An efficient, objective index for predictive disease incidence ranking of COVID-19 vaccine trial sites

Authors: Bradley G. Wagner[1*], Prashanth Selvaraj[1] and Stewart T. Chang[1]

November 13th, 2020

1. Institute for Disease Modeling, Global Health, Bill and Melinda Gates Foundation

* Contact author: **bwagner@idmod.org**

What is the purpose of this report: The aim of this report is to provide a validated method and predictive subnational results for selection of vaccine-trial sites based on future COVID-19 disease incidence. The method implicitly accounts for the time-gap between site selection and trial initiation. The output of the analysis is a normalized, ranking index we denote as "G."

Target audience for report: The intended audience includes vaccine developers and partner Contract Research Organizations (CROs) involved in site preparation for phase 3 COVID-19 vaccine efficacy trials.

Geographic areas represented in analysis: Areas represented in the analysis were chosen both due to the availability of validated COVID-19 disease incidence data as well as representation in the COVAX trial site network. Future updates may expand this analysis based on availability of (subnational) COVID-19 disease data and the needs of CROs and vaccine developers. Updates are intended to be on a two-week cadence.

How to read this document:

Geographic regions for which we have computed the predictive index G are denoted in Table 1. For each country the geographic level of estimation is noted (country or state/province).

Values, the dates used in computation, and dates for the intended prediction are given in Table 2. In addition to **the non-technical summary explaining interpretation and use of the index,** a complete description of methods, use, and limitations is given in the Methods section.

Validation of the method is shown in section: Validation. The validation done for counties over 500,000 population in the United States using reported COVID-19 disease incidence for the month of August 2020. A full definition of the components of the validation process is given in the Definitions section.

In addition to Table 2, maps showing the geographic distribution by state/province for each country are given in Figures section 1 (Spatial heterogeneity).

Locations where we have computed historical reproduction numbers (Rt) are shown in Figure section 2: Historical Reproduction Numbers. Those not shown have been taken from those computed by Epiforecasts[1] using the same methodology (and the equivalent curves can be accessed within these references).

Non-technical summary: We compute a normalized index (ranging from 0 to 1) designed to give a ranking prediction for trial sites in terms of confidence in COVID-19 case incidence beginning after a two-month lag from the selection date (corresponding roughly to site prep time). Higher values indicate more confidence in sustained transmission of the pathogen and therefore higher COVID-19 disease incidence. The method is based on historical reproduction numbers (Rt) which may be estimated by any method; however those presented in this report have been estimated from historical disease incidence data.

The index represents the average probability over a defined historical look-back time that the epidemic is in an exponential growth phase for any window corresponding to a typical trial-duration (chosen here to be 2 months). The historical look-back period is context dependent. For example, if novel interventions will reduce disease incidence, the relevant historical window will be reduced as historical performance in the early epidemic becomes less relevant to future control.

For example, an index value, $G > 0.5$ implies that over the defined historical look-back period, the epidemic was in an exponential growth phase for most of the time period. Note that the **index is continuous,** therefore it can be useful to consider the relative difference in the index in addition to using it to form a ranking.

Note that the index was chosen parsimoniously in order to minimize bias introduced by changes in surveillance occurring over the course of the epidemic that may cause transient changes in Rt. Therefore, the index tracks confidence in growth or decay but would not distinguish between two regions Rt = 2.3 and Rt=2.4 as both are in growth phases.

The index is designed to be used as a **rule-in** tool (see Definitions) only, as low index values may simply represent uncertainty due to low surveillance. In order to use as a rule-out it is also necessary to examine the uncertainty in Rt estimates simultaneously. **We present only the rule-in analysis.**

The index is based on two primary assumptions:

1. Past ability to control the epidemic is a good indicator of future ability to control the epidemic
2. Maximizing case-incidence can be thought of as optimizing the time spent in an exponential growth phase.

We note that assumption 2 is particularly applicable when seroprevalence is low, however the index will still distinguish (subject to unbiased disease-surveillance) epidemic decline due to high seroprevalence.

What the index does not explain is **endemic-SARS-COV-2 transmission** in which dynamics would be sustained by entry of new susceptible individuals into the population via births and decaying immunity among older exposed individuals. Currently (November 2020) we are not yet at this point in the pandemic.

Table 1: Countries and regions represented in the trial site analysis and geographic level of analysis. References indicate where the collated disease incidence data underlying the model was obtained if applicable.

Country	Geographic level of analysis
Argentina	subnational[2]
Belgium	subnational
Brazil	subnational[3]
Colombia	subnational[3]
Gambia	national[4]
India	subnational[3]
Indonesia	subnational
Mexico	subnational[4]
Pakistan	subnational[4]
United Kingdom	subnational[3]

Table 2: Index Values by Region. G-index values computed by region. The lookback period used is indicated as well as target trial start date. Here the target trial start date is 2 months from the decision point (the last data collected) as was empirically validated (see Validation section and Definitions). Maps showing the geographic distribution of the index by country are given in section Figures: Spatial

Heterogeneity. Historical Rt estimates for each region are shown in section Figures: Historical Rt estimates. Note that look-back periods and target trial dates were chosen at the country level.

Country	Region	Index Value (G)	Lookback period	Target Trial Start Date
Argentina	**Chaco**	**0.989637**	**20-08-09 - 20-10-09**	**20-12-09**
Argentina	Rio Negro	0.922339		
Argentina	Tucuman	0.897289		
Argentina	Neuquen	0.866284		
Argentina	Cordoba	0.862309		
Argentina	San Luis	0.782485		
Argentina	Formosa	0.870725		
Argentina	Santiago del Estero	0.864504		
Argentina	Santa Fe	0.715519		
Argentina	Chubut	0.901497		
Argentina	Misiones	0.930672		
Argentina	Tierra del Fuego	0.711411		
Argentina	Entre Rios	0.602428		
Argentina	Corrientes	0.743995		
Argentina	Mendoza	0.59185		
Argentina	La Rioja	0.587658		
Argentina	Salta	0.487292		
Argentina	La Pampa	0.673786		
Argentina	Catamarca	0.662824		
Argentina	San Juan	0.553809		
Argentina	Buenos Aires Province	0.293879		
Argentina	Jujuy	0.287858		
Argentina	City of Buenos Aires	0.189637		
Belgium	**VlaamsBrabant**	**0.897322**	**20-08-05 – 20-10-05**	**20-12-05**
Belgium	BrabantWallon	0.830622		
Belgium	Hainaut	0.817898		
Belgium	Limburg	0.827329		
Belgium	Namur	0.690436		
Belgium	Luxembourg	0.772605		
Belgium	Brussels	0.637608		
Belgium	OostVlaanderen	0.624335		
Belgium	WestVlaanderen	0.685778		
Belgium	Liege	0.553027		
Belgium	Antwerpen	0.506354		
Brazil	**Amazonas**	**0.669936**	**20-08-28 – 20-10-28**	**20-12-28**
Brazil	Espirito Santo	0.705443		

