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Duncan Mahood Date

Timeliness and impact of public health responses to measles outbreaks in the United States 2001-2017

By

Duncan Mahood
Master of Public Health

Global Epidemiology

Dr. Benjamin Lopman, PhD, MSc
Committee Chair

Dr. Paul Gastañaduy, MD
Committee Member

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By

Duncan Mahood

Bachelor of Science
University of Wisconsin-Madison
2013

Thesis Committee Chair: Dr. Benjamin Lopman, PhD, MSc

An abstract of
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Rollins School of Public Health of Emory University
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Master of Public Health
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2019

Abstract

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By Duncan Mahood

We assessed the timeliness of public health response to measles cases and outbreaks in the United States from 2001-2017 and quantified reductions in transmissibility (measured by the case reproduction number, R_c, or average number of secondary cases generated per case) following initiation of public health responses. Incidence time-series and the distribution of the serial interval (time between symptom onset of primary case to symptom onset of secondary attributable case) were used to quantify the R_c. The median number of days from rash onset to health department notification or case investigation was 2 days (sd: 10.66) and 5 days (sd: 10.50) respectively, while the median earliest date of public health response (either notification or investigation) to outbreaks was 8 days (sd: 8.68). For each daily increase in delay of public health response, case reproduction number went up an average of 0.038 (95% CI: 0.028, 0.047) for unvaccinated cases, 0.015 (95% CI: 0.01, 0.02) for vaccinated cases, and 0.020 (95% CI: 0.012, 0.028) for cases with unknown vaccination status. During the period of infectivity, the difference between response on the first day of infectivity (4 days before rash onset) and the last day of infectivity equates to 0.45 (0.41 to 0.85) additional transmissions per case. During outbreaks, R_c on or before and after index case response date was 1.47 and 0.15, respectively; absolute difference of 1.31, 95% CI (1.16, 1.46) additional infections per case. Overall, R_c for cases that were responded to before or during and after their period of infectivity was 0.60 and 0.84, respectively; absolute difference of 0.24 (95% CI: 0.10, 0.38) additional infections per case. These findings support the hypothesis that public health response reduces the probability of per-case transmission for (1) individual cases and (2) outbreaks overall, and that these trends are 2.5 times stronger for unvaccinated cases compared to vaccinated cases. To minimize local transmission, public health response should aim to investigate cases as soon as possible during the period of infectivity.

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BACKGROUND

Measles is a highly infectious airborne viral pathogen that causes a febrile rash illness, and sometimes serious complications and death in humans. In 2000, the United States successfully eliminated endemic measles transmission, largely due to the attainment of high MMR (combination Measles-Mumps-Rubella) vaccination rates(1)(2). However, elimination does not mean that there are no measles cases in the United States, rather that any chains of local transmission that occur when an infected person imports the disease from a measles endemic country are short-lived(3)(4). Recently, large measles outbreaks in the United States among predominantly unvaccinated communities have raised alarms among public health officials about the impact of vaccine hesitancy and public health response capacity(5).

When measles outbreaks occur in the United States, state and local health departments respond by performing case investigations, and implementing vaccination campaigns and social distancing strategies (e.g., isolation and quarantine) to limit measles transmission(6). Such interventions may be more critical to reducing transmission and final outbreak sizes when the disease is occurring among disproportionately vulnerable populations with low or moderate vaccination rates. In 2014, an outbreak among a predominately unvaccinated Amish population in Ohio resulted in 383 confirmed cases over 121 days – then the largest outbreak in the United States in 2 decades. Using stochastic compartmental transmission modeling and probabilistic reconstruction of the transmission tree, investigators were able to show that public health interventions (especially a vaccination campaign) during this outbreak likely contributed to a substantial reduction in the transmissibility of measles (as measured by the effective reproduction number) and effectively reduced the size and duration of the outbreak compared to a counterfactual model in which no interventions were initiated(7). Probabilistically inferring the effective reproductive number can be applied to a larger number of outbreaks throughout the United States in order to compare the impact of public health interventions during measles outbreaks in different populations. Such an investigation would shed light onto the public health impact of reactive vaccination, isolation, and quarantine interventions within an elimination context.

In this analysis we aimed to describe the promptness of public health responses to measles cases and outbreaks in the United States post-elimination, and whether decreases in transmissibility are noted after cases are reported and investigated.

METHODS

Summary Analysis

Confirmed measles cases are reported to the Centers for Disease Control and Prevention through the National Notifiable Disease Surveillance System (NNDSS) and to the National Center for Immunization and Respiratory Diseases (NCIRD) via telephone or e-mail(8)(9).

We evaluated singleton cases (i.e., cases that did not transmit), 2-case chains, and outbreaks. For surveillance purposes, an outbreak is defined as a transmission chain beginning with a single imported case and resulting in at least 2 additional locally acquired infections associated with the index case (a cluster of 3 or more epidemiologically-linked cases). In some outbreaks, an imported case may not have been identified, in which case the first locally-acquired case is considered the index case.

We first describe the number of unique cases and outbreaks, the distribution of chain sizes and chain durations, the promptness of case notification and investigation, and compare the delay from health department notification to health department investigation.

To describe the overall timeliness of responses to measles cases, we defined the public health response time as the difference between a case's date of rash onset and either (1) the date that the health department was notified of that case, or (2) the date that the health department investigated that case, whichever came first. When describing the timeliness of response to each separate outbreak, the public health response time refers to the difference between the date of rash onset for the index case in that particular outbreak and either (1) the date that the health department was notified of that index case, or (2) the date that the health department investigated that index case, whichever came first.

Relationship between Response Time and R_c

The primary goal of public health responses to measles cases is to minimize measles transmission(7). The key parameter that characterizes the transmission potential of a disease is the reproduction number, R, or average number of cases each case generates during their infectious period(10). The net or effective R describes transmissibility when a certain proportion of a population is immune, while the basic R, or R_0, describes transmissibility in a totally susceptible population. Case reproduction number, R_c, describes the number of secondary cases that were generated as a result of transmission from a specific primary case. In general, net $R > 1$ at any time during an outbreak indicates that on average, each case generates more than one other case, and thus transmission will likely continue, and the outbreak might grow. In contrast, net $R < 1$ indicates that on average, each case generates less than one other case, and thus the number of cases wanes with each generation, and the outbreak is likely to stop. The goal of public health response is to reduce net R below the critical value of 1 and thus bring the outbreak under control.

