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## The importance of timely contact tracing – A simulation study

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### ABSTRACT

**Background:** While the role of contact tracing in the containment of the COVID-19 epidemic remains important until vaccines are widely available, literature on objectively measurable indicators for the effectiveness of contact tracing is scarce. We suggest the diagnostic serial interval, the time between the diagnosis of the infector and infectee, as a new indicator for the effectiveness of contact tracing.

**Methods:** Using an agent-based simulation model, we demonstrate how the diagnostic serial interval correlates with the course of the epidemic. We consider four scenarios of how diagnosis and subsequent isolation are triggered: 1. never, 2. by symptoms, 3. by symptoms and loose contact tracing, 4. by symptoms and tight contact tracing. We further refine scenarios 3 and 4 with different lengths of target diagnostic serial intervals.

**Results:** Scenarios 1 and 2 did not yield a notable difference. In scenarios 3 and 4, however, contact tracing led to a decrease of the height of the epidemic as well as the cumulative proportion of infected agents. Generally, the shorter the diagnostic serial interval was, the smaller the peak of the epidemic became, and the more proportion of the population remained susceptible at the end of the epidemic.

**Conclusion:** A short target diagnosis interval is critical for contact tracing to be effective in the epidemic control. The diagnosis interval can be used to assess and guide the contact tracing strategy.

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### Introduction

In many countries that managed to contain the earlier COVID-19 outbreaks through extensive social distancing or a large-scale lock-down, a second or third wave of the outbreak took place. Although a lock-down or strict social distancing seem to be effective in containing the epidemic, these come with very high socioeconomic costs. The contact tracing strategy of “Diagnose, Trace, Isolate” has been highlighted as a more sustainable alternative in addition to personal hygiene measures such as wearing masks and washing hands (Rajan et al., 2020; World Health Organization, 2020a). While the importance of contact tracing has been emphasized, little literature is available on how to assess the effectiveness of contact tracing. Furthermore, many countries have experienced a surge of new

infections even though they have implemented contact tracing strategies, casting doubt around the usefulness of contact tracing (Mueller, n.d.).

Some authors suggested that reducing the delay from infection to diagnosis or from symptom onset to diagnosis is key (Rong et al., 2020). However, these approaches do not offer an objectively measurable parameter to assess the effectiveness of contact tracing, as the time of infection is often unknown and pre- or asymptomatic carriers may account for more than 50% of all transmission events (Moghadas et al., 2020). The total number of infected individuals or disease mortality also do not provide reliable information on the effectiveness of contact tracing since they may depend on other factors such as the number of tests performed, compliance of the public with mitigation measures, the variation in viral strains, weather, the age distribution of the population and medical care quality. The controversial change of testing guidelines by the U.S. Centers for Disease Control and Prevention to not test asymptomatic patients, which was reversed after heavy criticism (Sun, 2020), demonstrated how the absence of an objectively measurable quantity for the effectiveness and

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usefulness of contact tracing complicates political decision making.

We have previously suggested a novel indicator for the effectiveness of contact tracing that can be easily measured, namely the diagnostic serial interval, which we define as the time between the infector's diagnosis and the infectee's diagnosis (Mettler et al., 2020). In this paper, we study the relationship between the diagnostic serial interval and the growth of the epidemic using an agent-based simulation model. The diagnosis of SARS-CoV-2 infection is assumed to be made either via contact tracing and subsequent serial lateral flow antigen (LFA) testing or via symptomatic presentation and polymerase chain reaction (PCR) testing. We find that short diagnostic serial intervals correlate with a successful containment of the epidemic. Our findings imply that (1) fast contact tracing is important, and (2) diagnostic serial intervals can be used as an indicator for the speed of contact tracing.

Diagnosed agents are subsequently placed in isolation for 14 days and released if no longer symptomatic. The symptom status, diagnosis status, and isolation status are updated when certain conditions are fulfilled. One iteration corresponds to one day, and one simulation run (experiment) contains 100 iterations. Algorithm 1 is a pseudocode description of our simulation design. Each operation is explained in detail in Appendix A.

LFA tests detect SARS-CoV-2 infection by collecting a nasal swab sample and running a liquid sample along a surface with reactive molecules. We assumed the use of LFA testing for daily testing for its affordability, detection speed, and ease of use compared to traditional PCR testing (Mina et al., 2020). In December 2020, the United States Food and Drug Administration issued an emergency use authorization for a commercially available LFA test (U.S. Food and Drug Administration, 2020).

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**Algorithm 1** Pseudocode for Agent Based Simulation

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**Require:** Parameter set  $P$ , Diagnosis condition  $D$ , Number of iterations  $T$ , Number of experiments  $E$

**for**  $e$  in  $1:E$  **do**

Agent population  $\Theta_{t=0} \leftarrow \text{initialize}(P)$

**for**  $t$  in  $1:T$  **do**

$\Theta_{t+1}^{(1)} \leftarrow \text{move}(\Theta_t, P)$

$\Theta_{t+1}^{(2)} \leftarrow \text{update}(\Theta_{t+1}^{(1)}, P)$

$\Theta_{t+1}^{(3)} \leftarrow \text{contact}(\Theta_{t+1}^{(2)}, P)$

$\Theta_{t+1}^{(4)} \leftarrow \text{diagnosis}(\Theta_{t+1}^{(3)}, D)$

$\Theta_{t+1} \leftarrow \Theta_{t+1}^{(4)}$

**end for**

**return** Data set  $S_1^e = \{\Theta_t \text{ for all } t \text{ in } 1:T\}$ , Data set  $S_2^e = \{\text{Summary statistics of } \Theta_t \text{ for all } t \text{ in } 1:T\}$

**end for**

**return**  $S_1^e$  and  $S_2^e$  for all  $e$  in  $1:E$

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## Methods

While the majority of currently published simulation studies on COVID-19 are equation-based (Adam, 2020), such models typically do not allow for simulation of infection chains. We therefore employ an agent-based model, by modifying an existing simulation design and code (Silva et al., 2020). Our modifications entail both simplifications and additional features as described in the following paragraphs.

### Simulation design

We simulate the movements of 1000 agents in a two-dimensional space and track the spread of the epidemic within the population. Agents are in one of four states, namely, susceptible, infected, recovered/immune or dead. Unless dead, agents make a random move at every iteration within the predefined space. When susceptible agents come into close contact with an infected agent, they become infected at a given transmission probability. Infected agents develop symptoms after a random incubation time. According to the diagnostic testing triggering condition of the simulation scenario, infected agents may be diagnosed either via contact tracing and daily LFA testing for 5 days or via symptomatic presentation and PCR testing.

### Epidemiological assumptions

Table 1 describes the epidemiological assumptions of our simulation. The incubation time denotes the time between infection and symptom onset. The relative infectiousness refers to the infectiousness at time  $t$  relative to the maximum infectiousness  $\max_s g(s) = 1$ . Here,  $t$  is the number of days since the onset of symptoms and can be negative. The probability that an agent infects their close contacts at time  $t$  is given by the maximum secondary attack rate of 0.35 multiplied by the relative infectiousness at time  $t$ . The detection probability can be thought of as the sensitivity of diagnostic testing. The detection probability by LFA testing is assumed to depend on the relative infectiousness (Quilty et al., 2021). Although the true detection probability may remain high even after the agent is no longer infectious (Wölfel et al., 2020), this assumption does not significantly alter our results as we are mainly interested in case detection during the infectious phase. The detection probability by PCR testing during the symptomatic phase is assumed to be 100% for simplicity.

