Evaluating the use of the reproduction number as an epidemiological tool, using spatio-temporal trends of the Covid-19 outbreak in England

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Abstract

*Background*

The time-varying reproduction number (Rt) can be used to assess changing transmission dynamics during an epidemic outbreak. However, methods and data sources for estimating Rt vary. Nonetheless, one might expect all methods toshould in principle arrive at the same estimate when applied to one population given some true rate of transmission in that population. This study explores whether Rt estimates of Covid-19 remain consistent and comparable when derived from different data sources using a standardised approach.

*Methods*

We estimated and compared differences in time-varying Rt using publicly available sources of time-series count data for confirmed Covid-19 cases in England. These included: test-positive cases via public and private laboratories; hospital admissions; and all reported confirmed deaths, over March through August 2020.

*Results*

Estimation of Transmission potential appeared to varidy by data source despite having been estimated using the same method and over the same epidemic, time period, and population.  Rt estimates derived from test-positive cases were rarely entirely consistent with estimates from hospital admissions or deaths at any point in time. The extent of inconsistency itself varied over time, both towards and away from parity of Rt estimate. Spatially, these patterns were consistent across regions when using hospital admissions and deaths data to derive Rt. Potential mechanisms driving observed differences may include changing transmission patterns in sub-populations, and artefacts in data collection, reporting, or estimation methods.

*Conclusions*

We conclude that the data source used to estimate Rt has an important and potentially useful influence on resulting transmission estimates. This influence may reflect different epidemic dynamics in sub-groups of the general population. This has implications for the selection of data when estimating Rt estimation, for the communication of Rt estimates used in policy, and for detecting real-time transmission in vulnerable populations.

Keywords

Introduction

From its emergence in 2019, the novel coronavirus SARS-CoV-2 had caused over six million cases of disease (Covid-19) worldwide within six months [1]. This prompted global policy interventions to prevent continued transmission, with widespread temporary bans on social interaction outside the household [2,3]. Introducing and adjusting such policy measures depends on a value judgement in balancing continued transmission potential with the multidimensional consequences of interventions. It is therefore critical to inform the implementation of policy measures with clear and near real-time estimates of ongoing epidemic dynamics [4,5].

Such an understanding can be partly obtained from the numbers of confirmed cases and deaths due to the virus. Yet these numbers do not directly reflect current transmission potential, with delays from infection to displaying symptoms, then to reporting in official statistics gathered at the point of hospital admission, community testing, or death. Alternatively, an epidemic can be tracked in terms of transmission intensity by estimating the time-varying reproduction number (Rt, the average number of secondary infections generated by each new infectious case [6] on imputed infections. In principle, this provides a clearer picture of an underlying epidemic than using case counts. Estimating R quantifies relative transmission potential over time, accounting for the time taken from becoming infected to being infectious to others, and independent of reporting artefacts.

Different methods exist to model the reproduction number, and in the UK a number of mathematical and statistical methods have produced estimates used to inform policy [7–10]. For example, the incidence of transmission events can be estimated by taking some lagged time-series indicator of infection, such as symptomatic cases, and working back through the biological, behavioural, and reporting processes that take place after infection to arrive at a distribution of infections and transmission [8,11].  However, there is extensive variation among methods even within the same model family. This can include the source and handling of data used to parameterise infection counts, and key assumptions including the generation time or the degree of variation that Rt can display over time [12–17].

One major source of difference is in the source of data used as a reference point for modelling earlier transmission events [18]. In England, three publicly available reporting pathways identify confirmed cases of Covid-19. Recent cases are notified by laboratories testing for cases in the wider community, and separately by hospitals, from new confirmed diagnoses among admissions. Meanwhile, deaths with confirmed disease are notified from either local public health authorities, or from hospitals in which death occurred.

