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Department of Health
Republic of South Africa
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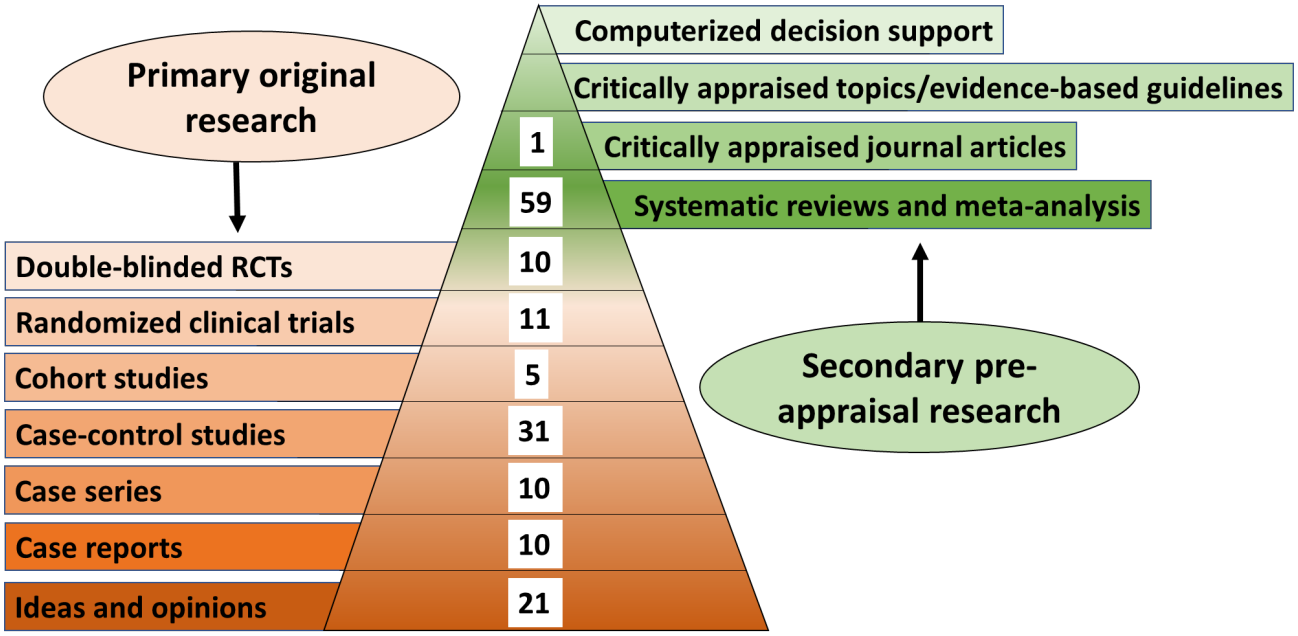
URGENT: REQUEST FOR IMMEDIATE REAPPRAISAL OF IVERMECTIN IN THE CONTEXT OF A SEVERE THIRD WAVE COVID-19 EPIDEMIC IN SOUTH AFRICA

Dear Colleagues,

Our correspondence refers to the update of the 25 January 2021 evidence review of Ivermectin for the treatment of COVID-19: Evidence review of clinical benefits and harms dated 18 June 2021.

The review by the NEMLC Therapeutic Sub-Committee concludes there not be use of Ivermectin based on a review of clinical studies. The key findings include that the current evidence for the use of ivermectin for COVID-19 does not suggest any clear benefits with respect to mortality, clinical improvement or viral clearance.

The Aldous-Makhetha ivermectin in COVID-19 living bibliography is summarized in the evidence-based pyramid in the figure below showing the extent of the current body of literature. It includes 13 papers concluding lack of efficacy of ivermectin. These studies include those with low and infrequent doses or inappropriate participant selection, and conclude that further studies are required. To date not a single publication has expressed harm incurred and few, if any, suggest pursuing ivermectin for COVID-19 treatment is futile. The rest of the 158 publications indicate safety and efficacy of ivermectin in the treatment of COVID-19, from small cases series, to double blinded randomized control trials, to city-wide, state-wide and country-wide population-based studies, and meta-analyses.



We present further below, key points that in our view, support an alternate conclusion to those of the NEMLC. More importantly, however, we wish to raise our concerns regarding conclusions drawn and recommendations made in the context of a severe COVID-19 pandemic that is rapidly moving; a pandemic that requires adaptive and realistic approaches to evidence-based medicine that are holistic, and that place ethical obligations and commitment to the rights to health and life in the centre.

Evidence-based medicine in the context of a novel viral pandemic necessitates an acceptance that knowledge is fluid, timeframes are compressed and that heterogeneous evidence must be brought to bear on prevention and treatment of the disease. New ways of thinking are needed that are adaptive and pragmatic, without dropping of standards. The quest for perfect evidence in the form of a large randomized controlled trial for a drug no longer supported financially by big pharma is difficult to achieve. The totality of all current evidence and on the ground implementation, need to be accepted as enough evidence to make a Type I error decision to save lives.

