Sharp reductions in COVID-19 case fatalities and excess deaths in Peru in close time conjunction, state-by-state, with ivermectin treatments

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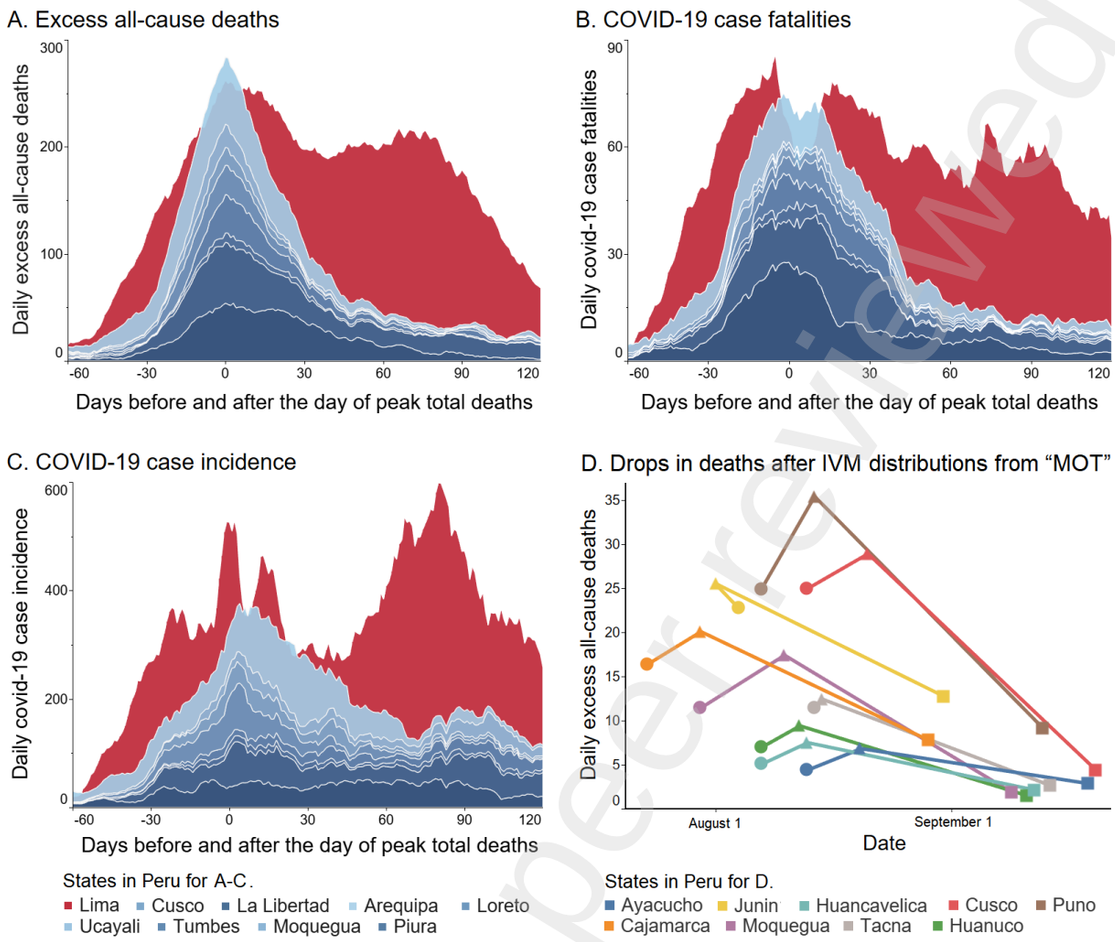

Figure 1: Graphical Abstract. A) Excess all-cause deaths; B) COVID-19 case fatalities; and C) case incidence data for eight states in Peru that deployed mass ivermectin (IVM) treatments early in their pandemic spread (blue) and for Lima, which deployed IVM treatment four months later (red). D) Excess deaths for nine states having mass IVM distributions in a short period through national operation "MOT" (see results section for sources). ● MOT start date; ▲peak deaths; ■ day of peak deaths + 30 days. Junin (yellow) distributed IVM to health centers beginning on July 22, 13 days before MOT start. Population-weighted mean deaths for these nine states dropped sharply, -74% at +30 days, beginning (except for Junin) 1 to 11 days after MOT start. All y values are 7-day moving averages, ages ≥ 60.

Abstract

On May 8, 2020, Peru's Ministry of Health approved ivermectin (IVM) for the treatment of COVID-19. A drug of Nobel Prize-honored distinction, IVM has been safely distributed in 3.7 billion doses worldwide since 1987. It has exhibited major, statistically significant reductions in case mortality and severity in 11 clinical trials for COVID-19, three with randomized controls. The indicated biological mechanism of IVM is the same as that of antiviral antibodies generated by vaccines—binding to SARS-CoV-2 viral spike protein, blocking viral attachment to host cells.

