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Transmission dynamics of the COVID-19 epidemic in India and modeling optimal lockdown exit strategies

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ABSTRACT

India imposed one of the world's strictest population-wide lockdowns on March 25, 2020 for COVID-19. We estimated epidemiological parameters, evaluated the effect of control measures on the epidemic in India, and explored strategies to exit lockdown.

We obtained patient-level data to estimate the delay from onset to confirmation and the asymptomatic proportion. We estimated the basic and time-varying reproduction number (R_0 and R_t) after adjusting for imported cases and delay to confirmation using incidence data from March 4 to April 25, 2020. Using a SEIR-QDPA model, we simulated lockdown relaxation scenarios and increased testing to evaluate lockdown exit strategies.

R_0 for India was estimated to be 2·08, and the R_t decreased from 1·67 on March 30 to 1·16 on April 22. We observed that the delay from the date of lockdown relaxation to the start of the second wave increases as lockdown is extended farther after the first wave peak—this delay is longer if lockdown is relaxed gradually.

Aggressive measures such as lockdowns may be inherently enough to suppress an outbreak; however, other measures need to be scaled up as lockdowns are relaxed. Lower levels of social distancing when coupled with a testing ramp-up could achieve similar outbreak control as an aggressive social distancing regime where testing was not increased.

Introduction

Originating out of Wuhan, China, in December 2019 (Zhu et al., 2020), the coronavirus disease 2019 (COVID-19) was declared a pandemic by the WHO on March 11, 2020 (WHO, 2020). As of May 2, 2020, there have been more than 3 200 000 cases and 230 000 deaths worldwide and close to 40 000 cases and 1200 deaths in India (Johns Hopkins CSSE, 2020). India reported its first COVID-19 case on 30 January 2020, although the actual epidemic growth started from early March (COVID19India.org, 2020).

For any novel infectious disease, the scale of its public health impact is determined by the basic reproduction number 'R_0' which is the average number of secondary infections generated by an infectious index case in a wholly susceptible population. The R_0 of an infection determines its potential to start an outbreak, the severity of control measures needed to contain the spread, and the fraction of the population that will be infected in the absence of interventions (Longini et al., 2005). However, once an outbreak is underway, the time-varying effective reproduction number 'R_t' is more relevant as it tracks the subsequent changes in transmission and can thus be used to monitor the efficacy of control measures and adjust them accordingly (Kucharski et al., 2020; Leung et al.,

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2020; Pan et al., 2020). However, any given transmission event is reflected in the data only after a delay, which must be accounted for in the estimation of such indicators for accurate interpretation (Kucharski et al., 2020). Previous studies have shown that a severe epidemic with $R_0 \sim 2{\cdot}4$ can be contained by combining effective quarantine, behavioral change to reduce social mixing, targeted antiviral prophylaxis, and pre-vaccination (Longini et al., 2005). However, in the absence of targeted therapeutics and vaccination for COVID-19, an unprecedented one-third of the world's population is currently under lockdown with the primary target of reducing the R_t below the threshold of 1 (Ferguson et al., 2020; Leung et al., 2020).

India responded to the COVID-19 pandemic rapidly and decisively by imposing a nation-wide lockdown on March 25, 2020 when there were 536 cases and 10 deaths. This 'suppression strategy', though effective, has its limitations—the social and economic cost of such population-wide social distancing is huge, which limits the long-term implementation of these measures (Lee et al., 2020). Additionally, containing COVID-19 in India is a unique challenge due to its high population density, underprepared healthcare system, and wide socio-economic disparity. A large proportion of India's labor force works as daily-wage laborers or migrant workers and are especially affected during such times, making lockdowns untenable without parallel social support (Lee et al., 2020). There could be yet unseen adverse effects in the form of non-COVID-19 morbidity and mortality due to aggravation of malnutrition, chronic diseases, and lack of access to healthcare during this time (Bhargava and Shewade, 2020). At the same time, premature withdrawal of lockdowns without adequately planned interventions for the post-lockdown phase may lead to re-emergence or a second wave (Ferguson et al., 2020; Leung et al., 2020). Thus, there arises a need to create a balance to ensure that the disease is contained and the healthcare system remains well-prepared while minimizing the collateral damage from intensive blanket interventions. Comprehensive lockdown exit strategies will be central to the future course of the pandemic. In such scenarios with limited primary information, dynamic mathematical models can provide actionable insights for researchers and policymakers (Ferguson et al., 2020; Hellewell et al., 2020; Kucharski et al., 2020).

Evidence suggests that COVID-19 has a wide clinical spectrum that ranges from asymptomatic to fatal infections which, when coupled with high infectivity, can lead to a large number of infections and deaths (Hu et al., 2020). It may be possible that COVID-19 transmission is driven significantly by undetected asymptomatics while fatality is driven by severe cases, which is a devastating combination (Gudbjartsson et al., 2020; Lavezzo et al., 2020). Some have deemed asymptomatic transmission to be the "Achilles' Heel" of the current control strategies against COVID-19, and it is important to consider the range of uncertainty regarding the same when simulating COVID-19 transmission (Gandhi et al., 2020).

In this study, we estimate the key transmission parameters for COVID-19 in India and its states and analyze how interventions affected transmission levels across time. Considering that blanket lockdowns are an initial rather than a final step in controlling this pandemic, we model the effect of relaxing public health interventions at various time-points. We evaluate the impact of increased detection of infections in the community through expanded testing strategies in containing transmission when restrictions are relaxed.

Methods

Data sources

For estimating the proportion of asymptomatic cases and the delay from symptom onset to confirmation, we obtained data from 140 COVID-19 patients admitted to a tertiary care hospital near Delhi, India (Appendix p5). For estimating the basic reproduction number (R_0) and effective reproduction number (R_t) for India and various states, we used data from COVID19India from March 4 to April 25, 2020, which is curated based on multiple verified sources (COVID19India.org, 2020). For model fitting and parameter estimation, we used time-series data for India from the Johns Hopkins University COVID-19 database, from March 16 to April 18, 2020 (Johns Hopkins CSSE, 2020). A laboratory-confirmed case irrespective of symptoms is counted as a confirmed COVID-19 case in India. Testing criteria are provided in Appendix p9. We used the World Bank Population Database for population data for India (World Bank, 2019).

Estimation of basic reproduction number (R_0)

The best-fit R_0 was calculated for the national and state level incidence data using the *R_0 package* in R 3·6·3 using two independent methods: Maximum Likelihood (ML) method and the Exponential Growth (EG) method after adjusting the incidence data for imported cases (Obadia et al., 2012; Wallinga and Lipsitch, 2007; White and Pagano, 2008). We assumed the serial interval to be gamma-distributed with a mean of 3·96 days (95% CI 3·53–4·39) and standard deviation (SD) of 4·75 days (95% CI 4·46–5·07), based on a large study of 468 infector-infectee pairs in China (Du et al., 2020). We analyzed the sensitivity of the estimated R_0 to the choice of the time period over which the R0 was estimated and the serial interval (Appendix p8). The *R_0 package* uses R^2 as the goodness-of-fit statistic.

