BMJ Global Health

Comparison of WHO versus national COVID-19 therapeutic guidelines across the world: not exactly a perfect match

Mia Cokljat,[1,2] Cintia Valeria Cruz ,[1,3] Verena Ilona Carrara,[4] Kanoktip Puttaraksa,[3] Camila Capriglioni,[5] Sabrina Marcela Insaurralde,[6] Maximo Rousseau-Portalis,[5,7] Agustina Roldan,[5] James A Watson ,[1,2] Joel Tarning,[1,3] Nicholas J White,[2,3] Philippe J Guerin [1,2]

To cite: Cokljat M, Cruz CV, Carrara VI, *et al*. Comparison of WHO versus national COVID-19 therapeutic guidelines across the world: not exactly a perfect match. *BMJ Glob Health* 2024;**9**:e014188. doi:10.1136/bmjgh-2023-014188

Handling editor Seema Biswas

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/bmjgh-2023-014188).

MC and CVC contributed equally.

Received 8 October 2023
Accepted 26 February 2024

For numbered affiliations see end of article.

Correspondence to
Professor Philippe J Guerin; philippe.guerin@iddo.org and Professor Nicholas J White; nickwdt@tropmedres.ac

ABSTRACT

Background The COVID-19 pandemic affected all WHO member states. We compared and contrasted the COVID-19 treatment guidelines of each member state with the WHO COVID-19 therapeutic guidelines.

Methods Ministries of Health or accessed National Infectious Disease websites and other relevant bodies and experts were contacted to obtain national guidelines (NGs) for COVID-19 treatment. NGs were included only if they delineated specific pharmacological treatments for COVID-19, which were stratified by disease severity. We conducted a retrospective review using the adapted Reporting Checklist for Public Versions of Guidelines (RIGHT-PVG) survey checklist and a derived comparative metric based on the WHO guidelines was performed.

Results COVID-19 therapeutics NGs could be obtained from 109 of the 194 WHO member states. There was considerable variation in guidelines and in disease severity stratifications. Therapeutic recommendations in many NGs differed substantially from the WHO guidelines. Overall in late 2022, 93% of NGs were recommending at least one treatment which had proved to be ineffective in large randomised trials, and was not recommended by WHO. Corticosteroids were not recommended in severe disease in nearly 10% of NGs despite overwhelming evidence of their benefit. NGs from countries with low-resource settings showed the greatest divergence when stratified by gross domestic product per year, Human Development Index and the Global Health Security Index.

Discussion Our study is limited to NGs that were readily accessible, and it does not reflect the availability of recommended medicines in the field. Three years after the start of the SARS-CoV-2 pandemic, available COVID-19 NGs vary substantially in their therapeutic recommendations, often differ from the WHO guidelines, and commonly recommend ineffective, unaffordable or unavailable medicines.

WHAT IS ALREADY KNOWN ON THIS TOPIC?

⇒ There has been a suspicion of significant variations in COVID-19 treatment recommendations among different countries since the beginning of the pandemic. However, these variations have not been formally quantified or studied in-depth.

WHAT THIS STUDY ADDS?

⇒ The study assesses the state of each country's national guidelines (NGs) in comparison to those of the WHO for COVID-19 treatment which are used as the gold standard. The study reveals substantial variations between NGs. Some countries lack a national guideline altogether. Some NGs omit WHO-recommended therapies, continue to recommend unproven therapies or differ in their classification of COVID-19 severity. Many NGs have not been updated for over 6 months.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY?

⇒ The study suggests that there is a significant global variation in COVID-19 treatment recommendations. The findings highlight a healthcare deficit that needs to be addressed. The study emphasises the need for a careful update of NGs, especially in countries that still omit strongly recommended proven treatments, such as corticosteroids, for patients with severe disease.

BACKGROUND

The COVID-19 therapeutic landscape has evolved substantially since the pandemic began in late 2019. In early May 2023, after more than 1100 days, the WHO declared an end to COVID-19's public emergency phase. With increasing vaccine coverage and frequent infections boosting immunity, and viral evolution attenuating pathogenicity, the global burden of morbidity and mortality from COVID-19 has fallen substantially. But COVID-19 has not gone away. The highest societal and economic impact has been in the poorest countries.[1] The global reported death toll of nearly 7 million is likely a substantial underestimate. The estimate of around 20 million deaths by the end of 2022 is now accepted by WHO as closer to the truth. The

future is uncertain as viral evolution continues and the infection is still active throughout the world.[2]

The effective vaccines and drugs which have been developed have not been distributed equally. In the past 3 years there have been approximately 4000 clinical trials recorded in clinical trial registries.[3 4] Although many of these trials have been completed, robust evidence has come mainly from a few large, well-conducted randomised controlled trials, either in hospitalised patients or in high risk outpatients, using clinical end-points.[5–8] In contrast, there have been very few pharmacometric comparisons to inform choice of drugs or dosing. When antiviral interventions were shown to be effective compared with placebo in pharmaceutical company-sponsored trials, they were not then compared with each other to inform therapeutic guidelines. The vast majority of individual studies were observational or small, and thus underpowered, prospective open clinical trials which, unfortunately, have not contributed significantly to the evidence. Nevertheless, many authorities have either recommended or supported specific anti-COVID-19 treatments based on these small studies or preclinical information and, in some cases, even anecdotal evidence.[9]

As a consequence, there has been substantial variation between countries in their COVID-19 treatment recommendations. Different conclusions derived from the same evidence, different timing of treatment guideline development, lack of evidence in early infections, lack of pharmacometric evaluation, lack of comparative information, the high cost of new therapeutics and political pressures have all contributed to the heterogeneity in guidance observed between countries.[10]

WHO has regularly updated its 'living' COVID-19 therapeutic guidelines,[11] making this recommendation on the basis of a standardised review of the latest evidence. With some exceptions,[12] its recommendations have been delineated by disease severity.

Many countries, particularly in low-resource settings, rely on guidance from WHO to develop and update their infectious diseases national treatment guidelines. We reviewed WHO member state national guidelines (NGs) for COVID-19 treatment and compared them to the WHO therapeutic guidelines.[13]

METHODS

We conducted a retrospective review of all the national COVID-19 treatment guidelines in the 194 WHO member states.

Search strategy

The search was conducted between 1 September 2022 and 30 November 2022. To identify NGs, the following stepwise approach was followed:

1. Guidelines collected previously by the COVID-19 Clinical Research Coalition were requested.
2. The countries' Ministries of Health or the National Infectious Disease websites were then searched and contacted when possible.
3. Key opinion leaders or researchers were contacted; this was either the first author of a previous iteration of a guideline or a local researcher located via literature databases.

If all three search criteria were undertaken and there was no response within the above time period the country-associated guideline was considered 'missing'. A publicly available repository will be created with all the guidelines obtained at iddo.org.

Inclusion and exclusion criteria

NGs were included if they recommended pharmacological treatments for COVID-19, as categorised by disease severity. Only the latest available versions of NGs were included. Guidelines were excluded if they were regional or local hospital COVID-19 treatment guidelines, vaccination guidelines, infection control policies or if no drug recommendation was made. Data pertaining to treatment for complications of COVID-19 (eg, thromboembolism and bacterial pneumonia) were also not included.

Data extraction

Relevant information was extracted using a REDCap database.[14] This database was developed from the Reporting Checklist for Public Versions of Guidelines (RIGHT-PVG).[15] The data extracted included publishing dates, language and body; disease severity classification; each recommended drug including indication and dosage; regulatory status; and any regulatory information gathered by the national body such as adverse effect profile. Antibiotic recommendations were excluded with the exception of an antibiotic used clearly for COVID-19 specifically and not for complicating bacterial pneumonia[13] (full extraction form is in online supplemental table 1). Country regions were defined as per the WHO classification: African Region (AFR), European Region (EUR), Region of the Americas (AMR), South-East Asian Region (SEAR), Eastern Mediterranean Region (EMR) and Western Pacific Region (WPR).

Eight physicians and one clinical nurse performed the data extraction between September and December 2022. Native and fluent speakers were used where possible; otherwise an automated online translator was used. In order to reduce interobserver variability, a pilot training extraction was performed in advance. All researchers extracted the same five guidelines (Japan, Germany, United Arab Emirates, Brazil and South Africa). Further training was provided for areas of low agreement.