Mass distributions of IVM for COVID-19 treatments, inpatient and outpatient, were conducted in different timeframes with local autonomy in the 25 states (*departamentos*) of Peru. These treatments were conducted early in the pandemic's first wave in 24 states, in some cases beginning even a few weeks before the May 8 national authorization, but delayed four months in Lima. Analysis was performed using Peruvian public health data for all-cause deaths and for COVID-19 case fatalities, as independently tracked for ages 60 and above. These daily figures were retrieved and analyzed by state. Case incidence data were

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not analyzed due to variations in testing methods and other confounding factors. These clinical data associated with IVM treatments beginning in different time periods, April through August 2020, in each of 25 Peruvian states, spanning an area equivalent to that from Denmark to Italy and Greece in Europe or north to south along the US, with a total population of 33 million, provided a rich source for analysis.

For the 24 states with early IVM treatment (and Lima), excess deaths dropped 59% (25%) at +30 days and 75% (25%) at +45 days after day of peak deaths. Case fatalities likewise dropped sharply in all states but Lima, yet six indices of Google-tracked community mobility rose over the same period. For nine states having mass distributions of IVM in a short timeframe through a national program, *Mega-Operación Tayta* (MOT), excess deaths at +30 days dropped by a population-weighted mean of 74%, each drop beginning within 11 day after MOT start. Extraneous causes of mortality reductions were ruled out. These sharp major reductions in COVID-19 mortality following IVM treatment thus occurred in each of Peru's states, with such especially sharp reductions in close time conjunction with IVM treatments in each of the nine states of operation MOT. Its safety well established even at high doses, IVM is a compelling option for immediate, large scale national deployments as an interim measure and complement to pandemic control through vaccinations.

Background

The first identified case of Covid-19 in Peru was a pilot who flew in from Europe on February 26, 2020.[1] On May 8, 2020, by decree, the Peruvian Ministry of Health, Victor Zamora, approved the use of ivermectin (IVM) as a treatment agent for COVID-19.[2] IVM is a drug of Nobel Prize-honored distinction that has been distributed in 3.7 billion doses worldwide since 1987.[3-6] Its known safety margins and availability provided a backdrop for this decision.

This May 8 national authorization of IVM treatments was implemented independently in each of Peru's administrative departments. Peru is divided into 24 *departamentos*, one of these being the Lima capital region, plus the independent *provincia* of Callao.[7] For simplicity of reference, these are designated as the 25 states of Peru. Mass distributions of IVM occurred autonomously in these 25 states through public and private channels for both inpatient and outpatient treatments of COVID-19. 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. These 25 states span terrain from jungle to desert to mountain, equivalent to an area from Florida to Minnesota to New York in the United States or from Denmark to Italy and Greece in Europe, with a combined total population of 33 million. This state-by-state clinical data, independently tracked for excess deaths and COVID-19 case fatalities, provided a boon for data analysis.

As detailed below and for nine individual states in Supplementary Appendix I, public compliance with IVM treatments was achieved due to well-publicized reports of successful outcomes for IVM treatment of COVID-19 by Peruvian celebrities. As a result, in each state of Peru but Lima, 24 of its 25 states, IVM treatments were widely deployed prior to or within a few weeks after an initial surge of pandemic cases and deaths, that surge period varying among the states between April and August 2020. In the Lima capital region, however, restrictive measures on IVM distribution, including police raids on pharmacies, delayed mass IVM treatments for COVID-19 four months after the initial pandemic surge in April. Finally in August, after 10,386 COVID-19 case fatalities had been recorded in Lima (all ages), 1.0 per thousand total population, IVM treatments began also in that state.

Analysis was performed using data independently compiled by the Peruvian government for total deaths and for COVID-19 state fatalities, each tracked daily, state by state. This analysis began by examining such data for nine states, including Lima, which had major outbreaks of COVID-19, closely reported distributions of IVM, population densities, and jungle, coastal and mountain terrains representative of all of Peru. As shown in Figures 1A-B and detailed in Appendix I, for eight of these states with IVM treatments early in their first waves of the pandemic, sharp mortality reductions likewise began early, but not for Lima, which had a four-month IVM treatment delay.

Analysis was then extended to all 25 states of Peru, as summarized in Tables 1 and 2, to determine if the same sharp mortality reductions emerged. A final phase of analysis was then performed to identify certain states for which particular dates of IVM distributions could be pinpointed and compared with dates at which downward slopes in mortality began. Nine states had mass IVM distributions and treatments in a short timeframe through a national program, *Mega-Operación Tayta* (MOT), for which such a time conjunction analysis could be performed.

