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Safety of high-dose ivermectin: a systematic review and meta-analysis

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Background: Ivermectin is a key anthelmintic for the control of neglected tropical diseases. The main indications for population-level control with ivermectin through mass drug administration are onchocerciasis and lymphatic filariasis; however, there is interest in using higher, fixed-dose regimens for the control of scabies, soil-transmitted helminths and malaria. Safety data for these higher-dose regimens are needed.

Methods: A systematic literature review and meta-analysis on the safety and doses of ivermectin was conducted. Eligible studies reported patient-level data and, for the meta-analysis, clinical trials reporting data on doses ≥200 and ≥400 μg/kg were included. Incidence ratios were used to compare adverse events by severity and organ system affected.

Results: The systematic search identified six studies for inclusion, revealing no differences in the number of individuals experiencing adverse events. A descriptive analysis of these clinical trials for a variety of indications showed no difference in the severity of the adverse events between standard (up to 400 μg/kg) and higher doses of ivermectin. Organ system involvement only showed an increase in ocular events in the higher-dose group in one trial for the treatment of onchocerciasis, all of them transient and mild to moderate in intensity.

Conclusions: Although within this review the safety of high-dose ivermectin appears to be comparable to standard doses, there are not enough data to support a recommendation for its use in higher-than-approved doses. Ocular adverse events, despite being transient, are of concern in onchocerciasis patients. These data can inform programme managers and guide operational research activities as new approaches for the use of ivermectin are evaluated.

Introduction

Preventive chemotherapy through mass drug administration (MDA) is the main strategic intervention implemented for the control of human helminthiasis on a global scale.[1] The provision of safe and effective drugs to communities with the highest burden in terms of morbidity and prevalence has been demonstrated to be a powerful tool for the programmes aimed at the elimination of onchocerciasis or lymphatic filariasis (LF) and for the control of soil-transmitted helminth (STH) infections and schistosomiasis.[2–4]

Anthelmintics available through drug donations are being used according to manufacturer recommendations and a large body of experience and knowledge has been gained through their use in millions of individuals.[5] Ivermectin is probably the most remarkable anthelmintic drug owing to its impact on onchocerciasis and LF, with an efficacy and safety that have made it the most relevant tool for the control of those diseases.[6] Beyond its microfilaricidal activity against filarial nematodes, its horizons have been expanded through new findings of significant activity against *Trichuris trichiura* when co-administered with benzimidazole drugs, its efficacy for the treatment of scabies and a potential role in malaria control due to its endectocidal activity against *Anopheles* mosquitoes.[7–10] As the drug of choice for the treatment of *Strongyloides stercoralis* infections, rising awareness about this STH adds to the increasing demand for ivermectin.[11,12] These newly defined opportunities in the role of ivermectin as a tool for disease control beyond its original uses is also defining more ambitious public health goals of disease elimination, as is the case for LF, where a triple-drug regimen of albendazole, ivermectin and

diethylcarbamazine citrate has demonstrated its superior efficacy, which has prompted its recommendation in the most recent WHO guidelines for the treatment of LF.[13,14]

The main obstacles for an expanded use of ivermectin have been its limited supply and the severe adverse events (AEs) (encephalopathy) experienced by patients coinfected with *Loa loa*.[15–17] Despite these issues, widespread use has demonstrated that ivermectin is a very safe drug with infrequent and mostly mild AEs.[5,18] Currently, ivermectin is prescribed at doses of 150–200 μg/kg against most filarial and *S. stercoralis* infections and approved in doses of up to 400 μg/kg against infections with *Wuchereria bancrofti*.[19,20] Among the new indications under evaluation for ivermectin like STH and malaria control, doses >400 μg/kg are being evaluated with the purposes of improving efficacy through the achievement of higher peaks and/or extending the intervals with detectable drug levels.[21] With the aim of simplifying the implementation of MDA activities, the potential use of ivermectin at a fixed rather than a weight- or height-based dosing regimen is under evaluation, in order to lead to coformulations with drugs like albendazole or mebendazole, which are prescribed as fixed-dose regimens. Provided it can demonstrate a proper safety profile, high-dose ivermectin would allow large groups of the population to be adequately treated with just a few, or even a single, fixed-dose formulation of ivermectin. In a recent study using 18 mg ivermectin tablets, a safety and pharmacokinetic (PK) trial in 54 healthy adult volunteers demonstrated the possibility of using fixed-dose regimens of 18 and 36 mg.[22] The aim of this study was to systematically review the safety profile of high-dose ivermectin in order to contribute to the exploration of opportunities for expanded uses of this drug.

Methods

The study protocol was registered with the Prospero International Prospective Register of Systematic Reviews on 11 November 2017 (CRD42017078101).

The review question was to assess the safety of ivermectin in humans when used at doses of >200 and >400 μg/kg/day, regardless of the duration of the treatment.

Search strategy and selection criteria

A systematic literature search was carried out in several databases from inception until January 2018. The following databases were searched for relevant studies: MEDLINE (PubMed); Web of Science Core Collection; Cumulative Index to Nursing and Allied Health Literature (CINAHL database); Tropical Diseases Bulletin; CAB Direct; Scopus (Elsevier API); Science Direct; International Pharmaceutical Abs (Ovid); and Conference Papers Index (CSA) (ProQuest XML).

All relevant studies were reviewed, regardless of language or publication status (published, unpublished, in press and ongoing). The reference lists of all included studies for other potentially relevant research and authors' personal collections (grey literature) were also reviewed.

Search terms

Searches were conducted by combining the following three groups of terms: (i) ivermectin; (ii) dosage 400, 600, 700, 800, high-dose, high dose; and (iii) adverse effects, side effects. Studies were filtered to include only human studies (Table S1, available as Supplementary data at *JAC* Online). Authors of recently published abstracts and manuscripts in press were contacted to retrieve full articles.

Selection of studies

Two reviewers (M.N. and D.C.) independently reviewed the titles and abstracts yielded by the search and identified all studies that potentially met the inclusion criteria for this review. Thereafter they independently assessed whether each study met the inclusion criteria using an eligibility form. When the reviewers did not initially reach a consensus, a third reviewer (A.R.-M.) made the final inclusion decision. All excluded studies were documented with their reason for exclusion.

We included all studies evaluating the safety of ivermectin in humans, including case–control studies. For studies that evaluated the administration of ivermectin at high doses co-administered with other drugs, we tried to disaggregate the data or we contacted study authors to request disaggregated data. In the systematic review we included all studies on patients receiving ivermectin regardless of the indication; however, the underlying condition was recorded. Studies conducted on immunosuppressed patients were also considered for inclusion. Further, we performed a meta-analysis including studies where a group of participants receiving higher doses was compared with a control group (participants receiving standard doses).

Data extraction and data analysis

Two reviewers (M.N. and D.C.) independently performed data extraction using a pre-designed data extraction form. They resolved any disagreements regarding the data extraction by discussion between the two reviewers. When necessary, a third reviewer (A.R.-M.) facilitated discussion until consensus was reached. They entered the extracted data into an Excel database (Microsoft, Redmond, WA, USA).

Data about the study design, study population (including number of individuals, whether patients or healthy individuals), inclusion and exclusion criteria and statistical methods were collected. The analysis was done stratifying between those using any doses >200 μg/kg and those using any doses >400 μg/kg. The reference standard was a dose of ivermectin of 150 to 200 μg/kg. The primary outcomes were the AEs of ivermectin at doses >200 μg/kg and >400 μg/kg (as ivermectin doses up to 400 μg/kg are indicated for some pathologies such as LF) compared with standard doses.

For the meta-analysis, we considered for inclusion only studies where the following information was available: (i) the absolute number of patients treated with standard dose and higher doses; and (ii) the absolute number of patients who experienced any AE, both in the standard-dose arm and in the higher-dose arm. The AEs reported were considered drug related unless specifically attributed and documented to other causes in the publication. A descriptive analysis was performed in relation to the type (ocular, neurological, cutaneous and other AEs) and grading (mild, moderate, severe, life-threatening) of AEs, ivermectin indication, age (older/younger than 15 years), different study setting (by geographical continent), clearing dose (administration of a standard 150 μg/kg dose 3 months before the high dose, in order to reduce the risk of ocular AEs in subjects with high ocular microfilarial densities) and single versus multiple dosing.

Quality assessment

All studies included in the meta-analysis were randomized clinical trials (RCTs). The methodological quality of these studies was assessed using the NICE methodology checklist for RCTs.[23] In studies subject to risk of bias, and lacking information, we contacted the corresponding authors in order to attempt to obtain missing data and clarify unclear methodology. Two reviewers independently assessed the quality of the studies included in the meta-analysis (M.N. and D.C.). The report of the systematic review followed the PRISMA-harm checklist, specific for systematic reviews including harm outcome (Table S2).

Statistical analysis and data synthesis

The absolute frequencies of any AE related to drug use in each treatment group were extracted from all considered studies. First, ORs for the association between any AE and higher-dose treatment with ivermectin were calculated for each study, together with their corresponding 95% CIs. The Cochran–Mantel–Haenszel method with random effect was then used to obtain a pooled estimate of the effect of higher-dose treatment. Measures of heterogeneity such as the I^2 and the DerSimonian–Laird estimator for τ^2 were also calculated. Forest plots were used to illustrate the point estimate with 95% CI. Such meta-analysis was performed using R version 3.4.3 (meta package). Incidence ratios (IRs) were calculated for comparisons between dosing groups in terms of AE severity and organ system involvement.

