Time-varying reproductive rates for SARS-CoV-2 and its implications as a means of disease surveillance on lockdown restrictions

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Mini-Abstract

There was variation over both time and geography in calculated basic reproductive number ($R_0$) and effective reproductive number ($R_e$ or $R_t$) values for SARS-CoV-2. Generally, as time has progressed, predicted $R_0$/$R_t$ values had decreased globally. As locations around the world begin to lift restrictions, monitoring of infectious spread is warranted.

Abstract

Objective: To quantify the time-varying reproductive rates for SARS-CoV-2 and its implication in Louisiana.

Summary Background Data: Basic reproductive number ($R_0$) and effective reproductive number ($R_e$ or $R_t$) are two measures of the ability of an infectious agent to spread in the environment. They differ in that $R_0$ assumes zero immunity in the population, while $R_e$ or $R_t$ accounts for change over time. Reproductive number modeling is influenced by several factors, including serial interval, the time between the onset of symptoms in an infector, and a secondary case. Quantification of the ability of a pathogen to spread is essential in guiding policy.

Methods: Here, we construct epidemic curves and calculate daily $R_t$ values for the state of Louisiana and each of its nine regions.

Results: Our results demonstrated variation over both time and geography in calculated $R_0$ and $R_t$ values. Generally, as time has progressed, predicted $R_0$ and $R_t$ values have decreased. In Louisiana, mean $R_t$ was calculated at 3.07 in March and 0.82 by May. A reproductive number less than one is important as it indicates infectious spread will decline with time. The most recent finding of mean $R_t = 0.82$ is important. It stands in stark contrast to the situation in April when New Orleans, Louisiana, had the highest per capita coronavirus mortality rate in the United States – twice that of New York City and four times the rate in Seattle.

Conclusion: As locations around the world begin to lift restrictions, monitoring of infectious spread will be essential.

Keywords: Coronavirus; Outbreak; SARS-CoV-2; Serial interval; reproduction number; transmission; Louisiana
Introduction

In December 2019, a novel and highly contagious viral outbreak emerged in Wuhan, China \(^1\). It has since been identified as a zoonotic coronavirus formally known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or more commonly as Coronavirus Disease 19 (COVID-19). In Louisiana, the first COVID-19 case was confirmed on March 9, 2020, and the outbreak grew particularly fast relative to other states \(^2\). Louisiana became the fourth state to receive a major disaster declaration, prompting serious concern about the state's healthcare capacity \(^3\). Mitigation efforts began in Louisiana soon after the identification of the first case. On March 13, the governor of Louisiana prohibited public mass gatherings over 250 people. This order was soon followed by the closure of educational facilities on March 16, closure of non-essential businesses on March 17, and a stay at home order on March 23 \(^4\). Despite these efforts, by April, New Orleans, Louisiana had the highest per capita coronavirus mortality rate in the nation – twice that of New York City and four times the rate in Seattle \(^2,5\).

To design and adjust public health responses such as those seen in Louisiana and around the world, quantification of transmissibility during epidemics is essential \(^6,7\). Furthermore, as cities, states, and countries begin to reopen, as is currently the case, a means of disease surveillance will be essential. Basic reproductive number (R naught or \(R_0\)) is defined as the average number of secondary cases generated by an infected individual in a population with no pre-existing immunity, otherwise known as complete susceptibility \(^8\). A value of \(R_0\) greater than 1 indicates that the infection may spread or persist among the population, while a value of \(R_0\) less than 1 indicates that the infection will decline as time progresses \(^9\).

Because the basic reproductive number (\(R_0\)) assumes zero immunity in a given population, it cannot reflect changes in time. Conversely, an effective reproductive number (\(R_e\) or \(R_t\)) is defined as the number of infections caused by any case and does not assume zero susceptibility. Both measures are affected by three factors, as described in the Susceptibility – Infectivity – Removal (SIR) model by Kermack & McKendrick \(^10\). Susceptibility, as discussed, is the proportion of the population that can become infected. Infectivity refers to the capacity of a pathogen for horizontal transmission, or, simply, its ability to establish an infection. Removal is the rate of case disappearance, either by recovery or death. The larger the population, the more susceptible the individuals in that population, and the more infective the virus, the larger \(R_0\) will be for a given pathogen. The faster the rate of removal of infected individuals, by recovery or death, the smaller the \(R_0\) value will be \(^8,11,12\). On the other hand, \(R_e\) is time and immunity dependent and is more a measure of the current situation. As a result, \(R_e\) is better estimated during the latter course of an epidemic when the population has acquired resistance to infection \(^9,13\).