At the time of the May 8 authorization of IVM treatments for COVID-19 in Peru, few results of clinical trials for such treatments had appeared. The clinical relevance of an in vitro study[8] demonstrating activity

of IVM against SARS-CoV-2 at a 1,000-fold physiological tissue concentration was widely questioned.[9-11] These gaps in scientific understanding of IVM effects that existed at the time of Peru's IVM treatment authorization prompted criticism by, among others, Carlos Chaccour, an internationally prominent researcher of IVM treatments for tropical diseases worldwide.[9] Yet as clinical trial results for IVM treatment of COVID-19 subsequently appeared, including ultimately one by Chaccour himself,[12] the application of IVM to COVID-19 treatment elicited greater interest. Satoshi Omura, the 2015 Nobel laureate for the discovery of IVM, presented clinical and epidemiological data indicating IVM efficacy against COVID-19 in September[13] and October[14] 2020 and offered a greeting of introduction for a December videoconference on such use of IVM.[15]

Since the May 8 authorization in Peru, 11 clinical trials of IVM for COVID-19 treatment,[12,16-25] three of these with randomized controls,[17,19,20] have shown major reductions in mortality and severity. Mortality rates for IVM treatment at higher doses, totaling at least 400 μg/kg over two consecutive days, were about one-tenth those of controls, with statistically significant improvement in other case parameters.[17-19] In a randomized controlled trial 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.[26]

The biological mechanism of IVM clinical benefits for COVID-19, as indicated in seven molecular modeling studies,[27-33] is the same as that of antiviral antibodies generated by vaccines currently deployed or under development.[34] That mechanism for both of these therapeutics is binding to SARS-CoV-2 spike protein, which blocks viral attachment to host cells and other viral functions.[35] Of interest in examining the specific such activity of IVM is that SARS-CoV-2 is a hemagglutinating virus, as established *in vitro*,[36] clinically from red blood cells of COVID-19 patients,[37] and from its biochemical binding properties.[35,38] Clumping by SARS-CoV-2 with red blood cells, platelets and other blood cells via attachments to cell surface sialic acid 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.[35] The specific type of binding by IVM to viral spike protein of SARS-CoV-2 may block such blood cell clumping without requiring a precise match to specific spike protein sequences, with efficacy of IVM thus conserved against viral mutant strains.[35]

Distribution of IVM and deployment for COVID-19 treatment in Peru, April through October 2020

Following the May 8 decree by the Peruvian Ministry of Health, Victor Zamora, approving IVM treatment of COVID-19, a new Minister of Health, Pilar Mazzetti, ratified it on September 8, 2020,[39] despite having received numerous requests to suspend its approval.[40-42] IVM treatments were provided for both inpatients and outpatients with a typical dosage of 200 μg/kg for a single day for mild cases, and repeated a second day for more serious cases.[2]

National distribution of IVM had three main components: use of this drug in the treatment of hospitalized patients, drug distribution through regional health offices and private groups, and a distribution campaign called *Operación Tayta* in which groups of health professionals treated COVID-19 positive patients house by house.[43] At the end of July 2020, *Operación Tayta* was extended and renamed as *Mega-Operación Tayta* (MOT). MOT was spearheaded by the Peruvian Ministry of Defense and army but also engaged other groups and health professionals. Its aim was to reach every part of the country, detecting COVID-19 cases, treating patients as well as family members in their households with IVM and giving them food to encourage their isolation for 15 days.[44]

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.[45] 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 potential to take it at 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.[45] From its inception at the end of July through the end of August 2020, MOT covered these ten states: Cajamarca, Junin, Pasco, Moquegua, Huánco, Huancavelica, Puno, Tacna, Ayacucho and Cusco.

While *Operación Tayta* and MOT were the largest individual programs for distributing IVM in Peru, localized distributions of the drug began in April and May 2020, as detailed for nine states in Supplementary Appendix 1. These initial distributions of IVM were mainly through volunteer channels and at the initiative of individual patients to obtain this medication. Loreto had the most extensive intervention led by a voluntary organization, with other such voluntary interventions in, for example, Ucayali, Piura, and Cusco. Local authorities, including those in Piura, La Libertad, Tumbes, and Arequipa, started other campaigns in June and July. However, for reasons specified in Appendix 1 (case 9: Lima),

only token distribution of IVM was achieved in Lima prior to the MOT distribution in August, although COVID-19 deaths had reached peak levels three months earlier in May 2020.

Several personal testimonies about successful treatment of COVID-19 with IVM were widely covered by the press and social media.[46,47] One the first of these reports emerged in April 2020, which described such successful treatments of members of the Peruvian Congress from the political party "Podemos Peru."[48] On May 11, a newspaper published a front page story, "*El milagro de la Ivermectina*" (the IVM miracle), sharing the successful treatment of 58 patients by the cardiologist Walter Mogrovejo.[49] On May 16th, a video from a policeman, Darvin Condezo, describing his own recovery from COVID-19 after treatment with IVM was shared widely.[50-55] The day after the release of this video, the number of google searches of "*ivermectina*" in Peru increased dramatically.[56]

On May 17 and in subsequent broadcasts, Armando Massé, a physician and radio and TV show host, repeatedly promoted IVM to treat COVID-19.[57-59] A high level of popular interest in IVM treatment for COVID-19 as spurred by these reports led to an IVM shortage in Peruvian pharmacies,[60] which motivated smugglers[61] and counterfeiters[62] to cover the demand. Major interest among the Peruvian populace in IVM treatments of COVID-19, as detailed further for nine states in Appendix 1, translated into high compliance with such treatments.