Modern methods for estimating R were pioneered by Wallinga and Teunis (2004)(11) and later developed into a user-friendly framework (EpiEstim package for R) by Cori et al. (2013)(12). This method uses incidence time series data and a distribution of the serial interval (time between symptom onset of a primary case to symptom onset of a secondary case infected by that primary case)(13), to estimate R_c for each case during an outbreak. The method probabilistically reconstructs the transmission tree and calculates the number of secondary cases attributable to each primary case, with quantified uncertainty. We applied the algorithm separately to each chain of measles transmission reported during the study period. We used a serial interval distribution for measles estimated from household studies (gamma distribution with mean of 11.1 days and a standard deviation of 2.47 days)(14).

To assess the impact of delays in reporting and investigation of measles cases on their transmissibility, we evaluated the relationship between the public health response time and the estimate of the R_c for individual cases. To assess effect measure modification, we stratified these results by the vaccination status for each case and fitted linear regression coefficients stratified by vaccination status. To assess the combined effect of response time on R_c, we fitted a single linear model, controlling for state and vaccination status, and allowing for interaction between state and vaccination status, and reported an overall regression coefficient and adjusted r-squared for the relationship between response time and R_c. Finally, because public health responses are more likely to have an impact in the case's reproduction number if these are initiated during the period of infectivity, we restricted the analysis to cases that were responded to during their contagious period (for measles this is defined as 4 days before rash onset to 4 days after rash onset)(15), and assessed how R_c changed as public health response was increasingly delayed within this period.

Impact of Public Health Response: R_c Estimation

We assessed the potential impact of public health outbreak responses by comparing R_c before and after the initiation of public health outbreak response. An average R_c before and after intervention was calculated by taking the arithmetic mean of all R_c estimates on or before the earliest date of public health response, after the earliest date of public health response, or set to zero if the earliest date of public health response was after the last case in the outbreak. A sensitivity analysis was performed in which we excluded outbreaks that had their last case presenting before public health responses began.

Finally, we compared R_c for cases that were responded to during or before the period of infectivity to R_c for cases responded to after the end of the period of infectivity.

RESULTS

Summary Analysis

Between January 1, 2001 and December 31, 2017 there were a total of 2,218 unique measles cases reported in the United States, including a total of 490 single cases and 201 chains of transmission with 2 or more cases. Figure 1 shows the distribution of outbreak sizes and outbreak durations. Among chains of transmission with 2 or more cases, the median number of cases per chain of transmission was 3 cases (sd: 29.67), with a range of 2 - 383 cases (Figure 1a), and the median chain duration was 17 days (sd: 18.72), with a range of 1 - 123 days (Figure 1b).

Public Health Response Time

Of the 2,218 total cases, 1,723 (78%) had both rash onset and date of health department case notification values to compare. The median number of days from rash onset to health department notification was 2 days (sd: 10.66) with a range from -11 days to 149 days (Figure

2a, Table 1). Of these, 80 cases (5%) had a date of health department notification before their rash onset.

Of the 2,218 total cases, 1,380 (62%) had both rash onset and date of health department case investigation values to compare. The median number of days from rash onset to case investigation was 5 days (sd: 10.50) with a range from -21 days to 149 days (Figure 2b, Table 1). Of these, 54 (4%) cases had a date of case investigation before their rash onset.

Of the 2,218 total cases, 1,319 (59%) had both date of health department case notification and date of health department case investigation values to compare. The median number of days from health department notification to case investigation was 0 days (sd: 7.66), with a mean of 2.9 days, and a range from -65 days to 65 days (Figure 2c, Table 1). Of these, 42 cases (3%) had a date of case investigation before the date of health department notification.

Among the 201 reported chains during the study period, the median number of days from the earliest date of rash onset (index case) to the earliest date of public health response (i.e., notification or investigation) to any case in that outbreak was 8 days (sd: 8.68) with a range of -3 days to 46 days (Figure 2d, Table 1).

Figure 3a shows a visual representation of the typical case response timeline, in which case notification takes place 2 days after the case's rash onset, followed by a case investigation 3 days later. In contrast, Figure 3b shows a visual representation of a less common, case response timeline, in which case notification takes place a day after initial symptom onset (3 days before rash onset), and case investigation takes place one day after notification.

Relationship between Case Response Time and R_c

Figure 4 shows the distribution of R_c estimates output from the method. Of the 2,218 total cases, 1,716 (77%) cases had both R_c and a case response time to compare. Figure 5a shows the relationship between R_c and corresponding public health response time. After controlling for the state within which the case was reported, the vaccination status of the case, and allowing for interaction between state and vaccination status, a daily delay in public health response resulted in an average increase of 0.028 (95% CI: 0.022, 0.035) in R_c. Variability in response time accounted for 3.6% (adjusted $r^2 = 0.036$, F-statistic =1.631, $p = 0.0001$) of the variability in R_c.

Figure 5b shows the relationship between R_c and corresponding public health response time, stratified by case vaccination status. For 1,151 unvaccinated cases (red line), 220 vaccinated cases (blue line), 345 cases with unknown vaccination status (green line), separate regression lines were calculated and graphed. For each daily increase in delay of public health response, R_c went up an average of 0.038 (95% CI: 0.028, 0.047) for unvaccinated cases, 0.015 (95% CI: 0.01, 0.02) for vaccinated cases, and 0.020 (95% CI: 0.012, 0.028) for cases with unknown vaccination status.

Figure 5c shows the relationship between R_c and corresponding public health response time during the period of infectivity, as well as the linear regression relating R_c to public health response, controlling for state, vaccination status, and allowing for interaction between state and vaccination status for all cases with response time during this period. During the period of infectivity, each day that public health response is delayed causes an increase in R_c of 0.058 (95% CI: 0.014, 0.097) on average, such that the difference between response on the first day of infectivity (4 days before rash onset) and the last day of infectivity results in an predicted prevention of 0.45 (0.41 to 0.85) additional transmissions per case.

Impact of Public Health Response to Outbreaks

Of the 201 reported outbreaks during the study period, R_c were estimated for all cases in 197 (98%) outbreaks. Figure 6a shows R_c over the course of these 197 outbreaks; outbreaks are aligned relative to each other based on the date of public health response.

Figure 6b shows scatter plots and boxplots of R_c before and after the index case in each of the outbreaks was notified or investigated. The average R_c on or before and after index case response date was 1.47 and 0.15, respectively; absolute difference of 1.31, 95% CI (1.16, 1.46) additional infections per case ($p < 2.2e\text{-}16$ by paired t-test).

