

Serial interval, basic reproduction number and implications for control measures: 120 days experience of COVID-19 outbreak from Jodhpur, India

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Serial interval, basic reproduction number and implications for control measures: 120 days experience of COVID-19 outbreak from Jodhpur, India

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Abstract

We aimed to estimate the serial interval and basic reproduction number (R_0) for Jodhpur, India and to use it for epidemic projection for next one month. Contact tracing of SARS-CoV-2 infected individuals was done to obtain the serial intervals. Aggregate and instantaneous R_0 values were derived and epidemic projection was done using R software v4.0.0. Median and 95 percentile values of serial interval were 5.23 days (95%CI 4.72 – 5.79) and 13.20 days (95%CI 10.90 – 18.18), respectively. R_0 during the first 30 days of outbreak was 1.62 (95%CI 1.07 – 2.17) which subsequently decreased to 1.15 (95%CI 1.09 – 1.21). Instantaneous R_0 ranged from a peak of 3.43 (95%CI 1.71 – 5.74) to 1.12 (95%CI 1.03 – 1.21) as on 6 July 2020. Epidemic projection over next one month was 2131 individuals (95%CI 1799 – 2462). Reduction of transmission by 25% and 50% could lead to 58.7% and 84.0% reduction in epidemic size, respectively. Aggressive control measures reduced R_0 indicating prevention of COVID-19 transmission. Further strengthening of control measures could lead to substantial reduction of COVID-19 epidemic size. A data-driven approach at local level was found useful in guiding the public health strategy and surge capacity planning.

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TITLE PAGE

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ABSTRACT

We aimed to estimate the serial interval and basic reproduction number (R_0) for Jodhpur, India and to use it for epidemic projection for next one month. Contact tracing of SARS-CoV-2 infected individuals was done to obtain the serial intervals. Aggregate and instantaneous R_0 values were derived and epidemic projection was done using R software v4.0.0. Median and 95 percentile values of serial interval were 5.23 days (95%CI 4.72 – 5.79) and 13.20 days (95%CI 10.90 – 18.18), respectively. R_0 during the first 30 days of outbreak was 1.62 (95%CI 1.07 – 2.17) which subsequently decreased to 1.15 (95%CI 1.09 – 1.21). Instantaneous R_0 ranged from a peak of 3.43 (95%CI 1.71 – 5.74) to 1.12 (95%CI 1.03 – 1.21) as on 6 July 2020. Epidemic projection over next one month was 2131 individuals (95%CI 1799 – 2462). Reduction of transmission by 25% and 50% could lead to 58.7% and 84.0% reduction in epidemic size, respectively. Aggressive control measures reduced R_0 indicating prevention of COVID-19 transmission. Further strengthening of control measures could lead to substantial reduction of COVID-19 epidemic size. A data-driven approach at local level was found useful in guiding the public health strategy and surge capacity planning.

KEY WORDS

SARS-CoV-2, COVID-19, serial interval, basic reproduction number, projection

MANUSCRIPT TEXT

Introduction

COVID-19 has emerged as the largest pandemic of 21st century with 14.3 million confirmed

cases and around 0.6 million deaths worldwide, as on 20 July 2020.¹ India has become the third most affected country worldwide with around 1.1 million confirmed COVID-19 cases.¹ COVID-19 is an emerging infectious disease with the onset of symptoms of first case having been reported from Wuhan, China in early December 2019.² Various epidemiological studies are being done to understand the transmission dynamics of the disease. Consequently, the estimated parameters such as serial interval and basic reproduction number (R_0) are being used to guide the control strategies and to enable disease forecasting.³⁻⁵

In the early phase of the COVID-19 pandemic, India had adopted the policy of universal health-facility based isolation of all SARS-CoV-2 infected individuals irrespective of symptomatic status. However, in view of the increasing number of COVID-19 cases, home isolation of asymptomatic and mild cases was introduced on 10 May 2020.⁶ Therefore, it is important to achieve an epidemiological understanding of COVID-19 situation at district level in the changed scenario so that it could be used to guide control measures and surge preparedness on a real-time basis.