Methods

Three 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: A) deaths from all natural causes (excluding violent deaths), hereinafter denoted as "all-cause deaths"; B) COVID-19 case fatalities; and C) COVID-19 case incidence. These figures, as publicly accessible,[63] sources detailed below, at the end of this section, were separately tracked by these agencies for the subgroup age 60 and above, as used exclusively in this analysis.

COVID-19 mortality was tracked using these independent measures of all-cause deaths and COVID-19 case fatalities. 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 S7). 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 S11).

For each of these 25 states, the day of peak (all-cause) deaths was calculated 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 calculated at the day of peak deaths and at 30 and 45 days following. The day of peak case fatalities was likewise calculated using its 7-day moving average, and case fatalities were then calculated at that day of peak fatalities and at 30 and 45 days following. As noted above, analysis was performed in three stages: 1) for the nine states of Appendix I, including Lima, per the selection criteria noted; 2) for all 25 states of Peru, details and summary statistics for excess deaths and COVID-19 case fatalities; 3) for the nine states of operation MOT, time conjunction analysis of dates of IVM treatments with dates of subsequent sharp reductions in excess deaths.

Case incidence statistics, although shown in state-by-state tables of Appendix 1, were disregarded in this analysis as they are generally unreliable in any nationwide pool of subjects. Among confounding factors is variation in the extent of PCR and antibody testing at different periods of time. There were also variations between states and over time in the mix of antibody and PCR testing performed, as shown in Table S5.[64] Also, the reporting of cases with mild symptoms is at the discretion of the patient. Indeed, gross inaccuracy in statistics for case incidence is indicated by tenfold difference between detected cases and the data from seroprevalence studies. At the end of September, the official case incidence count in Peru was 818,297,[65] but the government projected that of the country's population of 33 million, between 30 and 35%, or about 10 million, had already been infected.[66] These uncertainties, however, are reduced when considering only serious cases of COVID-19 that result in death, which constitutes the figure for COVID-19 case fatalities. Although a comparison of numbers of excess deaths and COVID-19 case fatalities indicates undercounting of the latter, as noted in another report,[67] both figures were observed to rise and fall in parallel in each state, as reflected in Figure 1 and Figures S1-S9.

To factor out effects of non-pharmaceutical interventions on changes in excess deaths and COVID-19 case fatalities in the 24 states that provided early IVM treatment vs. those effects in Lima, potential effects of Peruvian policies to limit social interaction must be considered. Peru implemented a two-week national

lockdown on May 16, 2020, extended through the end of June, which ordered the closing of national borders and restriction of domestic travel and all non-essential activity.[68] 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."[68] However, Google community mobility data from cell phones within a given locality allows objective quantification of social interactions, whatever the intended effect of such official orders.[69-72] 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,[70] while in others, official mandates had limited impact on actual mobility.[71,72]

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.[72] COVID-19 transmission was found closely associated with actual mobility patterns in another model.[69] 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,[70] had a 42% reduction in its 7-day moving average of daily deaths from its peak in April to thirty days later in May.[73] The corresponding figure for the US state of Georgia was a 10% reduction,[74] while the US state of Florida had no reduction in daily deaths in this period.[75] 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 eight states having early IVM treatment and for Lima, with comparisons made for trends in mobility vs. mortality.

The sources of COVID-19 case and fatality statistics used in this analysis were the Peruvian Open Source Database.[76] Information regarding IVM distribution was retrieved from official communications and press releases, as individually cited, and the CENARES drug distribution database.[77] Information regarding the total deaths in the selected age group was obtained from the registry of the National Death Information System (SINADEF);[78] and on regional populations, by age groups, from the National Institute of Statistics and Informatics. Information regarding case incidence and case fatalities for COVID-19 was obtained from the Open Data National Platform.[79] Aggregated on a national level, the COVID-19 data from Peruvian health information sources as used in this study matches the data compiled by the Johns Hopkins Coronavirus Resource Center.[80] Comparing values for all age groups at the national level, case incidence and case fatalities for COVID-19 in Peru from March 6 through January 4, 2021 match exactly (Figure 14).

Results

Analysis was performed using figures for all-cause deaths and for COVID-19 case fatalities, as independently tracked by Peruvian health agencies, all restricted to the subset of populations age 60 and above. Mortality trends were tabulated for each of the 25 states of Peru. Data for 24 states, all but Lima, where IVM treatments for COVID-19 were widely deployed early in the initial surge of pandemic deaths, were then compared with data for Lima, where such IVM treatments were deployed four months after its initial surge of pandemic deaths in April. Additional analysis was performed for Lima and eight other states, selected per the criteria described above, as reported in Supplementary Appendix I. Time conjunction analysis of dates of IVM treatments with dates of subsequent reductions in excess deaths was performed for the nine states of operation MOT.

