Ivermectin for COVID-19 in Peru: 14-fold reduction in nationwide excess deaths, p=.002 for effect by state, then 13-fold increase after ivermectin use restricted

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Abstract

Introduction. On May 8, 2020, Peru's Ministry of Health approved ivermectin (IVM), a drug of Nobel Prize-honored distinction, for inpatient and outpatient treatment of COVID-19. As IVM treatments proceeded in that nation of 33 million residents, excess deaths decreased 14-fold over four months through December 1, 2020, consistent with clinical benefits of IVM for COVID-19 as have emerged in several RCTs. But after IVM use was sharply restricted under a new president, excess deaths then increased 13-fold.

Methods. To evaluate possible IVM treatment effects suggested by these aggregate trends, excess deaths were analyzed by state for ages ≥ 60 in Peru's 25 states. To identify potential confounding factors, Google mobility data, population densities, SARS-CoV-2 genetic variations and seropositivity rates were also examined.

Results. The 25 states of Peru were grouped by extent of IVM distributions: maximal (mass IVM distributions through operation *MOT*, a broadside effort led by the army); medium (locally managed IVM distributions); and minimal (restrictive policies in one state, Lima). The mean reduction in excess deaths 30 days after peak deaths was 74% for the maximal IVM distribution group, 53% for the medium group and 25% for Lima. Reduction of excess deaths is correlated with extent of IVM distribution by state with $p<0.002$ using the Kendall τ_b test.

Conclusion. Mass treatments with IVM, a drug safely used in 3.7 billion doses worldwide since 1987, most likely caused the 14-fold reductions in excess deaths in Peru, prior to their 13-fold increase after IVM policy was reversed. This strongly suggests that IVM treatments can likewise effectively complement immunizations to help eradicate COVID-19. The indicated biological mechanism of IVM, competitive binding with SARS-CoV-2 spike protein, is likely non-epitope specific, possibly yielding full efficacy against emerging viral mutant strains.

Data links and a db map for the key data from Peruvian government sources on excess deaths are here.

Introduction

The COVID-19 pandemic swept through Peru beginning with its first identified case on February 26, 2020.[1] The national approval and widespread deployment of a drug for that disease resulted in a remarkable natural experiment. On May 8, 2020, the Peruvian Ministry of Health approved treatment for COVID-19 using ivermectin (IVM),[2] a drug of Nobel prize-honored distinction used in 3.7 billion doses worldwide since 1987.[3,4] Per that authorization, each of the 25 states of Peru implemented inpatient and outpatient treatments with IVM to different extents and in different timeframes, key parameters of which are precisely known, as detailed below. The government of Peru independently tracked two health statistics, state by state, daily, by which mortality could be assessed: COVID-19 case fatalities and excess all-cause deaths. Adding an additional twist to this epidemiological record, on November 17, 2020, a new president of Peru, Francisco Sagasti, took office.[5] The government then stopped distributions of IVM, the channel by which most patients had obtained it previously, and allowed its further use only by a doctor's prescription.[6-10]

The simplest yet least scientifically conclusive aspect of this epidemiological record was the change in the nationwide total of daily excess deaths (7-day moving average, all ages), before and after Peru's mass treatments of COVID-19 with IVM were sharply restricted beginning in mid-November. As shown in Figure 1A, between August 1 and December 1, 2020, nationwide excess all-cause deaths decreased from 660 to 48, a 14-fold reduction.[11] Excess deaths then increased 13-fold over the next two months to 608 on February 1, 2021. (For ages ≥ 60, excess deaths decreased from 506 to 45, 11-fold, and then increased to 442, 10-fold, for these same dates.[11]) To consider whether IVM treatments could explain this 14-fold nationwide decrease in mortality prior to their restriction, the state-by-state record of mortality trends and IVM distributions and treatments was analyzed using the methodology previewed in figures 1B-C.

Peru is divided into 24 *departamentos*, one of these being the Lima capital region, plus the independent *provincia* of Callao, which lies entirely within Lima.[12] For simplicity of reference, these are designated here as the 25 states of Peru. Mass distributions of IVM for inpatient and outpatient treatments of COVID-19 occurred autonomously in these 25 states through both public and private channels. IVM treatments began in different time periods between April and August 2020 in each of these 25 Peruvian states; in some, beginning even a few weeks before the May 8 national authorization. Details as to IVM distributions from such public and private sources in nine representative states, spanning different latitudes and terrains, have been provided.[13] The 25 states of Peru, with a combined total population of 33 million, span terrain from jungle to desert to mountain, equivalent to an extent from Denmark to Italy and Greece in Europe or from Florida to Minnesota to New York in the United States.

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A description of IVM distributions and treatments in Peru with state-by-state figures for excess deaths and COVID-19 case fatalities, with additional detail for nine states, was presented in a previous analysis.[14] As reported there, in each state of Peru but Lima, IVM treatments were widely deployed at the time of an initial surge of pandemic cases and deaths; that surge period varied among the states between April and August 2020. The typical IVM dose provided for both COVID-19 inpatients and outpatients was 200 µg/kg for a single day for mild cases, repeated a second day for more serious cases.[2]

