

Challenges in Estimating Time-Varying Epidemic Severity Rates from Aggregate Data

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Abstract

Severity rates like the case-fatality rate and infection-fatality rate are key metrics in public health. To guide decision-making in response to changes like new variants or vaccines, it is imperative to understand how these rates shift in real time. In practice, time-varying severity rates are typically estimated using a ratio of aggregate counts. We demonstrate that these estimators are capable of exhibiting large statistical biases, with concerning implications for public health practice, as they may fail to detect heightened risks or falsely signal nonexistent surges. We supplement our mathematical analyses with experimental results on real and simulated COVID-19 data. Finally, we briefly discuss strategies to mitigate this bias, drawing connections with effective reproduction number (R_t) estimation.

1 Introduction

Several public health metrics of interest express the probability that a second, often more ~~serious~~ severe outcome will follow a primary event. ~~For example, We refer to such metrics as “severity rates.” These include well-known examples such as~~ the case-fatality rate (CFR) and infection-fatality rate (IFR)~~are~~, commonly used to assess the deadliness of an epidemic (~~Garske et al., 2009; Russell et al., 2020b; Challen et al., 2021; Luo et al., 2021; COVID-19 Forecasting Team, 2022~~). ~~Another central example of a “severity rate”, which is a term that we use for metrics of this general form, is~~ (~~Garske et al., 2009; Russell et al., 2020b; Luo et al., 2021; COVID-19 Forecasting Team, 2022~~). ~~Another important example is~~ the hospitalization-fatality rate (HFR) (~~Bellan et al., 2020; Roth et al., 2021; Xie et al., 2024~~).

In an ideal setting, severity rates can be obtained directly from a comprehensive line-list or claims data set containing individual patient outcomes (~~Bellan et al., 2020; Challen et al., 2021; Roth et al., 2021; Xie et al., 2024~~) (~~Bellan et al., 2020; Challen et al., 2021~~). However, ~~in fast-moving epidemics like COVID-19~~, large-scale tracking of individuals ~~in fast-moving epidemics~~ has been infeasible, especially in real time. ~~For example, the CDC’s line list during the COVID-19 pandemic excluded large geographic regions, was only updated monthly, and had missing death statuses for a high proportion of individuals~~ (~~Centers for Disease Control and Prevention, 2023~~). Instead, severity rates are routinely estimated from aggregate count data. ~~While it is common to assume they~~ Aggregate case and death counts were widely used to estimate and report COVID-19 CFRs in the academic literature (~~Yuan et al., 2020; Horita and Fukumoto, 2022; Liu et al., 2023; Wjst and Wendtner, 2023~~), as well as in major news outlets including The Atlantic (~~Madrigal and Moser, 2020~~), Wall Street Journal (~~Kamp and Krouse, 2020~~) and New York Times (~~McNeil, 2020~~). They were also used by public health organizations like the CDC (~~Ahmad et al., 2023; Karimi, 2024~~), and reported by the Trump and Biden administrations (~~The White House, 2020, 2021~~).

Several works assume severity rates are constant in time (~~Ghani et al., 2005; Jewell et al., 2007; Reich et al., 2012; Baud et al., 2020~~). However, consequential shifts ~~in severity rates~~ can occur in response to factors such as new therapeutics, vaccines, and variants (~~McNeil, 2020~~). ~~Time-varying severity rates are often estimated~~. Therefore, many

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works estimate time-varying severity rates from aggregate data streams. Standard real-time approaches do so with a ratio of primary and secondary aggregate data streams. For example, aggregate case and death counts were widely used to estimate and report COVID-19 CFRs, both in the academic literature (Yuan et al., 2020; Luo et al., 2021; Horita and Fukumoto, 2022; Liu et al., 2023; Wjst and Wendtner, 2023) and also in major news outlets like The Atlantic (Madrigal and Moser, 2020) and The Wall Street Journal (Kamp and Krouse, 2020). In fact, ratio estimators are so common that CFR is often (mis)labeled the case-fatality *ratio* (Luo et al., 2021).

In this work, we show that these ratio estimators are prone to nontrivial statistical bias. We empirically validate our mathematical analysis, tracking the hospitalization-fatality rate (HFR) during COVID-19. Bias arises as a consequence of changing severity rates—precisely when rates—precisely what time-varying estimates should be most useful. It are employed to detect. For example, the ratio estimators failed to quickly signal increased risk in the onset of the Delta wave. Bias also arises due to misspecification of the delay distribution, which relates events, like cases and deaths in CFR that relates primary and secondary events. This is particularly troublesome during various stages of a surge, especially for the popular lagged ratio estimator, which divides values of two aggregate data streams. We validate these findings empirically, tracking the hospitalization-fatality rate (HFR) during COVID-19. The ratio estimators failed to quickly signal increased risk in the onset of the Delta wave; later, . Once again, these are periods in which it is critical to properly ascertain the severity rate. While the HFRs dropped in the aftermath of the initial Omicron wave, they surged while the true HFR fell. We provide initial Omicron surge, the lagged ratio’s estimates jumped 50% above the true values.

We provide practical heuristics for when to epidemiologists should expect this bias in practice, and discuss ideas for alternative. These may prevent poor decision-making based on biased estimates of severity rates. More broadly, our work exposes the limitations of existing approaches, motivating the use of alternatives. We point towards methodology which may avoid this bias, and offer suggestions to improve it. Code to reproduce our experimental results is available at <https://github.com/jeremy-goldwasser/Severity-Bias>.

2 Methods

In this section, we introduce the main estimators we study, and analyze their bias. Subsequently, we detail the data used for empirical study and validation.

2.1 Severity rate estimators

Severity rates convey the probability that a primary event will result in a secondary event in the future. In the case of CFR, for example, a primary event is a positive COVID-19 case and a secondary event is a death with a positive test result. Formally, a time-varying severity rate at time t is generally defined as:

$$p_t = \mathbb{P}(\text{secondary event will occur} \mid \text{primary event at time } t). \quad (1)$$

Here, t may represent a discrete interval of time, such as a given day or week. It also may be understood in a continuous-time fashion. Although this will not be our focus in this paper, the same general principles apply in the continuous-time case. For simplicity, we will consider only the discrete-time setting, and we index time steps via integers, as in $t = 0, 1, 2, \dots$.

Throughout, we denote by $\{X_t\}$ and $\{Y_t\}$ the aggregate time series of new primary and secondary events, respectively. These are often counts, and we will generally refer to them as such. At time t , we assume data for all past $s \leq t$ is available, but future data is not. Therefore real-time estimates of p_t can only rely on past counts $\{X_s\}_{s \leq t}$ and $\{Y_s\}_{s \leq t}$. In practice, to stabilize estimates, smoothed counts are often used in place of raw counts. This may be simply absorbed into the notation for X_t and Y_t , and we do not address smoothing explicitly in the formulation of the estimators, but refer back to this issue in Section 2.4.

Lagged estimator. The canonical estimator for time-varying severity rates is a ratio between the counts of primary and secondary events, offset by a lag ℓ . This estimator is widely-used in epidemiology, both in the academic literature and in public health practice and communication (e.g., Kamp and Krouse, 2020; Madrigal

and Moser, 2020; Yuan et al., 2020; Luo et al., 2021; Thomas and Marks, 2021; Horita and Fukumoto, 2022; Liu et al., 2023; Wjst and Wendtner, 2023). For concreteness, we define the *lagged ratio* at time t as:

$$\hat{p}_t^\ell = \frac{Y_t}{X_{t-\ell}}, \quad (2)$$

where $\ell \geq 0$ is a given parameter (often chosen to maximize cross-correlation between $\{X_t\}$ and $\{Y_t\}$).

Convolutional estimator. Alternative methods for estimating severity rates utilize a delay distribution, which relates the two time series. The delay distribution at time t and lag k is defined as:

$$\pi_k^{(t)} = \mathbb{P}(\text{secondary event at } t+k \mid \text{primary event at } t, \text{ secondary event occurs}).$$

Throughout

Throughout this work, we assume that the delay distribution has a finite support of d time steps. ~~We~~ For the sake of notational convenience, we also assume the delay distribution is stationary: $\pi_k^{(t)} = \pi_k$ for all k and t . ~~(In reality, delay distributions may themselves be time-varying, and this creates its own set of challenges, which only exacerbate the ones we highlight in this paper for a fixed delay distribution.)~~ However, our analyses hold in the case of time-varying delay distributions. While the delay distribution is generally unknown, several tools exist to estimate them from aggregate or line-list data (see Charniga et al., 2024 for a nice review). Given π , we can express the expected number of secondary events at time t as follows:

$$\begin{aligned} \mathbb{E}[Y_t \mid \{X_s\}_{s \leq t}] &= \sum_{k=0}^d X_{t-k} \mathbb{P}(\text{secondary at } t \mid \text{primary at } t-k) \\ &= \sum_{k=0}^d X_{t-k} \mathbb{P}(\text{secondary after } k \text{ time steps} \mid \text{secondary occurs, primary at } t-k) \\ &\quad \times \mathbb{P}(\text{secondary occurs} \mid \text{primary at } t-k) \\ &= \sum_{k=0}^d X_{t-k} \pi_k p_{t-k}. \end{aligned} \quad (3)$$

This is a convolution of the delay distribution against the product of primary incidence and the severity rate. If the severity rate remains constant, $p_{t-k} = p_t$ for all k between 0 and d , then the expression in (3) simplifies to $\mathbb{E}[Y_t \mid \{X_s\}_{s \leq t}] = p_t \sum_{k=0}^d X_{t-k} \pi_k$. As studied in Overton et al. (2022), we can rearrange this relationship in order to estimate the severity rate at t , after plugging-in an estimate γ of the delay distribution π :

$$\hat{p}_t^\gamma = \frac{Y_t}{\sum_{k=0}^d X_{t-k} \gamma_k}. \quad (4)$$

We call this the *convolutional ratio* estimator of the severity rate; ~~in the notation here, the superscript~~ in. The superscript in our notation \hat{p}_t^γ emphasizes that γ is the distribution used in the definition of the estimator (4). To reiterate, in moving from (3) to (4), we are implicitly assuming that the severity rate p_t is ~~constant-stationary~~ over the interval of time from $t-d$ and t . Of course, this runs in contradiction to the fact that we are trying to estimate a time-varying severity rate in the first place. As we will see shortly, this can create significant bias in the convolutional ratio.

Some further comments are in order. The convolutional ratio has a longer history of study and use in the literature on estimating stationary severity rates. Indeed, Nishiura et al. (2009) developed the estimator in this setting, and used it to analyze the CFR in the H1N1 influenza pandemic of 2009. (The ~~main-only~~ difference to (4) is that in the stationary case we aggregate both the numerator and denominator over all past data.) This estimator, which is sometimes called the *delay-adjusted* estimator of the severity rate, is popular in the academic literature and public health practice (e.g., Garske et al., 2009; Russell et al., 2020b,a; Unnikrishnan et al., 2021), though arguably less popular than the lagged ratio. The package `cfr` (Gupte et al., 2024) gives an R implementation, for both the stationary and time-varying cases.

Furthermore, we note that (4) can be seen as a generalization of the lagged ratio estimator (2): when we take γ to be a point mass at lag ℓ , i.e., $\gamma_\ell = 1$ and $\gamma_k = 0$ for all $k \neq \ell$, then (4) reduces to (2).

Connection with reproduction numbers. Severity rates bear a natural connection with reproduction numbers. Both the true severity rate as defined in (1) and the case reproduction number R_t are defined as the average number of secondary events produced by a single primary event at t , but in contrast to severity rates, reproduction numbers have infections as the primary and secondary events, where a single infection can produce more than one follow-on infection. Playing the role of the delay distribution π in our setting is the generation interval distribution in reproduction numbers, which measures the time in between primary and secondary infections.

Severity rates and reproduction numbers can also be estimated similarly. Because primary events at t produce secondary events after t , their effect is not observed in real time. Therefore, standard real-time estimators for severity rates (2), (4) and for R_t both analyze the number of secondary events at t produced by relevant primary events. In words, this adopts a “backward-looking” perspective (that is possible in real time), rather than the “forward-looking” perspective inherent to the definition in (1).

For reproduction numbers, the backward-looking quantity has its own name: *instantaneous* R_t , which is the average number of secondary infections at time t produced by a single primary infection in the past. One of the most popular traditional estimators of instantaneous R_t is based on an essentially identical idea to the convolutional ratio (Fraser, 2007; Wallinga and Lipsitch, 2007):

$$\hat{R}_t = \frac{I_t}{\sum_{k=1}^d I_{t-k} g_k}. \quad (5)$$

Here, I_t denotes the number of new infections at t , and g is the generation interval distribution. Note that the difference between (4) and (5) is that the latter uses the same aggregate time series, infections, in both the numerator and denominator. While more modern frameworks for estimating instantaneous R_t are often Bayesian (e.g., Cori et al., 2013), the underlying basic point estimates are still the same.

