# ISSUE NOTE v2
# Ivermectin; STROMECTOL® (Merck & Co.)
24 June 2021

## Essential Facts

- **About the Product:** Ivermectin (Stromectol®, Mectizan®; Merck & Co.) is a broad-spectrum antiparasitic and belongs to a class of drugs called anthelmintics.
- **Method of administration:** Ivermectin is administered intravenously (I.V.) and orally in studies for the treatment of COVID-19. It is also being evaluated as a prophylaxis in oral tablet form.
- **Approved use in Canada**:
    - Ivermectin is not authorized for any COVID-19 indication in Canada.
    - Health Canada has authorized ivermectin for the treatment of parasitic infections in humans and animals. In humans, ivermectin is indicated for the treatment of intestinal strongyloidiasis and onchoceriasis, or rosacea.
- **Approved use for COVID-19 internationally**
    - In May 2020, the Peruvian Ministry of Health recommended ivermectin for the treatment of mild and severe COVID-19. The recommendation was removed in June 2020.
    - Ivermectin has not been authorized for the prevention or treatment of COVID-19 in any other jurisdiction worldwide.
- **Key benefits:** Orally administered. In small RCTs, ivermectin may reduce viral load in patients with mild-to-moderate COVID-19. However,
    - Ivermectin is generally well tolerated for its approved indications.
- **Key challenges:**
    - More robust clinical trials with larger sample sizes are needed to determine its efficacy for COVID-19. The majority of trials on ivermectin in COVID-19 were limited to small sample sizes and mixed evidence on clinical benefits.

## Status of Agreements

- **Current procurement status**: Nil
- **Current distribution status**: Nil

## Considerations (optional)

- In June 2020, the Pan American Health Organization (PAHO) released a statement for ivermectin to be used only in the context of clinical trials.
- On January 14 2021, the National Institutes of Health (NIH) issued a statement on the lack of clear benefit or harm in the use of ivermectin for the treatment of COVID-19 due to the insufficient evidence.
- On February 4 2021, Merck and Co. announced they do not support the safety and efficacy of ivermectin for the treatment of COVID-19 based on an analysis of the available data and emerging studies. Their analysis identified no scientific basis for ivermectin as a potential therapeutic from

pre-clinical studies; no meaningful evidence for clinical activity or clinical efficacy in patients with COVID-19 disease; and the lack of safety data in the majority of studies.

## Positions

**CPTG Position:** The CPTG is monitoring emerging evidence of ivermectin as a treatment for COVID-19 and will conduct a detailed review once more evidence becomes available.

**TTF Position:** Nil

**P/T Position:** As of February 2021, the British Columbia COVID-19 Therapeutics Committee and the Alberta COVID-19 Scientific Advisory Group do not recommend ivermectin for the treatment or prophylaxis of COVID-19 outside of approved RCTs.

# ANNEX

## Key Findings (RCTs, Studies)

**Ongoing RCTs:**

- There are several ongoing randomized controlled trials (RCTs) evaluating the safety and efficacy of ivermectin for the prevention or treatment of COVID-19. The majority of trials are small with less than 100 participants.
    - NCT04527211: This RCT aims to determine the effectiveness and safety of ivermectin (200mcg/kg once a week for 7 days) as prophylactic treatment against SARS-CoV-2 infection in Columbian health workers with negative RT-PCR for SARS-CoV-2 infection (N=550). **Completion date: December 16, 2020.**
    - NCT04405843: The EPIC Trial is a Ph2/Ph3 RCT that aims to evaluate the efficacy of ivermectin treatment in adult patients with mild/moderate COVID-19 (N=476). **Completion date: December 21, 2020.**
    - NCT04529525: The IVERCORCOVID19 study is a single-center RCT that aims to evaluate the use of ivermectin in adults with mild/moderate COVID-19 disease (N=500) on incidence of hospitalizations. **Estimated completion date: January 31, 2021.**

**From:** Timmerman, Karen (PHAC/ASPC)
**Sent:** 2021-01-12 10:11 AM
**To:** Beique, Lizanne (PHAC/ASPC); Marinsky, Cheryl (PHAC/ASPC); Sarwar, Elaha (PHAC/ASPC); Ha, Shalane (PHAC/ASPC)
**Cc:** Timmerman, Karen (PHAC/ASPC)
**Subject:** Daily Titles for Tuesday January 12th

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**Importance:** High

Good morning everyone,

Here are the titles for today. If you could have them in the folder asap/by 3pm that would be very helpful.

| | |
|---|---|
| Lizanne | **Absent** |
| Cheryl | **Abstract**<br>**Ravikirti, Ravi, Roy, et al(2021). Ivermectin as a potential treatment for mild to moderate COVID-19: A double blind randomized placebo-controlled trial *medRxiv*,**<br>https://www.medrxiv.org/content/10.1101/2021.01.05.21249310v1 |
| Elaha | **Potential SR**<br>**Al-Abdouh, A, Bizanti, et al(2021). Remdesivir for the treatment of COVID-19: A systematic review and meta-analysis of randomized controlled trials *Contemp Clin Trials*,**<br>https://www.sciencedirect.com/science/article/pii/S1551714421000082?via%3Dihub<br><br>**Potential SR**<br>**Garcia-Albeniz, Xabier, Del Amo, et al(2021). Systematic review and meta-analysis of randomized trials of hydroxychloroquine for the prevention of COVID-19 *medRxiv*,**<br>https://www.medrxiv.org/content/10.1101/2020.09.29.20203869v4<br><br>**Potential SR**<br>**Li, Jianbo, Liao, et al(2021). Association Between Glucocorticoids Treatment and Viral Clearance Delay in Patients with COVID-19: A Systematic Review and Meta-Analysis *Research Square prepub*,**<br>https://www.researchsquare.com/article/rs-138544/v1<br><br>**Potential SR/MA**<br>**Vrachatis, DA, Giannopoulos, et al(2021). Impact of colchicine on mortality in patients with COVID-19. A meta-analysis *Hellenic J Cardiol*,**<br>https://www.sciencedirect.com/science/article/pii/S1109966620302852?via%3Dihub<br><br>**Potential SR/MA**<br>**Han Q, Guo M, Zheng Y, et al. Current Evidence of Interleukin-6 Signaling Inhibitors in Patients With COVID-19: A Systematic Review and Meta-Analysis. Front Pharmacol. 2020 Dec 15;11:615972** |

| | |
|---|---|
| | https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7769953/pdf/fphar-11-615972.pdf |
| Shalane | Abstract<br>**Zhang, J, Rao, et al(2021). Pilot trial of high-dose vitamin C in critically ill COVID-19 patients *Ann Intensive Care*,** https://annalsofintensivecare.springeropen.com/articles/10.1186/s13613-020-00792-3 |
| Karen | **Triage all titles**<br>**Send titles to review team**<br>**Review all summaries/abstracts**<br>**Email prep and send out to MCM group** |

