Progression of COVID-19 in six South American countries with different vaccination coverage

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ABSTRACT
COVID-19 seems to have progressed under two general assumptions: a) every new variant of SARS-CoV-2 should bear the worst consequences, thus justifying extension of government-mandated lock-downs, school and border closures, face mask wearing and other restrictive measures and b) that hastily developed experimental vaccines employing novel technologies would quickly and efficiently stop the pandemic by protecting from infection or, at the very least, by preventing complications and death. We tested these two hypotheses by analyzing the epidemiological data officially released by the governments of six countries in South America. We found that vaccination failed to prevent contagion by Omicron or by previous variants of SARS-CoV-2. Mortality has decreased with time since the start of global COVID-19 in early 2020 with Omicron showing the lowest mortality to date. This finding cursorily agreed with a beneficial effect of vaccination in each individual country but failed when countries with similar mortalities and different vaccination rates were analyzed. Thus, the slight but continued reduction in mortality through the duration of the pandemic and sharp decrease with Omicron do not correlate with the level of national vaccination among the countries studied. A more plausible explanation for the decrease in mortality through time is the natural attenuation of SARS-CoV-2 from successive passage through millions of susceptible and healthy hosts, as dictated by well-established principles of virology, immunology, and vaccinology dating at least from the mid 1950’s. The failure to prevent infection or to substantially reduce mortality as reported here should raise questions about the value of the massive vaccination campaigns in South America, particularly, considering the potential risks of adverse reactions (still to be fully determined) to experimental vaccines and the considerable cost to the stressed national economies of the region.

Keywords: COVID-19, SARS-CoV-2, pandemic, variants, vaccination, Argentina, Bolivia, Brazil, Chile, Paraguay, Uruguay
1. Introduction
A long established method of vaccine production before the use of recombinant DNA technology has been virus attenuation by passages through susceptible hosts. Attenuation by passage become firmly established after 1960 when live attenuated polio vaccine became available on a large scale.\textsuperscript{1-3} In contrast to the concept of natural attenuation, identification of every new variant of SARS-CoV-2 has been generally assumed to result in a worsening of the public health impact of COVID-19. This notion seemed supported in South America by continued increase in the number of infections, since the initial SARS-CoV-2 variants (Alpha, Beta [reported in Brazil in February 2020], Gamma [reported in Brazil in early 2021], Kappa, Zeta, and Andina.\textsuperscript{4-6} The assumption that every new variant was worse than its predecessors was bolstered in early 2022 by the large peak of infections during circulation of Omicron.\textsuperscript{7,8}

In this study we analyzed the progression of infections and deaths attributed to COVID-19, the appearance of different variants, and advance of the vaccination campaigns according to the official data released by the governments of Argentina, Bolivia, Brazil, Chile, Paraguay, and Uruguay.\textsuperscript{9-14} These countries were selected because all are located south of the equator, thus receiving through a considerable portion of their territory comparable germicidal solar radiation\textsuperscript{15}; and the governments of these countries presented timely and relatively stable data. The progression of COVID-19 in some of these countries up to December 2020, before the initiation of the vaccination campaigns, has been discussed previously.\textsuperscript{16} The impact of stringent restrictive measures imposed in Argentina has been previously compared to COVID-19 in Uruguay, a country that did not impose lock-downs and fared relatively well during the pandemic until vaccination started.\textsuperscript{17}

The World Health Organization (WHO) states that all of the vaccines that have achieved WHO Emergency Use Listing\textsuperscript{18} are safe and effective vaccines that prevent people from getting seriously ill or dying from COVID-19.\textsuperscript{19} The US Food and Drug Administration (FDA) has approved for emergency use a different list of Covid-19 vaccines than those approved in the WHO Emergency Use Listing.\textsuperscript{18,20} In a similar statement to that of WHO above, the US Center for Disease Control and Prevention (CDC) assures that vaccination remains highly effective against COVID-19 hospitalization and death caused by SARS-CoV-2.\textsuperscript{21} Table 1 lists the vaccines administered in each of the six studied countries.\textsuperscript{22-27}
Table 1: Vaccines administered by countries