Results

Included studies

The search strategy yielded 452 studies after removing duplicates. The authors identified six additional studies with relevant information for the systematic review that were included and assessed for eligibility. Two hundred and ninety-two studies were excluded after reading the title because they did not address our questions (studies about other topics, studies on animals, non-oral ivermectin) and, when any doubt remained, abstracts and/or whole articles were scanned; 109 were excluded after reading the abstract (mainly because they were reviews, case reports or about standard-dose ivermectin) and 48 were excluded after examining their full text. Nine of the 452 studies met the selection criteria. Finally, six studies were included for the meta-analysis (Figure 1).[21,22,24–27]

Quality assessment

The quality of the studies was evaluated; regarding allocation, half of the six studies showed unclear methods of randomization[22–24] and an adequate concealment of allocation was confirmed in only three.[18,24,25] Baseline characteristics of study groups were comparable in all but one study, which was a paediatric study not balanced for gender.[27] Three of the six studies were described as double-blind RCT.[18,22,24] The study by Wimmersberger *et al.*[27] was a single-blind RCT and the two remaining trials were open-label RCTs (Dembele *et al.*[24] and Muñoz *et al.*[22]). Consequently, risk of bias should be considered due to investigators' lack of blindness to participants' intervention and to other confounding and prognostic factors. Moreover, lack of blindness of participants to allocation was detected in two of the studies.[22,24] Blindness of individuals administering care was lacking in three of the studies.[22,24,27]

Regarding the received care and the length of follow-up between study groups, no risks of bias were detected in any of the manuscripts included. Treatment completion was comparable

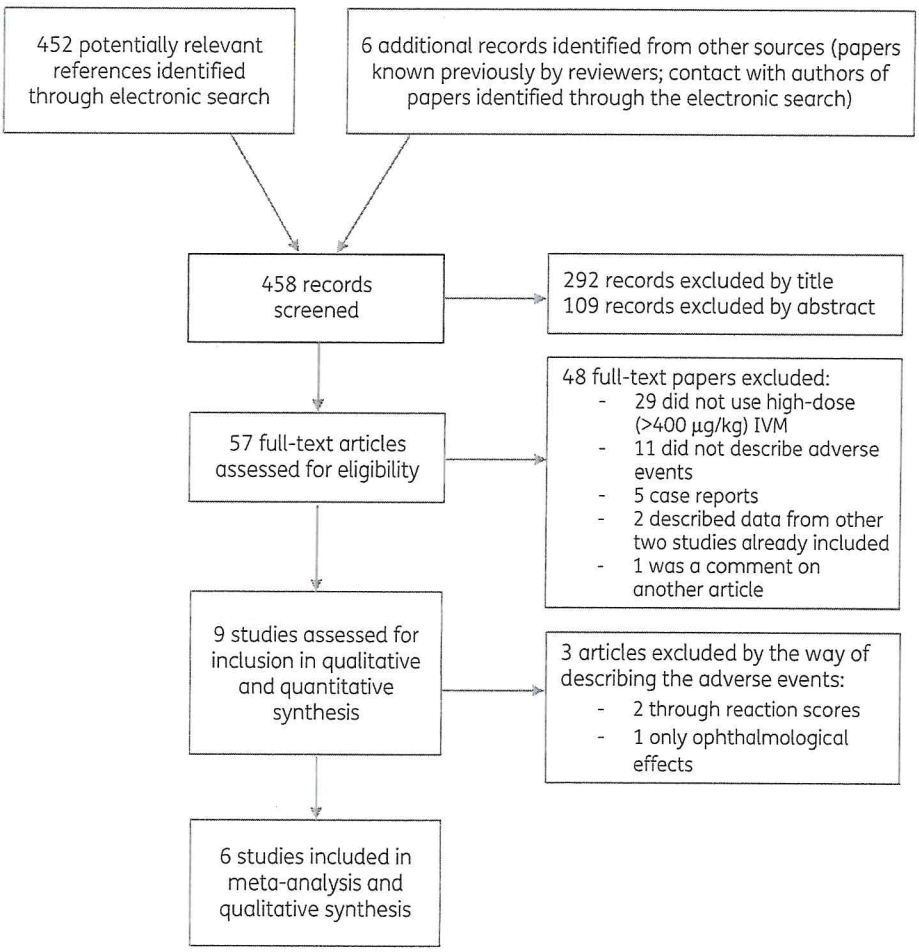

Figure 1. PRISMA flow diagram of systematic literature search. IVM, ivermectin.

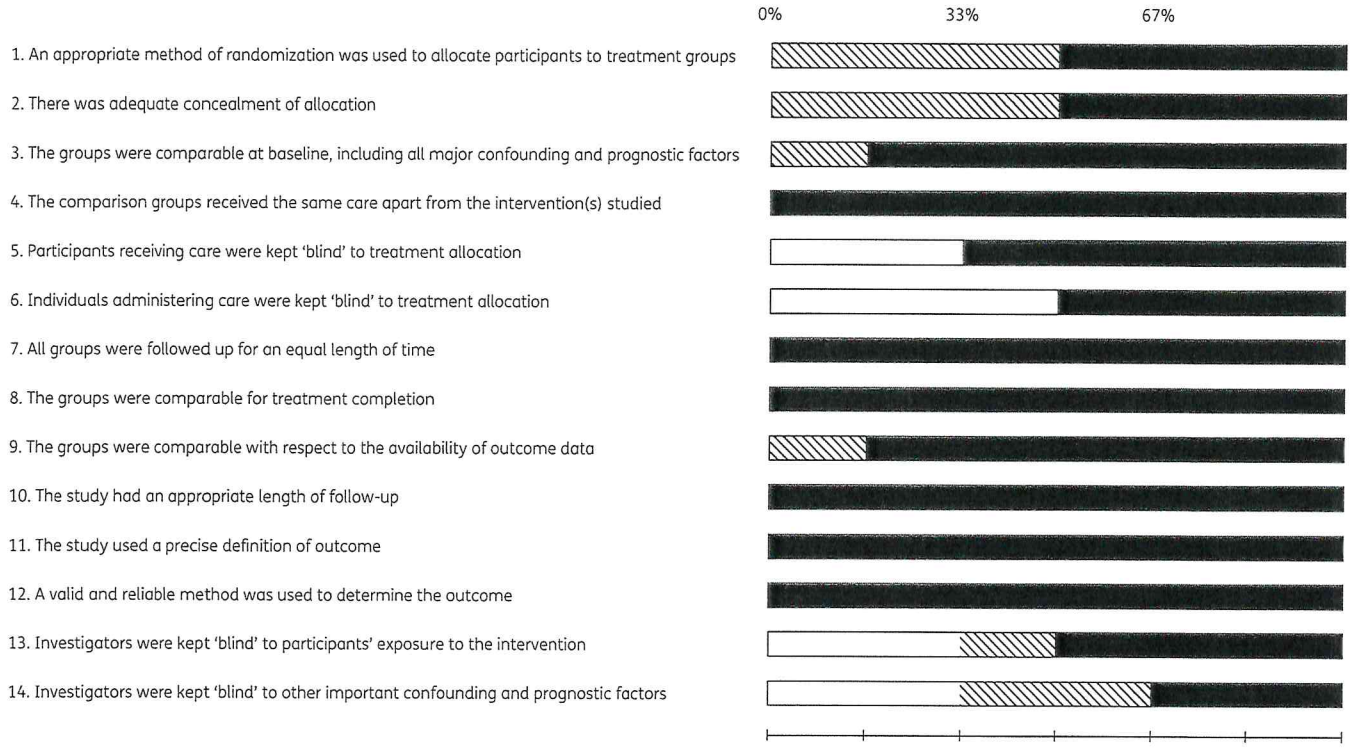

Figure 2. Quality assessment of the studies included in the meta-analysis using the NICE Methodology Checklist for RCTs. White, 'no'; striped line, 'unclear'; black, 'yes'.

between study groups in all articles. All studies included used a precise outcome definition and a reliable method to determine the outcome. Regarding risk of selective reporting bias, outcome data were comparable between study groups in all articles except those in which these data were unclear.[26] Length of follow-up was considered appropriate in all studies. The overall risk of bias is presented graphically in Figure 2.

Descriptive analysis

The four studies included in the meta-analysis with doses either up to 400 μg/kg or higher doses were also analysed in order to describe the total number of AEs, their severity and the involvement of particular organ systems (Table 1). In this analysis that included trials for diverse indications, including healthy volunteers, the high-dose arm included doses of up to 800 μg/kg. Since trial participants could experience more than one AE, IRs were calculated to evaluate the involvement of particular organ systems (ocular, neurological and cutaneous) most frequently described in the literature in the safety profile of ivermectin, revealing in just one clinical trial, for the treatment of onchocerciasis,[26] a significant increase in AEs related to the ocular system (IR 2.797, 95% CI: 1.226–6.377). Ocular AEs evaluated in this trial were subjective ocular symptoms such as transitory blurring of vision, itching or pain of the eye and dyschromatopsia. Severity of AEs showed that all studies reported 100% of the AEs as mild or moderate in both arms (standard and high dose), with serious AEs, described as life-threatening, reported in just one study with one case in the standard dose (anaphylactic reaction) and another in the high-dose group (QTc prolongation in the ECG, most likely due to a concomitant drug).[21] All studies were performed in Africa except one that was performed in Europe in healthy volunteers.[22] Ages of treated patients/individuals ranged from 2 to 60 years; one of the studies was performed in children (2–12 years) and the rest among adults (>18 years). Only one study administered a clearing dose of 150 μg of ivermectin before treatment.[26]

Meta-analysis

A total of six studies qualified for the different meta-analyses. Five studies published between 1993 and 2018 were included in the meta-analysis using 400 μg/kg as the cut-off, with moderate heterogeneity ($I^2 = 39\%$).[22,24–27] The random-effects model was 1.06 (95% CI 0.67–1.69), showing no difference between the study arms (Figure 3a). The meta-analysis was then repeated to compare ivermectin doses up to 200 μg/kg with higher doses. In this case, the analysis included four studies,[21,22,26,27] for which the results showed no difference in OR between study arms, according to both fixed and random-effects models; in this case, the random-effects model was 1.16 (95% CI 0.89–1.52) with very low heterogeneity (Figure 3b).

Discussion

This study describes the safety of ivermectin when used at higher daily doses than the standard regimens through the oral route of administration in humans. The methodological approach using a systematic review of the literature and meta-analysis allowed the comparison and joint analysis of different published trials using diverse underlying clinical conditions including healthy volunteers.