**From:** Cortés-Kaplan, Serena (PHAC/ASPC)
**Sent:** 2021-05-06 4:55 PM
**To:** Arthur, Jacqueline (PHAC/ASPC); Gale-Rowe, Margaret (PHAC/ASPC); Lawuyi2, Niyi (PHAC/ASPC); Marinsky, Cheryl (PHAC/ASPC); Sarwar, Elaha (PHAC/ASPC); Dave, Jaahnavi (PHAC/ASPC); Gadient, Stephan (PHAC/ASPC); Poon Young, Celisse (PHAC/ASPC); Djiometio, Joseph (PHAC/ASPC)
**Cc:** COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC)
**Subject:** COVID-19 Therapeutics Daily Updates for May 6th 2021

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Hello Everyone,

Here are the **COVID-19 Therapeutics Daily Updates for Thursday, May 6th, 2021:**

May 5th 2021: Alberta Health Services updates their recommendation on antimicrobial and immunomodulatory therapy in adult patients with COVID-19:

- **For critically ill patients** (hospitalized, ICU, requiring respiratory support): remdesivir is not recommended, dexamethasone is strongly recommended, tocilizumab is recommended and bamlanivimab is not recommended.
- **For severely ill patients** (hospitalized or ward-based): remdesivir is not recommended, dexamethasone is strongly recommended, tocilizumab is recommended and bamlanivimab is not recommended outside of approved clinical trials.
- **For mildly ill patients** (ambulatory or outpatient): remdesivir is not recommended, oral corticosteroids are not recommended, inhaled budesonide may be considered, tocilizumab is not recommended and bamlanivimab is not recommended outside of approved clinical trials.
- **Agents not recommended except for use in clinical trials:** ivermectin, lopinavir/ritonavir, baricitinib, colchicine and convalescent plasma.
- **Agents not recommended:** chloroquine or hydroxychloroquine, and interferon.

May 3rd 2021: Emergency use authorization for Baricitinib use for COVID-19 treatment in India:

- Baricitinib tablets, 1mg, 2mg and 4mg received emergency use authorization from India's national regulatory body for pharmaceuticals, The Central Drugs Standard Control Organization.
- India is currently facing a shortage of various COVID-19 therapeutics including remdesivir and tocilizumab.
- Baricitinib is marketed in Canada but is not authorized for use in COVID-19 indications. Submission to Health Canada for COVID-19 use by Eli Lilly (sponsor) is anticipated.

Have a good evening,
Serena

Serena Cortés-Kaplan
**Student Analyst | Analyste Étudiant**
(she | elle)
COVID-19 Therapeutics | thérapeutiques
CCDIC, PHAC | CLMTI, ASPC
Email: serena.cortes-kaplan@canada.ca

**From:** Gale-Rowe, Margaret (PHAC/ASPC)
**Sent:** 2021-06-04 12:48 PM
**To:** Ephrem, Bersabel (PHAC/ASPC); Arthur, Jacqueline (PHAC/ASPC)
**Subject:** Draft response: I-Mask+ Protocol for early treatment of Covid-19

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**Categories:** DO pending

I would like to offer some points of clarification to my original message.

One of the Public Health Agency of Canada's (PHAC) roles to support Canada's COVID-19 response is to acquire medications to treat COVID-19. This is to ensure that Canadians will have access to safe and effective treatments in the context of substantial global demand. PHAC monitors the emerging evidence around therapeutics to inform the decisions around procurement. Please note that PHAC does not issue recommendations as such, for or against the use of medications for COVID-19.

A manufacturer seeking market authorization will submit safety and efficacy data to Health Canada (HC). As the regulator, HC grants market authorization when it is satisfied that the benefits outweigh the potential risks. The provinces and territories have primary responsibility for decisions around choice and use of therapeutics - including for COVID-19 – within their jurisdictions. In Canada, a health care professional's decision to prescribe or use a particular drug for a labelled or off-label indication is part of the practice of medicine, which falls under the jurisdiction of provincial and territorial professional regulatory authorities.

Of note, domestic demand for ivermectin has increased this year. Ivermectin is also used to treat parasitic infections in COVID-19 patients treated with immunomodulating therapies (e.g., corticosteroids), where it can be lifesaving. This illustrates the importance of using a limited supply of a therapeutic judiciously.

Could integrate this as well from ML:

The list of applications received for drugs and vaccines for COVID-19 is available online.

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**From:** Ephrem, Bersabel (PHAC/ASPC) <bersabel.ephrem@canada.ca>
**Sent:** 2021-06-04 11:10 AM
**To:** Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>; Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>
**Subject:** RE: I-Mask+ Protocol for early treatment of Covid-19

Call me.
Bersabel

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**From:** Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>
**Sent:** 2021-06-04 11:03 AM
**To:** Ephrem, Bersabel (PHAC/ASPC) <bersabel.ephrem@canada.ca>; Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>
**Subject:** RE: I-Mask+ Protocol for early treatment of Covid-19

Can we have a quick call to discuss?

