tests per averted infection.

Threshold analysis of Rt and COVID-19 prevalence

When transmission and prevalence of COVID-19 is high and 20% of the population were tested once a week, the percent infections averted was only 20.78% (95% SI: 12.55% to 22.96%) when isolation effectiveness was low (20%), 63.53% (95% SI: 54.70% to 66.5%) when isolation effectiveness was 50%, and 96.51% (95% SI: 94.79% to 97.20%) in the best case scenario (isolation effectiveness=80%). There was also increased efficiency with greater isolation effectiveness. In the same scenario, the number of tests per averted infection is 60.85 (95% SI: 38.00 to 173.54) if diagnosed individuals isolate 20% of the time with similar testing (20% of the population once a week). This decreased to 19.90 (95% SI: 13.12 to 39.83) when isolation effectiveness was 50%, and 13.10 (95% SI: 8.98 to 22.98) when isolation effectiveness was 80% (Figure 3.2B). Moreover, there was a greater percentage of infections averted (greater impact) and more tests required per averted infection (less efficient) when the effective reproductive number and prevalence were low.

Secondary outcomes

The number of infections averted followed the same trend as percentage infections averted (Appendix 6.3), 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 I only tested 15% of symptomatic infections, 50% of severe cases, and all hospitalized cases) ranged from 1.1 to 8.2 million, or 11% to 82% of the population depending on the epidemic parameters. Appendix 6.4 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. Overall, confidence intervals to account for the stochasticity of the model demonstrated that my main findings were consistent across scenarios and outcomes and did not vary greatly due to stochasticity (Figure 3.3 and Appendix 6.5). The number of tests per 100,000 population/month is illustrated in Appendix 6.5.

3.4 Discussion

A greater percentage of infections were averted with more frequent and widespread community-wide Ag-RDT COVID-19 testing across all epidemic scenarios. However, the extent of infections averted in all scenarios strongly depends on the reduction in post-diagnosis contacts – diagnosis must be accompanied by changes in behavior for any testing strategy to be effective. Additionally, my findings suggest that community-wide testing has a small impact when disease transmission is high and is most useful when an epidemic is waning or before an epidemic wave (low *Rt*).

Health systems in limited resource settings are unlikely to be able to scale up COVID-19 testing to a large percentage of the population. For example, when disease transmission and COVID-19 prevalence is high (*Rt*=2 and prevalence=1%), even in the most modest

scenario considered in Appendix 6.5 – community testing 2.5% of a population once every two weeks – would require 5,000 Ag-RDT tests per 100,000 population per month and would yield only small reductions in infections (11% reduction in infections when assuming 50% reduction in contacts following a positive test). This level of testing would require 160% of the current testing procurement target for LMICs of 3,000 tests per 100,000 population/month,[44] and would require that all tests be performed in addition to tests allocated for symptomatic testing. For substantial impact of a community testing strategy, more widespread and frequent testing is needed; for example, to achieve an 88% reduction in infections, holding epidemic and other testing parameters constant, when 50% of the population are tested once a week, this would require 200,000 tests per 100,000 population per month (66x the current testing procurement target). As Omicron becomes the main SARS-CoV-2 variant globally, the US is providing increased support for access to testing, including a commitment to providing 500 million at-home Ag-RDTs, in addition to current facility testing capabilities.[45]

Other countries have implemented population-wide community-level SARS-CoV-2 testing to varying levels of success, and my results shed light on the relative success or failure of each national-level testing effort for epidemic mitigation. The UK is an example of having recently implemented an Ag-RDT mass screening program since April 2021 that offers access to tests twice a week. Testing data in the UK as of November 2021 for both PCR and Ag-RDT showed that approximately 41,375 tests per 100,000 population per month were conducted in November 2021,[10] which according to my findings is likely not enough to substantially reduce infections. A study also found

that only 20% of individuals complied with isolation measures.[46] The inadequate levels of testing and isolation effectiveness in the UK likely contributed to the ineffectiveness of the initiative, which corresponds with my study findings that demonstrate that in order for mass testing to be effective, widespread frequent testing and high isolation adherence is imperative.

Denmark also focused on a voluntary mass testing approach. Even though approximately 90% of the Danish population was tested at least once since the start of the pandemic, there may have been large differences in the frequency of testing of each individual given that the program was voluntary.[11] Further, research has shown that the contact number was only reduced by 25%,[11] which is likely to not have a large effect since my study demonstrated that high levels of frequent and widespread testing are needed to reduce a marked number of infections at a population-level. In contrast, Slovakia reported to have reduced COVID-19 infection prevalence in counties by 80% after two rounds of mass Ag-RDT testing.[9,47] Slovakia's success may be due to the high proportion tested in the population (83% and 84% in each round, respectively) in a short time frame, as well as the timing of testing (October and November 2020), which was early on in the country's outbreak, before an epidemic wave, with low *Rt*.[12] This is consistent with my finding that testing is more impactful before an epidemic wave. When Slovakia implemented mass testing, arrivals from some regions were being quarantined, reducing prevalence, which is consistent with my observation that testing is more impactful in low prevalence settings. Moreover, my findings are consistent with two modeling studies in France[48] and the Netherlands[49], which both concluded routine community-level testing with isolation of

infectious individuals only has a substantial impact on disease transmission with very widespread frequent testing, similar to the levels demonstrated in this study.

Differences in the effect of mass testing on COVID-19 outcomes in Denmark, Slovakia, and the UK is likely to be associated with the different NPIs in place as mass testing occurred, but even so, results from mass testing programs in various countries and my findings provide additional evidence to suggest that the epidemic trajectory in a given geographic region is as important as the screening program itself. While my findings suggest that mass asymptomatic community testing accompanied by viable mechanisms of isolation can facilitate disease control, the number of tests needed likely make it feasible only in small, defined settings in limited resource settings. Additional modeling, operational, and cost-effectiveness studies extending these findings need to be conducted to identify key candidate settings for asymptomatic community testing.

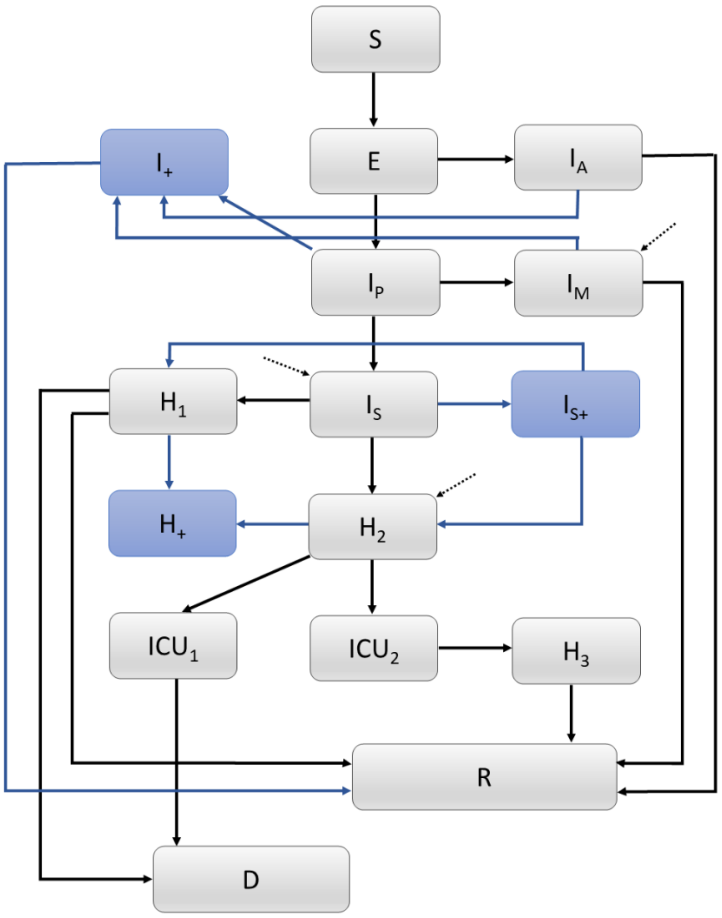
There are some limitations to this study. The model used several simplifying assumptions as a tradeoff between complexity and parsimony, which introduced several limitations in the interpretation of the findings. For example, the model was unconstrained by the total number of tests and healthcare workers, for my goal was to quantify the impact of Ag-RDT without considering resource limitations. Additionally, the model did not assume a contact tracing infrastructure, as these findings were meant to be generalizable across all countries. Contact tracing may not be feasible in many LMICs given the substantial human resource burden. However, the implementation of contact tracing in addition to widespread community testing would only further improve the effectiveness of routine community testing if human resources were available and trained to conduct this type of

large-scale public health program. I also did not incorporate age structure into my model, as the focus of the model was random mass testing of the population, which was assumed to be age-agnostic. Additionally, I assessed the number of infections, rather than deaths, which have not been shown to be age-dependent.[18,50,51] Finally, in order to evaluate the value of Ag-RDT at various stages of the epidemic trajectory, I had to make non-dynamic assumptions about each scenario (e.g. artificially setting *Rt* and prevalence) at the beginning of the model runs. In reality, these processes are dynamic, and a dynamic evaluation of each strategy across varying epidemic trajectories will be required in future research.

Overall, speed and frequency of testing to provide real-time SARS-CoV-2 case data make Ag-RDTs a valuable tool for case detection, outbreak investigation and contact tracing.[8] However, I found that in order for random routine community testing to be impactful, testing would need to be frequent and widespread, requiring a likely infeasible increase in required resources. Countries that have implemented or are rolling out expanded access to testing have not been reaching the number of diagnostic tests required to substantially reduce the percentage of infections by testing alone. However, testing in conjunction with other non-pharmaceutical interventions could have a substantial impact.

3.5 Tables and Figures

Figure 3.1 Adapted NCEM model. Additional compartments and transitions for diagnosed mild infections, severe infections, and hospitalizations are in blue. Dotted arrows are imported cases at the start of the epidemic.



Compartments: S – Susceptibles, E – Exposed Ia- Asymptomatic infections, Ip – Presymptomatic infections, Im – Mild infections, Is – Severe infections, H1 – non-ICU hospitalizations, H2 – ICU hospitalizations, ICU1 – ICU deaths, ICU2 – ICU recovereds, H3 – post-ICU hospitalizations, R – recovered, D – deaths, I+ - Asymptomatic/presymptomatic/mild infections diagnosed, IS+ - Severe infections diagnosed, H+ - Hospitalizations diagnosed

Table 3.1 Testing scenario parameters varied under different epidemic conditions

Parameters	Values
Ag-RDT testing scenario	
Proportion of community tested	2.5%, 5%, 20%, 50%, 90%
Frequency of community testing	Once/two weeks, once/week, twice/week
Isolation effectiveness	20%, 50%, 80%
Epidemic conditions	
Effective reproductive number	0.8, 1.2, 2.0
Prevalence of SARS-CoV-2	0.1%, 1%

Figure 3.2 (A) Percent of infections averted (impact) and (B) test per averted infection (efficiency) 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.