Estimation of reporting lag, lag adjusted incidence, and time-varying effective reproduction number (R_t)

A variable delay occurs from symptom onset to case confirmation (henceforth referred to as the reporting lag) which is attributed to multiple factors including time taken to seek care (patient dependent) and time taken to detect and test the case (healthcare-system dependent). As all included patients were tested and confirmed positive within a day of hospitalization, the time from symptom onset to hospitalization obtained from the data approximates the reporting lag of these cases. We assume these to be same for the purpose of our study. Due to lack of data, we assume that the reporting lag for India and each state is statistically the same as the estimated reporting lag for the 53 patients from Delhi whose onset date was known. For each reported case, onset dates were sampled to generate 1000 lag-adjusted datasets for incidence by onset (Appendix p5–6) from which, the time-varying R_t was calculated using *EpiEstim* package in R 3·6·3 which uses the Time Dependent Maximum Likelihood approach (Cori et al., 2013; Wallinga and Teunis, 2004). The same serial interval distribution was used as for R_0 estimation. We determined both the import-adjusted R_t and unadjusted R_t for India, where cases in the national incidence data not explicitly labeled as 'imported' were considered to be locally transmitted. The R_t trends were overlaid with major epidemic events and mobility data to analyze possible temporal correlations (Google LLC, 2020).

Modeling the pandemic using dynamic compartmental models

In order to model the spread of SARS-CoV-2 in the population, we generalize the extensively used SEIR model for infectious diseases to account for (1) time lag from symptom onset to case being reported in data, (2) underreporting of actual infections due to testing constraints, (3) varying proportion of infections being asymptomatic, (4) varying infectivity levels of asymptomatics, and

(5) time-dependent effect of implementing and relaxing control measures (Sun and Hsieh, 2010). For introducing the required complexities, we build a model as shown in Figure 1. Model parameters are defined in Table 1. Through a positive protection rate (α), the susceptible population gradually decreases to account for the effect of increasingly intensive social distancing policies and improved public behavior in reaction to the epidemic (Peng et al., 2020). We introduce a deprotection rate (σ) which increases the susceptible pool once social distancing policies are relaxed. Using deprotection rate (σ) in a SEIR model may be worthwhile in multiple scenarios. When estimating σ by fitting the model to data, one can incorporate the 'leakiness' of a lockdown into the predictions. In addition, allowing time-dependent estimation of σ in such a model can indicate the waning adherence to the lockdown over time. At last, altering the values of σ when simulating lockdown relaxation allows one to evaluate a gradual return to normal vis-a-vis a sudden return to normal.

We set the probability of an infected case being asymptomatic (p_a) to 0·2, 0·4, 0·6, and 0·8, as reported estimates for the percent of infections that are asymptomatic range widely from 18% to 80% (Gudbjartsson et al., 2020; Kumar et al., 2020; Lavezzo et al., 2020; Mizumoto et al., 2020). We set the relative infectivity of an asymptomatic to 25% (a_i = 0·25) based on reliable evidence from transmission studies (Buitrago-Garcia et al., 2020; He et al., 2020a).

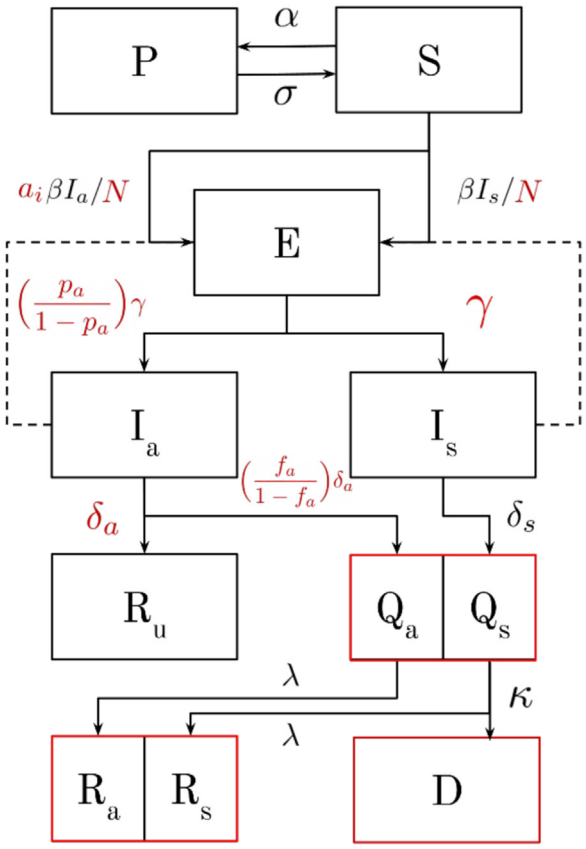

Figure 1. Schematic for SEIR-QDPA model.
Compartments include S (susceptible), E (infected but not yet infectious), Ia (undetected asymptomatic; infectious), Is (undetected symptomatic; infectious), Qa (detected and quarantined asymptomatic), Qs (detected and quarantined symptomatic), Ru (undetected recovered asymptomatic), Ra (recovered detected asymptomatic), Rs (recovered detected symptomatic), D (dead), and P (protected; non-susceptible). Compartments in red are fitted to data; Q = Qa + Qs to active cases, R = Ra + Rs to cumulative recovered cases, and D to cumulative deaths. Transition rates in red are inputs to the model, while others are estimated (Table 1). The governing differential equations for the model are available in Appendix p3–4.

We set the fraction of detected asymptomatics (f_a) at baseline to 0·1 based on underreporting estimates for the model time period from Russell et al. (2020). We sample the latent period (γ^{-1}) from a calculated distribution with a mean of 3.49 days and a standard deviation of 0.39 days based on previous studies and the infectious period for asymptomatics (δ_a^{-1}) from a calculated distribution with a mean of 4.31 days and a standard deviation of 0.55 days based on virologic and epidemiologic studies (Ali et al., 2020; He et al., 2020a,b; Lauer et al., 2020; Li et al., 2020b; Liu et al., 2020b). Details on how the distributions were generated are available in Appendix p28. We assume that all symptomatic patients are detected, and that no asymptomatic dies from the disease. Further details of the model, including the governing equations, are available in Appendix p3–4.

We estimated the unknown parameters of the model by fitting time-series data for active cases (=cumulative confirmed cases − cumulative recoveries − cumulative deaths), cumulative recoveries, and cumulative deaths to the Q(t) = Q_s(t) + Q_a(t), R(t) = R_s(t) + R_a(t), and D(t) compartments, respectively. We fitted for the values of transmission rate (β), protection rate (α), delay to confirmation for symptomatic cases (δ_s^{-1}), recovery rate (λ), mortality rate (κ), and initial exposed and infected individuals (E_0 and I_0). As a counterfactual, we explored the size and temporality of the first wave in an ideal scenario where strict control measures could be maintained for long periods by simulating the model with the estimated parameters. This continually enforces the estimated protection rate, thus assuming that control measures continue with initial stringency till the end of simulation. Here, we defined three key time points that are inherent to epidemic progression: time at peak of daily new reported cases (t1), time at peak of active cases (t2), and time when recovered cases > active cases (t3). The sensitivity of our results to assumptions of p_a, f_a and a_i was analyzed. The following terms in the article signify values obtained by combining multiple compartments: 'Symptomatic cases'—cumulative symptomatic cases once detected; 'Detected cases'—cumulative detected cases including symptomatic and asymptomatic cases; 'Total infections'—cumulative infections including detected cases and undetected asymptomatic infections.