Table 1. 7-day moving average of excess deaths, ages ≥ 60, 30 and 45 days after day of peak deaths. Mean values for deaths Jan-Feb, peak excess deaths, and values and percent change at +30 and +45 days are all weighted by populations of the states designated in each row. Data for this table and all tables and figures are from the official COVID-19 databases of the Peruvian *Ministerio de Salud* (MINSA)[63] unless otherwise noted.

State	Mean deaths Jan-Feb	Peak excess deaths	+30 days		+45 days	
			Value	Change	Value	Change
Lima	80	264	198	-25%	197	-25%
Eight other states in Appendix 1	58	292	105	-64%	59	-80%
Nine states for operation MOT	54	153	40	-74%	22	-86%
24 states (all 25 but Lima)	143	562	230	-59%	143	-75%

Table 2. 7-day moving average of case fatalities, ages ≥ 60, 30 and 45 days after day of peak case fatalities. Mean values for peak COVID-19 fatalities and for values and percent change at +30 and +45 days are all weighted by populations of the states designated in each row.

State	Peak COVID-19 fatalities	+30 days		+45 days	
		Value	Change	Value	Change
Lima	86	70	-18%	57	-34%
Eight other states in appendix 1	92	36	-60%	23	-75%
Nine states for operation MOT	41	14	-65%	15	-65%
24 states (all 25 but Lima)	205	78	-62%	67	-67%

As shown in Table 1, the 24 states that had IVM treatment early in their respective first waves of the pandemic had a population-weighted mean drop in excess deaths of 59% at +30 days and 75% at +45 days, days counted from the day of peak deaths. But in Lima, these respective drops in excess deaths were much less, 25% at both +30 and +45 days. As shown in Table 2, these respective figures for COVID-19 case fatalities for these 24 states (and for Lima) were 62% (18%) reductions at +30 days and 67% (34%) reductions at +45 days.

As shown in Tables 1 and 2, these drops in both mortality figures for the eight states (excluding Lima) chosen for close analysis vs. for all 24 early IVM-treated states are within 5% for excess deaths and 2-8% for case fatalities. Figures 1A and 1B show changes in the 7-day moving average of these mortality figures for the eight states and Lima, each normalized such that its day of peak excess deaths occurs at x=0. These graphs strikingly illustrate the sharp reductions in these two mortality figures for the eight early IVM treatment states of Appendix 1, representative of the 24 states, as compared to Lima.

In several states of Peru, as detailed, for example, in Loreto and others in Appendix 1, IVM was distributed through different channels at different times, eluding examination of date conjunctions between IVM distributions and mortality reductions. However, operation MOT, as described above, distributed IVM in a short time period in each locality. In each targeted region, local officials first identified vulnerable populations and then MOT staff distributed IVM beginning a week later. Because IVM was freely available in pharmacies without prescription and as local preparatory efforts may have spurred some informal such self-treatments prior to mass IVM distributions, the start date of MOT in each state was taken to be the beginning of the preparatory week of local health efforts. MOT began in late July 2020 and reached these states at the following start dates: Cajamarca (July 23),[81] Moquegua (July 30),[82,83] Junín (August 4),[84] Puno (August 7),[85,86] Huánuco (August 7),[87,88] Huancavelica (August 7),[89] Ayacucho (August 13),[90] Cusco (August 13),[90] and Tacna (August 14).[91] In Junin, MOT efforts were supplemented by state distributions of IVM to health centers beginning July 22,[92,93] 13 days earlier than its MOT start date. The state of Pasco was covered by MOT but at three different IVM distribution dates: July 23, August 5 and August 25.[94-96]

Figure 1D shows changes in the 7-day moving average of excess deaths after MOT start date in all states listed above except for Pasco, which had three different dates of IVM distribution. As shown, excess deaths dropped sharply in close time conjunction with MOT start dates. The lag time between MOT start day and day of peak deaths varied from 1 to 11 days, except for Junin, which had an additional IVM distribution 13 days before its MOT start date and which had its day of peak deaths 3 days before MOT start. For these nine states, the population-weighted mean reduction in the 7-day moving average of excess deaths at +30 days from day of peak deaths was 74%.

