Canadian Covid Care Alliance
Alliance canadienne pour la prévention et prise-en-charge de la covid

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To: The College of Physicians and Surgeons of Alberta (CPSA) February 17, 2023
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RE: EXPANDING THERAPEUTIC OPTIONS FOR THE EARLY TREATMENT OF COVID-19

EXECUTIVE SUMMARY

Approximately one year ago, the Canadian Covid Care Alliance (CCCA) wrote to the Canadian professional colleges requesting that the colleges support early COVID-19 (C19) treatment with various approved medications. Much has changed since then, including Health Canada's approval and the subsequent promotion by professional colleges across Canada of the novel antiviral agent, Paxlovid™, for use in the early treatment of COVID-19. While the CCCA applauds the federal and provincial decisions to promote the use of pharmacotherapy for early treatment, we ask that consideration be expanded to include additional medication options, including and especially ivermectin (IVM), for the following reasons:

- Since you acknowledge and promote the importance of early C19 intervention with Paxlovid™, it is prudent to acknowledge the value of other early treatments, especially those with lower cost and with comparable, and in some cases superior, effectiveness and safety.
- Estimates for one life saved are $78,000 for Paxlovid™ and $22 for generic ivermectin.
- Ivermectin is much safer than Paxlovid™ as the WHO database lists >20,000 adverse events for Paxlovid™ in less than a year after Interim Order approval, compared with <7000 for ivermectin after decades of use.
- The novelty of Paxlovid™ precludes knowing its long-term safety; ivermectin has been safely administered to billions of people over decades of use.
- The potential for drug interactions with Paxlovid™ is significant, and minimal with ivermectin.
- Ivermectin has been tested in more than 93 studies with more than 134,223 subjects revealing substantial benefits including significant reduction of disease severity and deaths.
- Delaying ivermectin use in early treatment of C19 is unethical, because ivermectin could obviate many C19 deaths in Canada.
- A recent (Jan 2023) randomized controlled trial conducted in 399 participants demonstrated a reduction of 72% of COVID-19 infection in the group treated with daily oral administration of ivermectin compared to the placebo group.

Given this new information, the Canadian Covid Care Alliance wishes to explore with your organization the possibility of opening a discussion on the broader scope of early treatment (ET) options for COVID-19.

For convenience of review, this letter is organized as follows:

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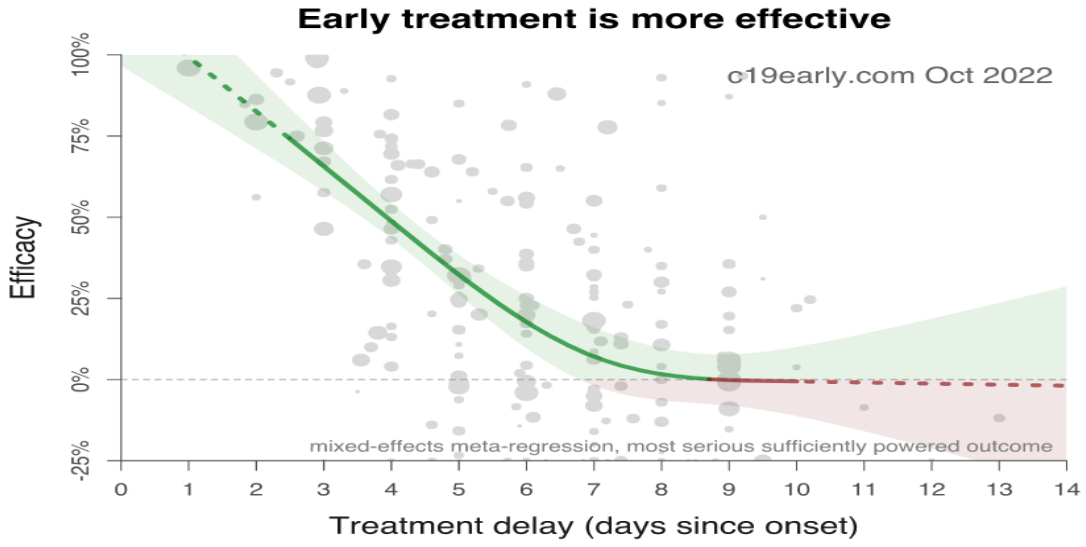
INTRODUCTION

The Canadian Covid Care Alliance (CCCA) is a group of over 700 independent research scientists, doctors, registered nurses and nurse practitioners, pharmacists and other health care practitioners, as well as lawyers, ethicists and other professionals from across Canada. The Alliance is dedicated to providing balanced, scientific, evidence-based information related to the prevention, tracking and treatment of COVID-19 so that hospitalizations can be reduced, lives saved, and our country safely restored as quickly as possible.

The CCCA wishes to discuss with your organization the use of early treatment (ET) options for COVID-19 (C19). More than a year has passed since we started reaching out to Canadian professional medical and pharmacy colleges highlighting the importance of ET, including the consideration for use of ivermectin (IVM), to reduce the development and severity of C19 disease.

Over the past year, much has changed in the understanding and treatment of C19. Key points that have been widely recognized include:

- COVID-19 genetic vaccines do not sufficiently reduce the risk of contracting or transmitting C19;
- ET represents a critical opportunity for combatting C19 at its earliest stages and for reducing risk of severe illness (see figure below);
- A variety of therapeutics continue to be studied in C19 ET, most notably IVM, and many have shown substantial evidence of efficacy.
- There have been occasions of insufficient accessible community resources such as family health teams and community pharmacies for C19 testing and ET;
- There has been increasing interest to move testing and ET from in-hospital locations to in-community health/pharmacy locations to preserve critical hospital manpower and resources.



Graph of efficacy of treatment of C19 as a function of time after symptom onset. This is a summary of all ET reports on C19 as compiled by c19early.com as of 2022 October 29.

ACCEPTANCE OF EARLY TREATMENT (ET)

In light of new information regarding the availability, efficacy, and safety of new and existing therapeutics for treating C19, and the changing COVID-19 landscape with the evolution of new viral variants, many jurisdictions around the world have approved and promote access to ET for C19, including Health Canada's earlier approval of monoclonal antibody (MAb) therapy and its more recent approval of Paxlovid™.

As allied advocates for frontline health care professionals, we applaud the recognition that ET for C19 promotes the health of Canadians while reducing the burden on valuable, limited healthcare resources. However, limiting the ET scope to only promote use of MAb or Paxlovid™ as the sole choices for reducing disease severity and death, has been impacted by, or resulted in, the following unfortunate experiences:

- Abandonment of MAb treatments as SArS-CoV-2 variant drift resulted in treatment failure;
- Significant limitations unique to Paxlovid™ including:
    - limited patient eligibility;
    - requirement of a positive C19 test;
    - requirement for treatment initiation within 5 days of symptom onset;
    - need for monitoring of liver and renal function;
    - potential drug interactions;
    - high rebound rates; and
    - high expense.
- Wide-spread shortages of cough & cold medications used for treating C19 symptoms as parents and patients, who are unaware of, or ineligible for, the use of Paxlovid™ seek convenient at-home treatment options for the management of C19 symptoms;

Because of these considerations, additional C19 prevention/treatment-related options should be considered for implementation in the community. Choices should reflect the need for equitable and positive patient outcomes from safe products at a sustainable and efficient cost. See below for some products identified in the literature as being potentially useful ET therapeutics:

COST PER LIFE SAVED from NNT in 2233 Studies (October 2022)			
Ivermectin	$22	Paxlovid™	$78,000+
Vitamin D	$11	Molnupiravir	$88,000+
Zinc	$30	Remdesivir	$208,000+

Table of costs per lives saved compiled from https://c19early.org/ as of October 29, 2022.