Simulating the effect of lockdown relaxation

To model complete lifting of the nationwide lockdown, α was set to zero and σ was set to a large value such that the entire protected population was emptied into the susceptible population in a short interval ($t_{1/2}$∼1 day). We triggered this change on May 4, 2020 (tentative date of lockdown relaxation in India at time of study) and 7-day intervals thereafter to compare outcomes if lockdown is lifted on different dates. We also considered the scenario where the lockdown is re-enforced after a fixed relaxation period which we modeled by setting σ to zero and re-enforcing the same α as before lockdown relaxation. Additionally, we simulate a more gradual lockdown relaxation using a relatively smaller value of σ (Supplementary p26).

Simulating the effect of increased testing

We hypothesized that increased testing after lockdown relaxation will decrease the epidemic growth enough to allow for greater resumption of normal social mixing, thus minimizing the social and economic fallout resulting from vigorous restrictions. To model the effect of increased testing capacity and subsequent improved detection, we assumed that it increased the asymptomatic detection rate f_a from 0·1 in lockdown, to 0·2, 0·3, 0·4, 0·5, 0·6, and 0·8 after lockdown relaxation starting May 4. An alternate interpretation of testing which is independent of clinical severity is discussed in Appendix p4. To model the effect of varying

Table 1
Parameters for SEIR-QDPA model.

Parameter	Value	Source
Protection rate (α)	–	Estimated
Deprotection rate (σ)	0·5 for fast lockdown relaxation (largest possible value for stable simulation)	Tested in Figure 4
Transmission rate (β)	– 0·9, 0·8, 0·7, 0·6, 0·5, 0·3 of estimated β for social mixing levels	Estimated Tested in Figure 5
Latent period (γ^{-1})	Mean 3.49, SD 0.39 (sampled from distribution)	He et al. (2020b), Lauer et al. (2020), Li et al. (2020b), Liu et al. (2020b)
Delay to confirmation for symptomatic (δ_s^{-1})	–	Estimated
Infectious period for asymptomatic (δ_a^{-1})	Mean 4.31 SD 0.55 (sampled from distribution)	Ali et al. (2020) and He et al. (2020b)
Mortality rate (κ)	–	Estimated
Recovery rate (λ)	–	Estimated
Infectivity of asymptomatic compared to symptomatic (a_i)	0·25 (0·5 for sensitivity analysis)	Buitrago-Garcia et al. (2020) and He et al. (2020a)
Probability of infected case being asymptomatic (p_a)	0·2, 0·4, 0.6, 0·8	This study, Gudbjartsson et al. (2020), Kumar et al. (2020), Lavezzo et al. (2020), Mizumoto et al. (2020), Buitrago-Garcia et al. (2020)
Probability of detection of asymptomatic case (f_a)	0·1 (0·05, 0·2 for sensitivity analysis) 0·2, 0·3, 0·4, 0·5, 0·6, 0·8 for increased testing	Russell et al. (2020) Tested in Figure 5

Sensitivity analysis to the choice of assumed parameters a_i, f_a, and p_a was performed for the fitted parameters α, β, δ_s^{-1}, κ and λ in Appendix p16–18.

levels of residual social distancing and positive behavior change after the lockdown is lifted, we changed the transmission rate to 90%, 80%, 70%, 60%, 50%, and 30% of the original rate β, starting May 4. Varying levels of social mixing mainly influence the number of contacts, while behavior changes such as wearing masks and hand washing affects the infectiousness of each contact—the transmission rate β captures both these changes (contact rate and infectivity per contact).

Results

Basic reproduction number 'R_0'

The exponential growth (EG) method had a better best-fit R^2 over a larger time period and was less sensitive to the choice of the time period (Appendix p7–8). The best fit R_0 for India was found to be 2·083 (95% CI 2·044–2·122; R^2 = 0·972). Taking into consideration the uncertainty in reported serial intervals (SI), the R_0 ranged from 2 to 2·5 for SI ranging from 4 to 4·6 days (Du et al., 2020; Nishiura et al., 2020; Tindale et al., 2020; You et al., 2020). Results were found to be sensitive to the SI distribution, and thus we report R_0 based on reliable SI estimates from 468 infector-infectee pairs in China (Du et al., 2020) and also consider a range of possible SIs based on other studies. The R_0 estimates for various states of India are provided in Appendix p7.

Reporting lag, lag adjusted incidence, and time-varying effective reproduction number 'R_t'

Out of 140 laboratory confirmed COVID-19 patients, 85 (60.7%) were asymptomatic while 55 (39.3%) were symptomatic. For 53 symptomatic patients, the reporting lag was found to have a mean of 3·40 days (95% CI 2·87–3·96) with SD of 2·09 days (95% CI 1·52–2·56) and a median of 2·68 days (95% CI 2·00–3·00) with IQR of 2.03 days (95% CI 1.00–3.00). The gamma distribution with shape parameter 3·45 (95% CI 2·42–5·19) and rate parameter 1·02 (95% CI 0·70–1·60) was the best fit to the distribution (Appendix p5–6).

The first cases of local transmission in India were reported on 4 March and were family members of an initial imported case. The number of imported cases in India started increasing from early-March, peaked a day after the international travel ban on March 23, and gradually came to a halt on April 5 with a total of 546 imported cases (Figure 2A). Incidence by onset and time-varying R_t could be ascertained up to April 22, 2020 as some cases with onset after this date may not have been reported yet in the data, due to the reporting lag. The R_t trends for India showed visible fluctuations over time (Figure 2B). The first uptick in unadjusted R_t (blue band) starting around March 13, 2020 was presumed to be an artifact due to imported cases, as it coincided with increasing imported case onsets and was not accompanied by a concurrent uptick in import adjusted R_t (pink band). The second uptick in unadjusted R_t correlated with the rise in adjusted R_t, indicating that local transmission was driving this rise. This rise started around the imposition of the nationwide lockdown on March 25 and peaked on March 30 at an adjusted R_t of 1·665 (95%CI 1·539–1·789). After this peak, the R_t continued to decrease to 1·300 (1·247–1·353) on April 8, 1·213 (1·175–1·251) on April 15, and further to its lowest yet value of 1·159 (1·128–1·189) on April 22. A sharp dip in mobility is noted during the voluntary public curfew on March 22, which is sustained after the nationwide lockdown was enforced on March 25, except for a rise in residential neighborhood mobility (Figure 2C). The daily R_t values for India and R_t trends for states of India are provided in Appendix p11–14.