Table 1. Descriptive analysis of AEs of ivermectin by organs and systems in clinical trials comparing standard (up to 400 μg/kg) versus high-dose (>400 μg/kg) ivermectin

Condition under study	IVM dosage (μg/kg)[a]	Follow-up	AE/*N*	OR (95% CI)	Ocular		Neurological		Cutaneous		Other		Reference
					n	IR (95% CI)	*n*	IR (95% CI)	*n*	IR (95% CI)	*n*	IR (95% CI)	
Onchocerciasis													
high dose	800	3 years	149/172	1.135	13	2.797	25	0.960	63	1.369	48	0.956	[26]
standard dose	150–400		273/370	(0.834–1.545)	10	(1.226–6.377)	56	(0.599–1.539)	99	(0.998–1.877)	108	(0.681–1.343)	
Healthy volunteers (PK)													
high dose	401–700	7 days	8/49	0.907	0	—	2	0.512	0	—	6	1.258	[22]
standard dose	200–400		20/113	(0.369–2.228)	0		9	(0.111-2.372)	0		11	(0.465–3.401)	
Trichuriasis													
high dose	600	3 days	9/33	1.346	0	—	2	1.018	1	1.018	6	1.328	[27]
standard dose	100–400		38/168	(0.532–3.405)	0		10	(0.223–4.647)	5	(0.119–8.715)	23	(0.541–3.261)	
Malaria													
high dose	600	28 days	13/45	3.286	4	2.133	2	1.067	0	—	7	2.489	[21]
standard dose	300		7/48	(0.951–11.355)	2	(0.391–11.648)	2	(0.150–7.573)	0		3	(0.644–9.625)	

IVM, ivermectin; *N*, number of participants in each treatment group.
[a]High (>400 μg/kg) and standard (≤400 μg/kg) doses are defined based on the study definition of this analysis, which may differ from the categorization of high and standard doses for each individual study by the authors of these publications.

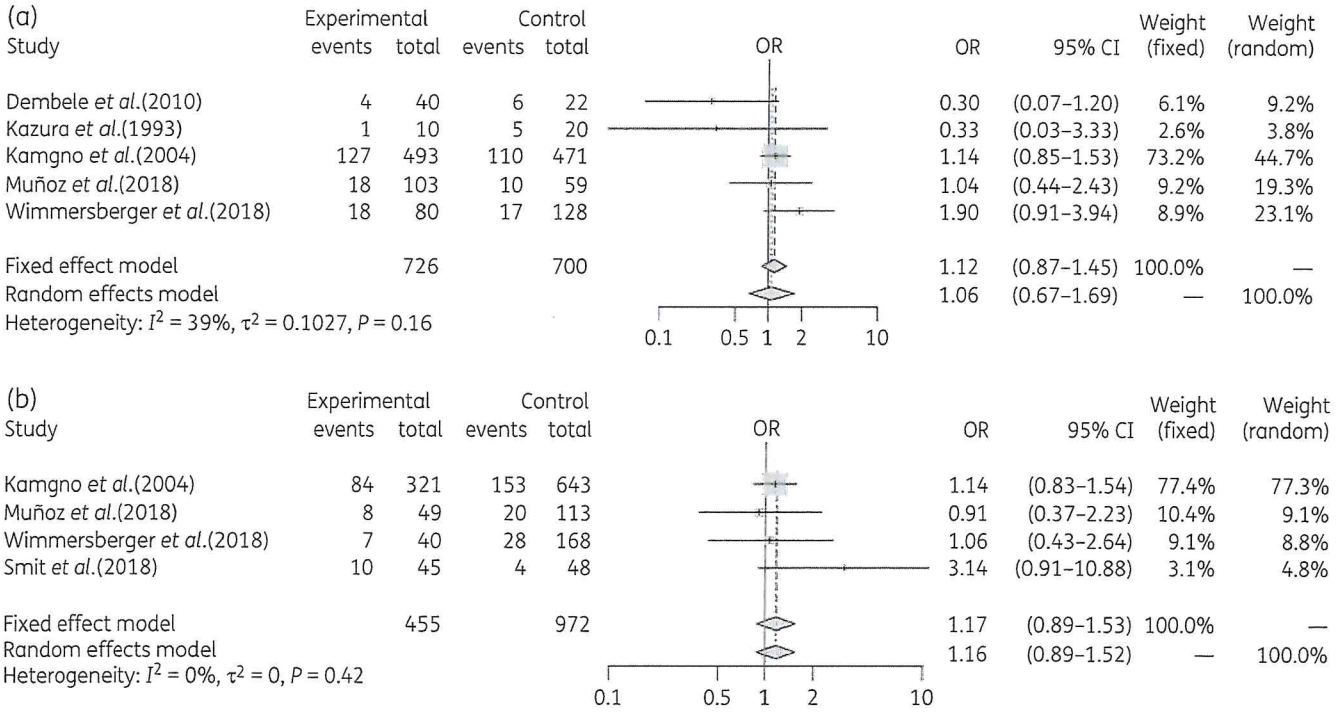

Figure 3. Meta-analysis of the association between AEs and standard- versus high-dose ivermectin using standard doses of 400 μg/kg (a) or 200 μg/kg (b) as reference.

Since the aim of the study was to understand the safety profile of higher doses of ivermectin to allow the consideration of their use at higher doses, in order to achieve higher efficacy or as a path to fixed dosing as an alternative dosing regimen to the weight-based approach currently recommended, the comparator of choice was the safety at regular doses (up to 400 μg/kg), which are well known, rather than comparing the safety of higher doses to that of placebo or no treatment. Through this approach, a fixed-dose regimen would provide a variable amount of μg/kg of ivermectin, therefore exposing a significant proportion of individuals to doses higher than those in the usual regimens. A proper understanding of the safety of these higher doses, which offer potential

advantages in the prevention of the emergence of drug resistance, is for this reason necessary.[28]

For the purpose of the meta-analysis, the treatment regimens were grouped into two arms, but it should be considered that in the 'higher doses' arm we had a wide range of doses. Although it was not possible to analyse further the influence of increasing doses of ivermectin, the results here do not suggest a trend in increasing AE with increasing doses. Only one study in patients with onchocerciasis demonstrated a higher risk of AE in the higher ivermectin-dose group,[26] which in further analysis was not able to link these AEs to microfilaraemia or disease-related lesions.[29] The most common complaints were transient blurred vision, itching or pain in the eye, scotomas or seeing flashes of light, all of them disappearing gradually over a few days. Another study included in our analysis found a non-significant increase in transient minor visual disturbances between subjects receiving 600 μg/kg compared with those receiving 300 μg/kg.[21] These findings are consistent with previous reports concluding that the type and severity of the underlying conditions is the most relevant variable that determines the safety of ivermectin.[30] Notably, the safety profile and AEs of ivermectin are generally not dose-related, as shown in a study that determined no relationship between serum ivermectin drug levels at 24 and 48 h post-administration and AEs among 71 patients with onchocerciasis.[31] In a clinical trial for the treatment of onchocerciasis, incremental doses of up to 800 μg/kg of ivermectin showed equal results in both efficacy and safety;[32] still, in a large intervention for onchocerciasis with over 50 000 treated individuals receiving between 130 and 200 μg/kg, there was a statistically significant relationship between the incidence of all reactions and ivermectin dosage after correction for microfilarial load, although no such relationship existed for moderate or severe reactions.[33] The limited number of studies that qualified for this review did not permit us to conduct subanalyses, for instance evaluation of the possible influence of underlying conditions in the development of AE or the geographic location of the trial.

The findings, although limited by the small number of studies and lack of blinding, add evidence to the safety of ivermectin at doses up to 800 μg/kg, which demonstrated an overall comparable safety to standard doses, which in this meta-analysis was tested in separate analyses using the 200 and 400 μg/kg doses as the highest standard dose since, for *W. bancrofti* infections, 400 μg/kg has been used for MDA campaigns.[34] Moreover, AEs observed in both groups were entirely of mild or moderate intensity. Remarkably, the largest study included in this analysis, which was performed in individuals with onchocerciasis, describes previously unpublished data of AEs categorized by the affected organ system revealing an increased IR for events affecting the vision with an IR of 2.80 (95% CI: 1.23–6.38) (Table 1). AEs categorized as systemic, neurological and cutaneous were present without significant increased frequency between groups. All other studies included in this analysis did not show a statistically significant increased risk of visual disturbances between groups. Some subjective ocular troubles (transitory blurring of vision, itching or pain of the eye and dyschromatopsia) appeared, but no patient developed any severe AE and none withdrew from the trial because of an adverse reaction. These results agree with a recent review of studies evaluating AEs in the treatment of LF, identifying the level of microfilaraemia rather than drug or dose as the variable most related to toxicity.[30] In a study including a limited number of healthy volunteers receiving doses up to 2000 μg/kg (10 times the recommended doses), ivermectin was well tolerated and ocular AEs were similar to those with placebo.[35]

With over 30 years of ample use and over 300 million people using it annually, ivermectin is, through its use in MDA campaigns, among the most relevant public health interventions in the developing world.[36] Despite this wide experience, there are still concerns and areas in need of evidence for a better understanding of the safety of ivermectin in order to expand its benefits to new indications and groups, like pregnant women and children <15 kg. The lack of safety data among these population groups results in their exclusion from MDA campaigns. However, recently published PK data from children receiving ivermectin for *T. trichiura* infections showed lower exposure profiles than adults receiving similar doses of 200 μg/kg, therefore suggesting that higher doses might be necessary in this age group.[37] A recent analysis of the databases of an international pharmacovigilance system concluded that even at regular doses, neurological serious AEs are rare without *L. loa* infections but research on other risk factors for these AEs is still needed.[38] Other relevant aspects for the understanding of PK/pharmacodynamic parameters of ivermectin are those related to the relationship of PK parameters, mostly C_{max}, with the appearance of toxicity. The high variability in PK parameters observed in humans may mask the effect associated with increased exposure if clinical trials are not accompanied by PK data.[22] In that study, the parameters related to drug exposure (AUC and C_{max}) showed a high interindividual coefficient of variation (CV) (CV = 37.4% and CV = 32.5%, respectively) and intraindividual variability (CV = 39.6% and CV = 33.2%, respectively),[22] therefore placing limitations on the results and conclusions from studies based purely on the relationship between dose and AEs.