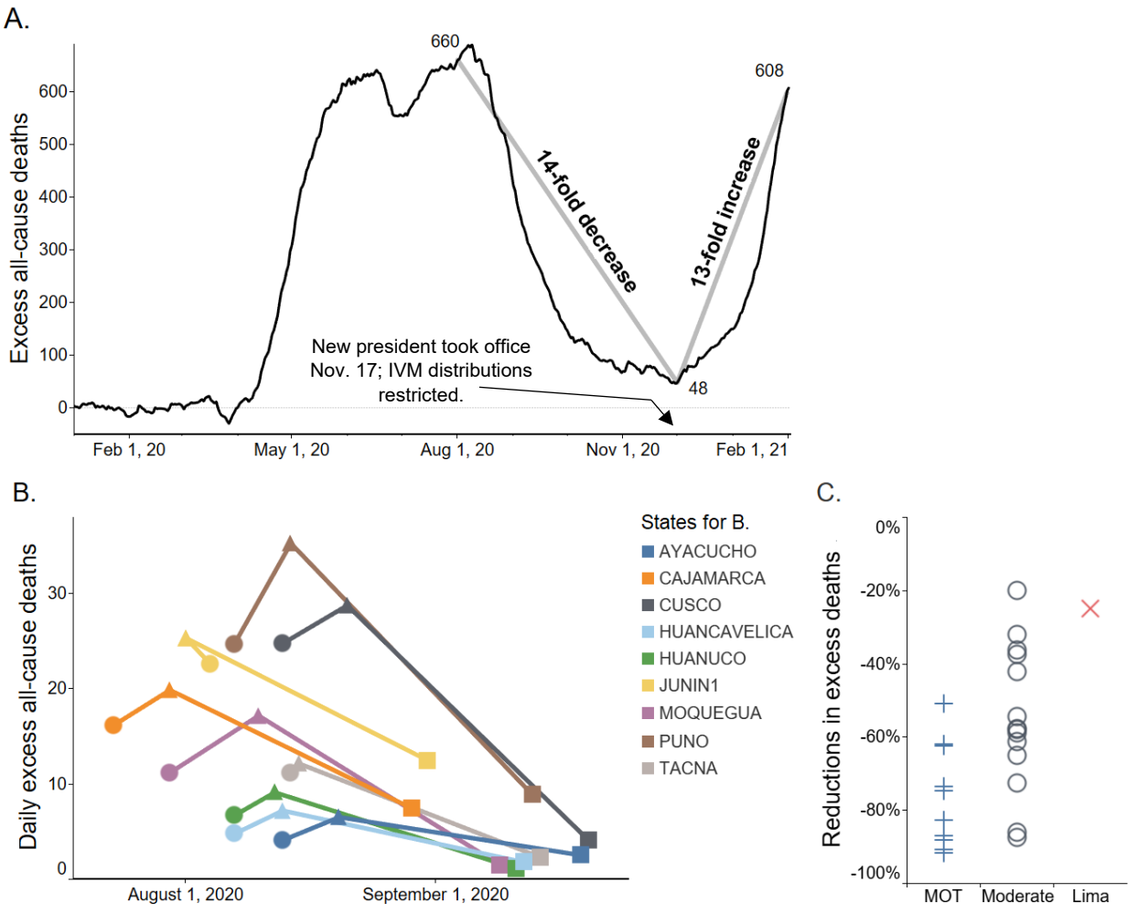

Figure 1. A) Excess all-cause deaths (all ages), national population of Peru. These decreased 14-fold August 1 through December 1, 2020; then, after IVM use was restricted, increased 13-fold through February 1. All y values are 7-day moving averages; for B and C, ages ≥ 60. Data are from Peru's National Death Information System (SINADEF).[11] B) Drops in excess deaths for all states of operation *MOT*, an army-led program of mass IVM distributions, but Pasco, which had them on 3 dates. ● *MOT* start date; ▲ peak deaths; ■ day of peak deaths + 30 days. Junin also distributed IVM 13 days before *MOT* start. C) Reductions in excess deaths at +30 days after peak deaths for the 25 states by extent of IVM distributions: maximal-*MOT* (+), mean -74%; moderate-local distributions (○), mean -53%; and minimal-Lima (x), -25%. These reductions by state correlated with extent of IVM distributions with Kendall τ_b = 0.524 (p<0.002).

Public compliance with these IVM treatments was achieved due to well-publicized reports of successful outcomes for IVM treatment of COVID-19 by Peruvian celebrities, as reviewed in the prior analysis.[14] The level of popular interest in IVM treatment for COVID-19 as spurred by these reports was so high that it led to an IVM shortage in Peruvian pharmacies,[15] which motivated smugglers[16] and counterfeiters[17] to cover the demand. In the Lima capital region, however, restrictive measures on IVM distribution, including police raids on pharmacies, delayed mass IVM treatments for COVID-19 for four months after the initial pandemic surge in April.[13,18,19] Finally, after 10,386 COVID-19 case fatalities had been recorded in Lima through July 31, 2020,[20] 1.0 per thousand of its total population, IVM distributions and treatments began there in mass quantities in August.[13]

IVM was typically distributed through regional health offices, voluntary channels and other private groups, as detailed for several states.[14] But ten states distributed IVM on a mass scale through a national program led by the Ministry of Defense, *Mega-Operación Tayta* (*MOT*). Two of these states had confounding factors for their distributions of IVM. Pasco had three different distribution dates, July 23, August 5 and August 25,[21-23] while Junin's *MOT* deployment, which began August 4, had been preceded by state distributions of IVM to health centers beginning July 22,[24,25] 13 days earlier.