Estimated model parameters and ideal first wave scenario

The model was able to fit the data well for the early exponential phase of the growth and also captured the recent slowdown in epidemic growth through the protection rate. The estimated model parameters for the range of assumptions are provided in Appendix p15–18. With the baseline assumption (asymptomatics are 25% infectious compared to symptomatics, 40% of total infections are asymptomatic, and 10% of asymptomatics are detected), the estimated reproduction number was 2.9 (2.5–3.3). Assuming that control measures continued with initial stringency, our model predicted the first wave (Figure 3) at 19 364 (95% CI 9452–36 313) maximum active cases and 50 566 (25 425–93 725) cumulative detected cases, of which 30 397 (15 314–56 293) were

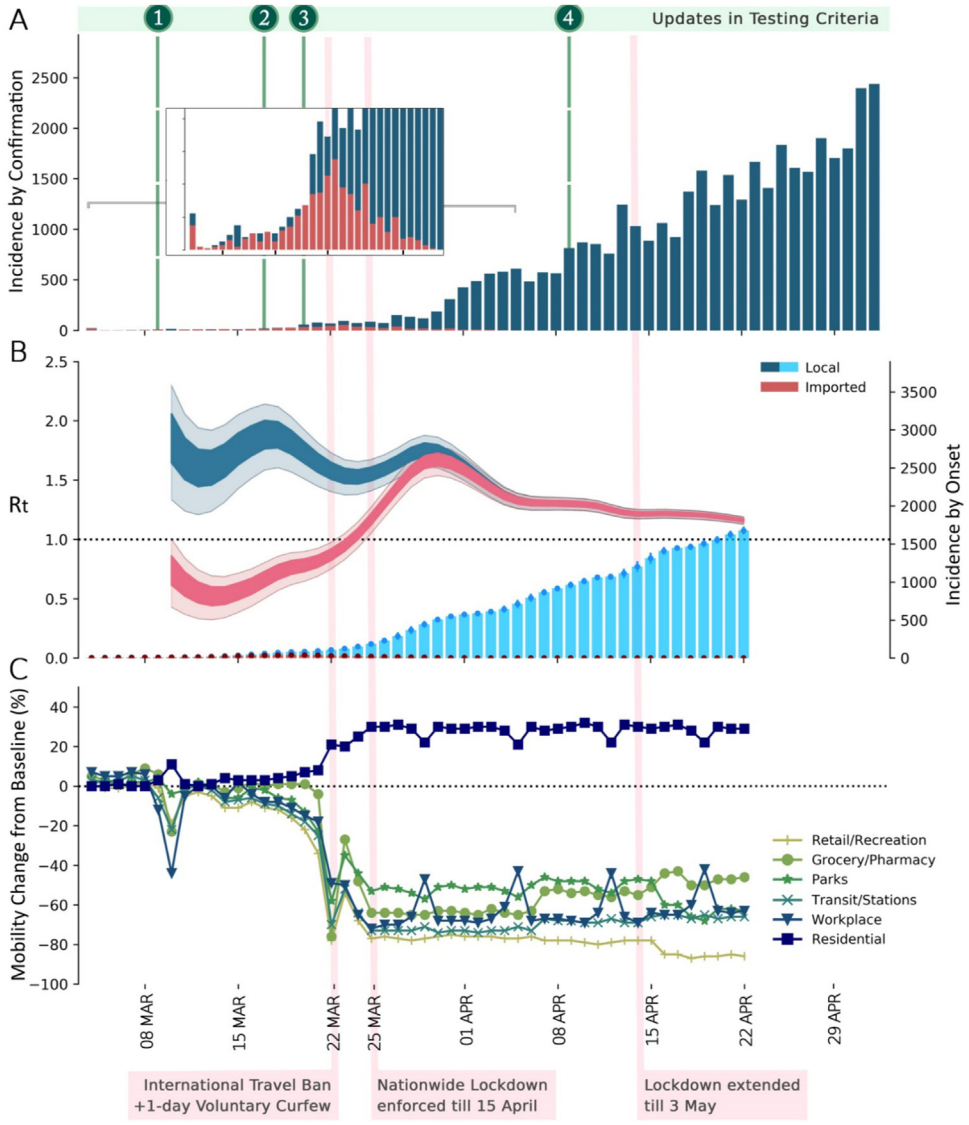

Figure 2. Transmission dynamics and incidence of COVID-19 in India, overlaid with major events and mobility trends. [A] Daily new cases by confirmation date in India up to May 2, 2020 stratified as imported (red) and local (dark blue). The dates of testing criteria updates are overlaid as the scope of testing influences the number of confirmed cases (Appendix p9). **[B]** Daily new cases by onset date (estimated epidemic curve) up to April 22, 2020 in India stratified as imported (red) and local (light blue); and the time-varying effective reproduction number R_t adjusted for importations (pink) and without adjusting for importations (blue), over 5-day windows. Dark bands indicate 50% CI, and light bands indicate 95% CI for estimated R_t. Similar graphs for states of India are provided in Appendix. **[C]** Mobility trends in India, compared to a baseline median value for the corresponding day of the week, during the 5-week period Jan 3–Feb 6, 2020. Holiday due to the Holi festival on March 10, 2020 caused a dip in mobility. A sharp dip in mobility is noted at the voluntary public curfew on March 22 and after the nationwide lockdown was enforced on March 25, except for a rise in residential neighborhood mobility. The weekly rise in workplace mobility appears to be an artifact due to comparison with normal weekends at the baseline. Source—Google LLC (2020). Major interventions are shown, the effects of which are best correlated with R_t trend and mobility changes, as these changes occur in real-time. R_t = time-varying effective reproduction number.

symptomatic, till the end of first wave. The total infections were 50 566 (24 425–93 725) Key time points were predicted as — time at peak of daily new reported cases (t1) between April 13 and April 18, 2020, time at peak of active cases (t2) between April 29 and May 5, 2020, and time when recovered cases > active cases (t3) between May 19 and May 24, 2020. Ninety-five percent CI of 1000 bootstrapped predictions are reported here. The epidemic size increased, and key points were delayed with higher assumptions of asymptomatic proportion (Appendix p19). It is important to note that the model does not consider a parallel leakage of protected compartment back into the susceptible compartment, which tends to happen in reality as lockdowns are not perfect. In addition, control measures cannot be practically maintained indefinitely with initial stringency. Thus, these first wave estimates will obviously be lower than actual data in future; however, they give us the valuable opportunity to model various interventions and explore alternate scenarios.