Sensitivity analysis excluding outbreaks for which the last case presented before public health response began provided similar results. For these 124 (63%) outbreaks, the average R_c on or before and after index case response date was 1.74 and 0.20 respectively; absolute difference of 1.54 95% CI (1.35, 1.73) additional infections per case ($p < 2.2e\text{-}16$ by paired t-test).

Figure 6c shows scatter plots and box plots of reproduction numbers for cases identified before or during the period of infectivity compared to that of cases identified after the period of infectivity. The average R_c for cases that were responded to before or during and after the end of their period of infectivity was 0.60 and 0.84, respectively; absolute difference of 0.24 (95% CI: 0.10, 0.38) ($p = 0.008$ by two sample t-test).

DISCUSSION

Our findings support the hypothesis that public health response reduces the probability of per-case transmission for (1) individual cases and (2) outbreaks overall. The reduction in transmission potential attributable to early public health response is higher for unvaccinated cases compared to vaccinated cases or cases with unknown vaccination status. Public health response that happens during or before the period of infectivity is more likely to reduce the per-case transmission potential compared to response that happens after a case is no longer contagious. During the period of infectivity, each additional day that public health response is delayed results in a measurable increase in average per-case transmission potential.

Even early during a few outbreaks, estimated R_c values were generally below 1, consistent with subcritical transmission of measles in the United States, and indicating elimination of endemic measles virus transmission is sustained in the country(16). When transmission does occur following introductions of measles from imported cases, transmission chains are generally short-lived and localized, taking place predominantly in unvaccinated communities. These successes are attributed to overall high population immunity (primarily a result of high coverage with measles-containing vaccines), as well as rapid responses to measles outbreaks.

Public Health Response Time

The timeliness of responses by public health officials to individual measles cases was remarkable; the median number of days from notification to investigation was 0 days, and the median number of days from rash onset to investigation was 5 days, highlighting how each measles case is treated as a public health priority. While responses to index cases (i.e., the first identified case in each chain of transmission) were longer than for individual cases (a median of 8 days), this difference highlights how although measles surveillance initially depends on passive reporting, identification of a single case triggers enhanced surveillance so that public health officials are ready to respond more quickly to subsequent cases(9). In fact, in some cases, we found that case notification and/or investigation took place before the recorded case's rash onset. This might occur when unvaccinated contacts are under active monitoring and are investigated at the onset of the prodrome (e.g., household members or daycare attendees).

Nonetheless, our findings also demonstrate the challenge of recognizing and responding to measles in time. First, the infectious period of measles starts 4 days prior to the onset of the classic rash, and prodromal symptoms are nonspecific, so measles might not be suspected early during the illness. Second, notification to health departments by healthcare providers occurred a median of 2 days after rash onset, which could be related to delays in (1) seeking care, (2) considering measles in the differential diagnoses, and/or (3) reporting suspected cases. Finally, because case investigations occurred a median of 5 days after rash onset, the contagious period (which extends through 4 days post rash onset) had already elapsed by the time any forward transmission could have been prevented for at least half of the cases. It is thus essential for the public health and healthcare providers to maintain a high awareness for measles, particularly among unvaccinated travelers presenting with febrile rash illness.

Relationship between Case Response Time and R_c

R_c estimates were positively correlated with public health response time, although our findings indicate that the variation in public health response time only accounted for a small percentage (3.6%) of the variation in R_c. Delays in public health response seemed to have a greater impact on the R_c of unvaccinated cases, compared to the R_c of vaccinated cases and cases with an unknown vaccination status, supporting observations that vaccinated cases with prior immune responses are thought to be inefficient transmitters(3). Measles transmissibility is also likely dependent on a variety of other factors, e.g., the vaccination status of cases and contacts, age-related contact patterns, crowding, and disease severity(7). Prompt public health responses to individual cases can play an important role in counteracting some of these factors. For example, administration of post-exposure prophylaxis (vaccine and immunoglobulin within 3 and 6 days from exposure, respectively) to susceptible contacts to prevent or modify illness, as well as social distancing strategies (isolation, quarantining), can directly impact the number of transmissions from any particular case. This is supported by an absolute difference in R_c of 0.45 for cases detected in the first day versus the last day of their contagious period. Similarly, the positive trend between R_c and response time held for responses that took place shortly after the end of the period of infectiousness (i.e., response times between 5 days and 10 days after case rash onset). These findings highlight the importance of identifying, reporting, and responding to cases as early as possible to stay ahead of the virus, and that public health responses targeted at contacts of cases even beyond their infectious period, i.e., administration of post-exposure prophylaxis, might have an impact in transmissibility.

Impact of Public Health Response to Outbreaks

Overall, the results suggest that public health response to outbreaks have an impact on measles transmission, i.e., cases with symptom onset after public health interventions, on average, contributed less to transmission than cases with symptom onset before public health interventions (an absolute difference of 1.31 secondary cases averted per case before versus after public health responses began). However, because R_c can vary for a number of reasons, these results should be interpreted cautiously(11). First, R_c naturally declines during outbreaks as a result of a depletion of available susceptible, so all or some of the decrease in R_c may instead be driven by a lack of susceptibility of the surrounding community, particularly in a setting with high immunization coverage. Second, outbreaks might end due to chance if an infectious person does not encounter a susceptible person, so the density of the population is important (e.g., a rural community versus and urban setting). Third, community behavior is expected to change during measles outbreaks. For example, cases might generally prefer to stay at home due to illness, and other persons might avoid social gatherings or other public places where they might be exposed. Fourth, case under-ascertainment might have occurred, and sudden increases and decreases in reporting might affect estimates of the reproduction number. However, identification of a single case in the United States quickly triggers enhanced surveillance, so decreases in reporting during the course of an outbreak are not expected. Finally, we considered public health response as a single uniform exposure, without consideration for which interventions were actually performed during each outbreak (social distancing, reactive vaccination, post-exposure prophylaxis), and disentangling the effect of each intervention is challenging.

Limitations

In addition to these various possible reasons for decline in the reproduction number, there are other limitations to our study. Our analysis was limited by the quality of the surveillance system which generated our dataset. We identified 4 outbreaks out of 201 total outbreaks for which the Wallinga and Teunis method could not be applied, specifically because of gaps in surveillance (e.g., an unidentified common source, or missing cases). There were some extraneous values in regards to the timing of reporting and investigation, that seemed unlikely and might be attributed to data entry errors. We assumed linear relationships between R_c and response time, which might not describe the association between these variable correctly, and the regression models we used likely do not account for all potential confounders that might affect transmissibility of measles over time.