### Simplicity assumptions

For the purpose of simplicity, we did not consider truly asymptomatic transmissions, i.e., agents who never develop

**Table 1**  
Control parameters – epidemiological assumptions.

Epidemiological parameters	Value	Reference
Population size	1000	(Arbitrarily chosen)
Initial percentage of infected	0.5%	(Arbitrarily chosen)
Initial percentage of immune	0%	(Arbitrarily chosen)
Incubation time distribution	Log-normal distribution with $\mu = 1.63$ and $\sigma = 0.50$	McAloon et al. (2020)
Relative infectiousness	$g(t) = \frac{\exp(-(t+4)/1.85)}{c(1 + \exp(-(t+4)/1.85))^{6.85}}$ where $c$ is chosen so that $\max_s g(s) = 1$	Ferretti et al. (2020)
Maximum secondary attack rate	0.35	Liu et al. (2020)
Detection probability	By LFA testing after contact tracing $\begin{cases} 0.95, & \text{if relative infectiousness} \geq 0.5, \\ 0.65, & \text{if } 0.1 \leq \text{relative infectiousness} < 0.5, \\ 0, & \text{otherwise.} \end{cases}$	Quilty et al. (2021) (for simplicity)
Time to recovery	By PCR testing while symptomatic 100%	Lechien et al. (2020)
Infection fatality ratio (IFR)	11.5 days after symptom onset unless dead 1%	World Health Organization (2020b)

symptoms. Also, we assume that every symptomatic patient either recovers and becomes immune or dies after 11.5 days of symptom duration. Furthermore, isolated agents are assumed not to infect others. We do not consider isolation of individuals without a diagnostic confirmation nor precautionary quarantine.

### Scenarios

We consider the following four scenarios as diagnostic testing triggering conditions.

**Scenario 1** Never (do nothing).

**Scenario 2** Time since symptom onset is  $\geq 3$  days (only symptom-based testing).

**Scenario 3** Time since symptom onset is  $\geq 3$  days or Infector's Time since diagnosis is  $\geq 5$  days (loose contact tracing).

**Scenario 4** Time since symptom onset is  $\geq 3$  days or Infector's Time since diagnosis is  $\geq 2$  days (tight contact tracing).

The scenarios where the Time since diagnosis of an infector is given as a diagnosis triggering condition are to simulate contact tracing. When agents are contact-traced, they undergo daily LFA testing for 5 days and are placed in isolation only if the test result is positive. Agents who are symptomatic for 3 days or longer are diagnosed by PCR testing and subsequently isolated.

### Target and observed diagnostic serial intervals

As the detection probability of the virus by LFA testing is relatively low (65%) during the early phase of infection, not all infectees are diagnosed on the day they are contact-traced. For example, even though infectees are contact-traced 2 days after the infector's diagnosis in scenario 4, the observed diagnostic serial interval may be greater than 2 days, because the virus was not detected by earlier tests. We call this contact-tracing interval of 2 days for scenario 4, or 5 days for scenario 3, the *target diagnostic serial interval*. We use the terms *observed diagnostic serial interval* and *diagnostic serial interval* interchangeably.

### Simulation output

After 100 iterations, two data sets are returned. The first data set contains all agent variables at every iteration. The second data set

contains summary statistics of the overall population at each iteration. Using the first data set, the clinical onset serial intervals and diagnostic serial intervals are calculated. The second data set is used to visualize the dynamic development of the epidemic over time.

All simulations are performed using Python version 3.7.1. The resulting simulated data are analyzed using the software R version 4.0.2. All code is available on our github repository (<https://github.com/DSI-COVID-Simulation/code/>).

### Results

The basic reproductive numbers, effective reproductive numbers, and distribution of contacts in scenario 1 can be found in Appendix B.

The epidemic development in each scenario is shown in Figure 1. As each simulation run entails a certain degree of randomness, each scenario is run 100 times with the same initial conditions to show stochastic variation. The ranges between the 5th and 95th percentiles as well as the median values are shown.

### Dynamic of the epidemic

#### Scenario 1. Nothing triggers diagnostic testing (do nothing)

The first scenario we consider is the “do nothing” scenario. As shown in Figure 1(a) the epidemic reaches a peak when 49.0% of the population are infected. The epidemic ends with no infected individuals when immunity is at 84.1% of the population, which is often referred to as herd immunity, leaving only 15.1% of the population susceptible. Assuming an infection fatality ratio of 1%, 0.8% of the population die in this scenario.

#### Scenario 2. Symptom duration of 3 days or longer triggers diagnostic testing (only symptom-based testing)

In the second scenario patients are diagnosed and subsequently isolated if they had symptoms for 3 days. The epidemic reaches its peak when 45.0% of the population are infected. Interestingly, while 35.2% of the population are isolated at maximum in contrast to no isolation in scenario 1, the epidemic ends after infecting 80.1% of the population in total and causing death in 0.8% of the population, showing little difference to the first scenario.

**Scenario 3. Symptom duration of 3 days or longer or infector's time since diagnosis of 5 days or longer trigger diagnostic testing (loose contact tracing)**

The third scenario simulates a contact tracing strategy with a target diagnostic serial interval of 5 days on top of the symptom duration condition defined in scenario 2. The epidemic is contained after reaching a maximum proportion of infected individuals of 34.2%. The epidemic ends after infecting 68.0% of the population and causing death in 0.7% of the population.

**Scenario 4. Symptom duration of 3 days or longer or infector's time since diagnosis of 2 days or longer trigger diagnostic testing (tight contact tracing)**

In the last scenario the target diagnostic serial interval is shortened to 2 days. The outbreak peaks with 4.2% of the population infected and 4.2% of the population isolated. The epidemic ends after infecting only 10.5% of the population and causing death in 0.1% of the population.

