RESEARCH ARTICLE

A mathematical model to assess the effectiveness of test-trace-isolate-and-quarantine under limited capacities

Julian Heidecke1,3,4*, Jan Fuhrmann2, Maria Vittoria Barbarossa1

1 Frankfurt Institute for Advanced Studies, Frankfurt, Germany, 2 Institute of Applied Mathematics, Heidelberg University, Heidelberg, Germany, 3 Interdisciplinary Center for Scientific Computing, Heidelberg University, Heidelberg, Germany, 4 Heidelberg Institute of Global Health, Heidelberg University, Heidelberg, Germany

* julian.heidecke@iwr.uni-heidelberg.de

Abstract

Diagnostic testing followed by isolation of identified cases with subsequent tracing and quarantine of close contacts—often referred to as test-trace-isolate-and-quarantine (TTIQ) strategy—is one of the cornerstone measures of infectious disease control. The COVID-19 pandemic has highlighted that an appropriate response to outbreaks of infectious diseases requires a firm understanding of the effectiveness of such containment strategies. To this end, mathematical models provide a promising tool. In this work, we present a delay differential equation model of TTIQ interventions for infectious disease control. Our model incorporates the assumption of limited TTIQ capacities, providing insights into the reduced effectiveness of testing and tracing in high prevalence scenarios. In addition, we account for potential transmission during the early phase of an infection, including presymptomatic transmission, which may be particularly adverse to a TTIQ based control. Our numerical experiments inspired by the early spread of COVID-19 in Germany demonstrate the effectiveness of TTIQ in a scenario where immunity within the population is low and pharmaceutical interventions are absent, which is representative of a typical situation during the (re-)emergence of infectious diseases for which therapeutic drugs or vaccines are not yet available. Stability and sensitivity analyses reveal both disease-dependent and disease-independent factors that impede or enhance the success of TTIQ. Studying the diminishing impact of TTIQ along simulations of an epidemic wave, we highlight consequences for intervention strategies.

Introduction

In the absence of effective medication or vaccination, mitigation of an infectious disease relies on so called non-pharmaceutical interventions. For person-to-person transmitted diseases these include mask mandates, hygiene measures, contact restrictions or test-trace-isolate-and-quarantine (TTIQ). They aim to reduce epidemiologically relevant contacts (effective contacts),
viz., those between infectious and susceptible individuals during which the pathogen is successfully transmitted. In contrast to population-wide measures, TTIQ is directly targeted at individuals at risk of being infected. In principle, an effective implementation of TTIQ could thus allow to reduce the need for population-wide contact restrictions and thereby lower their socio-economic consequences.

The TTIQ process begins with searching infected individuals within the population, potentially using some kind of diagnostic test which is typically conducted symptom- or risk-based. Once detected, the so-called index cases are asked to isolate and information concerning their close contacts is collected. For this, public health authorities (PHA) provide criteria for defining close contacts, depending on available information on the transmissibility of the disease. This definition aims to target contact persons who have potentially been infected by the detected index cases. Based on this information, attempts are then made to reach the close contacts (they are traced). Successfully approached close contacts are hence asked to self-quarantine for a period sufficient to cover their potential incubation and infectious phase. In this way, PHA aim at catching infected individuals in an early phase of their infection, potentially asymptomatic or presymptomatic, in order to prevent further transmission. From here on another round of contact tracing can be initiated by tracing contacts of contacts.

TTIQ is considered a cornerstone of infectious diseases control and was adopted by many countries worldwide to combat the spread of the coronavirus disease 2019 (COVID-19), the disease caused by infection with severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2). However, its effectiveness is hampered by several factors. Some of these factors are inherent to the TTIQ process:

- Interviewing index cases about their close contacts and eventually approaching these requires time and results in the so-called tracing delay.

- Limited capacities of PHA and testing laboratories cause the efficiency and speed of the TTIQ process to decrease if the prevalence of the considered disease, and thus the workload, increases.

- A variety of reasons can prevent individuals from complying with the request to participate in the TTIQ process.

Other limitations depend on the nature of the disease in question. For COVID-19 these include:

- The airborne transmission limits the proportion of identifiable infected contacts of any given detected infectious person, the so-called tracing coverage, and implies that many potential contacts have to be traced per detected index case.

- Many infected individuals show weak or unspecific symptoms [1, 2]. Moreover, there is a reportedly high proportion of presymptomatic transmissions [3–6]. Therefore, a symptom-based testing strategy will lead to a limited detection ratio (the proportion of infectious individuals detected by testing before recovery) and a significant testing delay (the combined time between turning infectious, administration of a test, obtaining the test result and starting to isolate) has to be expected. Moreover, tracing the contacts of all symptomatic individuals, which might include many individuals with a common cold or other respiratory disease, is virtually impossible. Therefore, tracing was usually limited to the contacts of cases confirmed as infected through a polymerase chain reaction test.

- COVID-19 is associated with a relatively short latency period (time between infection and onset of infectiousness) and infectious period [3, 6–10]. When the delays caused by testing...
and tracing become too large as compared to the timescale of disease progression, a small detection ratio is achieved and the contacts of an identified index case will already have caused infections themselves before they are successfully traced.

In light of these limitations, it is important to evaluate the contribution of TTIQ to disease control and to assess how this depends on (i) disease characteristics and (ii) non-disease-specific factors like maintaining low prevalence (to prevent exhaustion of TTIQ capacities), or a high compliance with isolation mandates. For this purpose, mathematical modeling provides a powerful tool. However, incorporating TTIQ into standard mean-field models is challenging due to the individual-based character of contact tracing. Information about the timing, proximity, and traceability of contacts of identified index cases has to be lifted from the individual-level to the population-level scale [11]. Moreover, in-host processes like the course of infectivity influence the population-level effect of TTIQ. To more readily include such fine-grained mechanisms many models use agent- and network-based approaches [12–17], or the branching process at the onset of the epidemic is studied [18–26]. Ordinary (ODE) and delay differential equation (DDE) models [27–34] are often less complex, allow for full simulation of the epidemic and are more amenable to analytical investigation. However, to derive quarantine rates in these population-level settings certain approximations have to be applied. Striking the right balance between an accurate representation of contact tracing and model simplicity is rather challenging. Several proposed models are based on simplified approaches where contact tracing is represented by an increased removal rate of infectious individuals [30] or a certain fraction of close contacts is assumed to be instantly quarantined [33]. In more rigorous model formulations, contact tracing is directly correlated to the identification of index cases [27, 34], though these works assume the efficiency of TTIQ to be independent of disease prevalence. In contrast, the model introduced in [29] accounts for limited TTIQ capacities assuming perfect efficiency until a certain prevalence/incidence is reached. The later was extended to account for a tracing delay which led to a model based on DDEs [28]. Delays in the testing and contact tracing process have also been modeled using alternative approaches, without necessarily relying on delay equations. One such approach is to introduce additional compartments in the model to account for individuals who will be traced or confirmed as positive in the future. Those individuals then reside in these compartments until they are successfully quarantined or isolated [35, 36]. Another approach is presented in [32] where expressions for the probability that individuals had recent contact with an infectious individual are derived. This probabilistic argument is then used to derive tracing terms that aim at matching the individual- and population-level scales. The model is shown to be in good agreement with an agent-based model for most scenarios. The model in [31], which similarly to [28, 29] includes a limited testing capacity, focuses on contact heterogeneity by deploying a contact exposure distribution. Based on the idea of digital contact tracing, terms are derived to account for tracing of those contacts that are above a certain exposure threshold. This approach aims at finding an optimal notification threshold that manages to balance disease control and quarantine cost by minimizing unnecessarily quarantined contacts. Among those of the above ODE and DDE models that address COVID-19 [28–33], only the one in [31] explicitly accounts for presymptomatic transmissions, a key characteristic of infection with SARS-CoV-2. Models that keep track of the age of infection of infected individuals offer suitable frameworks to incorporate more realistic infectivity profiles and to derive exact contact tracing rates. Such age of infection approaches have been studied previously [4, 16, 25, 26, 37–39], considering also the effect of tracing delays [4, 25] or of limited capacities [39], yet again assuming perfect TTIQ efficiency below a certain incidence threshold.
To aid knowledge and preparedness for future infectious disease outbreaks we derive a new DDE model that refines and extends approaches previously proposed in the literature. To consider limited laboratory testing capacity, we introduce state-dependent testing rates which are motivated by the considerations in [40]. Based on mechanistic assumptions and a series of simplifying approximations, we derive phenomenological contact tracing terms that link the success of index case identification to the quarantine rates achieved by contact tracing. The structure of the resulting delay equations is similar to those presented in [28]. However, as with the testing terms, our model does not assume the contact tracing efficiency to be constant below a certain prevalence. Instead, the efficiency of testing and tracing is assumed to decrease smoothly with increasing prevalence due to the growing workload. Additionally, we account for the possibility of transmission by individuals in an early, potentially presymptomatic, phase of their infection by introducing a compartment of short duration in which individuals are already infectious but do not yet have an increased chance of being tested unless they are successfully traced, as they cannot yet have developed signs of infection. As a working example we consider a scenario inspired by the spread of COVID-19 in Germany during the second wave in late summer and fall of 2020. This specific situation is of interest for our study as in Germany, and many other European countries, an epidemic wave emerged after a summer of low prevalence, most of the population was still susceptible, pharmaceutical interventions were not widely available, and TTIQ was the main control measure applied in addition to population-wide hygiene and contact interventions. As such a situation is not unusual for (re-) emerging diseases, focusing on this specific example does not restrict the general applicability of our results to other infectious diseases. Our modeling approach sheds light on the effectiveness of TTIQ in this critical early phase of an epidemic, underlines factors that limit the success of this strategy, and demonstrates how its performance is impeded once case numbers begin to increase. Our results highlight implications for intervention strategies and underline conditions for an effective implementation of TTIQ.