Amongst these options, evidence shows ivermectin to be safe, have favourable results as an ET therapeutic, and is readily available at a favourable cost point. In contrast, Canadian health authorities appear to deem Paxlovid™ as the sole focus for out-patient ET use. Because of this disparity, we present herein a detailed rationale for expanding the ET options to include ivermectin by **presenting the current data on Paxlovid™ in comparison with ivermectin for ET in C19.**

PAXLOVID™ AND IVERMECTIN COMPARISON

CRITERIA	PAXLOVID™ OVERALL	IVERMECTIN OVERALL
A. Quality of the evidence	Minimal	Significant
B. Safety for targeted population	High risk	Extensive long-term safety
C. Efficacy a. Impact on viral load/ transmission b. Symptom reduction c. Reduction in disease severity	 Minimal Moderate Moderate	 Robust Robust Significant
D. Mechanism of action	Singular	Multiple
E. Criteria for use	Limited	Broad
F. Long Covid-19 prevention/treatment	No evidence	Positive evidence
G. Economic costs	Significant	Modest

A. QUALITY OF THE EVIDENCE

While there have been many publications that addressed the efficacy of IVM in the various phases of the SARS-CoV-2 infection, meta-analyses are usually considered to be the highest form of evidence. We suggest that the most useful and objective meta-analysis of IVM in C19 is that of Bryant *et al. (*1). Co-author Dr. Tess Lawrie is one of the most experienced and respected analysts in this field, and has over 50 Cochrane reviews to her credit. In comparison, there are publications cited by opponents of IVM use in C19, and these have been embraced by the legacy media, some Canadian MPs and public health officials, as well as professional bodies such as the ACP and CPSA. These latter publications have serious shortcomings that we suggest have led the authors to make erroneous conclusions and recommendations. We address some of these papers below and add information from the latest randomized, double-blind, placebo-controlled trial of ivermectin at the end of this section.

The review by Popp *et al.* suggests: “The lack of good quality evidence on efficacy and safety of ivermectin arises from a study pool that consists mainly of small, insufficiently powered RCTs with overall limited quality regarding study design, conduct and reporting. Current evidence does not support using ivermectin for treating or preventing of COVID-19 unless they are part of well-designed randomized trials” (2).

Fordham *et al.* have highlighted 11 major issues with the Popp *et al.* Cochrane review, which may be summarized as inclusion criteria that were too stringent resulting in a generalized exclusion of many clinically relevant and valid studies (3). In doing so, they effectively disregarded the large pool of evidence supporting the benefit of ivermectin as part of a multi-faceted approach to the outpatient management of SARS-CoV-2 infection.

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Bounfrate 2021	✓	✓	✓	✓	✓	✓
Chaccour 2021	✓	✓	✓	✓	✓	✓
I-TECH 2022	✓	✓	✓	✓	✓	✓
López-Medina 2021	✓	~	✓	✓	✓	~
TOGETHER 2022	✓	✓	✓	✓	✓	✓
Vallejos 2021	✓	✓	✓	✓	✓	✓

Popp et al., 21 Jun 2022, preprint, 10 authors.

Table from https://c19ivm.org/popp2.html as of October 29, 2022.

The results of the ACTIV-6 (Accelerating COVID-19 Therapeutic Interventions and Vaccines) Trial of Ivermectin 400 has been published after peer-review (4). Sadly, even a cursory view of this paper reveals several shortcomings of methodology and statistical analysis that negatively impact the authors' interpretations. Some of these shortcomings are:

1. The treatment drug in the Ivermectin 400 arm, was under-dosed.
    a. The doses were approximated on patient bodyweight ranges to accommodate for dose per tablet. People at the upper end of the weight range would be under-dosed for the variants circulating at the time.
    b. Maximum dose of ivermectin was capped, leaving patients over 88 kg (44% of participants) in receipt of inadequate dosing. This was even more problematic for obese patients, because IVM is lipophilic and distributes into fat tissue leaving less drug available for therapeutic effect.
    c. Authors instructed patients to take IVM on an empty stomach—*"Ivermectin should be taken on an empty stomach with water"* (protocol section 16.3.3). Taking IVM on an empty stomach is suitable for treatment of intestinal parasites but not systemic diseases because IVM is lipophilic and administration with a fatty meal facilitates absorption.
    d. IVM following a high-fat meal has resulted in ~2.5-fold higher bioavailability relative to administration in the fasted state (5).
    e. The lead author of the ACTIV-6 trial acknowledged that there is supporting evidence in the clinical literature for the use of higher doses of IVM. At the 47:57-minute mark of the presentation available in reference (6) she states that, "*when we looked at the data, frankly we thought it justified a study with a higher dose*" (6). As such, a second IVM arm was introduced in the study of 0.6 mg/kg/day for 6 days.

2. Delayed or no treatment.
   ET (≤5 days following symptom onset) is recognized as a key component for the successful management of C19. Table 1 of the JAMA publication (4) summarizing the baseline characteristics of the ACTIV-6 Trial, shows that treatment was not started until a median time of 6 days following symptom onset (typically Days 5-8 for the IVM arm and Days 4-7 for the placebo arm) (4). Moreover, some patients did not receive their treatment for as long as two weeks after symptom onset, thereby negating the potential benefit of early treatment that could have prevented progression to the more severe inflammatory phase of the illness that would require a more aggressive treatment regime.

   In her grand rounds presentation (6), Dr. Naggie acknowledges, at minute 21:15 of her summary presentation (6), that the one patient who died in the treatment arm had, in fact, not received their medication. Of additional concern is that "*participants had already consented to participate but had not received study drug, and these participants continued in their assigned study group"* (4). Allocating patients to a treatment group when they in fact did not receive treatment skews the results in favour of the placebo group.

3. Monotherapy
   COVID-19 is a multifaceted disease with recognized treatment protocols using multi-drug regimens based on addressing the known underlying physiologic disease mechanisms. In ACTIV-6, IVM was used as a monotherapy.

4. Participants in the treatment arm were sicker than those in the placebo arm.
   The Supplemental Online Content Table 1 indicates that a higher proportion of patients assigned to the treatment group experienced severe shortness of breath (dyspnea) compared to the patients assigned to the placebo group (7).

5. Preprint results show benefit for the IVM treatment arm.
   Despite these methodological concerns, a benefit for the treatment arm was reported in the study's preprint. Bayesian statistical analysis was used and Table 2 shows a treatment benefit of 97% and 98% probabilities on days 7 and 14, respectively (8).

6. Conflict of Interest.
   The study was funded by the USA National Institutes of Health (NIH), which is involved in public-private partnerships with numerous pharmaceutical companies. The lead authors received funding from pharmaceutic companies, including those that make patented antiviral treatments for C19.

The TOGETHER trial, published in the New England Journal of Medicine in March, 2022, was a large randomized control trial whose IVM arm has been used by vested interests as conclusive evidence against the use of IVM in C19 (9). Of the many shortcomings identified, the ivermectin dosage regimen is very problematic; 0.4 mg/kg/day for three days on an empty stomach is clearly inadequate for the reasons described above. Moreover, the trial was conducted in an area of Brazil where IVM was freely available to control subjects via over-the-counter sales. Even with these design flaws that would deter the detection of positive impacts of IVM treatment, the data nestled in the supplemental section actually still supported the validity of IVM use in C19. A full critique of

this IVM study has been written by Halgas (10). The TOGETHER trial's lead authors also receive funding from pharmaceutic companies, including those that would financially gain from a preferential marketing and sale of patented antiviral treatments for C19. Regretfully, the public pronouncement of the failure of the IVM arm of the TOGETHER trial was made several months before the altered and flawed methodology of the study was revealed at the time of publication (9).

Most recently, in early January 2023, MedinCell Pharmaceutical released the data from their SAIVE study (NCT 05305560) that was conducted from March until November 2022 (11). This was a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group clinical study, evaluating the safety and efficacy of ivermectin tablets taken orally for 28 days (200 µg/kg on day 1 then 100 µg/kg daily until day 28). The study targeted unvaccinated adults who had been exposed to the virus within 5 days of screening after documented close contact with a person who had a PCR-confirmed SARS-CoV-2 infection. Participants in the ivermectin group showed no signs of drug safety concerns and experienced a significant 72% reduction in laboratory-confirmed infections (30/200) versus placebo (105/199), $p<0.0001$. This most recent evidence of ivermectin's significantly favourable level of protection against SARS-CoV-2 infection, especially during the highly-transmissible Omicron-circulation phase of the pandemic, supports the Canadian Covid Care Alliance's position that medical and pharmacy colleges should not be barring their members from considering the off-label use of ivermectin in a multifaceted C19-prevention and early treatment toolbox.

B. SAFETY FOR TARGETED POPULATION

PAXLOVID™

In Canada, Paxlovid™ is recommended only for patients who are at high risk of progressing to serious COVID-19 disease, hospitalization or death. Administration must begin within five days of symptom onset. The Canadian Covid Care Alliance has written a detailed evaluation of Paxlovid™ including multiple references (12).