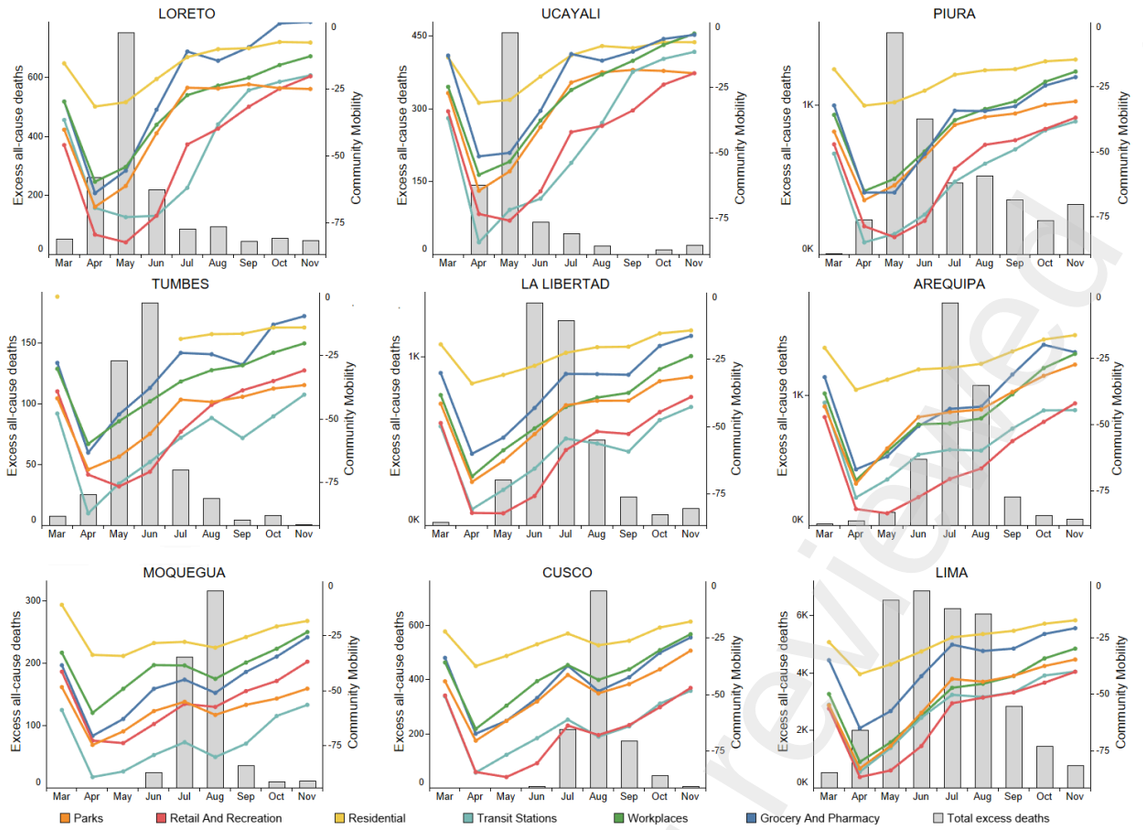

Figure 2. Google community mobility trends[97] (line graphs) and excess all-cause deaths for ages ≥ 60 (bars). These mobility indices show percentage changes in trips to different categories of destinations.

As shown in Figure 2, for the eight states plus Lima used for close analysis, COVID-19 mortality fell sharply after peak deaths at different dates 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 2 and also shown in Figure 1 and Tables 1 and 2.

Discussion

The 25 states of Peru that autonomously conducted IVM treatments for COVID-19 at different time periods provide a robust set of subpopulations from which these treatment impacts can be evaluated. These 25 states span jungle to desert to mountain terrain, equivalent to an area from the southern to northern extents of the US or from Denmark to Italy and Greece in Europe. For the 24 states with early IVM treatment, excess deaths dropped sharply, by 59% at +30 days and by 75% at +45 days after the day of peak deaths. But in Lima, where IVM treatments began in August, four months after its initial pandemic surge in April, which claimed 10,386 COVID-19 case fatalities (all ages) in March through July 2020, excess deaths dropped by only 25% at +30 days and also by 25% at +45 days after the day of peak deaths in May.

Most striking, however, were results following IVM treatments in nine states having IVM treatments in a condensed time period through operation MOT. In each of those nine states, excess deaths peaked within 11 days after MOT start date, those dates varying between July 23 and August 15, 2020 (Figure 1D). Excess deaths then dropped by a population-weighted mean of 74% at +30 days after day of peak deaths.

To maximize data integrity, two statistics, COVID-19 case fatalities and total all-cause deaths, both independently tracked by Peruvian health agencies, were used to assess mortality. Case incidence statistics were disregarded due to several factors that limit the reliability of this measure for a national population, including dependence upon self-reporting for cases with mild symptoms. Even had distortions in case incidence statistics been consistent by time and region during the period of interest, this figure would be difficult to correlate with the effects of IVM treatment, since asymptomatic transmission is known to play a key role in COVID-19 contagion, and generally only symptomatic people were treated with IVM.

Given the association between IVM treatments and sharp mortality reductions revealed by multiple approaches in this analysis, neither random fluctuation nor an unidentified, extraneous cause of these reductions in deaths appears likely. But it is useful to consider potential confounding influences. 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 the population age 60 and above, it was found that no more than 2.2% of that population died during the period March through November 2020 (Table S3). However, total weekly 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 S11). 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.

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.[98] This genomic analysis found that the phylogenic clades in 11 states had a distribution similar to that of Lima and supported other indications that the pandemic spread from Lima to other regions of the nation.[98] 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 2. These data demonstrate that mobility patterns from March through November 2020 in Lima were roughly the same as for the other states, and that excess deaths fell as mobility rose in the 24 states with IVM treatment early in their first waves of the pandemic.