Materials and methods

The model used in this work extends the known SEIR-type model for infectious disease dynamics [41]. It comprises equations for compartments representing susceptible individuals (S) who can be infected, exposed individuals (E) who are infected but not yet infectious, infectious individuals (U) who can spread the disease, and removed individuals (R) who either recovered or died from the disease. Infections might be confirmed by testing previously undetected infectious individuals. These are assumed to self-isolate (U → I) and disclose infected contact persons that may be traced and quarantined while still being in the latency period (E → Q_E) or after turning infectious (U → Q_U). We consider here solely the tracing and quarantine of individuals who have been infected by the index cases. This means that in the model we neglect the temporary shift to a quarantined compartment for those people who happened to have close contact with the index case, but did not become infected during this event. We assume that quarantined infectious individuals can themselves become confirmed as infectious through testing and are then isolated (Q_U → I). Removed individuals are not involved in disease transmission, assuming permanent immunity upon recovery—at least for the short simulation times under consideration. To account for the reportedly high proportion of COVID-19 transmissions occurring prior to the onset of any potential symptoms [3–6], we separate the infectious phase into two periods. The first period (early infectious phase, all individuals in U_1, Q_U_1, I_1) starts immediately after the exposed phase and marks the onset of infectiousness. We characterize the transition to the second period (late infectious phase, all individuals in U_2, Q_U_2, I_2) by reaching a potential symptom onset. For simplicity, we do not differentiate the
individuals in the late infectious phase into those with a symptomatic and those with a completely asymptomatic course of infection (see e.g., [28, 42]) which would introduce additional highly uncertain parameters like the transmission rate and the duration of infectiousness for asymptomatic cases. However, we implicitly account for the presence of asymptomatic or weakly symptomatic cases in the average rate at which individuals in the late infectious stage are detected by testing.

All the state variables as well as their meanings are summarized in Table 1. We describe the dynamics of these compartments by the following system of differential equations

\[
\begin{align*}
\dot{S} &= -\lambda S \\
\dot{E} &= \lambda S - \alpha E - Tr_E \\
\dot{Q}_E &= Tr_E - \alpha Q_E \\
\dot{U}_1 &= \alpha E - \eta_{U_1} U_1 - \gamma_1 U_1 - Tr_{U_1} \\
\dot{Q}_{U_1} &= \alpha Q_E + Tr_{U_1} - \eta_{QU_1} Q_{U_1} - \gamma_1 Q_{U_1} \\
\dot{I}_1 &= \eta_{U_1} U_1 + \eta_{QU_1} Q_{U_1} - \gamma_1 I_1 \\
\dot{U}_2 &= \gamma_1 U_1 - \eta_{U_2} U_2 - \gamma_2 U_2 - Tr_{U_2} \\
\dot{Q}_{U_2} &= \gamma_1 Q_{U_1} + Tr_{U_2} - \eta_{QU_2} Q_{U_2} - \gamma_2 Q_{U_2} \\
\dot{I}_2 &= \eta_{U_2} U_2 + \eta_{QU_2} Q_{U_2} + \gamma_1 I_1 - \gamma_2 I_2 \\
\dot{R} &= \gamma_2 (U_2 + Q_{U_2} + I_2)
\end{align*}
\]

where

\[
\lambda = \beta_{U_1} U_1 + \beta_{U_2} U_2 + \beta_{Q_1} Q_{U_1} + \beta_{Q_2} Q_{U_2} + \beta_{I_1} I_1 + \beta_{I_2} I_2.
\]

The total population size \( N \) is assumed to be constant. For simplicity, we neglect demographics, including disease induced deaths, for the simulated period. A sketch of the corresponding transitions between compartments is given in Fig 1.

The parameters in model (1) are defined as follows: \( \beta_X \) denotes the rate of transmission of the disease to susceptibles via contacts with infectious individuals from compartment \( X \). We set \( \beta_{U_1} = \theta \beta_{U_2} \) for some scaling factor \( \theta \) describing the extent of early vs late transmission.

Table 1. Dynamic variables of model (1).

| Notation | Description |
|----------|-------------|
| S        | susceptible individuals |
| E        | undetected exposed individuals |
| Q_E      | traced and quarantined exposed individuals |
| U_{1,2}  | undetected (early, late) infectious individuals |
| Q_{U_{1,2}} | traced and quarantined (early, late) infectious individuals |
| I_{1,2}  | confirmed and isolated (early, late) infectious individuals |
| R        | removed individuals |

https://doi.org/10.1371/journal.pone.0299880.t001
Moreover, we assume that undetected infectious individuals, lacking the same knowledge about their risk of being infected, have a higher transmission rate than quarantined infectious individuals ($\beta_{Ui} > \beta_{Qi}$, $i \in 1, 2$) who are expected to restrict their contacts to a higher degree. We further assume that quarantined individuals who are not yet confirmed/isolated reduce their contacts less strictly than confirmed cases ($\beta_{Qi} > \beta_{Ii}$, $i \in 1, 2$). We express the transmission rate of quarantined and of isolated infectious individuals as

$$\beta_{Qi} = \rho_Q \beta_{Ui}, \quad \beta_{Ii} = \rho_I \beta_{Ui}, \quad i \in 1, 2.$$  

The parameters $\rho_Q, \rho_I \in [0, 1]$ describe the fractions of secondary infections caused per unit time by an average quarantined case and by an average isolated case as compared to an average undetected case, respectively. In this sense, $\rho_Q$ and $\rho_I$ capture the efficiency of quarantine and case isolation in reducing transmissions. Motivated by the above discussion we assume $1 > \rho_Q > \rho_I$. Disease progression is described by the rates $\alpha$, $\gamma_1$ and $\gamma_2$, that is, $1/\alpha$ is the average duration of the latent period and $1/\gamma_1$ and $1/\gamma_2$ are the average duration of the early and late infectious period, respectively.

Detection of infectious individuals by testing in compartment $X$ is described by the rates $\eta_X$. Since all the individuals in compartment $U_i$ are without any symptoms, whereas a certain fraction of individuals in $U_2$ show specific symptoms, we assume that the detection rate in compartment $U_2$ is significantly larger $\eta_{U2} \gg \eta_{U1}$. Furthermore, it is plausible to assume that the PHA strive to test all traced individuals during their quarantine (independently of whether they show symptoms or not) to identify which of the reported contacts are indeed infected. Thus, we consider the rate at which these individuals are detected to be significantly larger than the corresponding rate for undetected infectious individuals $\eta_Q := \eta_{QU1} = \eta_{QU2} \gg \eta_{U2}$.

The terms $Tr_X$ denote the rates at which infected individuals in compartment $X$ are quarantined due to contact tracing. We assume that both testing and contact tracing depend on the
availability of capacities, rendering their effectiveness state-dependent. In the following, we first describe expressions for the testing terms in consideration of this dependency. Subsequently, we approximate capacity limited contact tracing assuming that it follows successful index case identification with a time delay $\kappa$. The tracing terms $Tr_X$ therefore depend on the state of system (1) in the past. For simplicity of notation, we chose not to explicitly indicate this in the right-hand side of system (1).