The EPIC-HR study, which has been used to justify Paxlovid™ in C19, comprised mostly participants who were not at high risk of developing severe illness (13). In a February 23, 2022 document, the Ontario Science Table raised this concern, stating "*young age and lack of details on concomitant medication use limit study generalizability*" (14). Further, the study included only non-vaccinated patients, not the vaccinated who now comprise the vast majority of the Canadian population (15).

Currently no long-term safety data for Paxlovid™ are available as clinical trials have been too short to allow for this. The Canadian health professional risk communication from January 17, 2022 cautioned that as Paxlovid™ is still being studied '*'it is possible that all the side effects are not known at this time*." The July 6, 2022 update continues to warn that "*Paxlovid™* ***may interact with various medications, which could result in serious or life-threatening adverse reactions, or a loss of therapeutic effect"*** *(*16).

A recent Cochrane Review (Reis *et al.,* September 2022) found only low- to moderate-certainty evidence that nirmatrelvir/ritonavir is safe in people without prior or concomitant therapies including medications highly dependent on CYP3A4 17). The Paxlovid™ monograph substantiates these

concerns, including significant risk for potential harms in compromised individuals or populations that were absent or insufficiently studied in clinical trials (18). This includes subjects with liver impairment, renal impairment, pregnancy or lactation, elevated risk of carcinogenicity, elevated risk of genotoxicity.

Additional safety concerns are significant given the current recognized number of drug interactions for Paxlovid™. This is addressed in a recent report of the Ontario Science Table with over 160 concerns (Appendix 3).

The WHO VigiAccess database shows over 20,000 reported adverse events for Paxlovid™ as of October 28, 2022. Note that this is based on less than one year of reporting, in sharp contrast with IVM, which has fewer than 7000 reported events after over 35 years of use.

IVERMECTIN

Unlike Paxlovid™, IVM has been used internationally for decades, affording the accumulation of a large amount of data related to its potential for toxicity in human use. In March 2021, Dr. Jacques Descotes published an extensive analysis addressing the toxicity potential of this drug (19).

The overall summary comments: ‘’*Safety analysis of >350 articles showing that ivermectin has an excellent safety profile*.” The author notes that "*no severe adverse event has been reported in dozens of completed or ongoing studies involving thousands of participants worldwide to evaluate the efficacy of ivermectin against COVID-19*”(19).

Further key findings from the Descotes report include:
- Mild to moderate adverse effects have been infrequent and temporary;
- More severe neurological complications are possible, but rare, and affect susceptible individuals, especially those with a severe parasitic disease;
- Serious adverse events relate mainly to the body’s efforts to rid itself of an overwhelming parasite load as a result of IVM’s therapeutic effects—rather than any potential drug toxicity;
- IVM safety has been confirmed with its long history of therapeutic use, spanning over 30 years.

Dr. Descotes added this statement of particular interest: “*The often-reiterated claim, even today, that ivermectin can be lethal in treated patients only rests on a one-page correspondence to the Lancet published in 1997. This claim is deemed to be unfounded as it has never been further substantiated until today and instead, subsequent publications repeatedly showed this claim was either incorrect or methodologically inaccurate. … No severe adverse reactions have seemingly so far been described in relation to off-label studies or clinical trials of ivermectin as a potential prophylactic or curative treatment of COVID-19”* (19).

There are many additional resources pointing to extensive IVM safety data:
- IVM has been an approved medication internationally for human use for decades. It continues to be listed on the WHO list of essential medications (20).
- Safety data of standard doses of IVM is widely established; safety of doses up to 10 times the highest FDA approved dose of 200 µg/kg have been well tolerated (21).
- Adverse events, if they occur, are typically non-severe (22,23).
- The ACTIV-6 and TOGETHER trial data found no concerns with safety in their IVM arms. (4,9)
- The reporting of adverse events has remained extremely stable for IVM in VigiAccess® over these past two years, despite the additional use of millions of doses for SARS-CoV-2 across the

globe. The number of adverse event reports for IVM was less than 7,000 as of October 23, 2022 cumulative since 1992. This represents approximately 4 billion doses administered worldwide over 30 years. In contrast, paracetamol/acetaminophen (a drug that has been recommended for C19 pain) has more than 175, 000 adverse drug reaction records as of the same date. The C19 vaccines (in less than 2 years) have already garnered well over 4.5 million adverse drug reaction records (24).

Drug Interactions; Limitations of Use in Specific Populations

- In terms of drug interactions, the Stromectal® (ivermectin) monograph outlines limited impact of IVM on common hepatic detoxification pathways and states, "*The findings of in vitro studies using human liver microsomes suggest that clinically relevant concentrations of ivermectin do not significantly inhibit the metabolizing activities of CYP3A4, CYP2D6, CYP2C9, CYP1A2, and CYP2E1*"(25).
- Use of IVM in some populations remains cautionary. This includes pregnancy, breastfeeding, paediatric patients less than 15 kg, and geriatric patients (25).

C. EFFICACY

i. Impact on viral load/transmission

PAXLOVID™

Prevention of transmission of SARS-CoV-2 was not included in the EPIC-HR study, and there was no measurable difference in the viral load between the placebo and treatment group at the end of the study, as shown below in Figure 3A of the study publication (13). As such, any suggestions regarding an impact on transmission of clinical significance cannot be supported.

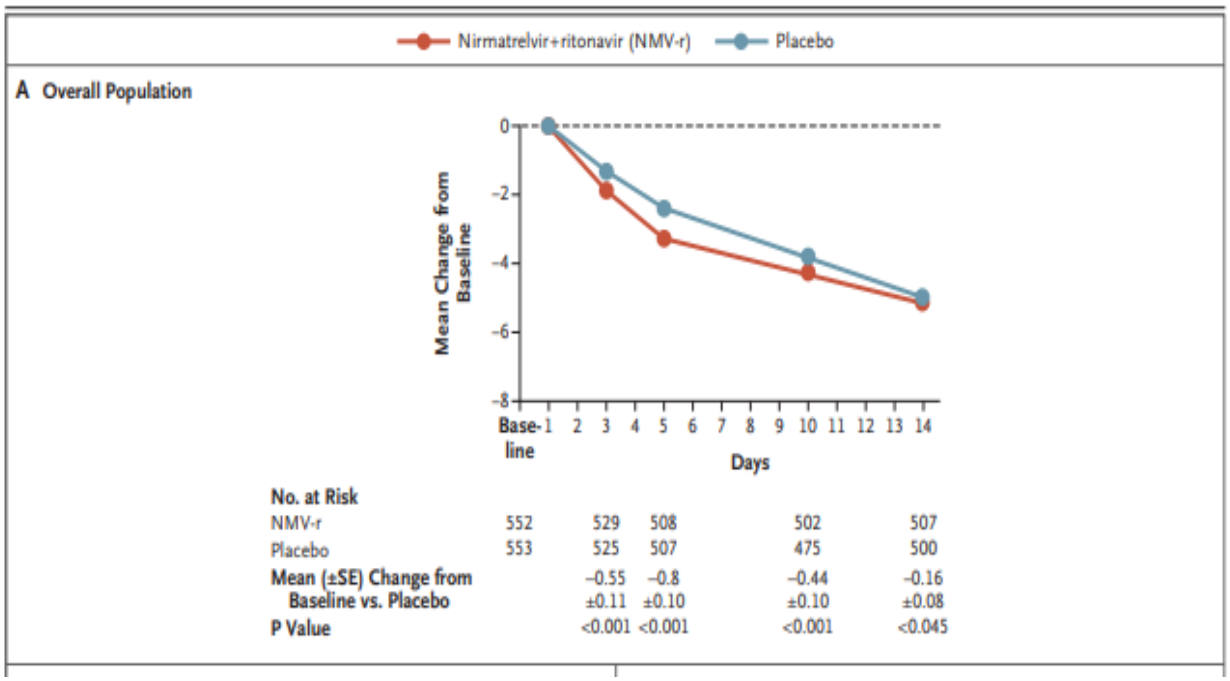


Figure 3A from the EPIC-HR study.