While this study used the daily rather than multiple-day cumulative doses of ivermectin as the unit of analysis, this approach is based on the little variation seen in the daily C_{max} of ivermectin over three doses of up to 600 μg/kg on consecutive days.[39]

Conclusions

This systematic review, including a meta-analysis, has shown that AEs following single-dose treatment with up to 800 μg/kg of ivermectin occur without significant differences of frequency or intensity to those at regular currently approved doses. Ocular AEs, despite being transient, are of concern in onchocerciasis patients, requiring caution and further studies if ivermectin is used at high doses for that indication. The AEs reported in the reviewed studies were mostly mild or moderate in nature, suggesting the safety of ivermectin. There is, however, a paucity of information able to be analysed and a lack of blinding in the studies included, therefore calling for consensus in the proper and standardized manner of reporting safety data, as has been suggested by other groups,[30] in order to have adequate information to provide to the programmes and healthcare workers participating in MDA campaigns on the management of AEs related to ivermectin. To conclude, more clinical trials evaluating the safety of ivermectin at higher doses, and in children <15 kg and pregnant women, are needed.

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Transparency declarations

None to declare.

Authors contributions

M.N.: First reviewer of all the papers and systematic review, leading analysis and writing; D.C.: Second reviewer of all the papers and systematic review, analysis of descriptive results; A.R.-M. Study design, conceptualization, third reviewer for discordant results and quality assessment; D.B.: Meta-analysis design; G.G.: Meta-analysis, statistics and graph; J.K.: Data processing; J.G.: Data processing; M.B.: Data processing; J.M.: Conceptualization and results interpretation; A.K.: Original idea, design, analysis and writing.

Disclaimer

The views and opinions of authors expressed herein do not necessarily state or reflect those of EDCTP.

Supplementary data

Tables S1 and S2 are available as Supplementary data at *JAC* Online.

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Productie 21

Annex 1

19th WHO Model List of Essential Medicines (April 2015)

Explanatory notes

The **core list** presents a list of minimum medicine needs for a basic health-care system, listing the most efficacious, safe and cost–effective medicines for priority conditions. Priority conditions are selected on the basis of current and estimated future public health relevance, and potential for safe and cost-effective treatment.

The **complementary list** presents essential medicines for priority diseases, for which specialized diagnostic or monitoring facilities, and/or specialist medical care, and/or specialist training are needed. In case of doubt medicines may also be listed as complementary on the basis of consistent higher costs or less attractive cost-effectiveness in a variety of settings.

The **square box symbol (□)** is primarily intended to indicate similar clinical performance within a pharmacological class. The listed medicine should be the example of the class for which there is the best evidence for effectiveness and safety. In some cases, this may be the first medicine that is licensed for marketing; in other instances, subsequently licensed compounds may be safer or more effective. Where there is no difference in terms of efficacy and safety data, the listed medicine should be the one that is generally available at the lowest price, based on international drug price information sources. Not all square boxes are applicable to medicine selection for children — see the second EMLc for details.

Therapeutic equivalence is indicated only on the basis of reviews of efficacy and safety and when consistent with WHO clinical guidelines. National lists should not use a similar symbol and should be specific in their final selection, which would depend on local availability and price.

The **a** symbol indicates that there is an age or weight restriction on use of the medicine; details for each medicine can be found in Table 1.1.

Where the ***[c]*** symbol is placed next to the complementary list it signifies that the medicine(s) require(s) specialist diagnostic or monitoring facilities, and/or specialist medical care, and/or specialist training for their use in children.

Where the **[c]** symbol is placed next to an individual medicine or strength of medicine it signifies that there is a specific indication for restricting its use to children.

The presence of an entry on the Essential Medicines List carries no assurance as to pharmaceutical quality. It is the responsibility of the relevant national or regional drug regulatory authority to ensure that each product is of appropriate pharmaceutical quality (including stability) and that, when relevant, different products are interchangeable.

For recommendations and advice concerning all aspects of the quality assurance of medicines see the WHO Medicines website http://www.who.int/medicines/areas/quality_assurance.

Medicines and dosage forms are listed in alphabetical order within each section and there is no implication of preference for one form over another. Standard treatment guidelines should be consulted for information on appropriate dosage forms.
The main terms used for dosage forms in the Essential Medicines List can be found in Table 1.2.

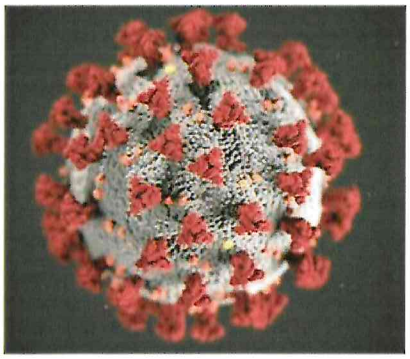
enalapril 28, 29
enoxaparin 25
entecavir 14
ephedrine 1
epinephrine (adrenaline) 3, 28, 38, 40
ergocalciferol 42
ergometrine 38
erythromycin 8
estradiol cypionate + medroxyprogesterone acetate 33
ethambutol 10
ethambutol + isoniazid 10
ethambutol + isoniazid + pyrazinamide + rifampicin 10
ethambutol + isoniazid + rifampicin 10
ethanol 31
ethinylestradiol + levonorgestrel 33
ethinylestradiol + norethisterone 33
ethionamide 11
ethosuximide 5
etonogestrel-releasing implant 34
etoposide 21
ferrous salt 25
ferrous salt + folic acid 25
filgrastim 22
fluconazole 11
flucytosine 11
fludarabine 21
fludrocortisone 33
fluorescein 30
fluorouracil 21, 30
fluoxetine 3, 39, 40
fluphenazine 39
folic acid 25
fomepizole 4
fresh frozen plasma 26
furosemide 29, 31
gemcitabine 22
gentamicin 9, 37
gliclazide 34
glucagon 34
glucose 41
glucose with sodium chloride 41
glutaral 31
glyceryl trinitrate 27
griseofulvin 11
Haemophilus influenzae type b vaccine 36
haloperidol 3, 39
halothane 1
heparin sodium 25, 26
hepatitis A vaccine 37
hepatitis B vaccine 36
HPV vaccine 36
hydralazine 28
hydrochlorothiazide 28, 29, 31
hydrocortisone 3, 24, 30, 32, 33
hydroxocobalamin 25
hydroxycarbamide 22, 26
hydroxychloroquine 43
hyoscine butylbromide 3
hyoscine hydrobromide 3
ibuprofen 2, 18, 43
ifosfamide 22
imatinib 22
imipenem + cilastatin 8
influenza vaccine 37
insulin injection (soluble) 34
intermediate-acting insulin 34
intraperitoneal dialysis solution (of appropriate composition) 39
iodine 42
iohexol 30
ipratropium bromide 40
irinotecan 22
isoflurane 1
isoniazid 10
isoniazid + pyrazinamide + rifampicin 10
isoniazid + rifampicin 10
isosorbide dinitrate 27
ivermectin 6
Japanese encephalitis vaccine 36
kanamycin 11
ketamine 1
lactulose 3
lamivudine (3TC) 12
lamivudine + nevirapine + stavudine 13
lamivudine + nevirapine + zidovudine 13
lamivudine + zidovudine 14
latanoprost) 38
ledipasvir + sofosbuvir 15
leuprorelin 24
levamisole 6
levodopa + carbidopa 25
levofloxacin 11
levonorgestrel 33
levonorgestrel-releasing implant 34
levonorgestrel-releasing intrauterine system 34
levothyroxine 35
lidocaine 1, 28
lidocaine + epinephrine (adrenaline) 1
linezolid 11
lithium carbonate 40
loperamide 3
lopinavir + ritonavir (LPV/r) 13
loratadine 4
lorazepam 5
Lugol's solution 35
magnesium sulfate 5
mannitol 31
measles vaccine 36
mebendazole 6
medroxyprogesterone acetate 34, 35
mefloquine 17
meglumine iotroxate 31
melarsoprol 18
meningococcal meningitis vaccine 37
mercaptopurine 22
mesna 22
metformin 34
methadone 40
methotrexate 23, 43
methyldopa 28
methylprednisolone 24
methylthioninium chloride (methylene blue) 4
metoclopramide 32
metronidazole 9, 15
miconazole 29
midazolam 1, 3, 5
mifepristone 39
miltefosine 15
misoprostol 38, 39
morphine 1, 2
mumps vaccine 37
mupirocin 30
naloxone 4
neostigmine 37
nevirapine (NVP) 13
niclosamide 6

levamisole	**Tablet:** 50 mg; 150 mg (as hydrochloride).
mebendazole	**Tablet (chewable):** 100 mg; 500 mg.
niclosamide	**Tablet (chewable):** 500 mg.
praziquantel	**Tablet:** 150 mg; 600 mg.
pyrantel	**Oral liquid:** 50 mg (as embonate **or** pamoate)/ mL. **Tablet (chewable):** 250 mg (as embonate **or** pamoate).
6.1.2 Antifilarials	
albendazole	**Tablet (chewable):** 400 mg.
diethylcarbamazine	**Tablet:** 50 mg; 100 mg (dihydrogen citrate).
ivermectin	**Tablet (scored):** 3 mg.
6.1.3 Antischistosomals and other antitrematode medicines	
praziquantel	**Tablet:** 600 mg.
triclabendazole	**Tablet:** 250 mg.
Complementary List	
*oxamniquine**	***Capsule:*** *250 mg.* ***Oral liquid:*** *250 mg/5 mL.* * *Oxamniquine is listed for use when praziquantel treatment fails.*
6.2 Antibacterials	
6.2.1 Beta-lactam medicines	
amoxicillin	**Powder for oral liquid:** 125 mg (as trihydrate)/5 mL; 250 mg (as trihydrate)/5 mL **[c]**. **Solid oral dosage form:** 250 mg; 500 mg (as trihydrate).
amoxicillin + clavulanic acid	**Oral liquid:** 125 mg amoxicillin + 31.25 mg clavulanic acid/5 mL AND 250 mg amoxicillin + 62.5 mg clavulanic acid/5 mL **[c]**. **Tablet:** 500 mg (as trihydrate) + 125 mg (as potassium salt).
ampicillin	**Powder for injection:** 500 mg; 1 g (as sodium salt) in vial.
benzathine benzylpenicillin	**Powder for injection:** 900 mg benzylpenicillin (= 1.2 million IU) in 5- mL vial **[c]**; 1.44 g benzylpenicillin (= 2.4 million IU) in 5- mL vial.
benzylpenicillin	**Powder for injection:** 600 mg (= 1 million IU); 3 g (= 5 million IU) (sodium **or** potassium salt) in vial.