<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>VACCINES</th>
<th>STARTING DATE</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARGENTINA</td>
<td>Astra-Zeneca&lt;sup&gt;W&lt;/sup&gt; (UK), Pfizer-Biontech&lt;sup&gt;WF&lt;/sup&gt; (USA-Germany),</td>
<td>12/29/2020</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>Covidicia/Cansino (China-Canada), Covishield&lt;sup&gt;W&lt;/sup&gt; (India), Moderna&lt;sup&gt;WF&lt;/sup&gt; (USA), Sinopharm&lt;sup&gt;W&lt;/sup&gt; (China), Sputnik V (Russia)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BOLIVIA</td>
<td>Astra-Zeneca&lt;sup&gt;W&lt;/sup&gt; (UK), Janssen-J&amp;J&lt;sup&gt;WF&lt;/sup&gt; (USA),</td>
<td>04/28/2021</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>Pfizer-Biontech&lt;sup&gt;WF&lt;/sup&gt; (USA-Germany), Sinopharm&lt;sup&gt;W&lt;/sup&gt; (China), Sputnik V (Russia)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRAZIL</td>
<td>Astra-Zeneca&lt;sup&gt;W&lt;/sup&gt; (UK), Coronavac-Sinovac&lt;sup&gt;W&lt;/sup&gt; (China),</td>
<td>01/18/2021</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Janssen-J&amp;J&lt;sup&gt;WF&lt;/sup&gt; (USA), Pfizer-Biontech&lt;sup&gt;WF&lt;/sup&gt; (USA-Germany)</td>
<td></td>
<td></td>
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<tr>
<td>CHILE</td>
<td>Astra-Zeneca&lt;sup&gt;W&lt;/sup&gt; (UK), Coronavac-Sinovac&lt;sup&gt;W&lt;/sup&gt; (China),</td>
<td>12/24/2020</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>Pfizer-Biontech&lt;sup&gt;WF&lt;/sup&gt; (USA-Germany)</td>
<td></td>
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<tr>
<td>PARAGUAY</td>
<td>Astra-Zeneca&lt;sup&gt;W&lt;/sup&gt; (K), Coronavac-Sinovac&lt;sup&gt;W&lt;/sup&gt; (China),</td>
<td>03/19/2021</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>Covaxin&lt;sup&gt;W&lt;/sup&gt; (India), Moderna&lt;sup&gt;WF&lt;/sup&gt; (USA), Pfizer-Biontech&lt;sup&gt;WF&lt;/sup&gt; (USA-Germany), Sinopharm&lt;sup&gt;W&lt;/sup&gt; (China), Sputnik V (Russia)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>URUGUAY</td>
<td>Pfizer-Biontech&lt;sup&gt;WF&lt;/sup&gt; (USA-Germany), Sinovac&lt;sup&gt;W&lt;/sup&gt; (China)</td>
<td>01/03/2021</td>
<td>27</td>
</tr>
</tbody>
</table>

Footnote: Vaccines approved by the WHO or by the US FDA are denoted with a W or a F, respectively. The date of initiation of vaccination in each country is also indicated according to the references listed in the Table.

The aim of the present study was to clarify the role of SARS-CoV-2 variants (from the initial variants in 2020 to the current, Omicron in early 2022), and the benefit of massive vaccination in South America by analysis of the epidemiological data reported by the governments of six countries.

2. Methods
2.1 Data sources. The timelines for the apparition and circulation of various variants of SARS-CoV2 has been documented previously.<sup>4-6</sup> COVID-19 epidemiological data officially released by the government of each studied country<sup>9-14</sup> was employed here after confirmation of the data as compiled by the John’s Hopkins’ Center for Systems Science and Engineering and presented in Our World in Data.<sup>28</sup> The total number of infections and deaths attributed to COVID-19 needed to be normalized for comparative purposes (everything being equal, large populations should have larger number of cases). Therefore, new daily infections attributed to COVID-19 per million inhabitants (infection rate) was presented. New daily deaths per 1000 infections is discussed in section 3.2. Since infection mortality rates (deaths per thousand or per million infections) are strongly affected by the number of infections,<sup>29</sup> which in turn varies with the level of testing, deaths per million inhabitants was preferred for Table 2 and the graphs in Figure 1 and 2. The 7-day rolling average of daily new confirmed COVID-19 infections and deaths per million inhabitants is presented in order to decrease artificial data oscillation due to
minimal government reporting on weekends and holidays and the release of several days’ worth of data on Mondays or other week days.