IVERMECTIN

IVM continues to demonstrate efficacy for clearance of the virus in both early and late treatment interventions. A summary calculation of IVM in C19 viral clearance revealed a mean 42% improvement (Appendix 4).

ii. Symptom reduction

PAXLOVID™

Paxlovid™ has not demonstrated improvement of C19 symptoms. In the EPIC-HR study, symptomatic improvement was measured but not reported (13). Similarly, the interim analysis of the EPIC-SR study revealed that '*the novel primary endpoint of self-reported sustained alleviation of all symptoms for four consecutive days as compared to placebo, was not met*" (15).

IVERMECTIN

IVM has continued to show positive impact on symptom reduction (26).

iii. Reduction in disease severity

PAXLOVID™

In the EPIC-HR study, Paxlovid™ was reported to dramatically lower the combined outcome of COVID-19 related hospitalizations or death compared to placebo when expressed as a relative risk reduction of 88.9% (13). However, these results are far less impressive when expressed as an absolute risk reduction of less than 6%. A recent Cochrane Review (Sep 2022) concluded only low-certainty evidence that nirmatrelvir/ritonavir reduces the risk of all-cause mortality and hospital admission or death, and this was in unvaccinated patients (27).

IVERMECTIN

IVM continues to be studied across a range of C19 indications, including impact on severity. For example, Akhtar *et al*. have shown that IVM reduced progression of C19 and reduced death (28).

D. MECHANISM OF ACTION

Several mechanisms of action are recognized to contribute to antiviral activity of drugs:

1. Inactivation of extracellular virus particles;
2. Prevention of viral attachment and/or entry into host cells;
3. Prevention of replication of the viral genome;
4. Prevention of synthesis of specific viral protein(s); and
5. Prevention of assembly or release of new infectious virions (29).

PAXLOVID™

Paxlovid™ is classified as a protease inhibitor, understood to prevent cellular SARS CoV-2 replication through inhibition of the SARS-CoV-2 3CL-like protease, which is critical for viral replication. It is considered to have 2000-times the potency of IVM for direct inhibition of the SARS-CoV-2 protease enzyme and appears to be the only known mechanism of action (30).

IVERMECTIN

IVM has significant additional mechanisms of action including: preventing entry of the virus into the cell, anti-inflammatory actions, and additional actions to prevent viral replication and prevention of the complications of the infection. In particular, the anti-inflammatory actions of IVM (notably in the ability to dampen the activity of two major inflammatory cytokines TNFa and IL-6) are critical to reducing the destructive cytokine storm; the severity of which is critical phase in determining disease severity and recovery (31).

IVM is understood to possess antiviral activity by targeting four key mechanisms via 20 unique actions (29):

Direct action on SARS-CoV-2
- Level 1: Action on SARS-CoV-2 cell entry.
- Level 2: Action on importin (IMP) superfamily.
- Level 3: Action as an ionophore.

Action on host targets important for viral replication
- Level 4: Action as an antiviral.
- Level 5: Action on viral replication and assembly.
- Level 6: Action on posttranslational processing of viral polyproteins.
- Level 7: Action on karyopherin (KPNA/KPNB) receptors.

Action on host targets important for inflammation
- Level 8: Action on interferon (INF) levels.
- Level 9: Action on Toll-like receptors (TLRs).
- Level 10: Action on nuclear factor-κB (NF-κB) pathway.
- Level 11: Action on the JAK-STAT pathway, PAI-1.
- Level 12: Action on p21-activated kinase 1 (PAK1).
- Level 13: Action on interleukin-6 (IL-6) levels.
- Level 14: Action on allosteric modulation of P2X4 receptor.
- Level 15: Action on high mobility group box 1 (HMGB1).
- Level 16: Action as an immunomodulator on lung tissue.
- Level 17: Action as an anti-inflammatory.

Action on other host targets
- Level 18: Action on plasmin and annexin A2.
- Level 19: Action on CD 147 on the red blood cell (RBC).
- Level 20: Action on mitochondrial ATP under hypoxia on cardiac function.

The direct “antiviral targets” may be useful in the early stages while the anti-inflammatory targets might be addressed in the later stages of the disease.

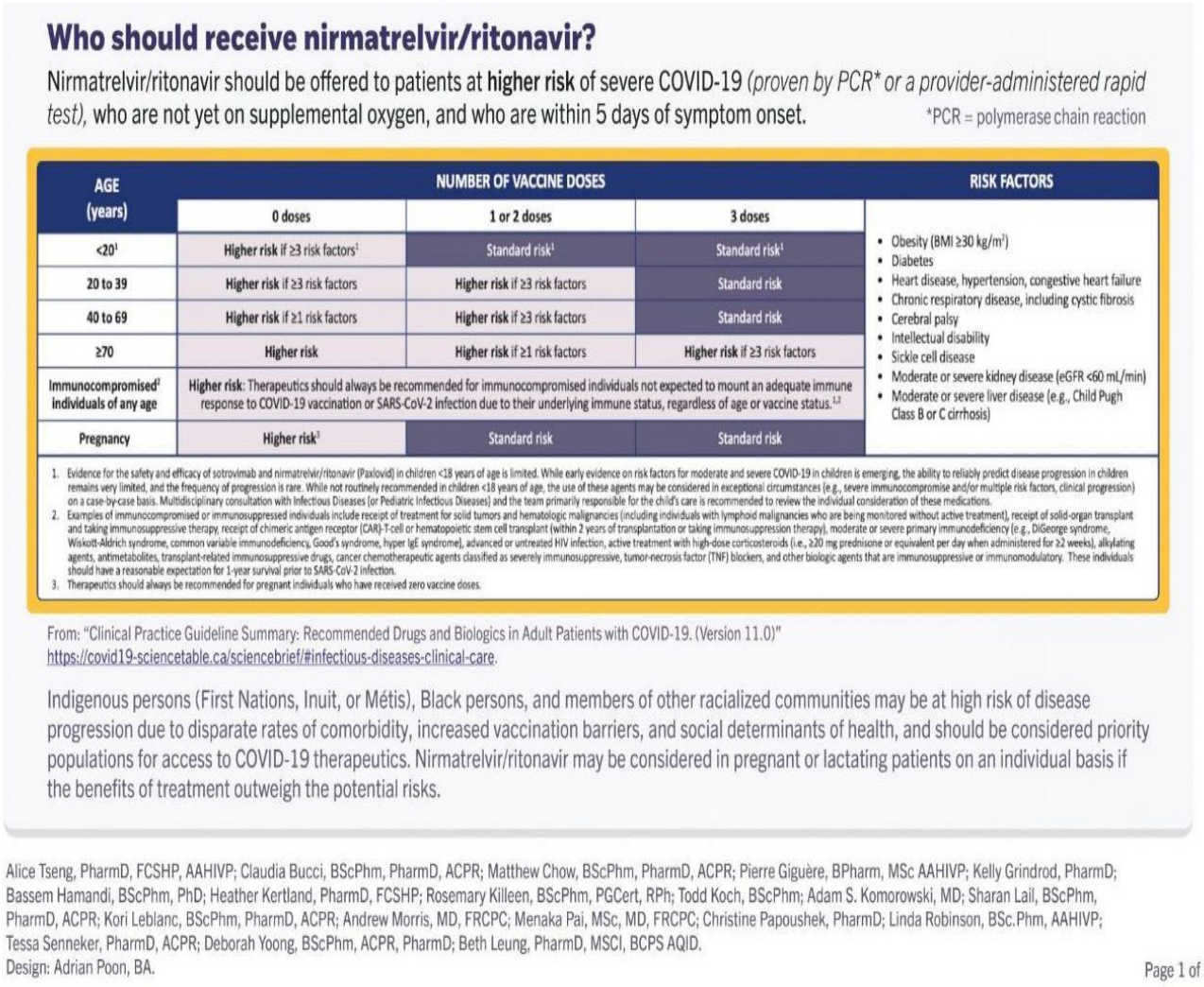
E. CRITERIA FOR USE

PAXLOVID™

Current indications for Paxlovid™ use are in those considered of higher risk of severe disease. Current Science Table recommendations outline specific criteria for use in Ontario but parallels other provincial recommendations (32).

Factors that contribute to higher risk classification include: age ≥ 60 years; body mass index (BMI) >25 kg/m^2; diabetes; chronic kidney disease; hypertension; current smoker; immunosuppressive disease or prolonged use of immune-modulating medications; chronic lung disease; cerebrovascular disease; neurodevelopmental disorders; genetic or metabolic syndromes; severe congenital abnormalities; active cancer (14).

