Test positivity – evaluation of a new metric to assess epidemic dispersal mediated by non-symptomatic cases

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Abstract

Epidemic control may be hampered when the percentage of asymptomatic cases is high. Seeking remedies for this problem, test positivity was explored between the first 60 to 90 epidemic days in six countries that reported their first COVID-19 case between February and March, 2020: Argentina, Bolivia, Chile, Cuba, Mexico, and Uruguay. Test positivity (TP) is the percentage of test-positive individuals reported on a given day out of all individuals tested the same day. To generate both country-specific and multi-country information, this study was implemented in two stages. First, the epidemiologic data of the country infected last (Uruguay) were analyzed. If at least one TP-related analysis yielded a statistically significant relationship, later assessments would investigate the six countries. The Uruguayan data indicated (i) a positive correlation between daily TP and daily new cases (r=.75); (ii) a negative correlation between TP and the number of tests conducted per million inhabitants (TPMI, r= −.66); and (iii) three temporal stages, which differed from one another in both TP and TPMI medians (p<0.01) and, together, revealed a negative relationships between TPMI and TP. No significant relationship was found between TP and the number of active or recovered patients. The six countries showed a positive correlation between TP and the number of deaths/million inhabitants (DMI, r=.65, p<0.01). With one exception –a country where isolation was not pursued−, all countries showed a negative correlation between TP and TPMI (r=.74). The temporal analysis of country-specific policies revealed four patterns, characterized by: (1) low TPMI and high DMI, (2) high TPMI and low DMI; (3) an intermediate pattern, and (4) high TPMI and high DMI. Findings support the hypothesis that test positivity may guide epidemiologic policy-making, provided that policy-related factors are considered and high-resolution geographical data are utilized.

Keywords: COVID-19; Test positivity; geo-epidemiology; resource-limited countries; infection.

1. Introduction

Unlike most other infections, COVID-19 is an infection characterized by a high percentage of asymptomatic cases: at least 40% and up to 80% of the cases may not reveal symptoms [1−3]. Such a feature creates an unprecedented problem; when this disease disseminates, in principle, the only way to identify all infected individuals would be through a universal testing program, i.e., testing, repeatedly, 100% of the population. At least in 2020, no country achieved such a high level of testing: on average, countries tested much less than 1 % of the population, on a given day. Given the scarcity of testing resources, in 2020, Austria and Germany reported that not more than 20% of the cases were likely to be detected [4].

Consequently, in 2020, the true epidemiologic status of the population was unknown. To remedy such a difficult and global problem, which may be encountered, again, in future epidemics caused by this, similar or other infections, new metrics may be required.

Testing populations seems to differ markedly from testing individuals. While clinical medical practices have historically emphasized personalized diagnostics, population-oriented testing is needed when epidemics are rapidly disseminating [5, 6].

Test positivity is a metric of potential relevance in situations in which the percentage of asymptomatic cases is high. Test positivity (TP) is the percentage of test-positive individuals reported on a given day out of all individuals tested the same day. TP is an indicator first mentioned in March 30, 2020: the World Health Organization described this metric in a public conference [7]. While now broadly used, TP has been used empirically. Hence, TP, as well as associated variables (including time), should be explicitly evaluated.

The ‘test positivity rate’ (TP) or ‘percent positive rate’ may help public health officials answer questions such as: ‘*Are we doing enough testing for the amount of people who are getting infected*?’ [8]. When the total number of tests conducted is too low, the test positivity (TP) percentage may be high. A high TP percentage may indicate that there are more people with coronavirus in the community who have not been tested yet [9]. A high TP percentage may reflect a rapid epidemic dissemination and, consequently, it may predict that places with a high TP will soon express a high or very high number of deaths/million inhabitants [6].

Vice versa, a low TP percentage may prognosticate the imminent cessation of an outbreak.

Other indicators that may influence TP or be influenced by TP are: a) the number of tests conducted per million inhabitants (TPMI), b) the number of deaths reported per million inhabitants (DPMI), c) the number of active cases (all test-positive cases minus deaths and recovered patients), and d) the number of recovered patients.

However, no variable may demonstrate utility or validity unless it is explored within an explicit –not an assumed− geographical and temporal context. That is so because the connectivity that explains epidemic dispersal is a geo-temporal structure [10-12].

Consequently, here the percentage of test positivity was investigated in Argentina, Bolivia, Chile, Cuba, Mexico y Uruguay –a group of countries selected because the first COVID-19 case, in these countries, was reported less than six weeks apart. Therefore, a relatively similar temporal timeframe allowed a hypothesis-generating study that considered both specific time points and geography. The purpose of this study was to generate the first geo-temporal evaluation of several epidemiologic variables associated with test positivity.

2. Methods

Daily epidemiologic reports corresponding to Uruguay were collected from the Uruguayan National System of Emergencies [13]. Because the data source was published in Spanish, it was corroborated with daily reports made by Worldometer [14]. Data corresponding to Argentina, Bolivia, Chile, Cuba, Mexico and Uruguay were collected from OurWorldInData [15]. Temporal data from these countries on test positivity, TPMI and DPMI are reported in Supplementary Table 1.

The period under study was the first 60-90 epidemic days, which correspond (for the group of six countries) to February-May, 2020. Specifically, daily and/or cumulative count data on: (i) the number of tests conducted in a given day, (ii) the number of test-positive individuals reported in a given day, (iii) the number of active cases, and (v) number of deaths were obtained. A commercial package (Minitab 19, State College, PA, Minitab Inc.) was used to perform statistical analyses and create plots. Population medians were analyzed using the non-parametric Mann-Whitney test.