2.2 Well-specified analysis

First we analyze the bias of the convolutional ratio (4) in what we call the *well-specified* case, where the true delay distribution π is known. Formally, for an estimator \hat{p}_t of p_t , we define its bias as:

$$\text{Bias}(\hat{p}_t) = \mathbb{E}[\hat{p}_t \mid \{X_s\}_{s \leq t}] - p_t.$$

Proposition 1. Assume the true delay distribution π is known. The bias of the well-specified convolutional ratio \hat{p}_t^π ~~(where the true delay distribution π is known)~~ is

$$\text{Bias}(\hat{p}_t^\pi) = \sum_{k=0}^d \left[\frac{X_{t-k} \pi_k}{\sum_{j=0}^d X_{t-j} \pi_j} (p_{t-k} - p_t) \right]. \quad (6)$$

The proof of Proposition 1 is ~~elementary and~~ given in Appendix A.1. ~~The bias (6) of the convolutional ratio estimator of the severity rate depends on three factors, which we discuss next.~~ Intuitively, the well-specified bias can be interpreted as a weighted average of the difference between trailing and current severity rates. The weights depend on the delay distribution and primary incidence curve. Figure 1 provides an accompanying illustration.

1. **Changes in severity rate.** The central component of this bias expression is the difference $p_{t-k} - p_t$. When the severity rate is constant over the d preceding time points, the convolutional ratio is unbiased (because this difference is zero). This falls in line with the motivation used to derive this estimator, as explained in the last subsection. But when severity rates change before t , these difference terms will be nonzero, in which case the estimator will be generally biased. Figure 1a shows a simple example of this: the estimated severity rates are most inaccurate in periods where the true rate is changing quickly.

To make matters worse, the bias is in the opposite direction of the trend we want to detect; for example, suppose the severity rate is monotonically falling, with $p_t < p_{t-1} < \dots < p_{t-d}$. The bias will then be positive, meaning the ratio estimates do not decline with the true rate. In fact, the estimated severity may even rise, not fall. Conversely, when true severity rates are rising, the estimates will be too low.

2. **The delay distribution.** How much the changing severity rates impact the bias depends on the shape of the delay distribution π . In general, the bias will be greatest when the delay distribution has a long enough tail to upweight significant differences in severity rate. While this distinction may appear subtle, Section 3 highlights its surprisingly large effects. The simple example in Figure 1b also shows significant differences in bias between shorter and longer delay distributions.
3. **The primary incidence curve.** Changing primary incidence X_t will also affect the bias, presuming the severity rate changes roughly monotonically in the recent past. Intuitively, this up- or down-weights the terms $X_{t-k}\pi_k(p_{t-k} - p_t)$ at times further from the present, which are likely to contribute the most bias. In general, falling primary incidences will amplify the bias, whereas rising events will minimize it. Figure 1c provides an illustration of this phenomenon.

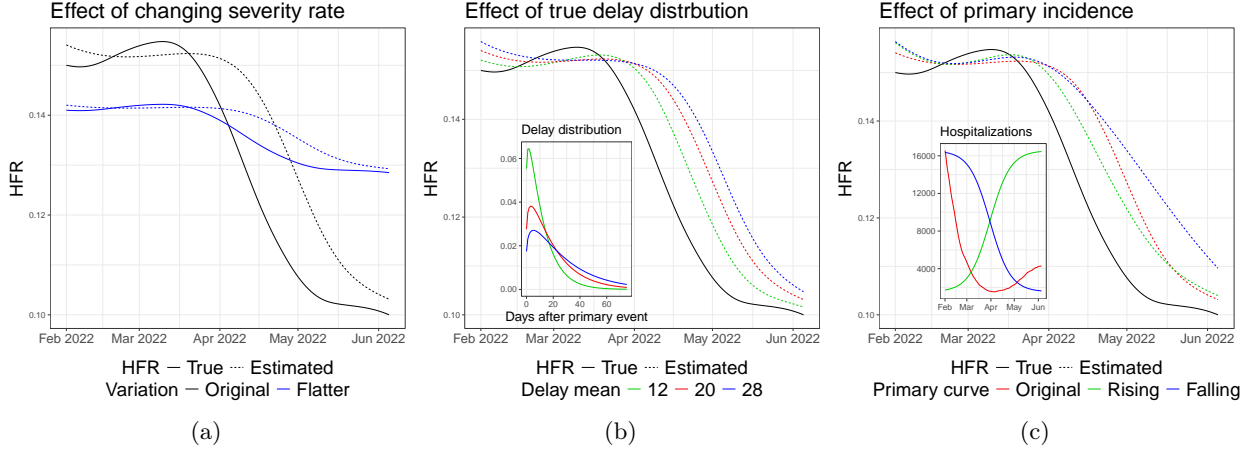


Figure 1: Simple examples which illustrate the effects of the three factors explained above on the bias of the well-specified convolutional ratio (6) in estimating p_t . In each figure, the severity rate colors correspond to different versions of the factor of interest. The primary incidence curve measures COVID-19 hospital admissions, as reported to the HHS in early 2022. We then simulate a secondary incidence curve, COVID-19 deaths, from (3), without noise. The underlying HFR curve p_t and delay distribution π used (in simulating deaths) were derived from external data sources, as explained in more detail in Section 2.4.

Appendix A.3 provides further analysis, by discussing simplified settings in which the bias (6) described in Proposition 1 itself simplifies in elucidating ways.

2.3 Misspecified analysis

We now analyze the bias of the convolutional ratio (4) for an arbitrary distribution γ . Recall that π denotes the true delay distribution in (3). We refer to the present as the *misspecified* case, as γ may differ from π .

Proposition 2. *The bias of the convolutional ratio \hat{p}_t^γ (where the true delay distribution π is unknown, and the working delay distribution γ is arbitrary, but also supported on d time steps) is*

$$\text{Bias}(\hat{p}_t^\gamma) = A_t^\gamma \text{Bias}(\hat{p}_t^\pi) + p_t(A_t^\gamma - 1), \quad (7)$$

where $A_t^\gamma = \sum_{j=0}^d X_{t-j}\pi_j / \sum_{j=0}^d X_{t-j}\gamma_j$. This compares how the delay distributions convolve against the most recent primary incidence levels.

The proof of Proposition 2 is again elementary, and given in Appendix A.2. Before delving into the technical details, we first summarize its implications for the lagged ratio. When primary incidence ℓ days ago is less than the average count weighted by the delay distribution, the lagged ratio is typically above the well-specified convolutional ratio. Otherwise, when counts ℓ days ago exceed the delay-weighted average, it tends to lie below. This leads to the following heuristics, which we justify subsequently.

1. **Heuristic #1:** When primary incidence is climbing rapidly, the lagged ratio tends to overestimate severity, at least relative to the well-specified convolutional ratio.
2. **Heuristic #2:** As incidence falls swiftly, the lagged ratio may drop just as sharply, even if true severity has not changed.
3. **Heuristic #3:** Once incidence stabilizes after a decline, the lagged ratio can exhibit sudden, counterintuitive jumps.

Under misspecification, the proposition gives an additive decomposition (7) of the convolutional ratio bias, based on the well-specified bias $\text{Bias}(\hat{p}_t^\pi)$ (as studied in Proposition 1), and a misspecification factor A_t^γ . At the outset, we note that if $\pi = \gamma$ (no misspecification), we have $A_t^\gamma = 1$, and (7) reduces to the well-specified bias. Generally, values of $A_t^\gamma > 1$ amplify the oracle bias and add positive misspecification bias $p_t(A_t^\gamma - 1) > 0$; meanwhile, values of $A_t^\gamma < 1$ shrink the oracle bias and add negative misspecification bias $p_t(A_t^\gamma - 1) < 0$.

Whether or not misspecification contributes a larger magnitude of bias overall hence depends on whether or not the sign of the misspecification term $p_t(A_t^\gamma - 1)$ agrees with the sign of the oracle bias $\text{Bias}(\hat{p}_t^\pi)$. This need not always be the case, though in our experience, it is often true in both real and simulated experiments, as we will see in Section 3. Here, to gain more insight, we study the behavior of the bias in three settings:

- Smooth γ with a lighter tail and smaller mean than π (more mass concentrated at recent time points).
- Smooth γ with a heavier tail and larger mean than π (less mass concentrated at recent time points).
- Nonsmooth γ , with a point mass at lag ℓ ; we reiterate that in this case the convolutional ratio reduces to the lagged ratio \hat{p}_t^ℓ in (2). We also note that its misspecification factor A_t^γ reduces to a quantity we similarly denote $A_t^\ell = \sum_{j=0}^d X_{t-j}\pi_j / X_{t-\ell}$, and its bias (7) reduces to:

$$\text{Bias}(\hat{p}_t^\ell) = \frac{\sum_{j=0}^d X_{t-j}\pi_j}{X_{t-\ell}} \text{Bias}(\hat{p}_t^\pi) + p_t \left(\frac{\sum_{k=0}^d X_{t-k}\pi_k}{X_{t-\ell}} - 1 \right). \quad (8)$$

We discuss the behavior of the bias in these three settings, as a function of the primary incidence curve (which drives bias through the misspecification factor A_t^γ). Figure 2 provides an accompanying illustration.

Primary incidence rising. Consider the case where primary events are rising—first slowly, then rapidly before leveling off. A lighter-tailed γ will place more weight on recent time points, with higher counts, than π ; thus $\sum_{j=0}^d X_{t-j}\gamma_j > \sum_{j=0}^d X_{t-j}\pi_j$, so $A_t^\gamma < 1$. The opposite occurs for a heavier-tailed γ : this places more weight on distant low-count time points and less on the ongoing surge, so $A_t^\gamma > 1$. A point mass distribution γ places all of its mass on $X_{t-\ell}$, and during the steepest phase of the rise, this is considerably less than X_t . The true delay π distributes mass across the d most recent time points, and a large fraction of its mass will be convolved against the last $\ell - 1$ time points, whose counts exceed $X_{t-\ell}$. The times before $t - \ell$ have less of an offsetting effect, because incidence has risen at a growing rate. Hence, during a surge we will see $X_{t-\ell} < \sum_{j=0}^d X_{t-j}\pi_j$, and $A_t^\ell > 1$. However, the behavior of A_t^ℓ will be generally more erratic than A_t^γ for a smooth distribution γ , as the denominator in the former is less smooth as t varies.

Figure 2 visualizes this as hospitalizations (primary events) rise between December 2021 and mid-January 2022. Throughout this period A_t^γ is below/above 1 for the light-tailed/heavy-tailed γ . Meanwhile, A_t^ℓ spikes to 1.25 in early January. Correspondingly, the lagged HFR rises to 20% when the true one drops to 15%.

Primary incidence falling. Next assume primary incidence reaches a maximum and begins to fall. The smooth distributions behave much the same as when incidence was rising. The light-tailed distribution has more mass around the peak than π , so $A_t^\gamma < 1$. Conversely, $A_t^\gamma > 1$ for the heavier-tail distribution because it convolves more mass before the top of the rise. The lagged bias changes its behavior in this period; while A_t^ℓ had exceeded 1 before the peak, it quickly plunges below 1. At exactly ℓ time points after the peak, the lagged estimator attains the smallest possible value of A_t^ℓ , as $X_{t-\ell}$ maximizes its denominator. Again, the lagged ratio is likely to have larger fluctuations of A_t^ℓ , since its denominator reaches extremes that are not witnessed in A_t^γ (the convolution in the denominator of A_t^γ acts as a smoother).