As described previously, there are a large number of potential drug interactions with Paxlovid™; this is concerning because populations for which Paxlovid is indicated are most likely to be the subjects of polypharmacy.



Who should receive nirmatrelvir/ritonavir?

Nirmatrelvir/ritonavir should be offered to patients at **higher risk** of severe COVID-19 *(proven by PCR* or a provider-administered rapid test),* who are not yet on supplemental oxygen, and who are within 5 days of symptom onset.

*PCR = polymerase chain reaction

AGE (years)	NUMBER OF VACCINE DOSES			RISK FACTORS
	0 doses	1 or 2 doses	3 doses	
<20[1]	**Higher risk** if ≥3 risk factors[1]	Standard risk[1]	Standard risk[1]	• Obesity (BMI ≥30 kg/m^2) • Diabetes • Heart disease, hypertension, congestive heart failure • Chronic respiratory disease, including cystic fibrosis • Cerebral palsy • Intellectual disability • Sickle cell disease • Moderate or severe kidney disease (eGFR <60 mL/min) • Moderate or severe liver disease (e.g., Child Pugh Class B or C cirrhosis)
20 to 39	**Higher risk** if ≥3 risk factors	**Higher risk** if ≥3 risk factors	Standard risk	
40 to 69	**Higher risk** if ≥1 risk factors	**Higher risk** if ≥3 risk factors	Standard risk	
≥70	**Higher risk**	**Higher risk** if ≥1 risk factors	**Higher risk** if ≥3 risk factors	
Immunocompromised[2] individuals of any age	**Higher risk**: Therapeutics should always be recommended for immunocompromised individuals not expected to mount an adequate immune response to COVID-19 vaccination or SARS-CoV-2 infection due to their underlying immune status, regardless of age or vaccine status.[1,2]			
Pregnancy	**Higher risk**[3]	Standard risk	Standard risk	

1. Evidence for the safety and efficacy of sotrovimab and nirmatrelvir/ritonavir (Paxlovid) in children <18 years of age is limited. While early evidence on risk factors for moderate and severe COVID-19 in children is emerging, the ability to reliably predict disease progression in children remains very limited, and the frequency of progression is rare. While not routinely recommended in children <18 years of age, the use of these agents may be considered in exceptional circumstances (e.g., severe immunocompromise and/or multiple risk factors, clinical progression) on a case-by-case basis. Multidisciplinary consultation with Infectious Diseases (or Pediatric Infectious Diseases) and the team primarily responsible for the child's care is recommended to review the individual consideration of these medications.
2. Examples of immunocompromised or immunosuppressed individuals include receipt of treatment for solid tumors and hematologic malignancies (including individuals with lymphoid malignancies who are being monitored without active treatment), receipt of solid-organ transplant and taking immunosuppressive therapy, receipt of chimeric antigen receptor (CAR)-T-cell or hematopoietic stem cell transplant (within 2 years of transplantation or taking immunosuppression therapy), moderate or severe primary immunodeficiency (e.g., DiGeorge syndrome, Wiskott-Aldrich syndrome, common variable immunodeficiency, Good's syndrome, hyper IgE syndrome), advanced or untreated HIV infection, active treatment with high-dose corticosteroids (i.e., ≥20 mg prednisone or equivalent per day when administered for ≥2 weeks), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, tumor-necrosis factor (TNF) blockers, and other biologic agents that are immunosuppressive or immunomodulatory. These individuals should have a reasonable expectation for 1-year survival prior to SARS-CoV-2 infection.
3. Therapeutics should always be recommended for pregnant individuals who have received zero vaccine doses.

From: "Clinical Practice Guideline Summary: Recommended Drugs and Biologics in Adult Patients with COVID-19. (Version 11.0)"
https://covid19-sciencetable.ca/sciencebrief/#infectious-diseases-clinical-care.

Indigenous persons (First Nations, Inuit, or Métis), Black persons, and members of other racialized communities may be at high risk of disease progression due to disparate rates of comorbidity, increased vaccination barriers, and social determinants of health, and should be considered priority populations for access to COVID-19 therapeutics. Nirmatrelvir/ritonavir may be considered in pregnant or lactating patients on an individual basis if the benefits of treatment outweigh the potential risks.

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Design: Adrian Poon, BA.

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Figure from the Ontario Science Table recommendations as of October 29, 2022 (32).

IVERMECTIN

IVM has been approved in Canada since 2018 for parasitic infections and its use for multiple phases of C19 continues to show extensive and supportive data. See https://c19ivermectin.com/ for a list of 186 studies as of October 29, 2022.

F. PREVENTION/TREATMENT OF LONG COVID

PAXLOVID™

There is no evidence to show that Paxlovid™ prevents or treats Long Covid-19 based on available study results. Long Covid-19 was not included in the primary endpoints of either the EPIC-HR or the EPIC-SR studies (13,15).

IVERMECTIN

In comparison to Paxlovid™, IVM has shown extensive efficacy in treatment and prevention of Long Covid-19 (33). Please also see Appendix 6 for a summary of IVM studies.

G. ECONOMIC COSTS AND GLOBAL MILIEU

PAXLOVID™

As described previously, the cost of treatment using Paxlovid is at least 1,000 times that of IVM. Considering this, and the superior pharmacology of IVM, it is unsurprising that IVM is a much more widely used drug internationally. IVM use for ET in C19 remains restricted throughout Canada. This is disconcerting, particularly when over a year ago two US states (Nebraska and Louisiana) had already recognized the importance of IVM in treatment and/or prevention of C19 (34,35).

IVERMECTIN

Global use of IVM has exploded, with more than half of the states in the USA now recognizing IVM for ET in C19 (36), as well as an array of regions around the world, including: South America, Japan, India and the European countries of Germany, Portugal, Ukraine and Slovakia. The figure below outlines global use as at May 2022—44% of countries and 28% of the world population.

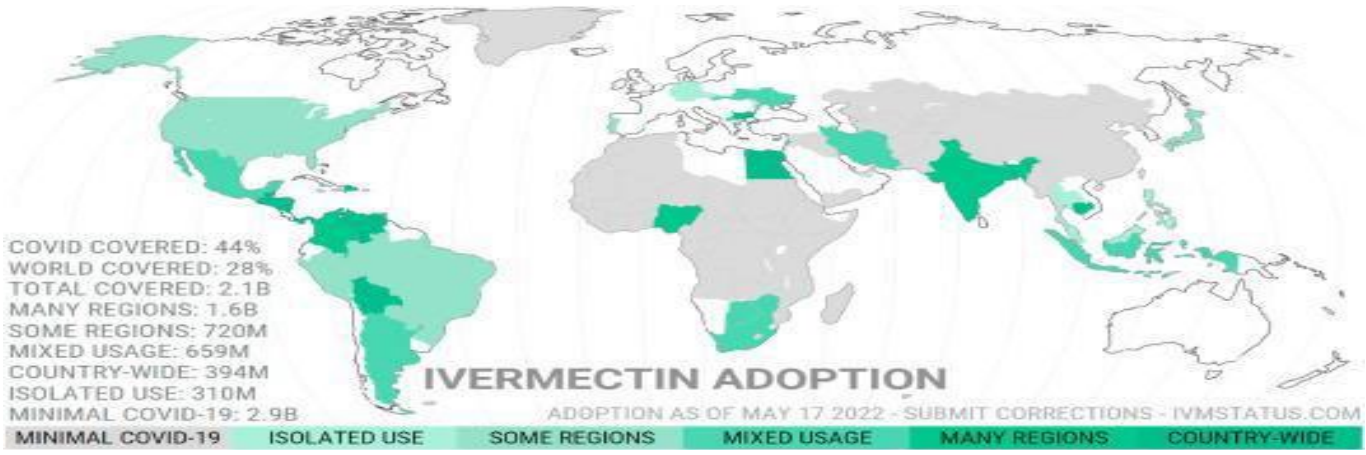

Figure from https://c19early.org/adoption.html as of October 29,2022.

CONCLUSION

With numerous Canadians still becoming ill with C19, large gaps in patient care remain when Paxlovid™ is the only available early outpatient treatment option. Those who cannot receive Paxlovid™ should be offered comparable or superior treatment options.