The figures of infections and the deaths per million inhabitants were calculated for each country utilizing the 2019 world population data. The reported mortality attributed to COVID-19 is not “excess mortality” as usually recorded in epidemiology; therefore, the mortality figures used here could be an overestimation if basal mortality (mortality occurring in absence of epidemics) would be discounted.

The percentages of each country's population that had received one dose (considered partially vaccinated) or two doses of vaccine (generally considered as fully vaccinated) were those compiled globally.

2.2 Statistical analysis. The date period of each peak of new daily deaths in each country was determined from the officially released national data. The date corresponding to the maximal daily new deaths of every peak was employed for statistical analysis. The dates of maximal new deaths were transformed to total number of days after January 1st 2020. The linear correlation between deaths and vaccination rate was calculated with Graph Pad Prism Version 2.0 statistical software (San Diego, California) which provided the correlation coefficient ($R^2$), the slope ± its standard deviation of the correlation (new daily deaths/million versus % vaccination), and the p-value. The significance of the difference between two correlation slopes was determined by input of the slopes, their standard deviation and degrees of freedom into the proper t-student test in online statistical calculators.

3. Results
3.1 Progression of COVID-19 in South America. Infections and mortality occurred from the starting of COVID-19 in South America with successive peaks and valleys. Plotting the two-year pandemic in a single graph with a single Y-axis scale necessarily reduced the apparent magnitude of these oscillations. Panel A in Figure 1 illustrates the progression of COVID-19 infections since the onset of the pandemic. The figure identifies main infection peaks during 2020, coinciding in Bolivia and Brazil (June-July 2020) with earlier peak in Chile and later peaks during October in Argentina and Paraguay (no infection peak in Uruguay during 2020). Several peaks of infection are detected during January 2021 in all countries. Two prominent infection peaks occurred in Argentina and Uruguay in March and June, with lesser peaks in Brazil, Chile, and Paraguay. In all countries the highest peak of infectivity to date has been reported during January 2022, when Omicron is circulating.
Figure 1: Progression of infections (A), Vaccination (B) and Deaths (C) from the beginning of the pandemic. The circulating variants of SARS-CoV-2 are shown at the top of panel A. The arrows indicate the start of the respective vaccination campaigns.
3.2 Infections and mortality of variants.
The peaks in infections during 2020 and early 2021 occurred while initial variants Alpha, Beta, Gamma, Kappa, Zeta, Mu and Andina were circulating.\textsuperscript{4, 6} Peaks in new daily infections appeared in all studied countries during mid 2021 (Figure 1A). The prominent peak occurring in January 2022 highlights the high infectivity of variant Omicron in comparison to the previous SARS-Co V-2 variants. The dates corresponding to different variants in the bar atop panel A are those reported in Argentina, as a representative South American example.

Mortality figures ascribed to SARS-Co V-2 are represented in Panel C, which shows that mortality during early 2022 is lower than that observed in previous mortality peaks. In contrast to its high transmissibility, the mortality under Omicron has remained to date relatively low at 1.56, 4.08, 2.31, 0.13, 7.20 and 0.47 deaths per 1000 infections at the peak of infectivity on January 18, 2022 in Argentina, Bolivia, Brazil, Chile, Paraguay and Uruguay, respectively. After appearance of Omicron, these figures are substantially lower than the new daily deaths per 1000 infections reported for those same countries of 14.2, 21.7, 45.0, 13.7, 32.5 and 28.5, respectively on May 28, 2021 when Alpha, Beta, Gamma, Kappa, Zeta, Mu and Andina variants were circulating in South America.