Given the quantification of the ability of a pathogen to spread plays a vital role in the selection and aggressiveness of mitigation measures required to slow disease transmission, here, we estimated the \(R_e\) in the state of Louisiana and across its nine-homeland security and emergency preparedness regions. A comparison between before and after social distancing and lockdown policies was performed.
Methods

Data source

Estimation of reproduction number relies on two inputs: a disease incidence time series (new cases observed over time) and an estimate of the distribution of serial intervals. We collected the cumulative incidence of new cases, death, and testing for each Parish in Louisiana from data available through the Louisiana Department of Health (http://ldh.la.gov/). Daily incidence rate and cases/100k were estimated from March 14 to May 10.

Serial interval distribution was determined as part of our meta-analysis. There was a wide variation of reported serial intervals in COVID-19 across studies. Estimation in some articles may be associated with significant uncertainty, especially early in the outbreak. Therefore, we used the pooled summary for the mean and standard deviation of the serial interval reported in 14 studies, which was equivalent to 5.45 ± 3.46 (Figure 1).

Scenario analysis and implementation

In our calculations, the 'case count' approach was applied to capture the transmission dynamics of the outbreak. We used daily case count data over 57 days for 64 Parishes in Louisiana to infer the initiation and the growth rate of the epidemic. All statistical analyses and model development were carried out using R version 3.6.3. Analysis of time-varying reproduction numbers (Rₜ) was implemented using the EpiEstim package (http://cran.r-project.org/web/packages/EpiEstim/index.html). The EpiEstim package supplied a framework to estimate Rₜ at each time-step with observed cases using branching processes, as described previously. Applied R script is available in the supplementary material, http://links.lww.com/SLA/C707. After calculations of the transmission chain in LA, the process was performed for each region and county separately. Results before and after mitigation procedure orders were compared.

Results

Estimation of reproduction rates in Louisiana statewide and by regions

According to the Louisiana Department of Health, in a state population of 4.5 million citizens, 31,600 confirmed cases had been reported (697.1 cases per 100K) on May 10, 2020, Figure 2. Of those, 2,286 (0.07%) people have died, while 20,316 (64.2%) have recovered. As of March 15, 2020, the time-varying reproductive number in Louisiana was estimated at 3.07 (95%CI = 2.81-3.34). It then gradually declined and reached a trough on April 11, 20 days after the stay at home order (0.58, 95%CI = 0.57-0.60), Fig. 2C. This decrease was subsequently followed by an upward drift, and Rₜ crossed the baseline of 1.0 by the end of April. The most recent calculations produce an Rₜ estimate of 0.85 (95%CI=0.82-0.89) in the first week of May. The epidemic curves for the incidence time series and maximum likelihood Rₜ values for Louisiana and its nine regions are depicted.
in Figure 3 and 4. Of note, New Orleans is located in Region 1.

Comparison before and after mitigation lockdown

Before the mitigation strategies were applied, initial median estimates of $R_t$ in the nine regions ranged widely from 2.60 to 23.3, with the highest values noted in regions 4, 5, and 6. In the three weeks following social distancing measures, the $R_t$ estimates declined below 1.0 in all regions. Some (regions 1, 3, and 7) were then quite stable until the end of the analysis, while others (regions 4, 6, 8, and 9) witnessed the elevation of $R_t$ coincident with peaks in the incidence time interval. The temporal trend of time-varying reproductive numbers in each parish is shown in Figure 5.

Discussion

The monitoring of $R_0$ over time provides feedback on the effectiveness of interventions and on the need to intensify control efforts\textsuperscript{24}. The goal of control efforts is to reduce $R$ below the threshold value of 1 and as close to 0 as possible, thus bringing an epidemic under control. Measures in Louisiana and around the world have included but are not limited to stay-at-home orders, closure of non-essential businesses, restricted hours for that business that remain open, and encouragement to wear masks in public\textsuperscript{3,4}.

Looking across all regions in Louisiana, there was a much higher variance in $R_t$ at the beginning of our study\textsuperscript{30,31}. The initial values, however, should be viewed with reservation. They are dependent upon the number of known infections, which relies on testing. In locations where testing began at or around the time of our study's initiation, there is a perceived explosive increase in the number of COVID-19 cases. In reality, the virus had probably spread undetected due to a lack of testing. By the final calculations reported, testing had become more widespread and consistent. In turn, $R_0$ values across regions stabilized and exhibited a much lower degree of variability.