IMPLICATIONS

Past research of measles transmissibility and response time has either assessed transmissibility during specific outbreaks with the goal of understanding which interventions are most effective, or sought to measure R from a national perspective to assess the status of measles elimination in a country. This analysis attempts to quantify the impact of response timeliness on transmissibility overall. Our results substantiate the public health value of rapid response to measles cases in the United States. Sensitive surveillance, reactive public health infrastructure, and early initiation of interventions are effective in reducing transmission potential for what is one of the most contagious infections in humans. Due to the timing of symptom onset and period of infectivity, public health response should aim to respond to cases as early as possible. For this purpose, active monitoring for symptoms among exposed persons helps identify cases early, and ensures quarantine recommendations are being followed.

While these results present an optimistic view of reactive control strategies to measles introductions in the United States, public health responses to measles outbreaks substantially diverts resources away from other pressing public health issues. Outbreaks of measles in pockets of susceptibility are readily preventable with a safe and effective vaccine, and preemptive vaccination to close these immunity gaps is the only foolproof and cost-effective public health strategy to limit measles spread from importations. Policies that increase routine vaccination and promote outreach to hesitant communities are essential for sustaining measles elimination in the United States.

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TABLES & FIGURES

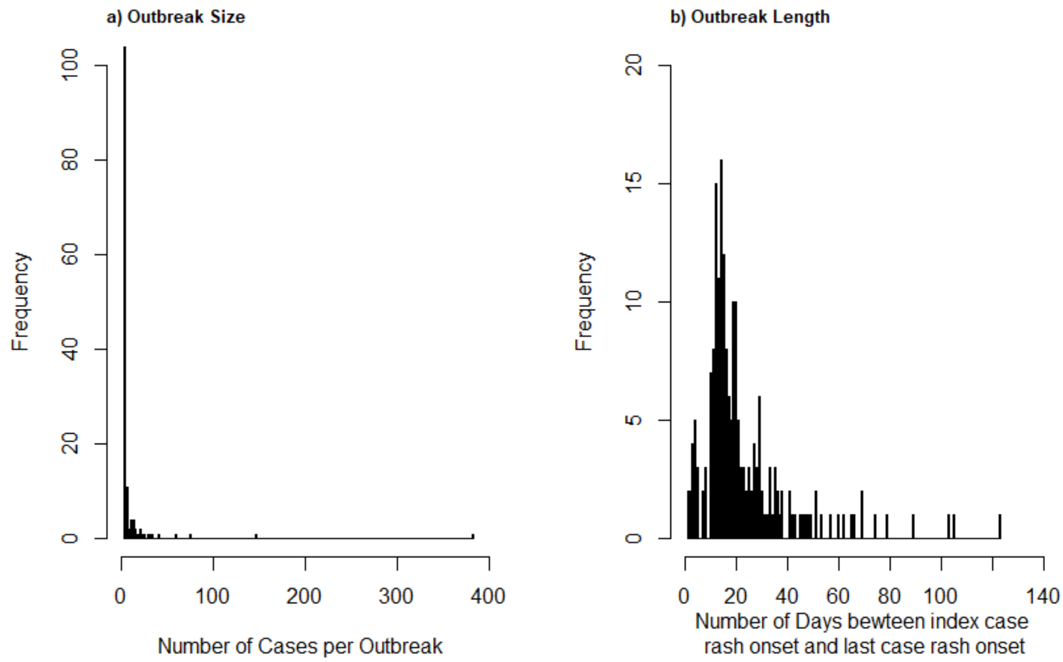


Figure 1. Histograms of a) outbreak size and b) outbreak duration.
Histograms include all outbreaks for which there were 2 or more associated cases (n=201) representing 1,707 (77%) of the total 2,218 cases.

Table 1. Public Health Response Time

	n (%)	Median (standard deviation)	Range	n (%) negative difference
Case Response				
Rash onset to case notification	1,723 (78)	2 days (10.66)	(-11 days, 149 days)	80 (5)
Rash onset to case investigation	1,380 (62)	5 days (10.50)	(-21 days, 149 days)	54 (4)
Case notification to investigation	1,319 (59)	0 days (7.66)	(-65 days, 65 days)	42 (3)
		2.9 days (mean)		
Outbreak Response				
Index response*	168 (81)	8 days (8.86)	(-3 days, 46 days)	-

*Time from earliest date of rash onset in a transmission chain to the earliest date of public health response (i.e., notification or investigation) to an case in that outbreak.