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Jacqueline Arthur, BScN, RN
(she | elle)
Senior Manager, AMR Division | Gestionnaire principale, Division de la RAM
COVID-19 Therapeutics | thérapeutiques
CCDIC, PHAC | CLMTI, ASPC
t. (613) 889-8455

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**From:** Ephrem, Bersabel (PHAC/ASPC) <bersabel.ephrem@canada.ca>
**Sent:** 2021-06-04 11:01 AM
**To:** Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>; Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>
**Subject:** FW: I-Mask+ Protocol for early treatment of Covid-19

Let's discuss our response.

be

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**From:** [redacted]
**Sent:** 2021-06-04 10:57 AM
**To:** Ephrem, Bersabel (PHAC/ASPC) <bersabel.ephrem@canada.ca>
**Subject:** RE: I-Mask+ Protocol for early treatment of Covid-19

Good morning

Thank you for your prompt response to my inquiry. If I may, I urge you to reconsider Canada's stance on this extremely important matter. Have you, personally, read the research studies? Have you been following new developments as more and more respected scientists and researchers become convinced of the efficacy of this treatment for Covid-19? I implore you and your committee to do your own research and that you be be willing to step out of the accepted norms. Would you consider even allowing it on a person by person basis with informed consent? I know many people who are considering self treatment with veterinary quality ivermectin which concerns me greatly. I believe that it's in the best interest of Canadian for Canada to reconsider.

Respectfully,
[redacted]

On Thu, Jun 3, 2021 at 3:23 PM, Ephrem, Bersabel (PHAC/ASPC) <bersabel.ephrem@canada.ca> wrote:

> Dear [redacted]
>
> Thank you for your correspondence concerning the use of the I-Mask Protocol for early treatment and prophylaxis for COVID-19 to support Canada's response to COVID-19.
>
> The Public Health Agency of Canada (PHAC) conducts a thorough analysis of the emerging scientific evidence regarding promising therapeutics to treat COVID-19, and Health Canada (HC) formally reviews these drugs to assess their safety, efficacy and quality before authorizing their sale in Canada. Many

drugs that show promise in laboratory studies are found to be ineffective in patients.

I-MASK+ Protocol is a prevention and early outpatient treatment protocol for COVID-19. While it includes a number of medications and supplements, it is centred on ivermectin, a broad-spectrum anti-parasitic agent authorized and approved by HC for human and veterinary applications to treat parasitic infections. At this time, HC has not authorized its use for the treatment of COVID-19.

Independent reviews of available clinical trial results that evaluate the effectiveness of ivermectin as a treatment for COVID-19 have been conducted by: the Canadian Agency for Drugs and Technologies in Health (CADTH); Alberta Health Services; British Columbia's COVID-19 Therapeutics Committee/COVID-19 Therapeutics Review and Advisory Working Group; and Ontario's COVID-19 Science Advisory table. These bodies of scientific experts all concluded that there is no clear benefit to ivermectin treatment among patients with COVID-19.

On March 31, 2021, the World Health Organization (WHO) issued a statement on ivermectin advising against its use outside of clinical trials, stating the current evidence was inconclusive. Further, the manufacturer - Merck - has also issued a statement against the use of ivermectin for the treatment of COVID-19.
https://www.merck.com/news/merck-statement-on-ivermectin-use-during-the-covid-19-pandemic/

In summary, there is currently no robust evidence (i.e., from high quality, well-designed clinical trials) to suggest that the I-MASK+ Protocol provides clinical benefit for the treatment or prevention of COVID-19, particularly in the Canadian context. Please be assured that PHAC continues to monitor the emerging evidence of clinical efficacy and safety from high quality trials on novel and repurposed therapeutics for COVID-19. The provinces and territories have primary responsibility for decisions around choice and use of therapeutics - including for COVID-19 – within their jurisdictions.

Thank you for writing to the Public Health Agency of Canada. I hope this information is helpful.

With best regards,

Bersabel
(She | Elle)

Bersabel Ephrem, BSc., MPA
Director General, Centre for Communicable Diseases and Infection Control
Infectious Disease Prevention and Control Branch
Public Health Agency of Canada
bersabel.ephrem@canada.ca / Tel: 613-948-6799 / Cell: 613-415-5897

Directrice générale, Centre de la lutte contre les maladies transmissibles et les infections
Direction générale de la prévention et du contrôle des maladies infectieuses
Agence de la santé publique du Canada

bersabel.ephrem@canada.ca / Tel: 613-948-6799 / Cell: 613-415-5897

-----Original Message-----
From: McLean, Hollie (HC/SC) <hollie.mclean@canada.ca> On Behalf Of Levesque2, Kaili (HC/SC)
Sent: 2021-05-31 3:54 PM
To: [redacted]
Cc: Ephrem, Bersabel (PHAC/ASPC) <bersabel.ephrem@canada.ca>; Levesque2, Kaili (HC/SC) <kaili.levesque2@canada.ca>; McLean, Hollie (HC/SC) <hollie.mclean@canada.ca>
Subject: RE: I-Mask+ Protocol for early treatment of Covid-19

Hi [redacted]

Thank you for your email. Note that I've recently assumed the role as Vice President, COVID-19 Vaccine Rollout at the Public Health Agency. I'm connecting you with Bersabel Ephrem, the Director General responsible for the therapeutics file.

Thanks

Kaili

Kaili Levesque (she/her/elle)
613.818.0492

-----Original Message-----
From: [redacted]
Sent: 2021-05-31 12:13 PM
To: Levesque2, Kaili (HC/SC) <kaili.levesque2@canada.ca>
Subject: I-Mask+ Protocol for early treatment of Covid-19

Good morning Ms. Levesque:

I am writing to ask for your assistance. I have been following a growing body of research on the use of the I-Mask Protocol for early treatment and prophylaxis for Covid-19. Early in the pandemic, this protocol was not well understood and had only anecdotal evidence of its efficacy. Recently, however, I've been encouraged to see multiple studies showing good evidence of efficacy. I am puzzled as to why this treatment is not being studied in Canada as we are still in a situation across the country where people are being hospitalized for Covid-19. I am not a medical professional, but I wonder if it is not prudent and compassionate to open the door to other treatment possibilities which could prevent further deterioration of newly diagnosed victims of this virus? I do not know if you are the right person to send this email to, but I do know that you believe that we should be doing absolutely everything to try to treat this disease. My sincere hope is that you and your Task Force are seeking to include the use of existing medicines that we know are not harmful in and of themselves, such as Ivermectin, which is one of the components in the I-Mask Protocol. While we all look forward to the day when vaccinations take effect Canada-wide, in the meantime there are still

many people who are falling ill and require medical treatment for this disease.

