Policy responses against the COVID-19 pandemic in Latin America: Statistical Analysis Plan

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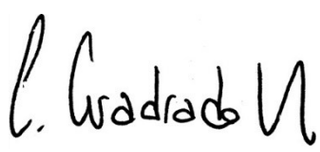

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Introduction

The COVID-19 pandemic is evolving quickly globally. By January 22, 2021, there were more than 112 million reported cases and more than 2.6 million deaths worldwide.[1] Latin America is one of the worst-hit regions and accounts for 20.3% of the SARS-COV2 cases and 30% of the global deaths, despite having only 8% of the global population. The effectiveness of policies to reduce the spread of COVID-19 has been analyzed in several empirical studies.[2-4] Nevertheless, few of these studies have included countries in Latin America or examined the effect heterogeneity and potential explanations for it. In this study we aim, first, to estimate the effectiveness of nonpharmaceutical interventions on SARS-COV2 transmission and COVID-19 mortality in Latin America; second, to examine the effect heterogeneity of transmission and mortality at the local level. Third, assuming we find evidence of moderate to substantial heterogeneity at the local level, we aim to explore potential explanations for this heterogeneity.

This Statistical Analysis Plan (SAP) provides an in-depth description of the statistical methods and definitions for the study analysis. More information on the rationale and data sources can be found in the Study Protocol.

Study methods

Design

The study is a natural experiment exploiting the variation in temporal and spatial implementation of nonpharmaceutical interventions (NPI) to reduce the spread of COVID-19 in Latin American local governments. The unit of analysis are third-tier subnational units (i.e. municipalities, districts, cantons). The setting is all Spanish and Portuguese speaking countries in Latin America that fulfil the inclusion criteria. We developed the plan following guidance from Gamble et al.[5]

Sample size

The study will use all available data that fulfils the inclusion criteria.

Timing of analyses and outcome assessments

We will use data from the date of the first case in each country until December 31, 2020. We will use publicly available daily data for all outcomes. We will use the enforcement date on data on interventions collected from PoliMap (www.polimap.org).

Protocol deviations

There have not been any deviations from protocol.

Study population

The study will focus on local governments, third-tier administrative units in each country. These receive different denominations in each country, primarily called municipality, district or cantón. The eligibility criteria are (1) Spanish or Portuguese speaking countries in the

Americas; and (2) availability of open data for any of the outcomes of interest at a subnational level. A flow diagram (similar to those recommended by CONSORT guidelines) will be reported describing the number of countries and subnational units eligible and how many of them fulfilled the eligibility criteria.

We will report (as a Supplementary Table) a summary of the baseline characteristics of the local governments included in the study.

Outcome definitions

The first outcome will be the 7-day moving average of daily confirmed cases of COVID-19/SARS-CoV-2. The second outcome is the time-varying reproductive number between the current and previous period.[6] The third outcome is the 7-day moving average of the daily number of deaths by COVID-19 in Latin American subnational regions. For the statistical modelling, these averages will be rounded to the nearest integer. We will consider a 7-day lag as the primary lag. We will use the definition of COVID-19 case and death which is valid at any given time in each country.

Analysis methods

The primary analysis will use interrupted time series (ITS) for each subnational unit to examine the causal effect of COVID-19 policies on primary outcomes. Interrupted time series is a widely used tool in causal inference that allows comparing trends before and after the introduction of an intervention.[7] The counterfactual outcome is the projection of the trend in the period before the introduction of the intervention into the time period was introduced. The unit of analysis in this study is days, starting from the date of the first case.

The standard model for an ITS regression is as follows

$$(1)\ Y_t = \beta_0 + \beta_1 time_t + \beta_2 post_t + \beta_3 timepost_t + \beta'_4 X + \mu_t$$

where $time_t$ is a variable which equals one at the first time point *t* and increases by one after each subsequent time point; $post_t$is a dummy variable that equals to zero prior to the introduction of the intervention (*p*) and equals one for every time point thereafter; $timepost_t$ is a variable that equals to zero until time *p-1*, and increases by one for each subsequent time point; and X is a vector of covariates. Coefficient $\beta_3$is the coefficient of interest and represents the change in slope after time *p*.

The validity of the ITS rests on three assumptions. Assumption 1 states that the expectation of the pre-intervention level and trends would be the same irrespective of whether the sample received the treatment. Assumption 2 states that in the absence of treatment, the outcome of interest would remain unchanged in the post-intervention period. Assumption 3 states that the time trends in the pre and post periods can be expressed as a linear combination of parameters.[8]

Using the potential outcomes framework, the estimated effect of a policy at time *p* could be defined as

(2) $\Delta_t = Y_t(1) - Y_t(0)$

These difference could also be expressed in terms of two equations

(3) $Y_t(1) = \alpha_0 + \alpha_1 time_t + \alpha_2 post_t + \alpha_3 timepost_t + \varepsilon_t$
(4) $Y_t(0) = \theta_0 + \theta_1 time_t + \theta_2 post_t + \theta_3 timepost_t + \nu_t$

where $Y_t(1)$ is the sequence of outcomes if we treat the unit at time *p* and $Y_t(0)$the sequence of outcomes in the absence of treatment. Assumption 1 implies no anticipation of treatment, i.e.$Y_t(1) = Y_t(0)$ for all $p \leq t_0$.[9] In other words, $\alpha_0 = \theta_0$ and$\alpha_1 = \theta_1$. Assumption 2 implies that $\theta_2$and $\theta_3$are equal to zero.