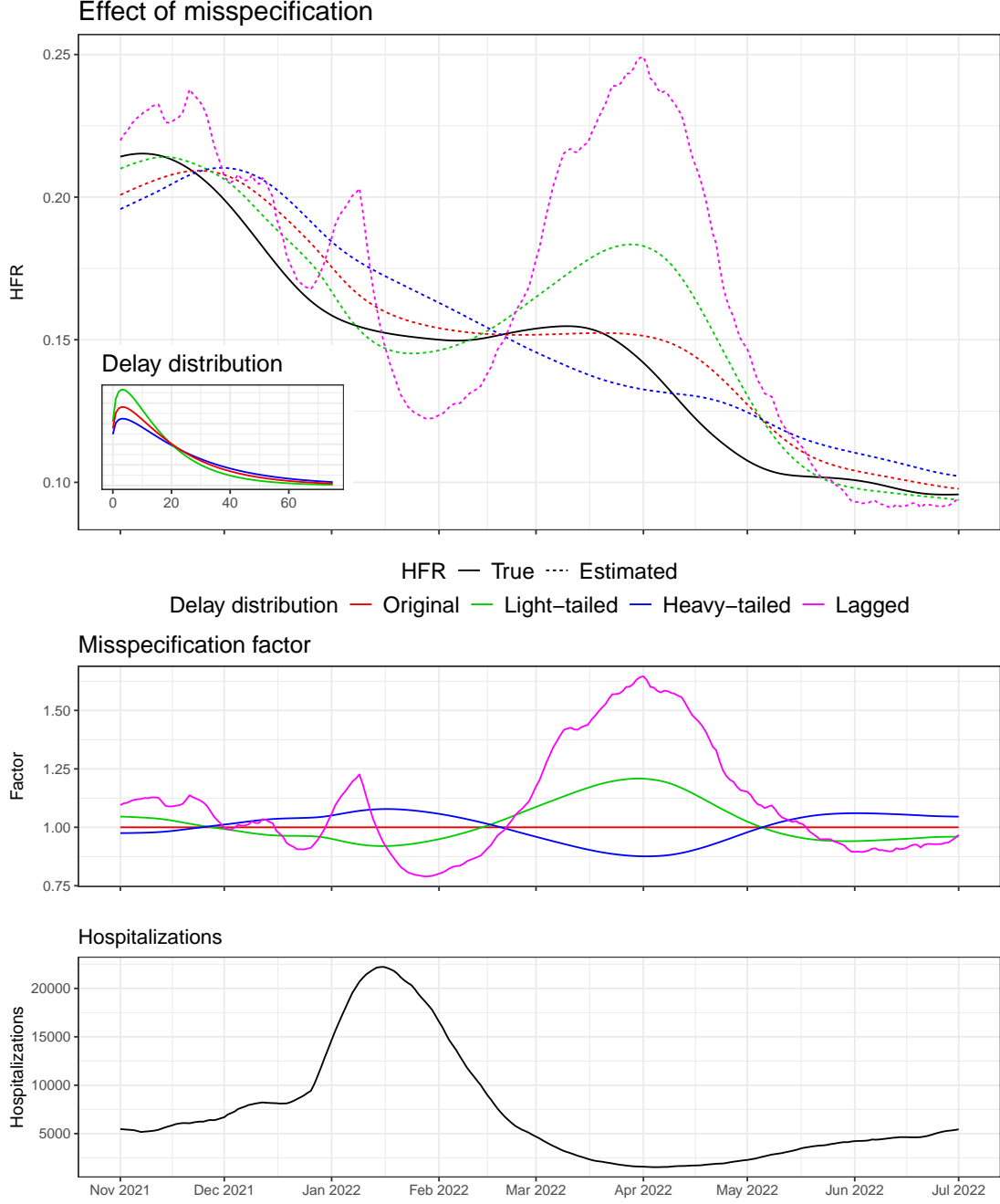


Figure 2: Examples of convolutional ratio estimates under misspecification of the delay distribution. As in Figure 1, the primary events are COVID-19 hospitalizations, as reported to the HHS, and secondary events are deaths simulated noiselessly from (3). The underlying HFR curve p_t and delay distribution π used in the simulation were fit using external data sources detailed shortly in Section 2.4. The lagged ratio estimator used $\ell = 16$, chosen to maximize cross-correlation (between hospitalizations and deaths).

In Figure 2, we can see A_t^ℓ drop below 0.8 near the start of February 2022; this happens precisely $\ell = 16$ days after daily new hospitalizations peak above 20,000 in mid-January. The lagged ratio falls from 20% to 12.5% accordingly, with the true HFR remains roughly constant, hovering around 15%. In the same period, the convolutional ratios (with light- or heavy-tailed γ) stay quite close to the true HFR.

Primary incidence levels out from a fall. The most jarring instance of misspecification bias occurs as primary incidence levels out. The true delay distribution π has a heavier tail than the low-mean, light-tailed distribution γ . It also has a heavier tail than the point mass distribution, which has no tail at all. This has important implications as the peak of the surge fades into the past. Compared to π , the light-tailed γ and point mass distribution convolve little to no mass with the high-count period of the wave. As a result, both A_t^γ and A_t^ℓ rise above 1, and severity rate estimates spike. The magnitude of this spike depends how quickly primary incidence is changing.

Figure 2 displays this false spike. Around the start of April 2022, we see A_t^γ (for light-tailed γ) and A_t^ℓ reach maximums near 1.25 and 1.68, respectively. Their corresponding HFR estimates reach 18% and 25% while the true HFR has fallen below 14%. This is of course highly problematic as it signals a rise in severity at a very counterintuitive time, when hospitalizations are at their lowest. The heavy-tailed delay γ has the opposite trend and underestimates the true HFR at this time, but by a smaller amount.

2.4 Experimental setup

Here we describe the data and general experimental setup used in Figures 1 and 2, and in Section 3.

Hospitalization-fatality rate. Our experiments analyze the HFR throughout the COVID-19 pandemic. While HFR may be less common as an object of study compared to CFR, it has a few advantages. First and foremost, hospitalization reporting was much more complete than case reporting throughout the pandemic. Hospitals were mandated to report new daily COVID-19 admissions to the Department of Health and Human Services (HHS) (Department of Health and Human Services, 2023). Due to changes in case ascertainment over time (cases as a fraction of infections), it is harder to interpret the CFR in a time-varying fashion, i.e., harder to understand what precisely this is reflecting over the course of the pandemic.

A second advantage is that hospitalization counts published by the HHS are aligned by admission date. This makes it more meaningful to interpret the HFR as a reflection of severity, especially in a time-varying fashion. In comparison, case counts as aggregated by John Hopkins University (JHU) (Center for Systems Science and Engineering (CSSE) at Johns Hopkins University, 2023) (the central resource for comprehensive COVID-19 case data in the US) are aligned by report date. Extreme reporting delays (sometimes cases were reported 45 days after infections, see, e.g., Jahja et al., 2022) make the CFR less meaningful to study as a time-varying quantity, even outside of ascertainment issues.

Thirdly, we were able to find a good “ground truth proxy” for the national HFR during the COVID-19 pandemic, as published by the National Hospital Care Survey (NHCS). This helps guide our simulations and also serves as validation data for us, as we describe in more detail below.

Aggregate data streams. To estimate the real-time HFR, we use aggregate counts of daily COVID-19 hospitalizations and deaths as made available in the Epidata API (Farrow et al., 2015), developed by the Delphi Group. Like HHS for hospitalizations, the JHU Center for Systems Science and Engineering (CSSE) provided the definitive resource for real-time death counts during the pandemic. These counts reflect times at which deaths were reported to health authorities, not necessarily when they actually happened. Hence raw JHU death counts are highly volatile due to reporting idiosyncrasies like day-of-week effects and data dumps. Hospitalizations are also subject to strong day-of-week effects. We thus smooth all data with a 7-day trailing average, for both hospitalizations and deaths.

Our real-time estimates of HFR actually use data that was available two days after the date in question. This was done to account for a typical two-day latency in the most recent data available. In this sense, one can actually view our real-time estimates as a two-day backcast of the HFR. In the rare event that counts were still unavailable at a two-day lag, we imputed their values with the most recently observed data (this is a common scheme, called last-observation-carried-forward or LOCF).

Hyperparameters. The ratio estimators of the HFR require choices of the lag ℓ and delay distribution γ . The experiments in Section 3 use a lag of $\ell = 20$ days, which roughly maximizes the cross-correlation between hospitalizations and deaths over the entire pandemic. For γ , we use a discrete gamma distribution, and set its support length to be $d = 75$ days, a conservative choice. For its mean, we use 20 again; this agrees nicely with a UK analysis that finds a median hospitalization-to-death time of 11 days (Ward and Johnsen, 2021),¹ and a CDC analysis that finds 63% of COVID-19 deaths are reported in 10 days (National Center for Health Statistics (NCHS) at Centers for Disease Control and Prevention, 2023). We set the standard deviation to 18, because the delay distributions fit by the UK study had standard deviations that were roughly 90% of their means.

Appendix C evaluates the robustness of findings against different hyperparameter values. We show our findings do not change across a wide range of lags (Figure 10) and delay distributions (Figure 11).

Validation data. While the true HFR curve is unknown, there are sound ways to approximate it; one way is to use estimates from the National Hospital Care Survey (NHCS) (National Hospital Care Survey (NHCS) at Centers for Disease Control and Prevention, 2023), which records weekly HFR based on a representative subset of 601 hospitals across the US. These estimates end up being consistently biased downwards because they are only based on deaths which occur in the hospital. A CDC analysis (Ahmad et al., 2023) found that roughly 60% of COVID-19 deaths occurred in hospitals in 2022, down from nearly 70% in 2021 and 2022. To account for non-inpatient deaths, we divide the NHCS estimates by these percentages. Lastly, we smooth the resulting HFR estimates with a spline, via the `smooth.spline` function in R (which chooses the smoothness hyperparameter by minimizing generalized cross-validation error). This results in our proxy for the ground truth HFR curve p_t .

This ground truth proxy is a useful benchmark to judge the fidelity of our HFR estimates; of course, it is not perfect (and derived from a relatively small subset of hospitals). Results in Section 3 suggest it may be too high in late 2022. Appendix B discusses alternative approximations to the ground truth HFR. These alternatives, shown in Figure 7, all exhibit similar qualitative behavior.

3 Results

We study the performance of the ratio estimators in greater depth, on real and simulated data. Throughout, we continue to use COVID-19 hospitalizations reported to the HHS as the primary incidence curve. Code to reproduce all results is available at <https://github.com/jeremy-goldwasser/Severity-Bias>.

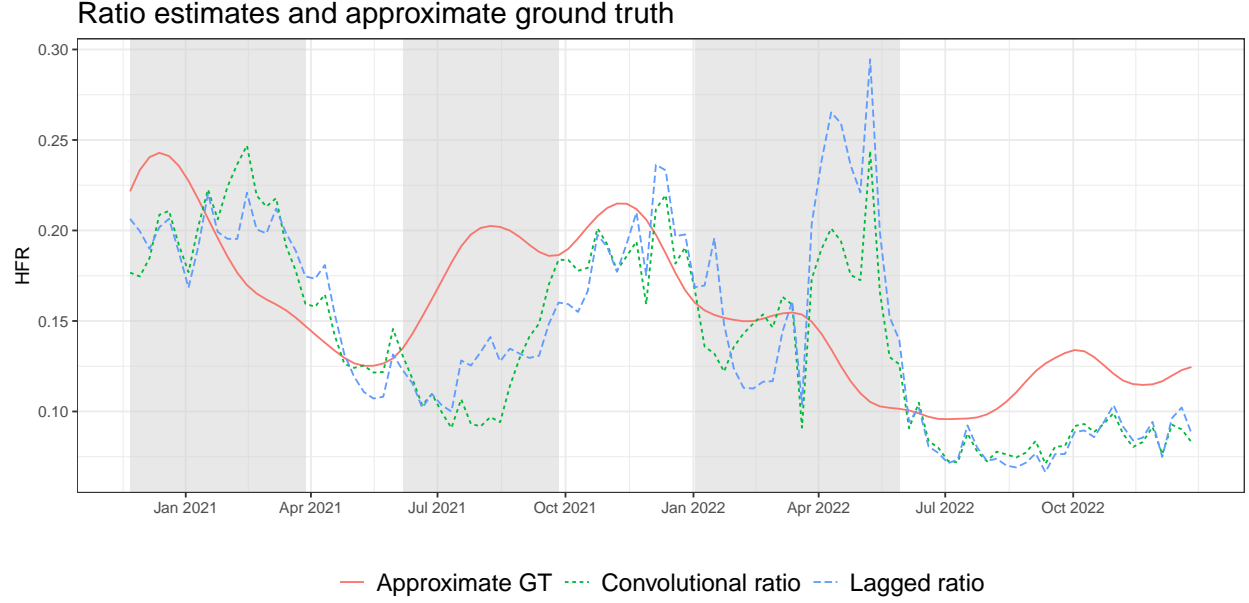
3.1 COVID-19 data

Figure 3 displays real-time HFR estimates from November 2020 to December 2022, which spans the major COVID-19 waves. These estimates were fit to the data described in Section 2.4. The real-time hospitalization and death counts exhibit a fair degree of instability, and recall, these were preprocessed with a 7-day trailing average. Even then, the convolutional (4) and lagged ratio (2) estimators each had wild spikes, so we further smoothed the estimates from both methods with a 7-day trailing average. Appendix C studies the sensitivity of the results to the choice of smoothing window in postprocessing. ~~This has~~ Figure 9 shows window size has very little qualitative effect on the main shape of the HFR estimates from either method.