Brazil	Sergipe	0.506424		
Brazil	Rio de Janeiro	0.526718		
Brazil	Rio Grande do Sul	0.454478		
Brazil	Santa Catarina	0.527224		
Brazil	Rio Grande do Norte	0.461819		
Brazil	Roraima	0.509008		
Brazil	Ceara	0.383401		
Brazil	Para	0.424367		
Brazil	Goias	0.269064		
Brazil	Amapa	0.320619		
Brazil	Alagoas	0.35644		
Brazil	Acre	0.294876		
Brazil	Bahia	0.338135		
Brazil	Piaui	0.235102		
Brazil	Pernambuco	0.198636		
Brazil	Mato Grosso do Sul	0.154976		
Brazil	Mato Grosso	0.132999		
Brazil	Minas Gerais	0.107998		
Brazil	Parana	0.112793		
Brazil	Tocantins	0.155129		
Brazil	Rondonia	0.15801		
Brazil	Distrito Federal	0.107406		
Brazil	Sau Paulo	0.096689		
Brazil	Paraiba	0.082121		
Brazil	Maranhao	0.056933		
Colombia	**Casanare**	**0.988298**	**20-08-27 – 20-10-27**	**20-12-27**
Colombia	Quindio	0.982653		
Colombia	Caldas	0.95237		
Colombia	Huila	0.864273		
Colombia	Arauca	0.856194		
Colombia	Boyaca	0.793081		
Colombia	Risaralda	0.639379		
Colombia	Antioquia	0.760729		
Colombia	Tolima	0.613276		
Colombia	Valle del cauca	0.700751		
Colombia	Guaviare	0.557836		
Colombia	Amazonas	0.601313		
Colombia	Atlantico	0.591293		
Colombia	Norte de santander	0.597701		
Colombia	Archipielago de san andres providencia y santa catalina	0.439534		
Colombia	San andres y providencia	0.358722		
Colombia	Vichada	0.349922		

Colombia	Vaupes	0.336193		
Colombia	Meta	0.335496		
Colombia	Cauca	0.329761		
Colombia	Caqueta	0.383793		
Colombia	Cundinamarca	0.386274		
Colombia	Santander	0.308711		
Colombia	Bolivar	0.304841		
Colombia	Sucre	0.308509		
Colombia	Bogota	0.363976		
Colombia	Cesar	0.241716		
Colombia	Narino	0.257426		
Colombia	Putumayo	0.181388		
Colombia	Choco	0.190034		
Colombia	La guajira	0.096913		
Colombia	Magdalena	0.122412		
Colombia	Cordoba	0.060002		
Colombia	Guainia	NA		
Gambia	**The Gambia**	**0.090153**	**20-08-19 – 20-10-19**	**20-12-19**
India	**Rajasthan**	**0.974266**	**20-08-14 - 20-10-14**	**20-12-14**
India	Kerala	0.951782		
India	Meghalaya	0.901641		
India	Arunachal Pradesh	0.802456		
India	Lakshadweep	0.781583		
India	Karnataka	0.770025		
India	Manipur	0.761661		
India	Madhya Pradesh	0.705975		
India	West Bengal	0.677397		
India	Sikkim	0.667221		
India	Chhattisgarh	0.623		
India	NCT of Delhi	0.583251		
India	Gujarat	0.575622		
India	Himachal Pradesh	0.529225		
India	Odisha	0.47682		
India	Haryana	0.457721		
India	Jammu and Kashmir	0.452309		
India	Goa	0.445062		
India	Uttarakhand	0.429534		
India	Nagaland	0.459068		
India	Punjab	0.411324		
India	Maharashtra	0.409806		
India	Mizoram	0.400686		
India	Chandigarh	0.384075		
India	Uttar Pradesh	0.339719		

India	Telangana	0.334627		
India	Puducherry	0.326916		
India	Tripura	0.320656		
India	Jharkhand	0.299488		
India	Assam	0.280098		
India	Andaman and Nicobar	0.263922		
India	Andhra Pradesh	0.201325		
India	Tamil Nadu	0.190701		
India	Bihar	0.179313		
India	Dadra and Nagar Haveli	0.024696		
Indonesia	Jakarta	0.987475	**20-07-15 – 20-09-15**	**20-11-15**
Mexico	**Mexico City**	**0.755289**	**20-08-09 – 20-10-09**	**20-12-09**
Mexico	Jalisco	0.59935		
Pakistan	**Sindh**	**0.500958**	**20-08-09- 20-10-09**	**20-12-09**
United Kingdom	**London**	**0.979071**	**20-08-25 - 20-10-25**	**20-12-25**
United Kingdom	Wales	0.97858		
United Kingdom	South West	0.969551		
United Kingdom	East of England	0.938264		
United Kingdom	East Midlands	0.933359		
United Kingdom	Scotland	0.920498		
United Kingdom	South East	0.906164		
United Kingdom	North East	0.873385		
United Kingdom	North West	0.867818		
United Kingdom	Northern Ireland	0.779647		
United Kingdom	Yorkshire	0.873385		
United Kingdom	West Midlands	0.933359		

Technical Details:

Problem statement: Motivated by the constraints of vaccine site selection can we design a framework which would prioritize sites based on future COVID-19 disease incidence over the period of 2-3 months

from the time-point of decision making. This framework should be robust to misclassification of low incidence sites as high incidence sites (type-2 error). Ideally methods should rely only on routinely collected historical data (e.g., disease incidence, testing volume) and be robust with respect to changes in surveillance happening over the course of the epidemic. Finally, it should be applicable at the subnational level and be suitably computationally efficient to allow for multi-country subnational updating at weekly or bimonthly intervals.