**Testing terms**

We assume that the per capita detection rates are state-dependent and decrease for larger prevalence of infectious individuals due to finite testing capacity. More precisely, as motivated in [40], we set

$$
\begin{align*}
\eta_{U_1} &= \sigma_{U_1} \bar{\eta}, \\
\eta_{U_2} &= \sigma_{U_2} \bar{\eta}, \\
\eta_Q &= \sigma_Q \bar{\eta},
\end{align*}
$$

where

$$
\bar{\eta} := \frac{\sigma_+}{S + \sum \sigma_X X + \sigma_-}, \quad X \in \{E, U_1, Q_{U_1}, I_1, U_2, Q_{U_2}, I_2, R\}.
$$

Here $\sigma_+$ is the maximal number of tests that can be administered and evaluated per unit time, $\sigma_-$ describes the fact that lab capacity cannot be stored and goes to waste unless quickly used, and $\sigma_X$ expresses the relative frequency of getting tested for individuals in compartment $X$ relative to the respective frequency for susceptibles. The essential meaning of the formulation of per capita detection rates as in Eq (2) becomes clear when considering the total detection rate in a specific compartment. The rate at which late infectious individuals are tested/detected can be written as

$$
\eta_{U_2} U_2 = \sigma_{U_2} \bar{\eta} U_2 = \sigma_{U_2} \frac{U_2}{S + \ldots + \sigma_{U_2} U_2 + \ldots + \sigma_-}.
$$

We can interpret

$$
\frac{\sigma_{U_2} U_2}{S + \ldots + \sigma_{U_2} U_2 + \ldots + \sigma_-}
$$

as the fraction of $\sigma_+$ that is allocated to late infectious individuals which depends on the current number of late infectious individuals $U_2$ as well as their relative likeliness of being tested compared to other individuals in the population encoded in $\sigma_{U_2}$. Similarly,

$$
\frac{\sigma}{S + \ldots + \sigma_{U_2} U_2 + \ldots + \sigma_-}
$$

denotes the fraction of tests that remain unused due to a lack of individuals meeting the symptom/risk-based testing criteria. We can imagine $\sigma_- = \sigma Y$ where $Y$ is a theoretical (constant) population consuming tests. Setting $\sigma_- = 0$ would correspond to full employment of available lab facilities on the population $N$ by administering as many tests as can possibly be processed independent of the prevalence of the disease. As discussed before, it is reasonable to assume that

$$
\sigma_Q \gg \sigma_{U_2} \gg 1 = \sigma_X, \quad X \in \{E, U_1, I_1, I_2, R\},
$$

with $\sigma_Q := \sigma_{Q_e} = \sigma_{Q_{U_1}} = \sigma_{Q_{U_2}}$, meaning that the chance of being tested is significantly increased for late infectious individuals, because they might show symptoms of the disease,
and quarantined individuals, because they were identified as a close contact of an infectious individual. This leads to reasonably high detection rates at low prevalence, but as the prevalence rises, there are more and more individuals who are considered important to receive one of the limited number of tests, the per capita detection rates decrease, and a greater proportion of infections goes undetected. In contrast, a setting where $\sigma_X = 1$ for all $X$ would correspond to a scenario where all available tests are used for randomly screening the population and leads to a constant but small detection rate of infections. In comparison to Eq (2), a high and constant detection rate in the compartment of late infectious individuals would lead to unrealistically high incidences of confirmed cases as the true prevalence increases. Although the detection rates in our model are not constant but state-dependent we usually omit this dependence in our notation and only specify it when referring to times in the past.

Contact tracing terms

To make the derivation of the contact tracing terms easier to follow, we describe it here without decomposing the infectious compartments ($U, I, Q$) into an early ($U_1, I_1, Q_{U_1}$) and late ($U_2, I_2, Q_{U_2}$) infectious phase. Thus, in the following we derive the rates at which infected contacts are quarantined from the exposed ($Tr_E$) and from the infectious stage ($Tr_U$). In the almost analogous derivation of the terms ($Tr_E, Tr_{U_1}, Tr_{U_2}$) for the full model (1), we take into account that the index cases detected by testing in $U_1$ and $U_2$, respectively, yield different numbers of secondary cases that have been infected on average for different lengths of time before being traced. The quite cumbersome derivation of these terms is included in Appendix A in S1 File.

The process of contact tracing is initiated upon detection of an index case by testing. Here we focus on the effect of manual forward contact tracing. This process is based on PHA interviewing the positively tested index case in order to identify contacts they might have infected. Digital contact tracing, which would support this process by using some kind of digital device that keeps track of contacts between individuals and ideally notifies close contacts instantly when index cases are confirmed as infected, as well as backward tracing, which aims to identify the individual that infected the index case, are not considered in this work. The contact tracing process is incorporated into model (1) based on the following assumptions:

(A1). Contact tracing is triggered by confirmation of infectious cases by testing.

(A2). Contact tracing is only triggered by confirmation of previously undetected infectious individuals ($U \rightarrow I$) (first-order tracing). More precisely, tracing contacts of contacts (recursive tracing) is neglected here.

(A3). There is a fixed delay of $\kappa$ units of time between the confirmation of an index case and the start of quarantine for their contacts. This delay represents the duration of the process of interviewing the index case and reaching out to close contacts.

(A4). Although we assume them to be imperfectly isolated, index cases only disclose contacts made before their time in isolation.

(A5). Only a certain fraction of secondary infections can be identified by PHA via contact tracing.

(A6). PHA rely on limited capacities to conduct contact tracing.

In reality, all traced close contact persons, including those who did not get infected during their contact to the index case, are asked to quarantine. At the time of contact notification, there is no way to pinpoint the truly infected contacts. Even if contacts quickly receive a laboratory test, some of them may still be in a phase where their infection is not yet detectable. This
means that in practice many susceptible individuals would quarantine, but also that additional undetected infected individuals, that were not necessarily infected by the index case, could be quarantined by chance. While we account for the tracing effort due to such contact persons, we do not explicitly consider the effects of their quarantine on the outbreak dynamics.

Assumptions (A1)-(A3) imply that the rate at which contacts are quarantined at time $t$ is proportional to the rate $Z_{U\text{U}}^{t_k}$ at which previously undetected infectious individuals are detected by testing at time $t - \kappa$. To calculate how this translates into the rate at which contacts are quarantined at time $t$, we approximate the number of contacts reported by each of the detected cases. To this end, consider an average index case that is confirmed as infectious by testing at time $t - \kappa$ and thus initiates contact tracing at time $t$. We assume that for the interview of this index case the PHA use a certain tracing window $T$ that determines the time interval $J_T(t) := [t - \kappa - T, t - \kappa]$ for which contacts of the index case are registered (tracing interval), neglecting that additional contacts made between time $t - \kappa$ and time $t$ could also be reported (see assumption (A4)).

Depending on the relationship between the tracing window $T$ and the age of infection $\tau(t)$, measuring the time for which the average index case initiating contact tracing at time $t$ was infectious by time $t - \kappa$ of being detected, the tracing interval $J_T(t)$ is composed of two subintervals:

- the, potentially trivial, part of $J_T(t)$ during which the index case was not yet infectious
  \[
  J_{\text{nin} T}(t) := \begin{cases} 
  \emptyset, & \text{if } T \leq \tau(t) \\
  [t - \kappa - T, t - \kappa - \tau(t)], & \text{if } T > \tau(t),
  \end{cases}
  \]

- and the time in $J_T(t)$ during which the index case has been infectious
  \[
  J_{\text{inf} T}(t) := \begin{cases} 
  [t - \kappa - T, t - \kappa], & \text{if } T \leq \tau(t) \\
  [t - \kappa - \tau(t), t - \kappa], & \text{if } T > \tau(t).
  \end{cases}
  \]

We approximate $\tau(t)$ by the expected residence time in the undetected infectious stage $U$ according to the recovery rate $\gamma$ and the detection rate $\eta_U$ evaluated at time $t - \kappa$, i.e., $\tau(t) = 1/(\eta_U|_{t-\kappa}^{\gamma})$ (the estimate for our full model (1) is given in Appendix C in S1 File). We want to note here that by considering an average index case instead of accounting for the full distribution of different index cases, we simplify our model which in a more detailed approach could be formulated as a system of partial differential equations where the infected compartments are structured by age of infection.

We further assume that PHA use a certain definition of close contact and ask the index case to report only contacts satisfying this definition. Along with the index case’s ability to recall such contacts this determines

- $\overline{c}_1$, the reported close contact rate corresponding to the time interval $J_{\text{nin} T}$,
- $\overline{c}_2$, the reported close contact rate corresponding to the time interval $J_{\text{inf} T}$, and
- $\overline{p}$, the infection probability corresponding to the close contacts made during $J_{\text{inf} T}$. 

We approximate $\tau(t)$ by...
On the one hand, it is reasonable to assume $\tilde{c}_\varepsilon \leq \tilde{c}_1$, since individuals in $U$ might reduce their contacts upon starting to show symptoms. On the other hand, this is countered by the fact that less recent contacts are harder to recall. Not trying to guess which of these effects is more pronounced, we work with the simplifying assumption $\tilde{c} := \tilde{c}_1 = \tilde{c}_\varepsilon$. The product $\tilde{\beta} = \tilde{p} \tilde{c}$ determines the rate at which the index case produced traceable effective contacts in $j_T^{\text{ind}}(t)$. Comparing $\tilde{\beta}$ with $\beta_U$ and $|j_T^{\text{ind}}(t)|$ with $r(t)$ gives a proxy for the fraction of infected contacts covered by the contact tracing process (see assumption (A5)). We call the fraction

$$\omega(t) = \frac{|j_T^{\text{ind}}(t)| \tilde{\beta}}{\beta_U} \leq 1$$

the tracing coverage at time $t$. In our specific parameterization, we assume that the tracing window $T$ is always sufficiently long to cover the infectious period of an index case (see Appendix C in S1 File). In this simplified setting, the tracing coverage reduces to the ratio between the tracing rate $\tilde{\beta}$ and the transmission rate $\beta_U$. Social and hygiene measures in place during the tracing interval obviously influence not only the transmission rates but also $\tilde{c}$, $\tilde{p}$, $\tilde{\beta}$. Moreover, the PHA might change their close contact definition over time or individuals might develop an increased awareness to keep track of their personal contacts to reduce recall issues further influencing these parameters. For the sake of clarity, we refrain from explicitly including this complexity for the moment and discuss how we handle such measures and time-dependent parameters in Appendix B in S1 File. Throughout the presentation of our results we chose to express changes in $\tilde{\beta}$ indirectly by specifying values for $\beta_U$ and the tracing coverage $\omega$ due to their straightforward interpretation.