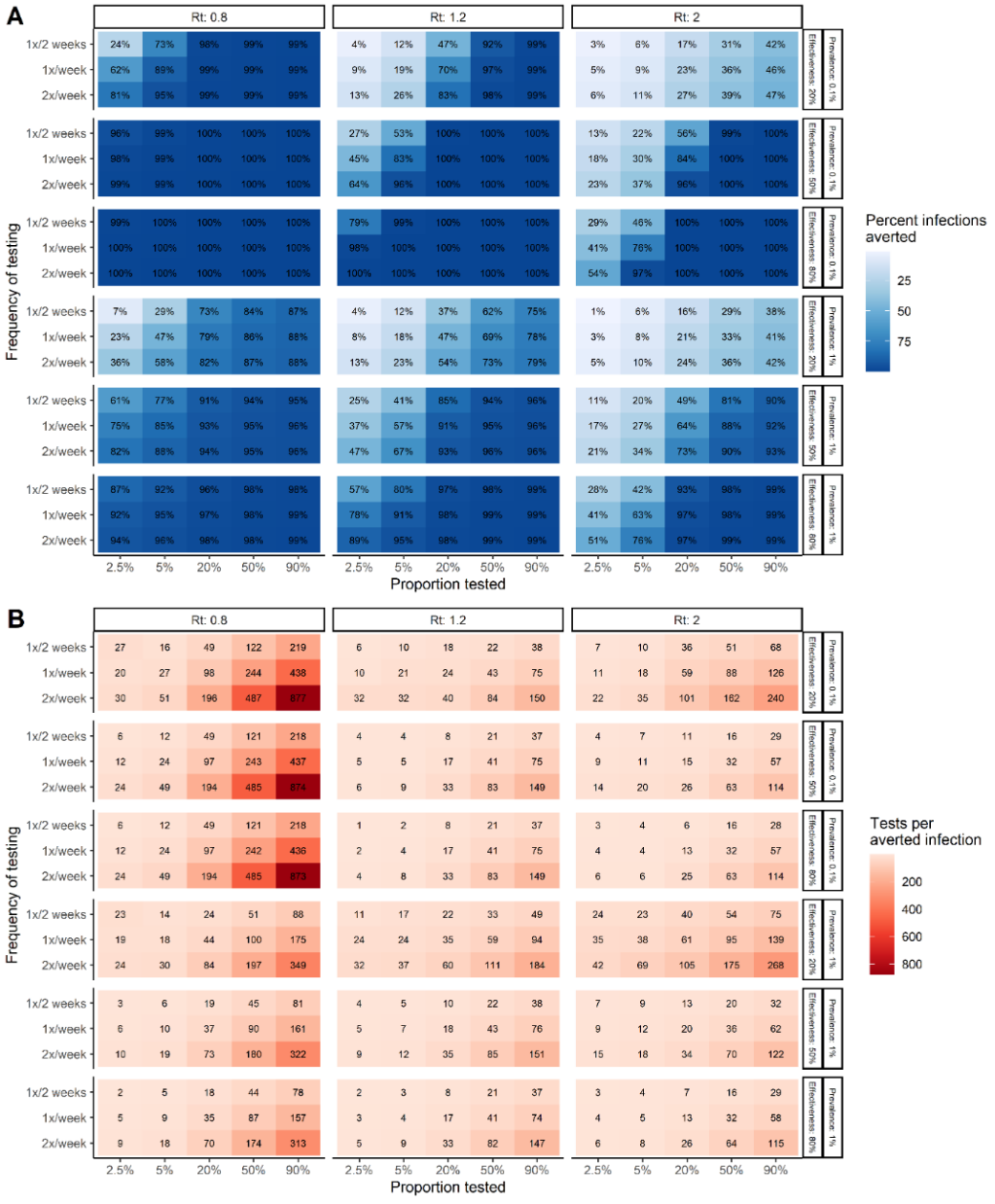
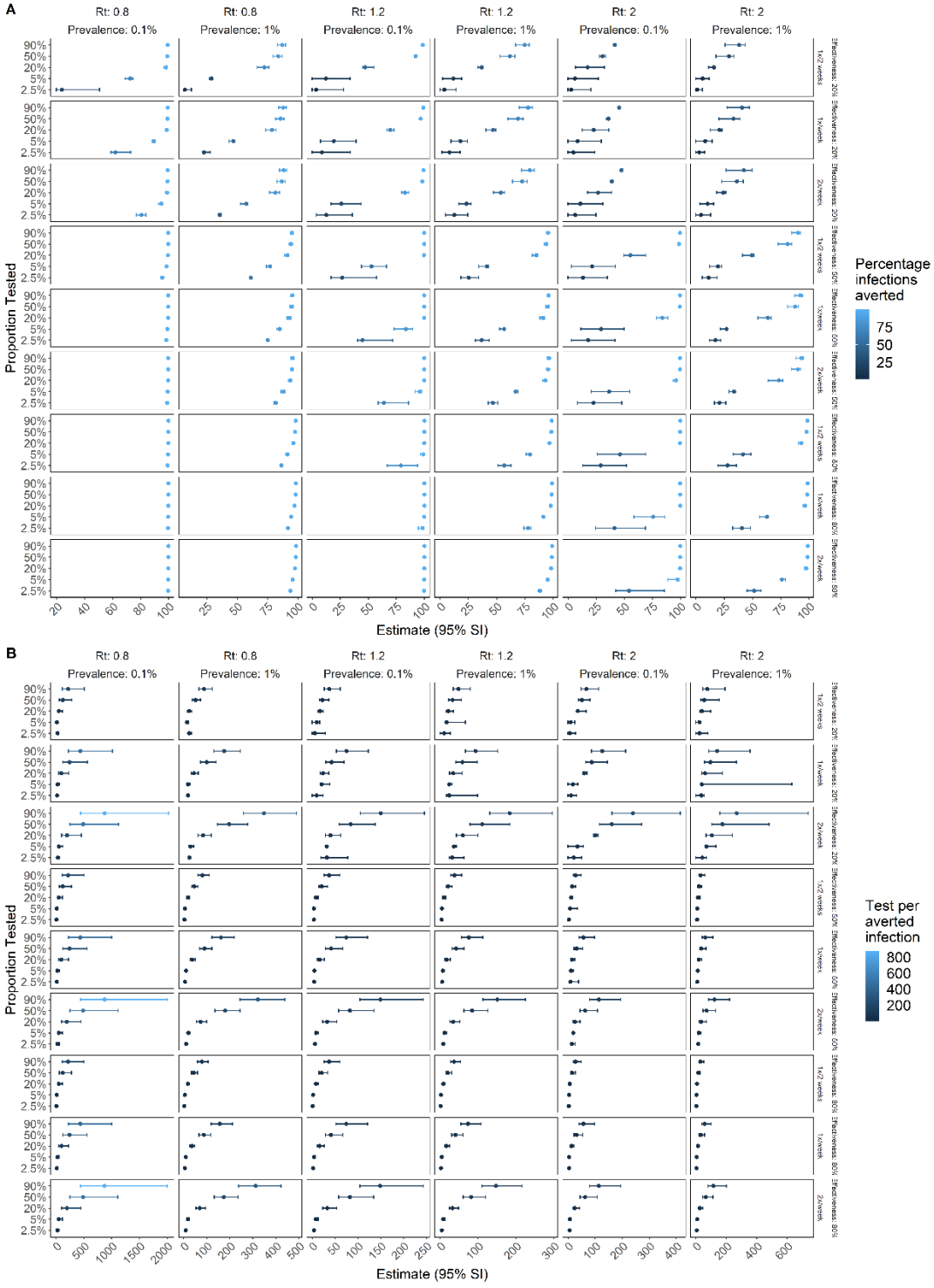


Figure 3.3 Estimates and 95% simulation intervals (SIs) for the (A) impact and (B) efficiency outcomes



4 RAPID ANTIGEN DIAGNOSTICS FOR SARS-CoV-2 MITIGATION: A COMPARISON OF EIGHT MATHEMATICAL MODELS

4.1 Introduction

Diagnostic testing for SARS-CoV-2 remains an effective pandemic response tool by allowing for the timely detection and isolation of infectious cases, particularly during the emergence of the Omicron variant. Early research demonstrates that the Omicron variant, which is now the most dominant strain globally, may evade vaccine-induced immunity, particularly without the booster shot.[52,53] Thus, other mitigation measures such as non-pharmaceutical interventions (NPIs) and diagnostic testing remain vital for reducing further SARS-CoV-2 transmission globally. 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 pandemic response. RT-PCR tests remain the gold standard for COVID-19 diagnostic testing, with higher test sensitivity and specificity than Ag-RDTs, making it the diagnostic most widely used to confirm COVID-19 infection. However, they require laboratory infrastructure, sample transport, skilled personnel, and can be plagued by long turnaround times.

As a surveillance and epidemic 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 (less than $2.50 per test)[54] and can be utilized

for the scale-up of diagnostic testing in limited resource settings such as low- and middle-income countries (LMICs) − where RT-PCR testing capacity is limited − and to support surveillance or response efforts where RT-PCR testing is readily accessible. While Ag-RDTs have lower test sensitivity (>80% in symptomatic individuals in the first 5-7 days of illness) than PCR tests, they can be performed at point of care and provide results within 10–30 minutes. Most importantly, Ag-RDTs perform very well when an individual has high SARS-CoV-2 viral load, where the most sensitive tests can detect 97% of infectious cases, and thus are able to detect COVID-19 cases when they are most infectious.[55]

Different diagnostic testing strategies are likely required in different settings to most efficiently reduce transmission. In limited resource settings, identifying the scenarios 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 such as 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 LMICs, by comparing outcome measures in several scenarios from multiple mathematical models. In doing so, I seek to provide an evidence base for the use of Ag-RDTs in various LMIC settings, quantify the impact and efficiency of expanded access to Ag-RDTs, and identify scenarios where use of tests can be optimized.

4.2 Methods

Overview and use cases

I conducted a multi-model comparison across six different scenarios, hereafter referred to as "use cases". Use cases are defined as the subnational settings and scenarios where I assess the impact of Ag-RDTs. In this study, the use cases were (a) in the general community, (b) at mass gatherings, (c) at K-12 schools (kindergarten to 12th grade/high school, or primary and secondary education), (d) at universities, (e) at border crossings, and (f) to exit quarantine. These use cases were identified by the Access to COVID-19 Tools-Accelerator (ACT-A) modelling consortium members[56] as high priority use cases, where Ag-RDTs are under consideration as a primary diagnostic tool. The ACT-A modelling consortium was established in conjunction with the World Health Organization (WHO) and Foundation for Innovative Diagnostics (FIND), with the goal of investigating the public health impact of Ag-RDTs to inform policy.

Outcomes

I calculated two outcomes relative to the base case scenario (counterfactual base case scenario with the same epidemic parameters, outlined in Table 4.1) in each use case:

(1) Impact – depending on the use case: the percent and number of infections averted, percent of infectious days averted, or the number of infectious imports averted per 100,000 travelers, and

2) Efficiency - the number of tests required to either: avert one infection, avert one infectious day, or infectious import per 100,000 travelers.

To calculate these outcomes, I determined the number of Ag-RDT COVID-19 tests that would need to be conducted, and the number of COVID-19 infections for each scenario. COVID-19 infections were defined as all diagnosed and undiagnosed asymptomatic, pre-symptomatic, mild, and severe (including hospitalized) COVID-19 infections. The *exiting quarantine* use case used a modified version of these outcomes (infection days instead of infections). I was interested in assessing the short- and medium-term relative impact of testing strategies, and depending on the use case the model trajectories were between 90 and 365 days. 95% simulation intervals were extracted from all models.

Multi-model comparison

A multi-model comparison is a formal process by which outcomes of two or more mathematical models of interventions are compared to provide evidence for decision making. In this study, I compared several use cases across different models. Guidelines on best practices for comparisons among different mechanistic disease models are outlined elsewhere, requested by the WHO Immunization and Vaccines-related Implementation Research Advisory Committee (IVIR-AC), and I followed that framework in this paper.[43] This comparison framework using multiple models has been used in multiple infectious disease studies in the past,[57-59] and multiple model approaches that predict the trajectory of the COVID-19 pandemic have previously been

published;[60,61] however, to date there have been no comparative studies that examine different Ag-RDT use cases. In the case of Ag-RDT recommendations, where evidence is scarce, the comparison of model results across various use case settings would put all findings in context within one overarching document, providing accessible guidance for decision makers.

4.2.1.1 Models

My study included eight mathematical models from different modeling groups to assess the potential impact of Ag-RDT testing for SARS-CoV-2 infection in different use cases. Most of the models included in the study were already created to model LMICs, but others were repurposed to represent the population structure, including age distribution and contact network, if applicable. All collaborators agreed to provide output from their models and make adjustments where relevant or required. All but one (border crossings) showed the results from a single modeling group**.** Table 4.1 outlines the mathematical models included in the analysis and a brief description. Models were a combination of compartmental, agent-based, algebraic, and statistical models. Additional background and methodological approach on all models are explained in detail in Appendix 6.6**.**

4.2.1.2 Model parameters and assumptions

Each modeling group was asked to run a set of scenarios. In order to have a unifying set of variables such that the models could be compared to each other, consortium members

modified their models to incorporate any missing parameters where appropriate. Moreover, modelling consortium members were given an acceptable range to use for test sensitivity for Ag-RDTs and base case scenarios across use cases, to preserve comparability across use case models. Across use cases, mean sensitivity ranged from 80% to 85%, or was conditional on intra-host viral load dynamics. Differences in model or parameter specification between models were systematically recorded in Appendix 6.7.

4.2.1.3 Ag-RDT testing scenarios

The impact of Ag-RDT testing scenarios were quantified to assess the utility of Ag-RDT across different conditions for all use cases. Table 4.2 outlines the parameters varied for each use case testing scenario. The parameters that were varied were use-case dependent, but most often the frequency of testing for asymptomatic infections (testing in the community, K-12 schools, and universities) was varied. Select use cases varied the proportion tested (community testing), isolation effectiveness (community testing), duration and timing of testing (mass gathering), groups tested (K-12), and days delay to contact tracing, quarantine, exit testing, and number of days (exit quarantine). All testing scenarios were compared to a counterfactual base case scenario with the same epidemic parameters as the base case (Table 4.1).

4.2.1.4 Threshold analysis under different epidemic conditions

I conducted threshold analysis of the Ag-RDT testing scenarios under different combinations of SARS-CoV-2 epidemic parameters (Table 4.1). Threshold analysis is

used to understand the drivers of variability in the impact and efficiency outcomes, as defined in section 4.2.2.[43] In these analyses, I assessed how changes to the effective reproductive number (*Rt*) and SARS-CoV-2 prevalence can affect the utility of a testing strategy, and whether results are robust to alternative assumptions about the epidemic characteristics. Initial *Rt* and prevalence were varied to assess the impact and efficiency of testing depending on the specific local stage of the epidemic; for example, high initial *Rt* and low prevalence would suggest the start of a new epidemic wave. I modelled different initial *Rt* values to account for differing vaccination rates nonpharmaceutical intervention (NPI) implementation. SARS-CoV-2 prevalence was set to either 0.1% or 1.0%. 95% simulation intervals (SI) were constructed for each model to account for the stochasticity of the model and incorporate uncertainty in the final estimates. All analyses of model output were conducted in R version 4.0.0.[26]

4.3 Results

Different use case settings require varying testing strategies to most efficiently and impactfully reduce infections across a range of epidemic conditions, with some global trends (Table 4.3). Overall, there were tradeoffs between impact (percent infections averted) and efficiency (number of tests to avert one infection). Across use cases, increasing test frequency (and/or more testing) was associated with greater percentage of infections averted (Figure 4.1). In contrast, lower testing frequency was generally more efficient. In community testing and university use case, testing was most effective and efficient when R_t and/or infection prevalence was low. In contrast, testing was most

effective and efficient when R_t and/or infection prevalence were high in defined settings such as border crossings (Table 4.3).