Patient and public involvement (PPI)

The nature and focus of this project precluded direct engagement with patients and the public, as the primary objective was to collect information on treatment guidelines from the health authorities responsible for it on each country. While recognising the inherent value of PPI in numerous research contexts, the deliberate exclusion in this instance stems from a conscientious consideration of the project's defined scope, ensuring that resources

Table 1 The WHO disease classification and treatment according to severity (extracted from WHO Therapeutics and COVID-19 11th version, dated 14 July 2022)

	Non-severe	Severe	Critical
Disease severity	Absence of signs of severe or critical disease	► Oxygen saturation <90% ► Signs of pneumonia ► Signs of severe respiratory distress	► Requires life-sustaining treatment ► Acute respiratory distress syndrome ► Sepsis ► Septic shock
Interventions			
Strong recommendation in favour	► Nirmatrelvir and ritonavir	► Corticosteroids ► IL-6 receptor blockers or baricitinib (depending on availability as well as clinical and contextual factors)	
Weak or conditional recommendations in favour	► Molnupiravir ► Sotrovimab ► Remdesivir ► Casirivimab and imdevimab*	► Casirivimab and imdevimab	

*If rapid viral genotyping is available and confirms infection with a susceptible SARS-CoV-2 variant.

and efforts were concentrated on the core investigative objectives.

WHO COVID-19 therapeutic guidelines references

The therapeutic recommendations and disease severity classification of all NGs were compared with the 'Therapeutics and COVID-19: living guideline, 14 July 2022',[11] the eleventh iteration of the WHO COVID-19 guidelines (table 1). NGs were compared with each other using World Bank gross domestic product (GDP) per capita in US dollars for 2021, the Human Development Index (HDI) 2021 and the Global Health Security Index (GHSI) 2021.

Creating a quantitative metric of guideline agreement

A specific metric was developed to quantitate the level of agreement between each country's guidelines and the WHO 11th version strength of recommendation classification. The goal was to measure objectively how closely each country's guidelines aligned with the WHO recommendations.

The metric application process is outlined as follows:

1. **Reference point**: The WHO guidelines' 11th version strength of recommendation served as the reference point for the assessment.
2. **Metric design**: the metric aimed to provide a numerical representation of the level of agreement between each country's guidelines and the WHO 11th version.
3. **Separate assessment**: The numeric quantification was performed separately for non-severe disease and severe/critical disease.
4. **Quantitative assessment:**
   i. Positive numeric weights: assigned to recommendations in a country's guidelines that matched the recommendations in the WHO guidelines.
   ii. No numeric weight: the absence of a WHO recommended treatment in a country's guidelines was considered neutral, with no numeric weight assigned.
   iii. Negative numeric weights: assigned if a country's guidelines recommended a therapeutic intervention that was discouraged by the WHO guidelines, or if there were additional non-evidence-based recommendations.
5. **Score calculation**: the assigned weights were then added together to calculate a final score for each country's guidelines. This score quantified how closely the country's guidelines aligned with the WHO recommendations. Extra points were awarded for guidelines that were updated within the last 6 months, for those that made recommendations in line with the strength of evidence and those that included assessments of both efficacy and adverse effects.
6. **Potential range**: the numeric metrics theoretically ranged from −31 to 21 for non-severe disease guidelines and −12 to 14 for severe and critical disease.

A detailed description of the metric, including the weights assigned and additional considerations, is provided in online supplemental appendix 1.

Statistical analysis

Statistical analysis was performed using Microsoft Excel V.16.72 and SPSS V.29. For significance testing between regions, one-way analysis of variance and Tukey's post-hoc tests were used. Pearson correlations were estimated between the numeric guidelines' agreement metric and GDP per capita, HDI and GHSI. Significance was set at $p<0.05$.

RESULTS

Of the 194 WHO member states, 109 countries had a national guideline that was included in the analysis (figures 1 and 2). Of the remaining 85, 9 countries confirmed that there was no national guideline, in most

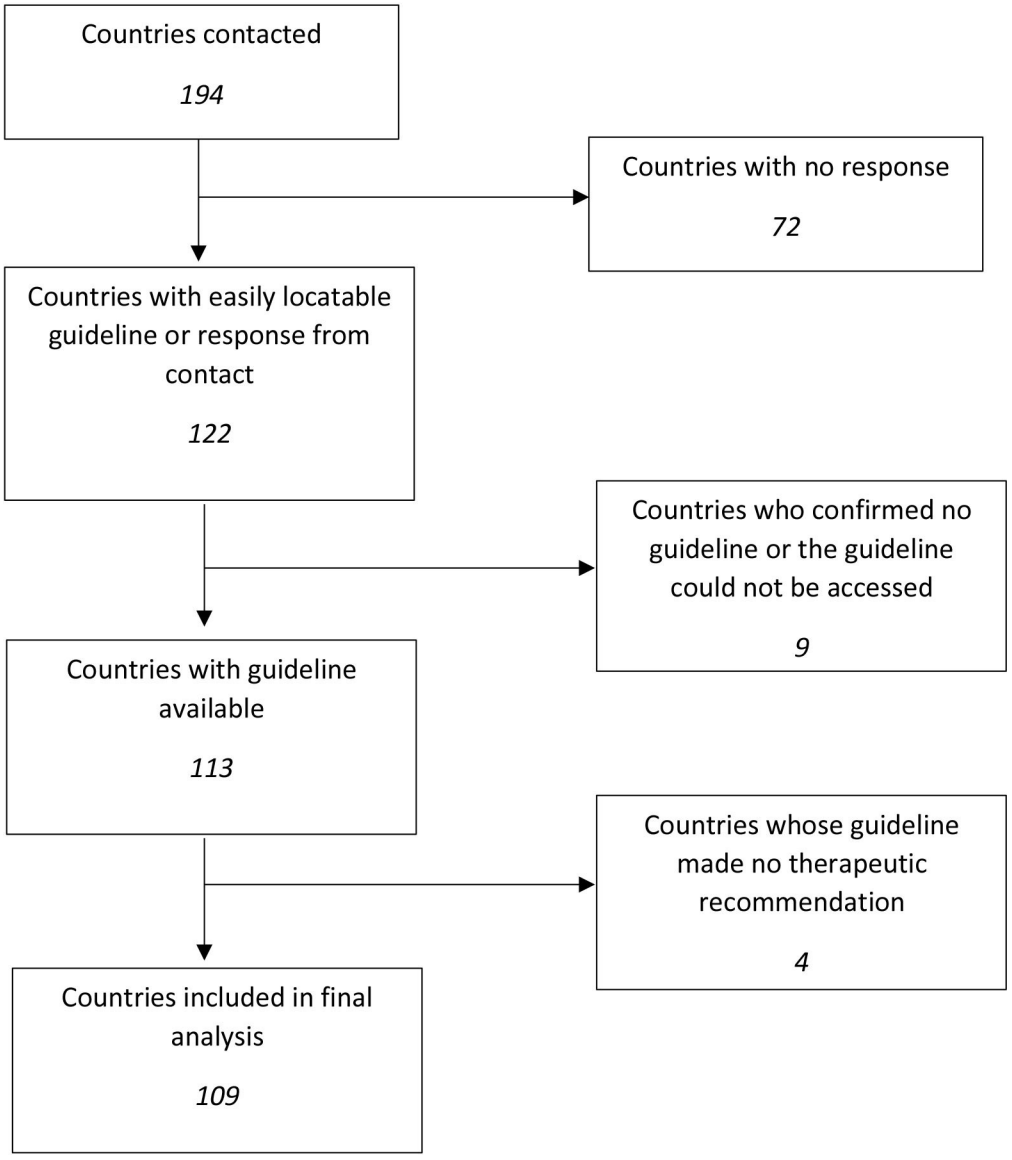

Figure 1 Flow chart demonstrating acquisition of the final guidelines included in the analysis.

cases because they used regional or hospital guidelines. Seventy-two countries made no response to contact attempts and no information was retrievable through our search method; in one country we were aware of the existence of a guideline but could not access it. Four countries were excluded after acquisition of their guidelines as they made no therapeutic recommendation. The median and IQR population in countries where guidelines were obtained was 14.2 million (IQR±42.6 million), compared with a median population of 5.5 million (IQR±34.4 million) for countries that confirmed no national guideline and 2.7 million (IQR±10.9 million) in those where we could not obtain the guidelines. Compared with countries with retrievable guidelines, the countries for which guidelines were not obtained had on average smaller populations, lower GDP per capita and a lower GHSI (table 2), indicative of greater economic challenges and less ability to respond to health emergencies. The full table of countries and indices is available in online supplemental appendix 2.