The possibility that the development of herd immunity was responsible for the observed reductions in mortality in the 24 states with early IVM treatment but not Lima is discounted by consideration of state-by-state seropositivity rates for November 2020 (Table S6). Although a high seropositivity rate for Loreto, which had reached 75% even by September,[99] 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 having IVM distributions through operation MOT, seropositivity rates even with increases through November were only 20%, 18%, 18%, and 15%, respectively. 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 Arequipa, Amazonas and Ucayali, to cite other examples of states deploying IVM treatment, seropositivity rates in November were 20%, 26% and 40%, but reductions in excess deaths 30 days after peak deaths were 65%, 84%, and 87%.

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,[100] 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.[100] 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 S4).[101] Thus, neither population densities per area or per household are markedly different in Lima vs. other states for which this analysis was performed.

An unpublished study from Duke University directed by professor Miguel Nicolelis proposed that cross-immunity from the dengue virus, which causes dengue fever, could explain lower than expected levels of mortality in some regions of South America.[102] His theory is based on a correlation between Brazilian regions with dengue outbreaks and lower COVID 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.[103,104] 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 S10, the pattern for most of the 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.

These data for mortality reductions associated with IVM treatment in Peru have parallels in the experience of one state in Mexico, Chiapas, the only one with IVM interventions. In Chiapas, beginning in early July 2020, 600 health workers traveled into communities, identified COVID-19 cases and distributed IVM along with other repurposed existing drugs for COVID-19 treatment.[105] On July 1, Chiapas had a 7-day moving average of 0.31 daily COVID-19 case fatalities per 100,000 inhabitants while Mexico City had 1.32 and the national average for Mexico was 0.51.[106,107] On September 1, these figures were .02 for Chiapas and 0.39 for Mexico. By December 1, these 7-day moving average figures had become 0 for Chiapas and 0.46 for Mexico. For the period of October 1 through December 31, 2020, cumulative case fatalities per 100,000 inhabitants in Chiapas was 2; Mexico City had 97, and the national average for Mexico was 44.[106,107]

Public and private decisions on prevention and treatment options for COVID-19

Eradication of the COVID-19 pandemic will depend not only upon effective therapeutics, but also on sound decisions by both public health officials and the populace. To consider a conspicuous such example,

the groundwork for successful immunizations against this virus was laid by national decisions to expedite clinical trials of vaccines such as those developed by Pfizer-BioNTec and Moderna. The scientific foundation for successful population-wide deployments of these vaccines was then demonstrated by their efficacy rates of 95% and 94.5%, respectively, that emerged from large randomized clinical trials.[108] But the actual success of this intervention will rest upon decisions of a sufficient percentage of individuals to be vaccinated.

For a given therapeutic option, a decision to expedite its deployment is appropriate based upon significant results of clinical trials, even with some gaps that can be identified under close critical scrutiny. The Pfizer-BioNTech vaccine, for example, was deployed in the US, UK and Canada based upon a 95% reduction in COVID-19 cases for 21,720 vaccinated subjects vs. 21,728 controls in a randomized, double-blind clinical trial.[109] This decision was sound despite a loophole that emerged in its blinding design: 77.9% of vaccinated subjects vs. 11.9% of control subjects reported pain at the injection site following the first injection. As COVID-19 cases were self-reported by study subjects, with follow-up RT-PCR testing only for reported cases,[110] subjects who had injection site pain may have felt protected and been less likely to have reported borderline symptoms.[111] Nevertheless, the magnitude of the disparity between 8 and 162 COVID-19 cases in the vaccinated vs. placebo groups is sufficient to establish preventative efficacy. Also, the difference in severe cases, 1 vs. 9, respectively,[109] which were not subject to self-reporting bias, confirms vaccine efficacy.

With hindsight, given the outcomes reported here, the May 8 authorization for mass IVM treatment of COVID-19 in Peru was likewise a sound public health decision. In 24 of the nation's 25 states and belatedly in Lima, both excess all-cause deaths and COVID-19 case fatalities, as independently tracked, fell sharply after IVM treatments. In nine states where most of the IVM was distributed in a short time period through a national program, these sharp drops in deaths averaging 74% over 30 days began within 11 days of their respective dates of IVM distribution. These sharp reductions in mortality occurred even though IVM treatments were performed at a low dose of 200 μg/kg,[2] yet greater reductions in mortality for COVID-19 have been observed in clinical trials at higher[17-19] vs. lower[16] doses. By conducting this analysis using two independently tracked figures for mortality associated with COVID-19, problems with case incidence data, including the self-reporting bias noted above, were avoided.