Approach: For subnational region we construct a normalized index G ($G \in [0,1]$) based on historical estimates of the effective SARS-CoV-2 reproduction number R_t up to the decision-making point. We define G such that higher values indicate a more confident site choice while lower scores represent less confidence. In its utilization of historical R_t the method is at minimum dependent on historical (daily) COVID-19 disease incidence data. It should be noted where there are differences in historical estimates of R_t from different methods, the index may be used to give weighted or ensemble estimates. These methods are limited to prioritizing for disease incidence; other factors such as severity of cases/presence of comorbidities, health access, and presence of competing trials within sites should be addressed separately.

Methods:

The index is defined as the following:

$$G = \frac{1}{\mathrm{T}} \min_{t_0 \in I} E\left(\int_{t_0}^{t_0 + T} 1\{R_t > 1\} dt \right)$$

- I represents the historical look back period over which we consider data. This may go back to the beginning of the epidemic or be weighted towards or include only more recent data. 1{Rt > 1} is an indicator function such that it takes on the value 1 if Rt > 1 and 0 otherwise.
- T represents the "ideal" duration of trial. For the purposes of results shown later this is chosen to be 2 months.
- R_t represents the time dependent effective reproduction number
- E represents the expectation taken over all trajectories inferred for R_t
- The minimum value is taken over any window of length T contained in the historical lookback period.

We note that in practice the integration is typically taken over daily case data.

Explained heuristically, the integrand scaled by the factor of 1/T describes the proportion of time that the epidemic is in an exponential growth phase for a given period of length T. This is averaged according to the probability of each Rt trajectory. The minimum across all possible intervals is then chosen to give the best (according to the average as defined) period of epidemic control in any such interval over the historical lookback period. If the best period of control historically remains mostly in a growth phase on average ($G > 0.5$) we may consider this a consistent candidate for a trial site.

Motivation and Assumptions:

The motivation for this method, underlying assumptions and appropriate use cases can be summarized as follows (key assumptions in bold font):

- **Historical ability to control the epidemic is the best indicator of future ability to control. This index will represent a composite of individual behavior, public policy and interventions and setting specific epidemiological factors including seroprevalence.**
- **Optimizing for COVID-19 disease incidence is dependent on selecting for periods of rapid exponential growth**. **This is most valid when herd immunity is low. Epidemic peaks and troughs, at this point in the epidemic, are driven primarily by policy and behavior and not herd immunity. See Figure 1.**
- **The time window gap between deciding on trial sites and study enrollment/ data collection is short enough that we do not expect substantial changes in seroprevalence over the gap period, however it is long enough for extrapolation of curve-fitting models (and raw extrapolation of mechanistic models without additional future assumptions) not to be appropriate. Gaps considered in validation were approximately 2 months in duration.**
- Computation of the index requires historical data of at least an interval T, so the method will not make predictions of future outbreaks in areas which there has not been previous observed circulation of the pathogen.
- The index is specifically constructed for site selection as a defensive index, it is not a forecasting model for every location. If an index value is high (close to 1) this indicates that an area's best period of control was still largely a period of growth. Therefore, it represents a confident choice based on past behavior. A low index value may simply represent a wide uncertainty bound in R_t which can result from limited surveillance.

- As constructed the method does not account for anticipated changes in policy or epidemiological conditions such as seasonality due either to weather-influenced behavior or virus survivability.(If there is a strong prior belief on the magnitude of these effects on R_t it is possible to adjust the index though this may strongly bias results)
- **An appropriate use of the index is to identify sites based on disease incidence as a rule-in tool. It is not appropriate to use this as a rule-out on its own and without addressing uncertainty in R_t as well as other factors. (See Definitions)**
- R_t can be estimated by any method. A standard method based on historical case counts alone is outlined in Abbot et al. [1]
- If new interventions which reduce transmission are introduced or there is a fundamental change in public health policy or individual behavior past epidemic features will be less predictive.
- **A value of G > 0.5 indicates that given any interval of length T in our chosen look-back period, the average proportion of time spent in a growth phase is greater than half.**

Use of EpiNow2 for computation of historical Rt curves

As noted previously, the method for computing the index G can utilize any estimates of the posterior distribution of R_t. Many of the estimates constructed here were computed using the package EpiNow2[5] [6] [1] which is built upon the MCMC package RStan [7]. A full explanation of the statistical method is given in Thompson et al. [5] . This method requires only the case-incidence time series and an independent (of the time epidemic time series) estimate of the distribution of the generation time[8] and incubation period[9] for COVID-19 (as well as any reporting and notification delays) [1]. At its essence this is a branching process model where the number of secondary disease cases from a single individual is given by Poisson(Rt). Therefore, given a generation time, incubation period, and delays, the method makes use of conjugate gamma priors for Rt with the assumption in the Rt prior (Rt ~ Gamma(1,1) = exp(1)) of mean of 1 and standard deviation of 1 (therefore with a slight skew below 1). For the Rt prior, this would correspond to a value of G = 0.37. As the method uses case data there is an implicit assumption that testing represents a random sample of the overall (symptomatic) population and that the testing coverage is consistent over time (but does not depend on estimating the reporting rate). It is notable that the shape parameter for the gamma posterior is given by the sum of weighted lagged cases over the smoothing time window used in estimation,(set at 7 days based on empirical performance in Abbot et al.[1]). Here the weighting is induced by the estimate of the serial interval distribution. This provides a heuristic rule for the distribution of Rt; once a few hundred cases are reported over the lagged window

the distribution of Rt (conditional on the serial interval and delay) is well approximated by a normal distribution and therefore approximately symmetric. This is seen in Figure 1 showing the COVID-19 epidemic estimates for Jalisco, Mexico. This also implies that an estimate of Rt distribution with mean 1, given a sufficiently large number of observed cases, would yield a value of $G \approx 0.5$

Model Validation

The model was validated using COVID-19 disease incidence data from US counties with populations over 500,000. This was chosen as a standard under the assumption that US metropolitan areas would have consistent and reasonably comparable detection rates. In general, lack of a gold standard is a challenge for model validation of this type. The method is constructed based on an unbiased surveillance/sampling (in both time and population group) of symptomatic cases but otherwise does not depend on the detection rate (other than indirectly in propagating uncertainty). However, validation of the method against case data requires some notion of knowing the symptomatic case detection rate to allow for a fair comparison. This fact should be noted in performing further validation of methods to other regions where detection rates may not be comparable.