National Guidelines for the treatment of COVID-19: countries and languages

Most successfully located guidelines came from the EUR: 34% (37/109) of located guidelines were from EUR, with 37 countries out of the 53-member countries having NGs (69.8%). The second region in terms of successfully located NGs was the AFR: 22.9% (25/109)—with 25 out of the 47-member countries providing guidelines (53.2%). About 65.1% of guidelines (71/109) were published prior to the 6 months before the July 2022 version of the WHO guidelines, while 31.2% (34/109) were published or updated within the 6 months preceding the WHO guidelines. The date of publication was not available for four NGs (3.7%). The most common publication language was English (35/109 guidelines; 32.1%), followed by

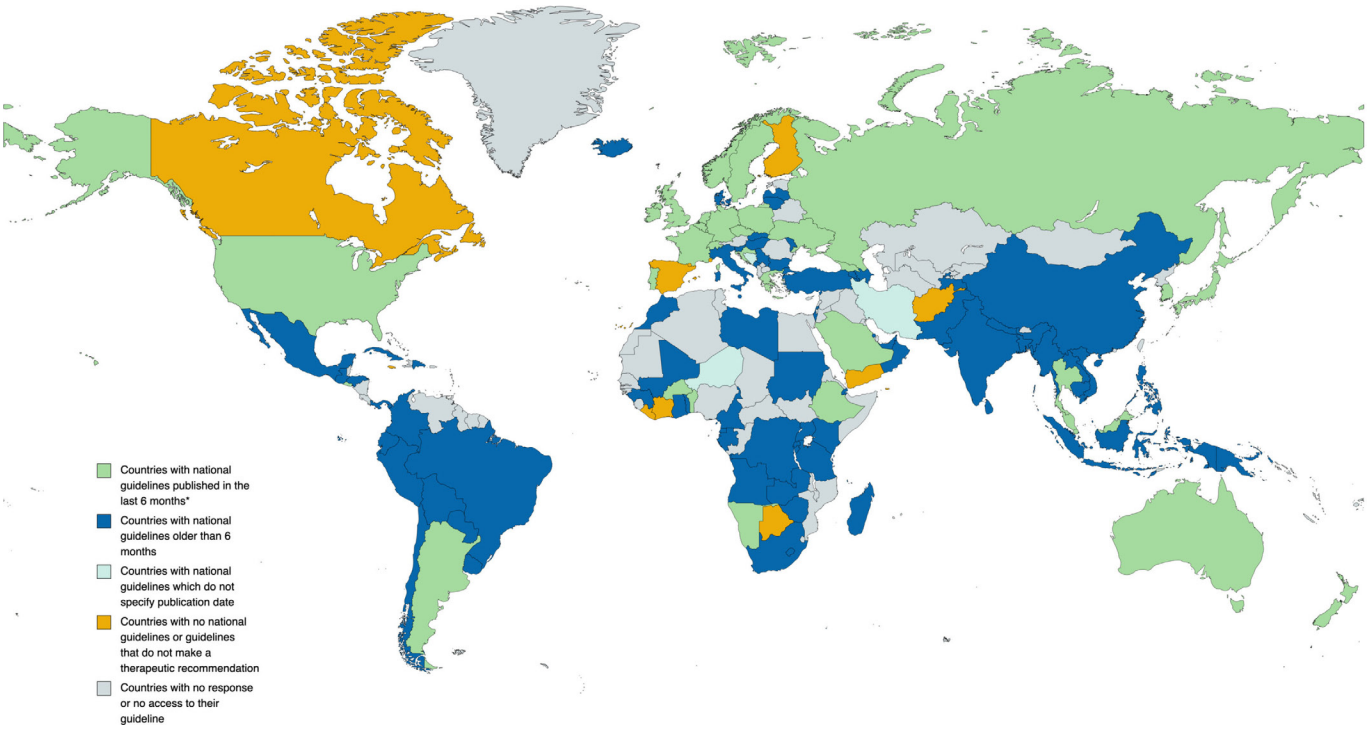

Figure 2 Schematic of the world map demonstrating each country by publication status of COVID-19 therapeutic guidelines. *Publication time-frame is relative to the July 2022 publication of the WHO guideline. Unknown status of COVID-19 therapeutic guidelines results from the absence of searchable guidelines and no response from contacted representatives of the country, or countries where the guideline could not be accessed.

Spanish (16/109 guidelines; 14.7%); French (16/109 guidelines; 14.7%) and Portuguese (3/109 guidelines; 2.75%). The remaining guidelines were published in the national language of the country (39/109 guidelines, 35.8%). In most cases, the NGs were published by the Ministry of Health (80/109 guidelines; 73.4%), 12.8% by a national infectious disease organisation (14/109) and 8.3% (9/109) were produced by a national advisory board to the government. Of the remaining guidelines, 5.5% (6/109) were published by other organisations, either by university hospitals, third-party organisation in one case or a bespoke consultancy group comprising healthcare practitioners. Online supplemental appendix 2 details the full demographic data of all the guidelines.

Therapeutic indications and recommendations

Even though the WHO therapeutic guideline was updated once during the extraction and analysis (15 September 2022 producing the 12th iteration of the guideline), we conducted all the comparison analyses using the WHO Therapeutics and COVID-19 11th version dated 14 July 2022, as described in the Methods section. This version of WHO guidelines divides disease severity into non-severe, severe and critical (table 1). The majority of the guidelines (84.4%; 92/109) did not define COVID-19 severity as in the WHO guideline. Some did not define severity at all (6.42%; 7/109). Only 10 guidelines (9.17%; 10/109) had severity definitions comparable to those of

Table 2 Comparative indicators for number of inhabitants, World Bank GDP per capita in US dollars for 2021, HDI 2021 and the GHSI for countries according to the availability of national guidelines

	Included	No national guidelines	Not found/not available*
n	109	9	76
Population in millions, median (±IQR)	14.2 (±42.6)	5.5 (±34.4)	2.7 (±10.9)
GDP per capita (US$), mean (±SD)	18 361 (±25 274)	52 765 (±71 613)	8748 (±10 975)
HDI, mean (±SD)	0.7 (±0.2)	0.8 (±0.2)	0.7 (±0.1)
GHSI, mean (±SD)	43.6 (±13.8)	43.8 (±21.1)	31.4 (±8.2)

*Includes 71 not found guidelines, 1 inaccessible and 4 excluded as no drugs were described.
GDP, gross domestic product; GHSI, Global Health Security Index; HDI, Human Development Index.