Impact

Impact was defined as the percentage of infections averted compared to the base case scenario for each use case. Across use cases, a higher frequency of testing (or more widespread testing) was associated with a greater impact in terms percentage of infections averted (Figure 4.1). 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, as long as positive cases comply with isolation (Figure 4.1a). With higher disease transmission (Rt=2) and high COVID-19 prevalence (1%), when the population was tested once every two weeks and test positive individuals isolated at 50% effectiveness, the percent infections averted increased from 11.3% (95% SI: 5.4% to 18.6%) when 2.5% of the population was tested to 90.3% (95% SI: 84.6% to 92.6%) when 90% were tested. Similarly, increased frequency of testing increased the impact of Ag-RDT testing. With a similar epidemic scenario and testing 20% of the population, increasing frequency of testing from once every 2 weeks to twice a week increased impact from 49.3% to 73.4% (95% SI: 63.8% to 76.7%). However, there is a plateau in the impact of Ag-RDT testing, after which more tests do not identify a higher percentage of infections.

Similarly, for the K–12 use case, an increased frequency of testing also resulted in a

larger proportion of infections averted. More widespread testing—testing all students plus all teachers—was the most effective scenario in reducing the percentage of new infections (Figure 4.1c). With testing twice weekly when disease transmission was high (*Rt*=2) and COVID-19 prevalence was high (1%), the percent of infections averted increased from 48.0% (95% SI: 47.9% to 48.0%) when all teachers and 13- to 18-year olds were tested to 73.0% (95% SI: 72.9% to 73.1%) when all teachers and students were tested. 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 (Figure 4.1d). When testing was conducted once every two weeks and both disease transmission and prevalence were high (*Rt*=2; 1%), percent infections averted increased from 15.0% (95% SI: 13.0% to 17.0%) when testing was done once every two weeks to 42.4% (95% SI: 40.5% to 44.4%) with twice weekly testing.

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 (Figure 4.1b). When COVID prevalence was 1% and an event was 3 hours long, testing the same day as an event averted 98.8% of infections (95% SI: 96.4% to 99.7%), compared to 56.4% of infections averted (95% SI: 56.4% to 65.9%) when testing was done 3 days prior.

In the case of immigrant/traveler screening, 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 (Figure 4.1e). In the LSHTM model, with 1% SAR-CoV-2 prevalence, percent infections averted increased from 48.4% (95% SI: 29.6% to 66.7%) with only Ag-RDT testing to 78.4% (70.8% to 83.1%) with an additional negative COVID-19 RT-PCR test result prior to Ag-RDT screening at the border.

When testing to exit quarantine, high frequency testing (daily testing without the need to quarantine for at least 5 days) averted the most infectious person-days, compared to a test to release strategy (individuals with positive tests will quarantine, and allows individuals to exit quarantine or isolation early with a negative test). Test to release strategies were very effective at reducing the percent of infectious days if testing induced individuals to adhere better than they would to a longer 14-day quarantine or 10-day isolation period (Figure 4.1f).

Efficiency

Efficiency was defined as the number of tests needed to avert one infection compared to the base case scenario across use cases. In general, lower frequency testing strategies are more efficient (fewer tests needed) (Figure 4.2). In terms of the community testing, lowering the frequency of testing in the community consequently increased the number of infections averted per test (Figure 4.2a). 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 reducing efficiency of 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 most epidemic conditions and testing frequencies (Figure 4.2c). The trade-off between impact and efficiency was less stark in the university setting when the *Rt* was low, and 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 of each test (Figure 4.2d).

In the mass gathering use case, 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 (Figure 4.2b). For border crossings, Ag-RDT screening only was the most efficient strategy for all three models (Figure 4.2e). When testing to exit quarantine, test to release strategies (individuals with positive tests will quarantine, and allows individuals to exit quarantine or isolation early with a negative test) were generally more efficient and utilized fewer Ag-RDT tests compared to a daily testing strategy (without the need for quarantine for at least 5 days) (Figure 4.2d). However, this efficiency comes at the expense of a smaller reduction in the percentage of infectious days averted.

Threshold analysis of Rt and COVID-19 prevalence

In general, testing strategies across most use cases were most impactful when *Rt* and/or prevalence was low and most efficient when *Rt* and/or prevalence was high, with some exceptions (Table 4.3). Testing strategies with more impact (greater percentage of infections averted) do not necessarily correspond to a greater number of infections averted (Appendix 6.8). Under widespread community testing, a high *Rt* and high prevalence necessitated a larger proportion of individuals be tested more frequently to minimize transmission (Figure 4.1a). Similarly, in mass gatherings, more testing strategies also require more tests to avert infections when *Rt* and/or prevalence are high (Figure 4.2e), but prevalence does not necessarily affect impact. The effect of COVID-19 prevalence on Ag-RDT screening at border crossings is less apparent but consistent with most of the other use cases; as COVID-19 prevalence increases, more infectious imports are averted and enter undetected (higher impact), but is also more efficient.

K-12 schools and universities had contrasting results. While both models predicted that a greater proportion of infections could be prevented under low COVID-19 prevalence, they presented 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 (Figure 4.1c and Figure 4.1d). Additionally, in the university setting, when the *Rt* is low, testing once weekly or bi-monthly would be sufficient at preventing a comparable percentage of infections to a higher frequency of testing (Figure 4.2d). When the *Rt* and prevalence are high, twice weekly testing prevented the greatest number of

infections, but required significantly more tests per averted infection. These differences are 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 *Rt* below 1.

Uncertainty across models

To compare uncertainty estimates (95% SIs) across use cases, scenarios which had similar parameters (Figure 4.3) were plotted. Some use cases do not model certain epidemic parameters (see Table 4.1 for the parameters each use case varies); thus, instead of excluding these use cases from the figure, I collapsed parameters of use cases with use cases without a parameter; i.e. I collapsed use cases with *Rt* 0.8 and use cases that did not model *Rt*; use cases with testing frequency 1x/week and use cases where frequency was not modeled. The outcomes for percent infections averted ranged from 15% [95% SI: 13% to 17%] (universities; *Rt*=1.2, prevalence=1%, frequency=1x/2 weeks) to 99.93% [95% SI: 99.89 to 99.95] (community testing; *Rt*=1.2, prevalence=0.1%; frequency=2x a week), and the simulation intervals varied slightly (Figure 4.3a). The test per averted infection ranged from 2 tests [95% SI: 1 - 3] (exiting quarantine; exposure prevalence=50%; frequency=1x to release) to 2049 tests [95% SI: 1319 - 4674] (Mass gathering; prevalence=0.1%) (Figure 4.3b).

4.4 Discussion

My results demonstrate that Ag-RDT can reduce SARS-CoV-2 infections across various use cases, and different testing strategies are needed to be most impactful (greater percentage of infections averted) and efficient (lesser number of tests per averted infection) across a range of epidemic conditions. Across use cases, increasing test frequency (and/or more widespread testing of a community) was associated with a greater percentage of infections averted. There was also a trade-off between impact (percentage of infections averted) and efficiency (number of tests per averted infection), where greater frequency and more widespread testing required more tests to avert one infection.

Moreover, the effective reproductive number (*Rt*) of SARS-CoV-2 and the prevalence of COVID-19 within the community are two influential factors in the success of a testing strategy, which suggests that testing strategies should be modified over time as *Rt* and SARS-CoV-2 prevalence changes. Similar to test frequency and proportion tested, there was also a trade-off between impact and efficiency in *Rt* and prevalence, where most testing strategies require more tests to avert infections when *Rt* and/or prevalence are low, and tests are more efficient when *Rt* and/or prevalence are high. Testing strategies across most use cases had the greatest impact when *Rt* and/or infection prevalence were low, because testing and isolation help to keep the number of cases below *Rt* of 1, since an outbreak of SARS-CoV-2 would more likely occur when *Rt* is above 1. The reduced efficiency when *Rt* and/or prevalence are high are due to the low probability of any individual testing positive when prevalence is low, and an Ag-RDT testing strategy for low COVID-19 prevalence captures fewer infectious days in the community for the same

number of tests, relative to a high prevalence setting.

These findings provide guidance to assist in determining how to allocate and optimize Ag-RDTs to reduce COVID-19 transmission and re-open societies safely: determining when schools and universities can re-open, determining when sporting events, concerts and places of worship can resume activity, reducing quarantine periods, halting outbreaks and resuming travel. Ag-RDTs, when accompanied by isolation following a positive test, have strong potential to play an important role in the control and mitigation of the COVID-19 pandemic. This is particularly beneficial in settings where access to RT-PCR testing is limited, and in cases where the turnaround time of available tests is not rapid enough to allow timely response. When resources are limited, allocation of diagnostic testing capabilities depend on whether the goal is to maximize impact or efficiency, or a combination of both. To maximize impact of Ag-RDTs, widespread and frequent testing, same-day testing, negative RT-PCR test result prior to Ag-RDT screening at the border, high adherence to quarantine, and daily frequency testing strategies should be prioritized. In contrast, more focused testing of higher risk groups, same-day testing, requiring only one Ag-RDT for border crossing, and test-to-release strategies are more valuable when maximizing efficiency. In limited resource settings where efficiency may be prioritized, testing resources may be best allocated to more defined use case settings where frequent and widespread testing can be implemented to maximize the utility of each test. Alternatively, rather than spend resources on random mass testing of the population with community testing, tests may be better spent when symptomatic or in close contact with a case. This is particularly the case if symptomatic testing demand is not yet saturated.

There has previously been limited guidance on the use of Ag-RDTs, as current WHO guidance focuses on symptomatic testing of individuals meeting COVID-19 case definition.[62] My findings provide greater support for the growing body of evidence that Ag-RDTs can significantly reduce transmission and are valuable in low prevalence settings.[63-66] There has previously been hesitance over using Ag-RDTs in low prevalence populations, due to the greater risk of false positive results (lower positive predictive value [PPV]) when prevalence is low.[67] Even so, at the population level, the feasibility of using Ag-RDTs 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.[55,64]

This study has a number of limitations. Since I compared multiple models with different structures, definite direct conclusions cannot be drawn from this study. The results of each use case cannot be fully and 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. Additionally, the models for the different use cases utilize various simplifying assumptions in order to reduce complexity, outlined in Appendix 6.6, which introduces several limitations in the interpretation of my findings. I have modeled the scenarios that would be most likely to provide insight into interventions that would facilitate epidemic control. As a balance between complexity and parsimony of the models, I could not model all possible testing scenarios, and only the ones I deemed most valuable. Additionally, the results presented only quantify the effectiveness of testing strategies

within each use case, and 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.

The results from this multi-model comparison 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. These findings emphasize the value of widespread, high frequency Ag-RDT COVID-19 testing across different settings, which are effective in reducing SARS-CoV-2 infections. In LMICs with limited resources that might have difficulty scaling up testing, efforts must be made to maximize the utility of each test by deciding who and where to focus testing effort, to optimize both impact and efficiency. The findings from this study provide an understanding of when and in what settings Ag-RDTs can best be utilized to most effectively reduce onward transmission, and such understanding is critical for global decision making and resource allocation.

4.5 Tables and Figures

Table 4.1 Details on the use case mathematical models included in the multi-model comparison.

Use case	Modelling group	Model type	Age structure	Network structure	Spatial structure	Sensitivity (95% CI)	Base case scenario
Community testing	Boston University	Compartmental model	N/A	N/A	N/A	85% (80%-90%)	No asymptomatic testing, 15% of symptomatic mild cases, 50% of severe cases, and 100% of hospitalized cases
Mass gathering	Harvard T.H. Chan School of Public Health	Bayesian statistical model	N/A	N/A	N/A	Conditional on intra-host viral load dynamics	No testing
K-12	New York University	Agent-based	Yes, divided into teachers, 5-12 yo pupils, and 13-18 yo pupils	N/A	N/A	85%	No asymptomatic testing, symptomatic testing for teachers and pupils
University	Boston University	Agent-based	Yes, continuous variable in the model	Yes, to conduct contact tracing	N/A	85%	No testing

Border crossings	Agency for Science, Technology and Research	Agent-based	N/A	N/A	N/A	80%	No testing
	Boston University	Algebraic algorithm	N/A	N/A	N/A	85%	
	London School of Hygiene and Tropical Medicine	Stochastic, Agent-based	N/A	N/A	Country-level	85%	
Exiting quarantine	London School of Hygiene and Tropical Medicine	Stochastic, Agent-based	N/A	N/A	N/A	Depends on Ct value at the time of testing, and is drawn from their individual Ct trajectory	No testing

Table 4.2 Parameters varied for each use case.