3. Results

The data corresponding to Uruguay were first investigated. The rationale for such a priority was the fact that it was the last country affected by this pandemic within the selected group and, consequently, epidemic patterns observed in Uruguay could follow and/or mimic patterns also exhibited by other countries prior to March 13, 2020 (when the first case was detected in Uruguay). The second reason for this research plan was that Uruguay started to develop diagnostic tests before the first case was detected and, consequently, the analysis of test positivity could be facilitated [16].

The first estimates of test positivity were rather high in Uruguay. However, after approximately two weeks, they decreased and remained low in the first 60 epidemic days **(**Fig. **1A**). TP was positively correlated with the daily number of new cases (r= 0.75, Fig. **1B**).

An alternative way to monitor the progression of this pandemic is to plot the cumulative number of test-positive individuals (cases) together with the cumulative number of SARS-CoV2-positive fatalities. This approach revealed two curves, which were not parallel (Fig. **1C**). Therefore, fatalities could not be predicted from the case data.

A similar finding was revealed when the cumulative number of cases was compared to the cumulative number of tests performed per million inhabitants (TPMI): the curves were not parallel (Fig. **1D**). One data inflection revealed that, between two and three epidemic weeks (after ~ 2000 TPMI were reached), the number of TPMI increased linearly over time (Fig. **1D**). A similar pattern was observed when the cumulative number of fatalities was compared to TPMI: after TPMI reached 1000, the number of deaths flattened out (Fig. **1E**). These patterns were also noticed when TPMI was compared to the cumulative number of deaths reported per million inhabitants (DPMI): only after TPMI exceeded 1000, the DPMI values flattened out (Fig. **1F**).

Several of these variables showed at least two phases (Figs. 1 **C, E, F**). The earliest stage displayed a quasi-exponential growth (i.e., the number of cases grew faster than time, which resulted in a quasi-vertical pattern). Later (after a data inflection was revealed) a quasi-linear phase was observed, in which the growth in the number of cases was slower than time and, therefore, cases exhibited a quasi-horizontal pattern (e.g., Fig. **1C**).