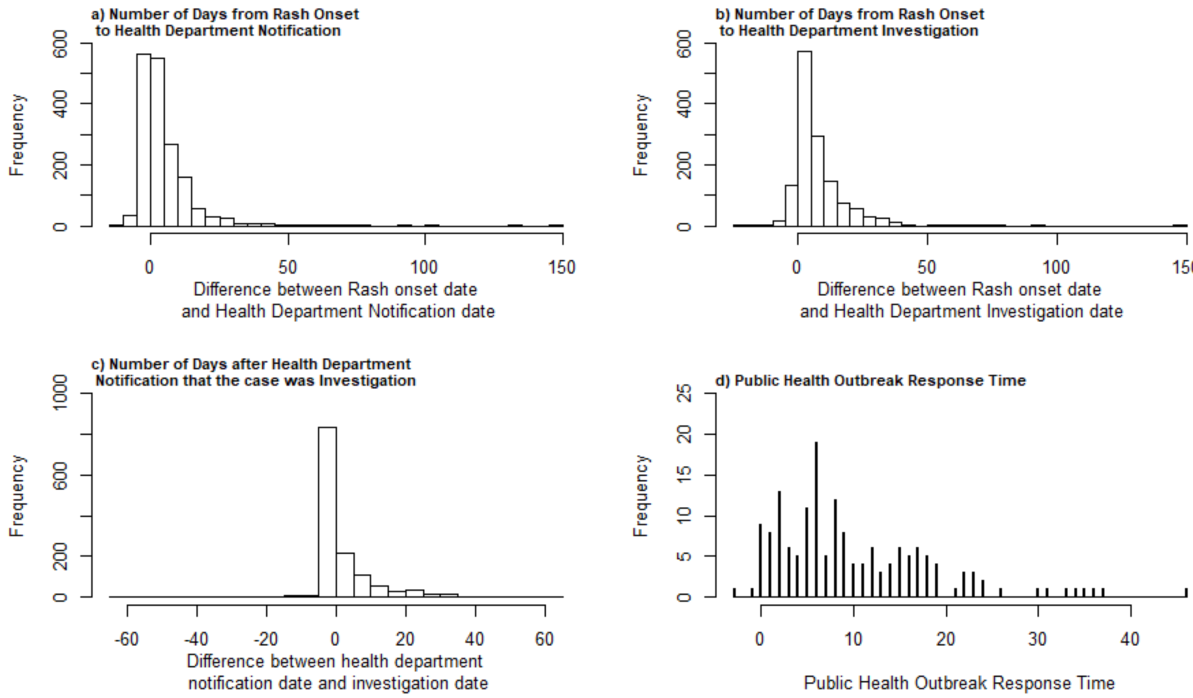


Figure 2. Histograms of a) notification delay for all cases, b) investigation delay, c) notification to investigation delay, and d) public health outbreak response time for 163 (81%) outbreaks with 2 or more associated cases.

Figure 3a. Visual representation of Typical Response Timeline

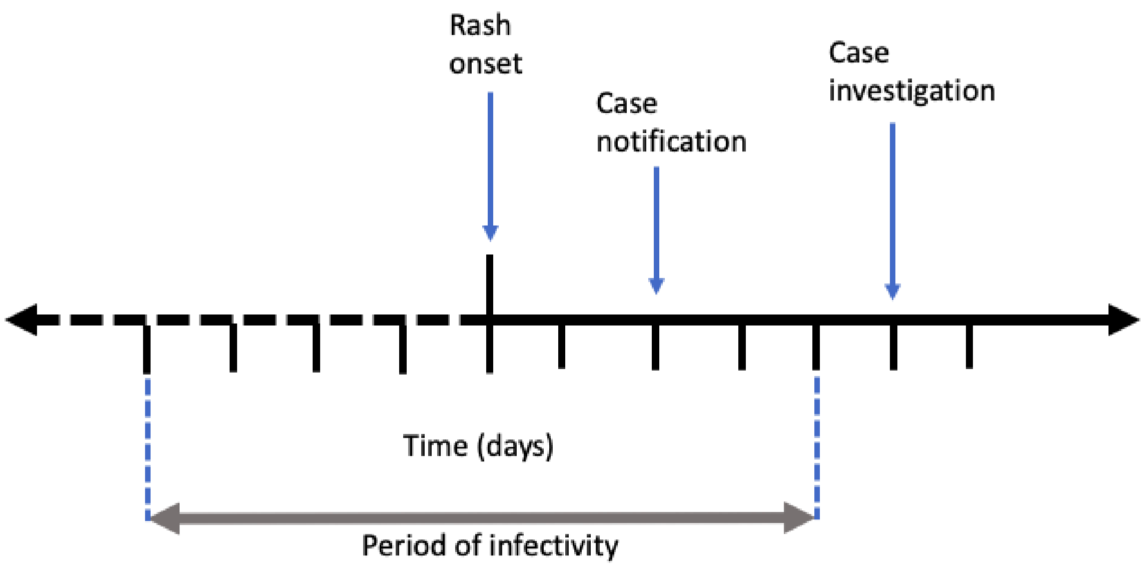
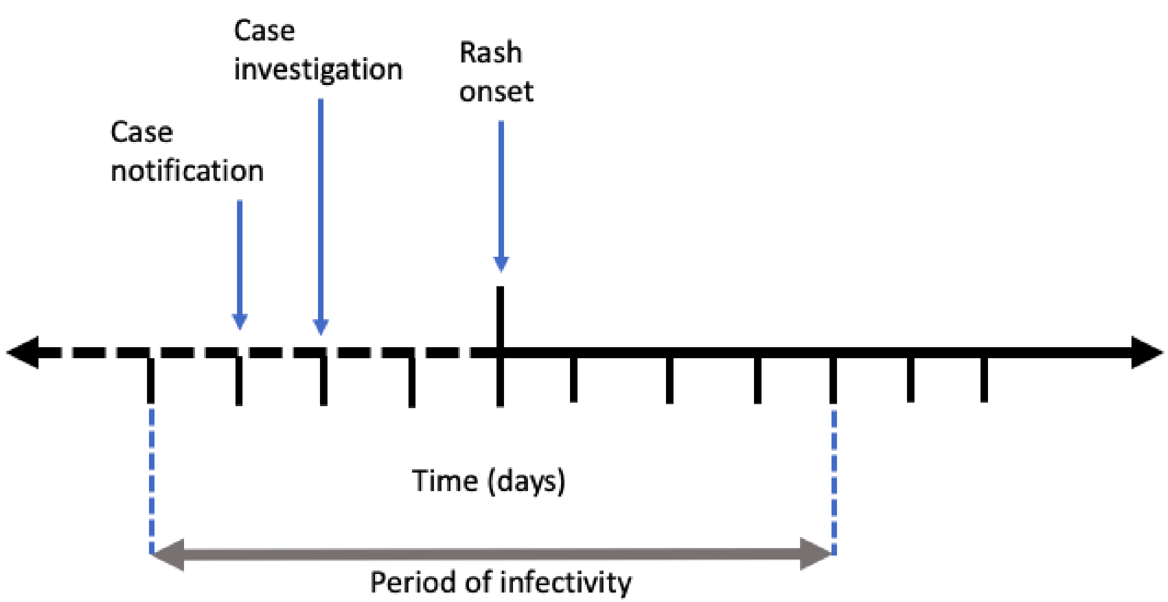


