

## BC COVID THERAPEUTICS

### Memorandum

Date: July 1st, 2021

To: BC Physicians, Family Medicine Specialists, & Pharmacists

From: BC COVID-19 Therapeutics Committee

Re: **Lack of Clinical Evidence to Support Ivermectin in Prophylaxis and Treatment of COVID-19 Patients**

Recently, there has been several reports and publications suggesting that ivermectin may be beneficial for the prophylaxis and treatment of COVID-19 patients. Based on a critical appraisal of the ivermectin literature, most data are cited from non-peer-reviewed clinical studies with methodological flaws and intrinsic limitations. Most of these trials are relatively small with *low to very low certainty of evidence* to support the outcomes. In addition, the studies vary widely in their designs, treatment regimens and duration, comparators, standards of care, endpoints, and statistical results. To date, there has not been a pivotal, well-conducted, randomized controlled trial (RCT) that is adequately powered to meet statistical significance. Based on these findings, there remains uncertainty in the benefits of ivermectin for prophylaxis and treatment of COVID-19.

#### Recommendations:

**For Critically, Severely, and Mildly Ill COVID-19 Patients:** Ivermectin is **not** recommended outside of approved clinical trials.

**For Prophylaxis with Known COVID-19 Exposure:** Ivermectin is **not** recommended outside of approved clinical trials.

#### Evidence used for these recommendations:

In a systematic review and meta-analysis of RCTs (6 published, 4 non-peer-reviewed) by Roman et al published in *Clinical Infectious Diseases* (June 2021), the benefits and harms of ivermectin in COVID-19 patients were evaluated.<sup>1</sup> Ten RCTs (1 in Spain and 9 in low- and middle-income countries) with sample sizes ranging from 24 to 398 patients were included (N=1173) [8 mild, 1 moderate, and 1 mild-moderate disease] with 5 to 30 days follow-up. Ivermectin did not reduce all-cause mortality (RR 0.37, 95% CI 0.12-1.13, I<sup>2</sup>=16%, *very low quality of evidence* (QoE)), length of stay (mean difference 0.72 days, 95% CI -0.86-2.29, I<sup>2</sup>=0%, *low* QoE), or adverse events (relative risk 0.95, 95% CI 0.85-1.07, I<sup>2</sup>=0%, *low* QoE) in mild COVID-19 disease. Main limitations included high risk of bias in 8 RCTs, differences in comparator groups (placebo or standard of care), and *low to very low quality of evidence* to support the outcomes. Based on this well-designed study, ivermectin does not appear to be effective for treatment of COVID-19.

Another systematic review and meta-analysis by Bryant et al was published in the *American Journal of Therapeutics* in June 2021. Twenty-four RCTs (N=3406) with 22 treatment and 3 prophylaxis trials (6 published, 18 non-peer-reviewed) ranging from 24 to 476 patients were included [16 mild-moderate, 6 severe disease].<sup>2</sup> Ivermectin appeared to reduce risk of death (2.3% vs. 7.8%, average risk ratio (aRR) 0.38, 95% CI 0.19-0.73, I<sup>2</sup>=49%, *moderate-certainty evidence*, [N=2438-15 trials]) with no differences in severe adverse events (aRR 1.65, 85% CI 0.44-6.09, I<sup>2</sup>=0%, *low certainty evidence*). For prophylaxis, ivermectin may reduce risk of infection but the studies were of low quality (5% vs. 29.6%, aRR 0.14, 85% CI 0.09-.021, *low certainty evidence*). Since the majority of studies were non-peer-reviewed trials with methodological variances and inadequate statistical significance, no definitive conclusions can be drawn.

The CTC will continue to update the “Clinical Practice Guidance for Antimicrobial and Immunomodulatory Therapy in Adult Patients with COVID-19” document based on any new studies and relevant data. Please refer to the BCCDC website for the most updated information: <http://www.bccdc.ca/health-professionals/clinical-resources/covid-19-care/clinical-care/treatments>

#### References

1. Roman YM et al. Ivermectin for the treatment of COVID-19: A systematic review and meta-analysis of randomized controlled trials. *Clinical Infectious Diseases*, 2021; ciab591, <https://doi.org/10.1093/cid/ciab591>
2. Bryant A et al. 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*. 2021 Jun 17. doi: [10.1097/MJT.0000000000001402](https://doi.org/10.1097/MJT.0000000000001402)