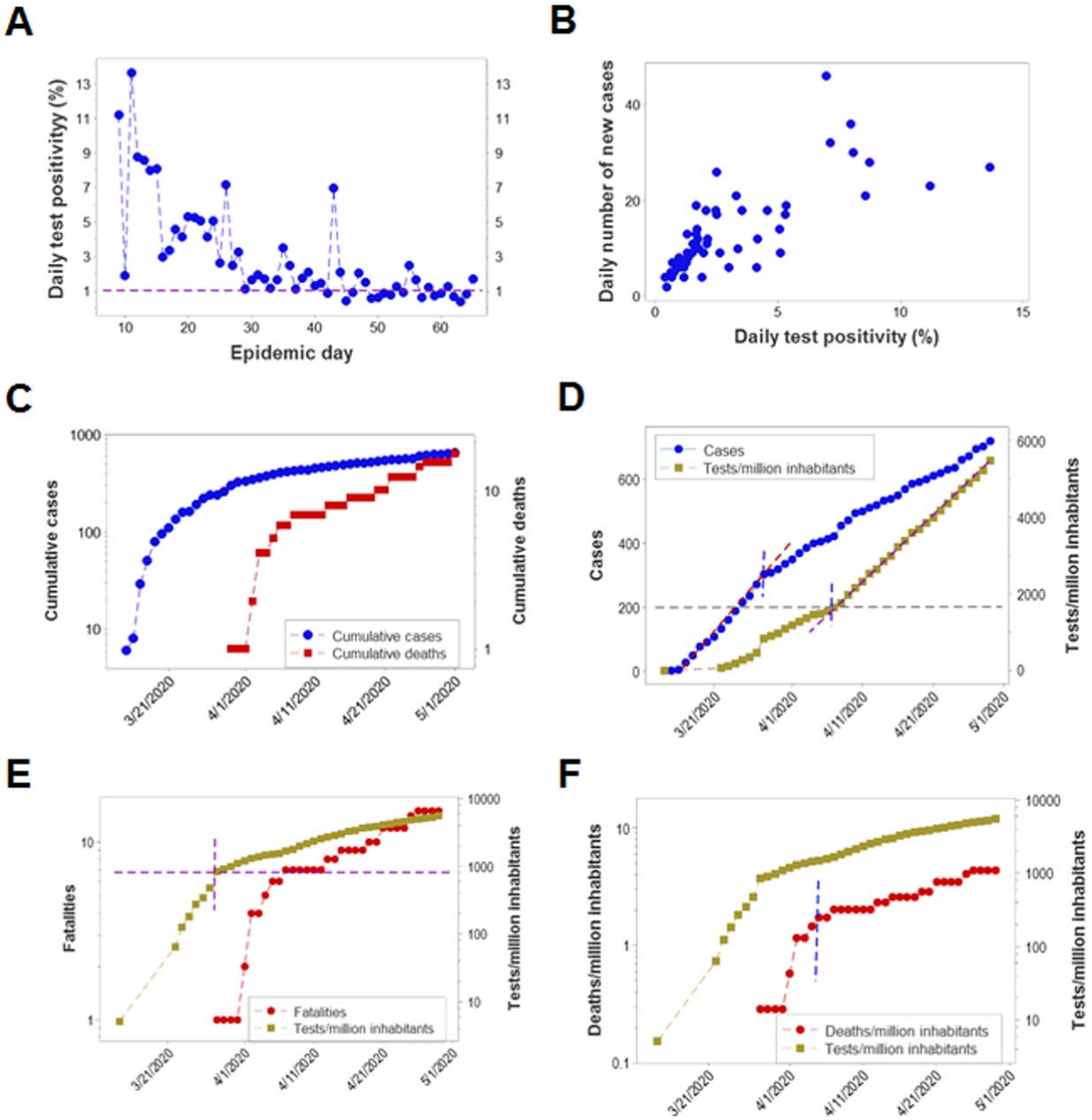

Fig. 1. Epidemic curve and early metrics for COVID-19 infections, Uruguay, March to May, 2020.
(A). Daily test positivity against epidemic days; (B). Daily number of new cases versus daily test positivity; (C). Cumulative cases and deaths over the period, March to May 2020; (D). Cases and tests per million inhabitants; (E). Fatalities and test per million inhabitants; (F). Deaths per million inhabitants and tests per million inhabitants.
There was a positive correlation between the daily number of new cases versus daily test positivity (r= 0.75 [CI= 0.61, 0.85]), Fig. 1B.

Test positivity was negatively correlated with testing in Uruguay (r= − 0.66, Fig **2A**). Three subsets of temporal observations showed decreasing values of TP, which corresponded to

increasing (and statistically significantly different) values of TPMI (p<0.01, Figs**. 2 B, C**). When the sub-group of active cases was compared to all cases (which included deaths and recovered cases), the cumulative number of active cases exhibited a data inflection followed by a decreasing trend which, together, supported the view that patterns displayed by the data on active cases may inform earlier than the alternative indicator (Fig. **2D**).

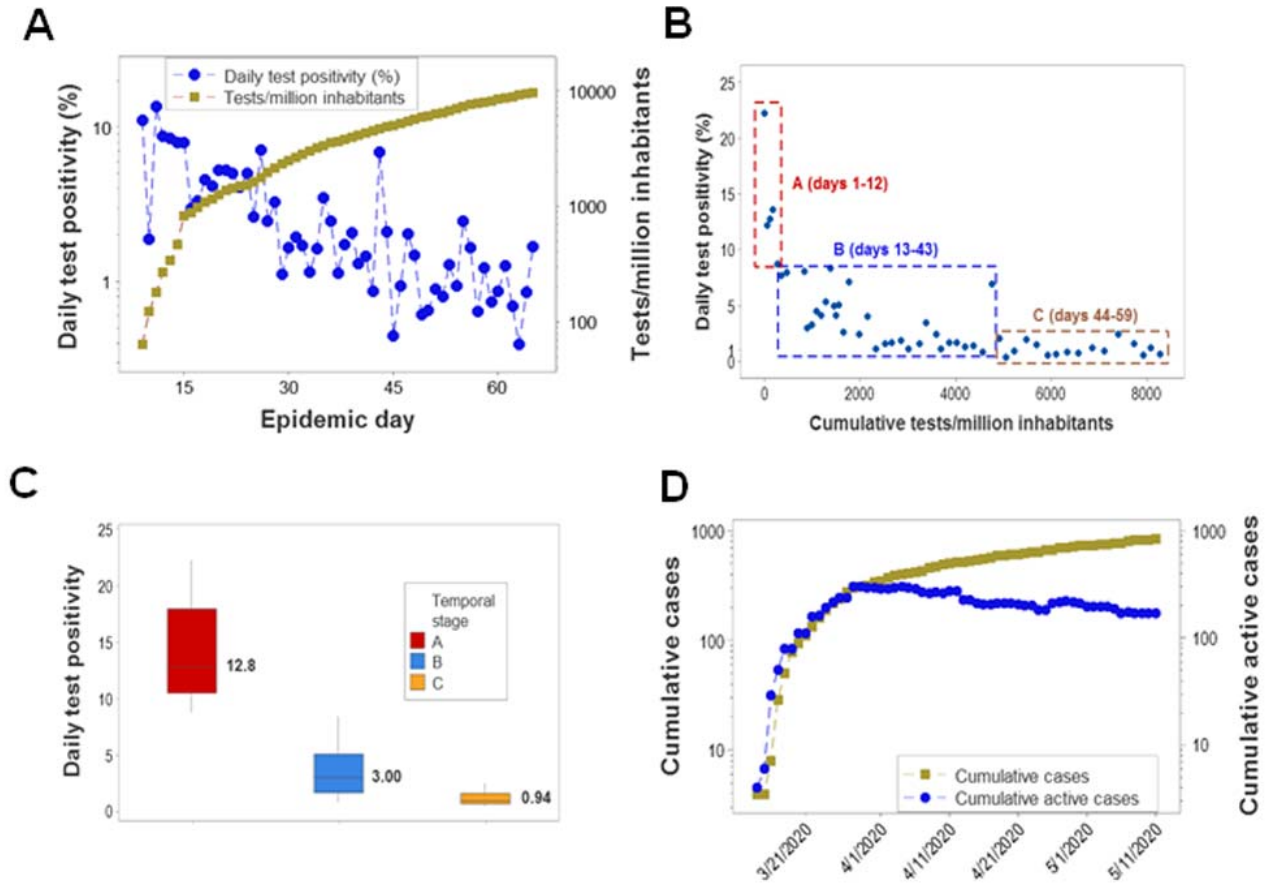

Fig. 2. Inferential statistics on COVID-19, Uruguay, March to May, 2020.
(A). Daily test positivity against epidemic days and tests per million inhabitants; (B). Daily test positivity versus cumulative tests per million inhabitants reveal L - shaped curve; (C). Temporal evaluation of daily test positivity reveals three distinct stage over the period, March to May 2020; (D). Cumulative cases and cumulative active cases plotted against a temporal timeline.
There was a negative correlation between the daily test positivity and epidemic days (r= - 0.66 [CI= - 0.79, - 0.48]), Fig. 2A.