Mega-Operación Tayta (*MOT*), an extension of a precursor program, *Operación Tayta,*[26] was spearheaded by the Peruvian Ministry of Defense and Army. Eleven other government agencies partnered in this effort, including the ministries of health, interior, agriculture, and education, while participating personnel included those from the Army, Navy, Air Force, and police.[27] *MOT*'s objective was to reach every part of a targeted region using rapid response teams that partnered with local health officials. These teams detected

COVID-19 cases house by house, treating patients with IVM and giving them food to encourage their isolation for 15 days.[28]

In each targeted locality, operation *MOT* began with outreach, including home visits, by local officials to identify people at highest risk for COVID-19 mortality, due to either age or other vulnerabilities.[29] No IVM was distributed through *MOT* during this preparatory period, but it was freely available everywhere in Peru without a prescription, and people identified as vulnerable had the capability to take it during that time on their own initiative. A week later, field workers from *MOT* then began distribution of IVM to everyone so identified as being at risk, whether they tested positive or were symptomatic for COVID-19 or not.[29] Other drugs commonly distributed along with IVM were acetaminophen and azithromycin.[8,30] *MOT* began in late July 2020 and reached these ten states, with *MOT* start dates as specified, designating the beginning of the preparatory week: Cajamarca (July 23),[31] Pasco (July 23, August 5 and August 25),[21-23] Moquegua (July 30),[32,33] Junín (August 4),[34] Puno (August 7),[35,36] Huánuco (August 7),[30,37] Huancavelica (August 7),[38] Ayacucho (August 13),[39] Cusco (August 13),[39] and Tacna (August 14).[40]

Since May 8, 2020, when IVM was authorized for COVID-19 treatment in Peru, results of 15 randomized clinical trials (RCTs) and many other clinical studies for IVM treatment or prevention of this disease have been reported worldwide.[41,42] Of particular interest are seven RCTs for IVM treatment of COVID-19 (four double-blind,[43-46] one single-blind,[47] two non-blinded[48,49]) plus four other clinical studies[50-53] that all tracked mortality or measures of morbidity in patients with moderate or severe symptoms. Major clinical improvements were seen in ten of these studies, with improvements just short of statistical significance in the 11th.[49] One meta-analysis of mortality statistics from such studies, restricted to RCTs, found totals of 14/658 (2.1%) deaths for IVM-treated patients and 57/597 (9.5%) deaths in controls, a 78% reduction.[41] In clinical studies using IVM doses totaling at least 400 μg/kg over two consecutive days, mortality rates for IVM treated patients were about one-tenth those of controls.[46-48] In an RCT for IVM prophylaxis, a group of 203 household contacts of COVID-19 cases given IVM had one-eighth the COVID-19 incidence (7.4% vs. 58.4%) and one-fourteenth the severe case incidence (0.5% vs. 6.9%) of the control group.[54]

Another RCT for IVM treatment of COVID-19, this one in a young population, median age 37, tracked time to resolution of symptoms as its primary outcome.[55] No statistically significant differences were found between the IVM and control groups for this outcome or for deaths (0 for IVM vs. 1 for controls). A striking anomaly, however, was that adverse effects characteristic of IVM use at this study's high cumulative dose occurred at almost identical rates in its IVM and placebo arms. This occurred against a backdrop of surging over the counter sales of IVM during the study period, in the study region.[56] Also, blinding was violated by use of glucose solution as the placebo for the first 64 of the 198 patients in the control group, clearly distinguishable in taste from IVM. Another flagrant protocol violation was the mistaken dosing of IVM for 38 designated control patients.[56]

The biological mechanism of IVM clinical benefits for COVID-19 is indicated in seven molecular modeling studies[57-63] to be binding to SARS-CoV-2 spike protein, thereby blocking viral attachment to host cells and other viral functions.[64] That is the same antiviral mechanism for antibodies generated by vaccines currently deployed or under development.[65] Of interest in examining such activity of IVM is that SARS-CoV-2 is a hemagglutinating virus, as established *in vitro* using a methodology refined by Jonas Salk,[66] clinically from red blood cells of COVID-19 patients,[67] and from its biochemical binding properties.[64,68] Clumping of red blood cells, platelets and other blood cells via attachments to cell surfaces by SARS-CoV-2 binding to sialic acid and/or sulfated glycoproteins may be an early trigger for vascular occlusion, which often develops in COVID-19 and appears to be key to its morbidities, as reviewed.[64] The specific type of binding by IVM to these viral spike protein sites appears likely to block such blood cell clumping and also block initial attachments to host infective target cells prior to ACE2 fusion without requiring a precise match to specific spike protein sequences (epitopes), with efficacy of IVM thus conserved against viral mutant strains.[64]

Methods

Two sets of health tracking figures were used for analysis, as compiled daily by the *Centro Nacional de Epidemiología, Prevención y Control de Enfermedades* (National Center for Epidemiology, Prevention and Disease Control) and *Instituto Nacional de Salud* (National Institute of Health) in Peru. These were deaths from all natural causes (excluding violent deaths), hereinafter termed "all-cause deaths," and COVID-19 case fatalities. As discussed in a prior comprehensive analysis of IVM distributions and mortality trends in Peru,[14] case incidence is an unreliable statistic across a national population and was not considered here.