A possible timeline of events for an index case detected by testing at time $t - \kappa$ whose contacts are quarantined at time $t$ is shown in Fig 2.

Following the above assumptions the rate at which contacts become traceable at time $t$ is given by

$$c_{\text{pot}}(t) = \int_{j_T(t)} \tilde{c} N_F(s) \eta_U|_I - \kappa U(t - \kappa) ds \approx |j_T(t)| \tilde{c} N_F(t - \kappa) \eta_U|_I - \kappa U(t - \kappa), \quad (4)$$

where $N_F := S + E + U + \rho_Q(Q_E + Q_U) + \rho I + R$. The approximation in Eq (4) assumes that changes in $N_F$ (approximated by $N_F(t - \kappa)$ throughout $j_T(t)$) are neglectable. The subpopulation $N_F$ accounts for the reduced contact rates with quarantined and isolated individuals represented by the same factors $\rho_X$ as in the transmission rates. Due to limited resources that can be provided to conduct contact tracing (assumption (A6)) not all traceable contacts necessarily end up being successfully contacted and quarantined. We assume an upper bound $\Omega$ (tracing capacity) for the actual rate at which contacts are quarantined due to contact tracing. As a rough approximation we could choose

$$c_{\text{act}}(t) = \min(\Omega, c_{\text{pot}}(t)) \quad (5)$$

for the actual rate at which contacts are quarantined at time $t$. However, we suppose the tracing efficiency, which we define as the share of successfully traced contacts among all traceable contacts while maintaining the constant tracing delay $\kappa$, to be continuously decreasing as the number of traceable contacts increases. That is, we assume that almost perfect efficiency can only be achieved for small rates of traceable contacts. For this reason, we smooth Eq (5) by a
saturating function of the form

\[
c_{ac}(t) = \frac{1}{\left(c_{pot}(t) + \Omega\right)^p}, \quad p > 0.
\]

As shown in Fig 3, a larger choice of \( p \) (which we call tracing efficiency constant) corresponds to a slower initial decrease in tracing efficiency as \( c_{pot}(t) \) rises whereas the limit case \( p \to \infty \) gives

\[
e(t) = \frac{\Omega}{\|c_{pot}(t) - \Omega\|_\infty},
\]

which exactly corresponds to Eq (5). Several factors determine whether the tracing efficiency can be kept high when the prevalence rises (large \( p \)) or whether it is quickly diminished (small \( p \)). These include the ease with which additional workforce can be recruited and the efficiency at which this additional workforce, that may have been trained for a different purpose,
operates. Moreover, when considering an epidemic outbreak in a large area, the outbreak is usually spatially heterogeneous, with some regions more affected than others. The tracing efficiency can only be kept high in regions with high prevalence when capacity from low prevalence regions can easily be shifted. If this is not the case (low $p$), then severely affected regions already have low tracing efficiency although the overall prevalence in the considered area might still be relatively low. In a spatially homogeneous model like (1) this is reflected in a fast decreasing tracing efficiency as prevalence rises. As the infection continues to spread, the outbreak is likely to approach states of high prevalence in all regions. As soon as the pool of additionally recruitable workforce is depleted, it is plausible to assume that the considered area makes use of its total capacity and a maximal rate at which contacts can be quarantined is approached.

Recapping the effective close contacts made in the time interval $J_{\text{inf}}(t)$, and accounting for the tracing efficiency, we can write the rate at which infected contacts are quarantined at time $t$ as

$$c_{\text{act}}(t) = \int_{J_{\text{inf}}(t)} \beta \bar{S}(s) \eta_{U|I\rightarrow\Lambda} U(t - \kappa) e(t) ds$$

$$\approx \left[ \frac{J_{\text{inf}}(t)}{J_{\text{inf}}(t)} \bar{\beta} S(t - \kappa) \right] \frac{\eta_{U|I\rightarrow\Lambda} U(t - \kappa)}{e(t)} , \quad (7)$$

where we approximate the susceptible population (approximated by $S(t - \kappa)$) to be constant in the short time interval $J_{\text{inf}}(t)$. The approximation in Eqs (4) and (7) allow us to simplify our model to involve only the constant delay $\kappa$, instead of integral equations with delays distributed over the (infectious part of) the tracing interval.

Fig 3. Illustration of Eq (6) for the choice $\Omega = 40,000$ and multiple values of $p$. The limit $p \to \infty$ recovers Eq (5). Mind the different scaling of the axes.

https://doi.org/10.1371/journal.pone.0299880.g003
Using our proxy Eq (7) for the actual rate at which infected contacts are quarantined at time $t$, we can now determine the contact tracing rates $\text{Tr}_E(t)$ and $\text{Tr}_U(t)$. Following a similar reasoning as in [28], we can approximate the fraction of Eq (7) originating from the exposed or infectious stage. Let us again consider the average index case detected by testing at time $t - \kappa$. Infection of close contacts reported by this index case took place during $f^u_T(t)$ and by the time of being quarantined all of these contacts are infected for at least a duration of $\kappa$ units of time due to the tracing delay. Assuming the infection events produced by our average index case to be uniformly distributed on $f^u_T(t)$, we approximate the age since infection of an average infected contact by the time $t$ of being quarantined as

$$\bar{\tau}(t) = \kappa + \frac{1}{2} f^u_T(t).$$

(8)

It should be noticed that the second term on the right-hand side of Eq (8) is a subtle but important addition to the derivation in [28] that takes into account the average time elapsed between infection of close contacts and detection of the index case.

After spending $\bar{\tau}(t)$ units of time in the infected chain, a fraction

$$\mu_E(t) := e^{-\bar{\tau}(t)}$$

of successfully traced individuals infected by the index case remains in the exposed state at the time of tracing ($E \to Q_E$). The remaining fraction described by the term $1 - \mu_E(t)$ have entered the $U$-compartment but might have been tested themselves or might have recovered by the time of being traced. Therefore, to approximate the fraction of quarantined contacts coming from the infectious stage ($U \to Q_U$), we keep following the first-order kinetics induced by recovery (rate $\gamma$) and testing (rate $\eta_U$) and solve the auxiliary equation

$$\frac{d\tilde{U}}{ds} = -(\gamma + \eta_{U|_{t=\kappa}})\tilde{U} + \alpha e^{-\bar{\tau}}, \quad \tilde{U}(0) = 0$$

(9)

up to time $s = \bar{\tau}(t)$. The initial condition $\tilde{U}(0) = 0$ accounts for the fact that each of the infected contacts is initially in the exposed stage. They eventually enter the infectious state which is described by the term $\alpha e^{-\bar{\tau}}$. Notice that in order to easily solve Eq (9), we have assumed the detection rate $\eta_{U|_{t=\kappa}}$ to be approximately constant (approximated by $\eta_{U|_{t=\kappa}}$) for the short time $\bar{\tau}(t)$. Replacing $\eta_{U|_{t=\kappa}}$ by $\eta_{U|_{t=\kappa}}$ in Eq (9), in which case Eq (9) would need to be solved on $[t - \bar{\tau}(t), t]$, would again require keeping track of distributed delays. The solution to the initial value problem (9) evaluated at time $s = \bar{\tau}(t)$ is given by

$$\mu_U(t) := \tilde{U}(\bar{\tau}(t)) = \frac{\alpha}{\eta_{U|_{t=\kappa}} + \gamma - \alpha} \left( e^{-\bar{\tau}(t)} - e^{-\eta_{U|_{t=\kappa}} + \gamma} \bar{\tau}(t) \right).$$

which continuously extends to $\mu_U(t) = \alpha \bar{\tau}(t) e^{-\bar{\tau}(t)}$ in the degenerate case $\alpha = \eta_{U|_{t=\kappa}} + \gamma$. This motivates us to set

$$\text{Tr}_E(t) = \mu_E(t) e_{\text{act}}^u(t),$$

$$\text{Tr}_U(t) = \mu_U(t) e_{\text{act}}^u(t).$$

In summary, the derivation of these contact tracing terms involved to approximate

- the age of infection of an average index case (note that in a model accurately tracking the age of infection $\tau$, the integral terms in Eqs (4) and (7) would have an additional outer integral running over all possible values of $\tau$ adjusting for each cohort of index cases $\eta_U(\tau)|_{t=\kappa} U(t - \kappa, \tau)$ the bounds of the inner integral),
parameters and subpopulations to be constant over (parts of) the tracing interval,
and the distribution of reported contacts over the infected compartments at the time of
being quarantined via their estimated age since infection.