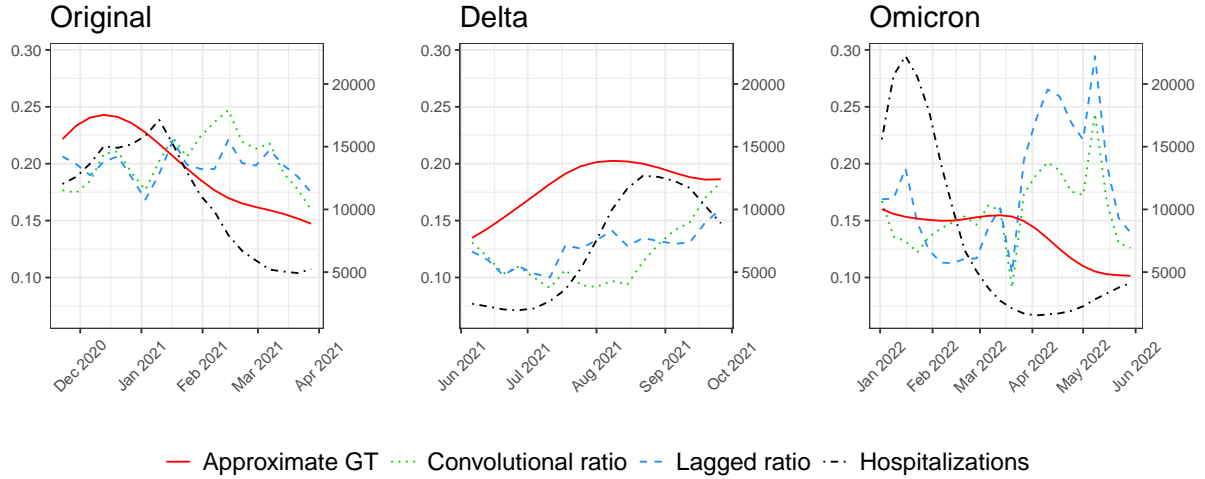
Overall, both ratio estimators perform poorly—their bias is consistent and nontrivial, especially for the lagged estimator. Both respond very slowly to changes in the HFR. As the HFR declines following the wave in winter 2021, both ratios hover near 20% for several months. More troublingly, they are too slow to detect the rise in HFR in the early Delta period (summer 2021). If the purpose of these estimators is to inform stakeholders of increased risks in real time, they failed during the Delta surge.

The most significant bias comes in the middle of the Omicron wave in spring 2022. In this period, the HFR remains around 15% until April, then sharply declines to 9% two months later. The ratio estimates first fluctuate around the true HFR, and then subsequently, both estimates surge as the true HFR nears its nadir,

¹Of course, conditions in the UK may be quite different from the US. However, we rely on the UK study because it provides the most comprehensive information on COVID-19 hospitalization-to-death delay distributions.



(a) Convolutional and lagged ratios against approximate ground truth HFR. Waves corresponding to the original, Delta, and Omicron variants are highlighted in gray.



(b) Zooming in to focus on major variants, with hospitalizations overlaid (right y-axis).

Figure 3: Comparing ratio estimates to approximate ground truth HFR on real-time COVID-19 data counts in the US, from November 2020 through December 2022.

with the lagged ratio approaching 30%. This dramatic upswing signals a serious false alarm. The analysis in Sections 2.2 and 2.3 explain each of these failure cases.

Well-specified analysis. We start by analyzing the convolutional ratio with respect to the well-specified bias expression in Proposition 1. While this expression assumes that the true delay distribution is known, we found that different choices of delay distribution generally yield similar bias ([Appendix C](#); see [Figure 11 in Appendix C](#)). This indicates that our convolutional ratio may not be far from the oracle (well-specified) ratio.

Proposition 1 indicates that the bias moves in the opposite direction of the true severity rate. This occurs during the Delta wave, when the HFR rises well before the ratio estimates do. On the other hand, falling

HFR produces positive bias, as observed in the original and Omicron waves.

The enormity of the bias during Omicron can partially be attributed to the precipitous decline in hospitalizations, as falling primary incidence has been shown to exacerbate the bias. Average daily hospitalizations declined from over 20,000 in mid-January to only 1,500 by April 1. Lastly, the delay distribution is relatively heavy-tailed, because the aggregate deaths here (from JHU) are aligned by report date. We find that this has a substantial impact on the bias, as analyzed in Appendix B. Figure 6 shows a large gap in bias between ratios computed on NCHS versus JHU deaths.

Misspecified analysis. The misspecification analysis explains central discrepancies between the convolutional and lagged ratios. Section 2.3 discusses why we expect $A_t^\ell < 1$ around the start of a decline in primary incidence (Heuristic #2). As a result, the lagged ratio will incur negative misspecification bias, ~~and we so it takes lower values than the convolutional ratio.~~ We observe this when hospitalizations with the original variant decline from their peak in mid-January 2021. Throughout February 2021, lagged estimates are about 2% below the positively biased convolutional ratios.

As primary incidence rises, we expect $A_t^\ell > 1$, contributing positive bias relative to the ~~(approximately)~~ well-specified ~~convolutional ratio ratio~~ (Heuristic #1). Correspondingly, when hospitalizations surge due to the Delta variant in August 2021, the lagged ratio is less negatively biased. Lastly, recall ~~we~~ we expect $A_t^\ell > 1$ after a fall in primary incidence (Heuristic #3). This accounts for the lagged ratio having higher bias in April 2022, when hospitalizations level out from the Omicron surge. There, the lagged HFR (and presumably also the misspecification factor A_t^ℓ) hits its maximum value.

We performed several robustness checks to assess the stability of these findings. Appendix C compares HFR estimates using finalized counts, rather than the data available in real time (Figure 8). It also studies the effect of different hyperparameter choices ~~and also~~ (Figures 9, 10, 11), and examines the ratio estimators on six US states ~~It also compares HFR estimates using finalized counts, rather than the data available in real time.~~ (Figure 12). By and large, the ratio estimators yield roughly the same type of bias throughout.

3.2 Simulated data

We further evaluate the ratio estimators in a variety of simulation settings. Keeping the primary incidence X_t as hospitalizations reported to the HHS, we simulate ~~a secondary incidence curve Y_t , deaths,~~ deaths based on the convolutional model (3) without noise. That is, we generate \div

$$Y_t = \mathbb{E}[Y_t | \{X_s\}_{s \leq t}] = \sum_{k=0}^d X_{t-k} \mathbb{P}(\text{die at } t | \text{hospitalized at } t-k) = \sum_{k=0}^d X_{t-k} \pi_k p_{t-k},$$

~~for a given HFR curve p_t and delay distribution π .~~

The simulations explore ~~different three three different~~ underlying HFR curves and two ~~delays.~~ ~~In addition to studying the delay distributions.~~ The delay distribution π is a discrete gamma with standard deviation 90% of its mean. We consider means of 12 and 24 to compare short and long distributions. For the HFRs p_t , we first use the approximate ground truth ~~give by NHCS,~~ ~~we mimic given by NHCS~~ In addition, we mimic the opposite trend by inverting and rescaling this curve. We ~~also consider a stationary HFR of 10%~~ do so with the following formula, preserving the minimum and maximum HFRs:

$$p^{\text{Inv}} = \frac{1}{p} \times \frac{\min(p)}{\max(p)}$$

The third HFR setting is a stationary $p = 10\%$ over all time. ~~For the delay distribution, we use a discrete gamma with standard deviation 90% of its mean, and consider means of 12 and 24 to experiment with short and long delay distribution.~~

For the This case elucidates the quantity A_t^ℓ that drives the lagged ratio's bias. This value is $A_t^\ell = \hat{p}_t^\ell / p$, the lagged ratio itself scaled by a constant. To see this, recall that the oracle convolutional ratio is unbiased under stationarity, so Proposition 2 simplifies to $\mathbb{E}[\hat{p}_t^\ell | \{X_s\}_{s \leq t}] = p A_t^\ell$ for the lagged ratio. Furthermore,

Ratio estimates under various simulation models

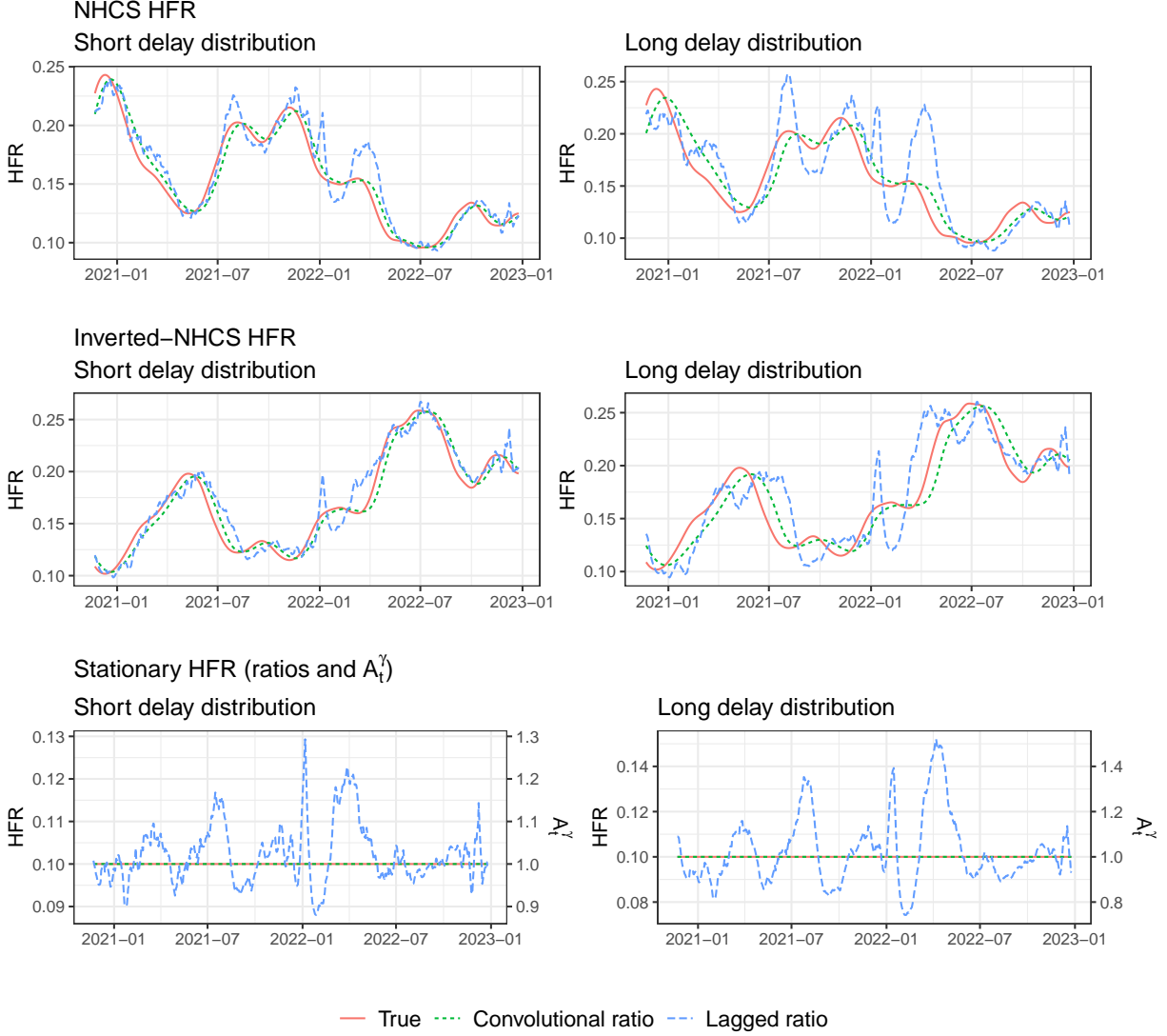


Figure 4: Convolutional and lagged ratios over various simulation settings, with three different underlying HFR curves (rows) and two delays (columns). The last row, for stationary HFR, also provides $A_t^\gamma = \hat{p}_t^\gamma / p$.

$\mathbb{E}[\hat{p}_t^\ell | \{X_s\}_{s \leq t}] = \hat{p}_t^\ell$ in this noiseless simulation, so $A_t^\ell = \hat{p}_t^\ell / p$. A_t^γ also is \hat{p}_t^γ / p for the well-specified convolutional ratio, we use $\gamma = \pi$ (the since the estimator is unbiased and $A_t^\pi = 1$ by definition.

To estimate the severity rates, the convolutional ratio is well-specified (ease) with $\gamma = \pi$. For the lagged ratio, we choose the lag ℓ by maximizing the cross-correlation between hospitalizations and deaths. In both cases, we do not smooth the data in any capacity. (The same is true for Figures 1 and 2.)

Figure 4 shows the results across the six settings in total. As expected, HFR estimates are significantly more biased when the underlying delay distribution is longer. This bias is most pronounced with the lagged ratio. For example, even when the true HFR is a constant 10%, the lagged ratio estimates hit 13% under the light-tailed delay, and 15% under the heavy-tailed one. In the NCHS HFR setting, it spikes (as we have seen before) as hospitalizations level out in spring 2022, reaching over 20% and 25% under the light- and heavy-tailed delays, respectively. Note the convolutional ratio does not share these dramatic oscillations. By and large, it tracks the general shape of the true curve, albeit at a delay. Its overall favorable performance

rests on the fact that we have chosen in this simulation to provide it with the benefit of the true delay distribution (no misspecification).