As we have outlined, the evidence supporting IVM has well exceeded that for Paxlovid™. It follows that IVM should be provided a place in C19 therapy equal to or greater than that of Paxlovid™. Moreover, the safety data shows that IVM is far safer than Paxlovid™. It is high risk patients that most require early treatment—and urgently— and yet many may not be candidates for Paxlovid™ due to concerns around hepatic and renal function, in addition to the extensive drug interactions.

Paxlovid™ has many additional disadvantages ranging from increased risk of toxicity, to overly stringent criteria for acceptance, to a plethora of potential drug interactions. In the face of this, Canadians require alternatives. The obvious alternative is IVM. We have outlined its efficacy and safety above, not to mention its orders of magnitude lesser cost.

The Colleges' reticence to accepting IVM (or other similar re-purposed drugs) for the ET of C19 has been catastrophic. Based on the effectiveness of IVM when used by numerous healthcare professionals and jurisdictions internationally, we suggest that thousands of C19-caused deaths in Canada could have been obviated. Specifically, deaths caused by C19, not simply deaths of persons with a positive C19 test result. Any further delays in facilitating the use of IVM by Canadian healthcare professionals is unethical; some may even consider it negligent. In any case, we ask that you reconsider your position vis-a-vis IVM and give full approval for pharmacists and doctors to dispense and prescribe this life-saving drug. Quoting Fordham *et al.,* "*The responsible physician knows that 'first do no harm' does not mean: 'do nothing'. Doing nothing, especially for the high-risk patient, is unacceptable. It is lethal folly to withhold a safe medicine that, when viewing the totality of the evidence, shows great promise at negligible cost. Such policies effectively deny to dedicated clinicians the ability to practice medicine"* (3).

We are aware that the objective of the college is to support quality practice and patient safety as well as promote patient-centered, collaborative health care that best uses the skills and knowledge of all health care professionals. Further, the Health Minister of Canada has stated: *"Healthcare practitioners may prescribe drugs, including ivermectin, outside of their authorized indications (also known as "off-label use"), based on other sources of information, such as medical literature. Off-label use falls under the practice of medicine and is regulated at the provincial and territorial level. Heath Canada has no jurisdiction over how health care professionals prescribe drugs once authorized*" (37). With this in mind, we suggest that the time is now to re-focus on patient-centred healthcare, and to utilize all the skills of our professionals.

The CCCA awaits your response to this important and urgent call for action.

Canadian Covid Care Alliance
Alliance canadienne pour la prévention et prise-en-charge de la covid

Sincerely,

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About the Canadian Covid Care Alliance

The Canadian Covid Care Alliance (CCCA) is a volunteer-run organization with over 700 Canadian physicians, researchers, healthcare practitioners, and legal & ethics professionals. These include virologists, vaccinologists, immunologists, psychologists, coroners, medical ethicists, medical doctors from a variety of specialities, professors from Canadian universities, allied healthcare professionals, and lawyers from across Canada. There are hundreds of additional members with diverse areas of expertise beyond healthcare and medical sciences. The Alliance is dedicated to providing balanced, scientific evidence-based information related to the prevention, tracking and treatment of COVID-19 so that hospitalizations can be reduced, lives saved, and our country safely restored as quickly as possible.

Our representative credentials and expertise within our Alliance include, but are not limited to, the following:

MD, Family Practitioner	PhD, Immunogenetics	PhD, Epidemiology	Chiropractic
MD, Coroner	PhD, Immunology	EdD, Psychology	Integrative Medicine
RN, Primary Care	PhD, Molecular Virology	DPhil, Bioanalytics	Pharmacy
PhD, Biomedical Research	PhD, Viral Immunology	PhD, Methodology	Physiotherapy
Doctor of Dental Surgery	PhD, Pharmacology	PhD, Ethics	Naturopathy
Doctor of Veterinary Medicine	PhD, Biochemistry	LL.B., B.B.A, Personal Injury	Occupational Therapy

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APPENDICES

Appendix 1. Global adoption of early treatments.
Appendix 2. Ivermectin improvement in C19—92 studies
Appendix 3. Paxlovid™ drug interactions
Appendix 4. Viral clearance by ivermectin.
Appendix 5. Chance of ivermectin being ineffective for C19 is 1 in 103 billion.
Appendix 6. Summary of ivermectin studies.

APPENDICES

Appendix 1. Global adoption of early treatments.

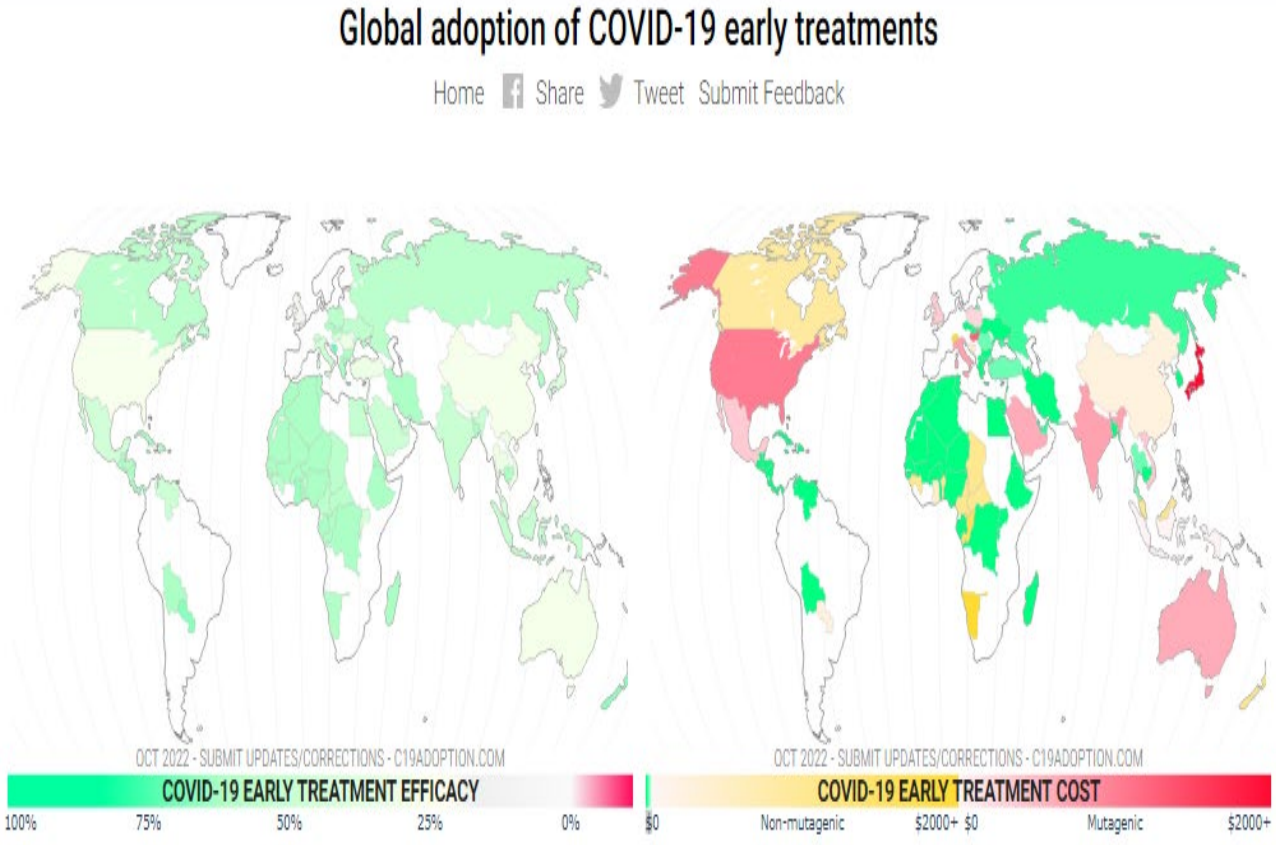

Figure from https://c19early.org/adoption.html as of October 29, 2022.