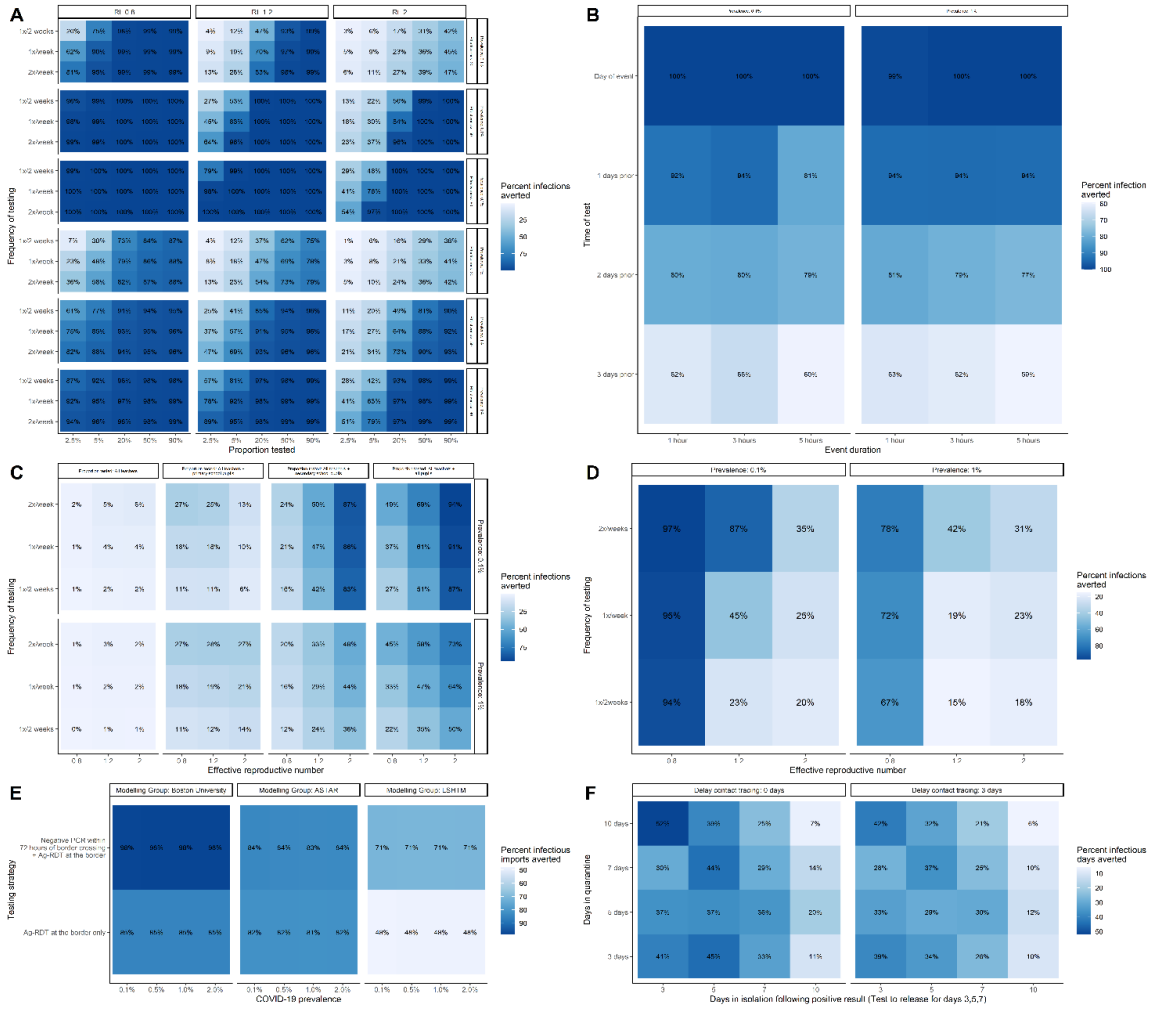
Use case	Parameter	Values
Community testing	Effective reproductive number (*Rt*)	0.8, 1.2, 2.0
	Prevalence of COVID-19	0.1%, 1%
	Proportion of community tested	2.5%, 5%, 20%, 50%, 90%
	Test frequency	Once/two weeks, once/week, twice/week
	Isolation effectiveness- reduction in number of contacts post positive test	20%, 50%, 80%
Mass gathering	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
K-12	Effective reproductive number (*Rt*)	0.8; 1.2; 2.0
	Prevalence of COVID-19	0.1%; 1%
	Groups tested	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
University	Effective reproductive number (*Rt*)	0.8; 1.2; 2.0
	Prevalence of COVID-19	0.1% or 1%
	Test frequency	Once/two weeks; once/week; twice/week
Border crossings	Prevalence of COVID-19	0.1%, 0.5%, 1.0%, 2.0%
	Test frequency	Ag-RDT on arrival alone; Ag-RDT on arrival plus a negative PCR test within 72 hours of travel
Exiting quarantine	Exposed prevalence of COVID-19	1%, 10%, 50%
	Delay to contact tracing (days)	0, 3 days
	Quarantine?	Yes, No
	Days in quarantine	0, 3, 5, 7, 10, 14 days

	Quarantine exit testing	Test to release, Daily, None
	Daily testing in quarantine (days)	1, 3, 5, 7, 10 days
	Days in isolation	1, 3, 5, 7, 10 days
	Isolation exit testing	Test to release, none

Table 4.3 Summary of the most impactful and most efficient scenarios for each Ag-RDT use case.

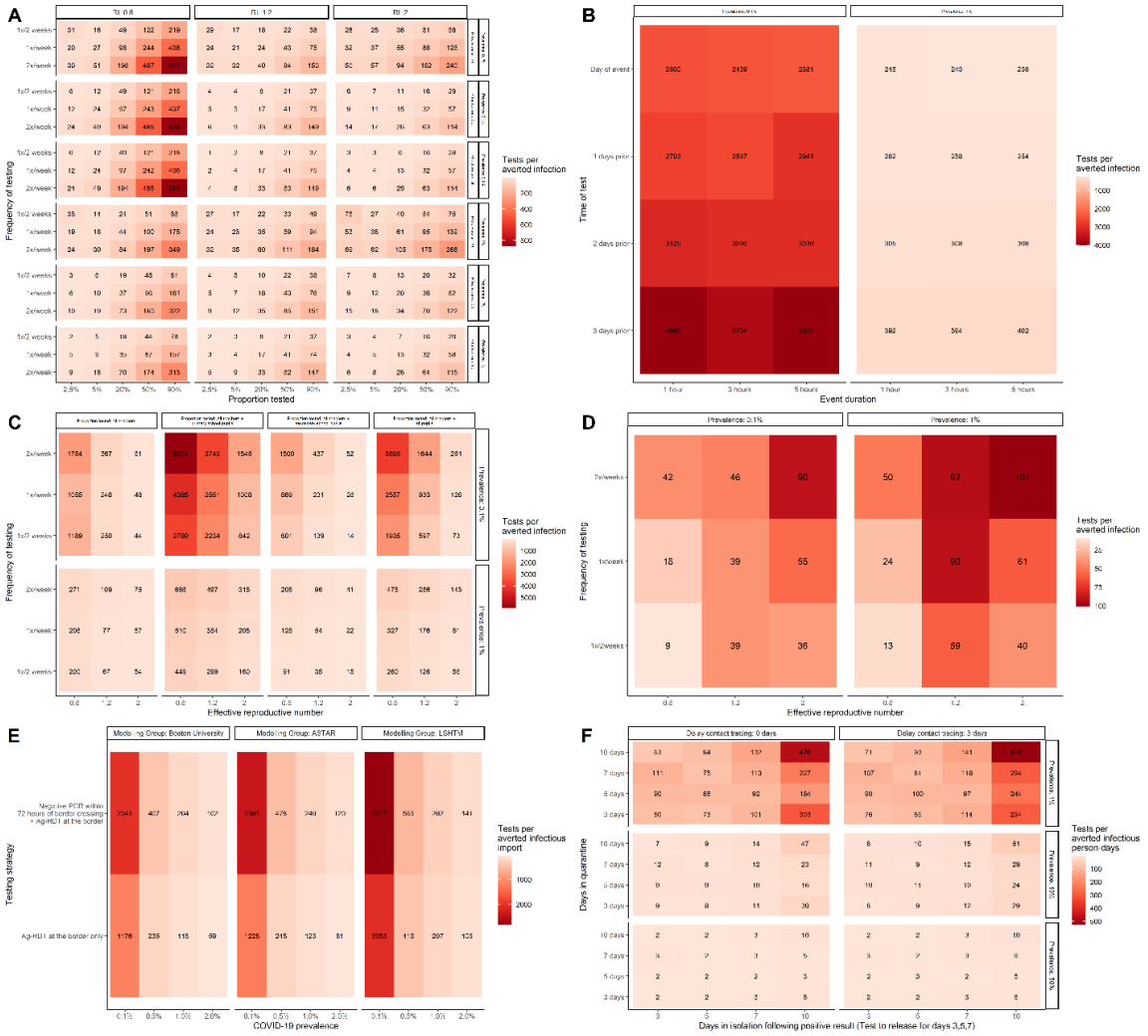
Use case	Most impactful (effective) scenarios					Most efficient scenarios				
	Rt	**Prevalence**	**Test frequency**	**Other parameter**	**Other parameter**	**Rt**	**Prevalence**	**Test frequency**	**Other parameter**	**Other parameter**
Community testing	Low (0.8)	Low (0.1%)	High (2x a week)	Test effectiveness – high (80%)	Proportion tested – high (90%)	High (2.0)	Similar for all	Low (1x every 2 weeks)	Test effectiveness – high (80%)	Proportion tested – low (2.5%)
Mass gathering		Similar for all		Duration of event – short (1 hour)	Timing of test – day of event		High (1%)		Duration of event – moderate (3 hours)	Timing of test – day of event
K-12	High (2)	Low (0.1%)	High (2x a week)	Groups tested – testing all teachers and all pupils		High (2)	High (1%)	Low (1x every 2 weeks)	Groups tested – testing all pupils aged 13-18	
University	Low (0.8)	Low (0.1%)	High (2x a week)			Low (0.8)	Low (0.1%)	Low (1x every 2 weeks)		
Border crossings (ASTAR, BUSPH, LSHTM)		High (2%)	Negative PCR + Ag-RDT at border				High (2%)	Ag-RDT at the border only		
Exiting quarantine		Exposed prevalence – similar for all	Daily testing strategy Days with daily testing – high (10 days)	Delay to contact tracing – low (0 days)	Days in quarantine – high (10 days) Days in isolation – low (3 days)		Exposed prevalence – similar for all	Test to release testing strategy Days with daily testing - low (3 days)	Delay to contact tracing – low (0 days)	Days in quarantine – moderate (5 days) Days in isolation – low (3 days)

Figure 4.1 Percent of infections averted (impact) with varying testing and epidemic parameters for use case (A) community testing (B) mass gathering (C) K–12 (D) university (E) border crossing (F) Exiting quarantine – test to release.[a]



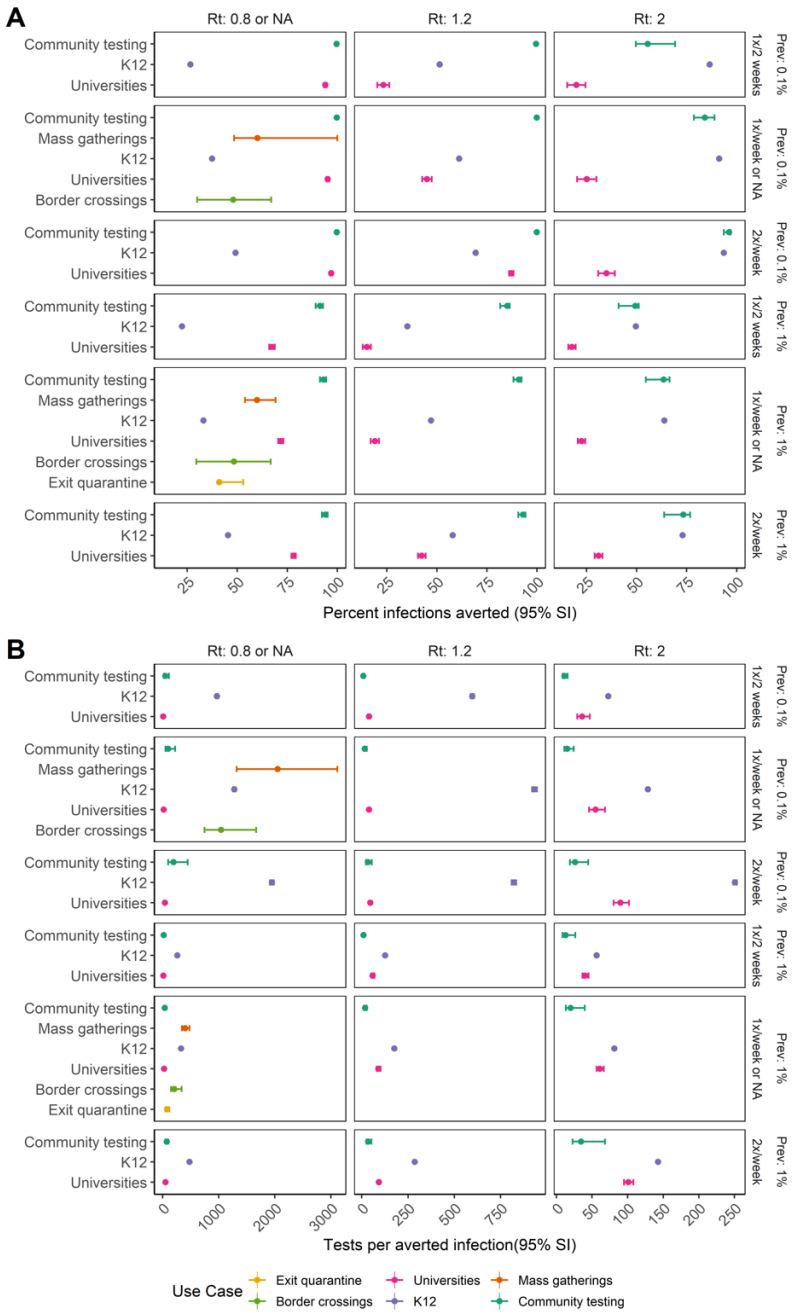
[a] shown for a 10% prevalence. There was a < 1% difference with a 1% and 50% prevalence.