Input data were Rt estimates (taken from COVIDactnow.org model[10] which is based on case data) from the beginning of the epidemic in February 2020 to May 31st 2020. The data used for validation was the per capita disease incidence over the month of August 2020. The model was compared in terms of rank correlation as well as comparison of average disease incidence over the highest quartile as well and type-2 error. Here the average incidence across the highest quartile can be thought of as the incidence arising from taking equally sized trials in each of the counties in the highest prediction quartile. The type-2 error refers to misclassification of a lowest quartile incidence county as a highest quartile county (a false positive).

The index G was compared against a current hotspot model, which is the most straightforward model of prediction, simply using the per capita incidence in the week prior to the decision point as a predictor of trial incidence rankings. Results are of the validation are shown in Table 3. The index model outperforms the hotspot model in all metrics. Particularly notable, as designed, it avoids misclassifying lowest quartile incidence sites as highest quartile ones, demonstrating that it avoids poor choices. In terms of highest quartile incidence, the G index outperforms the hotspot model by a ratio of 1.6 to 1. We note that the hotspot model rankings were not seen to be significantly correlated with the observed incidence rankings at this point in the epidemic.

Table 3: Validation of site-selection rankings generated by Index G against observed per capita COVID-19 disease incidence. Input data is comprised of that from US counties over 500,000 population from February to May 31st. Validation data is per capita disease incidence for the month of August 2020. Note the 2-month gap which is meant to represent typical site preparation time from decision making to trial data collection. The index model is compared to a hotspot model which is defined to be the per capita incidence the week before decision making. The Index G is seen to outperform the hotspot model in all measures of disease incidence for this period

Validation Metric	R_t predictor index (G)	Hotspot Model
Rank correlation (Spearman)	0.48 ($p < 10^{-6}$)	-0.18 ($p = 0.06$)
Highest quartile classification	13/27	4/27
Lowest quartile misclassification	0/27	6/27
Magnitude incidence in highest quartile	498* (1.6)	**313* (ref = 1.0)**

* Incidence per 100,000 population

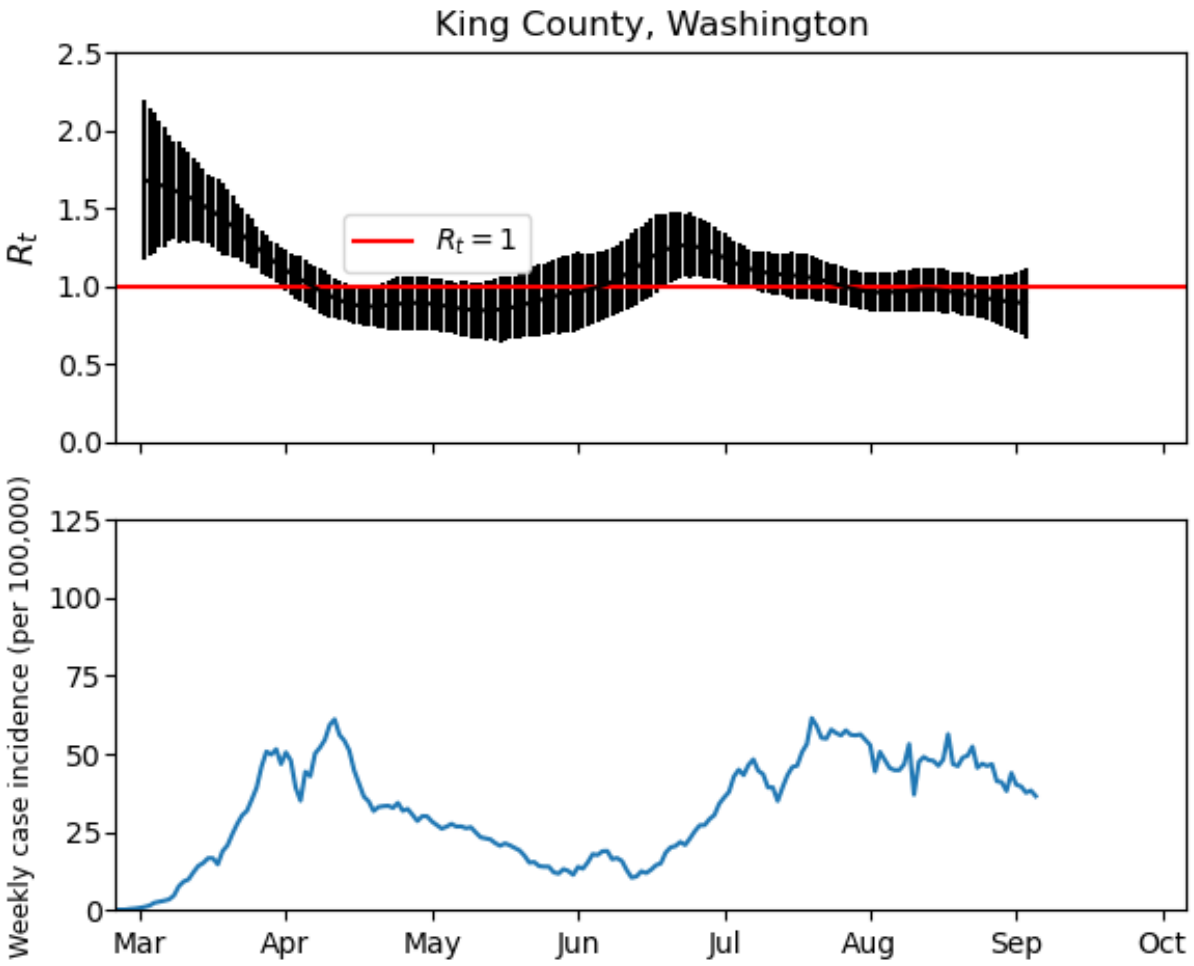


Figure 1: Historical estimates of Rt for King County, Washington, USA and corresponding COVID-19 disease incidence. Epidemic peaks and troughs are apparent but are not driven (as corroborated by serology) by herd immunity and recruitment of new susceptibles (i.e., births) as is observed for endemic childhood diseases.