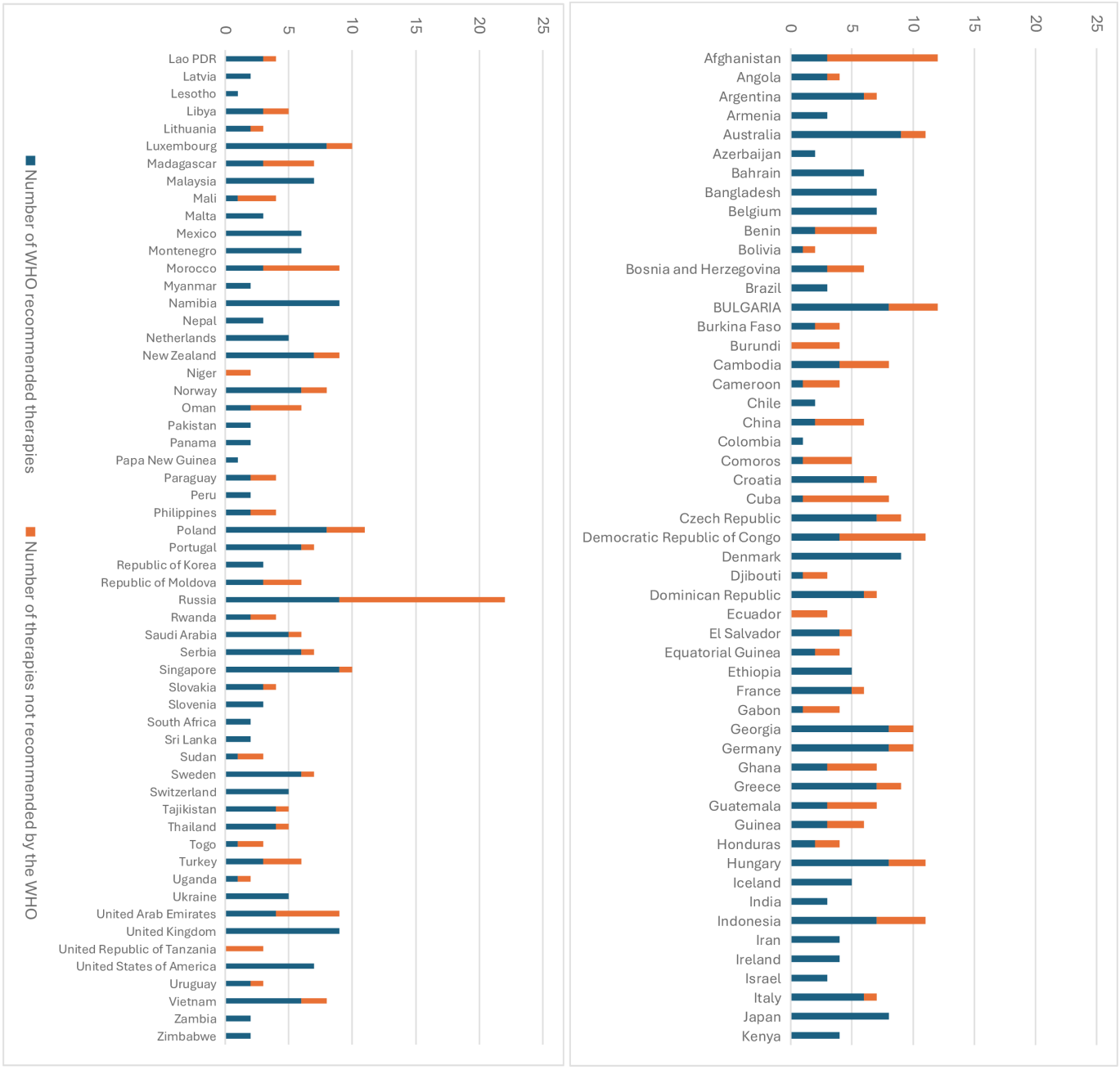

Figure 3 Number of WHO-recommended therapies, and those not recommended by the WHO, by country.

the WHO. The strength of the therapeutic recommendation was graded in 25 (23.8%; 25/109) of the guidelines assessed. Thus, the majority (77%; 84/109) did not report an assessment of the strength or certainty of the therapeutic recommendation.

The range of treatments in the guidelines recommended, irrespective of severity, varied from a single treatment to 22; the median was 5 (IQR=1-9). The WHO guidelines recommend a total of 10 drugs.

A total of 105 NGs recommended at least one WHO-recommended treatment, but in 4 NGs, none of the WHO-recommended therapies were recommended. The average proportion of WHO-recommended treatments per guideline was 70.9% (±29.4%, figure 3), and differed significantly between regions (p<0.001, F[5,103]). The AFR had a significantly lower proportion of WHO-recommended therapies, compared with the EUR and SEAR (p<0.001 and p=0.03 respectively; figure 4).

For all the WHO-advised drugs recommended by the NGs (table 3), 70.9% were indicated for the same severity of COVID-19.

The most commonly recommended drugs were corticosteroids; 92% (100/109) of the NGs featured corticosteroids, and 80% (88/109) recommended corticosteroids for the same disease severity as did the WHO. Remdesivir was indicated only for non-severe COVID-19 patients, as in the WHO guidelines, in only 16 (23%) of the 72 NGs, whereas, it was recommended in severe or critical disease

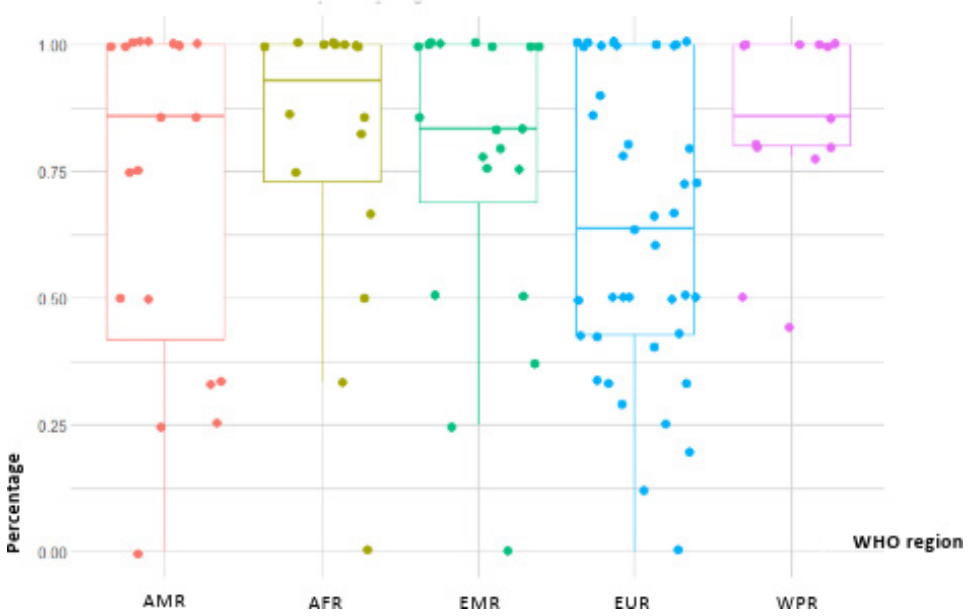

Figure 4 Proportion of WHO-recommended therapies by region. Bars represent mean±SD. AMR, Region of the Americas; AFR, African Region; EMR, Eastern Mediterranean Region; EUR, European Region; WPR, Western Pacific Region.

in 51% (56/72) NGs. This is contrary to the WHO guidelines, which only indicates remdesivir conditionally for non-severe patients at highest risk of hospitalisation. Tocilizumab was recommended for the same severity as the WHO guidelines (severe and critical disease, in the country's own classification) in 56 (79%) of the 71 guidelines. Figure 5 demonstrates the proportion of NGs that recommended each WHO-approved therapy for the same severity of COVID-19 compared with a different level of severity.

In late 2022 many NGs continued to recommend therapies that WHO has advised against (table 4). There was some regional variation. The majority of NGs (11/14; 78.6%) continuing to recommend lopinavir–ritonavir were from the AFR, EUR or the AMR. Eleven of the 12 (91.7%) NGs that recommended azithromycin were in the AFR. Twelve of the 15 (80%) NGs recommending vitamins and/or zinc were in the AFR and the AMR. Similarly, five NGs, four from the AMR and one in AFR, recommended ivermectin. Nine NGs, primarily from the EUR, recommended anakinra.

A total of 36 (36/109; 33.0%) NGs recommended at least one neutralising monoclonal antibodies directed against SARS-CoV-2. The NGs from the countries recommending neutralising monoclonal antibodies, the average GDP per capita, HDI and GHSI were US$32 096 (SD±29 663), 0.83 (SD±0.12) and 51.7 (SD±10.9) respectively. Of those not recommending any neutralising monoclonal antibodies, the average GDP per capita, HDI and GHSI were US$11 172 (SD±19 305), 0.7 (SD±0.15) and 39.4 (SD±13.3) respectively. Sotrovimab and casirivimab–imdevimab are neutralising monoclonal antibodies which were recommended at the time by the WHO. They were recommended by 24 (22%) and 25 (22.9%) NGs, respectively. Two neutralising monoclonal antibodies—bamlanivimab±etesivamab and regdanivimab—appeared consistently in NGs but were not recommended by the WHO. Ten (9.2%) NGs recommended bamlanivimab±etesivamab and four (3.7%) recommended regdanvimab (figure 5). Bebtelovimab and ambavirumab+romisevirumab were recommended by one NG each. Other monoclonal antibodies targeting proteins associated with the immune response, and typically used in autoimmune conditions (itolizumab, vilobelimab, levilimab, olokizumab and canakinumab) were all recommended by one or two NGs only. Thirteen (12%) NGs recommended the postexposure monoclonal antibodies tixagevimab+cilagavimab. This antibody was only

Table 3 List of drugs or monoclonal antibodies indicated by WHO and the corresponding number of NGs (as a percentage of total) that recommended these medicines

Drug or monoclonal antibody	Number of NGs (%) recommending the medicine
Corticosteroids	100 (92%)
Remdesivir	72 (66%)
Tocilizumab	71 (65%)
Nirmatrelvir–ritonavir	43 (39%)
Baricitinib	37 (34%)
Molnupiravir	34 (31%)
Casirivimab–imdevimab	25 (22.9%)
Sotrovimab	24 (22%)
Sarilumab	12 (11%)
Tofacitinib	7 (6%)
Ruxolitinib	2 (2%)

NGs, national guidelines.