We aimed to study the transmission of COVID-19 at district level by estimating the serial interval and R_0 . We wished to use it for epidemic projection for next one month in order to guide the COVID-19 response. We studied the COVID-19 outbreak in Jodhpur district which is situated in the western part of India in Rajasthan state (Figure 1). The first COVID-19 case was reported here on 9 March 2020.

Methods

We conducted a prospective observational study of the COVID-19 outbreak at Jodhpur, India. The study had been approved by the Institutional Ethics Committee (Ref: AIIMS/IEC/2020-21/3047).

Serial interval estimation

Individuals meeting suspect case definition for COVID-19 were tested with rRT-PCR (Real-Time Reverse Transcription-Polymerase Chain Reaction) at our institute in Jodhpur, India as per the national guidelines.⁷ Those found positive for SARS-CoV-2, were further assessed for their contact history with known COVID-19 cases in their household. Serial interval was estimated based on the time duration between the symptom onsets of the infector-infectee pairs thus identified. For asymptomatic individuals, the date of collection of first positive sample was taken as a proxy for symptom onset. Mean and standard deviation of serial interval was calculated. Further, the serial interval data was fitted to weibull, log-normal, log-logistic and generalized gamma distributions using Flexsurv package in R software version 4.0.0.⁸ The estimates of median serial interval were taken from the best fitting model based on minimum Akaike Information Criterion (AIC) value. Standard maximum likelihood approach was used to obtain the best model fit to actual data.

Estimation of R_0

The basic reproduction number (R_0) is defined as the average number of susceptible individuals infected by a single primary case.⁹ The daily COVID-19 case data of Jodhpur district was converted to incidence object using Incidence package in R software.¹⁰ EarlyR and EpiEstim packages in R software were used to estimate overall and instantaneous values of basic reproduction number using the parameter estimates of serial interval, respectively.^{11,12} Instantaneous R_0 values were calculated based on method of estimating daily incidence based on a Poisson process determined by daily infectiousness, as proposed by Jombart and Nouvellet *et al.*^{10,13} Here λ_t , the force of infection observed on day t is expressed by the following equation:

$$\lambda_t = \sum_{s=1}^{t-1} R_s y_s \omega_{t-s},$$

where y_s is the incidence of cases on day s . R_s is the instantaneous reproduction number

on day s . The value of ω_{t-s} is the probability mass distribution of the serial interval which represents the infectiousness of incident cases on day s in order to result in secondary cases on day t . As a practical approach used by earlier studies, we approximated day of reporting of the case as the day of onset, in the absence of exhaustive symptomatic history of each reported case.¹³

We also used another method by Wallinga and Teunis for estimation of the time varying R_0 based on probability of transmission between infector-infectee pairs.¹⁴ We used the parametric method of specifying the mean and standard deviation of serial interval distribution for both the methods. Time window of both 7 days and 14 days was used for calculation of instantaneous R_0 .

Forecasting of the epidemic size

Forecasting of daily and cumulative COVID-19 cases for the next 30 days was done based on the overall R_0 value and based on R_0 value of the past 30 days as input parameters using the Projections package in R.¹⁰ As required, serial interval distribution was specified as scale and shape parameters of gamma distribution. Forecasting of daily incidence was based on a Poisson process determined by daily infectiousness.¹³ The specified serial interval distribution is taken as a prior while utilizing the Bayesian methodology for Markov Chain Monte Carlo (MCMC) sampling using the Metropolis algorithm. The 95% confidence intervals of projected daily and cumulative incidence were calculated using bootstrap resampling method with 1000 samples.

Results

Serial interval

From the reporting of first case on 9 March 2020 till 6 July 2020, 3178 cases were reported from the district in a span of 120 days. Serial interval data for 103 infector-infectee pairs was obtained through contact tracing of known infected cases (multimedia appendix 1).

The mean serial interval was 6.23 days with a standard deviation of 3.49 days. The generalized gamma distribution was found to be the best fitting with serial interval with minimum Akaike Information Criterion value (Figure 2). The median and 95 percentile values of serial interval were 5.23 days (95% CI 4.72 – 5.79) and 13.20 days (95% CI 10.90 – 18.18), respectively estimated from the fitted generalized gamma distribution (Figure 2).