3.3 Infections and Vaccination. Panel B depicts the advance of the vaccination campaigns in the six South American countries studied. The arrows in the Panel A of the figure indicate the start of the vaccination campaigns in Argentina, Bolivia, Brazil, Chile, Paraguay and Uruguay, respectively. Partial vaccination (one dose), ranging from 68.6% of the population in Chile to 6.4% in Paraguay did not prevent the high peaks of infection occurring during winter 2021 (March-August 2021) in any of the countries (data not shown), when the initial variants as well as the Delta variant were circulating. The new daily infections in Brazil, Chile and Paraguay are similar during the infection peaks occurring in these countries in March to July 2021 (approximately 300 new daily infections per million inhabitants) in spite of considerable differences in the proportion of the fully vaccinated populations in those countries (as shown in Panel B of Figure 1). Bolivia had the fewest new daily infections among all countries in that peak, having started vaccination relatively late (see arrow in Figure 1A) and one of the lowest vaccination rates (4.7% fully- and 13% partially-vaccinated population) in that period (Table 2). In comparison, Uruguay, at that time, had the highest number of new daily infections per million inhabitants with nearly twice the vaccinated population (7.5% fully- and 29% partially-vaccinated) than Bolivia. Interestingly, the heights of the infection peaks after the start of vaccination campaigns were higher than before vaccination in all countries. In addition, Uruguay did not have any infection peak (actually very low infection levels) in 2020 and infections were the highest among all the six countries only after vaccination in Uruguay was in full progression.
Table 2: Vaccination rates at peaks of mortality

<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>PRE-VACCINATION</th>
<th>DURING VACCINATION 2021</th>
<th>OMICRON2022</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DEATHS PER MILLION</td>
<td>% FULLY VACCINATED</td>
<td>DEATHS PER MILLION</td>
</tr>
<tr>
<td>ARGENTINA</td>
<td>Aug 23 4.52 (235)</td>
<td>17.3 (274)</td>
<td>Jan 20 5.7 (760)</td>
</tr>
<tr>
<td></td>
<td>Oct 01 17.3 (274)</td>
<td>5.32 (93)</td>
<td>4.52 (235)</td>
</tr>
<tr>
<td></td>
<td>Jul 12 9.3 (55)</td>
<td>11.1</td>
<td>9.3 (55)</td>
</tr>
<tr>
<td>BOLIVIA</td>
<td>Jul 05 7.47 (517)</td>
<td>2.87</td>
<td>Jun 25 5.16 (755)</td>
</tr>
<tr>
<td></td>
<td>May 27 7.47 (517)</td>
<td>2.87</td>
<td>Jun 10 5.16 (755)</td>
</tr>
<tr>
<td></td>
<td>Sep 07 7.83 (532)</td>
<td>4.70</td>
<td>Feb 01, 2021 7.13 (406)</td>
</tr>
<tr>
<td>BRAZIL</td>
<td>Jul 08 4.96 (149)</td>
<td>3.62 (356)</td>
<td>Jul 08 8.86 (554)</td>
</tr>
<tr>
<td></td>
<td>Jun 14 12.64 (165)</td>
<td>14.90</td>
<td>Feb 01, 2021 3.62 (356)</td>
</tr>
<tr>
<td></td>
<td>Jul 21 11.96 (202)</td>
<td>20.09</td>
<td>Jan 04 1.84 (765)</td>
</tr>
<tr>
<td></td>
<td>Apr 14 0.48 (458)</td>
<td>6.97 (519)</td>
<td>Feb 01, 2021 8.86 (554)</td>
</tr>
<tr>
<td></td>
<td>Jun 03 5.70 (355)</td>
<td>11.43</td>
<td>Jul 08 8.86 (554)</td>
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<td>Jun 19 9.70 (555)</td>
<td>11.43</td>
<td>Jul 08 8.86 (554)</td>
</tr>
<tr>
<td>PARAGUAY</td>
<td>Sep 01 2.51 (249)</td>
<td>0.17</td>
<td>Jan 29 6.81 (759)</td>
</tr>
<tr>
<td></td>
<td>May 01 13.34 (986)</td>
<td>0.17</td>
<td>Jan 29 6.81 (759)</td>
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<tr>
<td></td>
<td>Sep 25 5.19 (565)</td>
<td>10.3</td>
<td>Sep 01 2.51 (249)</td>
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<tr>
<td></td>
<td>Oct 09 5.07 (282)</td>
<td>1.98</td>
<td>May 01 13.34 (986)</td>
</tr>
<tr>
<td></td>
<td>Dec 09 2.67 (354)</td>
<td>2.71</td>
<td>May 01 13.34 (986)</td>
</tr>
<tr>
<td></td>
<td>Dec 09 2.67 (354)</td>
<td>2.71</td>
<td>May 01 13.34 (986)</td>
</tr>
<tr>
<td>URUGUAY</td>
<td>Jan 15 16.49 (470)</td>
<td>7.48</td>
<td>Feb 04 1.99 (765)</td>
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<td></td>
<td>Jan 22, 2021 2.99 (387)</td>
<td>28.35</td>
<td>Feb 04 1.99 (765)</td>
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<tr>
<td></td>
<td>Mar 23 18.69 (508)</td>
<td>28.35</td>
<td>Feb 04 1.99 (765)</td>
</tr>
<tr>
<td></td>
<td>Jun 06 17.5 (322)</td>
<td>30.92</td>
<td>Feb 04 1.99 (765)</td>
</tr>
</tbody>
</table>