Impact of lockdown relaxation and its temporality

On a complete removal of the lockdown, irrespective of the date of relaxation, we observed that the number of active cases will start to rise exponentially after a variable delay (Figure 4A). We observed that delaying the lockdown relaxation increases the time lag from the date of relaxation to the date of new rise in active cases (start of second wave), in a linear fashion with Pearson's R = 0·985 (95% CI 0·984–0·985; $p < 0·0001$), as shown in Figure 4B. When we simulated limited duration relaxation periods, we found a rise in

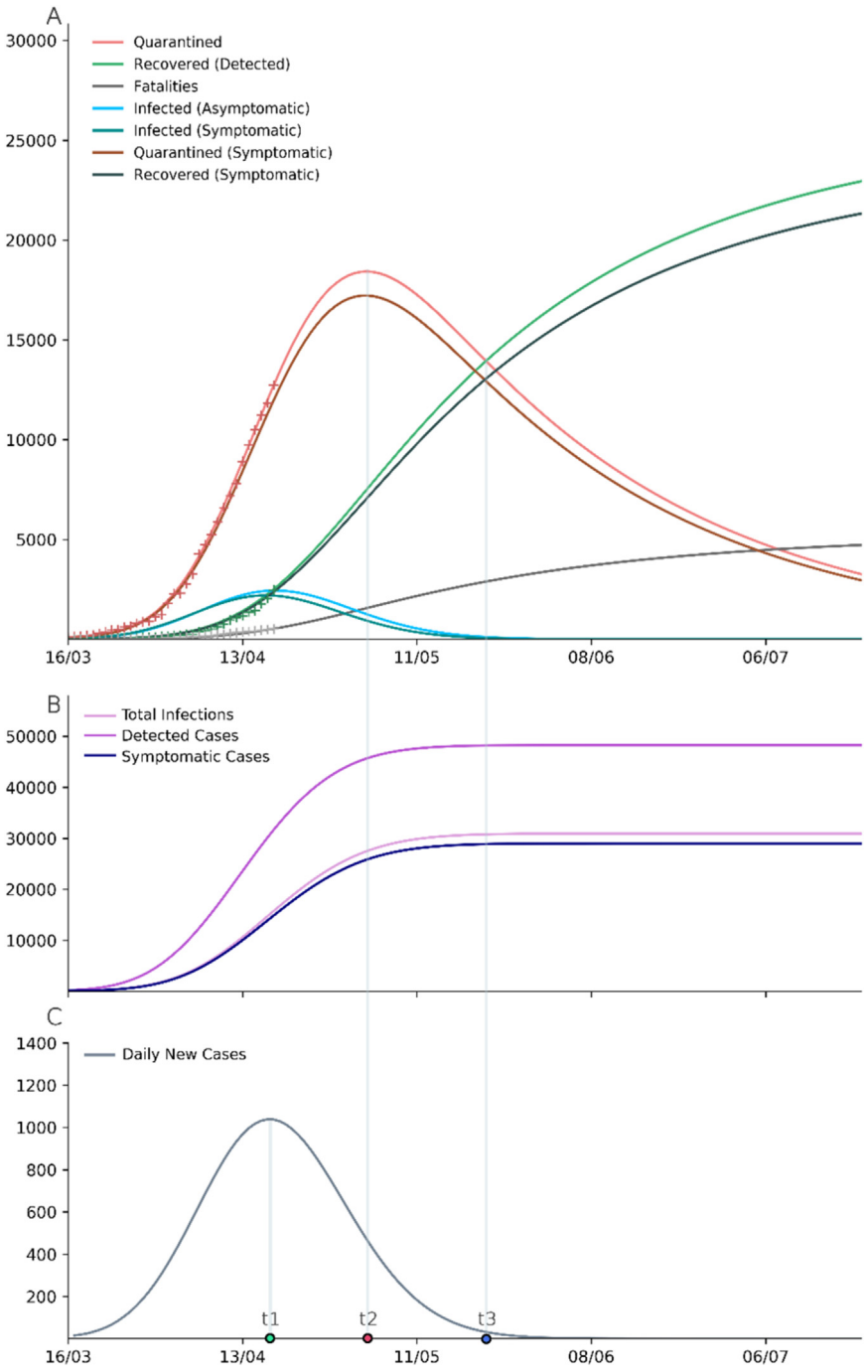

Figure 3. Model simulation of the first wave of COVID-19 in India assuming the lockdown continues indefinitely with the initial stringency. [A] Simulated values of model compartments over time. Quarantined cases are equivalent to the active cases at a particular time. '+' represents data with which the model was trained. **[B]** Predicted total infections, detected cases, and symptomatic cases over time. **[C]** Predicted daily new cases over time. Bands represent 95% CI for the mean prediction over 1000 bootstraps. Three key time points in epidemic progression are shown: time at peak of daily new reported cases (t1), time at peak of active cases (t2), and time when recovered cases > active cases (t3). Results shown for the baseline assumptions (asymptomatics are 25% infectious compared to symptomatics, 40% of total infections are asymptomatic, 10% asymptomatics are detected and quarantined). Results for other assumptions in Appendix.

active cases in all scenarios, but the extent of the rise was highly dependent on when the relaxation was started and the duration of the relaxation period (Figure 4C and D). Both delays in the lockdown relaxation and shorter relaxation periods reduced the number of active cases at the peak. In the case of a gradual lockdown release, the second wave was smaller and further delayed when compared to sudden relaxation (Appendix p26–27).

The result shown in Figure 4 shows that the peak of active cases is on May 4, 2020, while the actual peak of active cases may occur later than May 4, as discussed earlier. These findings may be generalized to any first wave scenario, when interpreted with respect to the actual peak date (which will be comparable to red point in Figure 4B), instead of the absolute dates that are simulated.