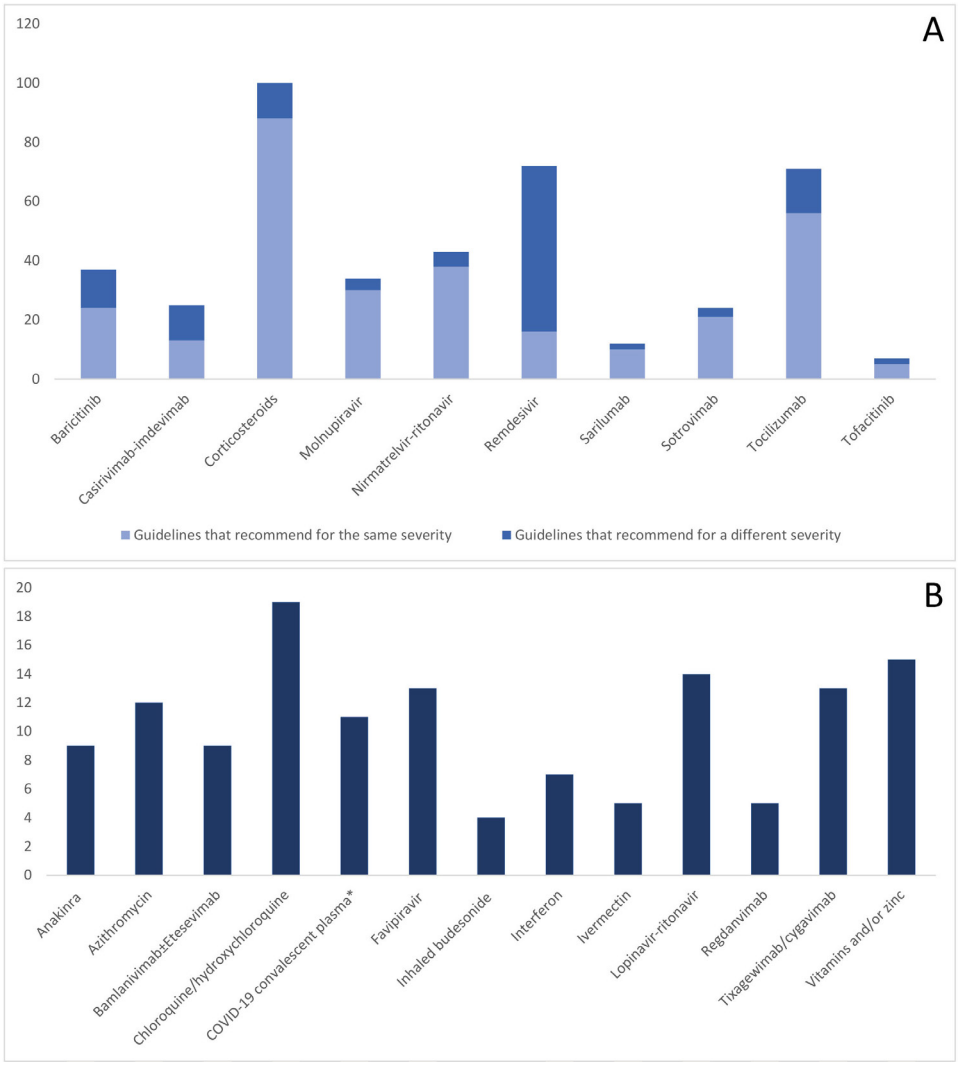

Figure 5 (A) Number of guidelines recommending individual WHO-recommended therapies, divided by same and different severity recommendations. (B) The number of guidelines recommending common non-WHO-recommended therapies. *Includes immunoglobulin.

recommended by NGs from countries with moderate to high-income from the EUR, as well as in Singapore, Australia and New Zealand.

The remaining therapies were also recommended only by either one or two NGs. One NG recommended the use of aspirin, a statin and famotidine as prevention and for reduction of symptoms (ie, treatment) of COVID-19. One NG recommended 'Covid-Organics', an herbal drink designed by a high-ranking politician. A different NG recommended 'PrevengHo-Vir', a homeopathic remedy, as well as the immune-modulatory medicines Jusvinza and Biomodulina-T. Finally, synthetic small interfering ribonucleic acid, ribavirin, umifenovir, colchicine, camostat and fluvoxamine were also recommended by one or two NGs.

Treatment dosages of the most commonly recommended drugs

Of the NGs that recommended corticosteroids, 88% (88/100) recommended dexamethasone as the first-line corticosteroid. Of these NGs, 80.7% (71/88) recommended a standard once a day dosing of 6 mg. In the remaining NGs, dose ranges were from 4 to 20 mg/daily. One country recommended twice a day dosing, and one did not specify a dose.

Tocilizumab (IL-6 receptor monoclonal antibody) dosing varied substantially i.e. 4–8 mg/kg, 4 mg/kg, 6 mg/kg or 8 mg/kg with or without a maximum of 400–600 mg per daily dose. Of the 72 NGs recommending remdesivir, 62 (62/72; 86.1%) used the same regimen of a loading dose of 200 mg on the first day and then 100 mg/day on the following days. Recommended treatment durations ranged from 3 to 10 days.

Regulatory status of recommended therapies

Only 45 (41.3%; 45/109) country guidelines mentioned the regulatory status of at least one of the drugs indicated. Fifty drugs recommended in 19 (17.4%; 19/109) NGs were accompanied by explicit mention that the drugs had been fully evaluated and approved. In all the

Table 4 List of drugs or monoclonal antibodies which WHO has advised against, and the corresponding number of National Guidelines that (as a percentage of total) recommended these in late 2022

Drug or monoclonal antibody	In late 2022, the number of NGs (%) recommending these medicines which WHO has advised against
Hydroxychloroquine or chloroquine	19 (17%)
Favipiravir	16 (15%)
Vitamins and/or zinc	15 (14%)
Lopinavir–ritonavir	14 (13%)
Azithromycin	12 (11%)
Anakinra	9 (8%)
Convalescent plasma or immunoglobulin	9 (8%)
Interferons	5 (5%)
Inhaled budesonide	4 (4%)

NGs, national guidelines.

Table 5 Quantification of strength of COVID-19 treatment guidelines according to region and disease severity using an adapted metric based upon the July 2022 WHO guideline[11]

Region	Therapeutic indication for non-severe disease Range: −14 to 21	Therapeutic indication for severe disease Range: −12 to 14
AFR	−2.2 (±5.8)	2.8 (±6.0)
AMR	1.3 (±8.1)	7.4 (±6.9)
SEAR	6.3 (±7.0)	7.4 (±3.7)
EUR	8.1 (±6.8)	8.1 (±4.3)
EMR	0.82 (±3.4)	3.5 (±6.6)
WPR	7.25 (±10.3)	5.8 (±4.8)

Data are presented as mean (±SD).
AFR, African Region; AMR, Region of the Americas; EMR, Eastern Mediterranean Region; EUR, European Region; SEAR, South-East Asian Region; WPR, Western Pacific Region.

other cases the status of the recommended therapy was approved for either emergency approval, compassionate or expanded use, off label use or with other categorisations.

Collection of efficacy and adverse effects data

Of the 109 guidelines, 46 (42%; 46/109) NGs mention ongoing clinical trials or some form of evidence to support the therapeutic indications. Twenty-one (21/109; 19.3%) NGs encouraged data collection on drug efficacy, and 27 (24.8%; 27/109) on drug adverse events. In 23 (23/109; 21%) NGs, the enrolment of patients in clinical trials was specifically encouraged.

Quantification of the strength of national guidelines using an adapted metric based on the contemporary WHO guideline

In the assessment of the strength of guidelines using an adapted metric, the metric values for non-severe guidelines were between −14 and 21 across all NGs. The regions differed significantly ($p<0.001$, $F[5,103]$). The AFR had significantly lower metric values compared with the EUR and WPR ($p<0.001$ and $p=0.003$, respectively); and AMR had significantly lower metric values compared with EUR ($p=0.015$).

For severe/critical disease recommendations, the metric values ranged between −12 and 14 across all countries. The regions also differed significantly ($p=0.005$, $F[5,103]$), where AFR had significantly lower metric values compared with EUR ($p=0.04$). The results are summarised in table 5.

The metric was correlated with the World Bank GDP per capita, HDI and GHSI (figure 6A–F). There was a significant correlation between each country's strength metric both for their non-severe and severe guidelines and all three indicators evaluated: GDP per capita ($r=0.54$ and $r=0.34$, $p<0.001$), HDI ($r=0.62$ and $r=0.45$, respectively, $p<0.001$) and GHSI ($r=0.66$ and $r=0.45$, respectively, $p<0.001$). Higher metrics of guidelines strength tended towards higher indices. This was especially the case when the non-severe guideline was correlated with HDI and GHSI. Equally, NGs from countries with higher income—for example from EUR—tended to have both higher metrics of strength for their non-severe and severe guidelines, as well as higher HDI and GHSI. Figure 7 demonstrates the geographical distribution of each metric.

DISCUSSION

In the third year of the COVID-19 pandemic national COVID-19 treatment guidelines varied considerably and often differed significantly from the latest WHO guidelines. Variations included omission of WHO-recommended therapeutics from the country guidelines, continued recommendation of unproven or ineffective therapies and differences in the classification of disease severity for which the drug is being recommended. Why do NGs differ so much in their treatment guidance for such a widespread and potentially serious infection when all have access to the same information? Apart from the prohibitive cost of some medications for low-resource settings we do not have a satisfactory explanation. Some of the following may contribute to these differences.