In the context of an emerging severe third wave of COVID-19 in South Africa, and among the more severe epidemics to date on the African continent, all resources at our disposal must be applied to minimize morbidity and mortality for all in South Africa.

In their review of making evidence and policy in public health emergencies in the COVID-19 context, Lancaster et al. (2020)[1] observe that adaptive evidence-making "should be the defining feature of an 'evidence-making intervention' approach to health". Carley et al. (2020)[2] highlight the need for agility and the adoption of new methods, with the weight of evidence being based on the "balance of probabilities". Deana (2020)[3] emphasises the importance of routine care practices and the role of clinicians in decision-making to treat patients, while Greenhalgh (2020)[4] argues the need for a dynamic approach that includes multidisciplinary perspectives, mixed methods, and the need to elevate the importance of 'practice-based evidence' in a pandemic context — *specifically questioning an over-reliance on evidence based on randomised control trials (RCTs) as the ultimate (and only) evidence to guide clinical decision-making.*

The Ivermectin Interest Group is a collective of doctors, pharmacists, scientists and public health specialists translating science into an effective response for COVID-19. We are focused on preventing and reducing severe COVID-19 and saving lives. We consider the totality of evidence. We are committed to science and evidence and we are applying what we know to the best of our abilities in the clinical, pharmaceutical and public health aspects of the COVID-19 pandemic in South Africa. Following a holistic and multidisciplinary approach to the science of ivermectin, and in our practice on the frontlines of this epidemic, we see clear benefits of our use of ivermectin. We celebrate the joy of a shortened and less severe course of illness among our patients — more so, when it is clear that our therapeutic efforts employing multiple interventions including ivermectin ensure that our patients survive. Such 'turnarounds' boost morale and energize our cadre of healthcare workers and invigorate our commitment in the most trying circumstances.

Regarding the NEMLC recommendation: "We suggest not use the option (conditional)" we draw your attention to the following regarding RCT evidence and ivermectin:

1. In the summary table presented by the NEMLC, among the included studies, eleven are assessed as having moderate overall risk of bias, and show promising findings. In our view, these studies offer sufficient evidence in an epidemic context to sway a recommendation from non-use to use (conditional or otherwise). How many lives still need to be lost before this evidence is accepted? Also, notably, in the analysis of change in clinical status, deference is given to the large study by López-Medina et al. (2021)[5] in Colombia, which finds no

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[1] Lancaster, K., Rhodes, T. and Rosengarten, M., 2020. Making evidence and policy in public health emergencies: Lessons from COVID-19 for adaptive evidence-making and intervention. *Evidence and Policy*, *16*(3), pp.477-490.

[2] Carley, S., Horner, D., Body, R. and Mackway-Jones, K., 2020. Evidence-based medicine and COVID-19: what to believe and when to change. Emerg Med J 2020;37:572–575

[3] Deana, C., 2021. The COVID-19 pandemic: is our medicine still evidence-based?. *Irish Journal of Medical Science (1971-)*, *190*, pp.11-12.

[4] Greenhalgh, T., 2020. Will COVID-19 be evidence-based medicine's nemesis?. PLoS Med. 17(6): e1003266

[5] López-Medina, E., López, P., Hurtado, I.C., Dávalos, D.M., Ramirez, O., Martínez, E., Díazgranados, J.A., Oñate, J.M., Chavarriaga, H., Herrera, S. and Parra, B., 2021. Effect of ivermectin on time to resolution of symptoms among adults with mild COVID-19: a randomized clinical trial. *Jama*, *325*(14), pp.1426-1435.

statistically significant outcomes for patients randomized to ivermectin versus a placebo. This study is assessed as having moderate risk of bias by the NEMLC. We draw your attention to an article by Scheim et al. (2021),[6] which suggest a higher than moderate risk of bias would be more appropriate.

2. A systematic review, meta-analysis and trial sequential analysis by Bryant et al. (2021)[7] following well-recognised and valid methods and assessment of evidence using the GRADE approach has been published in the American Journal of Therapeutics. This was released on 17 June, a day prior to the day of release of the NEMLC review, and may not have been included for that reason (although the openly available preprint was excluded). This review concludes: "Moderate-certainty evidence finds that large reductions in COVID-19 deaths are possible using ivermectin. Using ivermectin early in the clinical course may reduce numbers progressing to severe disease. The apparent safety and low cost suggest that ivermectin is likely to have a significant impact on the SARS-CoV-2 pandemic globally." In our view, the "moderate certainty" conclusion of the comprehensive, peer reviewed study published in a reputable journal by Bryant et al. (2021), in the context of a severe epidemic in South Africa with fatal consequences for many patients, is sufficient to merit a revision of the NEMLC guidance from non-use to suggest use (conditional or otherwise).