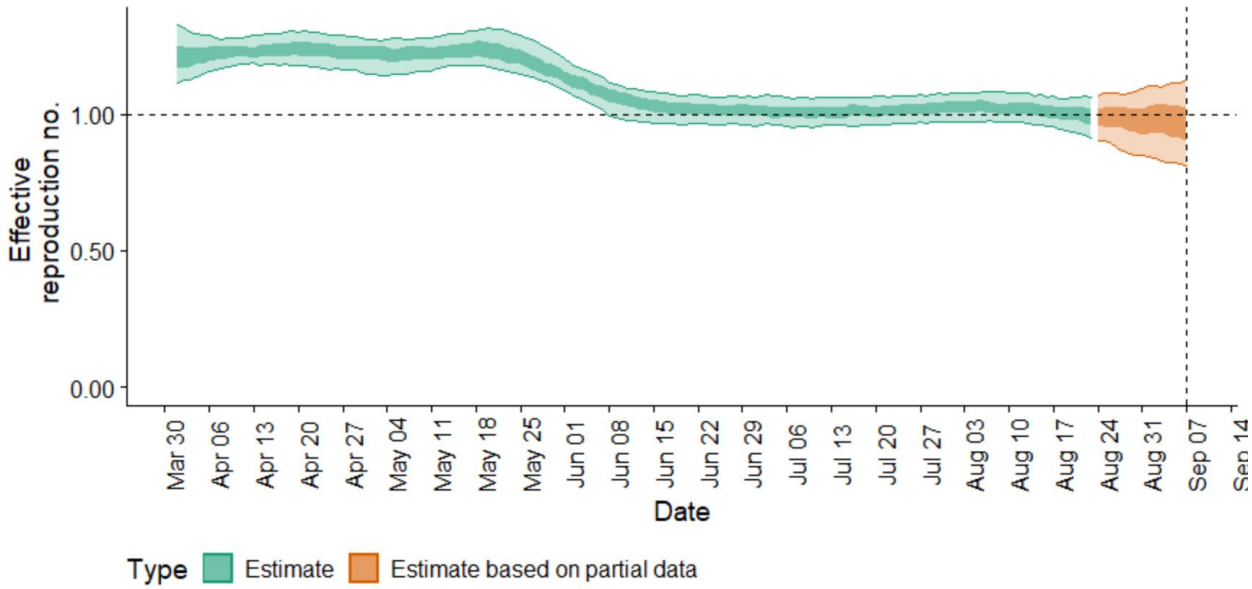


Figure 2: Estimates of Rt for Jalisco, Mexico over the course of the COVID-19 epidemic. Shading represents 50% and 90% credible intervals. Computations made using EpiNow2 package[1] with a 7 day smoothing window for the time-series.

Definitions:

Rule-in ranking tool/criteria: A criterion that with high specificity but potentially low sensitivity**.** As such it is designed to avoid making poor affirmative choices (i.e. choices of trial site) but may miss choosing some options which could possibly be classified as strong options by other tools/methods.

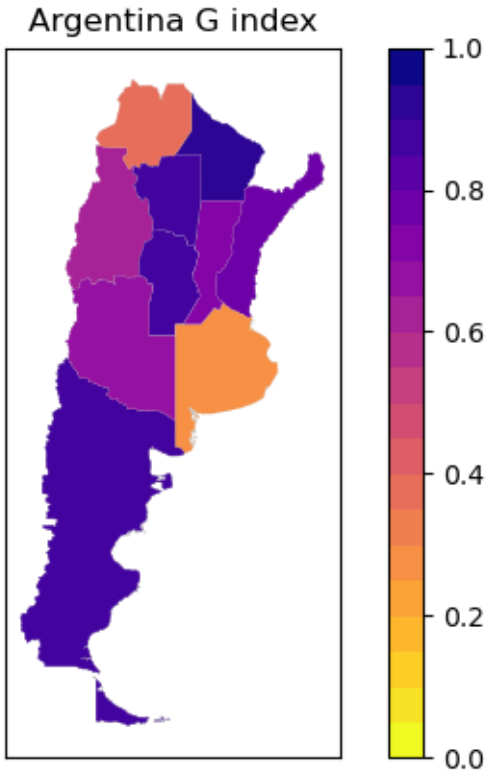
Current hotspot model: A mental model of ranking vaccine trial sites. Given a trial site preparation time, which we take to be 2 months, the current hotspot takes the per capita case incidence observed for the week prior to the decision point cutoff to use as a ranking for projected incidence after the 2month site preparation time.

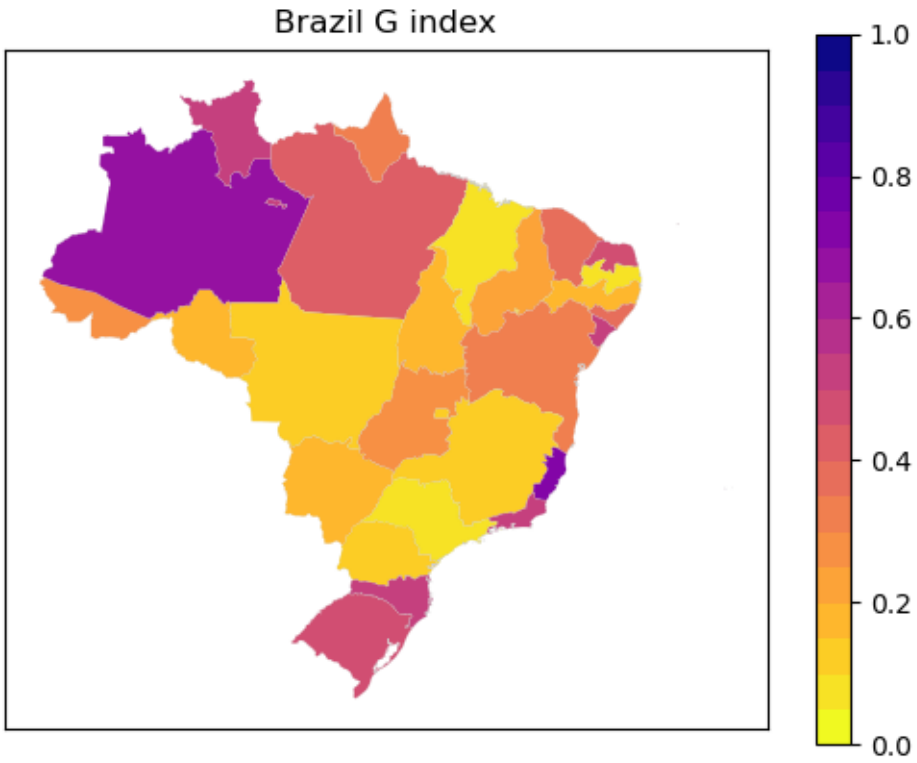
Validation: A 3 component comparison of model ranking to observed disease incidence based on historical COVID-19 epidemic data. The first component involves computing rank correlation. The second component is a quartile comparison a) how many highest quartile sites agree with the observed highest quartile and b) misclassification; how many predicted highest quartile sites are in fact in the lowest observed quartile. The third and last component is the computation of a weighted highest quartile incidence, which represents conducting a trial of equal size for every site in the predicted highest quartile. All of these measures are compared against the current hotspot model as a reference.