I respectfully submit to you this link to the growing body of knowledge and research studies around the I-Mask+ Protocol and I beg you to use your considerable influence to bring it to the attention of the Covid 19 Task Force and study it with all due diligence. If there is merit in this treatment, and your committee agrees to try it on a limited study basis, perhaps many Canadian lives could be saved and/or at the very least, saved from the longevity of hospitalizations for Covid 19 which they may be facing under the current treatment protocols. I believe that your committee has a moral and ethical obligation to fairly and diligently consider all possible treatments, irrespective of WHO or any other body who may be telling you otherwise. We are Canadians, first and foremost. We are responsible for one another.

Thank you so very much for your time. I ask you to please respectfully consider my request, and I very much look forward to your reply.

Sincerely,

[redacted]
Alberta, Canada

https://covid19criticalcare.com/covid-19-protocols/i-mask-plus-protocol/

**From:** Lawuyi2, Niyi (PHAC/ASPC)
**Sent:** 2021-03-24 11:23 PM
**To:** Lawuyi2, Niyi (PHAC/ASPC)
**Subject:** Emerging Therapeutics - FPT DSTF / Thérapeutique émergente - FPT PM
**Attachments:** FTP DSTF Emerging Therapeutics March 23 2021_mAbs.pptx

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Good afternoon,

Please see the attached slide deck that was presented to the FPT DSTF on March 23, 2021 on emerging COVID-19 therapeutics with special focus on neutralizing monoclonal antibodies. The French version of the presentation will follow.

Best regards,

COVID-19 Therapeutics Team

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Bonjour,

Veuillez consulter les diapositives ci-jointes qui ont été présentées au groupe de travail FPT sur les pénuries de médicaments le 23 mars 2021. Ces diapositives portent sur les nouvelles thérapies du COVID-19 et plus particulièrement sur les anticorps monoclonaux neutralisants. La version française de la présentation suivra.

Salutations distinguées,

Équipe Thérapeutiques COVID-19

**From:** Arthur, Jacqueline (PHAC/ASPC)
**Sent:** 2021-05-31 4:39 PM
**To:** Djiometio, Joseph (PHAC/ASPC); COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC)
**Cc:** Gale-Rowe, Margaret (PHAC/ASPC)
**Subject:** FW: I-Mask+ Protocol for early treatment of Covid-19
**Attachments:** Colchicine and Ivermectin and Vitamin D_CCDIC input.docx

---

Hi Joe;
We have received the correspondence below via our Director General's office regarding the I-Mask+ Protocol that centers around the main treatment, ivermection. Follow the link provided in the incoming correspondence.
Please review and prepare a draft response for Margaret's review by Wednesday.
I've attached previous correspondence we have done on ivermectin to assist - Adéle, could you track down the final correspondence that was sent under MECS#21-108019-10? It would be helpful for Joe to have the approved version sent.

Happy to discuss.
Jackie

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Jacqueline Arthur, BScN, RN
(she | elle)
Senior Manager, AMR Division | Gestionnaire principale, Division de la RAM
COVID-19 Therapeutics | thérapeutiques
CCDIC, PHAC | CLMTI, ASPC
t. (613) 889-8455

-----Original Message-----
From: Ephrem, Bersabel (PHAC/ASPC) <bersabel.ephrem@canada.ca>
Sent: 2021-05-31 4:07 PM
To: Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>
Cc: Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>; Hunt, Kelly (PHAC/ASPC) <kelly.hunt@canada.ca>
Subject: FW: I-Mask+ Protocol for early treatment of Covid-19

Hi Jackie,

Can we have a response? Please see below.

be

-----Original Message-----
From: McLean, Hollie (HC/SC) <hollie.mclean@canada.ca> On Behalf Of Levesque2, Kaili (HC/SC)
Sent: 2021-05-31 3:54 PM
To: [redacted]
Cc: Ephrem, Bersabel (PHAC/ASPC) <bersabel.ephrem@canada.ca>; Levesque2, Kaili (HC/SC) <kaili.levesque2@canada.ca>; McLean, Hollie (HC/SC) <hollie.mclean@canada.ca>
Subject: RE: I-Mask+ Protocol for early treatment of Covid-19

Hi [redacted]

Thank you for your email. Note that I've recently assumed the role as Vice President, COVID-19 Vaccine Rollout at the Public Health Agency. I'm connecting you with Bersabel Ephrem, the Director General responsible for the therapeutics file.

Thanks

Kaili

Kaili Levesque (she/her/elle)
613.818.0492

-----Original Message-----
From: [redacted]
Sent: 2021-05-31 12:13 PM
To: Levesque2, Kaili (HC/SC) <kaili.levesque2@canada.ca>
Subject: I-Mask+ Protocol for early treatment of Covid-19

Good morning Ms. Levesque:

I am writing to ask for your assistance. I have been following a growing body of research on the use of the I-Mask Protocol for early treatment and prophylaxis for Covid-19. Early in the pandemic, this protocol was not well understood and had only anecdotal evidence of its efficacy. Recently, however, I've been encouraged to see multiple studies showing good evidence of efficacy. I am puzzled as to why this treatment is not being studied in Canada as we are still in a situation across the country where people are being hospitalized for Covid-19. I am not a medical professional, but I wonder if it is not prudent and compassionate to open the door to other treatment possibilities which could prevent further deterioration of newly diagnosed victims of this virus? I do not know if you are the right person to send this email to, but I do know that you believe that we should be doing absolutely everything to try to treat this disease. My sincere hope is that you and your Task Force are seeking to include the use of existing medicines that we know are not harmful in and of themselves, such as Ivermectin, which is one of the components in the I-Mask Protocol. While we all look forward to the day when vaccinations take effect Canada-wide, in the meantime there are still many people who are falling ill and require medical treatment for this disease.