Figure 4.2 Test per averted infection (efficiency) with varying testing and epidemic parameters for use case (A) community testing (B) mass gathering (C) K-12 (D) university (E) border crossing (F) Exiting quarantine – test to release.[a]



[a] shown for a 10% prevalence. There was a < 1% difference with a 1% and 50% prevalence.

Figure 4.3 Estimates and 95% simulation intervals for (A) Percent of infections averted (impact) and (B) test per averted infection (efficiency) for all use cases[a]



[a] Community testing – proportion tested: 20%, effectiveness: 50%; K12 – group tested: all teachers and students; mass gathering – time of test: 3 days before, and event duration: 5 hours; border crossing – testing strategy: only Ag-RDTs, group was LSHTM; exit quarantine - test to release, no delay in contact tracing, days in quarantine: 3, days in isolation: 3.

5 CONCLUSION

In this dissertation, I conducted three studies that inform SARS-CoV-2 surveillance, mitigation, and control policies in low and middle income countries (LMICs). In the first study, I assessed the association between mobility, as measured by smartphone data, and SARS-CoV-2 case positivity in South African provinces and districts at the ecological-level using regression, cross-correlation and interrupted time series analysis. I found that increases in mobility were positively associated with future COVID-19 incidence at both the province and district-level, and the association of mobility and COVID-19 incidence remained even when adjusted for district-level confounders. Additionally, greater SARS-CoV-2 incidence is negatively associated with future human movement. My study reiterates previous studies in several settings demonstrating the relationship between human mobility and COVID-19 outcomes. [2-5,29,30] However, to my knowledge, this is the first study to assess this association in South Africa, which implemented numerous lockdowns to limit human mobility, with the goal of reducing SARS-CoV-2 transmission through chains of contact. My findings add to the body of evidence that restricting human movement continues to be a valuable mitigation and control measure during the pandemic, and digital smartphone data can be leveraged as a measure of human mobility in LMICs.

The second and third study focused on the impact and efficiency of rapid antigen testing (Ag-RDTs) in general LMIC settings. Impact was defined as the percentage of infections averted compared to the base case scenario, and efficiency was defined as the number of tests needed to avert one infection compared to the base case scenario. In study two, I

quantified impact and efficiency of population-level community testing using Ag-RDTs. I demonstrate that frequent and widespread Ag-RDT SARS-CoV-2 testing averts a substantial percentage of infections, corresponding to high impact, but the diagnosis must be accompanied by changes in behavior, such as quarantine. A reduction in the number of contacts after diagnosis is imperative for any testing strategy to be effective. However, the number of tests needed to substantially reduce infections likely make population-wide community testing feasible only in small, defined settings, particularly in limited resource settings. Testing in conjunction with other non-pharmaceutical interventions is likely more feasible, and could have more of a substantial impact.

The third study quantified the impact of SARS-CoV-2 Ag-RDT testing strategies on COVID-19 impact and efficiency in LMICs by comparing eight mathematical models from different modeling groups. Overall, there were trade-offs in impact and efficiency; increasing test frequency (and/or more widespread testing of a community) increased impact, but decreased efficiency. Furthermore, most testing strategies require more tests to avert infections when *Rt* and/or prevalence are low, and tests are more efficient when *Rt* and/or prevalence are high. These findings provide guidance in determining how to allocate and optimize Ag-RDTs to reduce COVID-19 transmission and re-open societies safely. Allocation of diagnostic testing capabilities depend on whether the goal is to maximize impact or efficiency, or a combination of both. In limited resource settings where efficiency is prioritized, testing resources may be best allocated to more defined use case settings where frequent and widespread testing can be implemented to maximize the utility of each test.

The second and third study adds to the body of evidence that Ag-RDTs can significantly reduce transmission and are valuable in low prevalence settings.[63-66] These results emphasize the value of widespread, high frequency Ag-RDT COVID-19 testing across different settings, which are effective in reducing SARS-CoV-2 infections. In LMICs that might have difficulty scaling up testing, efforts must be made to maximize the utility of each test by deciding on whether the goal is to maximize impact or efficiency. When efficiency is prioritized, testing resources may be best focused to more defined use case settings where frequent and widespread testing can be implemented to maximize the utility of each test, rather than population-wide community testing which would require a large amount of resources.

In conclusion, it is imperative to continue implementing mitigation and control measures that reduce SARS-CoV-2 transmission, such as NPIs and diagnostic testing strategies. This is particularly valuable in LMICs that have limited access to COVID-19 vaccines, particularly as new variants emerge that may evade vaccine-induced immunity.[52,53] The evidence generated from these studies provide further understanding critical for global pandemic decision making and resource allocation, which can be used for future SARS-CoV-2 resurgences, or adapted for use in future infectious disease outbreaks or pandemics.

6 APPENDICES

Appendix 6.1. Differential equations for the adapted compartmental model.†

$$\frac{dS_x}{dt} = -\Phi_x S_x$$

$$\frac{dE_x}{dt} = \Phi_x S_x - \gamma_1 E_x$$

$$\frac{dI_{A_x}}{dt} = p_a \gamma_1 E_x - [(1 - p_{ta})] r_1 I_{A_x} - p_{ta} se_i \varphi I_{A_x}$$

$$\frac{dI_{P_x}}{dt} = (1 - p_a)\gamma_1 E_x - [(1 - p_{ta})]\, \gamma_2 I_{P_x} - p_{ta} se_i \varphi I_{P_x}$$

$$\frac{dI_{M_x}}{dt} = [(1 - p_{tm}) + (1 - se_i)(p_{tm})] p_{m_x} \gamma_2 I_{P_x} - [(1 - p_{tm})(p_{tm})] r_2 I_{M_x} - p_{tm} se_i \varphi I_{M_x}$$

$$\frac{dI_+}{dt} = p_{ta} se_i \varphi I_{A_x} + p_{ta} se_i \varphi I_{P_x} + p_{tm} se_i \varphi I_{M_x} - \varrho_i recover I_{+_x}$$

$$\frac{dI_{S_x}}{dt} = [(1 - p_{ta})]\big(1 - p_{m_x}\big)\gamma_2 I_{P_x} - [(1 - p_{ts})]\tau_s I_{S_x} - p_{ts} se_s \varphi I_{S_x}$$

$$\frac{dI_{S+}}{dt} = p_{ts} se_s \varphi I_{S_x} - \varrho_i \tau_s I_{S_+}$$

$$\frac{dH_{1_x}}{dt} = [(1 - p_{ts})\,]\left(1 - \frac{p_{c_x}}{\big(1 - p_{m_x}\big)}\right)\tau_s I_{S_x} + \varrho_i \left(1 - \frac{p_{c_x}}{\big(1 - p_{m_x}\big)}\right)\tau_s I_{S_+} - [(1 - p_{th})] r_3 H_{1_x} - p_{th} se_h \varphi H_{1_x}$$

$$\frac{dH_{2_x}}{dt} = [(1 - p_{ts})] \frac{p_{c_x}}{\big(1 - p_{m_x}\big)} \tau_s I_{S_x} + \varrho_i \left(\frac{p_{c_x}}{\big(1 - p_{m_x}\big)}\right)\tau_s I_{S_+} - [(1 - p_{th})]\tau_p H_{2_x} - p_{th} se_h \varphi H_{2_x}$$

$$\frac{dH_{+_x}}{dt} = p_{th} se_h \varphi [H_{1_x} + H_{2_x}]$$

$$\frac{dC_{1_x}}{dt} = [(1 - p_{th})] d_{c_x} \tau_p H_{2_x} - \mu C_{1_x}$$

$$\frac{dC_{2_x}}{dt} = [(1 - p_{th})(p_{th})]\big(1 - d_{c_x}\big)\tau_p H_{2_x} - r_4 C_{2_x}$$

$$\frac{dH_{3_x}}{dt} = r_4 C_{2_x} - r_5 H_{3_x}$$

$$\frac{dR_x}{dt} = [(1 - p_{ti})] r_1 I_{A_x} + [(1 - p_{ti})] r_2 I_{M_x} + [(1 - p_{th})]\big(1 - d_{s_x}\big) r_3 H_{1_x} + r_5 H_{3_x} + \varrho_i I_{+_x}$$

$$\Phi_x * = \frac{\beta_x \delta_{x,t}\big(\zeta I_{A_x} + I_{P_x} + I_{M_x} + I_{S_x} + \Lambda\, I_+ + \Lambda\, I_{S_+}\big)}{N_x}$$

†List of symbols and corresponding parameter details are outlined in supplementary appendix 2.

*force of infection

Appendix 6.2. Model parameters.

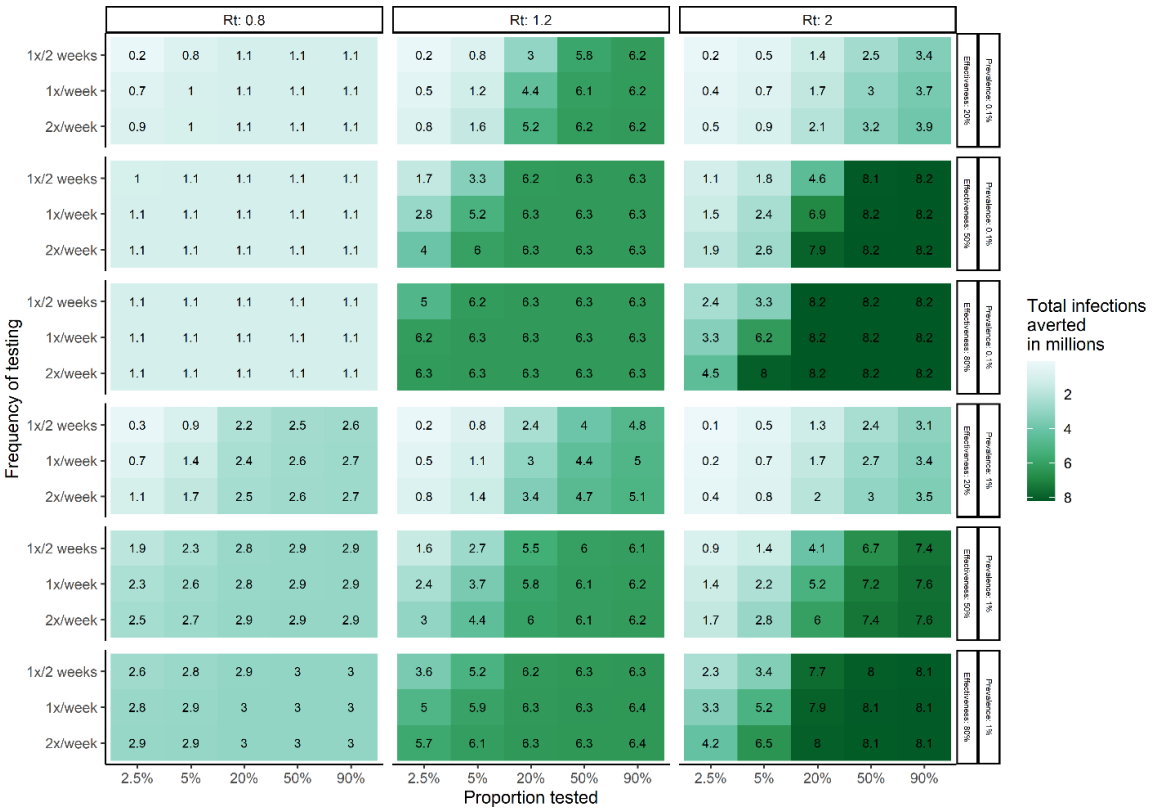
Constant parameters					
Symbol	**Details**	**Mode**	**Lower Bound**	**Upper Bound**	**Source**
γ_1	1/incubation period (years^{-1})	91.25	60.83	182.5	[39,40]
γ_2	1/dur presymp infectious (years^{-1})	182.5	121.666667	365	[39,40]
r_1	1/dur infectiousness (asymptomatic) (years^{-1})	52.143	45.625	60.83	[39,40]
r_2	1/dur infectiousness (mild untreated) (years^{-1})	73.000	60.83	91.25	[39,40]
μ	1/time to death (years^{-1})	73	60.83	91.25	[39,40]
τ_s	1/trt seeking severe cases (years^{-1})	73	60.83	91.25	[39,40]
p_a	proportion of cases that will be asymptomatic	0.31	0.24	0.38	[39,40]
p_m	proportion of symptomatic cases that are mild	0.95	0.76	1.14	[39,40]
p_s	proportion of symptomatic cases that are severe	0.035	0.028	0.042	[39,40]
p_c	proportion of symptomatic cases that will be critical	0.015	0.012	0.018	[39,40]
$\mathbf{d_{cx}}$	proportion of critical cases that die	0.26	0.208	0.312	[39,40]
τ_p	1/duration of progress to ICU (years^{-1})	91.25	73	182.5	[39,40]
ζ	relative infectiousness of asymptomatic	0.75	0.7	0.8	[42]
r_3	1/dur stay in hosp (severe) (years^{-1})	30.42	26.07	45.625	[39,40]
r_4	1/dur stay in hosp (critical) (years^{-1})	22.8125	20.28	26.07	[39,40]

r_5	1/dur stay in hosp (post critical) (years^{-1})	121.67	91.25	182.5	[39,40]
β_x	effective contacts per year	176.3758389	169.8434	182.908277	[39,40]
se	sensitivity of Ag-RDT	0.85	0.80	0.90	[41,68]
ϱ_i	1/dur infectiousness (tested mild) (years^{-1})	Calculated to equal the length of time undiagnosed mild cases are infective in the model			