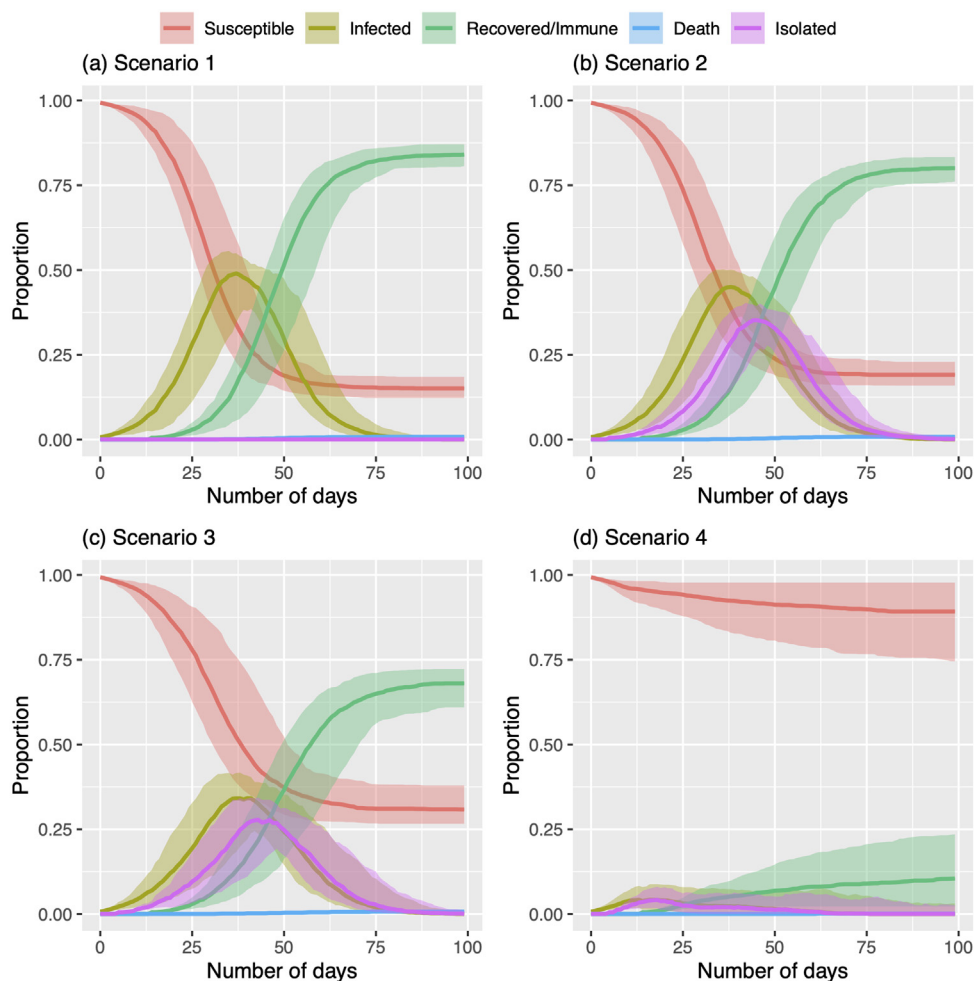
Interesting to note in Figure 1 is the time shift between the curve of infected agents and that of isolated agents in scenarios 2–4. It visualizes that the shortened target diagnostic serial interval leads to a smaller time shift between the curves of infected and isolated agents. This leads to the containment of the epidemic without reaching herd immunity.

*Cumulative proportion of cases with known transmission routes*

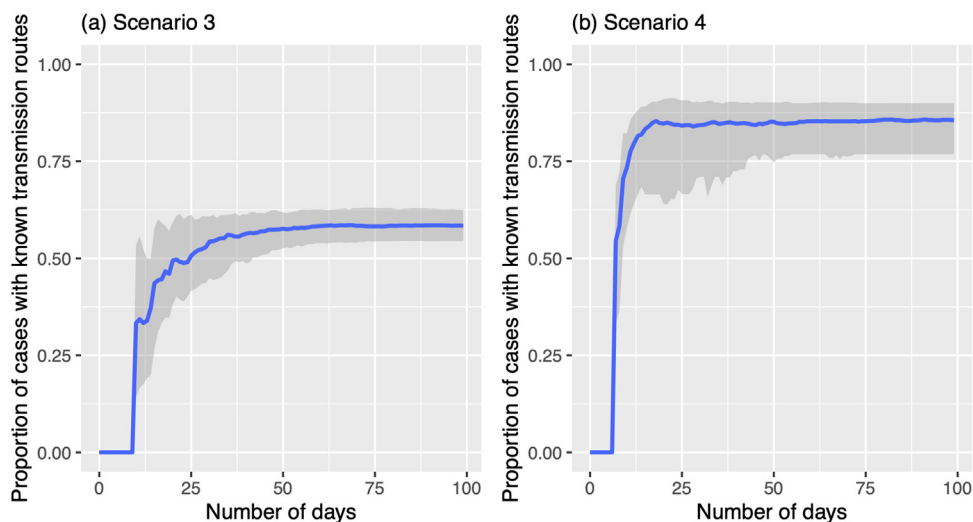
Figure 2 shows the cumulative proportion of cases with known transmission routes for scenarios 3 (loose contact tracing) and 4 (tight contact tracing). Cases are considered to have known transmission routes when they were diagnosed via contact tracing. The proportion of cases with known transmission routes is lower in scenario 3 than in scenario 4, indicating that scenario 3 leads to a larger proportion of cases spreading outside of the surveillance system.

*The serial intervals*

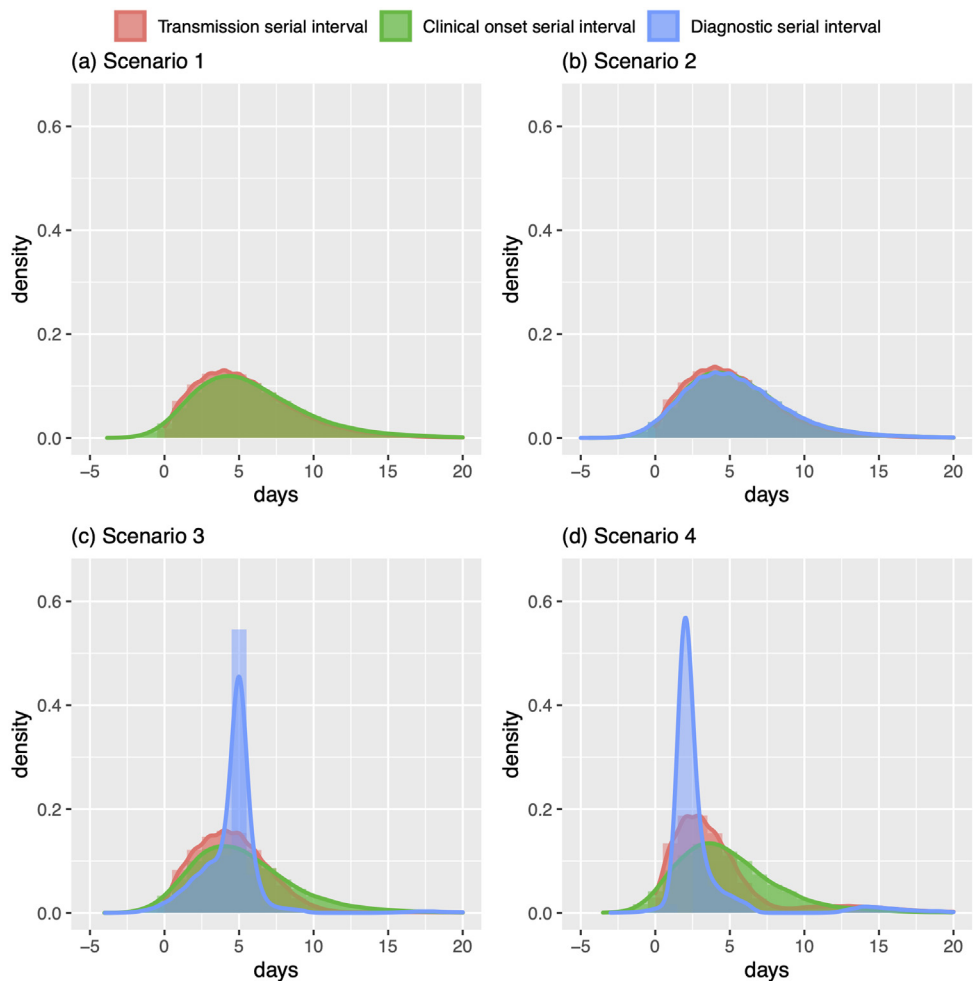
Using the simulation data, we compare the transmission serial interval (TSI), the clinical onset serial interval (COSI), and the diagnostic serial interval (DSI). The transmission serial interval, or the generation time, is the time between the infection events of the infector and the infectee (Fine, 2003). The clinical onset serial interval, commonly referred as the serial interval, is the time between the onset of symptoms of the infector and the infectee (Fine, 2003). The diagnostic serial interval is defined as the time between the infector's diagnosis and the infectee's diagnosis (Mettler et al., 2020). The latter two intervals are calculated using the agents' attributes at the end of the simulation using the formulae in Appendix C.