In theory, these three processes for generating data might be expected to be evenly distributed through the general population, all acting as lagged, partial indicators of transmission from which Rt can be estimated. Where resulting Rt estimates from each data source are not the same, this suggests that the proportion of cases which result in testing, hospital admissions, or deaths may have changed. This could be the case if, for instance, transmission increases among a younger population but remains stable among other ages. With younger cases less likely to require hospital admission or have fatal outcomes [19], then only an Rt derived from test-positive community cases would reflect this increase in transmission as long as testing covers the populations in which transmission occurs. The reverse would be true if there were an outbreak in a vulnerable subpopulation who are more likely to experience fatal outcomes [20]. If these differences by data source can be identified, this could provide a useful additional layer of real-time information about how transmission varies between sub-populations.

This approach suffers where it is unable to make strong or causal conclusions about varying transmission, given that data are noisy and assumptions about sampling and the representation of sub-populations remain implicit. An alternative way to explore differences in transmission would be to explicitly model varying assumptions about population structures and/or fit to multiple data sources while explicitly representing reporting processes. However, for rapid analysis during an outbreak, real-time analysis of Rt estimates is an efficient way to identify differences where these might have policy relevance, and we have used this extensively when providing Rt estimates to the Scientific Pandemic Influenza group on Modelling (SPI-M). This method is also useful for suggesting the comparability of existing Rt estimates.

In this study, we aim to compare regional Rt estimates of Covid-19 across England, using three sources of real-time public data. After assessing differences in Rt by data source, we identify why this variation may exist, and suggest that the usefulness of each data source depends on the purpose for which Rt is estimated.

Methods

Three sources of data provided the basis for Rt estimates. Public data were aggregated to seven English NHS regions. Data from other nations of the UK differed in both availability over time and in data collection and reporting practices. This made estimates incomparable with those from England, where the majority of cases had occurred [18].

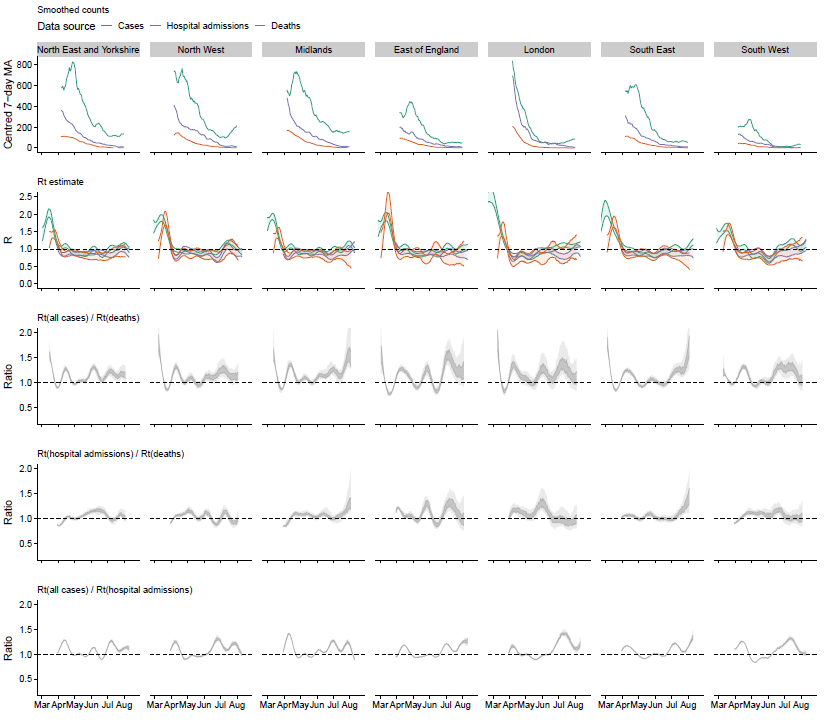
All data were publicly available and taken from the UK government source [18,21]. Time-series case data were available by specimen date of test. This was a de-duplicated dataset of Covid-19 positive tests notified from both NHS settings (Pillar One of the UK Government’s testing strategy, [22]) and by commercial partners in community settings outside of healthcare (Pillar Two). Hospital admissions were also available by date of admission, or by date of test if a patient had previously been in hospital. Deaths data were available by date of death, and included only those which occurred within 28 days of a positive Covid-19 test in any setting.