Footnote: a. Peak figures corresponding to pre-vaccination; b. Corresponds to the partial advance of the vaccination campaign and c. to a more advanced stage of the vaccination campaign. d. The 7-day rolling average of new daily deaths per million inhabitants is shown with the days after January 1 2020 indicated in parenthesis. e. The slope of the linear regression of daily new mortality as a function of % of the fully vaccinated population (with 2 doses) is indicated, followed by the correlation coefficient (R²) and the probability value (p) of the regression.

Similarly, the substantially high peaks in new daily infections when Omicron circulated in early 2022 (nearly 2,000 new daily infections per million inhabitants) do not correlate with the different rate of fully vaccinated populations, ranging from a high of nearly 85% in Chile, 70-80% in Argentina, Brazil and Uruguay, to as low as 42% in Bolivia and Paraguay (Figure 1B). This data demonstrates that COVID-19 vaccines administered in South America did not protect from SARS-CoV2 infection, and particularly, do not prevent infection with the Omicron variant.

3.4 Vaccination and mortality. A series of peaks in new daily mortality per million inhabitants (Panel C) occurred in the studied countries before any vaccines were available. Comparable mortality peaks occurred several months after the start of the vaccination campaigns in 2021 when variable proportions of the population of the countries studied were fully vaccinated (with two doses) as depicted in Panel B of Figure 1. We chose not to analyze the correlation between deaths and vaccination at every date to prevent the peaks and valleys masking any benefit from vaccination. Instead, we focused on major peaks of mortality that could be affected
more intensely by vaccination. The date of maximal mortality rate (7-days rolling average) occurring at the number of days after the arbitrary starting date of January 1st, 2020 (in brackets) is recorded for every country in Table 2. To maximize the potential benefit of vaccination we did not study partial vaccination (one-dose). Instead, the percentage of the population fully vaccinated (two doses) is reported in Table 2 for dates with maximal number of new deaths (per million). Peaks of deaths before start of the vaccination campaigns (during 2020) were similar to mortality after the campaigns have progressed (Figure 1 Panel B and C and data in Table 2). Mortality in Bolivia increased up to September 7 2020 (24.47 deaths/million) to decrease to 5.13/million in February 10 2021, just before the vaccination campaign started. The highest peak of mortality in Brazil (14.52/million) is three-fold higher than the highest mortality peak (4.86/million) before the vaccination campaign started in that country. Similarly, mortality in Paraguay and Uruguay after initiation of the vaccination campaigns is several-fold higher than mortality before vaccination started (Table 2). In Argentina mortality peaks are similar pre- and post-vaccination and in Chile mortality post vaccination is lower than pre vaccination.

We paired to 0% vaccination to the peaks pre-vaccination in Table 2 and calculated for each country the linear regression between mortality and vaccination as described in Methods with the results shown at the right in Table 2.

The slope of the linear regression between new daily deaths/million and % of the fully vaccinated population (2-doses) was slightly negative (smaller than 0.1 in all countries) not significantly different than zero\textsuperscript{31,32} and with small correlation coefficients (R\textsuperscript{2} lower than 0.11) except in Chile with a modest correlation (R\textsuperscript{2} = 0.69). The indecisive R\textsuperscript{2} in Chile induced additional study to detect a stronger correlation and steeper slope of the regression mortality versus vaccination. The results depicted in Figure 2 indicate that there is no correlation between the daily new deaths (per million) and the percentage of the Chilean population fully vaccinated (from 14.90% in March to 85.45% in December 2021, with a slope of +0.02225 \(\pm\) 0.01879, R\textsuperscript{2} = 0.2596, p= 0.3019). None of the regression lines showed an obvious inflection after the vaccination campaign started in any of the studied countries.