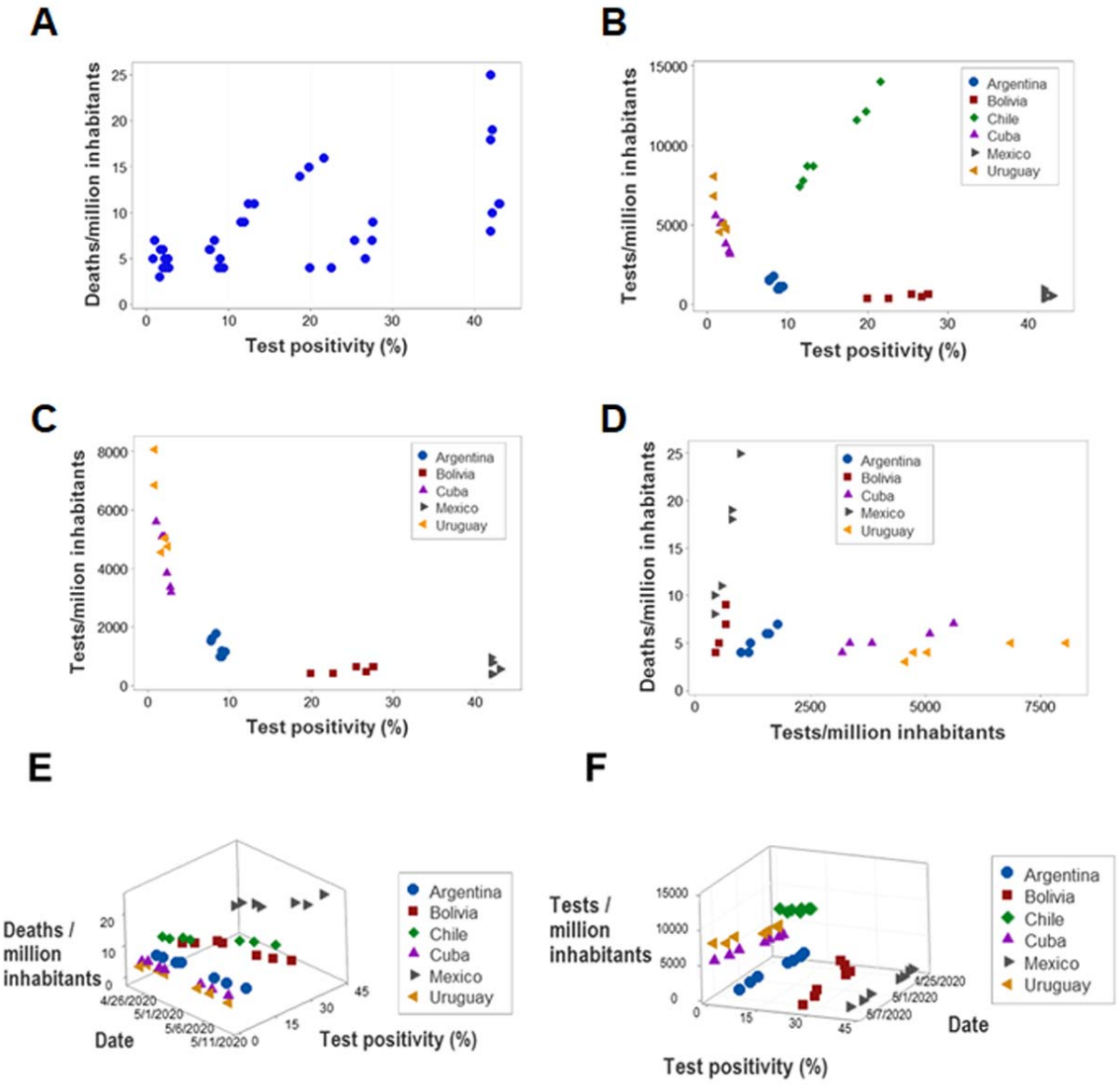

Fig. 3. External validity and comparison of observed patterns for COVID-19 in eleven countries.
(A). Deaths per million inhabitants against test positivity; (B). Tests per million inhabitants versus test positivity; (C). Tests per million inhabitants versus test positivity, excluding Chile; (D). Deaths per million inhabitants against test per million inhabitants, excluding Chile; (E). Three-dimensional plot of deaths per million inhabitants, temporal scale and test positivity; (F). Three-dimensional plot of tests per million inhabitants, temporal scale and test positivity.
There was a positive correlation for five countries except Chile, between the test positivity and death per million inhabitants (r= 0.65 [CI= 0.44, 0.80]), Fig. 3A. However, there was a negative correlation between test positivity and test per million inhabitants, after excluding Chile, (r= - 0.74 [CI= - 0.86, - 0.55]), (a demonstration that TP may be a reproducible metric, provided that the context and other variables are also considered).