**Figure 1.** (a) Scenario 1: do nothing. (b) Scenario 2: only symptom-based testing. (c) Scenario 3: loose contact tracing. (d) Scenario 4: tight contact tracing. The solid lines are the median values over all 100 simulations and the shadowed areas represent the 5th–95th percentiles.



**Figure 2.** The cumulative proportion of cases with known transmission routes for scenario 3 with the target diagnostic serial interval of 5 days (a) and for scenario 4 with the target diagnostic serial interval of 2 days (b). The solid lines are the median values over all 100 simulations, and the shadowed areas show the value ranges between the 5th and 95th percentiles.



**Figure 3.** Histograms of the transmission serial interval, clinical onset serial interval and diagnostic serial interval of each scenario, from all 100 simulations. The solid lines are density estimates.



**Table 2**

The mean values of transmission, clinical onset and diagnostic serial intervals for each scenario. The standard deviations are shown in parentheses.

	Scenario 1	Scenario 2	Scenario 3	Scenario 4
Transmission serial interval	5.52 (3.49)	5.26 (3.24)	4.56 (2.71)	4.29 (3.79)
Clinical onset serial interval	5.81 (3.87)	5.47 (3.58)	5.27 (3.53)	4.84 (3.46)
Diagnostic serial interval	– (–)	5.47 (3.60)	4.54 (2.34)	3.14 (3.31)

Figure 3 shows histograms and estimated density functions of the transmission serial interval, the clinical onset serial interval, and the diagnostic serial interval in each scenario aggregated from all 100 simulations. Table 2 shows the means and standard deviations of the three types of serial intervals.

The distribution of the diagnostic serial interval in scenario 2 (Figure 3(b)) is similar to that of the clinical onset serial interval. This is expected as diagnostic testing is only triggered by a symptom duration of 3 days or longer in scenario 2. In scenarios 3 and 4, the diagnostic serial intervals are targeted to be at 5 days and 2 days, respectively, and accordingly result in distributions shown in Figure 3(c) and (d).

It is interesting to note that the distributions of transmission serial interval and clinical onset serial interval depend on the mitigation strategies. The stricter the mitigation measures are, the shorter all three types of serial intervals become. This is likely due to the mitigation-based selection for infector-infectee pairs with shorter serial intervals because under mitigation measures, less transmissions occur in the later phase of the infector's course of infection. This may explain the variation of reported serial intervals in different countries.

#### *The target diagnostic serial interval and containment of the epidemic*

We ran a series of simulations with varying target diagnostic serial intervals from 0 day to 10 days while keeping the symptom-based testing condition at a symptom duration of 3 days or longer as in scenarios 3 and 4. For each target diagnostic serial interval, 100 simulations were performed.

Figure 4(a) shows how the observed mean diagnostic serial interval is correlated with the target diagnostic serial interval. The variation of the observed mean diagnostic serial interval is larger toward shorter target diagnostic serial intervals because the number of infected is small. As target diagnostic serial intervals become longer, the observed diagnostic serial intervals plateau at around 5–6 days, because more people are diagnosed due to symptoms rather than contact tracing.

Figure 4(b) and (c) show the relationship between the target diagnostic serial interval and epidemic control. The effect of contact tracing is shown to change drastically between target diagnostic serial intervals of 2 days and 6 days. For example, an increase in the target diagnostic serial interval from 3 days to 4 days (which corresponds to a mean observed diagnostic serial interval of 3.5 and 4.0, respectively) is associated with an increase in the proportion of infected agents at the height of the epidemic from 13.3% to 26.8%. Meanwhile, the cumulative proportion of infected individuals at the end of the epidemic increases from 32.1% to 57.1%.

## **Discussion**

Simulation studies are a valuable tool for planning public health interventions and assessing their potential impacts. They are especially useful when dealing with imminent public health crises such as the current COVID-19 pandemic. Our simulation study shows how timely contact tracing can help contain the current pandemic, the effectiveness of which can be measured by the

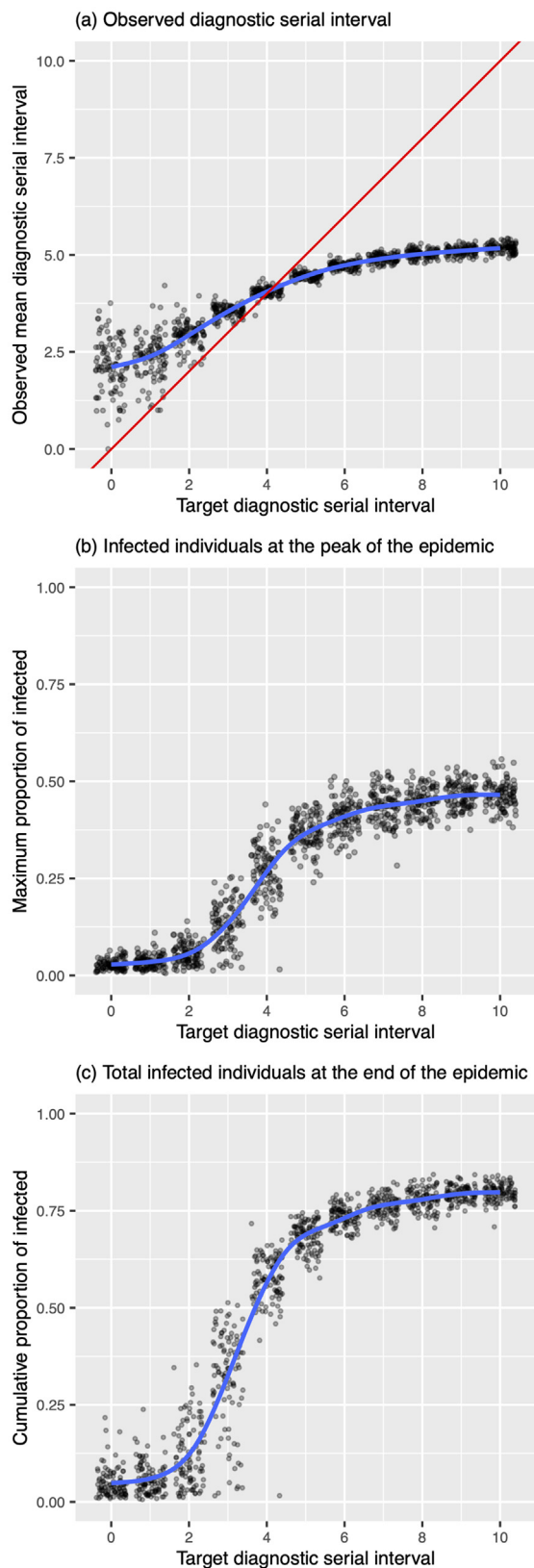
diagnostic serial interval together with the proportion of cases with unknown transmission routes. We conjectured in our previous publication that shortening the diagnostic serial interval below the transmission serial interval will break the infection chain and contribute to the containment of the epidemic (Mettler et al., 2020). The results of this simulation study are in line with this conjecture. Our study suggests that once the number of daily infection cases is brought down by a lock-down and extensive social distancing measures, the strategy of “Diagnose, Trace, Isolate” can be employed as a sustainable long-term measure for epidemic containment in addition to continuing personal hygiene measures. Considering that large-scale quarantine and isolation of individuals correlates with socioeconomic costs (Chu et al., 2020), extensive contact tracing efforts would inflict the least socioeconomic consequences by reducing the number of individuals put in isolation/quarantine.