~~Convolutional and lagged ratios over various simulation settings, with three different underlying HFR curves (rows) and two delays (columns).~~

The results in Section 2.3 explain the wide gap in performance between these estimators. ~~Proposition 2 expresses bias under misspecification as a function of the factor. This factor, denoted for the lagged estimator, can be read off from the third row in Figure 4. To see this, recall that given a constant severity rate $p_t = p$, the oracle convolutional ratio is unbiased, so (7) reduces to for the lagged ratio. Furthermore, we simulate deaths without noise. Consequently, or in other words, one can read off by simply multiplying the curves in the third row by $1/p = 10$.~~

~~As is to be expected~~ As anticipated, the lagged ratio is higher than the oracle convolutional ratio when $A_t^\ell > 1$, and lower when $A_t^\ell < 1$. Comparing A_t^ℓ to the estimated HFR curves, the bias moves very similarly. For example, during the Delta and Omicron waves, rapid rises in hospitalizations produced high values of A_t^ℓ . This accounts for the spikes in August 2021 and January 2022. ~~When hospitalizations level out from the Omicron surge, we see spike to 1.2 and 1.5 for the short and long distributions, respectively, hence the positive bias in spring 2022. Lastly, the 2022 (Heuristic #1). Heuristic #2 dictates the~~ lagged estimator should have ~~negative bias~~ lower bias than the well-specified ratio as primary events fall. We observe this in Delta (September 2021) and Omicron (February 2022). ~~Lastly, when hospitalizations level out from the Omicron surge, A_t^ℓ spikes to 1.2 and 1.5 for the short and long distributions. This explains the positive bias in spring 2022, per Heuristic #3.~~

The bias (7) rescales the oracle bias and adds a misspecification term. Studying Figure 4, we observe the misspecification term tends to dominate when A_t^ℓ strays away from 1. To understand this, consider periods in which the oracle bias is negative. As introduced in Section 2.3, the oracle and misspecification terms are at odds with each other when this is the case. Invariably, the lagged ratio moves in the direction of the misspecification term $p_t(A_t^\ell - 1)$. In the NHCS HFR setting, for example, the lagged estimates spike with A_t^ℓ in August 2021. In the inverted setting, the lagged bias tracks the down-up-down motion of A_t^ℓ during the first five months of 2021. That the misspecification term wins out in these conflicting settings indicates it comprises a disproportionate amount of the bias. Indeed, the oracle bias is low enough that multiplicative rescaling must not have a large effect.

4 Discussion

Our analyses and experiments illustrate that practitioners should take caution when using ~~(standard)~~ standard ratio estimators for time-varying severity rates. They exhibit nontrivial bias as severity rates change, particularly the popular lagged ratio. If a major purpose of such estimators is to inform stakeholders of changing risks in real time, then such bias indicates they may fail to do so in a reliable manner.

Analyzing the bias, as we have done in Propositions 1 and 2, allows us to form real-time heuristics about what to expect in practice. For example, based solely on the primary incidence curve, we generally expect the lagged ratio to make the following errors:

- unreasonably high severity estimates when primary incidence is rising quickly (Heuristic #1);
- rapid declines when primary incidence is falling quickly (Heuristic #2);
- unexpected surges when primary incidence has leveled out after falling (Heuristic #3).

Practitioners may be able to adjust their reactions accordingly; ~~for~~. For example, if the lagged HFR spikes shortly after hospitalizations have declined and reach a stable low point, then a savvy epidemiologist can temper ~~her~~ their alarm with the knowledge it may well be spurious.

While the lagged ratio seems ubiquitous in practice, the convolutional ratio (when a reasonable estimate of the delay distribution can be formed) can be better behaved and should probably be favored. While it is still subject to bias, this tends to be of a smaller magnitude.

Going beyond, there is still room to improve ~~the inherently upon the~~ backward-looking convolutional ratio. ~~Qu et al. (2022) proposed an approach that is meant to be retrospective in nature, and not real-time.~~

~~It is also inherently a promising forward-looking , and estimates severity estimator was proposed by Qu et al. (2022). This method obtains~~ all historical severity rates p_t at once, by minimizing

$$\sum_t (Y_t - \sum_{j=0}^d X_{t-j} \gamma_j p_{t-j})^2 + \lambda \sum_t |p_t - p_{t-1}|,$$

where $\lambda \geq 0$ is a parameter that controls the level of regularization. The regularizer above is a total variation ~~(also called fused lasso) penalty, and leads to penalty, also called the fused lasso; it produces~~ a piecewise constant ~~estimates .~~ Adapting this model so that it can be used to produce estimates in fit of the severity rates. Unlike the convolutional ratio, this method models the relationship between events without assuming severity rates are locally stationary. Therefore, it may be a less biased alternative. Since the severity rates are defined implicitly via optimization, their bias is analytically intractable and must be assessed empirically.

Unfortunately, while this method was introduced as a real-time , tool, it struggles with instability at the most recent timesteps. Improving its capabilities for real-time estimation, and extending it to fit smoother severity rates using trend filtering penalties (see, e.g., Tibshirani, 2014), are interesting directions for future work. Jahja et al. (2022) applied trend filtering to a similar deconvolution problem, reconstructing latent infections from case reports. Their insights on tail regularization may be useful to stabilize real-time severity estimates.

Severity rates may be biased in ways beyond the statistical bias our work focuses on. In Section 2.4, we mentioned that HFR estimation from line-lists can be subject to “survivorship bias”: the failure to account for deaths occurring outside the hospital (Lipsitch et al., 2015). Under-reporting is another central challenge, particularly for CFR. Not all infections are reported, reporting rates change across time, and severe cases are more likely to be reported than mild cases (Tsang et al., 2021). Reich et al. (2012) proposed an estimator for a time-invariant *relative* CFR—the ratio of CFRs between groups—which learns latent reporting rates via the EM algorithm. Angelopoulos et al. (2020) applied this in the context of COVID-19. Their work also identifies other sources of bias, like differences in case definition and testing eligibility. Finally, examining how hyperparameter tuning strategies affect the bias poses an opportunity for future work.

As discussed in Section 2.1, severity rates may be understood in connection with reproduction numbers. This connection extends to their bias as well. For example, we demonstrated that the convolutional ratio is unbiased if the severity rate and delay distribution in the d time points before t are stationary. In a similar vein, Fraser (2007) noted that instantaneous R_t is equal to case R_t if conditions remain unchanged. Future work along the lines of Eales and Riley (2023) could apply our framework to R_t bias, examining the fidelity of instantaneous R_t as a proxy for case R_t . Conversely, one could apply Bayesian perspectives on R_t to the context of severity rates.

References

- Adjei, S., Hong, K., Molinari, N.-A. M., Bull-Otterson, L., Ajani, U. A., Gundlapalli, A. V., Harris, A. M., Hsu, J., Kadri, S. S., Starnes, J., Yeoman, K., and Boehmer, T. K. (2022). Mortality risk among patients hospitalized primarily for COVID-19 during the Omicron and Delta variant pandemic periods — United States, April 2020–June 2022. *Morbidity and Mortality Weekly Report*, 71(37):1182–1189.
- Ahmad, F. B., Cisewski, J. A., Xu, J., and Anderson, R. N. (2023). Covid-19 mortality update — united states, 2022. *MMWR Morbidity and Mortality Weekly Report*, 72(18):493–496.
- Angelopoulos, A. N., Pathak, R., Varma, R., and Jordan, M. I. (2020). On identifying and mitigating bias in the estimation of the COVID-19 case fatality rate. *Harvard Data Science Review*, Special Issue 1.
- Baud, D., Qi, X., Nielsen-Saines, K., Musso, D., Pomar, L., and Favre, G. (2020). Real estimates of mortality following COVID-19 infection. *Lancet Infectious Diseases*, 20(7):773.
- Bellan, M., Patti, G., Hayden, E., Azzolina, D., Pirisi, M., et al. (2020). Fatality rate and predictors of mortality in an Italian cohort of hospitalized COVID-19 patients. *Scientific Reports*, 10:20731.
- Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (2023). COVID-19 data repository. <https://github.com/CSSEGISandData/COVID-19>.
- Centers for Disease Control and Prevention (2023). COVID-19 case surveillance public use data. https://data.cdc.gov/Case-Surveillance/COVID-19-Case-Surveillance-Public-Use-Data/vbim-akqf/about_data.
- Challen, R., Brooks-Pollock, E., Read, J. M., Dyson, L., Tsaneva-Atanasova, K., and Danon, L. (2021). Risk of mortality in patients infected with SARS-CoV-2 variant of concern 202012/1: Matched cohort study. *British Medical Journal*, 372:n579.
- Charniga, K., Park, S. W., Akhmetzhanov, A. R., Cori, A., Dushoff, J., Funk, S., Gostic, K. M., Linton, N. M., Lison, A., Overton, C. E., Pulliam, J. R. C., Ward, T., Cauchemez, S., and Abbott, S. (2024). Best practices for estimating and reporting epidemiological delay distributions of infectious diseases using public health surveillance and healthcare data. arXiv:2405.08841.
- Cori, A., Ferguson, N. M., Fraser, C., and Cauchemez, S. (2013). A new framework and software to estimate time-varying reproduction numbers during epidemics. *American Journal of Epidemiology*, 178(9):1505–1512.
- COVID-19 Forecasting Team (2022). Variation in the COVID-19 infection–fatality ratio by age, time, and geography during the pre-vaccine era: A systematic analysis. *Lancet*, 399(10334):1469–1488.
- Department of Health and Human Services (2023). COVID-19 guidance for hospital reporting and FAQs for hospitals, hospital laboratory, and acute care facility data reporting. <https://www.hhs.gov/sites/default/files/covid-19-faqs-hospitals-hospital-laboratory-acute-care-facility-data-reporting.pdf>.
- Eales, O. and Riley, S. (2023). Differences between the true reproduction number and the apparent reproduction number of an epidemic time series. arXiv:2307.03415.
- Farrow, D. C., Brooks, L. C., Tibshirani, R. J., and Rosenfield, R. (2015). Delphi Epidata API. <https://github.com/cmu-delphi/delphi-epidata>.
- Fraser, C. (2007). Estimating individual and household reproduction numbers in an emerging epidemic. *PLOS One*, 2(8):1–12.
- Garske, T., Legrand, J., Donnelly, C. A., Ward, H., Cauchemez, S., Fraser, C., Ferguson, N. M., and Ghani, A. C. (2009). Assessing the severity of the novel influenza A/H1N1 pandemic. *British Medical Journal*, 339:b2840.

- Ghani, A. C., Donnelly, C. A., Cox, D. R., Griffin, J. T., Fraser, C., Lam, T. H., Ho, L. M., Chan, W. S., Anderson, R. M., Hedley, A. J., and Leung, G. M. (2005). Methods for estimating the case fatality ratio for a novel, emerging infectious disease. *American Journal of Epidemiology*, 162(5):479–486.
- Gupte, P. R., Kucharski, A. J., Russell, T. W., Lambert, J. W., Gruson, H., Taylor, T., Azam, J. M., Degoot, A. M., and Funk, S. (2024). cfr: Estimate disease severity and case ascertainment. <https://cran.r-project.org/package=cfr>.
- Hodcroft, E. B. (2021). Covariants: SARS-CoV-2. <https://covariants.org/>.
- Horita, N. and Fukumoto, T. (2022). Global case fatality rate from COVID-19 has decreased by 96.8% during 2.5 years of the pandemic. *Journal of Medical Virology*, 95(1):e28231.
- Jahja, M., Chin, A., and Tibshirani, R. J. (2022). Real-time estimation of covid-19 infections: Deconvolution and sensor fusion. *Statistical Science*, 37(2):207–228.
- Jewell, N. P., Lei, X., Ghani, A. C., Donnelly, C. A., Leung, G. M., Ho, L.-M., Cowling, B. J., and Hedley, A. J. (2007). Non-parametric estimation of the case fatality ratio with competing risks data: An application to Severe Acute Respiratory Syndrome (SARS). *Statistics in Medicine*, 26(9):1982–1998.
- Kamp, J. and Krouse, S. (2020). Case-fatality metric points to increase in December deaths. Wall Street Journal.
- Karimi, M. (2024). Covid-19 case fatality rate, hypertension, and availability of federally qualified health centers (fqhcs), mississippi. Mississippi State Department of Health. Accessed from the CDC Chronic Disease Map Gallery.
- Lipsitch, M., Donnelly, C. A., Fraser, C., Blake, I. M., Cori, A., Dorigatti, I., Ferguson, N. M., Garske, T., Mills, H. L., Riley, S., Van Kerkhove, M. D., and Hernán, M. A. (2015). Potential biases in estimating absolute and relative case-fatality risks during outbreaks. *PLOS Neglected Tropical Diseases*, 9(7):e0003846.
- Liu, J., Wei, H., and He, D. (2023). Differences in case-fatality-rate of emerging SARS-CoV-2 variants. *Public Health in Practice*, 5:100350.
- Luo, G., Zhang, X., Zheng, H., and He, D. (2021). Infection fatality ratio and case fatality ratio of COVID-19. *International Journal of Infectious Diseases*, 113:43–46.
- Madrigal, A. C. and Moser, W. (2020). How many americans are about to die? The Atlantic.
- McNeil, D. G. J. (2020). The pandemic’s big mystery: How deadly is the coronavirus? New York Times.
- National Center for Health Statistics (NCHS) at Centers for Disease Control and Prevention (2023). Deaths by select demographic and geographic characteristics. https://www.cdc.gov/nchs/nvss/vsrr/covid_weekly/index.htm.
- National Hospital Care Survey (NHCS) at Centers for Disease Control and Prevention (2023). In-hospital mortality among hospital confirmed COVID-19 encounters by week from selected hospitals. <https://www.cdc.gov/nchs/covid19/nhcs/hospital-mortality-by-week.htm>.
- Nishiura, H., Klitkenberg, D., Roberts, M., and Heesterbeek, J. A. P. (2009). Early epidemiological assessment of the virulence of emerging infectious diseases: A case study of an Influenza pandemic. *PLOS One*, 4(8):e6852.
- Overton, C. E., Webb, L., Datta, U., Fursman, M., Hardstaff, J., Hiironen, I., Paranthaman, K., Riley, H., Sedgwick, J., Verne, J., Willner, S., Pellis, L., and Hall, I. (2022). Novel methods for estimating the instantaneous and overall COVID-19 case fatality risk among care home residents in England. *PLOS Computational Biology*, 18(10):e1010554.
- Qu, Y., Lee, C. Y., and Lam, K. F. (2022). A novel method to monitor COVID-19 fatality rate in real-time, a key metric to guide public health policy. *Scientific Reports*, 12:18277.