Test positivity was positively correlated with deaths/million inhabitants (DPMI) when the six countries were simultaneously investigated (r= 0.65, Fig. **3A**). However, when the same

countries were investigated in terms of TPMI and TP, a distinct, non-linear pattern was detected (Fig. **3B**). When one seemingly outlier country was removed from the analysis, a negative correlation was revealed (r= −0.74, Fig. **3C).** When DPMI and TPMI were investigated, a non-linear (L-shaped) distribution was noticed (Fig. **3D**). When time, TP, and DPMI were plotted, three patterns were detected, which were characterized by a) low TP and low DPMI (a pattern displayed by three countries), b) intermediate values (shown by two countries), and c) high TP and high DPMI, which were only revealed by one country (Fig **3E**). In contrast, when TPMI was plotted together with time and TP, four patterns were observed, which revealed a) high TPMI and low TP values (found in two countries), b) a lower TPMI but a higher TP than the previous subset (a profile shown in one country), c) the lowest TPMI and highest TP percentages (detected in two countries), and d) high TPMI and high TP values (a pattern observed in one country, Fig. **3F**).

When geography was considered, the association between TPMI and DPMI was further documented (Figures **4 A-F**). Within two weeks, one country partially predicted the fatalities associated with epidemic dispersal: the lowest TPMI values preceded an ~250% growth in DPMI. However, exceptions to this pattern were also noticed: in the same period of time, two countries that also displayed low TPMI values showed a negligible change in DPMI (Figures **4 A-F**).

The temporal fluctuation of TP values was minimal across countries. In the period under study and without exceptions, countries showed either one- or two-digit percentages (Fig. **5 A-F**).

In addition to TP-related geo-temporal assessments, the shape of the data on active cases was also informative. For instance, the detection of data inflections could be viewed as a positive outcome (Figures **6 A–C**). Similarly, both the directionality and numerical values of the ratio between recovered and active cases could be considered: when the ratio is greater than 1, a positive prognosis may be considered. In addition, when time progresses faster than the epidemiologic

metric (when a horizontal directionality predominates) a rather stagnant situation may be inferred. In contrast, when the ratio of recovered individuals over all active cases grows faster than time (when a vertical directionality is noticed), a positive prognosis is defensible (Figures **7A-C**).