I respectfully submit to you this link to the growing body of knowledge and research studies around the I-Mask+ Protocol and I beg you to use your considerable influence to bring it to the attention of the Covid 19 Task Force and study it with all due diligence. If there is merit in this treatment, and your committee agrees to try it on a limited study basis, perhaps many Canadian lives could be saved and/or at the very least, saved from the longevity of hospitalizations for Covid 19 which they may be facing under the current treatment protocols. I believe that your committee has a moral and ethical obligation to fairly and diligently consider all possible treatments, irrespective of WHO or any other body who may be telling you otherwise. We are Canadians, first and foremost. We are responsible for one another.

Thank you so very much for your time. I ask you to please respectfully consider my request, and I very much look forward to your reply.

Sincerely,

[redacted]
Alberta, Canada

https://covid19criticalcare.com/covid-19-protocols/i-mask-plus-protocol/

**From:** Arthur, Jacqueline (PHAC/ASPC)
**Sent:** 2021-04-22 5:50 PM
**To:** Gale-Rowe, Margaret (PHAC/ASPC); Lawuyi2, Niyi (PHAC/ASPC)
**Subject:** FW: Ivermectin and others

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Looping Margaret in to have a look at the FLCCC alliance:
https://covid19criticalcare.com/ivermectin-in-covid-19/
Interesting membership, all white males…

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Jacqueline Arthur, RN, BScN
(she | elle)
Senior Manager, AMR Division | Gestionnaire principale, Division de la RAM
COVID-19 Therapeutics | thérapeutiques
CCDIC, PHAC | CLMTI, ASPC
t. (613) 889-8455

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**From** [redacted]@gov.ab.ca>
**Sent:** 2021-04-22 5:43 PM
**To:** Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>; Lawuyi2, Niyi (PHAC/ASPC) <niyi.lawuyi2@canada.ca>
**Subject:** RE: Ivermectin and others

Thanks Jackie. Many callers to the government are referencing the FLCCC alliance and their evidence summaries (https://covid19criticalcare.com/ivermectin-in-covid-19/). I am sure that PHAC is aware of them but just wanted you to know who the public appears to be listening to these days!

thanks

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**From:** Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>
**Sent:** April-22-21 3:07 PM
**To:** [redacted]@gov.ab.ca>; Lawuyi2, Niyi (PHAC/ASPC) <niyi.lawuyi2@canada.ca>
**Subject:** RE: Ivermectin and others

CAUTION: This email has been sent from an external source. Treat hyperlinks and attachments in this email with care.

Thanks [redacted] for your email. PHAC does monitor the emerging evidence closely and summaries information about therapeutics showing promise. Our expert advisory group did issue public recommendations on hydroxychloroquine: Statement on hydroxychloroquine: COVID-19 Clinical Pharmacology Task Group - Canada.ca

As for ivermectin, our team continues to review the available evidence but no public recommendations are available at the federal level given the weak evidence. I know both Ontario and BC have updated guidance that includes ivermectin recommendations to not use it (attached for reference).

Our team at PHAC is working with Health Canada on the development of a new governance approach for COVID-19 therapeutics that we hope to discuss with provinces and territories soon that may be able to help in this area – for example, we think a regular therapeutics science/clinical/ table would be helpful to bring forward evidence summaries and analyses for a fulsome discussion with P/T clinical leads to help identify promising therapies. Do you think that would meet a need?
Would appreciate your thoughts.
Thanks,
Jackie

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Jacqueline Arthur, RN, BScN
(she | elle)
Senior Manager, AMR Division | Gestionnaire principale, Division de la RAM
COVID-19 Therapeutics | thérapeutiques
CCDIC, PHAC | CLMTI, ASPC
t. (613) 889-8455

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**From:** [redacted]@gov.ab.ca>
**Sent:** 2021-04-22 3:57 PM
**To:** Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>; Lawuyi2, Niyi (PHAC/ASPC) <niyi.lawuyi2@canada.ca>
**Subject:** Ivermectin and others

Hi Jackie and Niyi

In follow-up to the comment about evidence reviews raised in the ADM drug shortage meeting, I am wondering if Health Canada has any guidance/recommendations on any of the emerging therapies? We frequently get questions about ivermectin and hydroxychloroquine (among others) and why it is not being used for COVID. I recall a HC therapeutic committee mentioned in our meetings. Do they have public recommendations? Does HC monitor the every changing evidence based on these drugs and update recommendations as needed?

thanks very much

[redacted]
Alberta Health

**From:** Djiometio, Joseph (PHAC/ASPC)
**Sent:** 2021-06-03 5:53 PM
**To:** Arthur, Jacqueline (PHAC/ASPC); Gale-Rowe, Margaret (PHAC/ASPC)
**Subject:** FW: ivecmertin
**Attachments:** Ivecmertin statment.docx

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Sorry I forgot to cc you to the document sent to Nicole

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**From:** Djiometio, Joseph (PHAC/ASPC)
**Sent:** 2021-06-03 5:47 PM
**To:** Forbes, Nicole (PHAC/ASPC) <nicole.forbes@canada.ca>
**Cc:** Azad, Mina (PHAC/ASPC) <mina.azad@canada.ca>; Cortés-Kaplan, Serena (PHAC/ASPC) <serena.cortes-kaplan@canada.ca>
**Subject:** ivecmertin

Here you go

**Joseph Djiometio, PhD, MPH**
**Technical Lead**
COVID-19 Therapeutics | thérapeutiques
CCDIC, PHAC | CLMTI, ASPC
Tel: (343) 574-3635
Email: joseph.djiometio@canada.ca

**From:** Gale-Rowe, Margaret (PHAC/ASPC)
**Sent:** 2021-04-29 3:26 PM
**To:** COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC); Marinsky, Cheryl (PHAC/ASPC); Lawuyi2, Niyi (PHAC/ASPC)
**Cc:** Poon Young, Celisse (PHAC/ASPC)
**Subject:** For Senior Manager review: LISA AND THERAPEUTICS TEAM FOR INPUT BY APRIL 29 - 21-108019 - Vitamin D, Colcichine, Ivermectin
**Attachments:** Colchicine and Ivermectin and Vitamin D FOR SR MGR approval.docx; Correspondence on Vit. D Colchicine and Ivermectin-DRAFT-CM-_CKS_ES.docx; 21-108019-10 Incoming Apr 22.pdf; 21-108019_VitD_Colchicine, Ivermectin_Response_Apr2021.doc

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Hi,

Additional information has been included in this response for Jackie's approval. I just realized that we/I could have kept more detail, however it was very long.