We also highlight the critical importance of following a holistic approach to reviewing evidence that leads to Department of Health recommendations in the COVID-19 epidemic context. The following evidence is relevant:

- The mechanism of action of ivermectin for treating COVID-19 includes clearly demonstrable direct action, antiviral and anti-inflammatory effects as outlined in recent articles by Zaidi and Dehgani-Mobaraki (2021),[8] and Wehbe et al. (2021),[9] among others. These mechanisms of action remain valid for COVID-19 variants, and are of particular importance where vaccines are in short supply, vaccine rollout is complex and time-consuming, and where many health facilities in South Africa are under-resourced and inadequately staffed.
- Ivermectin has a long and well-documented safety history following billions of doses administered during antihelminth treatment campaigns, and numerous observational studies

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6 Scheim, D., Hibberd, J.A. and Chamie-Quintero, J., 2021. Protocol violations in López-Medina et al.: switched ivermectin (IVM) and placebo doses, failure of blinding, indicators of over-the-counter IVM use by controls, and blatant conflicts of interest. OSF.preprints

7 Bryant, A., Lawrie, T.A., Dowswell, T., Fordham, E.J., Scott, M., Hill, S.R. and Tham, T.C., 2021. Ivermectin for prevention and treatment of COVID-19 infection: a systematic review, meta-analysis and trial sequential analysis to inform clinical guidelines. American Journal of Therapeutics. e1–e27

8 Zaidi, A.K. and Dehgani-Mobaraki, P., 2021. The mechanisms of action of Ivermectin against SARS-CoV-2: An evidence-based clinical review article. *The Journal of Antibiotics*, pp.1-13.

9 Wehbe, Z., Wehbe, M., Iratni, R., Pintus, G., Zaraket, H., Yassine, H.M. and Eid, A.H., 2021. Repurposing Ivermectin for COVID-19: Molecular Aspects and Therapeutic Possibilities. *Frontiers in Immunology*, *12*, p.1040.

and RCTs include data that attest to the safety of ivermectin in the clinical management of COVID-19 (Guzzo et al).

- Ivermectin has been used as part of standard treatment protocols in many countries to date and is approved by many country health authorities, for example Mexico, some states in India, Egypt and others. It is also relevant to note the United States National Institutes of Health has a neutral position on ivermectin, being neither for nor against the use of the drug.
- Clinicians in many countries have shared their experiences administering ivermectin as part of the armamentarium for COVID-19 with many examples of positive outcomes. These experiences include low resource settings consistent with the facilities and resources available in many parts of Southern Africa, where very low mortality outcomes have been demonstrated—for example, the experiences of Dr Jackie Stone in Zimbabwe.[10] Clinicians in the IIG are in the process of documenting similar positive experiences, and this is also the case for others in practice in the country.
- There is currently no adequate national guidance on the use of ivermectin in South Africa. While there is much conflicting information, many people in South Africa are procuring and using ivermectin. Many patients with COVID-19 are requesting ivermectin, many pharmacists are legally dispensing it, and many clinicians are including ivermectin in the treatment of COVID-19. There is good evidence to support given dosages of ivermectin based on stage of disease, and there are opportunities to modify dosages based on clinical experience and emerging evidence. However, this vital process is severely inhibited by the absence of overarching national guidance which currently refutes the validity of ivermectin for treating COVID-19. On the basis of our experience, and the scientific evidence we have outlined, this contributes to increased morbidity and mortality of people in our country with COVID-19.

We appreciate that the Department of Health continues to reflect on therapeutic options for COVID-19 and makes recommendations accordingly. However, in an epidemic and pandemic context, it is vital that the approach to evidence-based medicine be revised to ensure the best care and health for all in South Africa. Decision-making on the basis of RCT's alone is inconsistent with the circumstances of a public health emergency. We urge the Department to expand its approach to include multidisciplinary perspectives in the COVID-19 epidemic context, and also to consider the concerns we have raised regarding the rejection of ivermectin as a therapeutic option by the NEMLC.

[10] The Palmer Foundation. Interview with Zimbabwe's Dr. Jackie Stone: COVID-19 Infection & death rates plummet post MCAZ green light for ivermectin use. 4 May 2021. https://www.palmerfoundation.com.au/interview-with-zimbabwes-dr-jackie-stone-covid-19-infection-death-rates-plummet-post-mcaz-green-light-for-ivermectin-use/

In our current emergency we need decision-making on interim strategies. Since ivermectin is well grounded in safety data, and evidence well within bounds for demonstrating improved COVID-19 outcomes, it is ethically appropriate to include ivermectin in the treatment regimen.

As the IIG, we stand ready to assist in any way possible, to alleviate the suffering wrought by COVID-19, especially in the urgent circumstance of the current third wave. We request an easing and endorsement of the compassionate use program and operational data collection as part of the process.

Signed off by members of the Ivermectin Interest Group:

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Prof Anisa Mosam

Dr Warren Parker

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