Since the May 8 authorization for IVM treatments of COVID-19 in Peru, results have emerged for 11 clinical trials of IVM for COVID-19,[12,16-25] three with randomized controls,[17,19,20] which aligned with the mortality reductions achieved in Peru. With these studies indicating about ten-fold reductions in mortality at higher doses,[17-19] and similar benefits in a randomized controlled trial for IVM prophylaxis,[26] it would be ethically questionable to conduct further such randomized trials. The life-saving interventions of IVM during the COVID-19 pandemic in 25 states of Peru should next be replicated in another national population. Such an initiative, interim and complementary to full vaccine deployment, is especially appropriate given a backdrop of safety: IVM doses used in Peru were 200 μg/kg,[2] while doses of 2,000 μg/kg were well tolerated in two clinical studies[112,113] and others as reviewed.[114] Since clear indications of mortality reductions appeared within 30 days after treatments in Peru, progress in such a treatment program could be rapidly assessed.

Public health policy decisions regarding two proven cures of the past century provide useful lessons for decision making about COVID-19 therapeutic options. In the early 1980s, an Australian physician, Barry Marshall, found that stomach ulcers were caused by a species of bacteria, H. pylori.[115,116] He developed a treatment consisting of a few weeks' course of two oral antibiotics and bismuth that permanently cured ulcers.[117] In 1988, he conducted a randomized, controlled clinical trial that established the efficacy of this treatment,[118] and in 2005 received the Nobel Prize for medicine for this research. Dr. Thomas Borody, also of Australia, conducted another clinical trial demonstrating 96% efficacy of such a therapy in 1990.[119] But patients and physicians were in the habit of taking and prescribing, respectively, two best-selling palliative medications for ulcers,[120,121] and the cure for H. pylori did not become widely used in clinical treatment until the late 1990s.[115,121] Of related interest, Dr. Borody has become an active investigator and proponent of IVM treatment of COVID-19.[122]

In contrast to the decade-long delay in the widespread clinical application of a proven cure for stomach ulcers was the rapid deployment of penicillin for bacterial infections, escalated by the urgent battlefield needs of World War II. The first successful treatment of a patient, a 90-year old women with a streptococcal infection, using penicillin was performed in March 1942.[123,124] A case series of penicillin treatments of 15 patients through oral, IV or intramuscular administration and of 157 other patients with local application was published in March 1943.[125] With a clear record of cures for most patients and no toxicity in these and subsequent case series,[126-128] production of penicillin was rapidly escalated and treatments extended to more patients limited only by supply.[123,128-130] By June 1944, enough penicillin had been produced to treat all

wounded Allied soldiers in the D-Day invasion.[129,130] At no time through 1944, however, had randomized clinical trials validating the efficacy of penicillin been conducted.

Two therapeutic approaches for COVID-19, vaccines and IVM, are each supported with much more clinical data than was penicillin for treatments of bacterial infections during World War II. The indicated biological mechanism for IVM, as noted, is the same as that for antiviral antibodies generated by vaccines: competitive binding with SARS-CoV-2 viral spike protein. Early IVM treatment of COVID-19 patients could significantly reduce mortality pending complete distribution of vaccines and for elements of the population declining immunization. Also, although the UK variant of SARS-CoV-2 appears to be protected by the Pfizer-BioNTech vaccine,[131] recent studies indicate that the South African variant, known as 501Y.v2 or B1351, may have five- to ten-fold less protection from current vaccines than the original viral strains[132-134] and that other emerging variants may likewise evade such protection.[135,136] The particular form of IVM binding to SARS-CoV-2 spike protein, which may entail steric interference through bindings at multiple sites, may be more likely to have its efficacy conserved across such emerging mutant strains.[35]

Conclusion

For the 24 states of Peru with early IVM treatment, both excess deaths and COVID-19 case fatalities dropped sharply over 30-45 days after peak deaths. Deaths fell as six indices of Google-tracked community mobility rose over the same period. For nine states in which IVM was distributed over a short period through operation MOT, excess deaths at +30 days dropped by a population weighted mean of 74%. Each drop began within 11 day after MOT start. Several potential incidental causes of mortality reductions were ruled out.

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 additional such national deployments, interim and complementary to full-scale vaccine deployments. As noted, the exceptional record of this Nobel Prize-honored drug in 3.7 billion doses worldwide since 1987 provides a backdrop of safety. IVM treatments offered early for symptomatic indications of COVID-19 can fill in the gaps of vaccination protection, providing major mortality reductions for individuals pending development of vaccine-generate antibodies. IVM is also likely to be effective against viral mutants, in particular, the South African variant, that may receive a lesser degree of protection with current vaccines. Yet with aggressive such complementary deployments of vaccinations and IVM, the risk of continued contagion through complacency among individuals spurred by diminished mortality rates must be avoided. Public policies of widespread, rapid testing, contact tracing and face coverings can ensure that both of these therapeutic tools, vaccinations and IVM treatments, are optimally applied toward the complete elimination of the COVID-19 pandemic.

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Supplementary information is retrievable at
https://drive.google.com/file/d/1bjm62m0NwL_1cGPSYyQjjgu3Xas0rkSR/view?usp=sharing

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