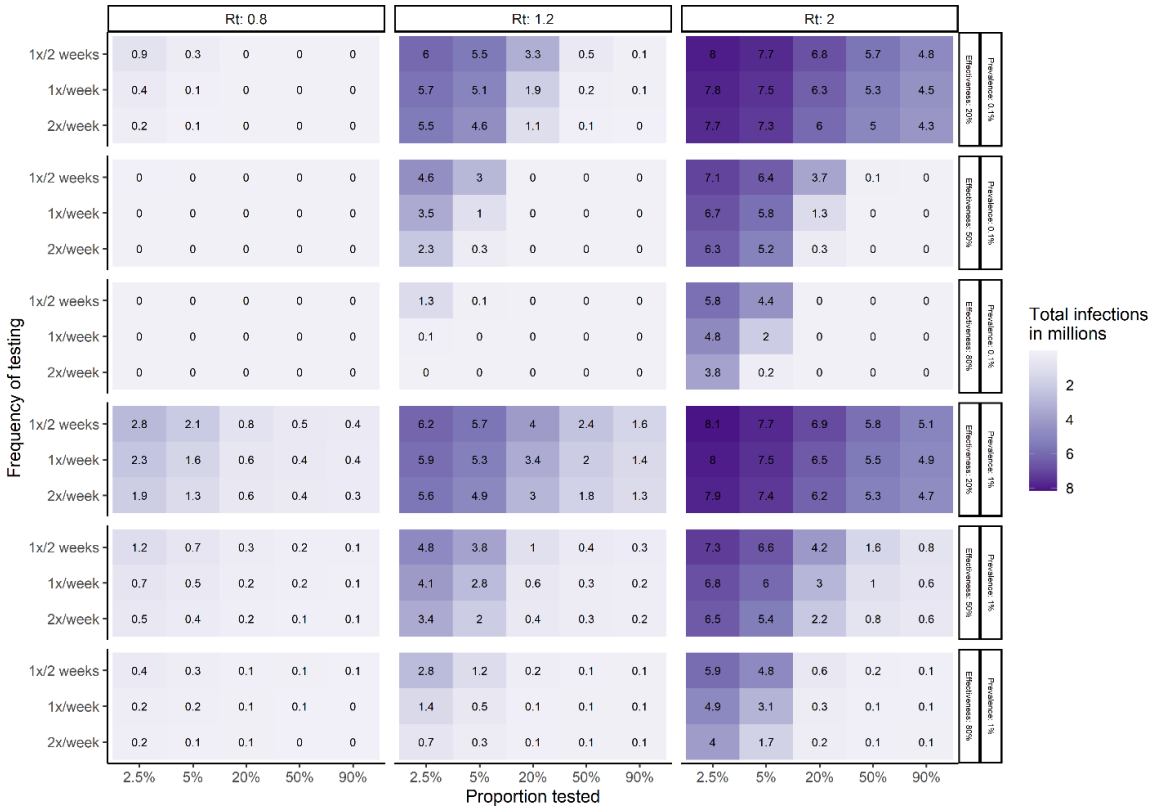
Varied parameters

Symbol	Details	Value
p_{ta}	probability of getting tested if mildly infected	0.25, 0.05, 0.20, 0.50, or 0.90 (proportion of community tested parameter)
p_{tm}	probability of getting tested if mildly infected	0.25, 0.05, 0.20, 0.50, or 0.90 (proportion of community tested parameter) + 0.15 (base case)
p_{ts}	probability of getting tested if severely infected	0.25, 0.05, 0.20, 0.50, or 0.90 (proportion of community tested parameter) + 0.50 (base case)
p_{th}	probability of getting tested if hospitalized (proportion of community tested)	1
Λ	relative infectiousness of diagnosed infections (Isolation effectiveness)	0.20, 0.50, or 0.80
φ	1/turn around time of Ag-RDT (frequency)	104.29 (frequency 1x/ 2 weeks), 52.14 (1x/ week), or 26.07 (frequency 2x/week)

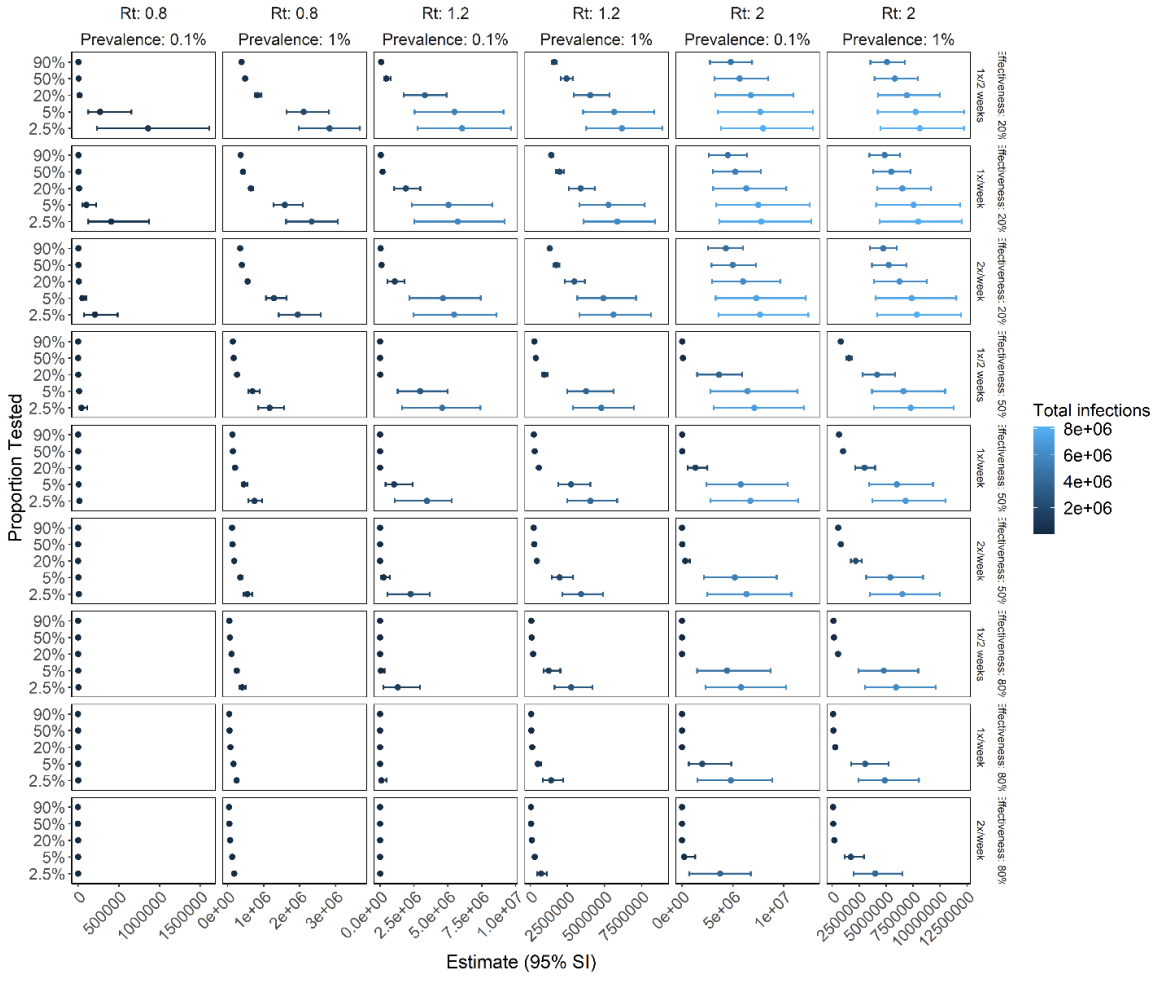
Appendix 6.3. Total infections averted with varying frequency of testing, effective reproductive number (Rt), COVID-19 prevalence, and isolation effectiveness (reduction in the force of infection when diagnosed) for a community testing strategy at various proportions of the community tested.



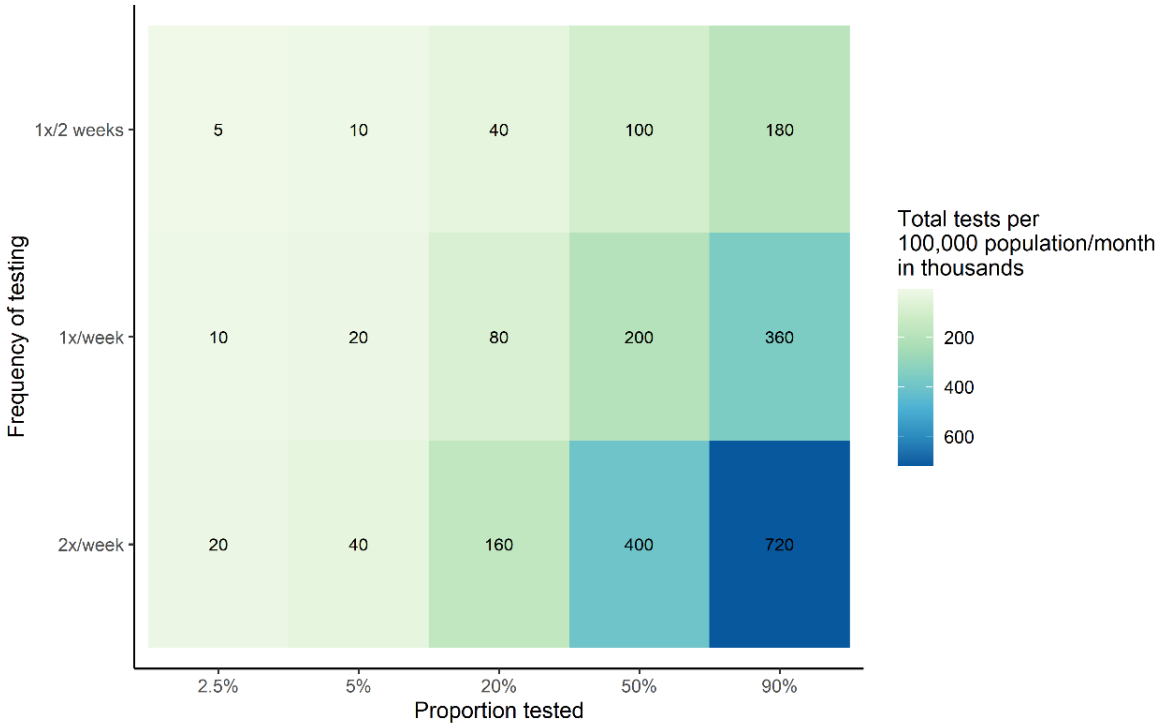
Appendix 6.4. Total infections with varying frequency of testing, effective reproductive number (Rt), COVID-19 prevalence, and isolation effectiveness (reduction in the force of infection when diagnosed) for a community testing strategy at various proportions of the community tested (total modeled population = 10 million).



Appendix 6.5. Estimate and 95% simulation intervals (SIs) for the total cumulative number of infections at the end of 365 days across various intervention scenarios (total modeled population = 10 million).



Appendix 6.6. Total tests per 100,000 population per month with varying frequency and proportion of testing.



Appendix 6.7. Background and approach of the different mathematical models for all use cases

Community testing

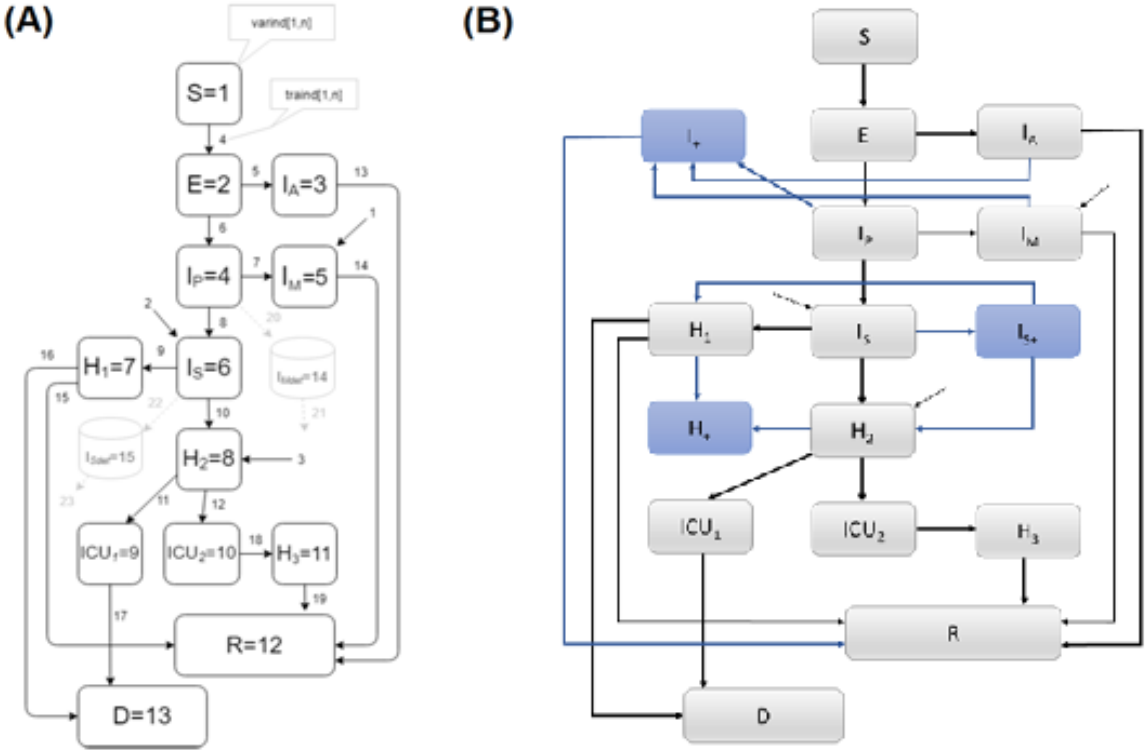
Background

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. Appendix 6.7 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.