Violations of assumption 1 include anticipation effects when the subjects of the policy can anticipate its initiation and change their behaviour.[9] In the case of the COVID-19 pandemic, the population might, for example, be more likely to adhere to social distancing recommendations during the discussion of a lockdown or take preventive actions when the incidence of cases increases, even before restrictions such as lockdowns are implemented. Violations of assumption 2 include concurrent changes due to history (other concurrent policy, program or societal changes), selection (changes in the composition of the sample at time *p*), instrumentation (changes in the way the outcome is measured) and mis-specification of the functional form of the time trend (in a classical ITS, time is assumed to be a simple linear term. Violations of assumption 3 can occur due to misspecification of the functional form, including failing to account for a delay of the policy to take effect or failing to account for autocorrelation (which can lead to artificially low standard errors).[10] In an epidemic process, cases over time follow a non-linear trajectory (often an exponential, Gompertz or other complex functional forms). Assuming a linear time trend can lead to incorrect counterfactuals and biased effect estimates.

We will examine and handle potential violations to assumptions in the following way:
Assumption 1. We will assess the existence of anticipation effects by visual exploration and examination of the slope prior to the intervention. If there is evidence of potential anticipation effects, we will use a "quasi-myopic" sensitivity analysis, i.e. an analysis that excludes a period of time where anticipation is expected to have happened from the analyses.[11]

Assumption 2. We will explicitly incorporate co-occurring interventions in a seven-day period as a combination of interventions. We will also adjust for changes in the case definition of COVID-19 cases and deaths for each of the respective outcomes. We will report in the Supplementary Appendix the exact dates considered in the analysis for each country/subnational unit and the interventions included in each intervention period.

Assumption 3. We will introduce flexible spline functions to account for seasonality and long-term trends. We will add a scale parameter, which will be the Pearson statistic divided by the residual degrees of freedom, to account for potential overdispersion (a violation of the Poisson regression assumption).[12] We will test for autocorrelation using the Durbin-Watson tests and visual plots of the autocorrelation function and partial autocorrelation function. If there is evidence of autocorrelation, we will use the Newey-West method to obtain adjusted standard errors.

Therefore, in the final analysis, we will use Poisson regression to model the count data.[13,14]. The final model is an extension of the regression described in equation 1 with the specifications described above.[4,15] The model will include each of the interventions (either as single interventions or combinations of), denoted $j = 1,...,J$. This method allows estimating simultaneously the effect of several interventions. We will consider interventions implemented within a 7-day period as a combination of interventions, following previous studies.[4] This means that the maximum number of combinations of interventions is 52, $t = 1,...,52$. We will estimate the effect of the interventions separately when interventions are separated by at least seven consecutive days and for a maximum period of 30 days.[4] The primary analysis will include a 7-day lag to account for the delay in the intervention to be effective, considering the incubation period of SARS-COV2.[16]

$$(5)\ ln(Y_t) = \beta_0 + \beta_{1j} time_{tj} + \beta_{2j} post_{tj} + \beta_{3j} timepost_{tj} + \mu_t$$

This model will be run at the municipal level and, therefore, we expect to run 10,000 regressions multiplied by the number of combinations of interventions at each municipal level. Coefficient β_{3j} is the coefficient of interest and represents the change in slope after the intervention j at period t.

In coefficient of interest at a second stage, we will pool the effects for each intervention -or combination of interventions- (i.e. the coefficient of interest β_{3j} from the local level regression) using a random-effects meta-analysis.[17] This meta-analysis will provide information to obtain a pooled effect estimate and a measure of heterogeneity. We will use the I^2 as a measure of heterogeneity.

If the heterogeneity is moderate or high (I^2 higher than 50%), we will carry out a meta-regression to assess whether subnational level determinants can explain the observed heterogeneity.[17] We will analyse the following covariates: (i) Population size, (ii) Population density, (iii) Proportion of population over 60 years old, as a proxy for age structure of the population, (iv) Household density, and (iv) Proportion of population with basic education, as a proxy of socioeconomic status.

The meta-regression has the effect size $\widehat{\theta_k}$ of a first-stage regression k as the outcome, covariates x_{ik}, a fixed effect $\rho_1 S_a$ for the second-tier level a (i.e. State or Region) and a random-effect $\delta_2 N_b$ for the national level b and a fixed effect $\rho_2 Y$ for the time of the year (quarterly periods)(equation 6). The equation includes two types of independent errors, where $\varepsilon_k$is the sampling error of the effect size and $\varsigma_k$is the random-effect error term.[17]

$$(6)\ \theta_k = \gamma_1 x_{1k} + \ldots + \gamma_n x_{nk} + \rho_1 S_a + \delta_2 N_b + \rho_2 Y + \varepsilon_k + \varsigma_k$$

These controls for higher levels of administration and time of the year will allow us to control for constant characteristics at the subnational and national level, as well as changes in the effectiveness throughout the pandemic.

We will carry out the following sensitivity analyses: (1) comparison of effect estimates using a 5-day and 10-day lag; (2) quasi-myopic analyses to control for anticipatory effects (if there is evidence of), and (3) placebo tests evaluating changes at times when no policy was implemented. In the analyses for the number of cases and time-varying R, we will run additional sensitivity analyses estimating the number of SARS-CoV-2 cases corrected by under-ascertainment derived from mortality statistics.[18]

Statistical software

We will use R (current version 3.6.3) for all analyses. We will use the *glm* function to run the Poisson model, using the code developed by Gasparrini et al as a reference source[19] and the *metareg* package for the meta-regression. Under-ascertainment will be estimated using code developed by Russell et al as a reference. [18]

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