Figure 2. COVID-19 deaths and vaccination in Chile. The 7-day rolling average of daily new deaths/million is shown in the Y-axis and the % of the population fully vaccinated (2-doses) at the same dates is depicted in the X-axis.
Conclusions similar to those resulting from the statistical analysis described above can be intuitively observed by comparing, for example the mortalities and vaccination rates during early 2022. The mortality and vaccination figures in Bolivia and Paraguay (5.2 deaths/million-43% vaccination and 6.8 deaths/million-43% vaccination, respectively) are similar to the 5.7 in Argentina and 8.0 deaths/million in Uruguay having these two countries nearly twice the percentage of fully vaccinated population (75% and 77%, respectively) than Bolivia and Paraguay (Table 2).

The two countries with the lowest mortality during the Omicron peak in 2022, Brazil (3.3 new daily deaths/million) and Chile (1.8 new daily deaths per million) differ considerably (18%) in their fully vaccinated populations (88% Chile versus 70% Brazil). The statistical analysis described above and the intuitive observation of the data summarized here agree in that the percentage of fully vaccinated population does not predict or correlate with the mortality ascribed to COVID-19.

4. Discussion
Vaccines had great success in controlling and even eradicating a number of serious diseases in the past and the benefits of immunization against bacterial (plague, typhus, botulism, tuberculosis, etc.) as well as viral diseases (poliomyelitis, smallpox, rabies, hepatitis, measles, mumps, influenza, etc.) have been recognized for many decades with recommendations regarding the risk-benefit of vaccination still valid today.\textsuperscript{2-3} One of the authors of the present article (JLS) had, in addition to a full complement of travel vaccines (typhus, yellow fever, cholera, etc) and of generally available vaccines (polio, tuberculosis, mumps, influenza, hepatitis, etc), received numerous experimental vaccines against warfare germs as part of his duties as Director of a military laboratory. The other author (DRA), in addition to the common vaccines listed above, is fully immunized against COVID-19. Therefore the findings reported in this article could be hardly ascribed to antivaccine scientists, an adjective frequently and rather quickly attached to anybody who dares to question the safety or efficacy of vaccines against COVID-19.

The present study covers the progression of the pandemics in six South American countries of various sizes and diverse demographics, where a wide variety of COVID-19 vaccines (listed in Table 1) of different design were administered. We do not understand why some of vaccines administered in the studied countries of South America were approved by WHO and others by the US-FDA (see Table 1). If COVID-19 vaccines were evaluated only by safety and effectiveness criteria, then, vaccines administered in South America should be approved by both WHO and the FDA. Although there is some overlap, the difference of institutional approval in the list of vaccines in Table 1 and the apparently different criteria for approval by the international and national institutions of developed countries should be clearer, especially when administered in developing countries with limited testing and monitoring resources.

Unfortunately, the data reported by the governments of the six countries depicted in Figure 1A and B demonstrate that the COVID-19 vaccines administered in South America failed to prevent infection during prevalence of every known variant. The high peak of infection during early 2022 further demonstrates that vaccination was particularly ineffective to protect against Omicron, the last variant reported to date (February 2022).
The lower mortality observed under Omicron has been explained by public health authorities mainly as a direct benefit resulting from massive vaccination.\textsuperscript{19,21} Cursory examination of the COVID-19 mortality data depicted in Panel C in Figure 1 (new daily deaths per million inhabitants) would seem to show a small decrease in the peaks of mortality with increasing vaccination (as shown in panel B). However, it can also be seen that peak mortality occurred in the mid 2021, several months after massive vaccination started in all the studied countries. The statistical analysis described in Methods and the reported Results failed to detect a significant benefit of vaccination on mortality. The data in Figure 1 and in Table 2 show that nearly two-fold variation in the proportion of population fully vaccinated did not correlate with a significant lower mortality. Still a benefit of vaccination could perhaps become detectable after including larger data sets and more refined statistical analysis than the classic and straightforward tests employed here. However, any beneficial effect of vaccination in mortality would be, at best, relatively low, in view that mortality at the peak in early 2022 in Bolivia and Paraguay (5.2 new daily deaths/million and 6.8 new daily deaths/million, respectively in Table 2) occurred when full vaccination was below 50% in both countries. Mortality in Argentina (4.8 daily deaths per million) with 75% of its population vaccinated does not differ significantly from the mortality in Bolivia and Paraguay. In contrast to the results of the massive vaccination campaigns against COVID-19, vaccination against poliomyelitis decreased the number of cases rather quickly after the start of massive vaccination and reduced total global cases by 99% in a few years (especially after live attenuated vaccine became available in large scale).\textsuperscript{33} A more plausible explanation for the slightly decreasing mortality through the pandemic and particularly the low mortality observed in January 2022 would be natural attenuation of the virus through vast number of susceptible hosts. The data presented here supports the notion that Omicron is a variant attenuated by passage through countless millions of susceptible humans known (by testing) or unknown to be infected by SARS-Co V-2. This hypothesis is based on data published as early as 1956, when Sabin reported that strains of poliovirus recovered from healthy individuals exhibited a wide range of neurovirulence (as measured by intracerebral inoculation in monkeys).\textsuperscript{1,34} Although some mechanisms may still need further elucidation, the general principles of virus attenuation have been established for long time.\textsuperscript{35} There is evolutionary pressure for high infectivity and low mortality that benefits the virus by increasing propagation through more hosts but without killing them, what would result in an end to replication and extinction of its clad. Accordingly, attenuation by multiple passages under evolutive pressure could explain attenuation of Omicron.