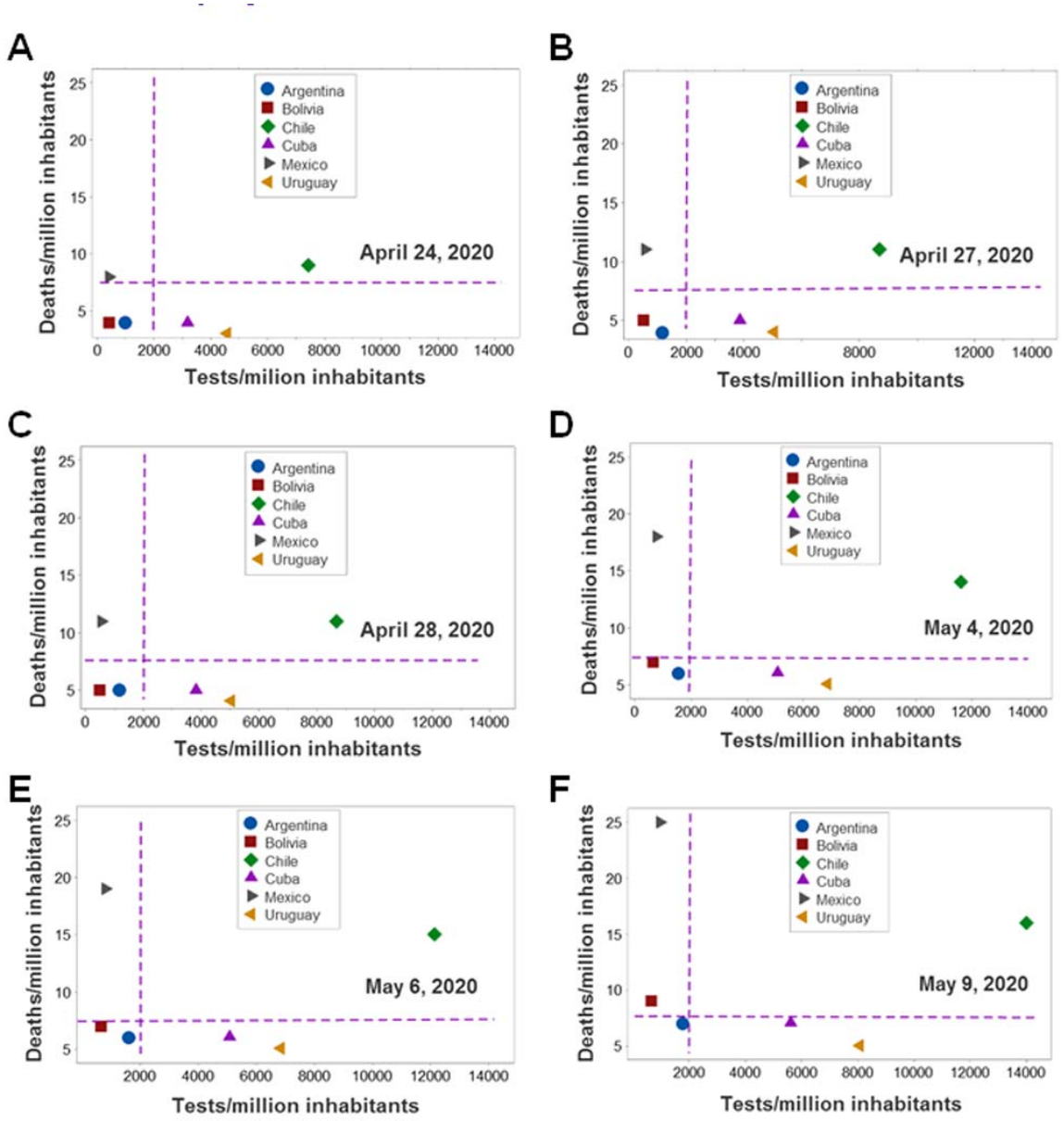

Fig. 4. Country-level comparison of cases, mortality and test positivity per million population for COVID-19. Plot of deaths per million inhabitants against tests per million inhabitants in (A). April 24, 2020; (B). April 27, 2020; (C). April 28, 2020; (D). May 4, 2020; (E). May 6, 2020; (F). May 9, 2020.
Fig. 4 (A – F) show a synopsis of a geo-temporal analysis; it includes (low-resolution or aggregate) geographical data and a temporal description of epidemics that started less than 6 weeks apart. For visual comparisons, each plot is divided into 4 quadrants ('low & low', 'high & low', 'low & high', and 'high & high') It is shown that high TP is associated with a faster growth of deaths/mill inh. The opposite pattern (low test positivity & low deaths/mil inh) shows one exception.

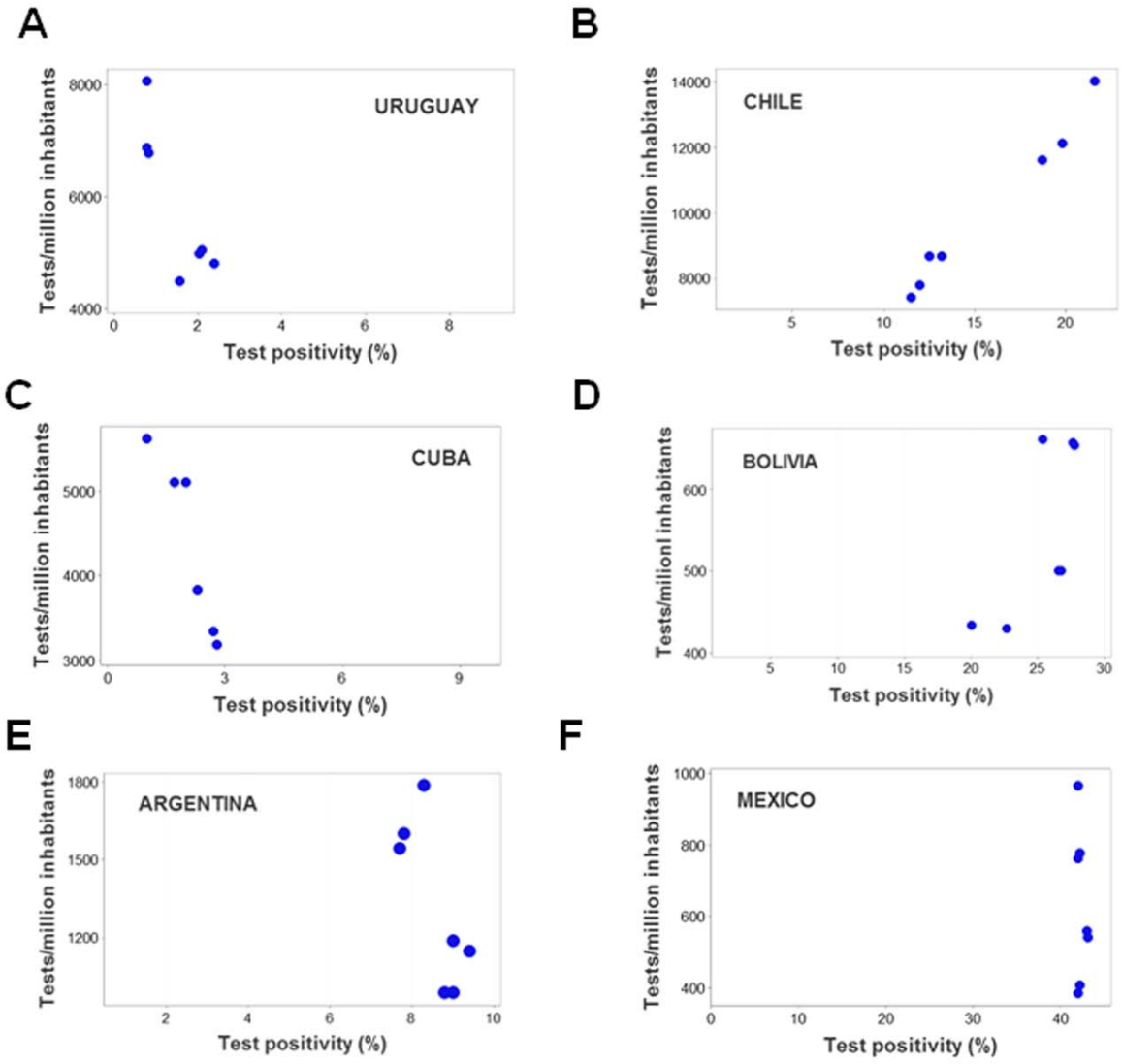

Fig. 5. Selected country classification by cases, mortality and test positivity for COVID-19.
Plot for (A). Uruguay; (B). Chile; (C). Cuba; (D). Bolivia; (E). Argentina; (F). Mexico.
Fig. 5 (A – F) show the same data depicted in fig 4, now at individual countries. The left column (A, C, E) displays countries with one digit of test positivity percentages. The right column (B, D, F) shows two-digit test positivity percentages.