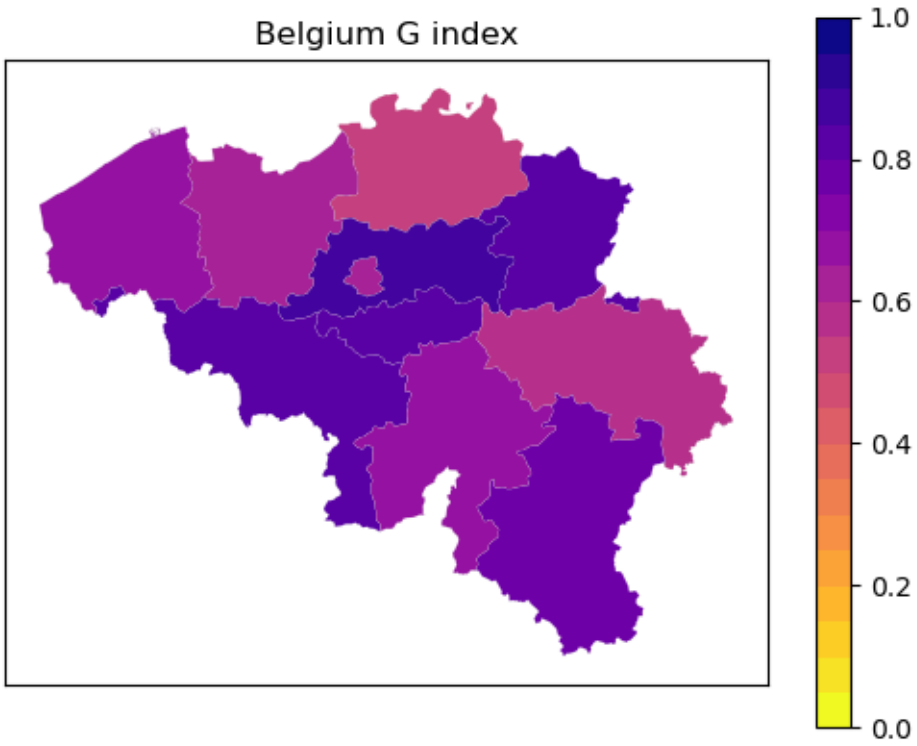
G index: The ranking metric defined in this paper, which is a normalized index (0 – 1) expressing future confidence in COVID-19 case-incidence for a given site. This is denoted “G” to emphasize that it selects for potential for historical periods of exponential growth.

Figures section 1: Spatial Heterogeneity in G index.

Note the color scale is identical for all maps shown. See Table 2 for values by region, look-back period used in input data and target trial dates. Note that for Pakistan (Karachi), Indonesia (Jakarta), Mexico (Jalisco, Mexico City) and The Gambia values are given in Table 2.




Brazil G index
1.0
0.8
0.6
0.4
0.2
0.0


Belgium G index
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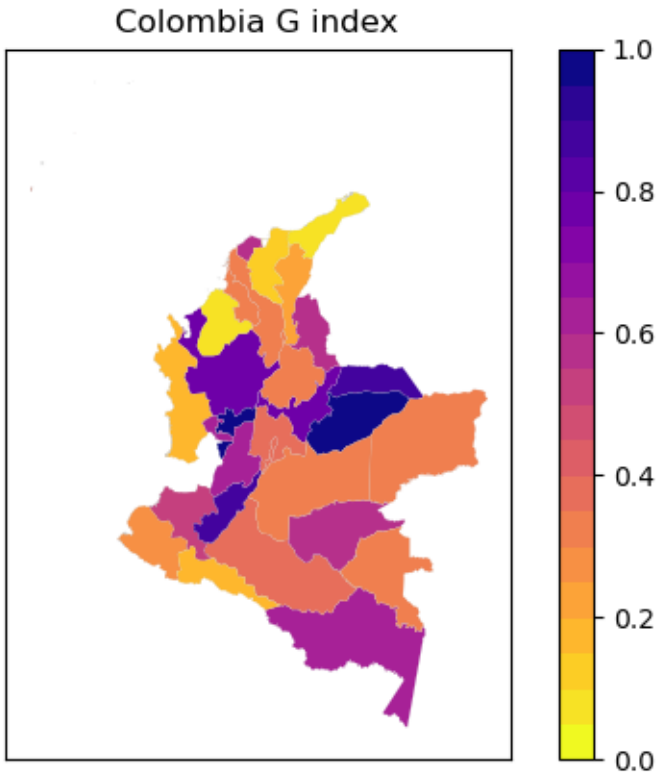
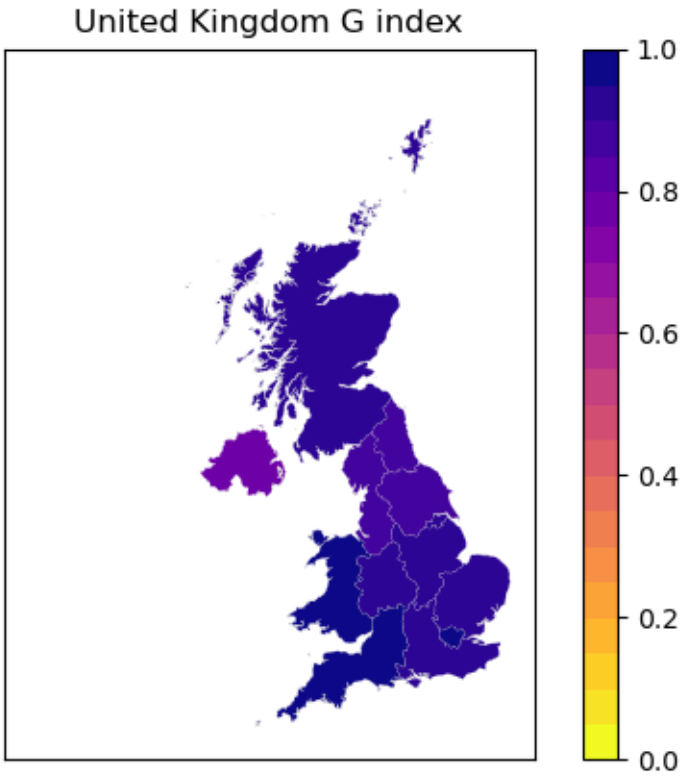
0.4
0.2
0.0