- Reich, N. G., Lessler, J., Cummings, D. A. T., and Brookmeyer, R. (2012). Estimating absolute and relative case fatality ratios from infectious disease surveillance data. *Biometrics*, 68(2):598–606.
- Roth, G. A., Emmons-Bell, S., Alger, H. M., Bradley, S. M., Das, S. R., de Lemos, J. A., Gakidou, E., Elkind, M. S. V., Hay, S., Hall, J. L., Johnson, C. O., Morrow, D. A., Rodriguez, F., Rutan, C., Shakil, S., Sorensen, R., Stevens, L., Wang, T. Y., Walchok, J., Williams, J., and Murray, C. (2021). Trends in patient characteristics and COVID-19 in-hospital mortality in the United States during the COVID-19 pandemic. *JAMA Network Open*, 4(5):e218828.
- Russell, T. W., Golding, N., Hellewell, J., Abbott, S., Wright, L., Pearson, C. A. B., van Zandvoort, K., Jarvis, C. I., Gibbs, H., Liu, Y., Eggo, R. M., Edmunds, W. J., Kucharski, A. J., and CMMID COVID-19 working group (2020a). Reconstructing the early global dynamics of under-ascertained COVID-19 cases and infections. *BMC Medicine*, 18(332).
- Russell, T. W., Hellewell, J., Jarvis, C. I., van Zandvoort, K., Abbott, S., Ratnayake, R., CMMID COVID-19 working group, Flasche, S., Eggo, R. M., Edmunds, W. J., and Kucharski, A. J. (2020b). Estimating the infection and case fatality ratio for coronavirus disease (COVID-19) using age-adjusted data from the outbreak on the Diamond Princess cruise ship, February 2020. *Eurosurveillance*, 25(12):2000256.
- The White House (2020). Press briefing by press secretary kayleigh mcenany. Trump White House Archives.
- The White House (2021). Press briefing by white house covid-19 response team and public health officials. Via teleconference. Archived content.
- Thomas, B. S. and Marks, N. A. (2021). Estimating the case fatality ratio for COVID-19 using a time-shifted distribution analysis. *Epidemiology & Infection*, 149:e197.
- Tibshirani, R. J. (2014). Adaptive piecewise polynomial estimation via trend filtering. *Annals of Statistics*, 42(1):285–323.
- Tsang, T. K., Wang, C., Yang, B., Cauchemez, S., and Cowling, B. J. (2021). Using secondary cases to characterize the severity of an emerging or re-emerging infection. *Nature Communications*, 12:6372.
- Unnikrishnan, J., Mangalathu, S., and Kutty, R. V. (2021). Estimating under-reporting of COVID-19 cases in Indian states: An approach using a delay-adjusted case fatality ratio. *BMJ Open*, 11(1):e042584.
- Wallinga, J. and Lipsitch, M. (2007). How generation intervals shape the relationship between growth rates and reproductive numbers. *Proceedings of the Royal Society B: Biological Sciences*, 274(1609):599–604.
- Ward, T. and Johnsen, A. (2021). Understanding an evolving pandemic: An analysis of the clinical time delay distributions of covid-19 in the united kingdom. *PLOS One*, 16(10):e0257978.
- Wjst, M. and Wendtner, C. (2023). High variability of COVID-19 case fatality rate in Germany. *BMC Public Health*, 23:416.
- Xie, Y., Choi, T., and Al-Aly, Z. (2024). Mortality in patients hospitalized for COVID-19 vs Influenza in fall-winter 2023-2024. *Journal of the American Medical Association*, 331(22):1963–1965.
- Yuan, J., Li, M., Lv, G., and Lud, Z. K. (2020). Monitoring transmissibility and mortality of COVID-19 in Europe. *International Journal of Infectious Diseases*, 95:311–315.

A Proofs and further analysis

The assumption of stationary delay distribution is not necessary for either bias expression. In the proofs in Appendix A.1 and A.2, the delay distributions π may simply be replaced with $\pi^{(t)}$.

A.1 Proof of Proposition 1

Proposition (1) establishes the bias of the well-specified convolutional ratio. Here and henceforth, we abbreviate $\mathbb{E}_t[\cdot] = \mathbb{E}[\cdot | \{X_s\}_{s \leq t}]$. Observe that

$$\begin{aligned} \text{Bias}(\hat{p}_t^\pi) &= \frac{\mathbb{E}_t[Y_t]}{\sum_{k=0}^d X_{t-k}\pi_k} - p_t \\ &= \frac{\sum_{k=0}^d X_{t-k}\pi_k p_{t-k}}{\sum_{k=0}^d X_{t-k}\pi_k} - \frac{p_t \sum_{k=0}^d X_{t-k}\pi_k}{\sum_{k=0}^d X_{t-k}\pi_k} \\ &= \sum_{k=0}^d \frac{X_{t-k}\pi_k}{\sum_{j=0}^d X_{t-j}\pi_j} (p_{t-k} - p_t). \end{aligned}$$

A.2 Proof of Proposition 2

Proposition (2) establishes the bias of the misspecified convolutional ratio, the lagged ratio being a special case. Observe that

$$\begin{aligned} \text{Bias}(\hat{p}_t^\gamma) &= \frac{\mathbb{E}_t[Y_t]}{\sum_{k=0}^d X_{t-k}\gamma_k} - p_t \\ &= \frac{\sum_{k=0}^d X_{t-k}\pi_k p_{t-k}}{\sum_{k=0}^d X_{t-k}\gamma_k} - \frac{\sum_{k=0}^d X_{t-k}\gamma_k p_t}{\sum_{k=0}^d X_{t-k}\gamma_k} \\ &= \sum_{k=0}^d \frac{X_{t-k}}{\sum_{j=0}^d X_{t-j}\gamma_j} (\pi_k p_{t-k} - \gamma_k p_t) \\ &= \sum_{k=0}^d \frac{X_{t-k}}{\sum_{j=0}^d X_{t-j}\gamma_j} (\pi_k p_{t-k} - (\pi_k + (\gamma_k - \pi_k))p_t) \\ &= \frac{\sum_{j=0}^d X_{t-j}\pi_j}{\sum_{j=0}^d X_{t-j}\gamma_j} \sum_{k=0}^d \frac{X_{t-k}\pi_k}{\sum_{j=0}^d X_{t-j}\pi_j} (p_{t-k} - p_t) - p_t \sum_{k=0}^d \frac{X_{t-k}}{\sum_{j=0}^d X_{t-j}\gamma_j} (\gamma_k - \pi_k) \\ &= \frac{\sum_{j=0}^d X_{t-j}\pi_j}{\sum_{j=0}^d X_{t-j}\gamma_j} \text{Bias}(\hat{p}_t^\pi) + p_t \left(\frac{\sum_{k=0}^d X_{t-k}\pi_k}{\sum_{j=0}^d X_{t-j}\gamma_j} - 1 \right). \end{aligned}$$

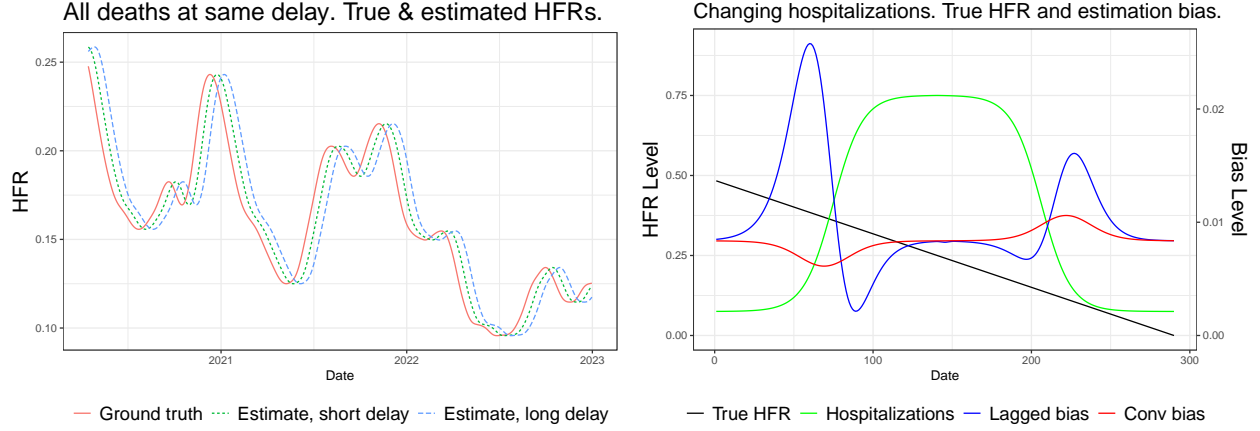
A.3 Further analysis of (6) well-specified bias

We present examples that further explain the well-specified bias. These are bias for the well-specified convolutional ratio (6). These examples are considerably more contrived than the ones in Section 2.2, for example, using unrealistic delay distributions. Nonetheless, their bias can be simplified to simple analytic formulas, isolating the three contributing factors.

To elucidate the relationship between changing severity rates and bias, let us consider the case where all secondary events occur after precisely ℓ time points. Note, the The well-specified convolutional and lagged ratio estimators coincide: $\hat{p}_t^\gamma = \hat{p}_t^\ell = p_{t-\ell}$. The bias in this setting is simply the change in the true severity rate, $p_{t-\ell} - p_t$, and the ratio estimator is unbiased only if the severity rate is stationary. Otherwise, say, the ratio will be 20% too low, for example, if the true severity rate was 20% lower ℓ time steps ago.

Typically

Figure 5a displays the results on the NHCS HFRs. In general, severity rates will be less similar to the present value p_t as we go further back in time, thus, for example, the The bias $p_{t-\ell} - p_t$ will be generally



(a) All deaths after ℓ days. HFR ratios equivalent; plotting delays of $\ell = 14$ and 28 days. (b) Changing primary incidence. Plotting bias of lagged and convolutional ratios.

Figure 5: Toy examples of biased severity rates.

tends to be larger when $\ell = 28$ versus $\ell = 14$. This supports the general overarching idea that estimates with heavier-tailed delay distributions tend to have more bias.

Now to elucidate the relationship between primary incidence and bias, let us consider a delay distribution π which places half its mass at lag 0, and the other half at lag q . Then the bias (6) has magnitude:

$$|\text{Bias}(\hat{p}_t^\gamma)| = \frac{\frac{1}{2}|X_t(p_t - p_t) + X_{t-q}(p_{t-q} - p_t)|}{\frac{1}{2}(X_t + X_{t-q})} = \frac{|p_{t-q} - p_t|}{1 + X_t/X_{t-q}}.$$

In other words, the absolute bias is monotonically decreasing in X_t/X_{t-q} , the proportion change in primary incidence. Rising primary incidence ($X_t/X_{t-q} > 1$) yields less bias, while falling levels yield more.

Figure 5b displays this setting with $q = 10$. Rising hospitalizations are defined as $X = \sigma(s) * 9000 + 1000$, where σ is the sigmoid function and s takes 300 evenly spaced steps from -9 to 7. These quantities are subsequently reflected to express a decline. The true HFRs fall from 0.5 to 0 over the same number of even steps. Accordingly, the absolute bias of the convolutional ratio is $c_q \frac{X_{t-q}}{X_{t-q} + X_t}$, where $c_q \approx 0.0167$. Shown in red, it dips as hospitalizations rise, and rises as they fall.

The figure also plots with lagged ratio with $\ell = \frac{q}{2}$, the mean of the delay distribution. When daily hospitalizations are close to constant, the two estimators converge towards the same ratio. During periods of change, however, the lagged estimator has different bias. It first moves upwards — the opposite direction as the convolutional bias — with far greater magnitude. This can be explained by the ratio $A_t^\ell = \frac{X_{t-2\ell} + X_t}{2X_{t-\ell}}$ from Proposition 2. As hospitalizations begin to steeply rise, $X_{t-2\ell}$ and $X_{t-\ell}$ are similar, but $X_t > X_{t-\ell}$. Hence, $A_t^\ell > 1$, contributing positive bias to both the oracle and misspecification terms. As hospitalizations level out near the top, $A_t^\ell < 1$, hence the bias falling lower. The opposite pattern occurs as hospitalizations fall.