All in all, these approximations simplify our model (1) to a system containing delay differ-
ential equations with a single constant delay \( \kappa \) instead of partial differential equations with dis-
tributed delays, which would result from a more precise but also more complex approach.

**Modeling of social and hygiene measures and assessment of TTIQ effectiveness**

Here, we briefly describe how population-wide social and hygiene measures (e.g., mask man-
dates, increased hand washing, contact restrictions) are modeled and how we evaluate the
effectiveness of TTIQ in controlling disease spread. For a detailed description on how we
account for the effect of these measures on the contact tracing terms we refer to Appendix B in
S1 File.

Population-wide social and hygiene measures are modeled by a time dependent factor
\( \phi(t) \in [0, 1] \), that scales the transmission rates, i.e.,

\[
\beta_U(t) = \phi(t) \bar{\beta}_U,
\]

where \( \bar{\beta}_U \) is the baseline transmission rate of individuals in the undetected late infectious
stage corresponding to a phase without any intervention. In case of COVID-19, this can be
seen as the transmission rate that would be observed given contact levels as before, or in a very
early phase during, the first occurrence of the disease. Thus, this baseline transmission rate is
associated to the basic reproduction number by

\[
R_0 = \left( \frac{\gamma_1}{\gamma_1 + \gamma_2} \right) N.
\]

The factor \( \phi(t) \) can be seen as the level of effective contacts at time \( t \) relative to the “pre-
COVID-19” scenario and leads to the control reproduction number

\[
R_c := \phi R_0.
\]

For the evaluation of the effectiveness of TTIQ in preventing an epidemic outbreak, we con-
sider \( \phi^* \), the critical level of effective contacts such that the disease-free equilibrium (DFE),
\((N, 0, \ldots, 0)\), is stable for \( \phi < \phi^* \) and unstable for \( \phi > \phi^* \). In the absence of TTIQ this is clearly
given by

\[
\phi^* = \frac{1}{R_0}.
\]

In the presence of TTIQ we can derive \( \phi^* \) from a numerical stability analysis of the DFE (see
Appendix D in S1 File for details). The higher the obtained \( \phi^* \), the higher the effectiveness of
TTIQ and the lower the need for social and hygiene measures. Comparison to the value
obtained in the absence of TTIQ (see Eq (11)) gives a measure of how much population-wide
contact restrictions can be relaxed by the addition of TTIQ. For a given TTIQ scenario and the
 corresponding \( \phi^* \) we can also interpret

\[
R_c^{\text{max}} := \phi^* R_0
\]

as the maximal control reproduction number for which the given TTIQ effort would still be
sufficient to prevent an outbreak. Later, we also consider scenarios with high prevalence that operate far from the disease-free state, where stability of the DFE does not offer sufficient information for disease control. In these cases we evaluate the effectiveness of TTIQ based on \( \bar{\phi} \), which we define as the critical level of effective contacts that yields a stagnation in the incidence of infected individuals. In other words, for \( \phi > \bar{\phi} \) the incidence would further increase and for \( \phi < \bar{\phi} \) it would decrease. Clearly, at low prevalence and low immunization we have \( \bar{\phi} \approx \phi^* \).

We remark that both \( \phi^* \) and \( \bar{\phi} \), as well as the corresponding values of TTIQ parameters, are threshold values that ensure stability of the DFE or the incidence of infected individuals (i.e., reduce the effective reproduction number to \( R_t \approx 1 \)). However, in reality the aim is usually to reduce \( R_t \) to a specified value below 1. Therefore, the derived parameter values should be interpreted as minimally required efforts. In particular, operating at or slightly below \( R_t = 1 \) would come with the risk of minor changes in some external parameters driving \( R_t \) above 1, initiating a new wave of exponentially increasing case loads.

**Results**

We apply model (1) to investigate the effectiveness of TTIQ in disease control. As an example of a disease spreading in a population with low immunity, we consider a scenario inspired by the early spread of COVID-19 in Germany. For this framework, we defined a baseline parameter setting that is motivated in detail in Appendix C in S1 File and summarized in Table 2. We start by considering the dynamics near the DFE and study the effectiveness of TTIQ in preventing an epidemic outbreak. Examining the sensitivity of our results to parameter changes reveals the disease- and non-disease-specific factors influencing the effectiveness of TTIQ. We then turn to the situation where disease spread is not fully controlled and the effect of TTIQ diminishes as the disease prevalence rises. Revisiting parameter changes reveals implications for intervention strategies.

**Table 2. Parameters of model (1).** The given values describe our baseline setting which is motivated in Appendix C in S1 File. The values of some parameters are shown in a more compact notation by incorporating the constant population size \( N \) in their expression. This is made for ease of representation only. Note that there is no difference in dimensionality between the units people and tests.

| Notation         | Description                                                                 | Value   | Units            |
|------------------|-----------------------------------------------------------------------------|---------|-----------------|
| \( \bar{\mu}_\infty \) | baseline transmission rate of undetected late infectious individuals          | 0.33/\( N \) | days \(^{-1}\) people \(^{-1}\) |
| \( \theta \)     | scaling factor for transmission rate in early vs late infectious period       | 1.5     | dimensionless    |
| \( (\rho > \rho_1) \) | strictness of quarantine and isolation                                       | (0.2, 0.1) | dimensionless    |
| \( \alpha \)     | exposed to early infectious rate                                            | 1/3.5   | days \(^{-1}\)   |
| \( \gamma_1 \)   | early to late infectious rate                                               | 1/2     | days \(^{-1}\)   |
| \( \gamma_2 \)   | late infectious to removed rate                                             | 1/7     | days \(^{-1}\)   |
| \( \sigma \)     | maximal number of tests administered and evaluated per day                   | 200 000 | days \(^{-1}\) tests |
| \( \sigma_\kappa \) | test loss constant                                                          | 1.353N  | tests            |
| \( (\sigma_{2}, \sigma_0) \) | relative frequency of testing undetected late infectious and traced individuals compared to susceptibles | (93, 300) | dimensionless |
| \( \Upsilon \)   | tracing window                                                              | 9       | days             |
| \( \zeta \)      | baseline reported close contact rate                                         | 0.8/\( N \) | days \(^{-1}\) people \(^{-1}\) |
| \( \omega \)     | tracing coverage                                                            | 0.65    | dimensionless    |
| \( \Omega \)     | maximal contact quarantine rate                                              | 40 000  | days \(^{-1}\) people |
| \( \kappa \)     | tracing delay                                                               | 2       | days             |
| \( \rho \)       | tracing efficiency constant                                                  | 2       | dimensionless    |
| \( N \)          | population size                                                             | 83 000 000 | people          |

https://doi.org/10.1371/journal.pone.0299880.t002
Effectiveness of TTIQ in preventing an outbreak

We compared values of the critical level $\phi^*$ of effective contacts for the stability of the DFE for (i) a scenario without TTIQ, (ii) a scenario in which only testing is performed, and (iii) a scenario in which both testing and contact tracing are performed (Fig 4A). In our baseline setting we assume $R_0 = 3.3$, and thus, get $\phi^* \approx 0.304$ in the absence of TTIQ from Eq (11). Adding testing activity controls the disease at higher rates of effective contacts $\phi^* \approx 0.407$. The addition of contact tracing to testing further increases $\phi^*$ to $\phi^* \approx 0.461$. These values for $\phi^*$ correspond to a maximal control reproduction number that can be contained (see Eq (12)) of at most $R_c^{\max} \approx 1.34$ when only testing is applied and $R_c^{\max} \approx 1.52$ when the full TTIQ approach is applied. That means that if the reproduction number would be brought to less than 1.34 by other measures, testing alone would be sufficient to suppress an outbreak, and if it were lower than 1.52, the full TTIQ approach could prevent an outbreak—assuming that the dynamics were still sufficiently close to the DFE. This shows that in our baseline setting the full TTIQ approach allows for an approximately 52% higher effective contact rate, testing contributes more to disease control than contact tracing, and even under the application of both testing and contact tracing a quite severe reduction of effective contacts by other measures to 46% of the pre-COVID-19 level is needed.