Estimation of R_0

The overall R_0 value in the first 30 days after reporting of first case was 1.62 (95% CI 1.07 – 2.17) which subsequently decreased to 1.15 (95% CI 1.09 – 1.21). The overall R_0 value for the entire outbreak duration was 1.07 (95% CI 1.04 – 1.11), whereas it was 1.20 (95% CI 1.14 – 1.27) for the last 30 days.

The instantaneous R_0 value calculated using the method by Jombart and Nouvellet *et al*¹³ yielded maximum values of 6.53 (95% CI 2.12 – 13.38) and 3.43 (95% CI 1.71 – 5.74) using sliding time-windows of 7 days and 14 days respectively (Figure 3). Similarly, using the method by Wallinga and Teunis¹⁴ the maximum values of instantaneous R_0 were 2.96 (95% CI 2.52 – 3.36) and 2.92 (95% CI 2.65 – 3.22), taking 7- and 14-day time-windows respectively (Fig 3). The peak R_0 values corresponded with the rising trend in COVID-19 cases being reported daily (Figure 2). The latest instantaneous R_0 value estimated on 6 July 2020, using the method by Jombart and Nouvellet *et al*¹³ were 1.21 (95% CI 1.09 – 1.34) and 1.12 (95% CI 1.03 – 1.21) taking 7- and 14-days sliding time-windows, respectively (Figure 3). Similarly, the latest instantaneous R_0 values estimated on 6 July 2020, using the method by Walling and Teunis were 0.32 (95% CI 0.27 – 0.36) and 0.61 (95% CI 0.58 – 0.63) taking 7- and 14-days sliding time-windows, respectively (Figure 3).

Projection of epidemic size

The number of daily cases projected for the next month while taking an overall R_0 value of 1.20 (corresponding to the most recent 30 days of transmission) ranged from 55 individuals

(95% CI 38 - 71) on 7 July 2020 (day 1) to 143 individuals (95% CI 110 – 175) on 5 August 2020 i.e. day 30 (Figure 4). Similarly, the number daily cases projected for the next month while taking the most recent 14-days rolling instantaneous R_0 value of 1.12 ranged from 52 individuals (95% CI 38 - 66) on day 1 to 91 individuals (95% CI 66 – 116) on day 30 (Figure 4). The cumulative projection of number of COVID-19 cases over the next 30 days while taking these R_0 values of 1.20 and 1.12 was 2817 individuals (95% CI 2374 – 3259) and 2131 individuals (95% CI 1799 – 2462), respectively.

A scenario of 25% and 50% reduction in the most recent transmissibility (i.e. reduction of R_0 from 1.12 to 0.84 and 0.56) assuming further strengthening of control measures resulted in monthly projection of 880 cases (95% CI 699 – 1061) and 341 cases (95% CI 265 – 418). This corresponded to 58.7% and 84.0% reduction in the epidemic size in Jodhpur, respectively.

Discussion

Implications of serial interval and R_0 estimation

Our observation of mean serial interval fell within the range of 4-8 days estimated by a meta-analysis of 7 studies conducted during the early phase of the COVID-19 pandemic.¹⁵ Another meta-analysis including studies only from China estimated a range of serial interval from 4.10 – 7.5 days.¹⁶ Our experience suggests that the median and 95% confidence interval estimate of serial interval should be reported alongside the mean and standard deviation as the latter approach is more susceptible to be influenced by extreme values. It has also been suggested that longer serial interval intervals can be noted due to preventive interventions and during the course of the epidemic.^{17,18} Therefore, it is preferable to estimate recent serial interval locally to better understand the transmission of SARS-CoV-2. The distribution of R_0 values was consistent with the observation from other countries indicating a similar transmission pattern.^{4,18} Once the peak of R_0 value was reached in the

first week of April, subsequent reduction towards April end could be attributed to aggressive testing, contact tracing and isolation measures in the urban area of Jodhpur during the April month. Earlier detection of infection followed by isolation is known to reduce the R_0 value through limiting both the duration of effective contact and the number of susceptibles an infected individual can come in contact with.⁹ Our findings further support that parameters such as serial interval, incubation period and R_0 values are likely to vary throughout the course of the epidemic and will depend on the local factors influencing transmission such as demographics, environmental conditions, modelling methodology and the stringency of the control measures.^{9,19}