We estimated Rt using EpiNow2 version 1.1.0, an open-source R package [9]. This implements a fully Bayesian latent variable approach, which works as follows. Initial seed infections are combined with time-varying estimates of Rt, via an uncertain estimate of the generation time using the Cori et al approach [16]. These infection trajectories are then mapped to reported case counts by convolving over an uncertain incubation period and report delay, and then applying a negative binomial observation model combined with a day of the week effect. Temporal variation is controlled using a Gaussian process with a squared exponential kernel, with the length scale and magnitude estimated during the model fitting process.

We used a gamma distributed generation time with mean 3.6 days (standard deviation 0.7), and standard deviation 3.1 (SD 0.8; based on [9,23]), but refit using an incubation period. We set the incubation period to a log-normal distribution with mean of 5.2 (SD 1.1) and SD 1.52 (SD 1.1; based on [8,24]). Report delays included that from onset to case report, with a mean of 4 (SD 1.4) and SD 2.3 (SD 1.1), and a report delay from onset to death, with a mean of 9.9 (SD 1.1) SD 2.1 (SD 1.1). This implementation of EpiNow2 is similar to the one used for SPI-M Rt and short term forecast submissions by the authors. See [9] for further details on the approach and <https://epiforecasts.io/covid> for an example implementation.

We compared results by data source, by plotting by region over time for simple descriptive differences and taking ratios of the daily median estimate and upper and lower credibility intervals (50% and 95% CIs). We also explored the binary daily outcome of whether the median Rt estimate from one data source fell within the 50% CI for that day’s Rt derived from a different data source. The Rt based on deaths was also shifted one and two weeks ahead to test whether it lagged the Rt from admissions. This was summed across the time-series to create a percentage of days with consistent estimates to total days by region, with a standard deviation (SD) among regions. Code for sourcing and cleaning public data, estimating Rt, and comparing outputs, is freely available ([github.com/epiforecasts/rt-comparison-uk-public](https://github.com/epiforecasts/rt-comparison-uk-public)).

Results

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*Figure #1.  Daily counts in centred seven day moving average; estimates of Rt,, 90% credible interval; and ratios of respective Rt. Data sources include test-positive cases (“all cases”), hospital admissions, and deaths with a positive test in the previous 28 days, available up to the 26 August 2020. Shown over March through August 2020, for English NHS regions.*

*Rt estimation*

Across England, regional epidemic peaks occurred in early to mid-April (figure #1). At this point, all English regions saw higher transmission among test-positive cases compared to cases that resulted in either hospital admission or death. However, transmission estimated from all data sources rapidly declined to an average of one onward case per infection. To varying degrees, estimates from all data sources fluctuated around one until late July. From this point there appeared to be an uptick in Rt among any measure of cases in comparison to transmission estimated from cases which resulted in death.

In London and the East of England there appeared to be several small waves and troughs of transmission among cases that resulted in death, while transmission among cases resulting in either a test alone or hospital admission remained stable. However, the reverse was true in the North East and Yorkshire, where transmission among test-positive cases saw similar small waves compared to stable transmission among eventual fatalities. As a result, the ratio of transmission from cases compared to deaths was the least consistent over time.

*Between-estimate consistency*

Compared to estimates from hospital admissions or deaths, the Rt from test-positive cases fluctuated more rapidly over time. This made comparing transmission to that from other data sources more difficult. To measure consistency among estimates, the median point estimate of Rt from test-positive cases was compared with the credible intervals of the Rt estimates from hospital admissions and from deaths. On average, the median Rt from cases fell within respective 50% CIs for only one-fifth of the time-series (17% (SD 5%) and 22% (SD 8%) respectively, average of days over the time-series across regions). For example, over the first three weeks of July in London, the median transmission potential among test-positive cases appeared to be around 40% higher than the median transmission among cases resulting in hospital admission (a mean average ratio of 1.38, 90% CI 1.33-1.45, over that period).