Figure 3b. Visual representation of Less Common Response Timeline



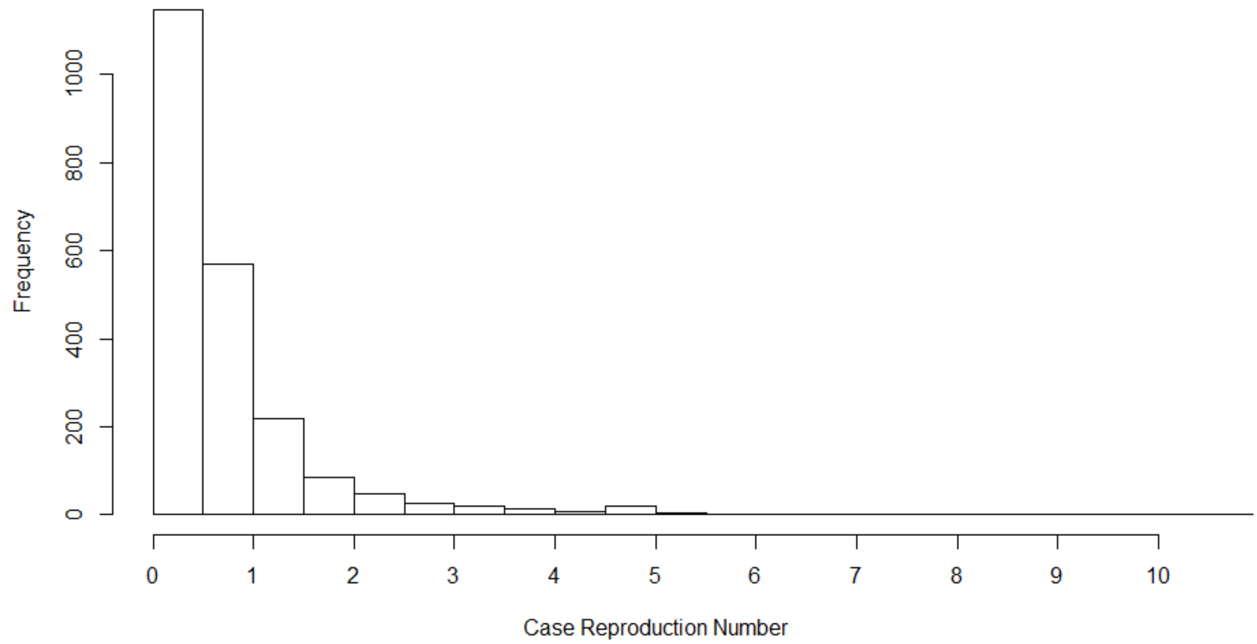


Figure 4. Distribution of Case Reproduction Number

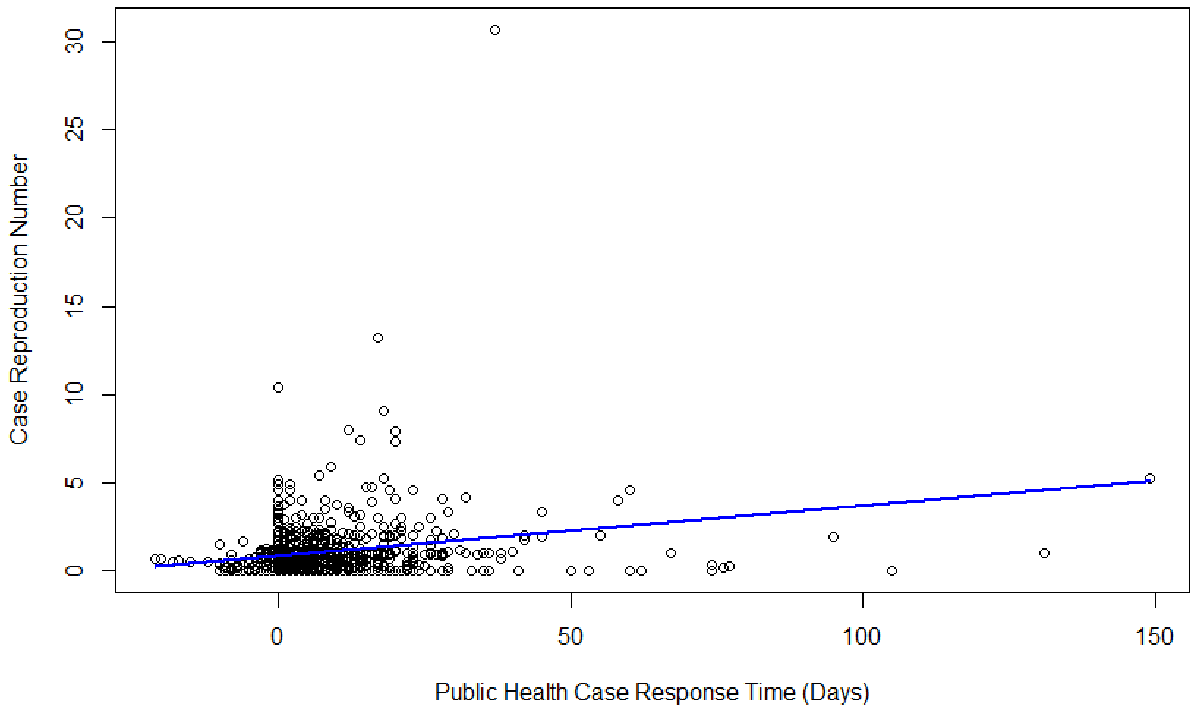


Figure 5a. Case Reproduction Number vs. Response Time