Appendix 2. Ivermectin improvement in C19—92 studies

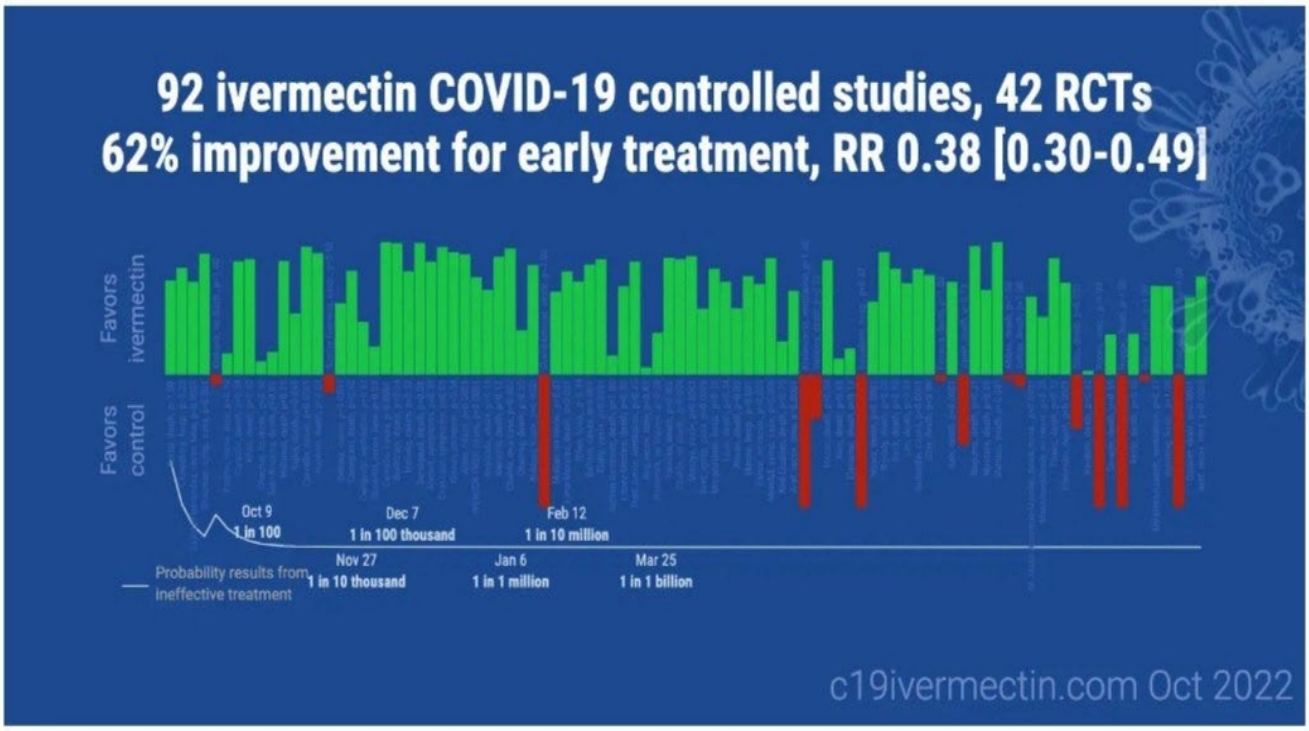

Figure from c19ivermectin.com as of October 29, 2022.

Appendix 3. Paxlovid™ drug interactions.

June 6, 2022

Nirmatrelvir/Ritonavir (*Paxlovid*) Drug Interactions:

This is not an exhaustive list. Consultation with a pharmacist who can obtain a complete medication, recreational, and natural health product history from the patient is recommended prior to prescribing nirmatrelvir/ritonavir.

Symbol	Severity	Recommendation	Rationale
▲	Contraindicated	Use alternative COVID agent. **Do not use nirmatrelvir/ritonavir.**	Stopping the drug will not mitigate the interaction (e.g., prolonged half-life, narrow therapeutic index, prolonged enzyme-inducing effects which may decrease effectiveness of nirmatrelvir/ritonavir). Do not coadminister due to risk of serious toxicity.
◬	Contraindicated (use within past 14 days)		
●	Do not coadminister	Hold and restart 2 days after completing nirmatrelvir/ritonavir.	Significant ↑ in drug concentrations expected. Do not coadminister due to risk of serious toxicity.
◆	Caution	Therapy modification required (see Appendix).	Significant ↑/↓ in drug concentrations expected, which may lead to serious toxicity or impaired efficacy. Only coadminister if the interacting drug can be safely held or dose-adjusted and closely monitored (see Appendix). Expert consultation may be useful.
✓	Drug interaction not likely to be clinically relevant	Continue with standard dosing.	Although mentioned in the monograph, clinically relevant interaction is not anticipated (e.g., minimal impact on certain metabolic pathways, wide therapeutic index, and short course of nirmatrelvir/ritonavir).

- ◆ Abemaciclib (*Verzenio*)
- ● Alfuzosin (*Xatral*)
- ◆ Alprazolam (*Xanax*)
- ▲ Amiodarone
- ✓ Amitriptyline
- ◆ Amlodipine (*Norvasc*)
- ◬ Apalutamide (*Erleada*)
- ◆ Apixaban (*Eliquis*)
- ◆ Aripiprazole (*Abilify*), oral
- ◆ Atorvastatin (*Lipitor*)
- ✓ Atovaquone
- ▲ Bosentan (*Tracleer*)
- ● Bosutinib (*Bosulif*)
- ◆ Brexpiprazole (*Rexulti*)
- ✓ Budesonide
- ✓ Bupropion
- ◆ Buspirone (*Buspar*)
- ◬ Carbamazepine (*Tegretol*)
- ◆ Ceritinib (*Zykadia*)
- ● Cisapride
- ✓ Citalopram
- ✓ Clarithromycin
- ✓ Clomipramine
- ● Clonazepam
- ◆ Clopidogrel (*Plavix*)
- ● Clorazepate
- ▲ Clozapine (*Clozaril*)
- ● Cobimetinib (*Cotellic*)
- ● Colchicine in renal/hepatic impairment
- ◆ Cyclosporine (*Neoral*)
- ◆ Dabigatran
- ◬ Dabrafenib (*Tafinlar*)
- ◆ Dasatinib (*Sprycel*)
- ◆ Dexamethasone, high dose
- ● Diazepam (*Valium*)
- ◆ Digoxin
- ◆ Diltiazem (*Tiazac, Cardizem*)
- ✓ Divalproex
- ● Dofetilide
- ✓ Dronabinol
- ▲ Dronedarone (*Multaq*)
- ◆ Edoxaban (*Lixiana*)
- ◆ Elagolix (*Orilissa*)
- ◆ Encorafenib (*Braftovi*)
- ◬ Enzalutamide
- ● Ergot alkaloids (e.g., dihydroergotamine, ergonovine)
- ◬ Eslicarbazepine
- ✓ Ethinyl estradiol
- ● Everolimus (*Certican*)
- ◆ Felodipine
- ▲ Fentanyl (*Duragesic*)
- ▲ Flecainide
- ✓ Fluoxetine
- ● Flurazepam
- ✓ Fluvoxamine
- ◆ Fostamatinib (*Tavalisse*)
- ✓ Fusidic acid, topical
- ● Glecaprevir/Pibrentasvir (*Maviret*)
- ◆ Hydrocodone
- ● Ibrutinib (*Imbruvica*)
- ✓ Imipramine
- ✓ Itraconazole
- ✓ Ketoconazole
- ✓ Lamotrigine
- ● Lomitapide (*Juxtapid*)
- ◬ Lorlatinib (*Lorbrena*)
- ● Lovastatin
- ▲ Lurasidone (*Latuda*)
- ✓ Maprotiline
- ✓ Maraviroc
- ● Meperidine (*Demerol*)
- ✓ Methamphetamine
- ✓ Metoprolol
- ● Midazolam, oral
- ◬ Mitotane (*Lysodren*)
- ◆ Modafinil
- ● Neratinib (*Nerlynx*)
- ◆ Nifedipine
- ◆ Nilotinib (*Tasigna*)
- ● Nitrazepam (*Mogadon*)
- ✓ Nortriptyline
- ◬ Oxcarbazepine
- ◆ Oxycodone (*Percocet, OxyNEO*)
- ✓ Paroxetine
- ◬ Phenobarbital
- ◬ Phenytoin (*Dilantin*)
- ▲ Pimozide
- ◬ Primidone
- ▲ Propafenone
- ◆ Quetiapine (*Seroquel*)
- ▲ Quinidine
- ● Quinine
- ✓ Raltegravir
- ▲ Ranolazine (*Corzyna*)
- ◆ Rifabutin
- ◬ Rifampin
- ◬ Rifapentine
- ◆ Risperidone (*Risperdal*), oral
- ▲ Risperidone, long-acting injection (*Risperdal Consta*)
- ● Rivaroxaban (*Xarelto*)
- ◆ Rosuvastatin (*Crestor*)
- ● Salmeterol (*Serevent, Advair*)
- ✓ Sertraline
- ◆ Sildenafil for ED† (*Viagra*)
- ▲ Sildenafil for PAH‡ (*Revatio*)
- ● Silodosin (*Rapaflo*)
- ● Simvastatin
- ● Sirolimus (*Rapamune*)
- ▲ Sonidegib (*Odomzo*)
- ◬ St. John's wort (*Hypericum perforatum*)
- ● Tacrolimus (*Prograf, Advagraf, Envarsus*)
- ◆ Tadalafil for ED† (*Cialis*)
- ▲ Tadalafil for PAH‡ (*Adcirca*)
- ● Tamsulosin (*Flomax*)
- ▲ Tepotinib (*Tepmetko*)
- ✓ Theophylline
- ● Ticagrelor (*Brilinta*)
- ✓ Timolol
- ◆ Tramadol
- ● Triazolam (*Halcion*)
- ✓ Trimipramine
- ● Vardenafil (*Levitra*) for ED†
- ▲ Vardenafil (*Levitra*) for PAH‡
- ▲ Venetoclax (*Venclexta*)
- ✓ Venlafaxine
- ◆ Verapamil
- ◆ Vinblastine
- ◆ Vincristine
- ✓ Voriconazole
- ◆ Warfarin
- ◆ Ziprasidone (*Zeldox*)
- ◆ Zolpidem (*Sublinox, Ambien*)
- ◆ Zopiclone (*Imovane*)