The second scenario, in which diagnostic testing is triggered after three days of symptom onset, was the strategy implemented in some parts of the world in the early phase of the pandemic. Using the most recently reported information on the epidemiological characteristics of the virus (incubation and infectiousness profile), our simulation shows that a mere symptom-based approach brings little benefit compared to the “do nothing” strategy, albeit perhaps reducing the strain on the health care system by delaying the peak of the epidemic and reducing its height.

While there have been promising results regarding possible vaccines, contact tracing will remain important until vaccines are widely administered. In particular, many low income countries will not be able to vaccinate most of their populations in 2021 (Dyer, 2020), and contact tracing will continue to be one of the few sustainable measures available against the COVID-19 pandemic in these countries. Our study underlines the importance of *fast* contact tracing. While the contact tracing thoroughness can be measured by the proportion of cases with known transmission routes, the diagnostic serial interval provides information on the timeliness of contact tracing. A shorter diagnostic serial interval implies timeliness in various steps of contact tracing, including fast identification of contacts, a short time between identifying contacts and conducting diagnostic tests, and quick return of test results. Our results suggest a close relationship between the epidemic control and the length of the diagnostic serial interval.

We have assumed that LFA testing was used for serial testing of those who have been identified through contact tracing. Nasopharyngeal PCR testing is considered a gold standard in diagnosing SARS-CoV-2 infection; however, it is not suitable for daily testing due to its high cost and turnaround time. Although LFA is less sensitive than PCR, this is not so important if the goal is to detect actively infectious patients (Mina et al., 2020). While LFA testing is inexpensive and quick, its effect in reducing transmission may be comparable to a 14-day quarantine, when used as daily serial testing accompanied by isolation of positive individuals (Quilty et al., 2021). LFA testing is a critical component in the response against COVID-19 pandemic especially in resource-limited settings (Boum et al., 2021).

There are several limitations to our simulation study. First, we considered a simplified setting with a small population and a two-dimensional space without complex social structures that can lead



**Figure 4.** The relationships between the target diagnostic serial interval and (a) the observed mean diagnostic serial interval, (b) the proportion of infected agents at the peak of the epidemic and (c) the cumulative proportion of infected agents at the end of the epidemic. Each point represents the result of one simulation run.

to super-spreading events. Second, we use the same maximum secondary attack rate of 35% for all infector-infectee contacts, regardless of the duration and nature of the contact. Current literature suggests a wide range of secondary attack rates ranging from 0.46% to 63.87% (Huang et al., 2020). This is likely due to different definitions of what constitutes close contact. For future studies, we may sub-categorize types of contacts and apply the contact-type specific secondary attack rate accordingly. Third, we assumed all contacts can be traced. The effect of this assumption may be partly offset by lowering the detection probability of LFA testing. Fourth, we did not consider asymptomatic carriers who never develop symptoms. According to recent literature, a significant portion of asymptomatic carriers remain asymptomatic (Zhou et al., 2020). However, asymptomatic carriers are less likely to form neutralizing antibodies and any antibodies formed tend to disappear quickly (Lei et al., 2021). Thus, we conjectured that asymptomatic carriers will contribute minimally in forming herd immunity. In addition, asymptomatic carriers are 65% less likely to transmit the virus than those with symptomatic infections (Buitrago-Garcia et al., 2020). For these reasons we decided to exclude truly asymptomatic carriers from our analysis. Furthermore, the number of deaths in our simulation is not a reliable estimate of the mortality for the following reasons. First, age is not considered for the purpose of simplicity. Second, the infection fatality ratio of 1% (World Health Organization, 2020b) is based on the assumption that proper medical care is provided. Our simulation, however, did not take medical care capacity into account. Finally, we assumed that all individuals are perfectly compliant with the isolation policy and that no infection occurs during isolation.

The largest changes in the benefits of contact tracing are observed in a range of target diagnostic serial intervals between 2 days and 6 days with an inflection point lying somewhere between 3 and 4 days (Figure 4) for this simulation setting. The role of the diagnostic serial interval in disease control should be studied further in relation to epidemiological parameters such as the incubation period, infectiousness profile or detection probability, which can be then generalized to other infectious diseases.

#### Patient or public involvement statement and ethics committee approval

Our research is based on simulation data and does not require to involve patients or the public in the design, or conduct, or reporting, or dissemination plans. Our research does not require ethics committee approval.

#### Conflict of interest statement

All authors declare no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

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#### Appendix A. Simulation design

##### 1. ) Initialization

A two-dimensional space is defined and populated with a given number of agents. Each agent has several attributes as listed in Table 3.



Agent attributes and their value ranges with initial values in italic. Time is measured in terms of the number of iterations (days).

Agent attributes	Possible values
ID	{1, 2, 3, ..., 1000}
Location	$(x, y) \in [0, 50] \times [0, 50]$
Infection status	{Susceptible, Infected, Recovered/Immune, Dead}
Activity degree	{0.3, 1, 3}
Symptom status	{Presymptomatic, Symptomatic, Postsymptomatic}
Diagnosis status	{Undiagnosed, Diagnosed}
Isolation status	{No isolation, Isolated}
Time since infection	{None, 0, 1, 2, ...}
Incubation time	{None, 0, 1, 2, ...}
Time since symptom onset	{None, 0, 1, 2, ...}
Time since diagnosis	{None, 0, 1, 2, ...}
Time since isolation start	{None, 0, 1, 2, ...}
Infector ID	{None, 1, 2, ..., 1000}
Transmission serial interval	{None, 0, 1, 2, ...}

Table 4 summarizes the control parameters for the model. It defines the number of agents, the movement amplitude of agents and the distance between two agents that qualifies as close contact.

Control parameters – model assumptions.