The source for all-cause deaths used in this analysis was the registry of the National Death Information System (SINADEF).[69] Data for populations, by state and by age groups, are from the National Institute of Statistics and Informatics.[70] Data for COVID-19 case fatalities are from the Peruvian government's COVID-19 Open Data Platform.[71] The databases for both all-cause deaths and COVID-19 case fatalities are subject to occasional retroactive adjustments, for example, if a death in a remote location were to be reported days after it occurred. These occasional adjustments have very small impacts on aggregate statistics, but access dates are cited and frozen database snapshots saved for all figures presented. Information and data for IVM distributions were retrieved from official communications and press releases, as individually cited, and the CENARES drug distribution database.[72]

Excess all-cause deaths were calculated from totals, state-by-state, by subtracting respective baseline means for January through February 2020. This simple normalization procedure was reasonable given the small variation in deaths per month in Peru from January 2017 through February 2020. During this period, monthly all-cause deaths fluctuated with a mean value of 5.2% and a standard deviation of 3.8% (Table

S1). However, total deaths for Peru beginning in May 2020 fluctuated by more than double the baseline value for January through February 2020, reflecting the impact of the pandemic (Figure S1). For each of Peru's 25 states, for ages 60 and above, the date of peak (all-cause) deaths was determined to be the day after March 1, 2020 when the 7-day moving average of deaths reached maximum value in that state's first wave of rising deaths from the pandemic. Excess deaths were then also tracked at 30 and 45 days following the day of peak deaths. Figure 2 provides examples of graphs of 7-day moving averages of excess deaths for three states, with line segments joining values of excess deaths at the day of peak deaths and 30 days following.

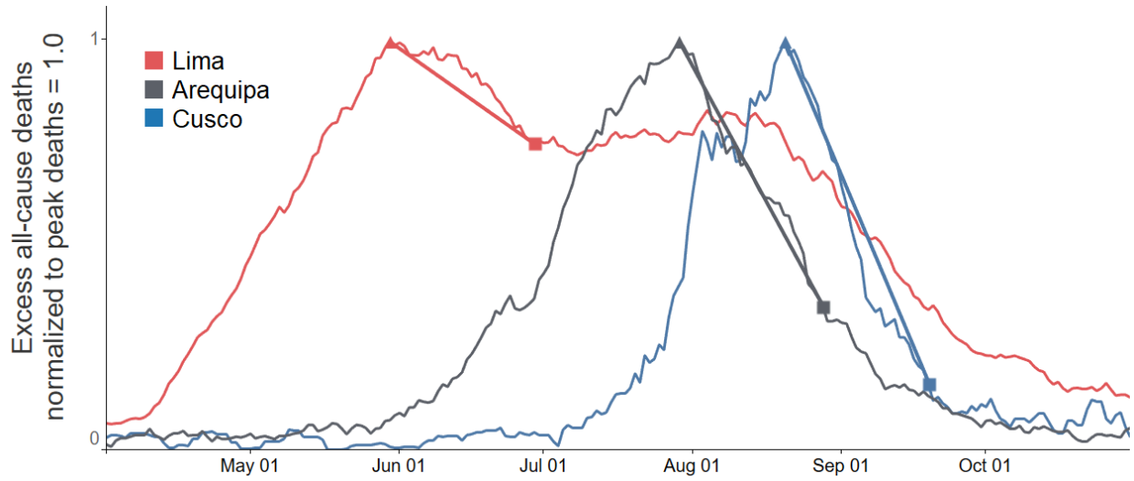

Figure 2. Excess deaths, normalized to peak deaths = 1.0 by state, for one state from each of the three tiers of IVM distribution: maximal, operation *MOT* (Cusco); moderate (Arequipa); and minimal (Lima). ▲designates peak deaths; ■ day of peak deaths + 30 days. In Lima, after restrictive measures on IVM distribution through July 2020, these distributions and treatments began on a mass basis in August.[13,18,19] Excess deaths are 7-day moving averages, ages ≥ 60; data are from the Peruvian National Death Information System (SINADEF).[11]

The databases for all-cause deaths and for COVID-19 case fatalities were both structured to record each death with one database record containing fields for age, sex, locality, and several other demographic characteristics. To minimize the confounding element of potential changes in percentage of COVID-19 cases across different age groups, all analyses with the exception of the graph presented in Figure 1A were performed restricted to the population age ≥ 60, as obtained by filtering these database records by age. Also, an independent analysis of excess deaths compared with COVID-19 case fatalities indicated undercounting of the latter.[73] Therefore, although case fatality figures by state are shown in Table S2, the more reliable figure of excess deaths is used exclusively here for analysis.

To evaluate possible effects of non-pharmaceutical interventions on changes in excess deaths by state, potential effects of Peruvian policies to limit social interaction were considered. Peru implemented a two-week national lockdown on May 16, 2020, that was extended through the end of June, which ordered the closing of national borders and restriction of domestic travel and all non-essential activity.[74] Yet as a Latin American policy official summarized, this lockdown "failed completely," because for 75% of Peruvian residents, "if they do not work one day, they cannot eat."[74] However, Google community mobility data from cell phones within a given locality allow objective quantification of social interactions, whatever the intended effect of such official orders.[75-78] Actual vs. mandated changes in social mobility have indeed been found to vary considerably during the 2020 pandemic period. In some countries such as Sweden, certain mobility restrictions were undertaken on individual initiative,[76] while in others, official mandates had limited impact on actual mobility.[77,78]

It was found that in one model of COVID-19 trends over time, inputs for official policies could be ignored and actual community mobility data used exclusively without sacrificing predictive efficacy.[78] COVID-19 transmission was found closely associated with actual mobility patterns in another model.[75] In localities without strictly enforced lockdowns, for which community mobility data indicated at most modest reductions in social interactions during April through May 2020, reductions in mortality were limited. Sweden, for example, in which certain mobility restrictions were undertaken on individual initiative,[76] had a 42% reduction in its 7-day moving average of daily deaths from its peak in April to thirty days later in May.[79] The corresponding figure for the US state of Georgia was a 10% reduction,[80] while the US state of Florida had no reduction in daily deaths in this period.[81] To factor out any potential effects of social isolation policies on mortality trends in Peru, six indices of Google community mobility data were retrieved for each of Peru's 25 states and compared with mortality trends.