Productie 22

UNIVERSITEIT GENT

Op weg naar antilichamen tegen COVID-19



(06-05-2020) UGent en VIB onderzoekers isoleerden antilichaam dat kan binden aan het SARS-CoV-2, het virus dat COVID-19 veroorzaakt.

Het labo van Xavier Saelens (VIB-UGent Centrum voor Medische Biotechnologie) heeft een antilichaam geïsoleerd dat kan binden aan het SARS-CoV-2, het virus dat COVID-19 veroorzaakt. Het werk werd verricht in samenwerking met Amerikaanse teams. De onderzoekers hebben vastgesteld dat het antilichaam bindt aan een deel van het 'spike-eiwit' dat het virus gebruikt om menselijke cellen binnen te dringen. Belangrijk is ook dat het antilichaam een laboratoriumvariant van het virus onschadelijk kan maken, een grote stap voorwaarts in de ontwikkeling van een potentieel antiviraal middel tegen COVID-19. Hun werk verschijnt in het vakblad Cell.

Een antilichaam tegen COVID-19

Sinds het begin van de COVID-19 uitbraak is de zoektocht naar het vinden van antilichamen onverminderd doorgegaan. Het team van professor Xavier Saelens heeft, in samenwerking met het labo van Jason McLellan (Universiteit van Texas in Austin, VS) **een klein antilichaam, geïsoleerd uit een lama, gekarakteriseerd dat bindt aan een belangrijk deel van het SARS-CoV-2 virus.**
Hun bevindingen laten precies zien waar het antilichaam zich bindt aan de **spike-eiwitten van het virus**. Deze eiwitten zijn van vitaal belang voor het virus omdat ze het in staat stellen gastheercellen binnen te dringen. **Door deze eiwitten in het vizier te nemen, kan het antilichaam het virus onschadelijk maken**. Dit is een belangrijke stap in de zoektocht naar een antiviraal middel tegen COVID-19.

Op weg naar bescherming

Deze nieuwe resultaten leveren het eerste bewijs dat het antilichaam mogelijk kan voorkomen dat het nieuwe coronavirus menselijke cellen infecteert. Belangrijk is dat het antilichaam ook op grote schaal kan worden geproduceerd met productieprocessen die gebruikelijk zijn in de biofarmaceutische industrie. Professor Saelens benadrukt: "Dit is een belangrijke stap voorwaarts in de strijd tegen COVID-19. Deze stap werd mogelijk gemaakt door de gezamenlijke inspanningen van mijn team en dat van Nico Callewaert (VIB-UGent Centrum voor Medische Biotechnologie)."

Dr. Bert Schepens, stafwetenschapper in het team van Xavier Saelens, beaamt: "**Goed teamwerk is cruciaal**. We kunnen rekenen op de expertise in het onderzoekscentrum, en op collega's van over heel VIB. De langdurige samenwerking met de labo's van Jason McLellan en Barney Graham is ook een essentieel element. Het moment waarop we in deze experimenten konden vaststellen dat het virus werd geneutraliseerd, voelde oprecht als een collectieve overwinning."

In vergelijking met vaccins, biedt een antilichaam **onmiddellijke bescherming – echter van kortere duur**. Het voordeel van deze benadering ten opzichte van vaccins is dat patiënten hun eigen antilichamen niet hoeven aan te maken. De meest kwetsbar groepen, zoals ouderen, vertonen vaak maar een beperkte respons op vaccins, waardoor hun bescherming niet optimaal is. Zorgverleners en andere mensen die een verhoogd risico lopen, kunnen ook voordeel halen uit een onmiddellijke bescherming. **Een antilichaam kan dus een belangrijk hulpmiddel zijn bij het bestrijden van de huidige pandemie**.

De volgende stappen

De VIB-onderzoekers zijn nu een preklinische testfase aan het voorbereiden met het oog op een behandeling van het coronavirus. Hoewel deze eerste resultaten veelbelovend zijn, is **verder onderzoek nodig** om het volledige potentieel van dit op antilichamen gebaseerde geneesmiddel tegen COVID-19 te bevestigen. De technologietransfer- en Discovery Sciences teams van VIB bieden waardevolle ondersteuning bij de klinische ontwikkeling van dit kandidaat-geneesmiddel voor COVID19.

> Lees het volledige verhaal over het COVID-19-werk van Xavier Saelens en Nico Callewaert, naar aanleiding van de voorpublicatie van hun artikel op BioRxiv eind maart 2020.

Meer informatie

→ Lees het artikel hier

→ Een doorbraak in onderzoek betekent niet hetzelfde als een doorbraak in de geneeskunde. De verwezenlijkingen van VIB-onderzoekers kunnen de basis vormen voor nieuwe therapieën, maar het ontwikkelingstraject neemt nog jaren in beslag.
Heb je vragen over medisch gericht onderzoek? Contacteer patienteninfo@vib.be

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Lees meer artikels over:

Productie 23

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

Juan J. Chamie-Quintero,[a] Jennifer A. Hibberd,[b] David E Scheim[c]

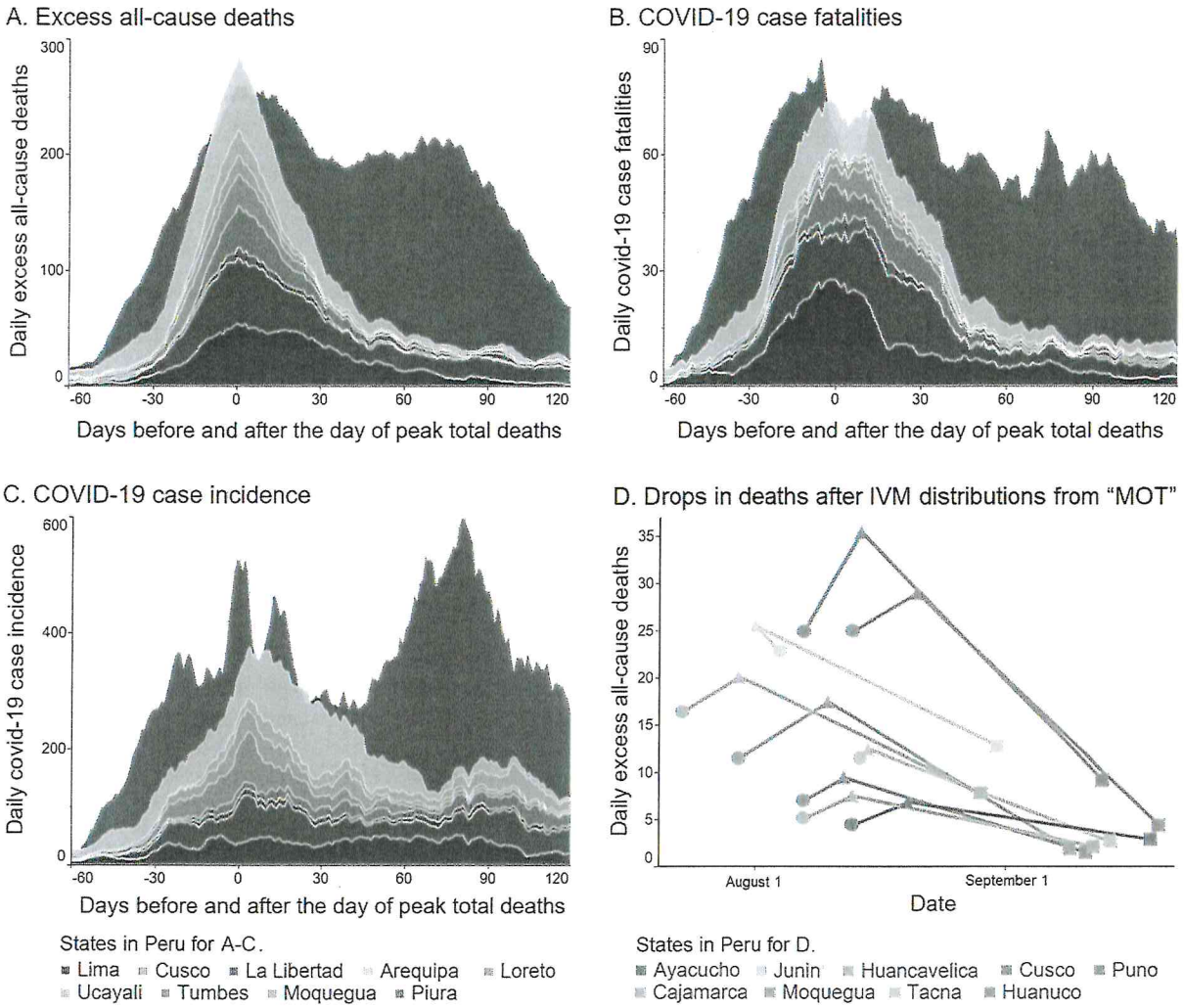

Figure 1: Graphical Abstract. A) Excess all-cause deaths; B) COVID-19 case fatalities; and C) case incidence data for eight states in Peru that deployed mass ivermectin (IVM) treatments early in their pandemic spread (blue) and for Lima, which deployed IVM treatment four months later (red). D) Excess 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

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.

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.

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

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%

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%.