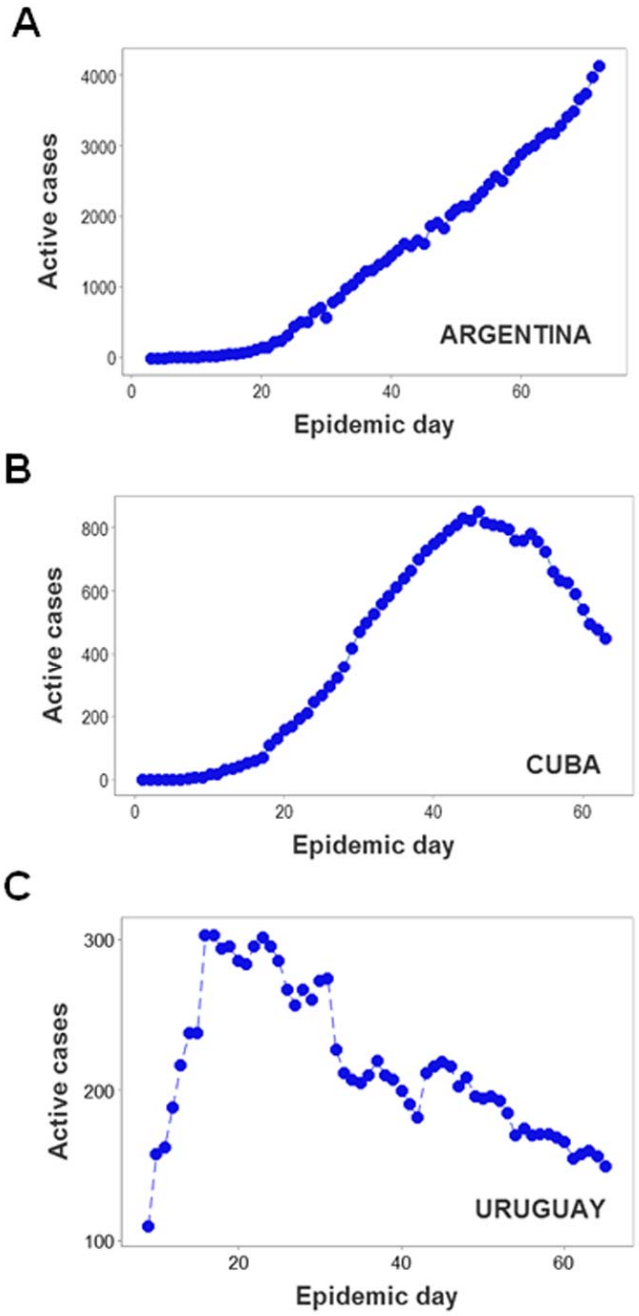

Fig. 6. Temporal-related metrics in the analysis of the COVID-19 cases in four countries. (A) Argentina; (B) Cuba; (C). Uruguay.