B Alternative data sources

B.1 Retrospective deaths

JHU aggregated daily deaths in real time, aligned by the date they were reported. In contrast, the National Center for Health Statistics (NCHS) provided weekly totals of deaths aligned by occurrence, which were not available in real time. Intuitively, the delay which relates hospitalization to death occurrence should have a lighter tail in comparison to that relating hospitalization to death report. Therefore, since that heavier-tailed delays generally introduce greater bias, we would expect the ratio estimates computed from JHU deaths to

have greater bias than those from NCHS deaths. Figure 6 shows that this is indeed the case. NCHS data, which was only available in retrospect, leads to lagged HFR estimates with substantially less bias.

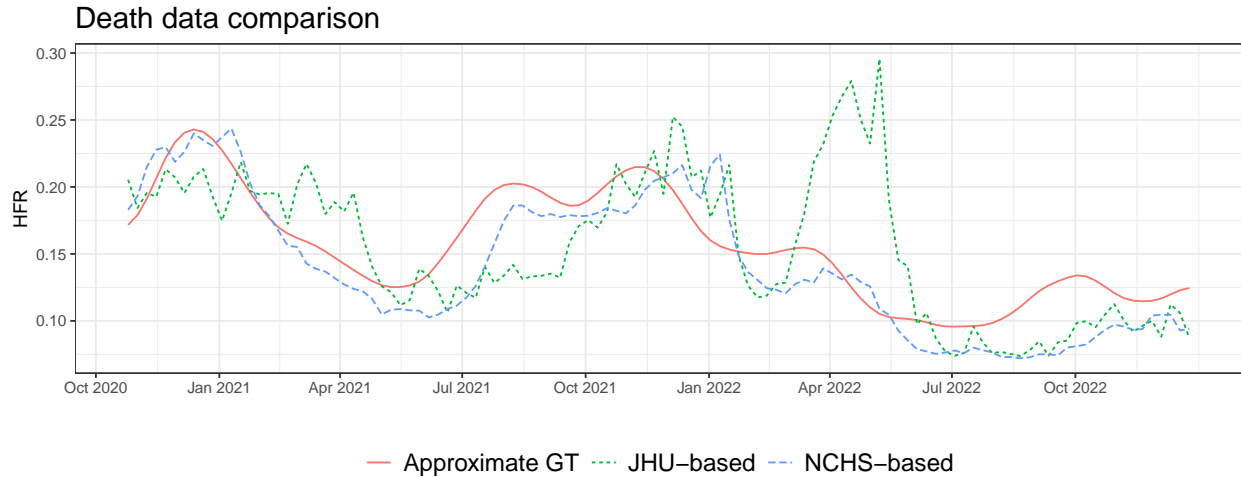


Figure 6: Comparing lagged ratios based on data from JHU versus NCHS.

B.2 Alternative ground truth

We consider two alternative approaches to approximate the ground truth HFR curve, over the COVID-19 pandemic. The first is simply to use the lagged ratio based on NCHS data. As discussed above, this benefits from a lighter-tailed delay distribution than JHU data. Further, as we are looking to approximate ground truth in retrospect, we modify this estimator to be forward-looking: $\hat{p}_t^\ell = Y_{t+\ell}/X_t$. The second approach we consider is to compute a single HFR by dividing total deaths by total hospitalizations in each major variant period, and then create a smooth curve by mixing these per-variant HFRs by estimates of the proportion of variants in circulation, obtained from CoVariants.org (Hodcroft, 2021). We only consider the four largest variants: the original strain, Alpha, Delta, and Omicron. However, because Omicron began with an enormous surge that quickly subsided, we split it into early and late periods, following (Adjei et al., 2022).

Figure 7 displays these two alternative ground truth curves, alongside that obtained from NCHS. They have nontrivial differences in magnitude, but reassuringly, the three curves move more or less in conjunction.

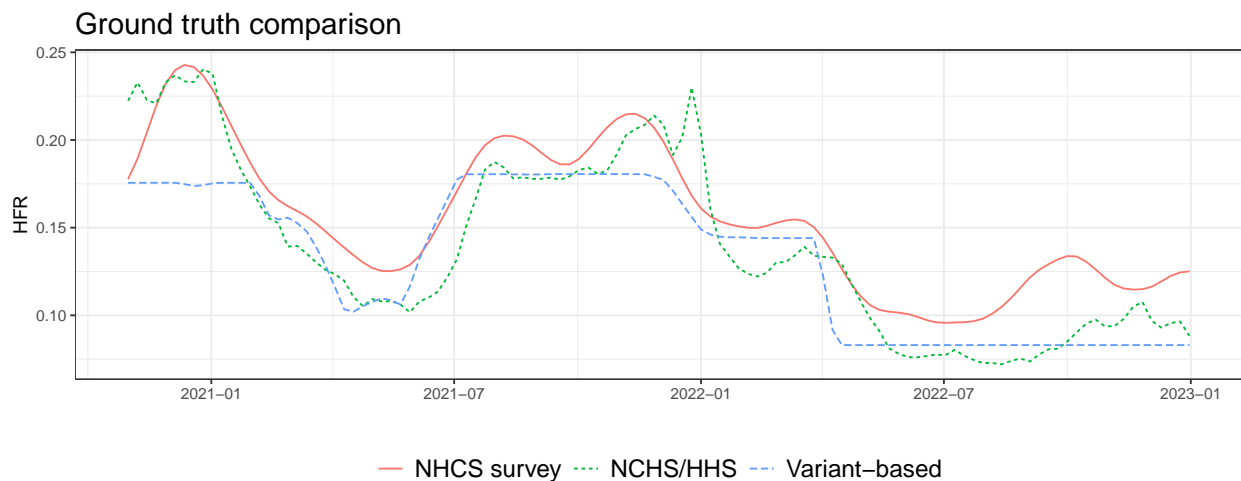


Figure 7: Comparing methods for approximating ground truth HFR.

The retrospective NCHS ratio is still subject to statistical bias (similar to (8)); the variant-based HFR curve is flatter, as it does not account for other sources of ~~(potential)~~ potential variability in the underlying severity rate.

C Robustness checks

C.1 Real-time versus finalized data

Recall, the results in Section 3.1 use hospitalization and death counts available in real time. To investigate the sensitivity of our findings, we recompute the lagged and convolutional ratios, this time using finalized counts. Figure 8 shows the real-time and finalized estimates track one another very closely. Therefore, the observed bias in Figure 3 cannot be attributed to real-time reporting quirks.

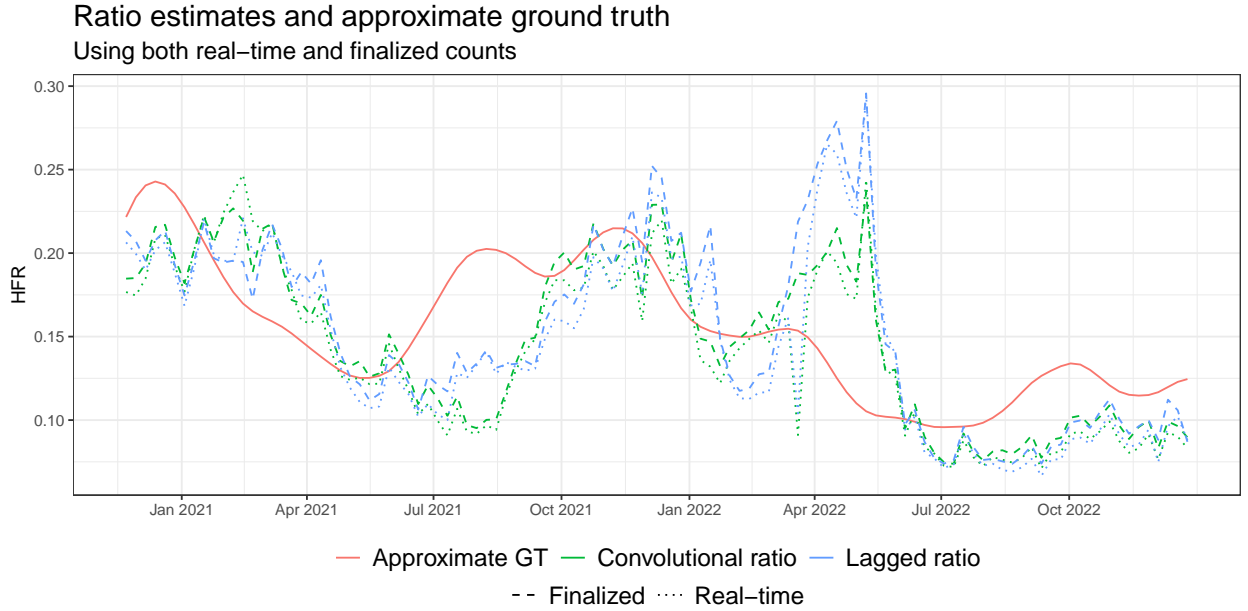


Figure 8: Comparing estimates based on real-time versus finalized counts.

C.2 Hyperparameters

We evaluate the robustness of our findings against choices of hyperparameters. First, we analyze smoothed versions of the ratio estimators, where we smooth the numerator and denominator separately:

$$\hat{p}_t^{\ell,w} = \frac{\sum_{s=t-w+1}^t Y_s}{\sum_{s=t-w+1}^t X_{s-\ell}},$$

$$\hat{p}_t^{\gamma,w} = \frac{\sum_{s=t-w+1}^t Y_s}{\sum_{s=t-w+1}^t \sum_{k=0}^d X_{s-\ell-k} \gamma_k}.$$

Figure 9 shows the results for varying window lengths $w > 0$. The results are very similar, indicating the bias does not disappear when smoothing over a longer history.

We next examine the time-to-death hyperparameters: The lag for the lagged ratio and delay distribution for the convolutional ratio. Figure 10 displays lagged HFR estimates where the lag ℓ ranges from 2 to 5 weeks. Unlike the window size, changing this parameter leads to notably different behavior. Some choices of lag are better than others; a 28-day lag, for example, falls appropriately in winter 2021, and rises less slowly during Delta. However, all are biased to varying degrees, most notably the huge spurious surge in spring 2022.

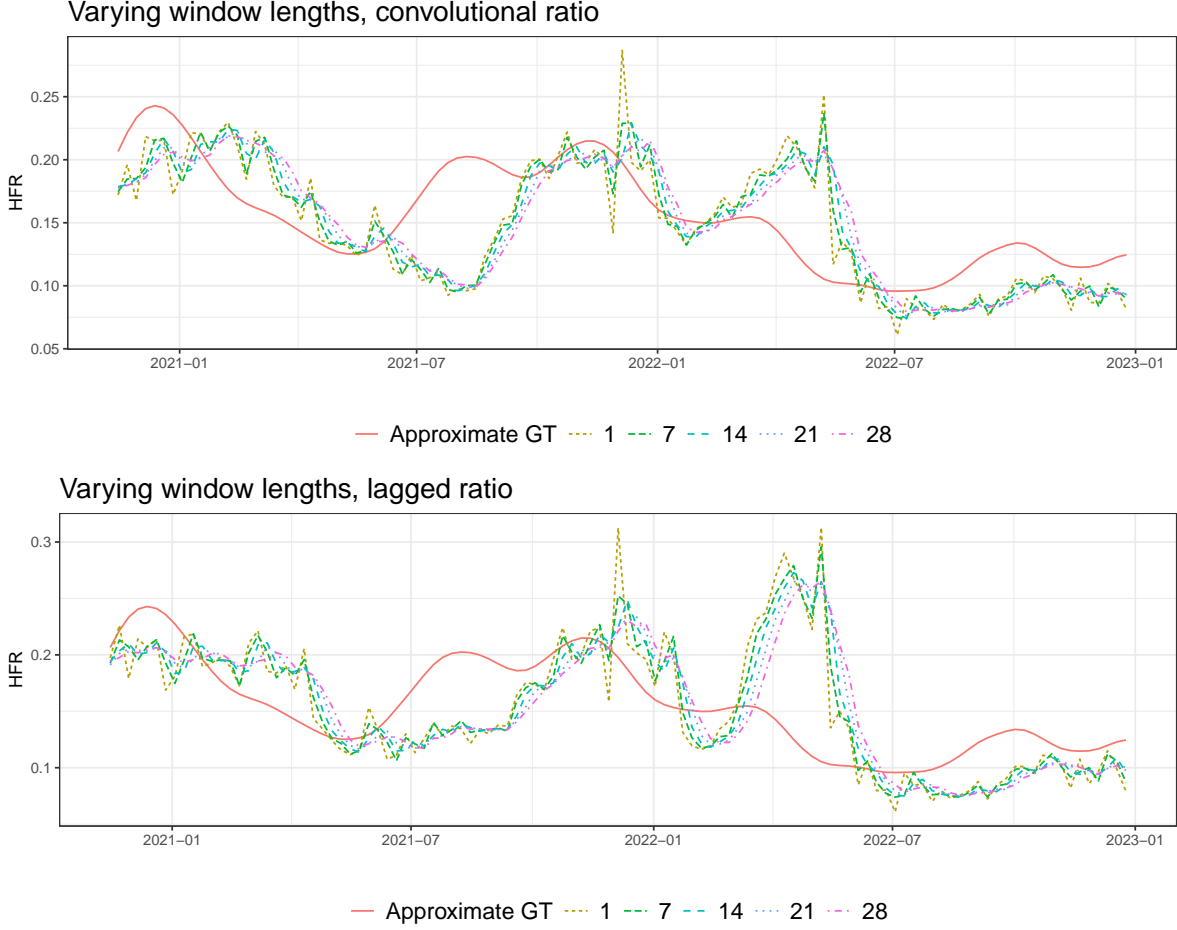


Figure 9: Comparing different choices of window length in post-smoothing.