No patients were involved in this study. All clinical data are from public Peruvian national databases.

Results

Analysis was performed state by state for excess all-cause deaths, ages ≥ 60. The 25 states of Peru were grouped by extent of IVM distributions: maximal (mass IVM distributions through operation *MOT*, 10 states); medium (locally managed IVM distributions, 14 states); and minimal (Lima, with restrictive

policies). For each state, the date of peak excess deaths in its first wave of the pandemic, as specified in the methods section, was determined. Decreases in excess deaths from date of peak deaths to 30 and 45 days afterwards were then tracked. Note that for Lima, as detailed in a previous analysis,[13] large distributions of IVM beginning in August marked the end of its prior policy of IVM restrictions, and a second peak in excess deaths occurred on August 4, followed by a decline, as shown in Figure 2. However, per the methodology of this analysis, the date of Lima's first peak in excess deaths, May 30, was used, which occurred during the period in which its IVM distributions were minimal, per restrictions then in place.

Table 1. Peak values of excess all-cause deaths (7-day moving averages, ages ≥ 60) and reductions at 30 and 45 days after day of peak deaths, grouped by maximal, medium or minimal extent of IVM distributions. All values for excess deaths are sums for individual states as shown in Table 2 below by the three categories of states. The Kendall tau and Spearman rho and their associated p values are shown for absolute value of reduction in excess deaths at +30 days and +45 days after peak deaths correlated with tier of IVM distributions, by state.

State	Peak excess deaths	+30 days		+45 days	
		Value	Change	Value	Change
Maximal IVM distributions through operation *MOT* (10 states)	164.9	42.3	-74.4%	22.7	-86.2%
Medium scale, locally managed IVM distributions (14 states)	396.8	187.3	-52.8%	120.3	-69.7%
Minimum scale, restricted IVM distributions (Lima)	263.6	197.6	-25.0%	197.2	-25.2%
All 25 states, TOTAL	825.3	427.2	-48.2%	340.2	-58.8%
Kendall tau			τ_b=0.5238 p=0.0019		τ_b=0.4869 p=0.0039
Spearman rho			ρ=0.6188 p=0.0010		ρ=0.5764 p=0.0026

Table 2. 7-day moving average of excess deaths for ages ≥ 60, 30 and 45 days after day of peak deaths, by state. Data are from the Peruvian *Ministerio de Salud,* National Death Information System (SINADEF).[69] Maximally IVM treated, *MOT* states are shown in blue; medium IVM treated states in black, and Lima, minimally IVM treated during the period of focus due to restrictive policies, in red.

State	Population age ≥ 60	Peak excess deaths		deaths +30 days		deaths +45 days	
		Date	Value	Value	Change	Value	Change
Amazonas	35,174	Jul 25	4.4	0.7	-84.1%	0.9	-79.5%
Ancash	150,716	Jun 15	22.0	13.2	-40.0%	14.6	-33.6%
Apurimac	41,253	Sep 23	5.4	2.3	-57.4%	1.6	-70.4%
Arequipa	212,228	Jul 28	64.3	22.5	-65.0%	9.5	-85.2%
Ayacucho	62,206	Aug 20	6.5	2.5	-61.5%	1.5	-76.9%
Cajamarca	133,274	Jul 30	19.9	7.4	-62.8%	6.9	-65.3%
Callao	178,909	May 21	42.0	28.5	-32.1%	18.8	-55.2%
Cusco	138,969	Aug 21	28.8	4.0	-86.1%	0.0	-100.0%
Huancavelica	30,834	Aug 13	7.2	1.8	-75.0%	1.8	-75.0%
Huánuco	63,505	Aug 12	9.1	1.1	-87.9%	1.8	-80.2%
Ica	118,348	Jul 13	25.5	16.7	-34.5%	10.9	-57.3%
Junín	149,830	Aug 1	25.3	12.5	-50.6%	4.0	-84.2%
La Libertad	257,655	Jun 22	55.0	35.2	-36.0%	22.4	-59.3%
Lambayeque	177,031	May 15	30.4	13.8	-54.6%	8.5	-72.0%
Lima	1,648,028	May 30	263.6	197.6	-25.0%	197.2	-25.2%
Loreto	84,137	May 6	36.3	10.0	-72.5%	6.4	-82.4%
Madre De Dios	15,441	Jun 24	4.8	1.9	-60.4%	1.1	-77.1%
Moquegua	29,157	Aug 10	17.2	1.5	-91.3%	0.9	-94.8%
Pasco	26,384	Aug 7	3.5	0.3	-91.4%	0.5	-85.7%
Piura	234,250	May 24	58.5	24.9	-57.4%	15.7	-73.2%
Puno	144,017	Aug 14	35.3	8.9	-74.8%	4.7	-86.7%
San Martin	79,911	Jun 22	16.4	10.3	-37.2%	5.9	-64.0%
Tacna	49,376	Aug 15	12.1	2.3	-81.0%	0.6	-95.0%
Tumbes	28,166	Jun 2	9.7	4.3	-55.7%	2.0	-79.4%
Ucayali	51,639	May 12	22.1	3.0	-86.4%	2.0	-91.0%