Projection of epidemic

The projected estimate of daily case and the final outbreak size were found to depend on the value of R_0 entered in the model.^{20,21} The method used to estimate the R_0 value and the time-window over which R_0 was calculated influenced the final projection by a wide margin. The 14-days-time window yielded less variable instantaneous R_0 estimates as compared to a 7-days-time window. We found that the method by Wallinga and Teunis was more sensitive to recent fluctuations in daily case count, as compared to the method by Jombart *et al*, while taking the same time window. Further, as per the renewal equation stated earlier, the values of R_0 are most influenced by the trend in daily cases reported within the range of the serial interval i.e. within 5-6 days. This also pre-assumes homogenous mixing, which becomes less applicable with larger populations with cases emerging from widely separated clusters. Also, the impact of methods of R_0 estimation and time windows were more pronounced when there was a fluctuating trend in cases or the R_0 value was close to 1. Therefore, R_0 values should be tested through sensitivity analysis by considering variations in time-windows and durations and using different methods so that reliable projections could be provided for larger populations.²⁰

Strengths and limitations

One of the strengths of our study was estimation of serial interval based on large data over a period of two months. Also, since our study was based on contact history of infected individuals instead of daily follow-up of contacts of infected individuals for disease onset, we minimized underreporting of longer serial intervals which is possible due to right-truncation in assessing serial interval based on follow-up method.²² Further, our use of time-varying method for daily R_0 estimation and maximum likelihood method for overall R_0 estimation had the benefit of less bias as compared to exponential growth and sequential Bayesian methods.²³ The time-varying method had the added advantage of providing daily R_0 values which were useful in assessing the effectiveness of control measures, as compared to other methods which provide only an aggregate R_0 value.²²

Population level estimates relying on daily reports could underestimate the value of R_0 as compared to those of closed populations, as many infected individuals are likely to be missed, especially if the testing capacity is limited or proportion of asymptomatics is high.²⁰ Further, modelling assumptions such as assuming a finite probability of interaction of infector-infectee pairs reported within a range of serial interval might not be applicable for large population cohorts.¹⁴ In order to overcome such limitations use of both spatial and temporally structured data has been proposed.²⁴

Conclusions

Public health measures such as testing, contact tracing and home isolation were found to reduce to instantaneous R_0 value and could thereby reduce the final outbreak size. The final epidemic size was found to be influenced by R_0 values, which in turn depended on the stringency of control measures. Even a marginal reduction in R_0 as a result of strengthening control measures was found to considerably reduce the projected COVID-19 burden in Jodhpur, India. Projections are feasible based on publicly released daily COVID-

19 case data and could be useful in guiding a data-driven COVID-19 response strategy at a local level. This could be utilized for both surge capacity planning of number of hospital beds and ventilators required, and also for the public health response such as number of staff required for contact tracing and for provisioning of institutional quarantine or isolation facility. Therefore, considering the increasing case load and dynamic situation of COVID-19, a decentralized evidence-driven approach appears to be the need of the hour.

AUTHOR STATEMENTS

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Authors' contributions – MKV, VG, NK and SS collected the data and SS conducted the analysis. SS wrote the draft manuscript with further inputs from MKV, VG, AG, MKG and PB. PB coordinated the data collection process. SM provided overall supervision of the lab testing, clinical care and research related to COVID-19 at AIIMS - Jodhpur, India. All authors approved the final manuscript.

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ABBREVIATIONS

AIIMS Jodhpur– All India Institute of Medical Sciences, Jodhpur, India

COVID-19 – Corona Virus Disease 2019

R0 – basic reproduction number

rRT-PCR – Real-Time Reverse Transcription Polymerase Chain Reaction

SARS-CoV-2 – Severe Acute Respiratory Syndrome Corona Virus 2

FIGURES

Figure 1: Location of Jodhpur district within Rajasthan state of India.