Liverpool's COVID-19 **Interaction Checker**
https://www.covid19-druginteractions.org/

University Health Network & Kingston Health Sciences Centre
Paxlovid-Oncology DDI

†ED = erectile dysfunction ‡PAH = pulmonary arterial hypertension

This document is intended for use by experienced clinicians, including prescribers and pharmacists. The information is not intended to replace sound professional judgment in individual situations, and should be used in conjunction with other reliable sources of information. Clinicians should always consider the risk/benefit profile for their individual patient, discuss these risks with the patient or caregiver before initiating therapy, and closely monitor for treatment benefit and adverse effects.

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Figure from the Ontario Science Table recommendations as of October 29, 2022 (32).

Appendix 4. Viral clearance by ivermectin.

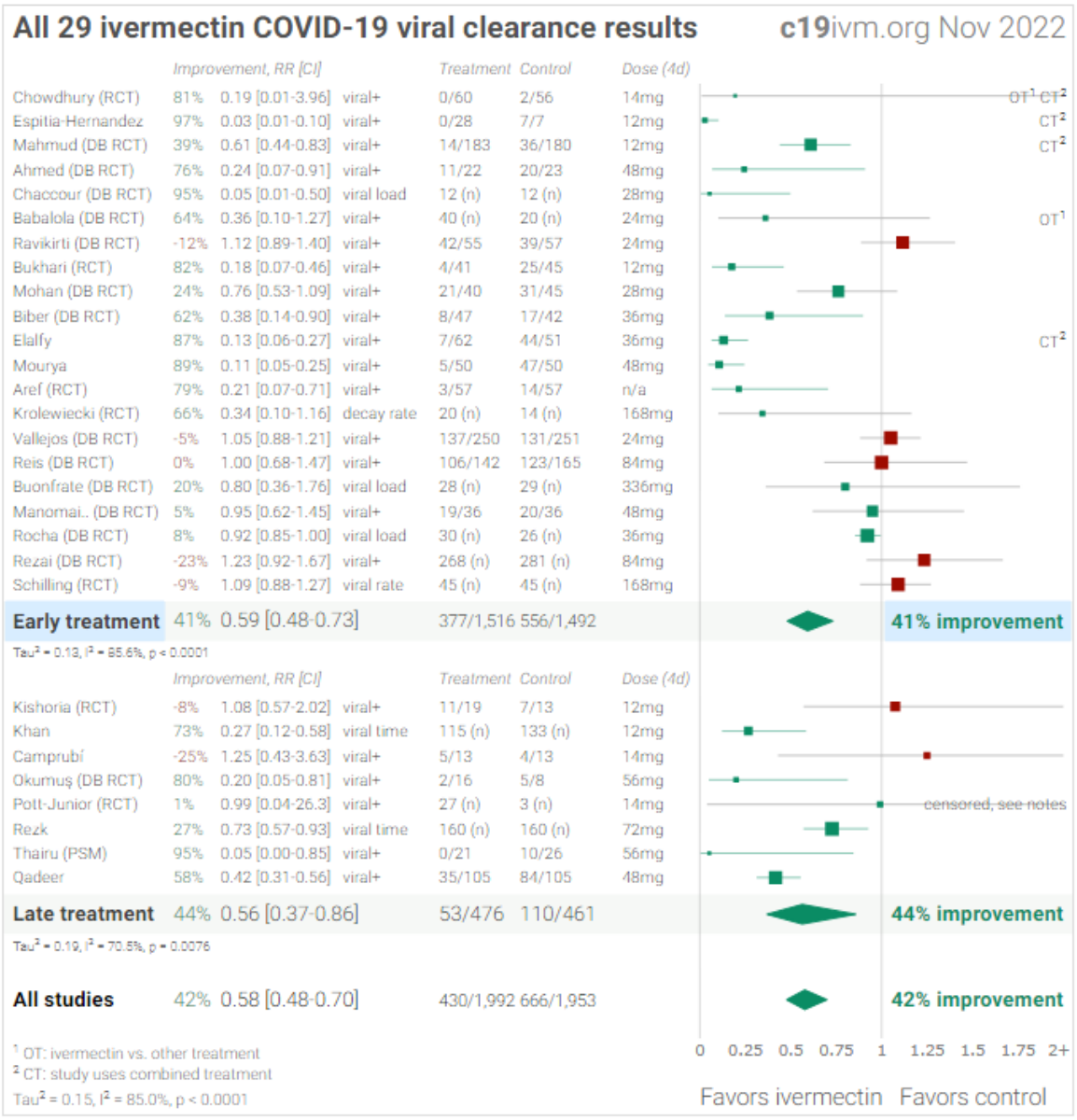

Figure 14. *Random effects meta-analysis for viral clearance.*

Figure from [c19ivm.org](c19ivm.org) as of November 1, 2022.

Appendix 5. Chance of ivermectin being ineffective for C19 is 1 in 103 billion.

Treatment time	Number of studies reporting positive effects	Total number of studies	Percentage of studies reporting positive effects	Probability of an equal or greater percentage of positive results from an ineffective treatment	Random effects meta-analysis results
Early treatment	29	37	78.4%	1 in 3 thousand	**62%** improvement RR 0.38 [0.30-0.49] p < 0.0001
Late treatment	33	40	82.5%	1 in 47 thousand	43% improvement RR 0.57 [0.45-0.72] p < 0.0001
Prophylaxis	16	16	**100%**	1 in 66 thousand	**83%** improvement RR 0.17 [0.11-0.26] p < 0.0001
All studies	78	93	83.9%	1 in 103 billion	**62%** improvement RR 0.38 [0.31-0.46] p < 0.0001

Table 1. *Results by treatment stage.*

Figure from c19ivm.org as of October 29, 2022.

Appendix 6. Summary of ivermectin studies.

	Studies	Prophylaxis	Early treatment	Late treatment	Patients	Authors
All studies	93	**83%** [74-89%]	**62%** [51-70%]	**43%** [28-55%]	134,223	1,014
Peer-reviewed	75	**83%** [73-90%]	**61%** [49-70%]	**45%** [26-59%]	123,956	834
After exclusions	62	**82%** [68-89%]	**69%** [61-76%]	**55%** [36-68%]	117,916	691
Randomized Controlled Trials	43	**84%** [25-96%]	**57%** [41-69%]	**33%** [14-47%]	11,312	612
RCTs after exclusions	34	**84%** [25-96%]	**65%** [53-74%]	**40%** [18-55%]	7,942	429

Table 2. *Results by treatment stage for all studies and with different exclusions.*

Figure from c19ivm.org as of October 29, 2022.