As noted above, operation *MOT* was an intensive effort that engaged the Army, Navy, Air Force and police in partnership with local health officials. Response teams were deployed in each targeted region, conducting

mass distributions of IVM to residents with COVID-19. The ten states covered by *MOT* from its inception on July 23, 2020 through August were identified in a previous analysis[14] and are listed above. *MOT* continued after August, but from that point forward, its target locales shifted frequently from one district to another in different states.[82-85] These ten *MOT* states extend from the southern tip to the north of Peru, including coastal and interior regions both adjoining and far from Lima. With its intensity of coordinated effort, the *MOT* program could be assumed, in general, to have resulted in significantly more extensive IVM distributions and treatments than for non-*MOT* states. If IVM were clinically effective against COVID-19, reductions in deaths would be expected to be correlated, state by state, with the extent of IVM distributions. But if IVM were as ineffective as sugar pills, then whichever set of states were selected for intensive distribution by *MOT*, no such effect would be seen.

As shown in Table 1, for the maximal, medium, and minimal IVM distribution states, respectively, the mean reductions in excess deaths 30 days after day of peak deaths were 74%, 53%, and 25%. Figure 1C shows these drops in excess deaths over 30 days for the 25 states, by tier of IVM distribution. At 45 days after peak deaths, these mean reductions were 86%, 70%, and 25%, respectively. For nine of the ten *MOT* states (excluding Pasco, which had three IVM distribution dates), *MOT* start dates were plotted together with dates of peak deaths in Figure 1B. As shown, excess deaths dropped sharply in close time conjunction with *MOT* start dates. Except for Junin, which had additional IVM distributions 13 days before its *MOT* start date, the lag time between *MOT* start date and date of peak deaths varied from 1 to 11 days.

For analysis using the Kendall τ_b correlation, the three groups of states were assigned extent of IVM distribution values of 0 for Lima, 1 for the 14 local IVM distribution states, and 2 for the 10 *MOT* states. For correlations between extent of IVM distributions and reductions in excess deaths (absolute values) at 30 days after peak deaths, the Kendall τ_b was 0.524, with (two-sided) $p<0.002$. For the extent of IVM distribution correlated with reductions in excess deaths at 45 days after peak deaths, the Kendall τ_b was 0.487, $p<0.004$.

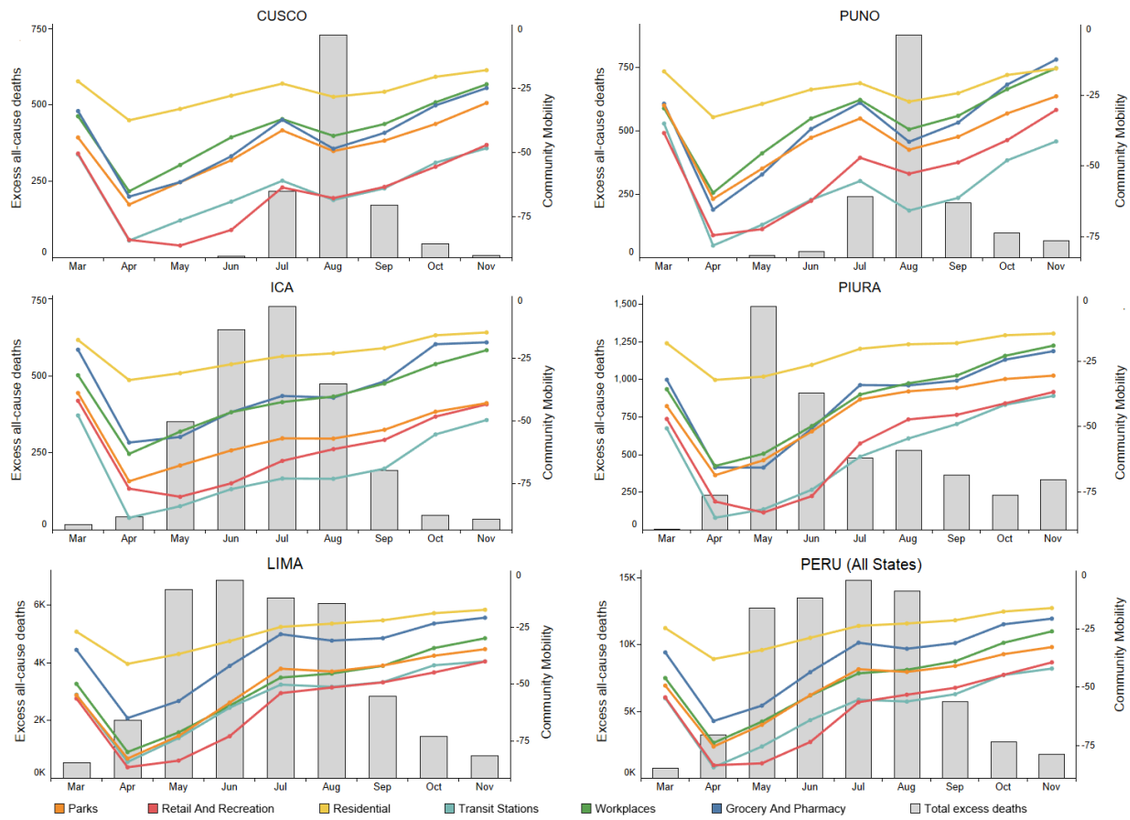

Figure 3. Google community mobility trends[86] (line graphs) and excess all-cause deaths for ages ≥ 60 (bars).[69] These mobility indices show percentage changes in different categories relative to the median of these daily figures for January 3 through February 6, 2020. Five of these categories, all but residential, show (reduced) percentages of trips to various destinations with respect to this baseline, while the residential index tracks hours spent at home; for this category, the sign is switched so that e.g. a 25% increased time at home appears as -25%. These graphs are for two *MOT* states (Cusco, Puno), two states with local IVM distributions (Ica, Piura), Lima, and all of Peru. These same graphs for each of the 25 states of Peru are shown in Figure S2.