I am also including the longer version that was provided by the technical team; that could be included if Jackie thinks it appropriate.

Please note that I have also attached the incoming as well as a draft response, parts of which were edited out of my response.

Margaret

---

**From:** Poon Young, Celisse (PHAC/ASPC) <celisse.poonyoung@canada.ca> **On Behalf Of** COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC)
**Sent:** 2021-04-26 1:54 PM
**To:** Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>; Marinsky, Cheryl (PHAC/ASPC) <cheryl.marinsky@canada.ca>; Lawuyi2, Niyi (PHAC/ASPC) <niyi.lawuyi2@canada.ca>
**Cc:** Poon Young, Celisse (PHAC/ASPC) <celisse.poonyoung@canada.ca>
**Subject:** FW: LISA AND THERAPEUTICS TEAM FOR INPUT BY APRIL 29 - 21-108019 - Vitamin D, Colcichine, Ivermectin
**Importance:** High

Hi everyone,

Please see the request that came to the Therapeutics inbox this afternoon. Sending to you all since I am not sure exactly who this should be directed to.

Thank you,

Celisse

**From:** Jamil, Marium (PHAC/ASPC) <marium.jamil@canada.ca>
**Sent:** 2021-04-26 12:21 PM
**To:** Waddell, Lisa (PHAC/ASPC) <lisa.waddell@canada.ca>; COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC) <phac.covid-19therapeutics-therapeutiques.aspc@canada.ca>
**Cc:** PHAC.F OCSO_ESGSecretariat / BCSC_SecrétariatGSE F.ASPC <phac.ocso_esgsecretariat-bcsc_secretariatgse.aspc@canada.ca>
**Subject:** LISA AND THERAPEUTICS TEAM FOR INPUT BY APRIL 29 - 21-108019 - Vitamin D, Colcichine, Ivermectin
**Importance:** High

Good morning Lisa and Therapeutics team,
**FOR INPUT/APPROVAL – BY APRIL 29**
**CONTEXT**

- Dr. Tam received correspondence on April 21, 2021 from a member of the public (please see attached '21-108019-10 Incoming Apr 22.pdf'), regarding the use of Vitamin D, Ivermectin and Colchicine as treatments for COVID-19.

**FOR INPUT**

- ESG Secretariat has drafted a standard response in regards to the use of Vitamin D (please see attached '21-108019-VitD_Colchicine, Ivermectin _ Response_Apr2021. doc') adapted from previous responses. The letter does not speak to Colchicine or Ivermectin however. We would be thankful if you could please provide **your input on:**
    - **Any evidence to support the use of Ivermectin and Colchicine**
    - **Any NEW evidence on the efficacy of Vitamin D**

Thank you so much for your time. We would be grateful if you could please provide us your input by April 29th.

Please let us know if you have any questions.

Regards,
Marium

*On behalf of the Office of Chief Science Officer and the PHAC Emerging Science Group Secretariat*

**Marium Jamil**
(she | elle)
Policy Analyst | Analyste des politiques
Office of the Chief Science Officer | Bureau du Conseiller scientifique en chef
Public Health Agency of Canada | Agence de la santé publique du Canada
NEW: phac.ocso_esgsecretariat-bcsc_secretariatgse.aspc@canada.ca

**From:** Forbes, Nicole (PHAC/ASPC)

**Sent:** 2021-06-03 9:00 PM

**To:** Arthur, Jacqueline (PHAC/ASPC); Gale-Rowe, Margaret (PHAC/ASPC); Djiometio, Joseph (PHAC/ASPC)

**Cc:** Azad, Mina (PHAC/ASPC)

**Subject:** Fwd: Ivermectin summary

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[redacted] Marina provided feedback for situational awareness of the rest of the team. This type of request is for TT's back pocket, which is nice as it doesn't need the formality of policy docs. Sounds like more requests will be headed your way :)

Nicole

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**Nicole Forbes, PhD**

**she | elle**

**Scientific Project Coordinator**

NACI Secretariat

Centre for Immunization Readiness

Public Health Agency of Canada I Agence de la santé publique du Canada

Tel: (613) 447-6450

Email: nicole.forbes@canada.ca

Begin forwarded message:

> **From:** "Salvadori, Marina (PHAC/ASPC)" <marina.salvadori@canada.ca>
> **Date:** June 3, 2021 at 9:55:20 PM ADT
> **To:** "Forbes, Nicole (PHAC/ASPC)" <nicole.forbes@canada.ca>
> **Cc:** "Azad, Mina (PHAC/ASPC)" <mina.azad@canada.ca>
> **Subject: RE: Ivermectin summary**
>
> Thank you. Just so you know Mina, These summaries need not be approved by the whole chain and are not issue notes.
>
> I brief Theresa on all things scientific.
>
> Fast and right is more impt than approvals.
>
> Welcome on board
>
> Marina

**From:** Forbes, Nicole (PHAC/ASPC) <nicole.forbes@canada.ca>
**Sent:** 2021-06-03 8:20 PM
**To:** Salvadori, Marina (PHAC/ASPC) <marina.salvadori@canada.ca>
**Cc:** Azad, Mina (PHAC/ASPC) <mina.azad@canada.ca>
**Subject:** FW: Ivermectin summary

Hi Marina,

Please see summary on ivermectin below, compiled by Mina Azad, a PhD Biochemist who recently joined the COVID-19 therapeutics technical team. [redacted] If Theresa needs a summary done for therapeutics in the future I suggest we route it through Mina. I am happy to review as she acquaints herself to the file. For this one it's a bit different as there was no recent trial that reported, instead a meta-analysis that suggested positive clinical benefit… see below.