(Modified from source file -https://commons.wikimedia.org/wiki/File:India_districts_map.svg, Creative Commons Attribution-Share Alike 4.0 International license)

Figure 2: Estimates of median and 95 percentile of serial interval data as fitted to weibull, log-normal, log-logistic and generalized gamma distributions (n = 103 pairs).

Figure 3: Daily COVID-19 cases at Jodhpur, India from 9 March 2020- 6 July 2020 (A) and instantaneous R0 values estimated using method by Jombart et al (B-C) and instantaneous R0 values estimated using method by Wallinga and Teunis (D-E) using time windows of 7 and 14 days, respectively.

Figure 4: Projection of daily and cumulative COVID-19 case-load over the next 30 days using instantaneous R0 value of 1.12 on 6 July 2020 (A-B) and overall R0 value of 1.20 for the most recent 30 days (C-D).

MULTIMEDIA APPENDIX

Appendix 1: Data for serial interval estimation of COVID-19 in Jodhpur, India (103 pairs).



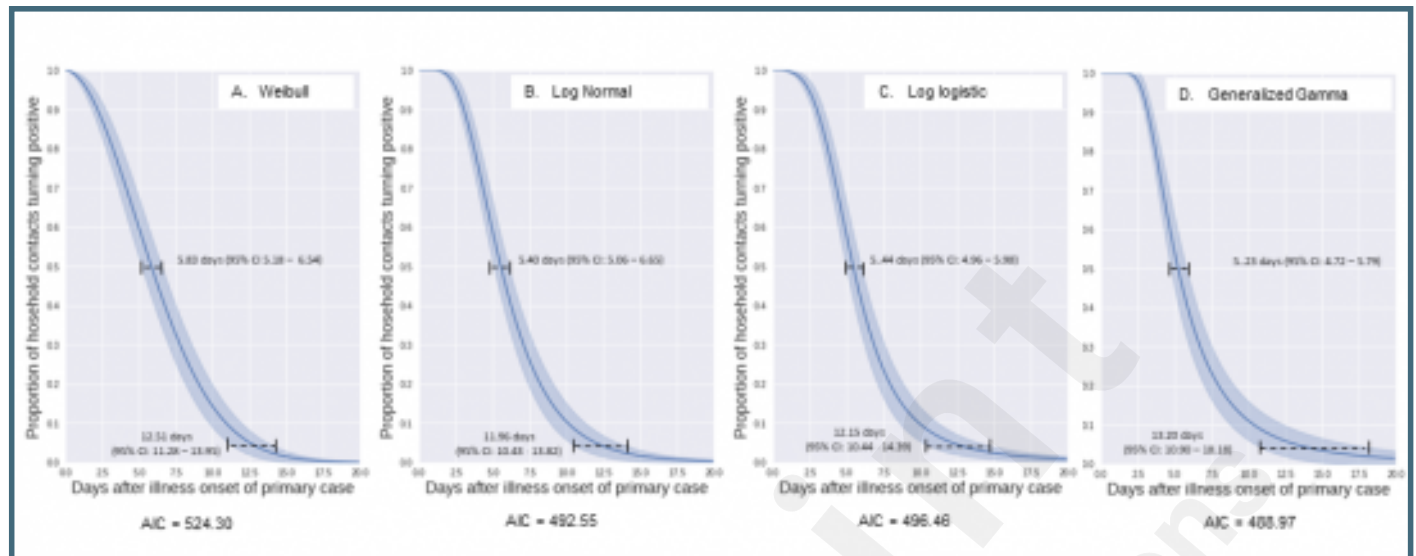
Supplementary Files

Figures

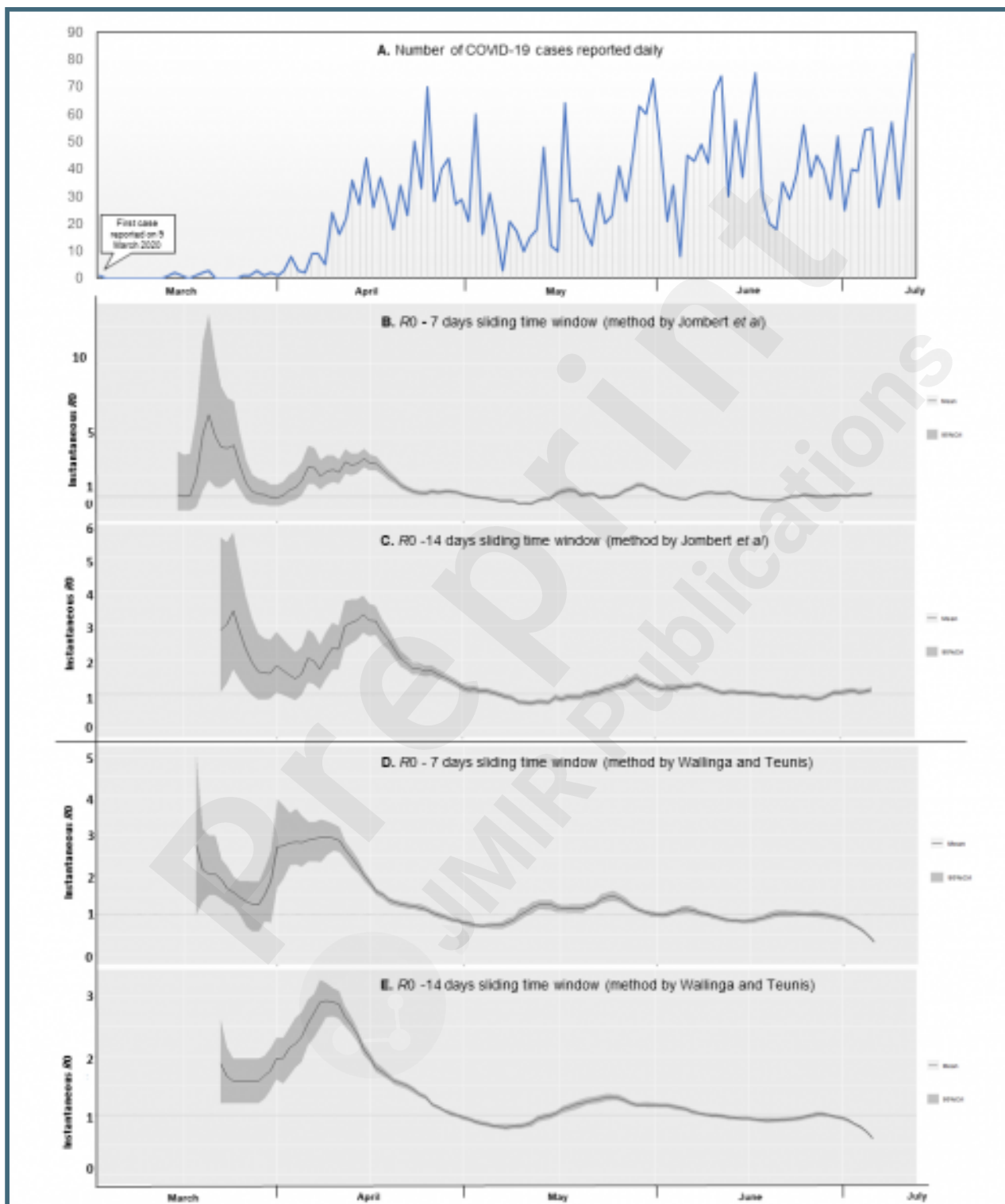
Location of Jodhpur district within Rajasthan state of India.