Appendix 6.7.1. (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, IS_+–Severe infections diagnosed, H_+–Hospitalizations diagnosed

In this use case, I assume a base case Ag-RDT testing scenario in which there is no large-scale asymptomatic community testing, and I only test 15% of symptomatic mild cases, 50% of severe cases, and 100% of hospitalized cases. I assessed the effect of additional percentages of Ag-RDT testing in the whole population, on top of the base case testing proportions. I 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 2**). To be realistic, the model does not assume a contact tracing infrastructure, given the substantial human resource burden. Additionally, I 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)

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 one-time events (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.

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 (**Supplemental Appendix 1 Table 1**). 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.

Appendix 6.7.2. Total denominator population of each scenario (representative of 1/5th of all schools in Malawi)[12–16]

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

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 symptomatic 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 2**). All scenarios were compared to counterfactual base cases with the same epidemic parameters and symptomatic 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. 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 Ag-RDT was assumed to be 85%.

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 2**, 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.

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 2**, 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. Daily travel volume was set at 100,000 individuals. The sensitivity for the BUSPH, ASTART, and LSHTM model were 85%, 80%, and 85% respectively. For the BUSPH model, the 72-hour pre-PCR sensitivity was assumed to be 88%[24], while the 72-hour pre-PCR sensitivity was based on viral load distribution in the other two models.

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 account for 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 (Appendix 6.6.1 Table 2). 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.

Appendix 6.7.3 Table 2. Main scenarios

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

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 account for assumed enhanced adherence from a reduction in the quarantine/isolation requirement (Appendix 6.6.4**)**

Appendix 6.7.4 Table 3. Adherence adjustments

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%	/

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]

Model simulations were run in R using the parameters shown in **Table 2**, 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.

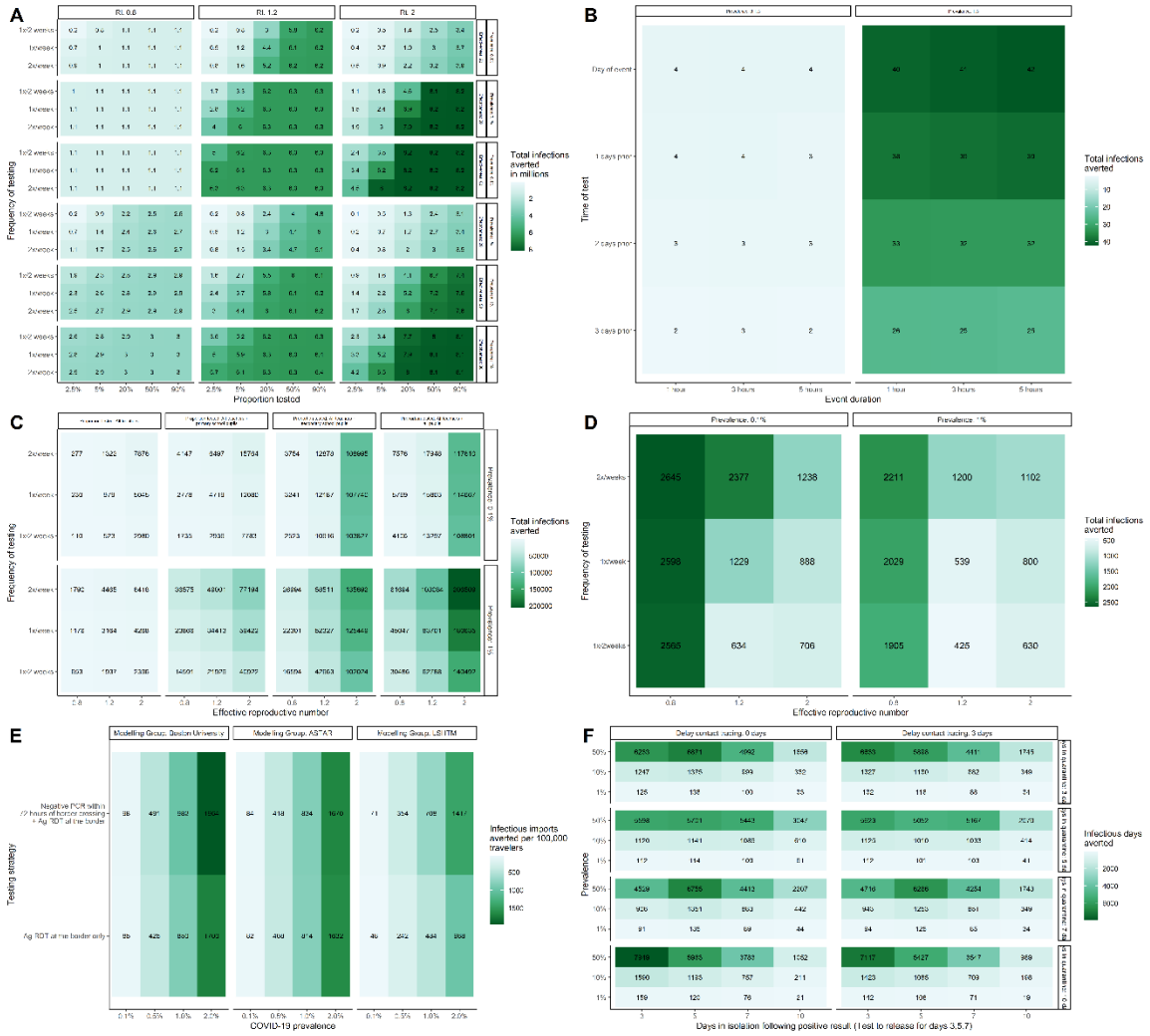
Appendix 6.8. Parameter and assumptions for all the models for all use cases

		Use cases							
Parameter group	**Parameter**	**Community testing**	**Mass gathering**	**K-12**	**University**	**Border crossings (ASTAR)**	**Border crossings (BUSPH)**	**Border crossings (LSHTM)**	**Exiting quarantine**
Infectious-ness/ duration	Time from point of infection to onset of symptoms (days)	2 (1-3)	Proliferation time 2.7 (1.2, 3.8)	5 days	1.1 days (τsym ~ lognormal (1.1, 0.9)	3-14 days	N/A	5.1 days (95%: 2.3, 11.5 days)	5.1 days (95%: 2.3, 11.5 days)
	Duration of infectiousness for asymptomatic cases (days)	7 (6-8)	N/A	N/A	8 days τra ~ lognormal (8.0, 2.0)	11-12 days	N/A	Duration of infectiousness for symptomatic cases	N/A
	Duration of infectiousness for mild cases (days)	5 (4-6)	Clearance time 7.4 (3.9, 9.6)	N/A	8 days τra ~ lognormal(8.0, 2.0)	Not differentiated	N/A	17 days (SD 0.94 days)	17 days (SD 0.94 days)
	Duration of infectiousness for severe cases (days)	5 (4-6)	Clearance time 7.4 (3.9, 9.6)	N/A	18.1 days τrs ~ lognormal (18.1, 6.3)	Not differentiated	N/A	17 days (SD 0.94 days)	17 days (SD 0.94 days)
	Duration of pre-symptomatic infectiousness	4 (2-6)	N/A	1-4 days	1 day τsym ~ lognormal (1.1, 0.9)	4 days before symptom onset	N/A	Individual infectivity conditional upon culture probability given viral load	Individual infectivity conditional upon culture probability given viral load
	Relative infectiousness of asymptomatic & pre-symptomatic cases compared to symptomatic cases	0.75 (0.7-0.8)	N/A	N/A	1	0.5	N/A	60%	60%
Severity	Proportion of cases that are asymptomatic	0.75 (0.7-0.8)	N/A	26 - 39%	Dependent on age	0.5	N/A	31% (24-38%)	31% (24-38%)
	Proportion of cases that are mild	0.2375 (0.23-0.24)	N/A	N/A	Dependent on age	N/A	N/A	N/A	N/A
	Proportion of cases that are severe	0.0125 (0.01-0.07)	N/A	N/A	Dependent on age	N/A	N/A	N/A	N/A
Treatment	Proportion of mild cases that seek treatment (outpatient)	N/A	N/A	N/A	0	N/A	N/A	N/A	N/A

	Proportion of severe cases that seek treatment (hospitalised)	0.6 (0.4-0.7)	N/A	N/A	Dependent on age	N/A	N/A	N/A	N/A
	Average days from symptom onset to treatment seeking for mild cases	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Average days from symptom onset to hospitalisation for severe cases	5 (4-6)	N/A	N/A	6.6 days (τsev ~ lognormal (6.6, 4.9))	N/A	N/A	N/A	N/A
Interven-tion assumption	Are there any interventions in place in the community (i.e. lockdown, social distancing, masks, vaccinations)?	Isolation with COVID-19 positive diagnosis	No	Masks, 6-foot social distancing, ventila-tion, hand-hygiene, class rotation, symptom screening	We can specify	Unspecified	Lock-downs, social distancing, mask-use	N/A	N/A
	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	N/A	Reduced secondary attack rate (SAR)	Reduction in beta, or reduction in network connectivity	Reduction in Rt	Reduction in Rt	N/A	N/A
	Are there any interventions in place in the use case (i.e. lockdown, social distancing, masks, vaccinations)?	Use case is same as the community	No	N/A	We can specify	Unspecified	N/A	(1) Pre-flight testing: no testing, PCR test, Lateral flow test (LFT) test. (2) Quarantine and/or testing on arrival..	(1) Test to release from quarantine: (2) Daily testing in lieu of quarantine (3) Self-isolation
	How are you representing these interventions (reduction in Rt, reduced proportion of	Use case is same as the community	N/A	N/A	Reduction in beta, or reduction in network connectivity	Reduction in Rt	N/A	Reduction in R of infectious arrivals	Effectiveness determined by the proportion of infectious distribution (from

	susceptible, reduction in network connectivity?)								culture) spent in quarantine or isolation
Contact rates	Average daily contact	0.483 (0.465-0.501)	N/A	9 to 13	N/A	N/A	N/A	N/A	N/A
	Probability of infection given an infectious contact	N/A	N/A	18.10%	N/A	N/A	N/A	N/A	N/A
	Transmission rate (beta)	*Rt*/average daily contact	N/A	$f(t) = (1/\Gamma(k)\theta k) * tk-1e-t/\theta$	0.16	N/A	N/A	N/A	N/A
Testing	Time from test to result (minutes/hours/days/ or assumed 'immediate')	Immediate	N/A	1 day	N/A	1 to 12 hours	Immediate	Assumed immediate	Assumed immediate
	Proportion of people in the use case that get tested	1%, 5%, 20%, 50%, and 90%	N/A	10, 20% / 10%, 20%, 100%	N/A	N/A	0% – 100%	0-100%	100%
	Frequency of testing	1x/week, 2x/week, and 1x/2 weeks	N/A	Monthly / Weekly	N/A	every 24 hours and above	Once at border	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)	Scenario dependent
	Criteria for accessing a test (e.g. in widespread community testing, is it age targeted, or symptomatic only?)	Widespread community testing	N/A	Randomly allocated surveillance testing	N/A	N/A	Randomly allocated to border crossers	Air-travel and quarantine	Scenario dependent. Upon symptom onset, or exit from quarantine, or daily in lieu of quarantine
	Time to return to testing pool after testing positive	Immunity assumed for the rest of the time period	N/A	2 weeks	None, after testing positive they go on to recover	N/A	N/A	N/A	N/A

Appendix 6.9. Number of infections averted with varying testing and epidemic parameters for use case (A) community testing (B) mass gathering (C) K–12 (D) university (E) border crossing (F) Exiting quarantine – test to release.[a]



[a] shown for a 10% prevalence. There was a < 1% difference with a 1% and 50% prevalence.

7 REFERENCES

1. COVID-19 modelling update: Considerations for a potential third wave 2021; https://www.nicd.ac.za/wp-content/uploads/2021/05/SACMC-Third-wave-report-290421.pdf. Accessed 2021, May 16.
2. Sy KTL, Martinez ME, Rader B, White LF. Socioeconomic Disparities in Subway Use and COVID-19 Outcomes in New York City. *American Journal of Epidemiology.* 2021;190(7):1234–1242. https://doi.org/10.1093/aje/kwaa277
3. Yechezkel M, Weiss A, Rejwan I, Shahmoon E, Ben-Gal S, Yamin D. Human mobility and poverty as key drivers of COVID-19 transmission and control. *BMC Public Health.* 2021;21(1):596.
4. Nouvellet P, Bhatia S, Cori A, et al. Reduction in mobility and COVID-19 transmission. *Nature Communications.* 2021;12(1):1090.
5. Kissler SM, Kishore N, Prabhu M, et al. Reductions in commuting mobility predict geographic differences in SARSCoV-2 prevalence in New York City. 2020. http://nrs.harvard.edu/urn-3:HUL.InstRepos:42665370
6. Guglielmi G. The explosion of new coronavirus tests that could help to end the pandemic. *Nature* 2020;583:506–509 https://www.nature.com/articles/d41586-020-02140-8. Accessed November 30, 2021.
7. Vandenberg O, Martiny D, Rochas O, van Belkum A, Kozlakidis Z. Considerations for diagnostic COVID-19 tests. *Nature Reviews. Microbiology.* 2021;19(3):171-183.