The findings reported in the present article raise the question whether a naturally attenuated viral strain conferring concomitant immunocompetence and resulting in lower mortality could have been attained earlier in the pandemic if social interactions would not have been prevented by lock-downs and other restrictive non-pharmaceutical measures of early implementation.\textsuperscript{16,17} In addition to natural attenuation, an increased proficiency of health care systems after two years of pandemic could have resulted in fewer hospitalizations preventing some nosocomial infections in intubated and ventilated COVID-19 patients leading to fewer deaths by...
common pathogens that instead were ascribed to SARS-CoV-2. Therefore, the effect of natural attenuation of SARS-CoV-2 through millions of human hosts, augmented by fewer hospitalizations and resulting fewer nosocomial infections and deaths ascribed to SARS-CoV-2, could explain fully a decreasing mortality without any contribution by massive vaccination.

The approach described in this study could serve as a blueprint for similar research in other countries located in different regions. Other scientists interested in clarifying the roles of: variants of SARS-CoV-2, hospital infections, and vaccination in COVID-19 infections and deaths are welcome to contact the authors regarding these topics.

The lack of a self-evident or substantial benefit in preventing infection or in reducing mortality as indicated by the data analyzed here should raise questions about the value of the massive vaccination campaigns in South America, particularly, considering the potential risks of experimental vaccines with adverse reactions still to be fully determined and the considerable cost to the stressed national economies of the region. Considering the effect on society and the economy, the burden of proof should fall heavily on proving a substantial benefit of massive vaccination and not on demonstrating their irrelevance.

5. Conclusions
The three main findings reported here indicate that:

i) Massive vaccination has not prevented COVID-19 infections in South America.
ii) The notion that vaccination prevents serious effects and death by COVID-19 is contradicted by similar mortality in countries with considerable differences in

the percentages of vaccinated population and non-significant results of statistical analysis.

iii) Not every new viral strain or variant should be assumed to be more lethal than its predecessors. In particular the Omicron variant which is highly transmissible and with low mortality, may be desirable for conferring natural immunity against SARS-CoV-2.

The findings supported by the epidemiological data discussed here should not be considered as a criticism of the established assumptions and dogmas developed during COVID-19. Instead it is hoped that the present article will promote free and honest discussion of its findings leading to improved public health responses in future pandemics. This goal will only be attainable without a) the censorship of some leading scientific journals, b) sensationalisms of news media, c) greed from pharmaceutical corporations, and d) expectations of personal gain (political or economical) by some high visibility governmental public health servants.

Author contribution: Dr. Daniel Aquilano gathered data from the Health Ministries and other sources in South America and produced the graphs. Dr. Jose-Luis Sagripanti drafted the manuscript and analyzed the data. Contribution was 50% by each author.

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government.

**Data Availability Statement:** The epidemiological data employed in this study is freely available from the sources listed in References. Most reprint of the listed References can be downloaded from the world wide web. Those articles not freely available can be requested from the authors.

**Animal and Human Experiments:** No experiments utilizing animals or humans were undertaken in this study.

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