The stronger correlations for extent of IVM distributions with drops in excess deaths over 30 vs. 45 days is consistent with the expectation that operation *MOT*, with its rapid response teams, would more likely have the most impact over a shorter time period. Nevertheless, for both 30 and 45 days, p values were significantly less than the confidence level of $p=0.05$ for an established clinical effect. The lack of perfect correlations between extent of IVM distributions and reductions in excess deaths may derive in part from anomalies such as high levels of public and private distributions of IVM in some states such as Loretto,[13] a non-*MOT* state, which had a 73% drop in excess deaths at 30 days after peak. Also, Callao is entirely contained within the state of Lima, having a 32.1% reduction in excess deaths over 30 days, the second

lowest after Lima's, which may reflect the same restrictions in IVM distributions through July 2020 as occurred in Lima.

As shown in Figure 3, with these charts for all 25 states shown in Figure S2, in each state, COVID-19 mortality fell sharply after its respective month peak deaths concurrent with a continuing increase in six Google-tracked indices of community mobility. These mobility indices show a similar pattern among states: a sharp decline from March to April 2020, followed by a steady rise through November, with a brief and modest decrease in August. There are no reductions in mobility that can explain the reductions in excess deaths shown in Figure 3.

Discussion

The 25 states of Peru that conducted IVM treatments for COVID-19 at different time periods provide a robust set of subpopulations from which these treatment impacts can be evaluated. For the 10 *MOT* states, excess deaths dropped most sharply, by 74% at +30 days and by 86% at +45 days after the day of peak deaths. For the 14 states with locally administered IVM distributions, excess deaths dropped by 53% at +30 days and by 60% at +45 days. In Lima, however, where IVM treatments were delayed until August, four months after its initial pandemic surge in April, excess deaths dropped by only 25% at +30 days and also by only 25% at +45 days after its day of peak deaths on May 30. The *MOT* states had sharp drops in excess deaths after reaching peak values in close time conjunction with *MOT* start dates (Figure 1B). For the 25 states, reductions in excess deaths correlated with extent of IVM distribution, maximal, medium, or minimal, with $p<0.002$ using the Kendall τ_b test.

Given the association between IVM treatments and sharp mortality reductions revealed in this analysis, neither random fluctuation nor an unidentified, extraneous cause of these reductions in deaths appears likely. But it is useful to consider the potential confounding influences of social isolation, changing seropositivity rates, variations in viral strains across states, and other factors. To begin with the most straightforward of these considerations, possible distortions caused by varying proportions of younger or older people in any given population were ruled out by including only the population age 60 and above in the analysis. Also, for each of the 25 states of Peru, for ages ≥ 60, it was found that no more than 2.2% of that population died during the period March through November 2020 (Table S3). Percentages of reductions in total populations age 60 and above of up to 2.2%, by state, were thus very small in comparison to pandemic-related fluctuations of more 200% in deaths in 2020 (Figure S1).

The possibility that a more virulent strain of SARS-CoV-2 caused more fatalities in Lima than elsewhere in Peru was discounted by an analysis of 149 genomes from COVID-19 patients in Peru obtained through July 4, 2020 from diverse geographical regions of the country.[87] This genomic analysis found that the phylogenetic clades in 11 states had a distribution similar to that of Lima.[87] Note that no conclusions have been offered, despite a suggestive conjunction, regarding the 13-fold increase in nationwide excess deaths, ages ≥ 60, over two months through February 1, 2021 that occurred after restrictions on IVM distributions were instituted in November 2020. No state-by-state variations in those IVM restrictions are apparent from which such conclusions might be drawn. Yet the UK variant of SARS-CoV-2, first detected in Peru on January 8, 2021,[88] cannot explain that post-November surge in deaths, since prior to then, excess deaths (all ages) had already tripled from 48 on December 1 to 150 on January 1.[11] A Pan-American survey found that no other mutations of potential interest to public health, including 501Y.V2 and P.1, was detected in Peru as of mid-January, 2021.[89]

The possibility that varying compliance with social isolation mandates in the different states of Peru could account for varying impacts of the pandemic is discounted by Google community mobility data shown in Figure 3. These data demonstrate that for Lima, the 10 *MOT* states, and the 14 states with local IVM distributions, mobility patterns from March through November 2020 were roughly the same and that excess deaths fell as mobility rose in all states but Lima in their respective first waves of the pandemic.