First, there is the definition of COVID-19 itself. From a therapeutic perspective, COVID-19 is a biphasic disease in which antiviral drugs are beneficial early in the infection during the viral replication period whereas, in the minority of patients who progress to pneumonitis and require hospitalisation, immunopathogenesis dominates. In the latter phase, immunomodulators (notably corticosteroids) reduce mortality, whereas antiviral medicines are most effective early in the course of infection.[13] Clinical severity is therefore a critical determinant of therapy

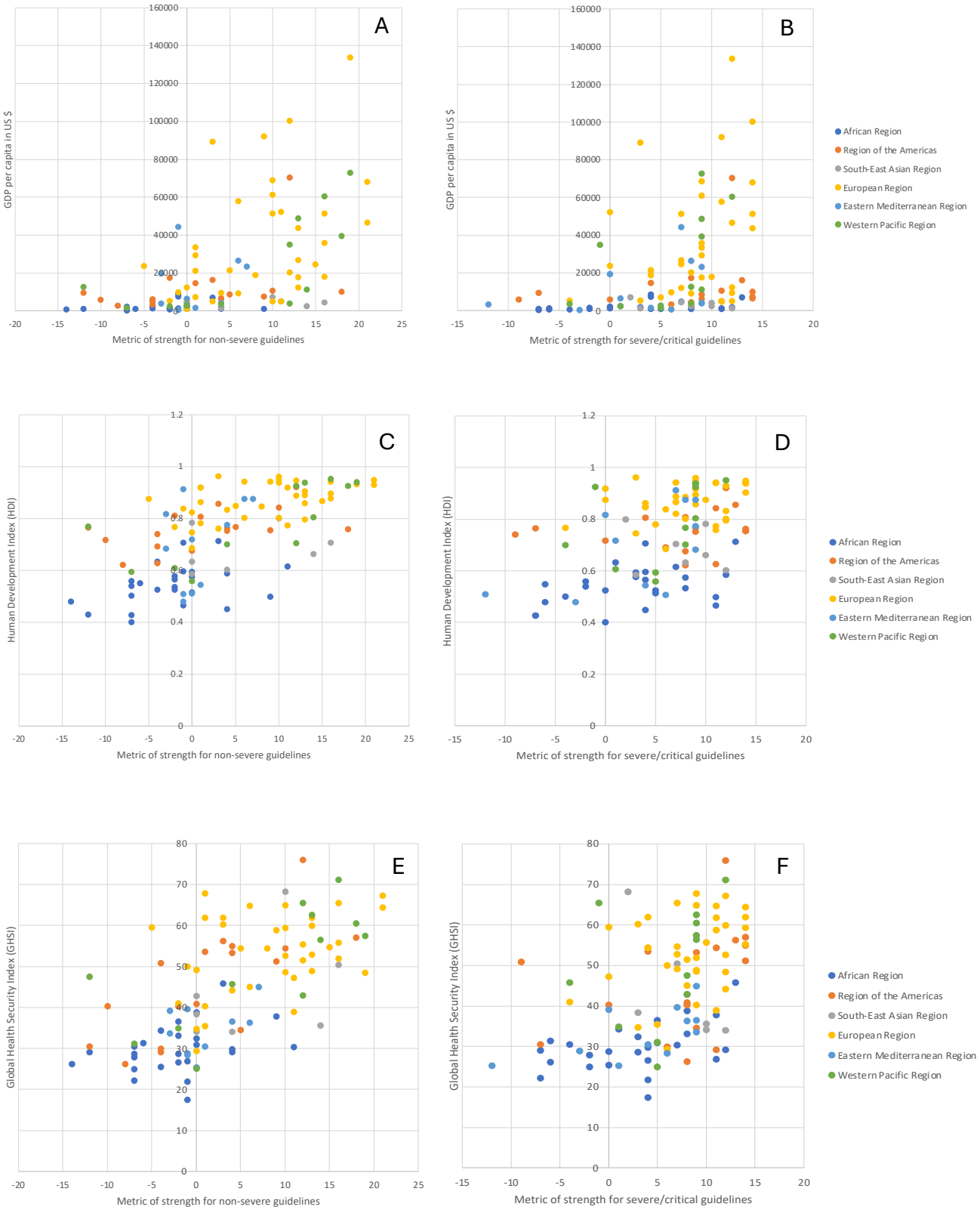

Figure 6 (A) Correlation between the metric of strength for each country's non-severe COVID-19 therapeutic guideline, and the World Bank 2021 GDP per capita in US dollars. (B) The metric of strength of each country's severe/critical guideline, correlated against the World Bank 2021 GDP per capita in US dollars. (C) The metric of strength for each country's non-severe guideline, against the HDI. (D) The metric of strength for each country's severe/critical guideline, against the HDI. (E) The metric of strength for each country's non-severe guideline, against the GHSI. (F) The metric of strength for each country's severe/critical guideline, against the GHSI. GDP, gross domestic product; GHSI, Global Health Security Index; HDI, Human Development Index.

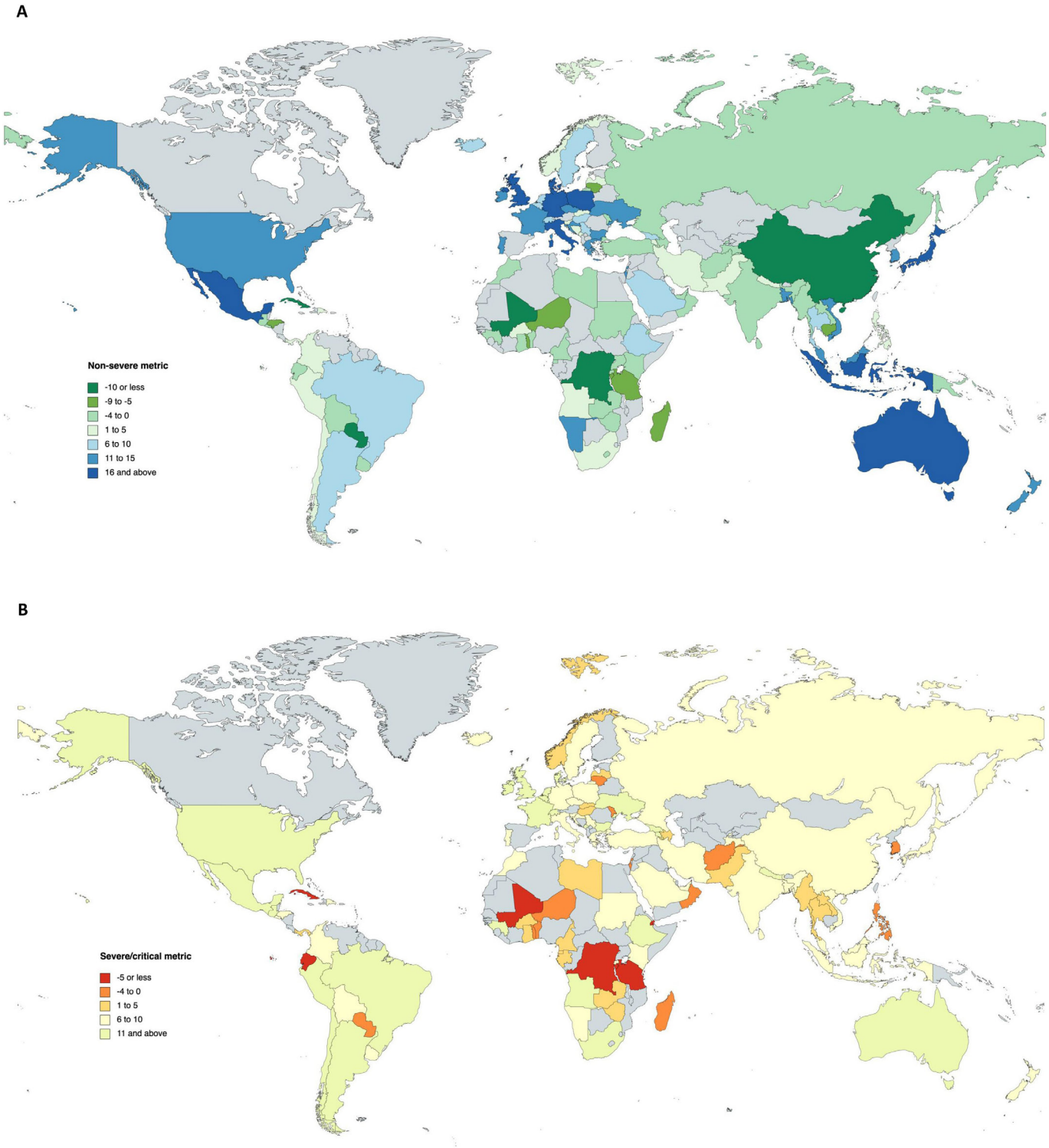

Figure 7 Worldwide geographical distribution of the non-severe (A) and the severe/critical (B) metric. Grey countries represent those which did not have accessible guidelines and therefore did not have data extracted. High values indicate concordance with the WHO COVID-19 therapeutic guidelines.

but, confusingly, there is substantial variation in the grading of COVID-19 severity between the reference organisations.[16] The majority of guidelines identified in this series (92/109 NGs; 84%) did not define severity as it has been defined by the WHO.