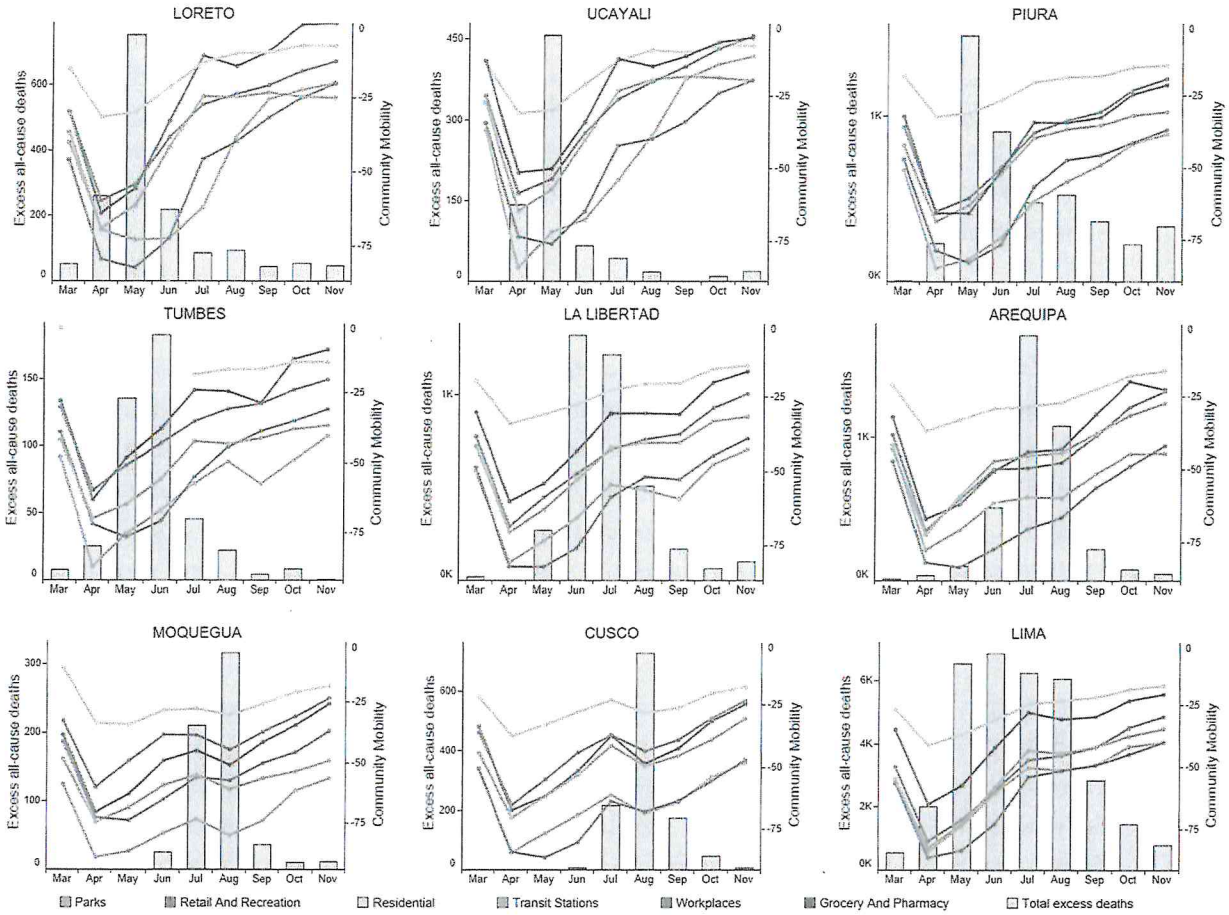

Figure 2. Google community mobility trends[97] (line graphs) and excess all-cause deaths for ages ≥ 60 (bars). These mobility indices show percentage changes in trips to different categories of destinations.

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

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

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]

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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Use of Ivermectin Is Associated With Lower Mortality in Hospitalized Patients With Coronavirus Disease 2019

The Ivermectin in COVID Nineteen Study

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BACKGROUND: Ivermectin was shown to inhibit severe acute respiratory syndrome coronavirus 2 replication in vitro, which has led to off-label use, but clinical efficacy has not been described previously.

RESEARCH QUESTION: Does ivermectin benefit hospitalized coronavirus disease 2019 (COVID-19) patients?

STUDY DESIGN AND METHODS: Charts of consecutive patients hospitalized at four Broward Health hospitals in Florida with confirmed COVID-19 between March 15 and May 11, 2020, treated with or without ivermectin were reviewed. Hospital ivermectin dosing guidelines were provided, but treatment decisions were at the treating physician's discretion. The primary outcome was all-cause in-hospital mortality. Secondary outcomes included mortality in patients with severe pulmonary involvement, extubation rates for mechanically ventilated patients, and length of stay. Severe pulmonary involvement was defined as need for $F_{IO_2} \geq 50\%$, noninvasive ventilation, or invasive ventilation at study entry. Logistic regression and propensity score matching were used to adjust for confounders.

RESULTS: Two hundred eighty patients, 173 treated with ivermectin and 107 without ivermectin, were reviewed. Most patients in both groups also received hydroxychloroquine, azithromycin, or both. Univariate analysis showed lower mortality in the ivermectin group (15.0% vs 25.2%; OR, 0.52; 95% CI, 0.29-0.96; $P = .03$). Mortality also was lower among ivermectin-treated patients with severe pulmonary involvement (38.8% vs 80.7%; OR, 0.15; 95% CI, 0.05-0.47; $P = .001$). No significant differences were found in extubation rates (36.1% vs 15.4%; OR, 3.11; 95% CI, 0.88-11.00; $P = .07$) or length of stay. After multivariate adjustment for confounders and mortality risks, the mortality difference remained significant (OR, 0.27; 95% CI, 0.09-0.80; $P = .03$). One hundred ninety-six patients were included in the propensity-matched cohort. Mortality was significantly lower in the ivermectin group (13.3% vs 24.5%; OR, 0.47; 95% CI, 0.22-0.99; $P < .05$), an 11.2% (95% CI, 0.38%-22.1%) absolute risk reduction, with a number needed to treat of 8.9 (95% CI, 4.5-263).

INTERPRETATION: Ivermectin treatment was associated with lower mortality during treatment of COVID-19, especially in patients with severe pulmonary involvement. Randomized controlled trials are needed to confirm these findings. CHEST 2021; 159(1):85-92

KEY WORDS: hospitalized COVID-19; in-hospital mortality; ivermectin; mechanical ventilation; number needed to treat; severe pulmonary involvement; survival

ABBREVIATIONS: COVID-19 = coronavirus disease 2019; IQR = interquartile range; MAP = mean arteria pressure; QTc = corrected QT interval; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

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Take-home Points

Study Question: Is ivermectin associated with lower mortality rate in patients hospitalized with coronavirus disease 2019 (COVID-19)?

Results: A retrospective cohort study of consecutive patients hospitalized with confirmed severe acute respiratory syndrome coronavirus 2 infection at a four-hospital consortium in South Florida. Analysis showed statistically significant lower mortality rates in the group treated with ivermectin as compared with the group treated with usual care (15.0% vs 25.2%).

Interpretation: Ivermectin was associated with lower mortality during treatment of COVID-19 patients, especially in patients who required higher inspired oxygen or ventilatory support.

Ivermectin previously was studied as a therapeutic option for viral infections, with data showing some in vitro activity against a broad range of viruses, including HIV, dengue, influenza, and Zika virus, likely through inhibition of importin $\alpha/\beta1$-mediated nuclear import of viral proteins.[1-3] Wagstaff et al[4] demonstrated that ivermectin was a potent in vitro inhibitor of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), showing a 99.8% reduction in viral RNA after 48 h. Reports can be found on the Internet of physicians worldwide treating Coronavirus disease 2019 (COVID-19) empirically with ivermectin since late April 2020. According to ClinicalTrials.gov, currently 37 studies are investigating the usefulness of ivermectin in COVID-19. However, in vivo efficacy of ivermectin in SARS-CoV-2 infection in humans has not been reported previously.

In the late 1970s, ivermectin was developed as a new class of drug to treat parasitic infections. Initially used in veterinary medicine, it soon was found to be safe and effective in humans. It has been used successfully to treat onchocerciasis and lymphatic filariasis in millions of people worldwide as part of a global drug donation program. About 3.7 billion doses of ivermectin have been distributed in mass drug administration campaigns globally over the past 30 years. Presently, ivermectin is approved for use in humans in several countries to treat onchocerciasis, lymphatic filariasis, strongyloidiasis, and scabies.[1]

Based on the data drug safety sheet for ivermectin (New Drug Application Identifier: 50-742/S-022), side effects were uncommon and limited. Reported side effects with more than 1% occurrence included elevation in alanine aminotransferase and aspartate aminotransferase (2%), nausea (2%), diarrhea (2%), decreased leukocyte count (3%), peripheral edema (3%), tachycardia (3%), dizziness (3%), and pruritus (3%). A pharmacokinetic study of 166 patients reported side effects of headache (6%), dysmenorrhea (5.5%), upper respiratory infection symptoms (1.8%), and diarrhea (1.8%).[5]

Methods

Patients

Sequentially consecutive hospitalized patients at four Broward Health-associated hospitals in South Florida with laboratory-confirmed infection with SARS-CoV-2 during their admission were reviewed in this study. The list of confirmed cases was provided by the hospitals' epidemiology departments. Enrollment dates ranged from March 15, 2020, through May 11, 2020. Confirmatory testing was performed by nasopharyngeal swab using a Food and Drug Administration Emergency Use Authorized COVID-19 molecular assay for the detection of SARS-CoV-2 RNA. Patients younger than 18 years and those who were pregnant or incarcerated were excluded from data collection based on institutional review board requirements. Patients who had at least two separate admissions placing them in both groups also were excluded.

Study Procedures

Records were abstracted by four of the authors (J. C. R., N. F., J. S., and J.-J. R.), and all data were reviewed subsequently and confirmed by the lead author. Baseline data were collected at the time of ivermectin administration for the ivermectin group; for the usual care group, baseline was either the time of administration of hydroxychloroquine or, if not used, at the time of admission. Information collected included COVID-19 testing results, patient demographics, pre-existing comorbid conditions, initial vital signs, laboratory results, and the use of corticosteroids, hydroxychloroquine, and azithromycin to describe the cohort and to identify potential confounders between groups. Severity of pulmonary involvement was assessed at the time of baseline data collection and was categorized

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as severe or nonsevere. Patients were considered to have severe pulmonary involvement if they required an Fio_2 of 50% or more, high-flow nasal oxygen, noninvasive ventilation, or intubation and mechanical ventilation. The nonsevere pulmonary criteria encompassed patients who required no supplemental oxygen or low Fio_2 (ie, venturi mask 40% or less or up to 6 L/min of low-flow nasal cannula), independent of laboratory findings.

Patients were categorized into two treatment groups based on whether they received ivermectin at any time during the hospitalization. Patients in the ivermectin group received at least one oral dose of ivermectin at 200 μg/kg in addition to usual clinical care. A second dose could be given at the discretion of the treating physician at day 7 of treatment. Ivermectin is not currently approved by the Food and Drug Administration for COVID-19 treatment. The decision to prescribe ivermectin, hydroxychloroquine, azithromycin, or other medications was at the discretion of the treating physicians; however, hospital guidelines were established for the safe use and dosing of these agents. These guidelines included a baseline ECG and mandatory cardiac and corrected QT interval (QTc) monitoring for patients receiving hydroxychloroquine (alone or in combination with azithromycin), avoidance of azithromycin if patient's baseline QTc was more than 460 msec, and discontinuation of hydroxychloroquine if a concerning elevation in QTc occurred or if the patient's cardiologist recommended discontinuation. Oxygen and ventilatory support were applied per the customary care. Empiric use of ivermectin was given explicitly for COVID-19.