Note: There are no current estimates for Guainía as indicated in Table 2.


United Kingdom G index
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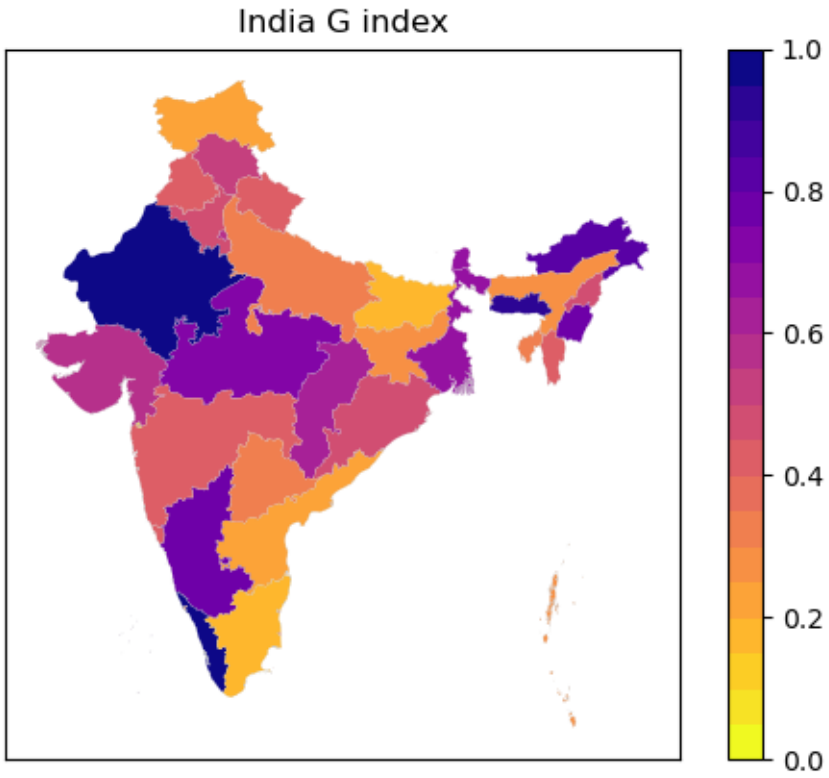
India G index
1.0
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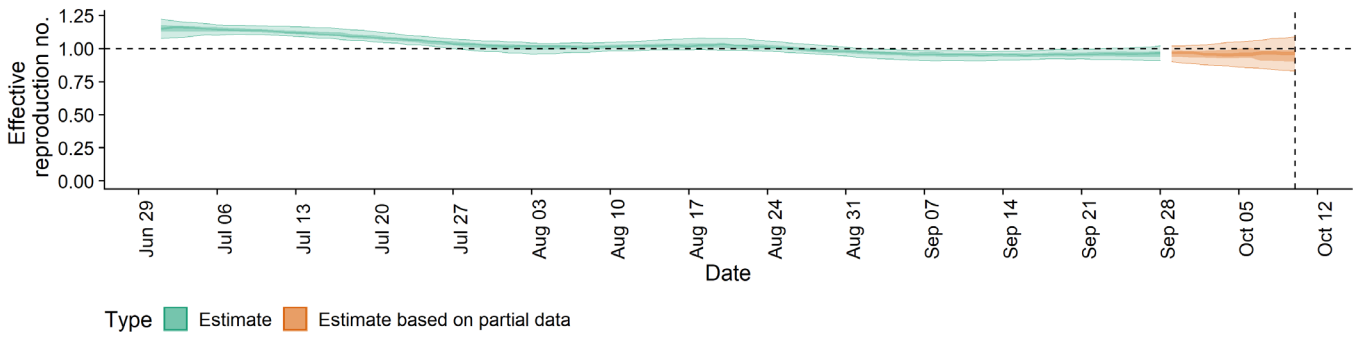
0.6
0.4
0.2
0.0

Figures section 2: Historical Rt Estimates

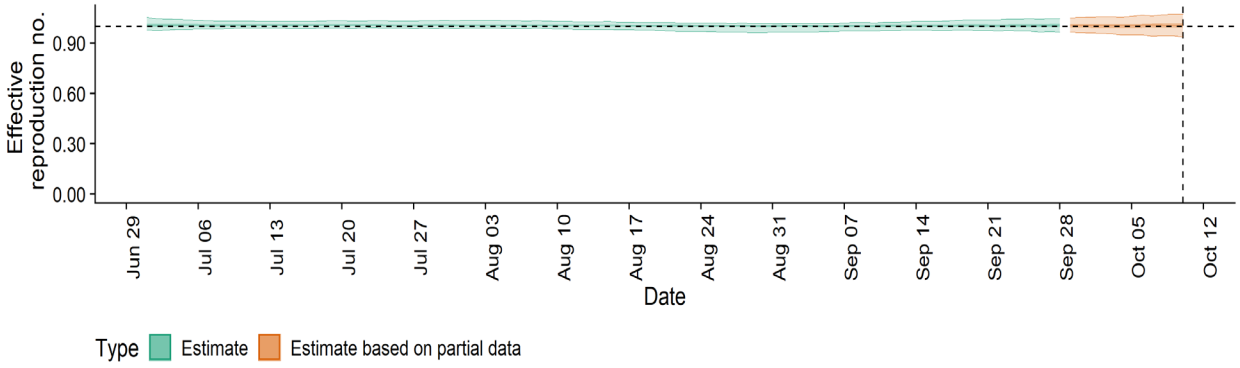
Regional estimates of Rt for Brazil, Colombia, the United Kingdom and India available at Epiforecasts.io

