IVERMECTIN TECHNICAL BRIEF ON COVID 19, February 16, 2021

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Background

Ivermectin is an antiparasitic drug used to treat a number of human neglected tropical diseases including onchocerciasis, strongyloidiasis due to the nematode parasite *Strongyloides stercoralis* and for the treatment of onchocerciasis due to the nematode parasite *Onchocerca volvulus.*

In the last couple of months, there has been a lot of discussion both among the scientific community and the general public in the USA, Europe and Africa regarding the potential positive effect of Ivermectin for COVID-19 treatment and/or prophylaxis. Within Africa, there has been strong advocacy to allow use of Ivermectin for COVID-19 patients in Zimbabwe and South Africa; resulting in the two countries allowing emergency use of Ivermectin for COVID-19 patients. Zambia received social media reports that some sections of the Zambian public may be using the drug **for** suspected COVID-19. This raised concern and NHRA sought guidance from MOH, ZAMRA, and other stakeholders in order to explore the current evidence and advice MOH on messaging to protect the public from unauthorized use of the unregistered and unapproved drug. A multi-stakeholder Taskforce was hence constituted to study available scientific data and issue a statement to the public. ZAMRA drafted the statement that the Taskforce reviewed and was issued. This statement was updated a week later. The message has been consistent; there is currently insufficient evidence to allow use of Ivermectin for COVID-19; hence the need to support researchers in Zambia to conduct studies that would investigate the efficacy and safety of Ivermectin for COVID-19.

Available evidence on efficacy and safety for COVID 19

The global evidence on the efficacy and safety of Ivermectin for COVID-19 is mixed and not conclusive. Some clinical trials have shown no benefits or worsening of disease after Ivermectin use [1-4], others reported shorter time to resolution of disease manifestations that were attributed to COVID-19 [5-8], greater reduction in inflammatory marker levels [6,7], shorter time to viral clearance [1,6], or lower mortality rates in patients who received Ivermectin than in patients who received comparator drugs or placebo [1,6,8]. However, most of these studies had methodological quality issues and therefore difficult to use them as conclusive evidence of efficacy or lack of it. See a summary of these studies in Annex 1[9].

Evidence from systematic reviews and meta-analysis, scientific methodology that gathers available research evidence and scientifically pools or adds it altogether, is mixed and not conclusive. In one systematic review and meta-analysis published in the Journal of Pharmacy on 23rd November, 2020, a total of 629 RT-PCR positive patients were included from 4 studies. 397 of these patients received Ivermectin together with standard of care. Pooled Odds Ratio (OR) was

0.53 (95% CI: 0.29 to 0.96) for all-cause mortality as primary outcome; which was statistically significant at P-value of 0.04. Random effect model also showed that adding Ivermectin resulted in significant clinical improvement compared to usual therapy (OR=1.98, 95% CI: 1.11 to 3.53; P=0.02). In all the studies included in the review, the safety profile of Ivermectin was reported to be favourable. The authors concluded as follows: Ivermectin is an established drug with a long history of clinical use and with minimal safety concern. Recent observational studies have reported the effectiveness of this drug as an add-on therapy in patients with COVID-19. Our meta-analysis also supports this finding and suggests the modest utility of Ivermectin in reducing all-cause mortality and improving clinical outcomes." However, the quality of evidence in the primary studies included in the meta-analysis was very low. See the Systematic Review Paper in Annex 2 [10].

However, a real-time meta-analysis published on 15th February, 2021 report that 100% of 40 studies they reviewed showed positive effects with random effects meta-analysis pooled RR of 0.19 (95% CI: 0.11-0.33); i.e. 81% reduction in early treatment outcomes. Prophylactic use showed a reduction of 89% in outcome measures assessed, RR 0.11 (95% CI: 0.05 – 0.24). They also report 78% lower mortality, RR 0.22 (95% CI: 0.12 – 0.41).

The authors concluded that Ivermectin is an effective treatment for COVID-19. They add in their conclusion that the probability that an ineffective generated results as positive as the 40 studies to date is estimated to be one in one trillion (p=0.00000000000091).