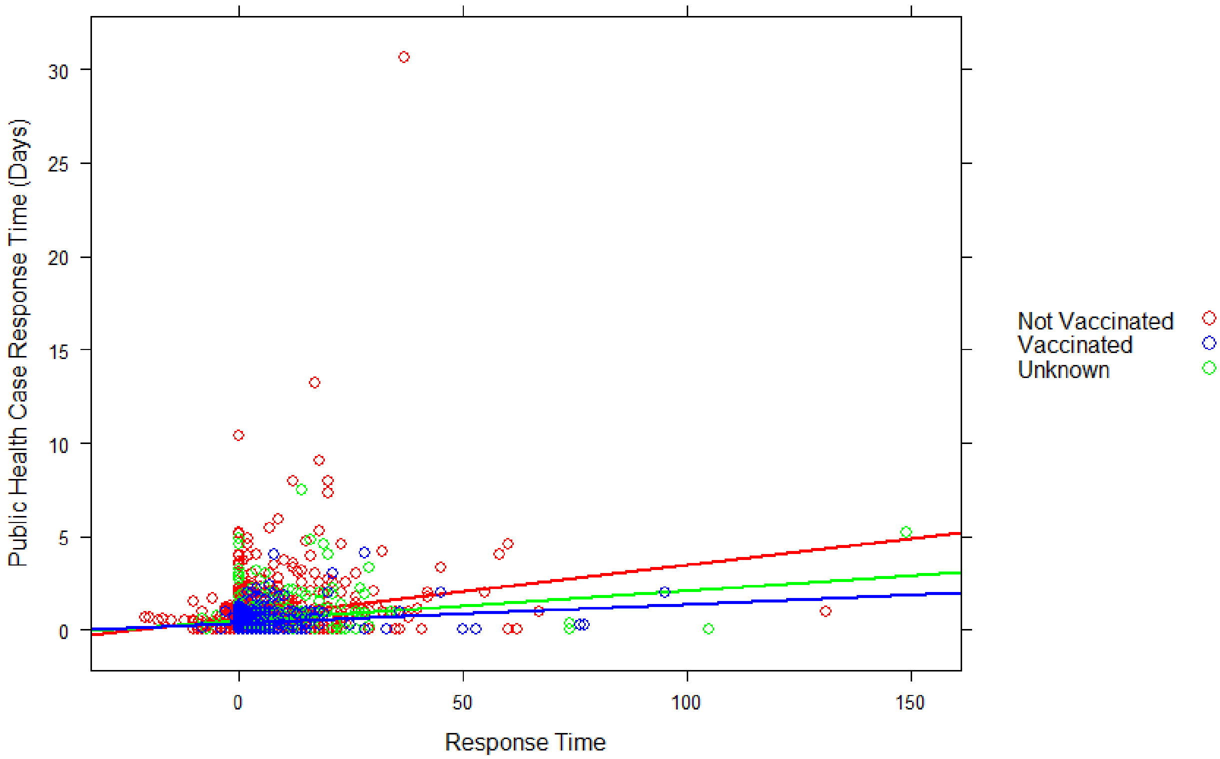


Figure 5b. Case Reproduction Number vs. Response Time, Stratified by Vaccination Status

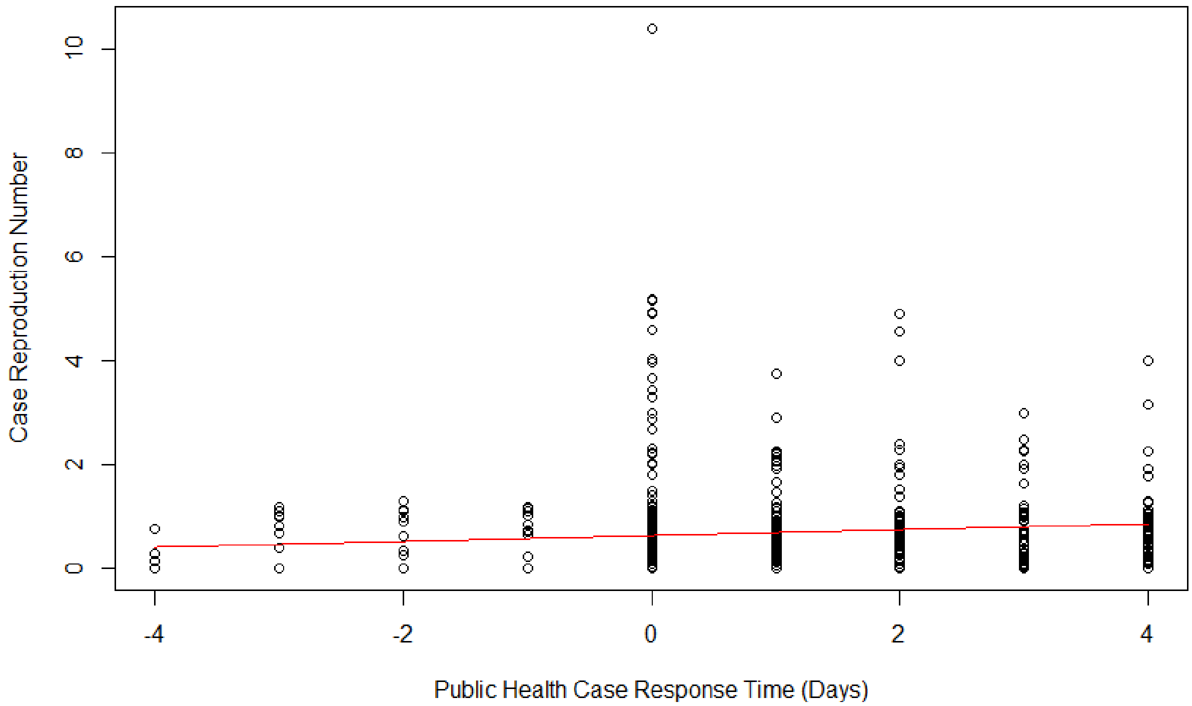


Figure 5c. Case Reproduction Number vs. Response Time, during period of infectivity

