

Significant global variation in national COVID-19 treatment guidelines

*Most countries recommend at least one treatment that definitely doesn't work
Greatest divergence from gold standard recommendations in under-resourced countries*

National clinical guidelines for the treatment of COVID-19 vary significantly around the world, with under-resourced countries the most likely to diverge from gold standard (World Health Organization; WHO) treatment recommendations, finds a comparative analysis published in the open access journal **BMJ Global Health**.

And nearly every national guideline recommends at least one treatment proven not to work, the analysis shows.

Significant variations in national COVID-19 treatment recommendations have been suspected since the advent of the pandemic, but these haven't been formally quantified or studied in depth, note the researchers.

And despite the fact that COVID-19 is no longer taking the toll on lives and health that it once did, the virus is still evolving and active around the globe, they emphasise. The WHO only rescinded COVID-19's status as a public health emergency in April 2023.

To assess how well national clinical practice followed the recommendations of the WHO (11th version; July 2022)—regarded as the gold standard—for the treatment of COVID-19, the researchers analysed the content of all 194 WHO member states' most recent national guidelines at the end of 2022.

Each set of guidelines was scored according to how closely they aligned with the WHO recommendations. Extra points were awarded for those that had been updated within the preceding 6 months; those that made recommendations in line with the strength of evidence; and those that included assessments of the effectiveness of treatments and their side effects.

The wealth and resources of each country were then compared using per capita World Bank gross domestic product (GDP) in US dollars for 2021, the Human Development Index 2021, and the Global Health Security Index 2021.

Of the 194 countries contacted, 72 didn't respond. Of the remaining 122, 9 had no formal guidelines or couldn't be accessed (1) and a further 4 didn't recommend any treatments, so these were excluded, leaving a total of 109.

The countries for which guidelines weren't obtained had, on average, smaller populations, lower GDP per head, and a lower Global Health Security Index, indicative of greater economic challenges and less ability to respond to health emergencies.

The 11th iteration of the WHO guidelines categorises disease severity, but most of the reviewed guidelines (84%; 92) didn't define COVID-19 severity in the same way, and

some didn't define severity at all (6.5%; 7). Only 10 guidelines (9%) used disease severity definitions that were comparable with those of the WHO.

Most (77%; 84) guidelines didn't include an assessment of the strength or certainty of the therapeutic recommendation. And the range of recommended drugs, irrespective of severity, varied from 1 to 22. The WHO guidelines recommend a total of 10.

In all, 105 guidelines included at least one treatment recommended by the WHO, but 4 didn't recommend any. Countries in the African region had a significantly lower proportion of therapies recommended by the WHO, compared with countries in Europe and SouthEast Asia.

The most commonly recommended drugs were corticosteroids (92%;100), with 80% (88) of guidelines recommending them for the same disease severity as the WHO. But corticosteroids weren't recommended in severe disease in nearly 1 in 10 guidelines despite overwhelming evidence of their benefit.

Remdesivir was recommended for severe or critical disease in half the guidelines (51%;72). But the WHO guidelines only indicate remdesivir conditionally for mild disease in patients at highest risk of hospital admission.

In late 2022, many guidelines continued to recommend treatments that the WHO had advised against, including chloroquine, lopinavir–ritonavir, azithromycin; vitamins and/or zinc.

One in three guidelines (36; 33%) recommended at least one neutralising monoclonal antibody directed against SARS-CoV-2, the virus responsible for COVID-19. These guidelines were issued by wealthier countries.

But 2 of these monoclonal antibodies—bamlanivimab plus or minus etesivimab and regdanivimab—appeared consistently in clinical guidelines, despite not being recommended by the WHO.

Doses of the most commonly recommended drugs also varied. And many guidelines hadn't been updated for more than 6 months.

Guidelines from under-resourced countries diverged the most from the WHO recommendations, when stratified by annual GDP, the Human Development Index, and the Global Health Security Index.

The researchers acknowledge several limitations to their findings, including the scoring used to assess the guidelines, which hasn't been validated by other studies, and the inability to assess all national guidelines.

But they nevertheless ask: “Why do [national guidelines] 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.”

They offer some possible explanations, including variations in how the severity of, and therefore the most appropriate treatment for, COVID-19 is defined; the evolution of the evidence; and the research chaos and confusion of the early stages of the pandemic, leading to claims and counterclaims, compounded by intense political and media interest.

“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,” explain the researchers. “But why many of these unproven remedies continued to be recommended as evidence of their ineffectiveness accrued is much less clear,” they add.

“There is clearly more variation in national guidelines for COVID-19 therapeutics than there should be to ensure optimum treatment,” which aren’t justified by significant differences between populations or geographic variation in SARS-CoV-2 antiviral susceptibility, they write.

Global health inequalities clearly have a part to play, leading to the recommendation of ineffective, unaffordable and unavailable therapies, they suggest.

“The formalisation of processes in the development of [national guidelines] for COVID-19 and other infectious diseases is essential for ensuring that these guidelines are grounded in the best available evidence,” they conclude.

“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.”