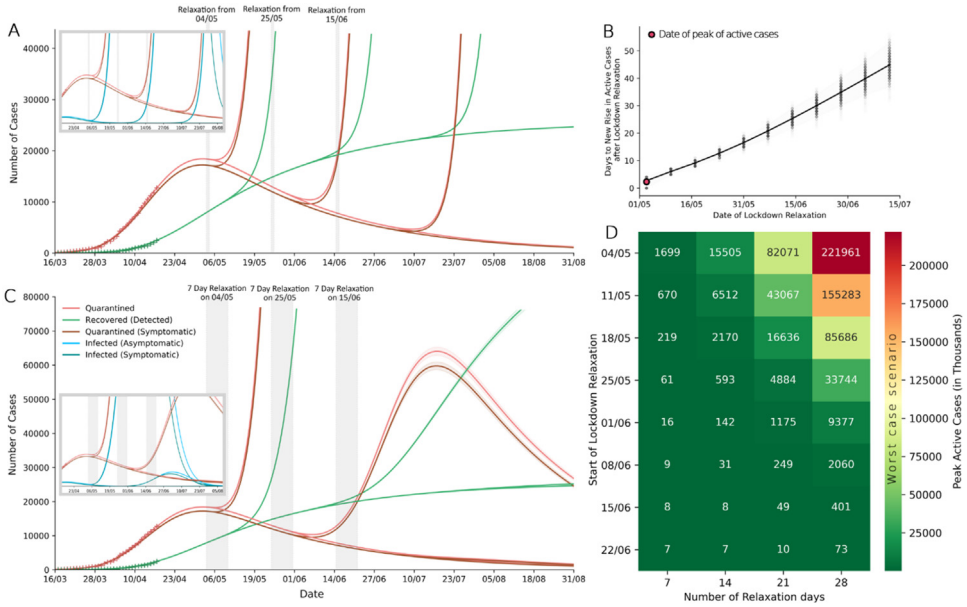

Figure 4. Effect of complete lockdown relaxation under various scenarios. Results are shown for the baseline assumptions (asymptomatics are 25% infectious compared to symptomatics, 40% of total infections are asymptomatic, 10% asymptomatics are detected and quarantined). Bands represent 95% CI for the mean prediction over 1000 bootstraps for all model plots. **[A]** Simulated values of the model compartments Q (active cases), Q_s (active symptomatic cases), and R (recovered) under complete and sustained lockdown relaxation starting May 4, May 25, and June 15, 2020, showing increasing delay to start of the second wave with later relaxation. Inlay shows the underlying depletion of undetected infectious pool as the first wave crosses the peak. **[B]** Days to new rise in active cases (time delay after respective relaxation date) at different dates for lockdown relaxation. This effect is expected to be generalizable when interpreted with respect to the actual date of peak of active cases (compare with red point). Black line represents the line joining the mean lag for 1000 bootstrapped simulations, and bands represent 95% CI. **[C]** Simulated values of the model compartments Q (active cases), Q_s (active symptomatic cases), and R (recovered) under complete relaxation lasting 7 days, starting May 4, May 25, and June 15, 2020, showing increasing delay to start of the second wave and lower magnitude of the second wave with later relaxation. **[D]** Heatmap for the peak active cases under different lockdown relaxation durations and dates of start of relaxation. These are hypothetical worst-case values, where lockdown has been completely lifted across the country at once.

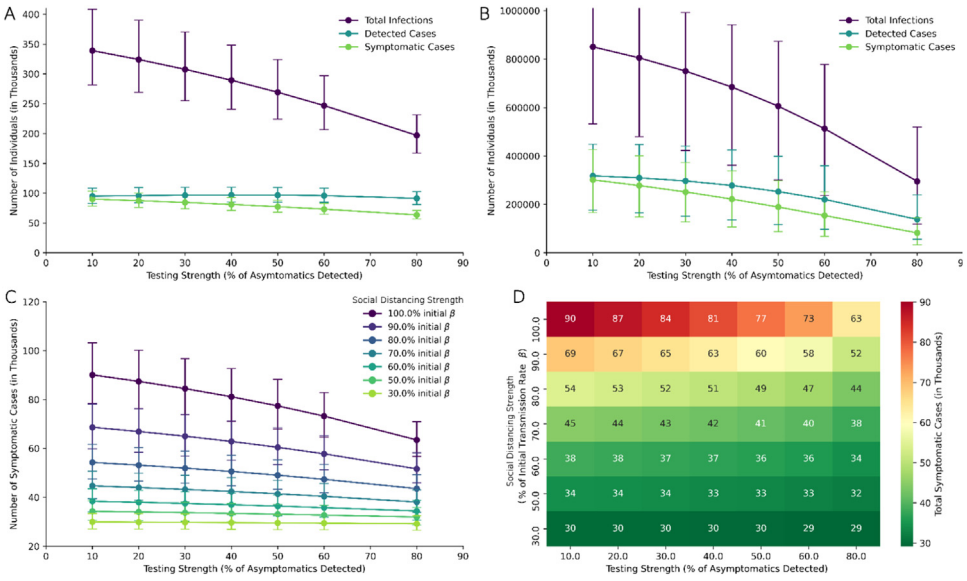

Figure 5. Effect of expanded testing and varying social mixing after complete lockdown relaxation. Results shown for the baseline assumptions (asymptomatics are 25% infectious compared to symptomatics, 40% of total infections are asymptomatic, 10% asymptomatics are detected and quarantined). Any increase in testing or any decrease in social mixing starts from the day of lockdown relaxation. Results for other assumptions in appendix. Error bars represent 95% CI for 1000 bootstrapped predictions. All values are given in thousands of individuals. **[A]** and **[B]** Total number of infections, detected cases, and symptomatic cases at 15 days and 45 days after lockdown relaxation with varying levels of testing. **[C]** Effect of increasing testing (along x-axis) and decreasing social mixing (lines from top to bottom) on the number of symptomatic cases at 15 days after the lockdown relaxation. **[D]** Heatmap for total symptomatic cases after 15 days under different reductions in transmission rate (proxy for social distancing policies) and asymptomatic detection rate (proxy for testing policy). An example of a feasible combination of testing and social distancing policy is indicated by the area between two watershed lines (grey) for a containment target of 50,000-100,000 cases. Similar heatmap for total infections is given in Appendix p24.

Effect of increased testing on epidemic size and restoration of normal social mixing

Increased detection through expanded testing resulted in a decrease in the number of total infections and symptomatic cases (Figure 5A and B). The number of detected cases may remain almost constant at various levels of testing due to a concurrent decrease in total infections and increase in the fraction of infections that were detected (ascertainment rate). However, a lower proportion of detected cases are symptomatic under higher testing, which highlights the significance of detecting more asymptomatic infections.

We further found that the positive impact of increased testing becomes more prominent at progressively higher values of transmission rate β (Figure 5C). As seen in Figure 5C, when prevailing levels of social distancing are very strong (low transmission rate β), increased testing and detection have very little effect on reducing symptomatic case load. For an increase in detection from 10% to 20%, the symptomatic cases after 15 days decreased by 2.9% at β, by 2.0% at 0·8β, and by 0.76% at 0·5β as compared to no increase in detection. For an increase in testing from 10% to 50%, the symptomatic cases decreased by 14.0% at β, by 9.6% at 0·8β, and by 3.5% at 0·5β. Here β, 0.8β, and 0.5β imply no, moderate, and strong social distancing levels that are residual after lockdown relaxation.

After lockdown relaxation, lower levels of social restrictions (high β) when coupled with increased testing, can achieve similar results as a more restrictive social distancing regime where testing was not increased (Figure 5D); increased testing allowed greater resumption of normal social mixing after lockdown relaxation. An example of a feasible combination of testing and social restrictions is indicated by the area between two watershed lines (grey) in Figure 5D. Due to uncertainty in the percent of infections that are asymptomatic, we evaluated the effect of testing across the range of p_a (Appendix p22–25).

Discussion

The trend of effective reproduction number (R_t) of COVID-19 in India indicates that control measures have been effective in slowing down the spread of COVID-19 across the country. To achieve sustained suppression, monitoring of the time-varying R_t at district, state, and national levels should be done to reach and maintain an R_t close to the threshold value of 1. If lockdown is to be extended, additional benefits can be achieved if it is extended farther after the peak of active cases has passed. As these restrictions are relaxed, increased detection through testing will be essential for limiting the resurgence of cases, and thus, testing capacity should be ramped up preemptively before lifting restrictions. Considering that asymptomatics play an undeniable role in transmission of COVID-19, dependence on presence of symptoms for control strategies, behavioral changes, and testing should be reduced.

The range of R_0 of SARS-CoV-2 in India was found to be 2–2·5, with 2·083 being the best fit. Our results align with recent studies which estimate the R_0 to be 2–2·7 (Li et al., 2020a; WHO, 2020; Wu et al., 2020). In comparison, the R_0 was 1·4–1·6 for the 2009 influenza (H1N1) pandemic, 2·0–3·3 for the 2003 SARS epidemic, and 2·0–3·0 for the 1918 Spanish flu pandemic, which reflects the seriousness of the current pandemic (Coburn et al., 2009; Mills et al., 2004; WHO, 2003). The proportion of population that must become immune in order to halt the epidemic is given by $1–1/R_0$—the herd immunity threshold (Fine et al., 2011). For COVID-19, our estimates imply that approximately 50–60% of the population must be infected or vaccinated in order to attain long-term epidemic control.