Sensitivity to TTIQ parameters

To explore alternative parameter settings and determine the most influential TTIQ parameters on $\phi^*$, we first considered single parameters one after the other and varied them in ranges according to Table 3 (Fig 5). As shown in Fig 5A, weak isolation of confirmed infectious cases $I$ ($\rho_I$ close to 1) leads to $\phi^* \approx 0.304$, thus, renders TTIQ completely ineffective. Contact tracing is dependent on prior index case identification and is more effective the shorter the testing delay. This explains why an improved relative frequency $\sigma_{U_t}$ of testing undetected late

![Fig 4. Critical level $\phi^*$ of effective contacts for the stability of the DFE. Here we compare a scenario without any TTIQ (no TTIQ), a scenario where only testing is conducted (only testing) and a scenario where testing and tracing is carried out (full TTIQ). This is shown for A the baseline parameter setting given in Table 2 and B a setting with improved testing such that $\sigma_{U_t} = 185$.](https://doi.org/10.1371/journal.pone.0299880.g004)
infectious individuals has the side effect of increasing the effectiveness of contact tracing (compare Fig 4A where \( s_{U_2} = 93 \) vs. Fig 4B where \( s_{U_2} = 185 \)) and why \( s_{U_2} \) has a significantly larger impact on \( \phi^* \) than the parameters associated with contact tracing \( (\omega, \kappa, \sigma_Q, \rho_Q) \) (compare Fig 5B with Fig 5C–5E). The tracing coverage \( \omega \) appears to be slightly more important than the tracing delay \( \kappa \) (compare Fig 5C and 5D). This, however, is mainly due to the baseline parameters we chose, with a relatively short tracing delay \( \kappa = 2 \) and only moderate tracing coverage \( \omega = 0.65 \). Either of these parameters being in an unfavorable range severely limits the effect of any change of the other. In particular, in a setting with long baseline tracing delay but high tracing coverage \( \phi^* \) is more sensitive to changes in the tracing delay (not shown here). The strictness of quarantine \( \rho_Q \) as well as the relative frequency \( \sigma_Q \) at which quarantined individuals are tested appear to be of minor importance (Fig 5E and 5F). It should be noticed, however, that we chose quite optimistic values for \( \rho_Q \) and \( \sigma_Q \) in our baseline setting (Table 2). Clearly, \( \rho_Q \)

---

**Table 3. TTIQ parameter ranges considered in the sensitivity analysis.**

| parameter | meaning | range |
|-----------|---------|-------|
| \( \omega \) | tracing coverage | \([0, 1]\) |
| \( \sigma_{U_2} \) | relative frequency of testing undetected late infectious individuals | \([1, 186]\) |
| \( \sigma_Q \) | relative frequency of testing traced individuals | \([1, 600]\) |
| \( \rho_Q \) | strictness of quarantine | \([0, 1]\) |
| \( \rho_I \) | strictness of isolation | \([0, 1]\) |
| \( \kappa \) | tracing delay | \([0.5, 14]\) |

[https://doi.org/10.1371/journal.pone.0299880.t003](https://doi.org/10.1371/journal.pone.0299880.t003)

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**Fig 5.** Critical level \( \phi^* \) of effective contacts for the stability of the DFE (solid lines) varying single TTIQ parameters. For comparison we also indicate the value of \( \phi^* \) derived from our baseline parameter setting given in Table 2 (dashed line).

[https://doi.org/10.1371/journal.pone.0299880.g005](https://doi.org/10.1371/journal.pone.0299880.g005)
becomes more important when $\sigma_Q$ is smaller and $\rho_Q$ gains importance when $\rho_I$ is close to unity (Fig 6A). In addition, $\sigma_Q$ may also be of importance for recursive tracing which is neglected in our equations. Simultaneous improvements of other parameters show synergistic effects. For example, stricter isolation and quarantine reinforces the benefits of improved testing (Fig 6B). A similar effect is present between improving tracing coverage and improving testing (Fig 6C), and between improvements of tracing coverage and tracing delay (Fig 10A).

To gain insight on the global sensitivity of $\phi^*$ we used latin hypercube sampling on the TTIQ parameter space as given in Table 3 ranges and calculated partial rank correlation coefficients (PRCCs). This allows us to assess which TTIQ parameters are most influential on $\phi^*$, even if other parameters are simultaneously perturbed [43]. We excluded the strictness of quarantine $\rho_Q$ of traced contacts from this analysis to rule out the unnatural cases $\rho_Q < \rho_I$ in which traced but so far unconfirmed cases reduce their contacts more strictly than confirmed cases since in these cases increases in $\sigma_Q$ would be predicted to have negative impact on $\phi^*$. Instead we allowed $\rho_I$ and all the remaining parameters given in Table 3 to vary and set

$$\rho_Q = \begin{cases} 2\rho_I, & \rho_I < 0.5 \\ 1, & \text{else} \end{cases}$$

The calculated PRCCs support our observations from the variation of single parameter values. The strictness of isolation $\rho_I$ of confirmed cases is predicted to be most influential on $\phi^*$ having the largest absolute PRCC, closely followed by the relative frequency $\sigma_{U2}$ of testing undetected late infectious individuals which is associated with a significantly larger absolute PRCC than all the parameters corresponding to contact tracing $\omega$, $\kappa$, $\sigma_Q$ (Fig 7).

### Impact of early infectiousness and other disease characteristics

We considered variations in parameters describing disease characteristics to investigate the impact of potential uncertainty in our parameter choices and to gain insight on how the effectiveness of TTIQ might be altered for other infectious diseases. All parameter changes studied below ensure that $R_0$ is kept constant according to Eq (10). In particular, in the absence of TTIQ the critical level $\phi^*$ of effective contacts for the stability of the DFE stays unchanged.
(compare Eq (11)) and all deviations in \( \phi^* \) can be attributed to increased or decreased TTIQ effectiveness.

A high incidence of asymptomatic infectious individuals implies a reduced frequency of testing in compartment \( U_2 \) which we demonstrated to have a major impact on \( \phi^* \) (Fig 5B). Therefore, TTIQ has to be expected significantly more effective if overt symptoms occur frequently upon infectious individuals.

The extent of transmission during the early infectious phase is characterized by the average length of the early infectious period \( 1/\gamma_1 \), and by the scaling factor \( \theta \) describing the relative transmission rate of early infectious individuals when compared to late infectious individuals. We investigated the effects of variations in these parameters on \( \phi^* \). When varying \( 1/\gamma_1 \), we adjusted \( 1/\gamma_2 \) such that we maintain the same average for the total duration of the infectious period \( 1/\gamma = 1/\gamma_1 + 1/\gamma_2 \), and adjusted the transmission rates in order not to alter \( R_0 \). Both larger \( 1/\gamma_1 \) and larger \( \theta \) increase the amount of transmissions that cannot be prevented by symptom-based testing. Larger \( 1/\gamma_1 \) additionally implies a smaller detection ratio achieved by testing (at least if \( 1/\gamma_1 + 1/\gamma_2 \) and \( \sigma_{U_2} \) stay unchanged) and a larger testing delay such that contacts have spent more time in the chain of infection before being quarantined. As shown in Fig 8, variations in both parameters notably affect \( \phi^* \).

To assess the sensitivity of TTIQ to the time scale of disease spread, we also considered changes in the mean duration of the latent period \( 1/\alpha \) and the mean duration of infectious phase \( 1/\gamma = 1/\gamma_1 + 1/\gamma_2 \). When varying \( 1/\gamma \) we adjusted the transmission rates to maintain \( R_0 \) constant and kept a constant ratio between \( \gamma_1 \) and \( \gamma_2 \) such that the proportion of transmissions occurring in the early infectious phase in the absence of TTIQ remains unchanged. Unsurprisingly, faster disease progression (smaller \( 1/\alpha \), \( 1/\gamma \)) leads to a smaller \( \phi^* \) (Fig 9). A longer latency period (larger \( 1/\alpha \)) implies that more infected contacts are still latent at the time of being traced.
Fig 8. Critical level $\phi^*$ of effective contacts for the stability of the DFE varying disease characteristics. Here we vary the average duration of the early infectious period $1/\gamma_1$ and the scaling factor $\theta$ for the early infectious transmission rate.

https://doi.org/10.1371/journal.pone.0299880.g008

Fig 9. Critical level $\phi^*$ of effective contacts for the stability of the DFE varying disease characteristics. Here we vary the average duration of the latent phase $1/\alpha$ and the average duration of the infectious period $1/\gamma$. This is shown for A the $(1/\gamma, 1/\alpha)$-plane and B-E different combinations of values for $1/\alpha$ and $1/\gamma$, comparing a scenario without any TTIQ to a scenario where only testing is conducted and a scenario where both testing and contact tracing is carried out.

https://doi.org/10.1371/journal.pone.0299880.g009
and thus more onward transmissions are prevented by their quarantine. This only affects the effectiveness of contact tracing and has no effect on a purely testing-based scenario (compare second bars in Fig 9B–9E). Larger $1/\gamma$ increases the detection ratio achieved by testing (at least if $\sigma_{ij}$ stays unchanged) and implies that less contacts will have recovered by the time of being quarantined. Fig 9B–9E demonstrates that this increases the benefit of both testing and contact tracing.

We found that disease characteristics not only influence $\phi^*$ directly but also its sensitivity with respect to the TTIQ parameters. For instance, the tracing delay gains relevance when compared to the tracing coverage in case of a shorter latent phase (compare slope of contour lines in Fig 10A and 10B).