Buenos Aires Province (Argentina):



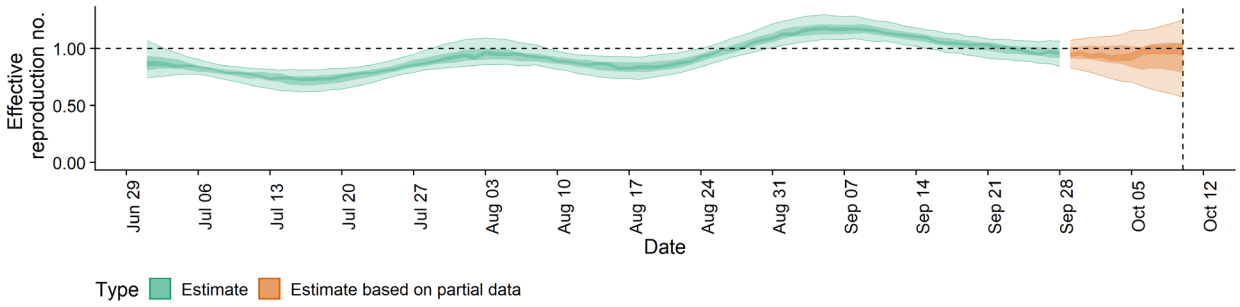
Estimated Rt values for Buenos Aires Province showing 50% and 90% credible intervals. (See supplementary material for other provinces).

Mexico City (Mexico):



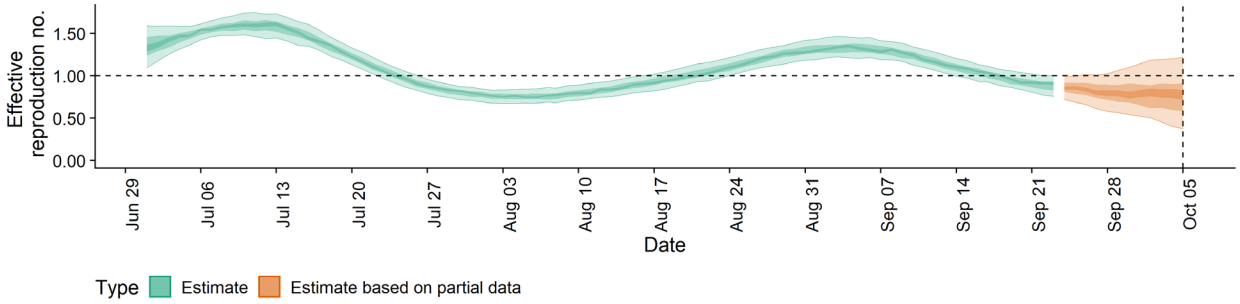
Estimated Rt values for Mexico City showing 50% and 90% credible intervals. (See supplementary material for other provinces).

Sindh Province (Pakistan):



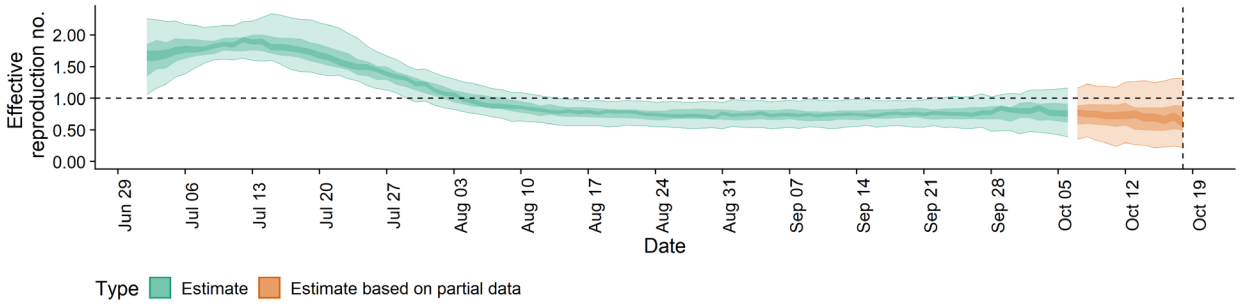
Estimated Rt values for Sindh province showing 50% and 90% credible intervals.

Antwerp Province (Belgium):



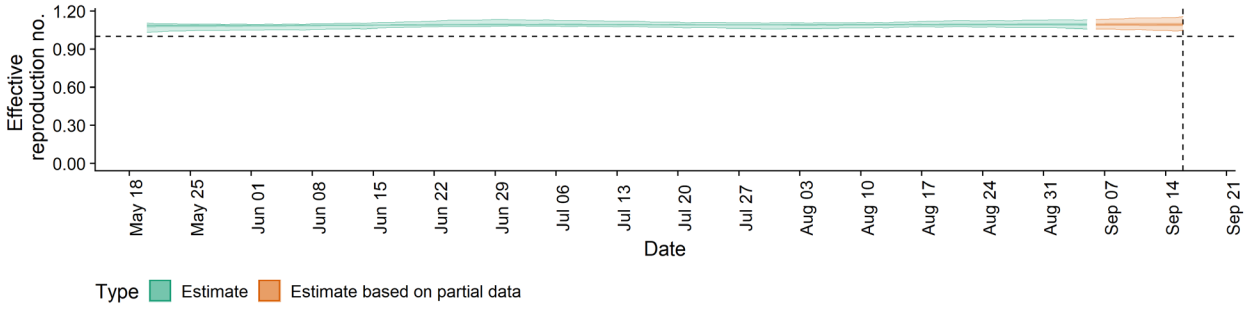
Estimated Rt values for Antwerp province showing 50% and 90% credible intervals. (See supplementary material for other provinces).

The Gambia:



Estimated Rt values for The Gambia showing 50% and 90% credible intervals.

Jakarta (Indonesia):



Estimated Rt values for Jakarta showing 50% and 90% credible intervals

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