Outcomes

The primary outcome was all-cause in-hospital mortality. A patient was considered a survivor if he or she left the hospital alive or if his or her status in the hospital changed from active care to awaiting transfer to a skilled facility. Two consecutive nasopharyngeal swab specimens showing negative results for SARS-CoV-2, collected ≥ 24 h apart, were necessary for a patient to be accepted to the local skilled nursing facilities.

Secondary outcomes included subgroup mortality of patients with severe pulmonary involvement, extubation rates for patients requiring mechanical ventilation, and length of hospital stay. Length of stay was calculated from day of admission to either the day of discharge or to patient death.

Statistical Analysis

Univariate analysis of the primary mortality outcome and comparisons between treatment groups were determined by the Student t test for parametric continuous variables or the Mann-Whitney U test for nonparametric continuous variables as appropriate, and by the Pearson χ^2 test for categorical variables. The method of Hodges-Lehman was used to estimate median differences with 95% CIs.

To adjust for confounders and between-group differences, a multivariate analysis was performed using stepwise binary logistic regression. Patient variables included in the analysis were age, sex, comorbidities of diabetes, chronic lung disease, cardiovascular disease, and hypertension, smoking status, severity of pulmonary involvement, need for mechanical ventilation at study entry, BMI, peripheral white blood count, absolute lymphocyte count, and use of corticosteroids based on bivariate associations within our data, a priori plausibility, and documented associations with mortality from previous studies. Adjusted ORs with 95% CIs were computed to show level of certainty. Analyses were based on nonmissing data, and missing data were not imputed. Missingness of 1% was found for peripheral WBC count, 5% for smoking status, and 7% for absolute lymphocyte count.

We performed a secondary analysis using propensity score matching to reduce the effects of confounding and the likelihood of selection bias. Propensity matching was performed using a nearest-neighbor algorithm with 1:1 matching without replacement and a caliper distance of less than 0.2. Variables for propensity scoring included those variables from the univariate between-groups analysis of the unmatched cohort that had a P value of less than .2 (age, sex, pulmonary condition, hypertension , HIV status, severe pulmonary presentation, and exposure to corticosteroids, hydroxychloroquine, or azithromycin). Race, WBC count, absolute lymphocyte count, and need for mechanical ventilation before or on the day of study entry also were added as potential clinical confounders.

All tests were two-sided and a P value $< .05$ was considered statistically significant. Statistical analyses were conducted using IBM SPSS version 26.0 software, R version 3.5.3 software (R Foundation for Statistical Computing), and SPSS PS-matching software (sourceforge.net).

This study was conducted in accordance with tenets of the amended Declaration of Helsinki. The protocol was approved by the institutional review board for the Broward Health Hospital System (Identifier: 2020-034-BHMC). The authors assume responsibility for the accuracy and completeness of the data and analyses, as well as for the fidelity of the study.

Results

Characteristics of the Patients

Three hundred seven patients were admitted for COVID-19 during the period studied. Four patients were not reviewed because of multiple admissions, 11 did not have COVID-19 confirmed at the time of the study, and 12 were excluded because their age was younger than 18 years, they were pregnant, or they were incarcerated. The remaining cohort of 280 patients comprised 173 treated with ivermectin and 107 in the usual care group. Most patients received a single dose of ivermectin; however, 13 patients received a second dose of ivermectin for ongoing signs or symptoms on day 7 of treatment. Follow-up data for all outcomes were available through May 19, 2020. No patients were lost to follow-up for the primary outcome. At the time of analysis, all patients in both groups had met the end point of death, discharge alive, or awaiting transfer to a skilled facility. Of those awaiting transfer, in the control group, one patient was awaiting transfer to hospice because of an unrelated terminal illness and one patient was awaiting negative COVID-19 test results to proceed with unrelated surgery. In the ivermectin group, five patients were in stable condition, awaiting transfer to skilled facility or rehabilitation, and one patient was improving clinically.

Baseline characteristics and between-group comparisons for unmatched and propensity-matched cohorts are shown in Table 1. Before matching, hypertension and

TABLE 1] Patient Characteristics by Treatment Group

Demographic Characteristic	Unmatched Cohort				Matched Cohort			
	Total (N = 280)	Usual Care (n = 107)	Ivermectin (n = 173)	*P* Value	Total (N = 196)	Usual Care (n = 98)	Ivermectin (n = 98)	*P* Value
Age, y	59.6 ± 17.9	58.6 ± 18.5	60.2 ± 17.6	.45	59.6 ± 17.5	59.04 ± 17.7	60.07 ± 17.4	.68
Female sex	127 (45.4)	43 (41.2)	84 (48.6)	.17	78 (39.8)	39 (39.8)	39 (39.8)	1.0
Race or ethnicity			.36				1.0	
Black	153 (54.6)	55 (51.4)	98 (56.6)		108 (55.1)	54 (55.1)	54 (55.1)	
White	76 (27.1)	35 (32.7)	41 (23.7)		55 (28.1)	27 (27.6)	28 (28.6)	
Hispanic	33 (11.7)	12 (11.2)	21 (12.1)		23 (11.7)	12 (12.5)	111 (11.2)	
Other or not identified[a]	13 (4.6)	5 (4.7)	13 (7.5)		10 (5.1)	5 (5.1)	5 (5.1)	
Current or former smoker	46/255 (18.0)	22/99 (22.3)	24/156 (15.6)	.40	31/180 (22.2)	20/90 (22.2)	11/90 (12.2)	.11
No. of comorbidities	1.66 ± 1.34	1.60 ± 1.46	1.70 ± 1.27	.57	1.56 ± 1.33	1.58 ± 1.43	1.53 ± 1.22	.79
Diabetes	90 ± 32.1	31 ± 29.0	59 ± 34.1	.37	59 ± 30.1	30 ± 30.6	29 ± 29.6	.88
Cardiac	43 ± 15.4	18 ± 16.8	25 ± 14.5	.59	27 ± 13.8	16 ± 16.3	11 ± 11.2	.30
Pulmonary	28 ± 10.0	14 ± 13.1	14 ± 8.9	.18	18 ± 10.1	10 ± 10.2	8 ± 8.2	.62
Obesity	114 ± 40.7	42 ± 39.3	72 ± 41.6	.70	79 ± 40.3	39 ± 39.8	40 ± 40.1	.88
Renal	24 ± 8.6	10 ± 9.4	14 ± 8.1	.72	16 ± 8.2	9 ± 9.2	7 ± 7.1	.60
Cancer	17 ± 6.1	8 ± 7.5	9 ± 5.2	.44	14 ± 7.1	7 ± 7.1	7 ± 7.1	1.00
Hypertension	50 ± 17.9	13 ± 12.2	37 ± 21.4	.05	26 ± 13.2	12 ± 12.2	14 ± 14.3	.67
Neurologic	28 ± 10.0	8 ± 7.5	20 ± 11.6	.27	17 ± 8.7	8 ± 8.2	9 ± 9.2	.80
HIV infection	9 ± 3.2	1 ± 1	8 ± 4.6	.09	3 ± 1.5	1 ± 1.0	2 ± 2.0	.56
Thyroid	23 ± 8.2	7 ± 6.6	16 ± 9.3	.42	15 ± 7.7	7 ± 7.1	8 ± 8.2	.79
BMI	30.0 ± 7.8	29.8 ± 7.2	30.1 ± 8.2	.81	29.4 ± 6.6	29.4 ± 6.3	29.4 ± 6.9	.95
Pulmonary severity				.46				
Severe	75 (26.8)	26 (24.3)	49 (28.3)	.12	47 (24.0)	22 (22.4)	25 (25.5)	.62
Intubated at study entry	38 (13.6)	15 (14.0)	23 (13.3)	.86	25 (12.8)	11 (11.2)	14 (14.3)	.52
Heart rate	86.0 (75.0-98.0)	86.0 (74.0-97.0)	86.0 (75.5-98.0)	.65	85.5 (74.0-98.0)	86.0 (73.0-97.5)	85.0 (74-98.0)	.88
MAP (mm Hg)	93 (82.3-103.0)	90 (81.0-103.0)	94 (83-103)	.24	92.5 (82.0-103.0)	91.0 (81.0-103.2)	93.0 (82.0-103.0)	.74
MAP ≤ 70 mm Hg	13/260 (5.0)	6/89 (6.7)	7/171 (4.1)	.35	7 (3.6)	4 (4.1)	3 (3.1)	.70
Corticosteroid	90 (32.1)	21 (19.6)	69 (39.8)	.001	46 (23.2)	21 (21.4)	25 (25.5)	.5
Hydroxychloroquine	260 (92.9)	104 (97.2)	156 (90.2)	.03	190 (96.9)	95 (96.9)	95 (96.9)	1.00
Azithromycin	243 (86.7)	99 (92.5)	144 (83.2)	.03	177 (90.3)	90 (91.8)	87 (88.7)	.47

(Continued)

TABLE 1] *(Continued)*

Demographic Characteristic	Unmatched Cohort				Matched Cohort			
	Total (N = 280)	Usual Care (n = 107)	Ivermectin (n = 173)	*P* Value	Total (N = 196)	Usual Care (n = 98)	Ivermectin (n = 98)	*P* Value
Peripheral WBC count (× 10^9/L)	7.3 (5.6-10.2; n = 277)	7.0 (5.7-8.9; n = 106)	7.6 (5.5-11.1; n = 171)	.41	6.9 (5.3-9.3)	7.0 (5.8-9.0)	6.9 (5.2-9.8)	.69
Lymphocyte count (× 10^9/L)	1.15 (0.78-1.56; n = 260)	1.14 (0.84-1.49; n = 102)	1.20 (0.77-1.67; n = 158)	.62	1.13 (0.77-1.52)	1.15 (0.87-1.45)	1.19 (0.75-1.57)	.88

Data are presented as No. (%), mean ± SD, or median (interquartile range), unless otherwise indicated. Current and former smoker is given as a proportion of the population with known smoking status documented in their medical records. MAP = mean arterial pressure.
[a]Asian, Native American, Pacific Islander, or not identified.

corticosteroid use were more prevalent in the ivermectin group, whereas the use of hydroxychloroquine and hydroxychloroquine plus azithromycin were higher in the usual care group.