Hospital admissions gave a more stable estimate over time, with Rt falling within the 50% CI of the Rt from deaths an average 41% (SD 9%) of the time. For the majority of the time-series, rates of transmission among hospital admitted cases were equivalent to transmission estimated from cases resulting in death, with a near 1:1 ratio from May through June. Rt estimates from deaths were hypothesised to be lagged behind Rt estimates from hospital admissions, because it is likely that the delay distribution from infection to either admission or death may have been mis-specified due to a lack of data. To explore this, estimates from deaths were shifted one and two weeks ahead and compared to admissions estimates. However, consistency between the two remained similar to non-lagged estimates (35% (SD 8%) and 24% (SD 7%) respectively).

Discussion

Using the same method, we have estimated the time-varying reproduction number over March to August across English NHS regions, using cases from hospital admissions, cases by lab report, and deaths. While theoretically these come from the same population, and therefore results could be expected to be consistent, in fact results differed depending on the source of data. This could arise from differing infection dynamics across the population, or misspecified delays in model estimation.

*Hypotheses*

Differences among Rt estimates by data source may give some insight into epidemic variation across the population. Each data source is likely to bias Rt estimates away from the general population and towards the specific sub-population in which the estimated infections arose and were detected. If sub-populations experience varying epidemic dynamics, then selecting one data source, or averaging separate Rt estimates into a combined estimate, would be unjustified and risk losing a potentially useful layer of information about uneven transmission.

For example, any difference in Rt from cases detected from laboratory testing compared to cases represented as newly diagnosed hospital admissions, might indicate a shifting epidemic where sources of transmission move between the community and within-hospital transmission. Alternatively, cases who are hospitalised are likely to be more severe than all cases who are tested. This severity could be due to other risk factors (such as age or sex) which have an independent and time-varying influence on transmission potential: for example, individual risk perception and resulting behaviour may change both with age and over time [25].

* Age dist of cases -> young people increasing ill -> higher test positive but no more admissions/deaths maybe. Indicates successful shielding if true.
* Further highlights we don’t really care about test positive cases only admissions (as similar to + lead to deaths). Care about test positive cases if predict deaths here you are saying not reliable.

These differences were only evident where Rt estimates were displayed individually by data source. Alternatively, varying epidemics in sub-populations could be addressed with mechanistic models that explicitly take into account transmission in different settings and are fitted to multiple data sources [26]. However, these require data to parameterise and may be complex to develop, and in the absence of data can introduce structural biases. Our approach contains few structural assumptions and therefore may be more robust when data are sparse or information is required in real-time.

Our results also suggested that Rt estimated from population testing was the least consistent in comparison to estimates based on more severe cases. This could be explained by changes in case sampling and detection, rather than actual transmission. For example, we might expect testing to scale up gradually over time, creating a linear divergence between Rt estimates from admissions and cases from wider testing. However, this linearity is not evident in our estimates. This could be due to rapid, inconsistent changes in testing, with expanded testing around policy targets or where a cluster of new, mild cases has been identified [27]. Our results support this explanation, with rapid oscillations in estimated transmission from test-positive cases not seen in estimates from more severe cases reported as hospital admissions or deaths.

An Rt from either hospital or tested cases was different again from an Rt taken only from cases where Covid-19 was fatal. For example, transmission among cases which eventually result in death may not be accurately reflected in other data sources, where cases may not receive hospital treatment. Where admissions and deaths vary, this suggests the proportion of cases resulting in death is different from the proportion admitted to hospital. This might indicate a vulnerable population with lower admission rates. For example, in England, cases in care homes were more likely to remain in the care home until death, compared to cases in the community who were more likely to be admitted to hospital before death [28,29]. Where the Rt estimated from deaths is greater than that derived from cases who may have survived, this might indicate a separate, and less controlled, epidemic with higher transmission intensity among those with higher case-fatality rates (for example, those in care homes), compared to those who are represented in lab testing or hospital treatment.