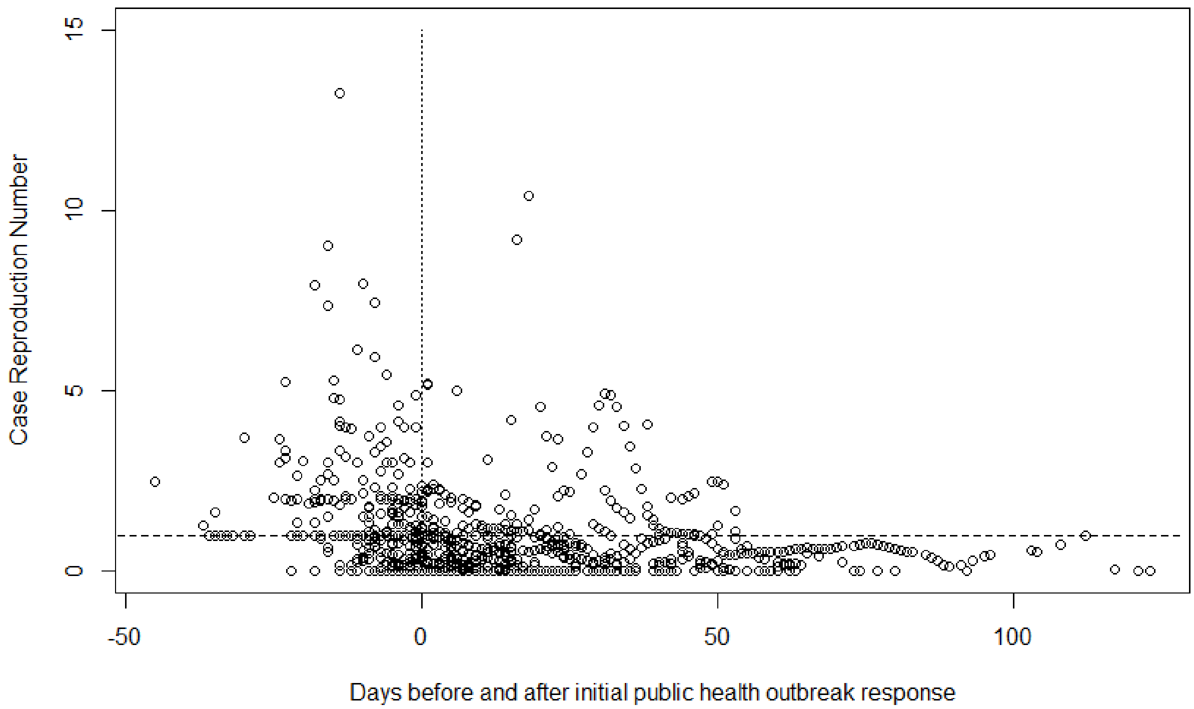


Figure 6a. Case Reproduction Number Before and After Initiation of Public Health Outbreak Response

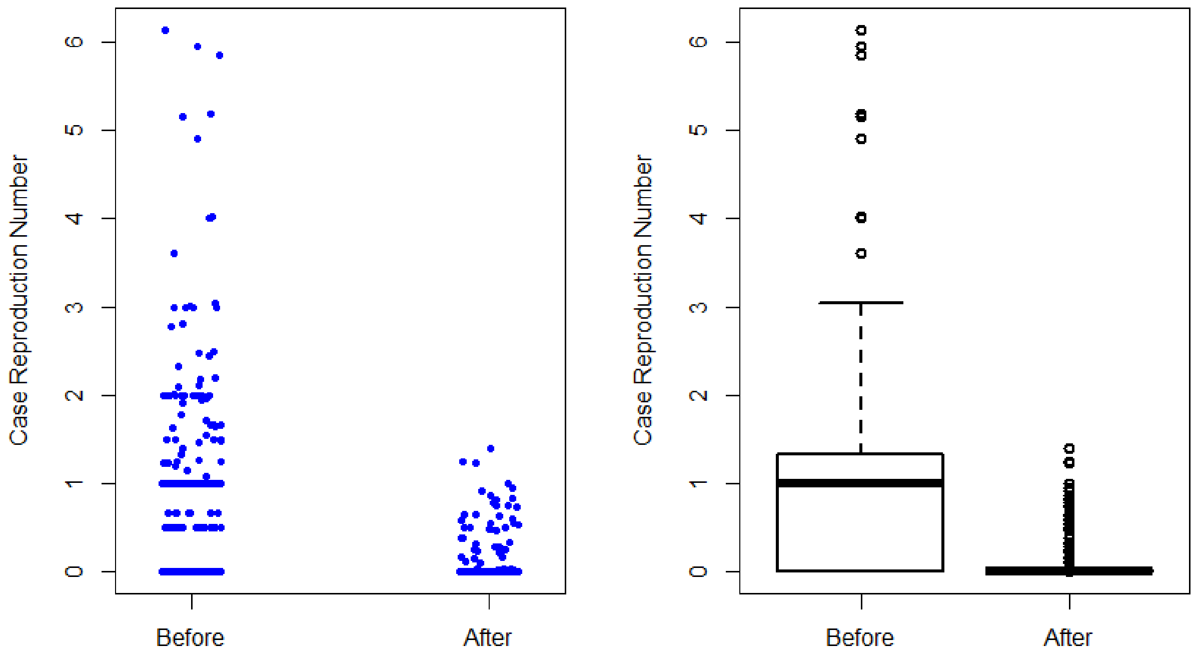


Figure 6b. Case Reproduction Number Before and After Initiation of Public Health Outbreak Response

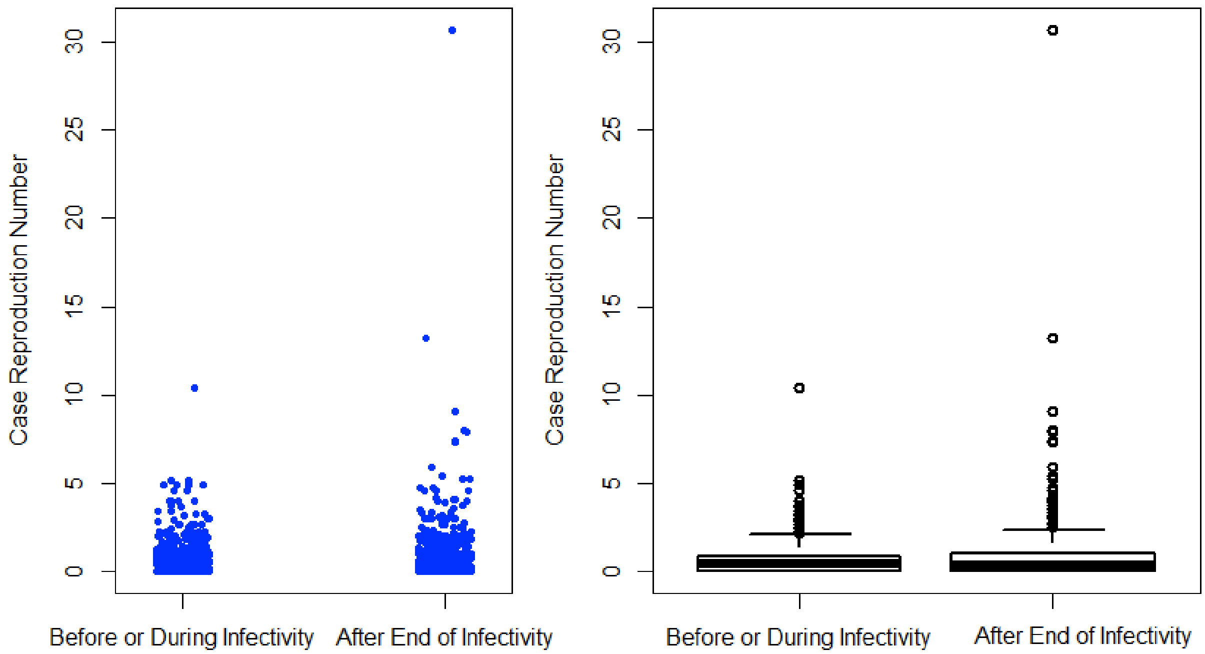


Figure 6c. Case Reproduction Number Before and After End of Period of Infectivity