Propensity score matching created a total of 98 matched pairs. After matching, no statistically significant differences were found between the two groups. Eight patients in the propensity-matched group received a second dose of ivermectin on day 7.

Outcomes

Unadjusted outcomes for the unmatched cohort and outcomes in the propensity-matched cohort are shown in Table 2. For the unmatched cohort, overall mortality was significantly lower in the ivermectin group than in the usual care group (15.0% vs 25.2% for ivermectin and usual care, respectively; $P = .03$). Mortality also was lower for ivermectin-treated patients in the subgroup of patients with severe pulmonary involvement (38.8% vs. 80.7% for ivermectin and usual care, respectively; $P = .001$). On univariate analysis, patients receiving corticosteroids showed a higher mortality than those who did not receive corticosteroids (30.0% vs 13.7%; OR, 2.7; 95% CI, 1.47-4.99; $P = .001$); however, corticosteroids were more likely to have been prescribed for severe patients (58.6% vs 22.4% for severe and nonsevere, respectively; OR, 4.91; 95% CI, 2.78-8.63; $P < .001$).

Results were similar, with lower mortality in the ivermectin-treated patients for the matched cohort for the group as a whole and for the subgroup with severe pulmonary involvement (Table 2). In the matched cohort, ivermectin was associated with an absolute risk reduction of 11.2% (95% CI, 0.38%-22.1%) and a corresponding number needed to treat of 8.9 (95% CI, 4.5-263) to prevent one death. We found no difference in median hospital length of stay or in extubation rates in either the unmatched or matched cohorts. Of note, 1 of the 13 patients who received a second dose of ivermectin died; this patient was not in the propensity-matched cohort.

Multivariate analysis was performed on the unmatched cohort, adjusting for demographic factors and between-group differences in mortality risks. Independent predictors of in-hospital mortality included treatment group, age, severe pulmonary disease category, and reduced lymphocyte count (Table 3). Because race was not a significant predictor after adjustment, a further analysis was performed that showed that White patients were significantly older than Black patients (mean age, 66.8 vs 59.1 y; mean difference, 7.7 y; 95% CI, 3.0-12.4 y;

TABLE 2] Univariate Clinical Outcomes by Treatment Group

Outcome	Unmatched Cohort					Matched Cohort			
	Control Subjects (n = 107)	Ivermectin (n = 173)	OR or Difference (95% CI)	*P* Value	Control Subjects (n = 98)	Ivermectin (n = 98)	OR or Difference (95% CI)	*P* Value
Mortality	...	...	...	...	...	...	...	...
Total	27 (25.2)	26 (15.0)	0.52 (0.29-0.96)	0.03	24 (24.5)	13 (13.3)	0.47 (0.22-0.99)	0.045
Severe	21/26 (80.7)	19/49 (38.8)	0.15 (0.05-0.47)	0.001	18/22 (81.8)	8/25 (32.0)	0.27 (0.08-0.92)	0.002
Nonsevere	6/81 (7.4)	7/124 (5.6)	0.75 (0.24-2.3)	0.61	6/76(7.9)	4/74 (5.4)	0.97 (0.61-1.54)	0.78
Successful extubation	4/26 (15.4)	13/36 (36.1)	3.11 (0.88-11.00)	0.07	3/22 (15.4)	7/18 (38.9)	1.91 (0.43-8.46)	0.14
Length of stay	7.0 (4.0-10.0)	7.0 (4.0-13.3)	0 (-1 to 2)	0.34	7.0 (4.0-10.0)	7.0 (3.0-13.0)	0 (-2 to 1)	0.88

Data are presented as No./Total No. (%) or median (interquartile range) unless otherwise indicated.

$P = .001$) and that Hispanic patients (mean age, 49.8 y; mean difference, 17.0 y; 95% CI, 9.6-24.4 y; $P < .001$).

Discussion

In this multihospital retrospective cohort study, we observed a significant association of ivermectin with improved survival for patients admitted with COVID-19. This association also was seen in the subset of patients with severe pulmonary disease. These findings were confirmed after multivariate adjustment for comorbidities and differences between groups, and also in a propensity score-matched cohort. Similar to other studies, we noted that older age, cardiac disease, current or former smoking, more severe pulmonary involvement at presentation, higher WBC counts, and lower lymphocyte counts emerged as risk markers for in-hospital mortality.

The overall mortality, and mortality in intubated patients, in our usual care group was similar to what was reported in previous studies. Richardson et al[6] reported an overall mortality of 21% in a New York City cohort, with a mortality of 88% in intubated patients. Zhou et al[7] reported 28.2% mortality in a cohort of hospitalized patients in Wuhan, China; the intubated patients showed a mortality of 96.9%. In contrast to Magagnoli et al,[8] we did not see a higher mortality effect for hydroxychloroquine. This may have been because of the small number of patients who were not treated with this agent; thus, our study was underpowered to detect a difference in mortality from hydroxychloroquine treatment. We also hypothesize that precautionary measures in the hospitals' protocol for hydroxychloroquine use could have prevented fatal arrhythmias from developing. These included baseline electrocardiography and daily QTc monitoring by telemetry for any patient receiving hydroxychloroquine or combination therapy, avoidance of azithromycin if patient's baseline QTc was more than 460 msec, and discontinuation of hydroxychloroquine if a concerning elevation in QTc occurred or if the patient's cardiologist recommended discontinuation. In contrast to Horby et al,[9] we did not find a mortality benefit for patients who were prescribed corticosteroids in our multivariate analysis, which included several severity covariates. These findings are likely explainable by physicians' choice to reserve use of corticosteroids for the most seriously ill patients, because the study was performed before the results of the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial were published.[9]

TABLE 3] Multivariate Analysis of Factors Associated With Mortality

Variable	OR (95% CI)	*P* Value
Treatment group	. . .	. . .
Ivermectin	0.27 (0.09-0.80)	.03
Control subject	Reference	. . .
Age	1.05 (1.02-1.09)	.003
Sex	. . .	. . .
Female	0.42 (0.24-1.82)	.42
Male	Reference	. . .
Smoking status	. . .	. . .
Current or former smoker	3.49 (0.71-17.32)	.13
Nonsmoker	Reference	. . .
Race	. . .	.18
Black	0.64 (0.21-1.94)	.43
Hispanic	0.14 (0.02-1.22)	.08
Other	0.62 (0.05-7.92)	.71
White	Reference	. . .
Comorbidities	. . .	. . .
Diabetes	1.17 (0.39-3.55)	.78
Cardiac	1.51 (0.43-5.22)	.52
Pulmonary	0.15 (0.20-1.84)	.15
Hypertension	0.72 (0.17-3.08)	.66
No comorbidities	Reference	. . .
BMI	0.97 (0.89-1.07)	.58
Severe presentation	11.41 (3.42-38.09)	< .001
Intubated at study entry	2.96 (0.73-12.06)	.13
MAP ≤ 70 mm Hg	1.82 (0.17-19.1)	.62
Corticosteroid treatment	1.71 (0.57-5.16)	.34
Peripheral WBC count	1.08 (0.96-1.23)	.22
Lymphocyte count	3.65 (1.25-10.60)	.02

MAP = mean arterial pressure.

We also did not confirm a higher risk of mortality in Black patients in comparison with White patients after controlling for age. Prior reports showed lower survival rates among Black and Hispanic patients[10]; however, Price et al[11] also found no racial differences in mortality. In our hospital population, White patients were significantly older, which is reflective of our catchment area and may be responsible for the discrepancy.

We did not observe a significant difference in hospital length of stay between the groups (median, 7 days for both groups) despite the lower mortality. Possible explanation could include delay in discharging patients to other facilities (skilled nursing facilities, inpatient rehabs, and so forth) because of a delay in obtaining required repeat COVID-19 testing results. Patients who died were included in length-of-stay measurements.

Use of mechanical ventilation was not adopted as an outcome of interest, because guidelines and practice patterns for intubation criteria changed throughout the length of the study. We were unable to determine ICU length of stay and ventilatory-free days in the ICU because overflow conditions during the pandemic placed critically ill patients in the emergency room and other non-ICU environments, and therefore, we could not determine ICU stay accurately. We did not find a lower mortality in the subgroup of nonsevere patients treated with ivermectin; however, our study was not powered to assess these differences because the overall mortality in nonsevere patients was low. Similarly, the study was not powered to determine whether extubation rates were higher in the ivermectin group. These should be investigated further with a larger randomized controlled trial.

Interpretation

Our study has several limitations. Because of the retrospective observational nature of the study, despite adjustment for known confounders and propensity score matching, we cannot exclude the possibility of unmeasured confounding factors. Although more of the control group was enrolled in the first weeks of the study, suggesting the possibility of timing bias, this may be offset by preferential treatment of more severe patients with ivermectin early in the study because of low initial availability. We also did not find consistently different mortality outcomes with time over the short duration of this study. We also did not find evidence of immortal time bias, because only one of the control patients died fewer than 5 days from admission, the average time from admission to death was 11 days, and the vast majority of patients received ivermectin in 2 days or fewer. If we omit the patient with potential immortal time from the analysis, the mortality difference remains significant in both unmatched (15.0% vs 24.5% for ivermectin and usual care, respectively; $P < .05$) and matched (12.4% vs 25.0% for ivermectin and usual care, respectively; $P < .03$) cohorts. Most of the studied patients received hydroxychloroquine with or without azithromycin, and we are unable to determine whether these medications had an added benefit or whether mortality would have been better in both groups without these agents.

We showed that ivermectin administration was associated significantly with lower mortality among patients with COVID-19, particularly in patients with more severe pulmonary involvement. Interpretation of these findings are tempered by the limitations of the retrospective design and the possibility of confounding. Appropriate dosing for this indication is not known, nor are the effects of ivermectin on viral load or in patients with milder disease. Further studies in appropriately designed randomized trials are recommended before any conclusions can be made.

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