*Limitations*

Methodological artefacts may be influencing some part of these variations, rather than underlying differences in transmission. For instance, Rt estimates become increasingly uncertain with lower case counts. Further, estimated unobserved infections were mapped to reported cases or deaths using two uncertain delay distributions: the time from infection to test-positive cases or admissions, and a longer delay from infection to death.

A mis-specified delay distribution would have created bias in the temporal distribution of all resulting Rt estimates. For example, if our specification of the delay distribution from infection to death from Covid-19 was longer than the true average time from infection to death, then our estimated dates of infection, and Rt, derived from deaths data would on average be shifted too far back in time compared to the true infection curve. However, there is currently very little UK data on the time from case onset to confirmation of Covid-19 in any of a positive test, hospital admission, or death. We mitigated this by using a subsampled bootstrap, adding extra uncertainty to the sampled delays. This remains a major contribution to uncertainty in both the central estimates, and their validity.

The data sources themselves may also have been inaccurate or biased, which would change the representation of the population we have assumed here. For example, the population characteristics of hospital admissions from Covid-19 may have changed over time, if clinical criteria for admission changed with better understanding of disease or hospital capacity.

In this analysis we have described trends in Rt across data sources, but cannot directly explain them. While we have suggested various hypotheses above, we are unable to test these without finer-scale data and a clear, consistent definition of the criteria for case detection in each data source.

*Conclusions and recommendations*

Despite the notional separation of data-generating processes from actual transmission, this work suggests the need to consider the influence of potential biases and sampling discrepancies in case detection. Therefore it may be important to base comparisons of Rt estimates on consistent and well-understood processes of case detection over time. More generally, there is no clearly superior choice of data source for estimating Rt. Each source of confirmed cases of Covid-19 considered here (all tested cases, moderately severe cases as hospital admissions, or fatalities), may represent either a different transmission rate or differing impacts of a disease on a subpopulation. This means there is additional useful information when they are considered in tandem, creating an overall picture of epidemic dynamics within the population as a whole.

This might inform the selection of data source depending on the use-case of the Rt model. For example, Rt estimates from hospital admissions may be more sensitive to recent changes in transmission than deaths, given a shorter time from infection to reporting. However, Rt estimates from confirmed deaths may be more robust to extraneous influences such as hospital admissions capacity or case detection and testing regimes, although death figures themselves can be subject to changes in, for example, post-mortem testing practices, or recording [30,31]. Therefore, the choice of data source in estimating Rt could be designed to reflect the purpose and context in which the model is built and used.

Similarly, the use of Rt estimates in policy could be more carefully informed by the specific advantages and limitations that each data source represents. If each data source gives a different estimate of Rt, then merging these into a combined average that is reported as the “true” Rt figure would conflate populations and would not necessarily be any more representative of transmission intensity in the general population. This might also unnecessarily inflate uncertainty. It would then be unclear what any policy recommendation should be and for whom. In contrast, keeping estimates separate could also provide useful information, indicating variation in transmission intensity among sub-populations. This could also help to clarify and target policy depending on the actual transmission intensity by sub-population.

For future work estimating Rt, any model that fits to data may benefit from comparing sensitivity to different data sources. Specifically this could include extending the comparison of Rt by data source to other countries, and clarifying the potential for comparing Rt estimates in real-time tracking of outbreaks. Further work should also explore the inconsistencies in case detection over time and space, where a cluster of cases leads to a  highly localised expansion of testing, creating an uneven spatial bias in transmission estimates.

Tracking differences in Rt estimates by data source may have potential as a useful tool in real-time epidemic monitoring. Our approach is simple to deploy and scale over time and space, using existing open-source tools, and all code and estimates used in this work are available to be used or re-purposed by others. This can quickly identify patterns in developing epidemics that might require further investigation and early policy intervention.

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