Best regards,

Nicole

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**From:** Azad, Mina (PHAC/ASPC) <mina.azad@canada.ca>
**Sent:** 2021-06-03 8:25 PM
**To:** Forbes, Nicole (PHAC/ASPC) <nicole.forbes@canada.ca>
**Cc:** Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>; Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>; Djiometio, Joseph (PHAC/ASPC) <joseph.djiometio@canada.ca>
**Subject:** Ivermectin summary

**Ivermectin Overview**

Ivermectin is a broad-spectrum anti-parasitic agent authorized by Health Canada for human and veterinary applications. Health Canada has not authorized its use for the treatment of COVID-19.

**Ivermectin Findings & Outcomes**

- In laboratory studies, ivermectin prevented SARS-CoV2 from replicating and has demonstrated anti-inflammatory properties, raising the possibility that ivermectin may have a role in COVID-19 prophylaxis or treatment.
- While preliminary *in vitro* and animal studies reported promising antiviral and anti-inflammatory effects of ivermectin in the context of SARS-CoV-2 infection, its use as a preventative or treatment for COVID-19 remains controversial due to mixed evidence of clinical benefit from numerous smaller, underpowered randomized trials.
- The British Medical Journal's living systematic review and network meta-analysis analysed 16 randomized trials. Based on their findings, they rated the effects of ivermectin on viral clearance, mechanical ventilation and mortality as uncertain, meaning it is uncertain whether ivermectin has an important impact on any patient-important outcome.
- Recently, a meta-analysis based on 18 randomized trials of ivermectin in COVID-19 found that ivermectin treatment reduced mortality, time to clinical recovery, and time to viral clearance.
- A powered, well-designed randomized trial is needed to clearly elucidate the appropriate role of ivermectin in the clinical management or prevention of COVID-19.

**Considerations**

***Canadian perspectives***

- The Canadian Agency for Drugs and Technologies in Health (CADTH; statement issued on February 08, 2021); Alberta Health Services (statement issued on February 02, 2021) ; as well as British Columbia's COVID-19 Therapeutics Committee/COVID-19 Therapeutics Review and Advisory Working Group (statement issued on May 25, 2021) have all concluded that there is no clear benefit associated with ivermectin treatment among patients with COVID-19. As of June 3, 2021, no statement has been issued by INESSS.
- On May 28, 2021, Ontario's COVID-19 Science Advisory Table issued a statement titled Ivermectin to Prevent Disseminated Strongyloides Infection in Patients with COVID-19. While stipulating ivermectin is currently not recommended as a treatment or preventative for COVID-19, the statement acknowledges patients with COVID-19 who receive therapies that alter immune system function may require ivermectin for the purposes of treating a pre-existing parasitic infection and to avoid severe complications of worsening parasitic infection.

***International perspectives***

- In South American countries, ivermectin is being prescribed routinely for COVID-19 infections; however, it is difficult to ascertain clinical benefit from use outside the context of randomized controlled trials.
- On March 31, 2021, the WHO issued a statement on ivermectin advising against its use outside of clinical trials, stating the current clinical evidence was inconclusive
- On March 22, 2021 the EMA issued an advisory notice against use of ivermectin for the prevention or treatment of COVID-19 outside randomised clinical trials.
- On February 11, 2021 the NIH COVID-19 Treatment Guidelines Panel issued a statement concluding there is insufficient evidence to recommend either for or against the use of ivermectin for the treatment of COVID-19.

Mina Azad, PhD

(She | elle)

Research Analyst | Analyste de recherche

COVID-19 Therapeutics | Thérapeutiques

CCDIC, PHAC | CLMTI, ASPC

mina.azad@canada.ca | Tel: (343) 574 4080

**From:** Arthur, Jacqueline (PHAC/ASPC)

**Sent:** 2021-02-07 11:18 AM

**To:** Forbes, Nicole (PHAC/ASPC)

**Subject:** Fwd: Weekly email #XLVI from your friendly neighbourhood infectious diseases specialist

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As discussed Friday. You can subscribe directly if interested.

See below.

J

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Jacqueline Arthur, RN, BScN

(she | elle)

Senior Manager, AMR Division | Gestionnaire principale, Division de la RAM

COVID-19 Therapeutics | thérapeutiques

Centre for Communicable Diseases and Infection Control | Centre de la lutte contre les maladies transmissibles et les infections

Public Health Agency of Canada | Agence de la santé publique du Canada

t. (613) 889-8455

Begin forwarded message:

**From:** "Andrew Morris, MD" <andrew@covidemails.com>
**Date:** February 5, 2021 at 10:01:08 PM EST
**To:** jackiearthur@rogers.com
**Subject: Weekly email #XLVI from your friendly neighbourhood infectious diseases specialist**
**Reply-To:** "Andrew Morris, MD" <andrew@covidemails.com>

View this email in your browser

## Weekly Email XLVI (46 if you don't speak Roman)

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I am a girls' basketball coach who doubles as an infectious diseases physician, and this is my 46th weekly email since the COVID-19 pandemic emerged.

This is one of my busiest weeks of the pandemic, so I am keeping the email relatively focused on the new variants and their implications. I hope it is enough to keep you both informed and entertained. I have interspersed some great Super Bowl ads of the past (and a few other videos) for your entertainment.

As always, please share widely. Social media is the most efficient way to share, but feel free to use any of the buttons at the bottom.

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## Weekly Overview

This week's newsletter brings the following to you prematurely:

- **Super Bowl LV**
- **Variants**
- **We are going into the second half with the lead**
- **Don't underestimate the young bench player**
- **Israel vs. Denmark**
- **Coming off the bench**
- **Where does that leave Canada?**

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## Super Bowl LV

As mentioned last week, this weekend is the 55th Super Bowl, pitting the Tampa Bay Buccaneers against the Kansas City Chiefs. Some will see it as a matchup between Tom Brady and Patrick Mahomes; Mahomes is the reigning champion quarterback, and Tom Brady is, well, Tom Brady. I'm just hoping for a great game and looking forward to hosting, yet again, a massive Super Bowl Party in my home.