Second, as evidence has accrued, the WHO guidelines have changed.[17] Remdesivir is a case in point. The current WHO guidelines do now recommend remdesivir for non-severe stages of the disease. However, earlier in the pandemic there was a diversity of guidance with some authorities recommending remdesivir for severe and critical disease, whereas WHO, based on the interim results of the SOLIDARITY[7] and DisCovery trials,[18] recommended against remdesivir. Approximately

two-thirds of the NGs were updated over 6 months before the publication of the WHO July 2022 guidelines. Many countries had published an initial guideline during the early months of the pandemic, and then no subsequent update was issued.

Third, the research landscape early in the pandemic was confusing and chaotic with laboratory reports of uncertain clinical significance,[3] involvement of organisations and specialties with little or no experience of respiratory virus infections, a plethora of small, often observational clinical studies, claims and counter claims, all compounded by intense political and media. In this 'fog of war' countries clearly felt the need to say something and do something, even if it was based on very little evidence. But why many of these unproven remedies continued to be recommended as evidence of their ineffectiveness accrued is much less clear.

Fourth, despite their detailed and apparently rigorous evidence synthesis pathway, the WHO guideline itself has not been consistent, and in some cases has also been confusing or contradictory. Initially WHO pooled together uncomplicated and severe illness despite very different therapeutic susceptibilities.[12] In the COVID-19 prevention guidelines,[19] the WHO guidelines have made errors in data extraction, and deduced lack of efficacy and raised concerns over toxicity without corresponding evidence.[16] The grading of evidence has also sometimes been confusing. For example, the evidence (based on the 980 deaths in the RECOVERY[6] trial) for corticosteroids providing mortality benefit in severe disease was considered to be of 'moderate certainty with a serious risk of bias'. In addition, strong recommendations against some monoclonal antibodies have been based only on in-vitro data. At first glance, this can appear confusing to healthcare professionals who are then accruing evidence for their NGs. Whether these inconsistencies in the WHO guidelines have contributed to the substantial variation between countries in the national recommendations is uncertain, but it does raise important questions about how evidence is synthesised, and policies are made in a timely manner.

The quality and strength of evidence have accrued unevenly during the COVID-19 pandemic. Large and definitive randomised control trials in severe disease cases, notably RECOVERY (Randomised Evaluation of COVID-19 ThERapY),[7] SOLIDARITY[8] and REMAP-CAP (Randomized Embedded Multifactorial Adaptive Platform for Community-acquired Pneumonia),[9] have produced consistent and clear results. There is no justification for ignoring their findings. In contrast, in early disease and prevention, the clinical trials have been compromised by a lack of pharmacometric data, limitations in statistical power and trial design, and the declining prevalence of severe end-points in phase III studies.[3] For example, the recent UK-based, multicentre, open-label, prospective randomised controlled trial of molnupiravir treatment in outpatients (PANORAMIC[20]) enrolled 26,411 patients, but was still underpowered with respect to the primary endpoint of death or hospitalisation within 28 days. Further definitive data from phase III type studies like this are therefore unlikely. Meanwhile, the pharmaceutical industry has made lucrative contracts with high-income countries, based on efficacies measured early in the pandemic when the disease was more serious, and have subsequently been very unwilling to provide their medicines for direct comparisons.[21] As a result, there have not been any head to head comparisons to inform policies. Billions of US dollars were spent on medicines, which were not used and have now expired.[22 23] The net result has been a lack of clarity in relative or absolute benefits in early disease. It is less surprising, therefore, that national recommendations vary widely in prevention and early treatment.

There is clearly more variation in National Guidelines for COVID-19 therapeutics than there should be to ensure optimum treatment. There is little evidence for significant differences between human populations or geographic variation in SARS-CoV-2 antiviral susceptibility to justify such divergence. Clearly, some recommendations are incorrect. Global health inequalities play their part in the discrepancies. The countries for which guidelines were not obtained had smaller populations and a lower GDP and GHSI. For both non-severe disease and severe/critical disease guidelines, countries with higher income and with higher health development and global security indices were more likely to recommend WHO-recommended therapeutics, and were less likely to make therapeutic recommendations that are either not approved by the WHO, or actively advised against. Cost of medicines is clearly an important factor.[24] The monoclonal antibodies at current prices are largely unaffordable in low resource settings (LRS) even if they are recommended (figure 8). Recommended drugs such as nirmatrelvir–ritonavir or remdesivir in high risk outpatients, and immunomodulators in hospitalised patients are also relatively expensive, and are often unavailable in lower to middle-income countries. This contrasts with the low cost of available repurposed, but ultimately ineffective therapies, which were recommended early in the pandemic. Recommending drugs which are ineffective, unavailable or unaffordable raises important ethical questions.

The formulation of effective NGs is paramount for mitigating the impact of the pandemic on public health. Formalised processes, which include (but are not limited to) the aggregation and assessment of evidence, structured decision-making, expert consensus, regular updates and transparent communication, play a crucial role in ensuring that elaborated guidelines are not only comprehensive but also reflect the most current and reliable evidence available. These formalised processes, as applied in the WHO guidelines and used as a reference here, could foster the development of more robust clinical guidelines worldwide and are strongly encouraged by the authors.

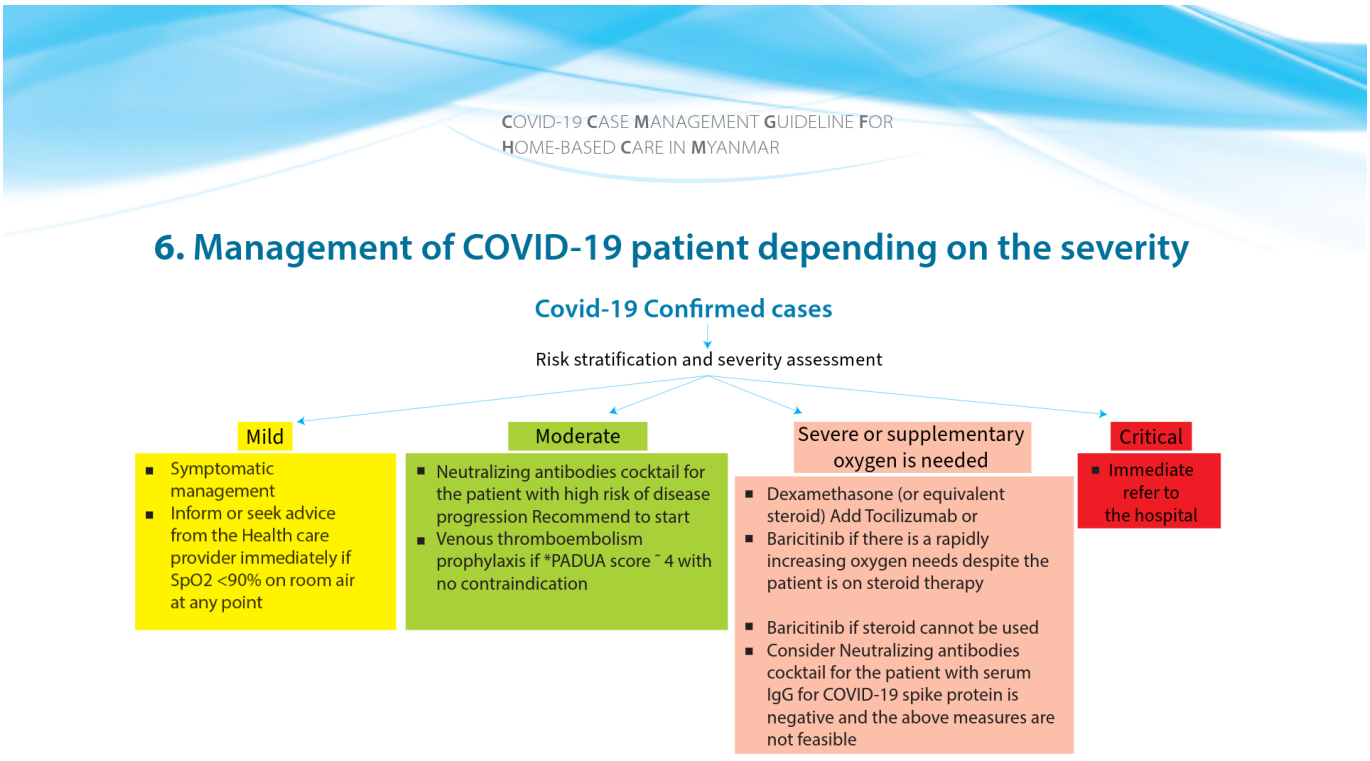

Figure 8 COVID-19 case management guideline for home-based care in Myanmar elaborated by WHO in 2021 . In Myanmar, with the exception of a limited supplementary oxygen availability and corticosteroids, these recommended therapeutic interventions were generally unavailable within the country, and tocilizumab, baracitinib and neutralising monoclonal antibodies were not available at all.