Analysis of Louisiana over time revealed that the value of $R_0$ is not constant, thus necessitating an evaluation of $R_t$. Given the decline in both $R_0$ estimates worldwide and $R_t$ over time in Louisiana, our analysis suggests that transmission may be affected by mitigation strategies as well as the population studied. These differing $R$ values observed are of genuine importance as they represent the difference between a pandemic that is controllable with less intensive mitigation strategies and one that requires the extreme measures that have been put into place worldwide.

Lockdowns profoundly impact the economy, which has significant social and medical consequences. Unemployment, psychological distress, and long-term economic harm need to be considered when deciding how to act. On the contrary, reopening too early without means to assess its consequences promptly and adequately can create the potential for exponential growth in infection rates and may erase the benefits derived from lockdowns thus far. The number of avoidable deaths could increase, the healthcare system could once again become overwhelmed, and a scenario could emerge in which we find ourselves in another prolonged lockdown. To mitigate this vicious cycle, it is imperative to adopt a mechanism that will closely monitor the reproductive rate in each state.
Conclusion

Quantification of the ability of a pathogen to spread is essential in guiding policy. There is variation over both time and geography in calculated $R_0$ and $R_t$ values. As time has progressed, estimated $R_0$ and $R_t$ values have decreased globally and in Louisiana. As locations worldwide begin to lift restrictions, viral spread monitoring is essential.

Declaration of Competing Interest

The authors declare the absence of conflict of interest.

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Author contribution

MH, ET, RE, MF, JD designed the study. MH, ET, RE performed all data analyses and created the table and figure. MH, ET, RE, MF, JD contributed to data interpretation. ET, RE, AH, DT, MF wrote the first draft. ET drafted the final manuscript. All authors critically reviewed and approved the final version of the manuscript.
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Figure legends

Figure 1. **Pooled analysis for the serial interval.** Last name of the first author, date of publication, and the geographical region of the affiliated authors. Each navy line represents the values for a study, plotted as effect size and confidence interval. Raw values are shown as mean and standard deviation reported in each study. The green diamond represents the pooled estimate for the 14 studies. Between-studies homogeneity was observed since $I^2$ was below 50%.

| Study                        | Effect Size (mean) | SD |
|------------------------------|--------------------|----|
| Teng, 07-Feb (China)         | 8.40               | 3.80|
| Pung, 16-Mar (Singapore)     | 5.00               | 2.70|
| Li, 20-Mar (China)           | 3.96               | 2.75|
| Zhang, 01-Apr (China)        | 7.50               | 3.40|
| Nishioka, 01-Apr (Japan)     | 7.50               | 3.40|
| Huang, 10-Apr (China)        | 1.60               | 1.50|
| Wu, 15-Apr (China)           | 7.00               | 4.50|
| Bi, 27-Apr (China)           | 6.30               | 4.20|
| Kadk, 30-Apr (China)         | 4.58               | 3.38|
| Srice, 04-May (Switzerland)  | 4.80               | 2.30|
| Acutea-Zegarra, 06-May (Mexico)| 4.70              | 2.00|
| You, Pre-print (China)       | 4.41               | 3.17|
| Du, Pre-print (China)        | 3.96               | 4.75|
| **Overall**                  | **5.45**           | **3.46**|

Random-effects Restriction Maximum Likelihood model

Figure 2. **Estimation of time-varying reproduction number in Louisiana.** (A) Timeline for mitigation measures in association with epidemic curve. X-axis represents the time and Y-axis shows the daily incidence of new cases. (B) Map of Louisiana colored according to cumulative incidence on May 10. (C) Time-varying reproduction number in Louisiana from March 14 to May 10. Estimates decline from 3.07 before mitigation measures to 0.82 by the end of the study period.
Figure 3. **Epidemic curves for daily incidence rates.** Graph shows daily confirmed new cases by day through May 10, representing in the nine regions of Louisiana. Horizontal x-axis shows the date of illness onset among cases and the vertical y-axis shows the number of cases.

Figure 4. **The estimated time-varying reproductive number across nine regions during the study period from March 14 to May 10, 2020.** Horizontal x-axis shows the date of illness onset among cases and the vertical y-axis shows the value of time-varying reproduction rate Rt. The first and last estimated Rt is presented. Red font for $R_t > 1.0$ while green is for $R_t < 1.0$. 
Figure 5. The estimated reproductive number across parishes. (A) Map for nine regions of Louisiana. (B) Effective Reproductive rate in Louisiana, 9 regions, and 64 Parishes during the study period from March 14 to May 10, 2020.