These results may be controversial on at least two grounds: 1.0 The authors appear to have pooled heterogeneous data in their meta-analysis. For example, for early treatment effects, the following were the different outcome measures all pooled into the forest plot: risk of fever at day 14, risk of unresolved symptoms, risk of no virological cure. The authors do however, acknowledge the heterogeneity in the studies. 2.0 The authors did not perform a quality assessment of the studies for inclusion, but included all studies. They justified their approach as follows: "Typical meta-analysis involves subjective selection criteria, effect extraction rules, and study bias evaluation, which can be used to bias towards a specific outcome. In order to avoid bias, we include all studies and use a pre-specified method to extract results from all studies." See the Systematic Review Paper in Annex 3 [11].

Conclusions and Technical Advice

There appear to be a fair amount of evidence indicating that Ivermectin has a potential role in the treatment of COVID-19. However, the current data is not conclusive due to methodological issues. It is therefore important that Zambia generates its local evidence in a well-designed and conducted randomized clinical trial, while at the same time closely monitors emerging evidence from across the globe.

Ivermectin and other remedies for COVID-19 Taskforce Members:

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References

1. Ahmed S, Karim MM, Ross AG, et al. A five-day course of Ivermectin for the treatment of COVID-19 may reduce the duration of illness. *Int J Infect Dis*. 2020;103:214-216. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33278625.
2. Chachar AZK, Khan KA, Asif M, Tanveer K, Khaqan A, Basri R. Effectiveness of ivermectin in SARS-COV-2/COVID-19 Patients. *Int J of Sci*. 2020;9:31-35. Available at: https://www.ijsciences.com/pub/article/2378.
3. Chowdhury ATMM, Shahbaz M, Karim MR, Islam J, Guo D, He S. A randomized trial of ivermectin-doxycycline and hydroxychloroquine-azithromycin therapy on COVID19 patients. *Research Square*. 2020;Preprint. Available at: https://assets.researchsquare.com/files/rs-38896/v1/3ee350c3-9d3f-4253-85f9-1f17f3af9551.pdf.
4. Soto-Becerra P, Culquichicón C, Hurtado-Roca Y, Araujo-Castillo RV. Real-world effectiveness of hydroxychloroquine, azithromycin, and ivermectin among hospitalized COVID-19 patients: results of a target trial emulation using observational data from a nationwide healthcare system in Peru. *medRxiv*. 2020;Preprint. Available at: https://www.medrxiv.org/content/10.1101/2020.10.06.20208066v3.
5. Hashim HA, Maulood MF, Rasheed AW, Fatak DF, Kabah KK, Abdulamir AS. Controlled randomized clinical trial on using ivermectin with doxycycline for treating COVID-19 patients in Baghdad, Iraq. *medRxiv*. 2020;Preprint. Available at: https://www.medrxiv.org/content/10.1101/2020.10.26.20219345v1/.
6. Elgazzar A, Hany B, Youssef SA, Hafez M, Moussa H, Eltaweel A. Efficacy and safety of ivermectin for treatment and prophylaxis of COVID-19 pandemic. *Research Square*. 2020;Preprint. Available at: https://www.researchsquare.com/article/rs-100956/v2.
7. Niaee MS, Gheibi N, Namdar P, et al. Ivermectin as an adjunct treatment for hospitalized adult COVID-19 patients: a randomized multi-center clinical trial. *Research Square*. 2020;Preprint. Available at: https://www.researchsquare.com/article/rs-109670/v1.

8. Khan MSI, Khan MSI, Debnath CR, et al. Ivermectin treatment may improve the prognosis of patients with COVID-19. *Arch Bronconeumol*. 2020;56(12):828-830. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33293006.
9. National Institutes of Health (NIH) Revised Treatment Guidelines on Ivermectin; 11th February, 2021. https://www.covid19treatmentguidelines.nih.gov/antiviral-therapy/ivermectin/
10. Padhy BM, Mohanty RR, Das S, Meher BR. Therapeutic potential of ivermectin as add on treatment in COVID 19: A systematic review and meta-analysis. J Pharm Sci. 2020;23:462-469. doi: 10.18433/jpps31457. PMID: 33227231.
11. file:///C:/Users/PROF~1.BIE/AppData/Local/Temp/ivm-meta-1.pdf

Annexes: See Separate documents