**Diminishing effectiveness of TTIQ during an epidemic outbreak**

When the disease prevalence rises the effectiveness of testing and tracing decreases and our stability analysis about the DFE does not offer sufficient information for disease control. To investigate how the effectiveness of TTIQ is affected by increasing prevalence, we considered a scenario where we assume moderately effective social and hygiene measures that are insufficient to control disease spread at the DFE ($\phi = 0.6 > 0.46 \approx \phi^*$). We initiated a simulation of our model near the DFE by choosing a constant history function such that the simulation starts with an incidence of roughly 300 confirmed cases per day. Although not being an exact representation, this setting is qualitatively resembling the surge in cases in late summer and early fall of 2020 in Germany: most of the population is still susceptible, the simulation starts at a low daily incidence of confirmed cases and disease spread is moderately suppressed by contact restrictions. For simplicity, and recognizing that transmission rates and TTIQ effort change much more dynamically in reality, all parameters in this scenario are held constant throughout the simulated period with values as in the baseline setting Table 2. In the considered scenario the DFE is unstable leading to an increase in the total number of infected
individuals (Fig 11A) and daily new confirmed cases (Fig 11B) over time. As more infectious individuals arise in the population the test positive rate increases (Fig 11C). Moreover, the finite testing capacity leads to decreasing per capita detection rates which decreases the detection ratio

$$\frac{\eta_{U_1}}{\gamma_1 + \eta_{U_1}} + \frac{\gamma_1}{\gamma_1 + \eta_{U_1}} \frac{\eta_{U_2}}{\gamma_2 + \eta_{U_2}}.$$  

The nevertheless increasing number of confirmed cases leads to an increase in reported contacts which gradually diminishes the tracing efficiency (Fig 11B)

$$\varepsilon(t) = \frac{\Omega}{(\epsilon_{pot}(t)^2 + \Omega^2)^{1/2}}.$$  

All in all these effects lead to a steep increase in the under-ascertainment of active infectious individuals

$$\frac{U_1(t) + U_2(t) + Q_{U_1}(t) + Q_{U_2}(t) + I_1(t) + I_2(t)}{Q_{U_1}(t) + Q_{U_2}(t) + I_1(t) + I_2(t)}$$

as prevalence rises (Fig 11D).

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Fig 11. Model outcomes simulating an outbreak starting from low case numbers. This simulation is initiated using the baseline parameter values given in Table 2 and a reduction of effective contacts corresponding to $\phi = 0.6$.  

https://doi.org/10.1371/journal.pone.0299880.g011
This scenario leads to a self-accelerating disease spread that gets harder to control the longer it remains uncontrolled. This is reflected in the critical level $\bar{\phi}$ of effective contacts that yields a timely stagnation in the incidence of infected individuals. We calculated $\bar{\phi}$ at multiple points in time $t^*$ by simulating an intervention that immediately decreases $\phi$, that is

$$
\phi(t) = \begin{cases} 
0.6, & t < t^* \\
\phi_{int}, & t \geq t^*
\end{cases}
$$

and scanned for the maximal value of $\phi_{int}$ that yields no further increase (thus approximately yields stagnation) in the incidence after two weeks post intervention for the rest of the additionally simulated period (+ 42 days). The result is shown by the dashed line in Fig 12A. Due to the loss of TTIQ effectiveness, later intervention timing $t^*$ requires a stricter reduction of

---

**Fig 12.** Critical level $\bar{\phi}$ of effective contacts that yields a stagnation in the incidence of infected individuals. $\bar{\phi}$ is calculated along the epidemic outbreak considered in Fig 11 and plotted against the timing of intervention $t^*$. This is shown for different values of A the tracing capacity $\Omega$, B the tracing efficiency constant $p$, C the testing capacity $\sigma$, and D comparing a scenario with high tracing capacity $\Omega$ and low tracing efficiency constant $p$ to a scenario with low $\Omega$ and large $p$.

https://doi.org/10.1371/journal.pone.0299880.g012
effective contacts (lower $\bar{\phi}$) in order to prevent a further increase in the incidence of infected individuals. However, at some point the effect of population-level immunization counterbalances the effect of a decreasing TTIQ effectiveness and $\bar{\phi}$ starts increasing as $t^*$ becomes larger. Note this ease of control comes at the cost of widespread infestation. Models that do not include limited capacities would predict this increase in $\bar{\phi}$ already for early intervention time points $t^*$.

**Impact of capacity parameters**

We investigated the impact of TTIQ capacities on the temporal evolution of $\bar{\phi}$ by simulating the epidemic outbreak considered in Fig 11 for multiple values of the tracing capacity $\Omega$, the tracing efficiency constant $p$, and of the testing capacity $\sigma_\Omega$. All three, larger tracing capacity $\Omega$, larger testing capacity $\sigma_\Omega$, and larger tracing efficiency constant $p$ (reflecting higher efficiency in allocating tracing capacity) increase the minimal value of $\bar{\phi}$ along the outbreak and delay its decrease with respect to $t^*$ (Fig 12A–12C). However, for larger $p$ the decrease in $\bar{\phi}$ happens more abruptly. In particular, a TTIQ system with relatively low tracing capacity but with efficient allocation of this capacity (large $p$) manages to maintain a high tracing efficiency for a longer phase of the outbreak than a TTIQ system with high tracing capacity but inefficient allocation of this capacity (small $p$). This is only true until a certain prevalence is reached. The system with low absolute tracing capacity experiences the drop in $\bar{\phi}$ in a shorter time frame and quite abruptly stricter reductions of effective contacts are needed to regain control over disease spread (Fig 12D).

**Implications for intervention strategies**

The decrease in TTIQ effectiveness along an epidemic wave implies that the success of intervention strategies is state-dependent. To see how this affects interventions based on changes in TTIQ parameters we considered the outbreak investigated before (see Fig 11) and simulated an intervention taking place either early at a daily case incidence of approximately 1500 ($t^* = 47$) or later at a daily case incidence of approximately 20000 ($t^* = 123$). At the start of the intervention we varied TTIQ parameters in ranges as in Fig 3 and additionally scanned for the associated critical level $\bar{\phi}$ of effective contacts that yields a stagnation in the incidence of infected individuals (Fig 13). While the curves corresponding to the early intervention unsurprisingly resemble those in Fig 5, the curves corresponding to the late intervention scenario are shifted. For optimistic TTIQ parameter values, the curves are shifted downwards, reflecting the decreased tracing efficiency and per capita testing rates. Conversely, for suboptimal TTIQ parameter sets, $\bar{\phi}$ is larger in the late intervention scenario due to the already greater depletion of susceptibles. In these cases, the beneficial effect of higher immunization outweighs the detrimental effect of lower TTIQ effectiveness, since TTIQ does not contribute much in the first place. For all TTIQ parameters, the curve corresponding to the late intervention is notably flatter, demonstrating less impact on $\bar{\phi}$ and decreased importance of these parameters for disease control.

The above observations have important implications for the outcome of intervention strategies. To demonstrate that, we report here simulated scenarios where at the day of intervention a stricter reduction of effective contacts (smaller $\phi$) is applied and, additionally, improve TTIQ parameters in some scenarios. As before we assumed that the interventions have an immediate effect on the parameters of the system. As a benchmark scenario we assumed that the intervention, applied either early or late as above, leads to a reduction in effective contacts from $\phi = 0.6$ to $\phi_{int} = 0.49$. When accompanied with no additional improvements of TTIQ, disease spread
Additionally increasing the tracing coverage from $\omega = 0.65$ to $\omega_{\text{int}} = 1$ (e.g., by increasing awareness in the population to keep track of personal contacts or by improving the close contact definition), improving the relative frequency of testing undetected late individuals from $s_{U_2} = 0.93$ to $s_{U_2\text{int}} = 1.18$, or implementing a stricter reduction of effective contacts corresponding to $\phi_{\text{int}} = 0.46$, show a similar response in case of low prevalence and timely lead to a slow decrease in the number of infected individuals (Fig 14A). However, the three enhanced interventions show different responses in the late intervention scenario with high prevalence. Improving the tracing coverage proves to be ineffective (see dashed line Fig 14B). The improvement in testing does not perform significantly better (see dotted line in Fig 14B). Only the stricter reduction of effective contacts significantly slows down disease spread (see triangles in Fig 14B). All three strategies, however, fail to stop the increase in the number of infected individuals in the late intervention scenario.

**Discussion**

We introduced a delay differential equation model to assess the effectiveness of TTIQ interventions for infectious disease control. To account for limited testing capacity, we introduced state-dependent detection rates of infectious cases that are based on the derivation presented in [40]. This leads to reasonably high detection rates at low prevalence that smoothly decrease when prevalence rises. Similar to the approach in [28], we model contact tracing as a delayed consequence of successful index case identification. However, in our derivation we did not
consider a sharp prevalence threshold above which the tracing efficiency is affected by disease spread. Instead, by contrasting the theoretical yield of detected infections per index case and the curtailment of this yield by the emerging burden on PHA, our model rather describes a smoothly decreasing tracing efficiency as disease prevalence rises. In addition, our model includes an early infectious phase in the course of infection during which infected individuals can transmit the disease prior to the occurrence of potential symptoms.