Figure 11 compares the performance of the convolutional ratio across different choices of delay γ ; we kept the discrete gamma shape for each, but varied the mean and standard deviation. We investigated a standard deviation equal to 90% of the mean, and also a more compact delay with standard deviation equal to 70% of the mean. All resulting HFR estimates are significantly biased. Regardless of delay distribution, the ratios are negatively biased during the onset of Delta, and surge after the peak of Omicron. This indicates the bulk of the error is fundamental to the estimator, and cannot be attributed to model misspecification.

C.3 State-level results

We repeat our analysis the six large US states, finding similar trends. The NHCS survey was conducted on a subset of hospitals meant to represent the US at large, so for the state-level approximate ground truth, we therefore use the forward-looking lagged ratio computed using NCHS deaths, as discussed above. Figure 12 compares this rough ground truth to the real-time convolutional and lagged ratios. For each state, we select the lag for the approximate ground truth curve to maximize cross-correlation between hospitalizations and NCHS deaths, and the lag in the real-time lagged ratio to maximize cross-correlation between hospitalizations and JHU deaths. We then use a discrete gamma distribution with mean equal to the latter lag, and standard deviation 90% of its mean, for the convolutional ratio.

Several states display similar biases to the US as whole (Figure 3). Estimates in California, Texas, and Florida are all slow to detect the uptick in HFR during Delta; they also spike during Omicron in California, and to a lesser extent Florida. Note these states are the ones with the largest cross-correlation optimal lags, an estimate of the average time-to-death. In contrast, New York, Pennsylvania, and Illinois have mean delays

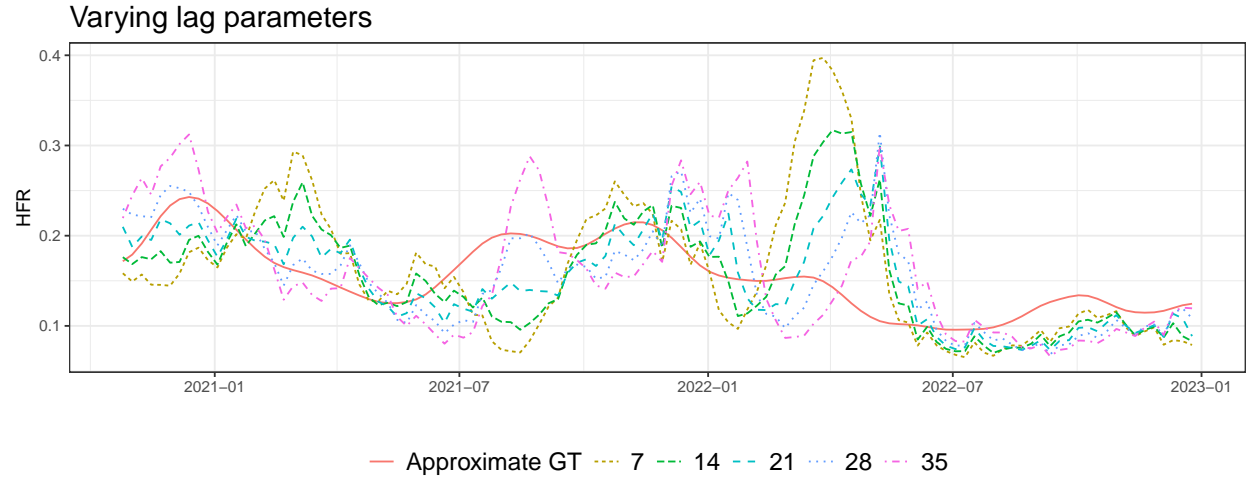


Figure 10: Comparing different choices of lag parameter in the lagged ratio.

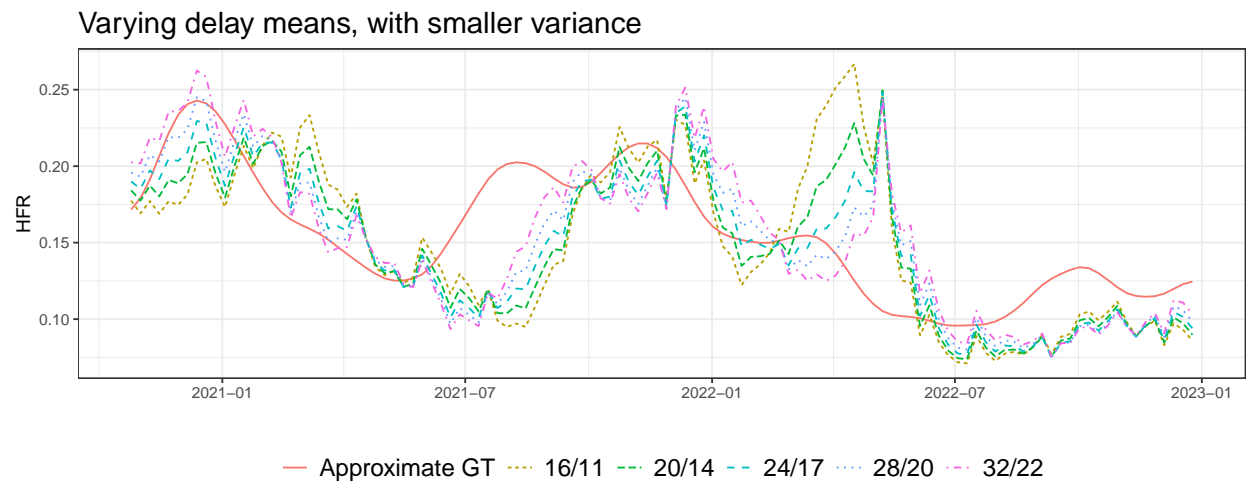
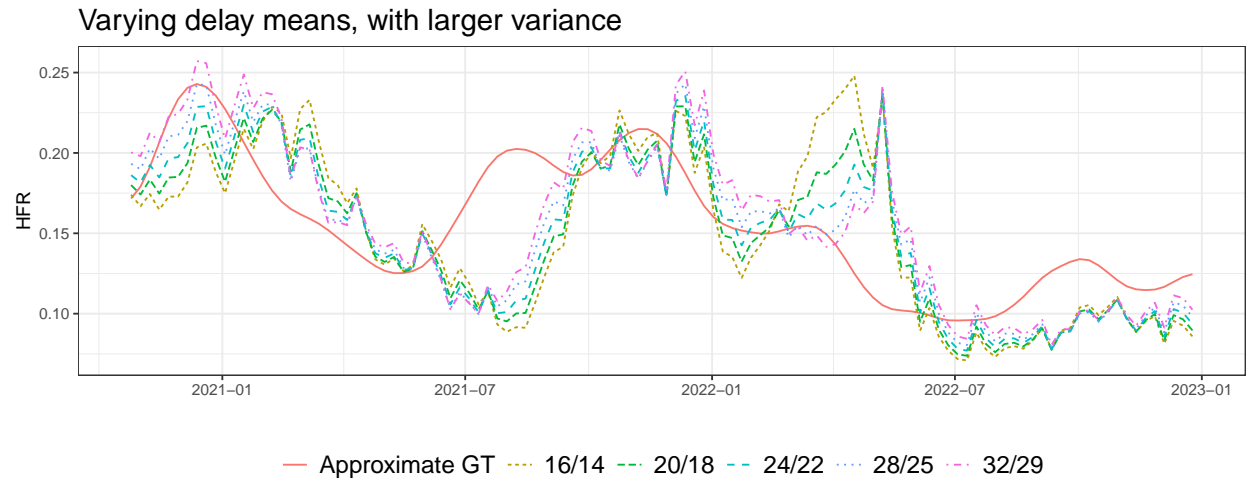


Figure 11: Comparing different choices of delay distributions in the convolutional ratio. The top panel shows gamma distributions whose standard deviation is 0.9 times the mean, versus 0.7 times the mean the bottom panel. The legend labels reflect the mean/standard deviation.

Ratio estimates and approximate ground truth

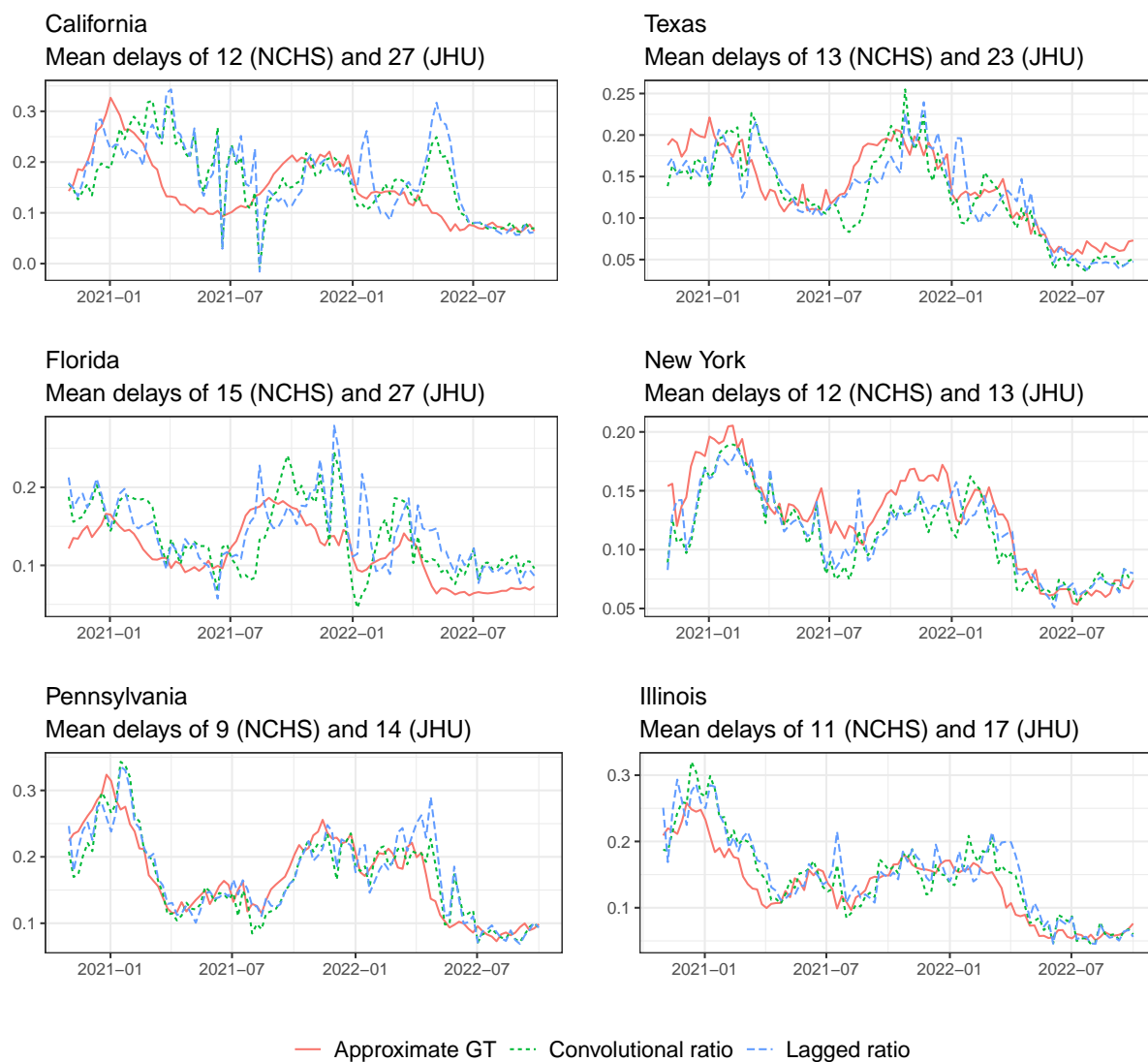


Figure 12: Comparing ratio estimates for individual US states.

of at most 17. Their HFR estimates are still biased, but overall less so. This once again emphasizes the role of the delay in bias. The takeaway: fatality ratios are generally less trustworthy in states that take longer to report deaths.