In the early stages of the epidemic in India, we found that restrictions on international travel were effective in limiting the number of imported cases in India, although this is of limited importance once local chains of transmission had been established (Mandal et al., 2020). As testing of travelers was based on appearance of symptoms, asymptomatic imported infections that remained undetected may have played a role in the early spread of COVID-19 (ICMR, 2020).

A 'suppression' strategy (e.g.: lockdown) aims to arrest epidemic growth by reducing R_t below 1 (Ferguson et al., 2020; Leung et al., 2020). After the nationwide lockdown was imposed on March 25, 2020, the mobility levels quickly dropped to low levels, but the R_t continued to increase till March 30 (Figure 2) probably due to inflation of estimated transmission by the Nizammudin cluster (a super-spreading event originating in Delhi) — which represented about 30% of total COVID-19 cases in India in early April, with latest data linking the cluster to 4291 cases across more than 15 Indian states (Ministry of Health and Family Welfare, Government of India, 2020). This event adds to the list of multiple COVID-19 super-spreader events around the world, which have caused unexpected spikes in cases (Liu et al., 2020a). It should be noted that clusters may disproportionately inflate transmission estimates because targeted testing of people linked to the cluster leads to higher test positivity rates. The R_t down-trended on 30 March onwards, with the most recent estimated R_t of 1·159 (95% CI 1·128–1·189) on 22 April, which was the lowest value of R_t yet. As there was no significant susceptible depletion, this decrease in transmission can be attributed to the intensive social restrictions in place. The trend of R_t from 23 April onwards is of particular interest, and it remains to be seen whether the R_t can reach sub-threshold levels (below 1) before the lockdown is relaxed.

India was under one of the strictest lockdowns in the world (OxCGRT: Oxford COVID-19 Government Response Tracker, 2020), and a comprehensive lockdown exit strategy is required to consolidate and build upon the gains of the lockdown. A sudden and complete lifting of the nationwide lockdown is not a feasible option as it will lead to a rapid exponential increase in cases due to the absence of herd immunity. A lockdown of adequate length and efficacy eventually causes the active cases to peak and then gradually decrease. Once the peak of active cases is reached, extending lockdown farther beyond the peak may have additional benefits due to progressive exhaustion of the infectious pool in the population, which is practically comparable to a lower pre-relaxation prevalence of COVID-19. This has 2 effects. First, the rebound epidemic growth is initially slower, which delays the resurgent rise in cases after relaxation of lockdown. This seems to imply that though extending a lockdown inherently buys time for preparation, it also adds a progressively longer preparation time after the lockdown is relaxed (Figure 4A, B). Second, we find that if lockdown is to be reimposed after a fixed relaxation period, the magnitude of the second peak can be reduced by relaxing the lockdown farther from the first peak (Figure 4C, D). This is of particular interest if an intermittent lockdown strategy is implemented in the future, where measures need to be imposed and relaxed repeatedly. The time gained should be used to strengthen surveillance systems, ramp-up testing capacity, and increase health-system preparedness. It is optimal to prevent a second wave from occurring at all, by fine-tuning lockdown relaxation based on serial monitoring of R_t to keep its value under 1 (Leung et al., 2020; Pan et al., 2020). In this scenario, a later relaxation will allow the stabilization of disease prevalence at a lower value, which can provide a buffer for response if and when a resurgent rise in cases is seen (maintaining $R_t = 1$ implies that the prevalence will remain constant at the pre-relaxation level). These observations may increase the benefit of lockdowns above what is

widely known and can better inform the delicate balance of cost and benefits of such intensive policies.

Massive scaling up of testing has been proposed as a lockdown exit strategy (Lavezzo et al., 2020; Peto et al., 2020). In this study, we present quantitative evidence based on modeling for the same (Figure 5). Extremely low transmission rates during intensive restrictions are inherently enough to contain the epidemic. However, as transmission rates increase with progressive restoration of normal socio-economic activities post lockdown relaxation, testing assumes an increasingly substantial role in containment. The extent of relaxation that will be possible without causing an untenable rebound in infections will highly depend on the amount of testing that is done, especially after lockdown relaxation. While having both intensive social distancing policies and very expansive testing may be nonviable, combining the effects of both to a feasible extent can effectively keep the epidemic under control (Figure 5D). Our findings align with results seen in countries with an aggressive testing approach, such as South Korea and Taiwan where severe restrictions have been avoided (Pueyo, 2020). As of May 2, 2020, 1 046 450 total COVID-19 tests were conducted in India with about 70 000 tests administered daily and growing. During the same time period, Russell et al. (2020) estimate that cases in India were underreported by a factor of 5–25 based on delay-adjusted case fatality rates; a finding that is consistent with the usual under-ascertainment seen in early phases of an epidemic. Even if the amount of testing being done during lockdown is deemed to be sufficient, a rapid and massive scaling up of testing capacity is needed preferably before relaxing restrictions. The monetary cost of expanding testing even at a large scale, is expected to be smaller than the cost of implementing intensive social distancing for long periods (Lee et al., 2020). In addition to supporting the economy, this approach can ameliorate the substantial social and humanitarian implications of imposing population-wide lockdowns, especially in a country such as India.

Blanket testing of health care workers (HCWs) can be a judicious use of the expanded capacity, considering they are highly exposed personnel and risk spreading the infection to patients, co-workers, and family members if infected. This will limit depletion of an already scarce workforce due to unnecessary quarantine, while also reducing spread from unrecognized asymptomatic infections in HCWs (Black et al., 2020). Other essential workforce like law enforcement personnel, grocery vendors, sanitation workers, and others with high contact rates should also be considered.

SARS-CoV-1 did not reach the scale of SARS-CoV-2 despite a comparable R_0 due to low community transmissibility and onset of infectivity well after symptom onset which allowed optimal efficacy of traditional control measures such as symptom-triggered isolation and contact tracing (Gandhi et al., 2020; WHO, 2003). Pre-symptomatic transmission occurs before the onset of symptoms in an eventually symptomatic patient, while asymptomatic transmission occurs through patients who never become symptomatic. The presence of both these features in COVID-19 is a significant deterrent for control strategies (Gandhi et al., 2020; Hu et al., 2020; Liu et al., 2020c; Tindale et al., 2020). In such a scenario and $R_0 \sim 2.5$, modeling studies indicate that controlling COVID-19 outbreaks through classical contact tracing and isolation alone is not possible. However, contact tracing systems should be strengthened as they are a prerequisite for expanded testing of contacts, and they may achieve significant containment at lower effective reproduction numbers (Hellewell et al., 2020). Contact definitions should include contacts made 48–72 h before symptom onset of index case to account for pre-symptomatic transmission. Technology-enabled contact tracing can reduce delay to isolation of contacts and thus cut off transmission when infectiousness is highest around the time of symptom onset.