Model parameters	Value
Number of agents	1000
Amplitude of movement	Susceptible: 3 Recovered/Immune: 3 Infected: 3 Dead: 0 Isolated: 0
Distance considered as contact	$\leq 1$

### 2. ) Execution and iterations

At every iteration the functions move, update, contact and diagnosis are executed. This is repeated for a given number of iterations which reflects the number of days of observation. We set the number of iterations to be 100.

#### Move

We simulate the movements of agents in a simplified manner. At each iteration every agent moves vertically and horizontally by a distance randomly chosen from the standard normal distribution  $N(0, 1)$  multiplied by the status-based amplitude of movement and the activity degree of the agent. The activity degree is randomly chosen at the beginning of the simulation for each agent and can be thought of the agent’s personal trait (age, personality, etc.) that determines the relative range of movement of the agent. The positions of agents at time  $t + 1$  are given by  $x_{t+1} = x_t + \Delta_{x_t} \times (\text{amplitude of movement}) \times (\text{activity degree})$  and  $y_{t+1} = y_t + \Delta_{y_t} \times (\text{amplitude of movement}) \times (\text{activity degree})$  where  $\Delta_{x_t}$  and  $\Delta_{y_t}$  are independent realizations of the standard normal distribution. All agents are only able to move within the two-dimensional space defined in the initialization step. Periodic boundary conditions are applied at the boundaries.

#### Update

At each iteration the Infection status, Symptom status, Isolation status, Time since infection, Time since symptom onset and Time since diagnosis of agents are updated as indicated in Table 5.

Agent variables which are updated at every iteration and the conditions for the update.

Agent variable	Update	Condition
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(Continued)

Agent variable	Update	Condition
Infection status	Infected → Dead	Happens with probability IFR (see Table 1) if Time since symptom onset is 11.5 days.
	Infected → Recovered/Immune	If Time since symptom onset is 11.5 days and agent is not dead.
Symptom status	Presymptomatic → Symptomatic	If Time since infection exceeds Incubation time.
	Symptomatic → Postsymptomatic	Happens when Infection status changes from Infected to Recovered/Immune.
Isolation status	Isolated → No isolation	If Time since isolation start is 14 days and Infection status is Recovered/Immune.
	No isolation → Isolated	When agent is diagnosed.
Time since infection	None → 0	When agent becomes infected.
	+1	At every iteration afterwards.
Time since symptom onset	None → 0	When agent becomes symptomatic.
	+1	At every iteration afterwards.
Time since isolation start	None → 0	When agent becomes isolated.
	+1	At every iteration afterwards.
Time since diagnosis	None → 0	When agent becomes diagnosed.
	+1	At every iteration afterwards.

### Contact

New contacts occur at every iteration as a result of agents’ movements. If a susceptible agent is located within the predefined contagion distance of an infected agent who is not isolated, the susceptible agent becomes infected at a given probability, namely, the maximum secondary attack rate multiplied by infectiousness as defined in Table 1. At the time of contact and subsequent transmission, the Infection status of the newly infected agent is updated from Susceptible to Infected and the Infector ID and Transmission serial interval, which is equivalent to the infector’s Time since infection, are recorded in the attributes of the newly infected agent. The recording of the Infector ID allows for tracking of transmission chains.

### Diagnosis

Based on the diagnosis triggering condition chosen for the simulation, agents who are infected and meet the diagnosis triggering condition become diagnosed and subsequently isolated. The variables Diagnosis status and Isolation status are updated from Undiagnosed to Diagnosed and from No isolation to Isolated.

### 3. ) Response variables

Table 6 summarizes the response variables of the simulation. Response variables

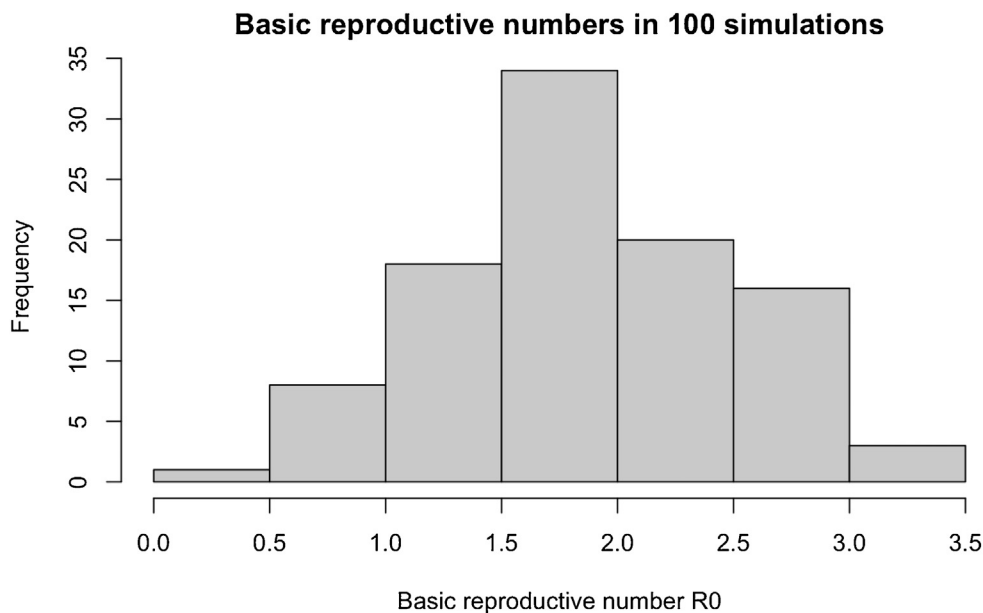
Response variables
Proportion of susceptible agents at each iteration
Proportion of infected agents at each iteration
Proportion of recovered/immune agents at each iteration
Proportion of dead agents at each iteration
Proportion of isolated agents at each iteration
Cumulative proportion of cases with known transmission routes at each iteration
Transmission serial intervals for all infected individuals
Clinical onset serial intervals for all symptomatic individuals
Diagnostic serial intervals for all diagnosed individuals

If the diagnosis of an infectee was triggered by contact tracing, then the infectee is considered to have a known transmission route. If both the symptom condition and the contact tracing condition are satisfied, the transmission route is considered to be known as well. The proportion of cases with known transmission routes reflects the proportion of cases that are identified by contact tracing.