As a working example representative of a (re-)emerging disease for which pharmaceutical interventions are not yet available, we applied our model to study the effectiveness of TTIQ in a scenario inspired by the spread of COVID-19 in Germany during the wave in late summer and fall of 2020. Under these conditions, in particular original strain of SARS-CoV-2, no vaccine, no rapid antigen tests, and low population immunity, our model results suggest that, as long as disease prevalence is low, TTIQ allows to control disease spread if the reproduction number is reduced to a value below 1.52 by other interventions alone. Thus, assuming a basic reproduction number of 3.3, TTIQ as described here would allow for approximately 52% more effective contacts within the population. Nevertheless, a reduction to approximately 46% of the pre-COVID-19 effective contact rate would be needed to prevent an epidemic outbreak. This is in line with previous modeling studies suggesting that additional interventions are required to control disease spread under realistic assumptions on imperfect TTIQ [4, 13, 16, 19, 20, 22–24, 28, 29, 39].

By means of a sensitivity analysis we identified the TTIQ parameters most influential to the effectiveness of TTIQ. Our results show that depending on how the TTIQ parameters are set, TTIQ may allow a significantly higher or lower effective contact rate than observed in our baseline setting. In agreement with previous findings in the literature, the compliance with isolation [13, 17, 19] and the rate of index case identification [13, 16, 18–20, 23, 27] play a central role in this regard. The significance of these parameters reflects simple causal relationships between the mechanisms described by the TTIQ parameters. It is irrelevant how many index cases are found by testing and how many contacts are traced when none of them effectively

**Fig 14. Number of infected individuals (both detected and undetected) simulating the baseline outbreak scenario from Fig 11 with different interventions.** Here an intervention takes place either A early at a daily case incidence of approximately 1 500 (\( t^* = 47 \)) or B late at a daily case incidence of approximately 20 000 (\( t^* = 123 \)). At the time of intervention the level of effective contacts is changed from its baseline value to \( \phi_{int} \). Additionally, in some considered scenarios, the tracing coverage is improved to \( \omega_{int} \) or the relative frequency of testing undetected infectious individuals to \( \sigma_{int} \). Parameters not mentioned in the legend are held constant throughout the simulation.

https://doi.org/10.1371/journal.pone.0299880.g014
reduces their contacts. Similarly, by definition contacts can only be traced and quarantined upon prior identification of index cases. This renders the success of testing a key factor for the effectiveness of TTIQ. Consistent with previous studies [27, 29, 32], we observed synergistic effects when varying TTIQ parameters simultaneously which highlights the benefit of combining strategies rather than concentrating on, e.g., testing exclusively.

To go beyond our consideration of COVID-19 and to further examine the effect of uncertainty in our baseline parameter setting, we also considered variations in parameters describing disease characteristics. Overall, our results underline that COVID-19 combines several characteristics adverse to TTIQ (asymptomatic and early transmissions, short latency and infectious period, airborne transmission resulting in imperfect tracing coverage) that explain its rather low effectiveness observed in our baseline setting. The central role of asymptomatic and presymptomatic transmission in diminishing TTIQ effectiveness has been repeatedly demonstrated in the literature [12, 16, 20, 22, 24, 27, 37].

When disease control is insufficient and an outbreak takes place, limited TTIQ capacities lead to a self-acceleration of disease spread [28, 29, 31, 39]. In our model, this effect takes place gradually along an epidemic wave until it is countered by sufficiently wide spread immunization. We show how the timing and intensity of the self-accelerating effect depend on the testing and tracing capacity parameters. It is weaker for higher capacities and a more efficient allocation of contact tracing expressed by larger tracing efficiency constant $p$. Moreover, a larger $p$ extends the period of almost perfect tracing efficiency and leads to a more abrupt decrease of tracing efficiency. The limit $p \to \infty$ offers a transition between the description of tracing capacity in our model and previous models that assume a sharp prevalence threshold for the decrease in tracing efficiency [28, 29, 39].

The self-accelerating effect observed in our working example appears to be only moderate. Our sensitivity results and the previous literature shows that it may be more or less pronounced depending on assumptions on the model structure and parameters (see for example [28]). It should be noticed, however, that the detrimental effect of limited capacity in our simulations, though less pronounced than under alternative modeling assumptions, is far from negligible and the transient acceleration of disease spread may have irreversible effects [39]. In particular, our results show that at states of high prevalence stricter measures are needed to control disease spread and interventions based on improvements of TTIQ parameters become less effective. In such situations, greater reduction of transmission rates by means of stricter social or hygiene measures might be the only feasible non-pharmaceutical intervention to effectively stop case numbers from rising.

There are several limitations to our model that offer routes for further research and should be considered when interpreting our results. We focused on first-order manual forward tracing. Other modeling studies consider the effect of recursive tracing [14, 16, 21, 25], backward tracing [15, 25, 26] and digital contact tracing [4, 16, 23, 24]. Under favorable conditions, like a high acceptance within the population in case of digital contact tracing, these processes may significantly increase the effectiveness of TTIQ. Moreover, in reality, a relevant proportion of contacts of confirmed cases is likely to be informed about their potential transmission by the index case before PHA reach out to the contact. This can lead to earlier quarantine of contacts and render parts of contact tracing independent of PHA capacities. Similarly, individuals might reduce their contacts due to an increase in reported cases. These and other behavioral factors are so far not considered in our model. Moreover, we only considered quarantine for close contacts that happened to be infected by one of the identified index cases. It should be noticed that quarantine of the remaining contacts (those that had contact but were not infected), which is for example considered in [16, 31, 32, 34], can effect the disease dynamics if sufficiently many susceptibles are quarantined or a substantial amount of additional infected
individuals are quarantined by chance, which is only likely in situations of high prevalence. In addition, the consideration of quarantine of all close contacts (infected and uninfected) would allow to assess the socioeconomic damage induced by contact tracing and to address TTIQ strategies that reduce quarantine costs (see for example [17, 24, 31, 44]). Furthermore, our approach considers the populations in the different compartments in our model as homogeneous. At the cost of an extended parameter space many additional factors that differentiate individuals could be considered, such as age, space, infectiousness, and disease severity. Not differentiating infectious individuals by the severity of their disease, for instance, implies that the significant benefit of increasing the relative frequency $\sigma_{U_2}$ of testing undetected late infectious individuals when compared to susceptibles shown in Fig 5C should be seen as harder to realize the larger $\sigma_{U_2}$ becomes. Every increase of $\sigma_{U_2}$ deviates the typical distribution of individuals in $U_2$ more and more towards asymptomatic individuals. This makes the average individual in $U_2$ less amenable to symptom-based testing and a further increase of $\sigma_{U_2}$ more difficult to achieve. Furthermore, our approach assumes that the considered population is well-mixed, at least as long as no individual is quarantined or isolated. However, the effect of contact tracing is dependent on the contact network underlying the considered population. Previous modeling studies found that, for instance, clustering benefits contact tracing [45, 46] and that mixing patterns can affect the efficacy of contact tracing [14]. Additionally, although our model splits the infectious phase into an early and late infectious stage, a more realistic infectivity profile and course of symptoms could be considered using an age of infection approach [4, 16, 25, 26, 37–39]. Finally, in order to reduce model complexity we applied a series of approximations to the contact tracing process. While this allowed us to readily gain insights into a vast range of scenarios, an age of infection model incorporating realistic state-dependent TTIQ effectiveness would offer a promising approach for a more precise description of contact tracing. An agent based framework [12, 13, 16, 17] would allow to include even more complexity, investigate effects of stochasticity, and to consider various of the factors outlined above. A comparison of our modeling outcomes to such direct formulations of contact tracing could be used to investigate the justification of a numerically inexpensive but approximate model as leveraged in the present work.

**Conclusion**

We derived a mathematical model of TTIQ interventions that accounts for challenges posed by disease characteristics and inherent limitations of TTIQ such as a tracing delay, imperfect compliance with isolation, and limited testing and tracing resources. Using the spread of COVID-19 as an example, we show how these factors can limit the effectiveness of TTIQ as a strategy for disease control. Our observations on the diminishing TTIQ effectiveness during simulations of an epidemic outbreak demonstrate that a careful evaluation of the contemporary load on TTIQ capacities is needed to predict the effect of different intervention strategies. A strength of our approach is that we disentangle the individual contributions to disease control which result from isolating index cases and tracing their contacts. Our model extends the literature on phenomenological models of TTIQ and is flexible enough to be adapted and applied to evaluate the effectiveness of TTIQ in controlling infectious diseases other than COVID-19. Further research is needed to investigate how well relatively simple population-level models approximate the effect of the individual-based process of contact tracing.

**Supporting information**

**S1 File.** Appendix A Derivation of contact tracing terms with early and late infectious individuals, Appendix B Modeling social and hygiene measures and changes in the tracing coverage,
Appendix C Parameterization, Appendix D Stability analysis.

Author Contributions
Conceptualization: Julian Heidecke, Jan Fuhrmann, Maria Vittoria Barbarossa.
Formal analysis: Julian Heidecke.
Investigation: Julian Heidecke.
Methodology: Julian Heidecke, Jan Fuhrmann, Maria Vittoria Barbarossa.
Software: Julian Heidecke.
Supervision: Jan Fuhrmann, Maria Vittoria Barbarossa.
Visualization: Julian Heidecke.
Writing – original draft: Julian Heidecke.
Writing – review & editing: Julian Heidecke, Jan Fuhrmann, Maria Vittoria Barbarossa.

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