Based on our findings, it is possible that detecting more asymptomatics through testing impedes transmission to an extent where the total number of infections, and thus the number of symptomatic cases, decreases (Figure 5), relieving burden upon the healthcare system and reducing mortality. This finding will increasingly approximate reality if asymptomatics play a larger role in transmission. A case in point is a blanket testing study done in a small town in Italy which achieved almost complete outbreak control (Lavezzo et al., 2020). Although blanket testing is not practical for larger implementation, it further highlights the importance of detecting and isolating asymptomatics in controlling COVID-19 outbreaks.

A symptom-based monitoring approach during quarantine will miss asymptomatic infections that will escape the quarantine net and go on to spread the disease. With emerging evidence of infectious asymptomatics, it is prudent to modify the public health response to address these concerns. Thus, all contacts should ideally be tested at the end of quarantine irrespective of symptoms. In settings where testing all contacts is not yet possible, close contacts may be tested and extended quarantine periods up to 28 days may be considered, which have two-fold benefits. First, almost all asymptomatics finish their infectious period before 28 days, and second, more symptomatics can be detected by day 28 (only 2 out of 10,000 symptomatic cases are missed by day 28, compared to 101 cases by day 14) (Lauer et al., 2020). Such extended quarantines are already in place in certain parts of India (Kerala) and China (Harbin). Currently, a 14-day quarantine is recommended based on studies of incubation period of COVID-19 (Lauer et al., 2020; Li et al., 2020a), but studying the incubation period inherently assumes an onset of symptoms. It is encouraging to note that the need for expanded testing can be supported by high-throughput machines and by pooling of samples (ICMR, 2020). Pooling can also be used for community surveillance and has the potential to drastically increase detection capabilities while saving costs and resources. Pooling should be used wherever possible, while also enhancing research to boost pool size and accuracy (Yelin et al., 2020).

While contact tracing, isolation, and testing are important, the role of behavior change in reducing transmission must not be underestimated. Asymptomatic people are themselves less likely to take appropriate precautions, and people use less caution around other people who do not have symptoms. Universal mask wearing in public spaces should be encouraged and, if required, mandated by policy (Abaluck et al., 2020). Considering that ensuring long-term compliance of citizens to health advisories and public restrictions will be another challenge, transparent and proactive communication by authorities along with continued social support for vulnerable groups will be essential.

Blanket interventions have been effective in suppressing the pandemic till now, but targeted interventions will be key as we move forward. Various interventions need to be stratified based on how effectively they suppress viral transmission and the amount of disruption they cause. Cost effectiveness analysis must be done, and bundles of interventions that together achieve high efficacy with least accompanying disruption should be deployed. Highly effective and disruptive interventions should be targeted at areas with active hotspots and high community transmission. It will be essential to build robust disease surveillance systems to assess the relative impact of each intervention in real-time and reduce the time delay to response. Expanded testing and strengthened contact tracing will enable this by reducing the reporting lag and rapidly detecting any surge in cases. Instead of adopting an intermittent lockdown policy, where lockdowns are treated as either ‘on’ or ‘off’ (Ferguson et al., 2020), some countries have adopted a staged alert system for responding to the COVID-19 pandemic (New Zealand Government, 2020), where a geographical

area may move up and down alert levels, to reflect the level of suppression that the local outbreak situation demands. Similarly, India has recently stratified its districts into red, orange, and green zones, based on surveillance trends, in preparation for a staggered relaxation of lockdown (Ministry of Home Affairs, Government of India, 2020). Such social distancing policies which are dynamic with respect to geography and time are direly needed as we move into a time of relative uncertainty post lockdown relaxation.

As with all analyses, our study has a few limitations which must be noted to better understand the findings. First, the estimation of reproductive numbers is based on detected cases which are only a fraction of the actual infections, and we do not account for variation in detection, which, if significant, may confound the changes in estimated R_t over time. Second, we assumed the delay from symptom onset to confirmation to be similar to the delay from symptom onset to hospitalization due to lack of data, and that this delay is uniform across India. Though the latter approximates the former, further studies to ascertain the true reporting lag in India are needed as it is critical for identifying R_t changes at correct points in time (Leung et al., 2020). Third, as our primary goal was to evaluate the effect of identifying asymptomatics, we assumed that increased testing increases the detection of asymptomatics only, while in reality it would detect more cases across the clinical spectrum. However, the interpretations regarding impact of increased testing are not sensitive to this assumption, which has been discussed through an alternate interpretation of the model (Appendix p4). Lastly, we assumed a constant death rate (κ), in contrast to reality where the death rate gradually decreases during an epidemic to ultimately converge at the near-actual death rate (Spychalski et al., 2020). Thus, we refrained from forecasting deaths due to obvious bias in the prevailing death rate at the time of the study.

Notwithstanding the limitations, we built a mathematical model which can account for the dynamics of lockdown imposition and relaxation, varying levels of case detection, and lag to symptom onset and case reporting, while simultaneously allowing to test the range of asymptomatic burden and transmissibility. As we have presented findings across the range of uncertainty regarding asymptomatics (Appendix), our results are robust with regard to emerging evidence. Though our model is fitted to data from India, we expect the insights into lockdown relaxation and testing impact to be generalizable to similar scenarios elsewhere.

In conclusion, though disruptive, the world's largest lockdown in India has been effective in reducing the transmission levels of COVID-19. To avoid a resurgence in cases, a dynamic relaxation approach guided by regional monitoring of effective reproduction numbers is recommended, and this relaxation should be farther from the peak of active cases as feasible. Asymptomatics could be a considerable challenge to long-term containment efforts, and increased detection will play an increasingly pivotal role once restrictions start to be lifted. The amount of testing will dictate the extent of resumption of socioeconomic activities, and authorities should scale-up testing capacity as a priority. Further, control measures should be appropriate and acceptable in the social context of a population, especially in low and middle-income countries across the world.

Contributions

MG and GGP conceptualized the study. MG and SSM designed the model. SSM programmed the model and performed formal analyses. MG wrote the original draft. SSM, AR, MAg, MAr, and AMa assisted in draft preparation and reviewed existing evidence. GGP, AL, PB, and AB consulted on the analyses and reviewed the draft. SSM and MG made the figures. RK, VPM, PT, SB, and AMo enabled patient participation, collected and curated primary patient data, and enabled inter-department coordination at the hospital. GGP and MG supervised the project. All authors interpreted the results, contributed to writing the manuscript, and approved the final version for submission.

Data sharing and code availability

The code for the simulations and detailed results are available at the following GitHub repository: https://github.com/CovidToday/covid19model-india. The primary data for calculation of reporting lag is available in the appendix. All other data are from publicly available datasets.

Declaration of interests

We declare no competing interests.

Ethics approval

All relevant ethical guidelines have been followed; necessary IRB and/or ethics committee approvals have been obtained (through *Institute Ethics Committee AIIMS Delhi; Ref. No. IECPG-166/23.04.2020*). All necessary patient/participant consent has been obtained.

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Appendix A. Supplementary material

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2020.11.206.

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