**Appendix B. Basic reproductive number, effective reproductive number and distribution of contacts in Scenario 1**

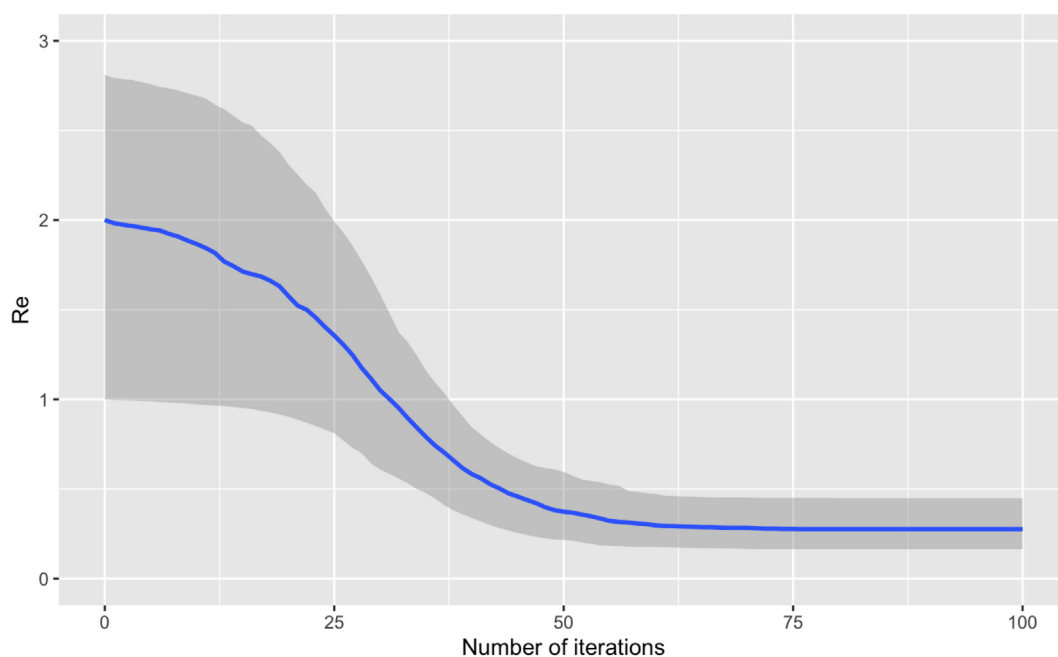
1. )  $R_0$

Under the default conditions without any intervention, one index case infects approximately 1.93 agents (averaged over 100 simulations). The basic reproductive number  $R_0$  varied in each simulation with the same initial condition but different seeds and its histogram is shown below.



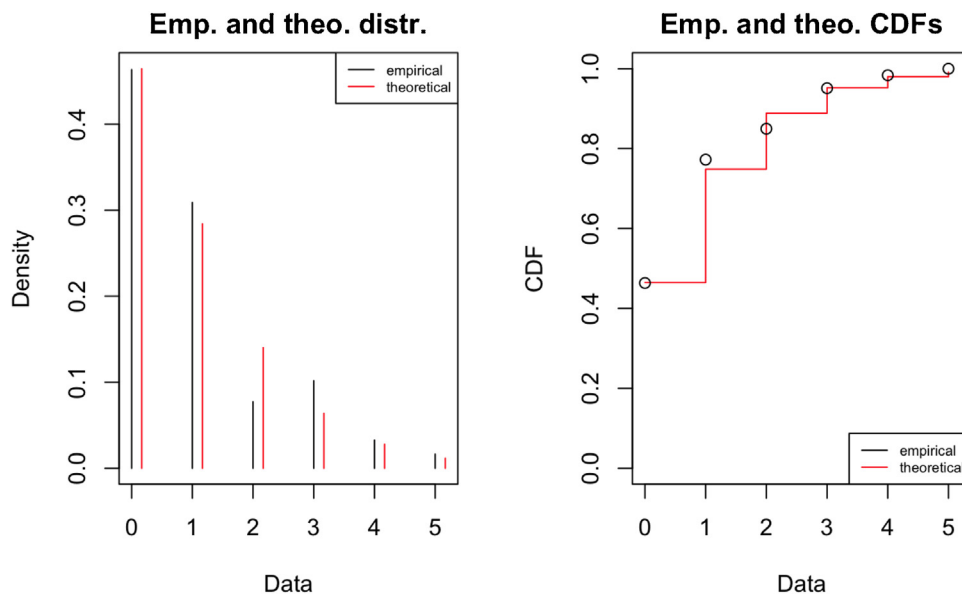
2. )  $R_e$

The trend of the effective reproductive number under no mitigation is shown below. The solid line is the median value of 100 simulations and the shadowed areas represent the 5th–95th percentiles. The values of  $R_e$  drop drastically as the proportion of susceptible population decreases.



3. ) Distribution of the number of transmissions per infector at day 33 (comparable to the distribution of contacts)

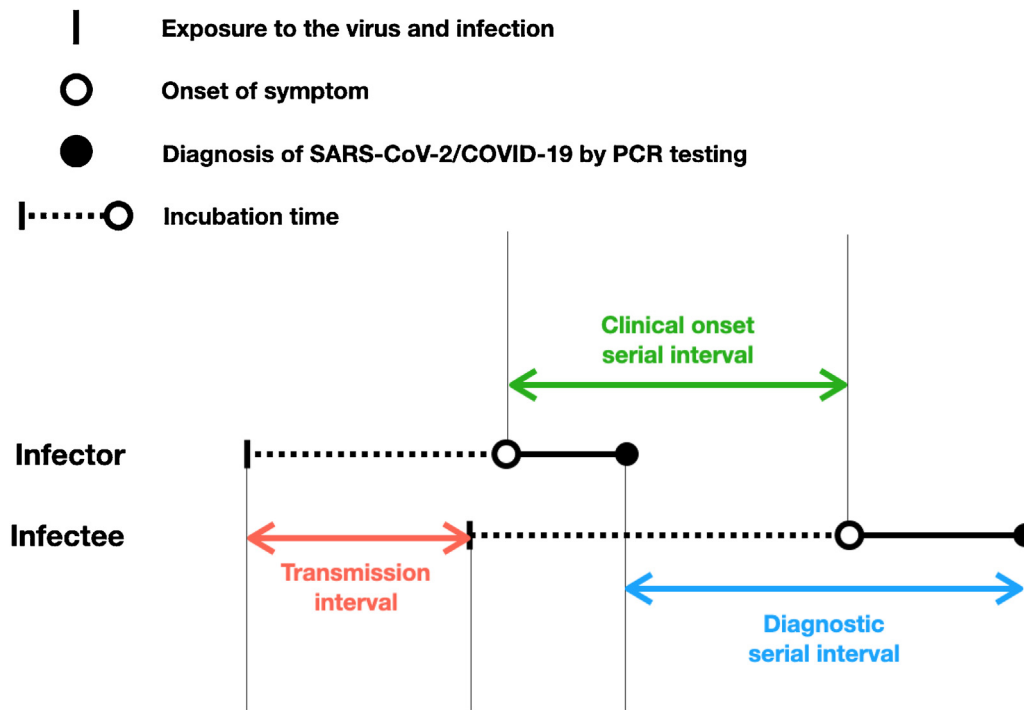
We supposed that the number of transmissions per infector during the earlier phase of the pandemic is comparable to the distribution of contacts as a large portion of the population are still susceptible. The function `fitdistrplus` in R library (`fitdistrplus`) gives a negative binomial distribution with overdispersion for Scenario 1 as displayed in the figure below (aggregated from 100 experiments).