8. World Health Organization. Antigen-detection in the diagnosis of SARS-CoV-2 infection using rapid immunoassays. 2020; https://www.who.int/publications/i/item/antigen-detection-in-the-diagnosis-of-sars-cov-2infection-using-rapid-immunoassays. Accessed May 17, 2021.

9. Pavelka M, Van-Zandvoort K, Abbott S, et al. The impact of population-wide rapid antigen testing on SARS-CoV-2 prevalence in Slovakia. *Science.* 2021;372(6542): 635–641.

10. Testing in England. Virus tests conducted. 2021; https://coronavirus.data.gov.uk/details/testing?areaType=nation&areaName=England.

11. Busk PK, Kristiansen TB, Engsig-Karup A. Assessment of the National Test Strategy on the Development of the COVID-19 Pandemic in Denmark. *Epidemiologia.* 2021;2(4).

12. Center for Systems Science and Engineering at Johns Hopkins University. COVID-19 Dashboard. https://coronavirus.jhu.edu/map.html.

13. Miller JC. Spread of infectious disease through clustered populations. *Journal of The Royal Society. Interface.* 2009;6(41):1121–1134.

14. Mei S, Chen B, Zhu Y, Lees MH, Boukhanovsky AV, Sloot PMA. Simulating city-level airborne infectious diseases. *Computers, Environment and Urban Systems.* 2015;51:97–105.

15. Smieszek T, Fiebig L, Scholz RW. Models of epidemics: when contact repetition and clustering should be included. *Theoretical Biology and Medical Modelling.* 2009;6(1):11.

16. Delamater P, Street E, Leslie T, Yang YT, Jacobsen K. Complexity of the Basic Reproduction Number (R0). *Emerging Infectious Diseases.* 2019;25(1):1–4. https://dx.doi.org/10.3201%2Feid2501.171901

17. *Moya Application* [computer program].

18. Bajema KL, Wiegand RE, Cuffe K, et al. Estimated SARS-CoV-2 Seroprevalence in the US as of September 2020. *JAMA Internal Medicine.* 2021;181(4):450–460.

19. Data Science for Social Impact research group. Coronavirus COVID-19 (2019-nCoV) Data Repository for South Africa. 2022; https://github.com/dsfsi/covid19za.

20. National Institute for Communicable Diseases. COVID-19 Testing Summary. 2020. nicd.ac.za. Accessed October 27, 2020.

21. Zeng C, Zhang J, Li Z, et al. Spatial-Temporal Relationship Between Population Mobility and COVID-19 Outbreaks in South Carolina: Time Series Forecasting Analysis. *Journal of Medical Internet Research.* 2021;23(4):e27045.

22. Liebhold A, Koenig WD, Bjørnstad ON. Spatial Synchrony in Population Dynamics. *Annual Review of Ecology, Evolution, and Systematics.* 2004;35(1): 467–490.

23. Brockwell PJ, Davis RA. *Time Series: Theory and Methods, second edition.* New York, Inc.: Springer-Verlag; 1991.

24. Bernal JL, Cummins S, Gasparrini A. Interrupted time series regression for the evaluation of public health interventions: a tutorial. *International Journal of Epidemiology*. 2017;46(1):348–355.

25. Bernal JL, Cummins S, Gasparrini A. Interrupted time series regression for the evaluation of public health interventions: a tutorial. *International Journal of Epidemiology*. 2016;46(1):348–355.

26. *R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing* [computer program]. Vienna, Austria 2017

27. Statistics South Africa. Mid-year population estimates 2019. https://www.statssa.gov.za/publications/P0302/P03022019.pdf.

28. Code for Africa. African Covid-19 Vulnerability Index (ACVI). 2022; https://africaopendata.org/dataset/africa-covid-19-vulnerability-index.

29. Nagata S, Nakaya T, Adachi Y, et al. Mobility Change and COVID-19 in Japan: Mobile Data Analysis of Locations of Infection. *Journal of Epidemiology*. 2021; 31(6):387–391.

30. Nouvellet P, Bhatia S, Cori A, et al. Reduction in mobility and COVID-19 transmission. *Nature Communications.* 2021;12(1):1090.

31. Potgieter A, Fabris-Rotelli IN, Kimmie Z, et al. Modelling Representative Population Mobility for COVID-19 Spatial Transmission in South Africa. *Frontiers in Big Data.* 2021;4:718351.

32. Number of smartphone users in South Africa from 2014 to 2023 (in millions). 2021; https://www.statista.com/statistics/488376/forecast-of-smartphone-users-in-south-africa/. Accessed May 16, 2021.

33. Health Budget Brief South Africa. 2018/2019. https://www.unicef.org/esa/sites/unicef.org.esa/files/2019-03/UNICEF-South-Africa-2018-Health-Budget-Brief.pdf.

34. Government SA. COVID-19 / Novel Coronavirus. 2021; https://www.gov.za/Coronavirus.

35. America IDSo. Nucleic Acid Amplification Testing (e.g. RT-PCR). 2021; https://www.idsociety.org/covid-19-real-time-learning-network/diagnostics/RT-pcr-testing/. Accessed November 30, 2021.

36. Corman VM, Landt O, Kaiser M, et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. *Eurosurveillance.* 2020;25(3):2000045.

37. Gill M, Gray M. Mass testing for covid-19 in the UK. *BMJ: British Medical Journal.* 2020;371:m4436.

38. Viana R, Moyo S, Amoako DG, et al. Rapid epidemic expansion of the SARS-CoV-2 Omicron variant in southern Africa. *Nature.* 2022. https://doi.org.10.1038/s41586-022-04411-y

39. South African COVID-19 Modelling Consortium. National COVID Epidemiology Model (NCEM). 2020; https://sacovid19mc.github.io/supplementaryInformation.

40. National Institute of Communicable Disease. *South African COVID-19 Modelling Consortium. NCEM Provincial Model Code Guide.* South African COVID-19 Modelling Consortium; 2021.

41. Foundation for Innovative Diagnostics (FIND). FIND Evaluation of SD Biosensor, Inc. STANDARD Q COVID-19 Ag Test: External Report. FIND. 2020. https://www.finddx.org/wp-content/uploads/2020/12/SDQ-Ag-Public-Report_20201210-v2-1.pdf.

42. Buitrago-Garcia D, Egli-Gany D, Counotte MJ, et al. Occurrence and transmission potential of asymptomatic and presymptomatic SARS-CoV-2 infections: A living systematic review and meta-analysis. *PLoS Medicine.* 2020;17(9):e1003346.

43. den Boon S, Jit M, Brisson M, et al. Guidelines for multi-model comparisons of the impact of infectious disease interventions. *BMC Medicine.* 2019;17(1):163.

44. *The ACT-Accelerator. The ACT-Accelerator Strategic Plan & Budget, October 2021 to September 2022.* 2021.

45. The White House. FACT SHEET: President Biden Announces New Actions to Protect Americans and Help Communities and Hospitals Battle Omicron. 2021; https://www.whitehouse.gov/briefing-room/statements-releases/2021/12/21/fact-sheet-president-biden-announces-new-actions-to-protect-americans-and-help-communities-and-hospitals-battle-omicron/.

46. Smith LE, Potts HWW, Amlôt R, Fear NT, Michie S, Rubin GJ. Adherence to the test, trace, and isolate system in the UK: results from 37 nationally representative surveys. *BMJ: British Medical Journal.* 2021;372:n608.

47. Mahase E. Covid-19: Mass testing in Slovakia may have helped cut infections. *BMJ: British Medical Journal.* 2020;371:m4761.

48. Bosetti P, Kiem CT, Yazdanpanah Y, et al. Impact of mass testing during an epidemic rebound of SARS-CoV-2: a modelling study using the example of France. *Eurosurveillance.* 2021;26(1):2001978.

49. Bootsma M, Kretzschmar M, Rozhnova G, Heesterbeek J, Kluytmans J, Bonten M. Regular universal screening for SARS-CoV-2 infection may not allow reopening of society after controlling a pandemic wave. *medRxiv.* https://doi.org/10.1101/2020.11.18.20233122

50. Fontanet A, Tondeur L, Grant R, et al. SARS-CoV-2 infection in schools in a northern French city: a retrospective serological cohort study in an area of high transmission, France, January to April 2020. *Eurosurveillance.* 2021;26(15): 2001695.

51. Madewell ZJ, Yang Y, Longini IM, Jr, Halloran ME, Dean NE. Household Transmission of SARS-CoV-2: A Systematic Review and Meta-analysis. *JAMA Network Open.* 2020;3(12):e2031756-e2031756.

52. Cele S, Jackson L, Khan K, et al. SARS-CoV-2 Omicron has extensive but incomplete escape of Pfizer BNT162b2 elicited neutralization and requires ACE2 for infection. *medRxiv.* 2021. https://doi.org/10.1101/2021.12.08.21267417

53. Pfizer and BioNTech Provide Update on Omicron Variant. 2021; https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-provide-update-omicron-variant.

54. Unitaid. Cost of rapid COVID-19 tests halved as global investment ensures availability of high volumes for low- and middle-income countries. 2022; https://unitaid.org/news-blog/cost-of-rapid-covid-19-tests-halved-as-global-investment-ensures-availability-of-high-volumes-for-low-and-middle-income-countries/#en.

55. Mina MJ, Parker R, Larremore DB. Rethinking Covid-19 Test Sensitivity — A Strategy for Containment. *New England Journal of Medicine.* 2020;383(22):e120.

56. Foundation for Innovative Diagnostics (FIND). ACT-Accelerator Access to COVID-19 Tools. 2020; https://www.finddx.org/covid-19/act-accelerator.

57. Menzies NA, Gomez GB, Bozzani F, et al. Cost-effectiveness and resource implications of aggressive action on tuberculosis in China, India, and South Africa: a combined analysis of nine models. *The Lancet. Global Health.* 2016;4(11):e816–e826.

58. Eaton J, Menzies N, Stover J, et al. How should HIV programmes respond to evidence for the benefits of earlier treatment initiation? A combined analysis of twelve mathematical models. 2013. World Health Organization. https://apps.who.int/iris/handle/10665/93524

59. Keebler D, Revill P, Braithwaite S, et al. Cost-effectiveness of different strategies to monitor adults on antiretroviral treatment: a combined analysis of three mathematical models. *The Lancet. Global Health.* 2014;2(1):e35–e43.

60. Borchering RK, Viboud C, Howerton E, et al. Modeling of Future COVID-19 Cases, Hospitalizations, and Deaths, by Vaccination Rates and Nonpharmaceutical

Intervention Scenarios - United States, April-September 2021. *MMWR: Morbidity and Mortality Weekly Report.* 2021;70(19):719–724.

61. Shea K, Runge MC, Pannell D, et al. Harnessing multiple models for outbreak management. *Science.* 2020;368(6491):577–579.

62. World Health Organization. Recommendations for national SARS-CoV-2 testing strategies and diagnostic capacities. Interim Guidance. 2021. https://apps.who.int/iris/bitstream/handle/10665/342002/WHO-2019-nCoV-lab-testing-2021.1-eng.pdf?sequence=1&isAllowed=y.

63. Peeling RW, Olliaro PL, Boeras DI, Fongwen N. Scaling up COVID-19 rapid antigen tests: promises and challenges. *The Lancet. Infectious Diseases.* 2021; 21(9):e290–e295.

64. Larremore DB, Wilder B, Lester E, et al. Test sensitivity is secondary to frequency and turnaround time for COVID-19 surveillance. *medRxiv.* https://dx.doi.org/10.1101%2F2020.06.22.20136309

65. Korenkov M, Poopalasingam N, Madler M, et al. Evaluation of a Rapid Antigen Test To Detect SARS-CoV-2 Infection and Identify Potentially Infectious Individuals. *Journal of Clinical Microbiology.* 2021;59(9):e0089621.

66. Regev-Yochay G, Kriger O, Beni S, et al. Real World Performance of SARS-CoV-2 Antigen Rapid Diagnostic Tests in Various Clinical Settings. *medRxiv.* https://doi.org/10.1101/2021.03.02.21252400

67. Rashid A, Sy KTL, Cabrejas JM, Nichols BE, Bhadelia N, Murray EJ. A clinician's primer on epidemiology for COVID-19. *Med (New York ,N Y)*. 2021;2(4):384–394. https://doi.org/10.1016/j.medj.2021.02.007

68. Foundation for Innovative Diagnostics (FIND). FIND Evaluation of Abbott Panbio COVID-19 Ag Rapid Test Device (NASAL): External Report. FIND. 2021. https://www.finddx.org/wp-content/uploads/2021/06/Panbio_Nasal_Ag-Public-Report_20210211v1.pdf

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