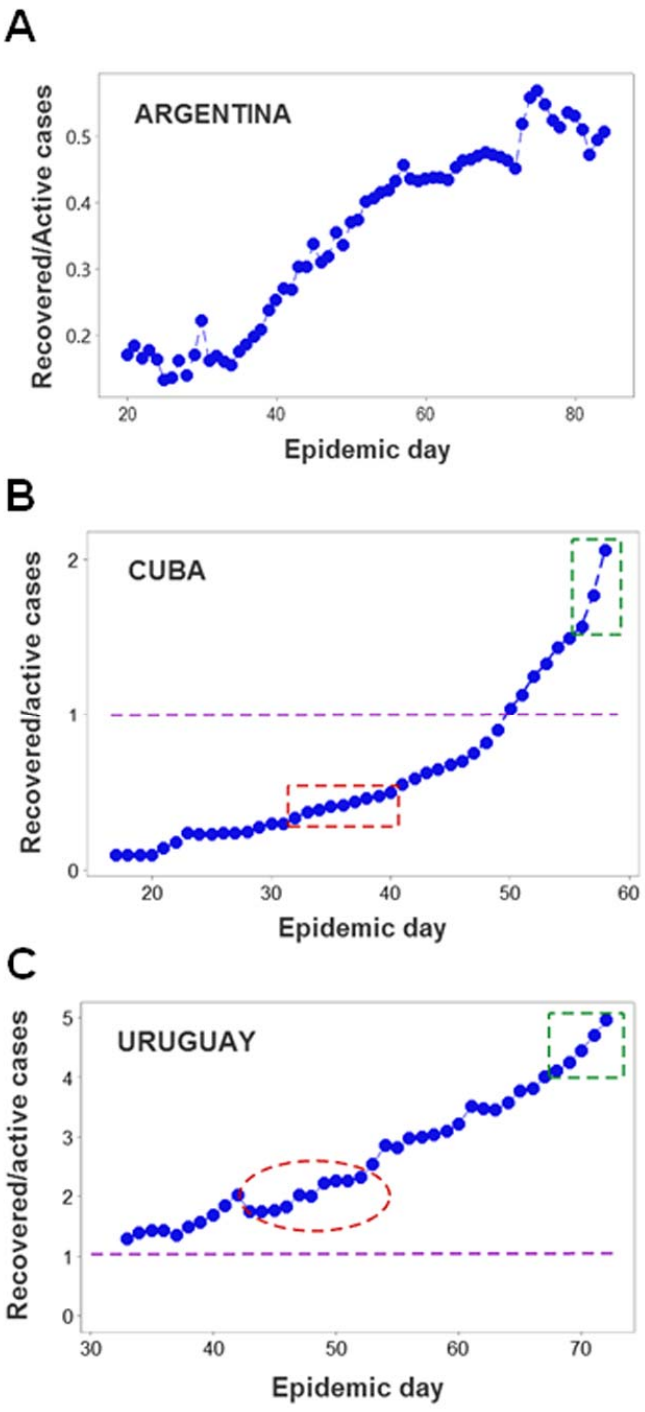

Fig. 7. Relationship between test positivity data and other metrics in selected countries. (A) Argentina; (B) Cuba; (C). Uruguay.

4. Discussion

Hoping to explore a novel metric –test positivity−, we evaluated several epidemic parameters associated with SARS CoV-2 for the first 60 to 90 epidemic days in six countries where the time when the first COVID-19 case was reported differed in six of fewer weeks. Given that test positivity is not a direct measure of health status at population level, it was wondered whether this metric could estimate –albeit indirectly− the progression (or lack of) of epidemic dispersal.

The answer to such a question is unlikely to be totally elucidated with a single study. However, one study may provide information that supports or rejects theories and/or technologies aiming at monitoring population health status when exposed to infectious diseases with a high or very high percentage of asymptomatic individuals.

Earlier studies have shown that test positivity predicts epidemic dispersal better than the simple number of tests performed per million inhabitants [5, 6]. In addition, this evaluation documented several statistically significant associations that may reflect biological relationships. For instance, when two sources of data were used, the Uruguayan case revealed a negative correlation between TP and TPMI, both when it was investigated alone and when four other countries were explored (Figures **2A** and **3C**). Such a double reproducibility (which involves two data sources and five countries) does not support random findings.

The fact that several variables also exhibited reproducible patterns (such as two temporal phases), provides a group of metrics associated with TP that may be worth considering in future studies. Some of these indicators may provide geography- (country-), and time-specific information potentially useful in epidemic monitoring. For instance, in the Uruguayan epidemic, at least 1000 tests per million inhabitants appeared to be needed to flatten out the growth of fatalities (Fig **1E**).

In all six investigated countries, the simultaneous consideration of TPMI and DPMI, over time, may help to find both similarities and differences (Figures **3 E and F).**

The observed relationships among TP, tests/million inhabitants, the shape of active cases, and the shape of the R/A ratio data supported WHO's recommendations on policies aimed at low TP percentages: the highest levels of testing (which may detect credible levels of disease prevalence) only occurred at the lowest levels of TP. The test positivity, together with the shape of the number of active cases, can determine whether and when the epidemic is / is not under control. Associated patterns –such as increasing or decreasing trends of the recovered/active ratio data− may inform policy makers whether an overflow of hospital beds and associated resources is not / is likely in the following weeks. When TP is analyzed together with tests/million inhabitants, it may indicate (in a country-specific manner and without pre-established assumptions) whether testing is sufficient or not. While the data analyzed in this study referred to nationwide levels and aggregated data tend to be less informative because it may lose resolution [17], these metrics could also be used with lower-scale, higher-resolution (county- or city-level) geographical data [11, 12].

While limited in scope, this study generated hypotheses. One example is the hypothesis that lack of explicit isolation policies may inhibit the effectiveness of massive testing. Such a hypothesis was illustrated by one country that showed a high level of testing, but did not pursue isolation [18]. Patterns observed were compatible with studies that have reported (a) lockdowns but no specific testing scheme, and (b) neither testing nor lockdowns [18].

Thus, this initial stdy on test positivity provides support for several recommendations. We advocate for a policy that focuses on four aspects: (1) massive and repeated testing, (2) border control, (3) tracing of every case, and (4) active isolation which, to be successful, must be implemented within a Critical Response Time, that is, before the exponential growth kicks in [19].

Effective responses are not likely to depend on piecemeal approaches that only consider one or a few strategies. Instead, new and accelerated educational programs are needed, which should provide training on several disciplines, including but not limited to (a) geography, (b) epidemiology, (c) the economics of public health, (d) development and use of new software packages that facilitate early (real time) and geographically specific interventions, and (e) the creation of new systems that both collect and disseminate data.

Provided that additional studies reproduce thee findings, one possible application of test positivity is to become an alternative to the quasi-centennial 'reproductive number' (or R_0), which estimates the ratio of secondary over primary cases. That is so because, at the present time, there are no real time estimates on how rapidlly epidemics may progress and such estimates are also prone to numerous sources of error [20, 21]. Unlike the lack of geographically explicit information and delayed calculations associated with the R_0 (which prevent real time, site-specific decision-making), test positivity can be calculated on daily basis and provide actual (not assumed) high-resolution, geographical information (e.g., neighborhood- or village-specific geographical coordinates). Such an application could improve policy-making: instead of assuming test positivity is homogeneously distributed over large territories and remains constant over time, daily changes at specific (and geographically small) sites could support context-specific, cost-benefot oriented interventions [6].

To win the war against the next epidemic, reactive responses are not acceptable. Proactive responses are the only alternative, which require a robust and immediate creation of novel educational programs of inter/transdisciplinary nature. To that end, further research on the advantages and limitations of test positivity is necessary.

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