**Appendix C. Formulae for different serial intervals and graphical illustration**

TSI: Transmission serial interval (also known as the generation time)  
 COSI: Clinical onset serial interval (often referred as the serial interval)  
 DSI: Diagnostic serial interval or diagnosis interval

$$\begin{aligned}
 TSI &= \text{infector's time since infection} - \text{infectee's time since infection} \\
 &= \text{infector's time since infection at the time of infectee's infection} \\
 COSI &= \text{infector's time since symptom onset} - \text{infectee's time since symptom onset} \\
 &= \text{infector's time since infection} - \text{infector's incubation time} \\
 &\quad - (\text{infectee's time since infection} - \text{infectee's incubation time}) \\
 &= TSI - \text{infector's incubation time} + \text{infectee's incubation time} \\
 DSI &= \text{infector's time since diagnosis} - \text{infectee's time since diagnosis}
 \end{aligned}$$



## References

- Adam D. Modelling the pandemic – the simulations driving the world's response to COVID-19. *Nature* 2020;580:316–8.
- Boum Y, Fai KN, Nicolay B, Mboringong AB, Bebell LM, Ndifon M, et al. Performance and operational feasibility of antigen and antibody rapid diagnostic tests for COVID-19 in symptomatic and asymptomatic patients in Cameroon: a clinical, prospective, diagnostic accuracy study. *Lancet Infect Dis* 2021; doi:[http://dx.doi.org/10.1016/S1473-3099\(21\)00132-8](http://dx.doi.org/10.1016/S1473-3099(21)00132-8).
- Buitrago-Garcia D, Egli-Gany D, Counotte MJ, Hossmann S, Imeri H, Ipekci AM, et al. Occurrence and transmission potential of asymptomatic and presymptomatic SARS-CoV-2 infections: a living systematic review and meta-analysis. *PLoS Med* 2020;17(9):e1003346.
- Chu IYH, Alam P, Larson HJ, Lin L. Social consequences of mass quarantine during epidemics: a systematic review with implications for the COVID-19 response. *J Travel Med* 2020;27(October (7)):taaa192, doi:<http://dx.doi.org/10.1093/jtm/taaa192>.
- Dyer O. Covid-19: Many poor countries will see almost no vaccine next year, aid groups warn. *BMJ* 2020;371:m4809, doi:<http://dx.doi.org/10.1136/bmj.m4809>.
- Ferretti L, Leda A, Wymant C, Zhao L, Leda V, Abeler-Dörner L, et al. The timing of covid-19 transmission. *medRxiv* 2020; doi:<http://dx.doi.org/10.1101/2020.09.04.20188516>.
- Fine PE. The interval between successive cases of an infectious disease. *Am J Epidemiol* 2003;158:1039–47, doi:<http://dx.doi.org/10.1093/aje/kwg251>.
- Huang Y-T, Tu Y-K, Lai P-C. Estimation of the secondary attack rate of COVID-19 using proportional meta-analysis of nationwide contact tracing data in Taiwan. *J Microbiol Immunol Infect* 2020;54(1):89–92, doi:<http://dx.doi.org/10.1016/j.jmii.2020.06.003>.
- Lechien JR, Chiesa-Estomba CM, Place S, Van Laethem Y, Cabaraux P, Mat Q, et al. Clinical and epidemiological characteristics of 1420 European patients with mild-to-moderate coronavirus disease 2019. *J Intern Med* 2020;288:335–44, doi:<http://dx.doi.org/10.1111/joim.13089>.
- Lei Q, Li Y, Hou HY, Wang F, Ouyang ZQ, Zhang Y, et al. Antibody dynamics to SARS-CoV-2 in asymptomatic COVID-19 infections. *Allergy* 2021;76(2):551–61.
- Liu Y, Eggo RM, Kucharski AJ. Secondary attack rate and superspreading events for SARS-CoV-2. *Lancet* 2020;395:e47, doi:[http://dx.doi.org/10.1016/S0140-6736\(20\)30462-1](http://dx.doi.org/10.1016/S0140-6736(20)30462-1).
- McAloon C, Collins Á, Hunt K, Barber A, Byrne AW, Butler F, et al. Incubation period of COVID-19: a rapid systematic review and meta-analysis of observational research. *BMJ Open* 2020;10:e039652, doi:<http://dx.doi.org/10.1136/bmjopen-2020-039652>.
- Mettler SK, Kim J, Maathuis MH. Diagnostic serial interval as a novel indicator for contact tracing effectiveness exemplified with the SARS-CoV-2/COVID-19 outbreak in South Korea. *Int J Infect Dis* 2020;99:346–51, doi:<http://dx.doi.org/10.1016/j.ijid.2020.07.068>.
- Mina MJ, Parker R, Larremore DB. Rethinking Covid-19 test sensitivity—a strategy for containment. *N Eng J Med* 2020;383(22):e120.
- Moghadas SM, Fitzpatrick MC, Sah P, Pandey A, Shoukat A, Singer BH, et al. The implications of silent transmission for the control of covid-19 outbreaks. *Proc Natl Acad Sci U S A* 2020;117:17513–5, doi:<http://dx.doi.org/10.1073/pnas.2008373117>.
- Mueller B. Contact tracing, key to reining in the virus, falls flat in the west. *New York Times*; October 2020.
- Rajan S, Cylus JD, Mckee M. What do countries need to do to implement effective 'find, test, trace, isolate and support' systems?. *J R Soc Med* 2020;113:245–50, doi:<http://dx.doi.org/10.1177/0141076820939395>.
- Rong XM, Yang L, di Chu H, Fan M. Effect of delay in diagnosis on transmission of COVID-19. *Math Biosci Eng* 2020;17:2725–40, doi:<http://dx.doi.org/10.3934/mbe.2020149>.
- Silva PCL, Batista PVC, Lima HS, Alves MA, Guimarães FG, Silva RCP. COVID-ABS: an agent-based model of COVID-19 epidemic to simulate health and economic effects of social distancing interventions. *Chaos Soliton Fract* 2020;139:110088, doi:<http://dx.doi.org/10.1016/j.chaos.2020.110088>.
- Sun L. CDC reverses controversial coronavirus guidelines for testing people without symptoms. *The Washington Post*; 2020 19 September 2020.
- Quilty BJ, Clifford S, Hellewell J, Russell TW, Kucharski AJ, Flasche S, et al. Quarantine and testing strategies in contact tracing for SARS-CoV-2: a modelling study. *Lancet Public Health* 2021;6(March (3)):e175–83, doi:[http://dx.doi.org/10.1016/S2468-2667\(20\)30308-X](http://dx.doi.org/10.1016/S2468-2667(20)30308-X).
- U.S. Food and Drug Administration. Coronavirus (COVID-19) update: FDA authorizes antigen test as first over-the-counter fully at-home diagnostic test for COVID-19. 2020 Retrieved from: <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-antigen-test-first-over-counter-fully-home-diagnostic> on 1 April 2021.
- World Health Organization. Director-General's opening remarks at the media briefing on COVID-19 16 March 2020. 2020.
- World Health Organization. Estimating mortality from COVID-19 4 August 2020. 2020.
- Wölfel R, Corman VM, Guggemos W, Seilmaier M, Zange S, Müller MA, et al. Virological assessment of hospitalized patients with covid-2019. *Nature* 2020;581:465–9, doi:<http://dx.doi.org/10.1038/s41586-020-2196-x>.
- Zhou X, Li Y, Li T, Zhang W. Follow-up of asymptomatic patients with SARS-CoV-2 infection. *Clin Microbiol Infect* 2020;26:957–9, doi:<http://dx.doi.org/10.1016/j.cmi.2020.03.024>.