The possibility that the development of herd immunity was responsible for the major reductions in excess deaths seen in almost every state of Peru but Lima is discounted by consideration of state-by-state seropositivity rates for November 2020 (Table S4). Although a high seropositivity rate for Loreto, which had reached 75% even by September,[90] could explain reduced pandemic impacts there, several other IVM-treated states with low seropositivity rates had sharp drops in COVID-19 mortality. For Cajamarca, Cusco, Huancavelica and Tacna for example, all *MOT* states, seropositivity rates were only 20%, 18%, 18%, and 15%, respectively, in November 2020. But within 1 to 8 days after *MOT* start, excess deaths peaked and then dropped over 30 days, respectively, by 63%, 86%, 75% and 81%. For the state-by-state correlation of reduction in excess deaths at peak deaths plus 30 days with seropositivity rate for November 2020, the Pearson's p-value was 0.486, while that correlation for reduction in excess deaths at +45 days had a p value of 0.415, showing no association and discounting any such dependence.

To consider the potential confounding influence of population density, even though Lima has the highest population density per area in Peru, with 10,577 inhabitants per km^2,[91] densities for other cities are not much lower. Inhabitants per km^2 in Trujillo, the capital of La Libertad, is 9,431; this figure is 8,216 for Piura and 8,195 for Cusco.[91] As for people living in the same household, a demographic study in 2017 showed that Lima households with more than 5 people represented 27% of the total; in Loreto, that figure was 42%, and in Ucayali, 36% (Table S5).[92] Thus, neither population densities per area or per household are markedly different in Lima vs. population centers of other states for which this analysis was performed.

An unpublished study from Duke University directed by Miguel Nicolelis proposed that cross-immunity from the dengue virus, which causes dengue fever, could explain lower than expected levels of COVID-19 mortality in some regions of South America.[93] His theory is based on a correlation between Brazilian regions with dengue outbreaks and lower COVID-19 spreads. This theory collapses in Peru, however, with the observation of parallel COVID-19 outbreaks in Peruvian states such as Moquegua, which has not had dengue cases in the last 20 years, and Loreto, the epicenter of dengue in Peru.[94,95] Finally, one other data artifact could be that several peaks and drops in Lima's different districts could explain the low reduction in excess deaths. However, as shown in Figure S3, the pattern of total deaths, ages ≥ 60, for most of these districts, those comprising the bulk of the population, is the same: rising deaths to a peak around late May 2020 and then a three-month plateau following.

With potential confounding factors discounted, the remarkable natural experiment that unfolded with the authorization of IVM for COVID-19 in Peru on May 8, 2020 had a conclusive outcome. For the 25 states of Peru, the extent of IVM distributions correlated with reductions in excess deaths over 30 days with $p < 0.002$. The ten states of operation *MOT*, having the greatest extent of IVM distributions, had a mean 74% reduction in excess deaths at 30 days after peak deaths. These reductions, except for one anomaly, occurred within 1-11 days after *MOT* start dates. This 74% reduction in mortality for *MOT* states is consistent with the 78% pooled mortality reduction vs. controls achieved in RCT's for IVM treatment of COVID-19.[41]

The system of large randomized clinical trials as a requirement for new drug approvals has served public health well. These allow screening for dangerous side effects and can also determine if important therapeutic gains obtained in relatively small percentages of subjects persist under more rigorous scrutiny. But this methodology is inappropriate for a national decision to deploy IVM against COVID-19 for several reasons. IVM has been safely used in 3.7 billion doses since 1987[3,4] and found well tolerated even at ten times the standard dose of 200 μg/kg[96-98] that was used in Peru (repeated a second day for serious cases).[2] It is already approved by regulatory authorities worldwide. Considering that these results for IVM in Peru align with mortality reductions of 78% for COVID-19 in several RCTs, it would appear no longer ethical to conduct further RCTs, except to test dose or adjunct effects with IVM, since no other therapy with that degree of expected clinical benefit is available for use in a control arm. Indeed, with mortality benefits for IVM at p=.002 for Peru's 25 states, each state having a mean population age ≥ 60 of 165,600, many times the total clinical trial subject pool tested for most drugs, it is questionable why more RCTs might be of significant interest.

Finally, COVID-19 is a life-threatening international emergency. During a prior such medical emergency with the urgent need for treatment of infected battlefield wounds during World War II, production of penicillin was ramped up rapidly. One year after the first small case series of patients treated with that drug, most with successful outcomes, in 1943, it was ready for full battlefield deployment in 1944.[14] Penicillin was then extended for civilian use without any RCT results or even complete data for its battlefield outcomes. In the current international emergency of COVID-19, with significant percentages of US residents, for example, unwilling to be vaccinated,[99,100] combined with lesser protection from immunizations against mutants and possibly waning of immunity over several months, COVID-19 could persist with $R_0 > 1$ as an enduring menace. Mass deployments of IVM treatments, a safe therapeutic with a compelling track record against COVID-19, can fill in these gaps, bringing COVID-19 deaths below influenza deaths while setting an example of public decision-making based on sound science.

Conclusion

Mass treatments with IVM most likely caused the 14-fold reduction in excess deaths in Peru through December 1, 2020, prior to a 13-fold increase after IVM policy was reversed. The appropriate clinical follow-up to IVM treatments for COVID-19 in the 25 states of Peru, with a combined total population of 33 million, is more national deployments of IVM treatments interim and complementary to immunizations. Since a likely biological mechanism of IVM against SARS-CoV-2 is non-epitope specific competitive binding to viral spike protein, the efficacy of IVM may well prove to be conserved against emerging viral mutant strains.[64] Given that for the ten *MOT* states of Peru, mean 74% reductions in mortality were accrued over just 30 days, rapid confirmation would be obtainable for success of such national IVM deployments.

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Abbreviations

IVM: ivermectin

MOT: *Mega-Operación Tayta*

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