This study is subject to several limitations. First, the numeric metric used to assess the guidelines was a novel approach, and therefore not validated by other studies. However, it was based on the WHO July 2022 guideline and provided a quantitative representation of concordance with the WHO guideline. Second, although the majority of countries' guidelines were obtained, the complete COVID-19 therapeutic guidelines landscape could not be assessed. As dissemination of guidelines through the internet is now standard, the absence of easily accessible national recommendations does raise concerns about optimal guidance and information access for local physicians. Our study also reflects only the NGs. It may be that some countries ceased to update NGs, instead focusing on local guidelines and still delivered up-to-date therapies. Equally, what is recommended by the NG does not necessarily reflect the availability and the access to the therapy within the country. It is hoped that in those countries which have not yet recommended corticosteroids in severe COVID-19, the treating physicians are using either updated local guidelines or are directly following the WHO recommendations. Thirdly, the quality assessment of the individual guidelines was out of our scope mainly because the WHO applied the grade approach and this was our reference; but this could impact the comprehensive assessment of the NGs reliability and robustness.

CONCLUSION

Publicly available COVID-19 National Guidelines vary substantially in their therapeutic recommendations. Ineffective, unaffordable and unavailable therapies are widely recommended, particularly in low-resource settings. The formalisation of processes in the development of NGs for COVID-19 and other infectious diseases is essential for ensuring that these guidelines are grounded in the best available evidence. A systematic and structured approach would not only enhance the credibility of the guidelines but could also contribute to their effectiveness in guiding public health interventions, especially in a pandemic setting.

Author affiliations
[1]Infectious Diseases Data Observatory (IDDO), University of Oxford, Oxford, UK
[2]Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford, Oxford, UK
[3]Mahidol Oxford Tropical Medicine Research Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand
[4]Institute of Global Health, Faculty of Medicine, University of Geneva, Geneve, Switzerland
[5]Laboratorio de Estadistica Aplicada a Ciencias de la Salud (LEACS), Facultad de Medicina, Universidad de Buenos Aires, Buenos Aires, Argentina
[6]Instituto de Investigacion, Swiss Medical Group, Buenos Aires, Argentina
[7]Hospital Italiano de Buenos Aires, Buenos Aires, Argentina

Correction notice The published version misspelled co-author's name as Kanoktip Puttaraska. The correct name should be Kanoktip Puttaraksa.

X Cintia Valeria Cruz @MedicaMigrante

Contributors CVC and MC are both first coauthors of this paper and responsible for the overall content as the guarantors. NJW, PJG, CVC and MC conceived the project. NJW, PG, JT, CVC and MC designed and implemented the study. CVC, MC and JAW conducted the statistical analysis. CVC led all aspects of project management and MC led all aspects of data extraction training and overseeing. CVC, MC, VIC, KP, CC, SMI, MR-P and AR were involved in acquiring the national guidelines and extracting the data. CVC and MC led the project and and wrote the first and final draft of the manuscript. VIC, KP, CC, SMI, AR, JAW, JT, NJW and PJG read and critically revised the manuscript. All authors read and approved the final manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. A repository of the guidelines will be available at IDDO COVID-19 platform (https://www.iddo.org/covid-19).

ORCID iDs
Cintia Valeria Cruz http://orcid.org/0000-0001-8393-8536
James A Watson http://orcid.org/0000-0001-5524-0325
Philippe J Guerin http://orcid.org/0000-0002-6008-2963

REFERENCES

1 Schellekens P. A life lost is a life lost, Available: https://pandem-ic.com/
2 WHO. WHO Coronavirus (COVID-19) dashboard. situation by region, country, territory & area. 2023. Available: https://covid19.who.int/table
3 McLean ARD, Rashan S, Tran L, *et al*. The fragmented COVID-19 Therapeutics research landscape: a living systematic review of clinical trial registrations evaluating priority pharmacological interventions. *Wellcome Open Res* 2022;7:24.
4 Infectious Diseases Data Observatory. A living systematic review of registered COVID-19 trials. 2023. Available: https://www.iddo.org/covid-19/live-systematic-review-trials
5 Dexamethasone in hospitalized patients with COVID-19. *New England J Med* 2021;384:693–704.
6 Horby PMM. RECOVERY collaborative group. 2023. Available: https://www.recoverytrial.net
7 WHO. WHO COVID-19 solidarity Therapeutics trial. 2020. Available: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments
8 REMAP. Publications and results — REMAP-CAP trial. 2023. Available: https://www.remapcap.org/covid19publications
9 Rome BN, Avorn J. Drug evaluation during the COVID-19 pandemic. *N Engl J Med* 2020;382:2282–4.
10 Burki T. COVID-19 in Latin America. *Lancet Infect Dis* 2020;20:547–8.
11 World Health Organization. Therapeutics and COVID-19: living guideline. 2022.
12 White NJ, Strub-Wourgaft N, Faiz A, *et al*. Guidelines should not pool evidence from uncomplicated and severe COVID-19. *Lancet* 2021;397:1262–3.
13 Echeverría-Esnal D, Martin-Ontiyuelo C, Navarrete-Rouco ME, *et al*. Azithromycin in the treatment of COVID-19: a review. *Expert Rev Anti Infect Ther* 2021;19:147–63.
14 Harris PA, Taylor R, Minor BL, *et al*. The Redcap consortium: building an international community of software platform partners. *J Biomed Inform* 2019;95:S1532-0464(19)30126-1.
15 Wang X, Chen Y, Akl EA, *et al*. The reporting checklist for public versions of guidelines: RIGHT-PVG. *Implement Sci* 2021;16:10.
16 Schilling WH, Callery JJ, Chandna A, *et al*. The WHO guideline on drugs to prevent COVID-19: small numbers- big conclusions. *Wellcome Open Res* 2021;6:71.
17 Li G, Hilgenfeld R, Whitley R, *et al*. Therapeutic strategies for COVID-19: progress and lessons learned. *Nat Rev Drug Discov* 2023;22:449–75.
18 Ader F, Bouscambert-Duchamp M, Hites M, *et al*. Remdesivir plus standard of care versus standard of care alone for the treatment of patients admitted to hospital with COVID-19 (DISCOVERY): a phase 3, randomised, controlled, open-label trial. *Lancet Infect Dis* 2022;22:209–21.
19 WHO drugs to prevent COVID-19: A WHO living guideline. 2021.
20 Butler C, Hobbs FDR, Gbinigie O, *et al*. Molnupiravir plus usual care versus usual care alone as early treatment for adults with COVID-19 at increased risk of adverse outcomes (PANORAMIC): preliminary analysis from the United Kingdom randomised, controlled open-label, platform adaptive trial [Lancet]. *SSRN Journal* 2023;401:281–93.
21 Heled Y, Rutschman AS, Vertinsky L. The problem with relying on profit-driven models to produce pandemic drugs. *J Law Biosci* 2020;7:lsaa060.
22 Agence France-Presse (AFP). *US buys up almost entire world supply of coronavirus drug remdesivir*. 2020. Available: https://www.abc.net.au/news/2020-07-02/us-criticised-hoarding-coronavirus-covid19-drug-remdesivir/12414154
23 MSF. New MSF report: high-income countries must stop Hoarding 870 million excess COVID-19 vaccines doses and Redistribute them to save lives - doctors without borders / Médecins Sans Frontières. 2021. Available: https://www.doctorswithoutborders.ca/new-msf-report-high-income-countries-must-stop-hoarding-870-million-excess-covid-19-vaccines-doses-and-redistribute-them-to-save-lives
24 Usher AD. The global COVID-19 treatment divide. *Lancet* 2022;399:779–82.