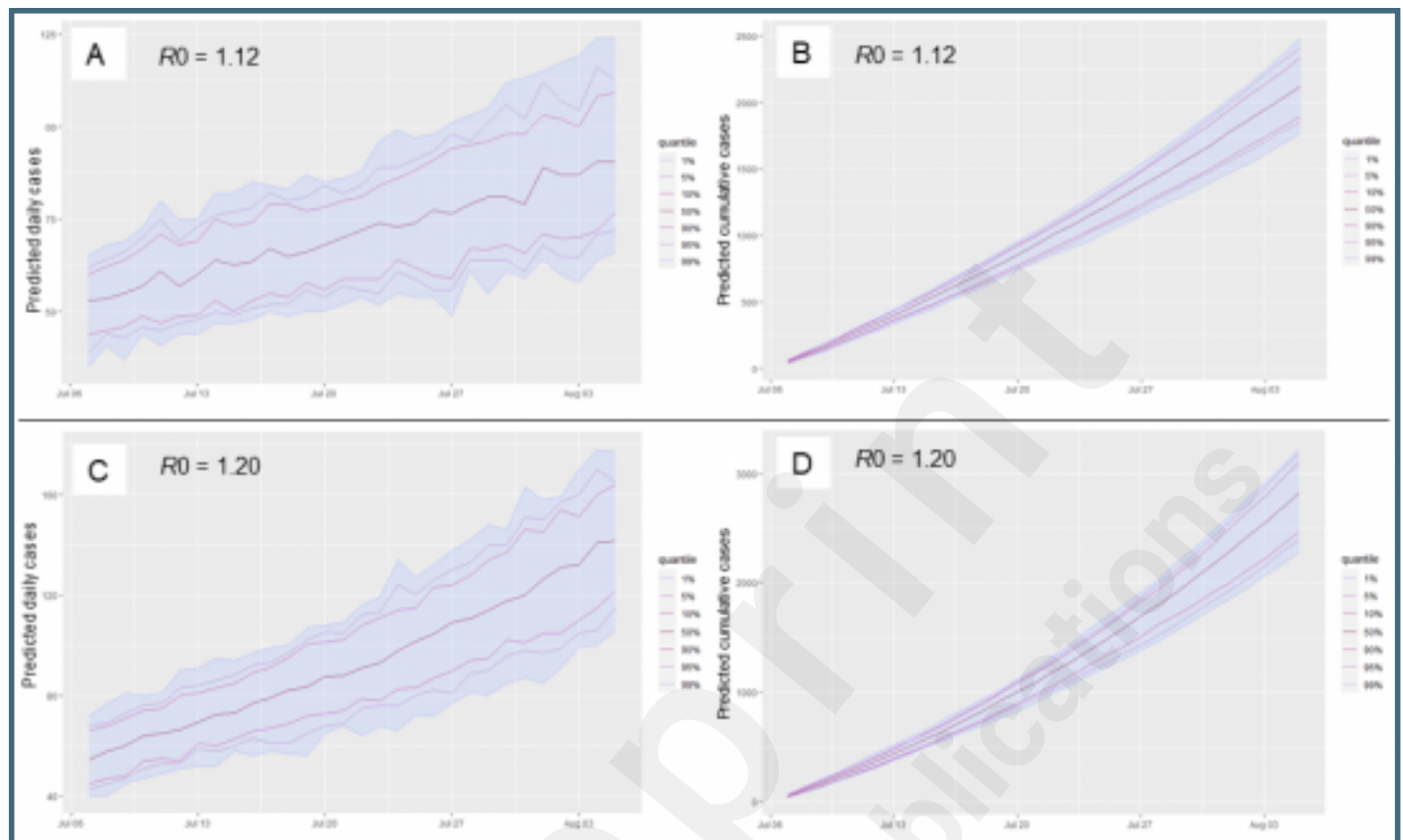
Estimates of median and 95 percentile of serial interval data as fitted to weibull, log-normal, log-logistic and generalized gamma distributions (n = 103 pairs).



Daily COVID-19 cases at Jodhpur, India from 9 March 2020- 6 July 2020 (A) and instantaneous R_0 values estimated using method by Jombart et al (B-C) and instantaneous R_0 values estimated using method by Wallinga and Teunis (D-E) using time windows of 7 and 14 days, respectively.



Projection of daily and cumulative COVID-19 case-load over the next 30 days using instantaneous R_0 value of 1.12 on 6 July 2020 (A-B) and overall R_0 value of 1.20 for the most recent 30 days (C-D).



Multimedia Appendixes

Data for serial interval estimation of COVID-19 in Jodhpur, India (103 pairs).
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