You are correct: there is zero chance anyone who doesn't live with me is coming into my home to watch. And I am asking for not only you to do the same, but to let people who you know know (yes, that is an intentional double "know") that you will not be watching with people from outside your home and why. Because we know that normalizing the right thing influences what other people do.

One other thing: the true star, in my mind, is Dr. Laurent Duvernay-Tardif, the KC lineman who took a year off to work as a doctor and also study public health. You can hear an interview with him on CBC radio's The Current and cannot help but be impressed. He won't be playing, but he is still a star.


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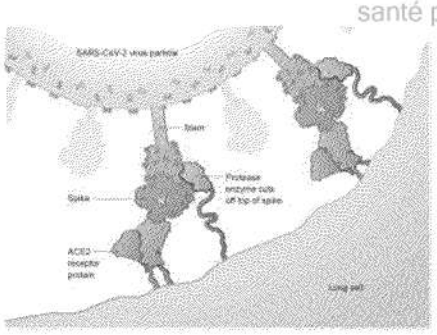
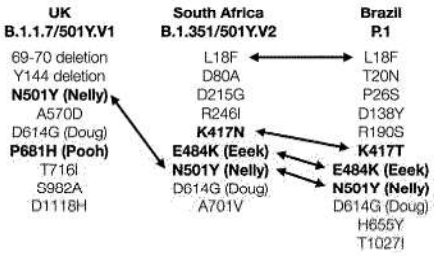
## Variants

Back in weekly issue #36, I showed you all SARS-CoV-2 and the spike (S) protein, explaining how it latches onto the human ACE2 receptor as the starting point for infection. Although the virus for COVID-19 has expected mutations, some mutations in this spike protein are causing lots of trouble. We call these variants "Variants of Concern" or VOCs. Kinda reminds me about several times when I received feedback from supervisors over the years: "Well, it's not the biggest thing, but I do have a few concerns ..." Yeah, right. Concerns.

There is a huge problem with naming all of them because there is nothing really memorable about all of the names, and there are even different naming systems. (I favour the approach that I saw Dr. Kristian Andersen from the Scripps Research Institute in La Jolla, California, use; it's shown below. 1. You name according to where the mutation occurs, for example S means spike protein. 2. You say what has changed, like N501Y means an N nucleic acid has become a Y at the 51st position. 3. You give each one a fun name based on what the coded name looks like. So N501Y becomes NellY or E484K becomes EeeK.)

There are some mutations that have made these variants pretty bad. I will be explaining why.

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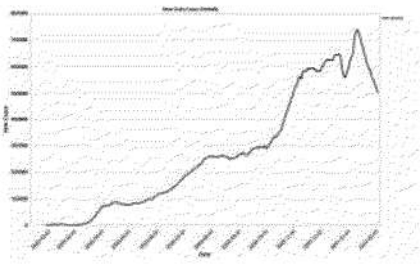
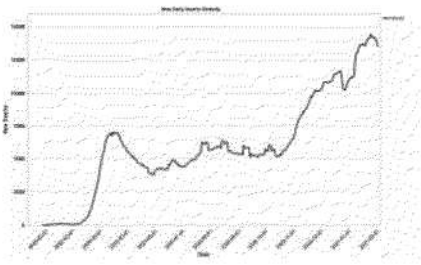
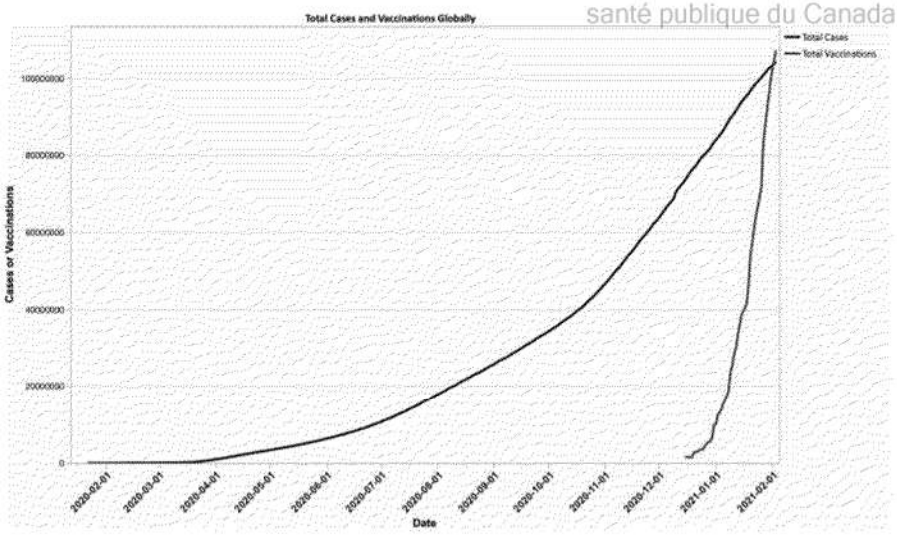
## Going into the second half with the lead

Many people participate in Super Bowl prop bets, like who will catch the first pass, who will make the first fumble, etc. You can also create your own COVID-19 prop bet sheet, like who will be the first person to pull their mask down on the sideline to talk, who will be the first to touch their face, who will be the first person to sanitize their hands on-air, etc. And you can also take bets on when the first time they mention COVID-19 for the first time on the broadcast, etc. If you do any of these things ... there is something wrong with you. Just watch and enjoy the damn game!

One other thing: when you are watching, it is likely that one team will be leading entering the second half. Well, please look at the two graphs below. The first one looks at daily cases of COVID-19, and the second one looks at daily deaths from COVID-19. What do you see? Yup—they are dropping. Why? Dunno. I am almost certain it isn't from vaccination. It might be a variety of factors related to global efforts to get things under control. Or it could be something entirely different that we have yet to understand. But this is good, and it suggests we're leading going into the second half of this pandemic.








One last sign that we are leading going into the second half: the total number of people vaccinated has exceeded the total number of people who have been infected.

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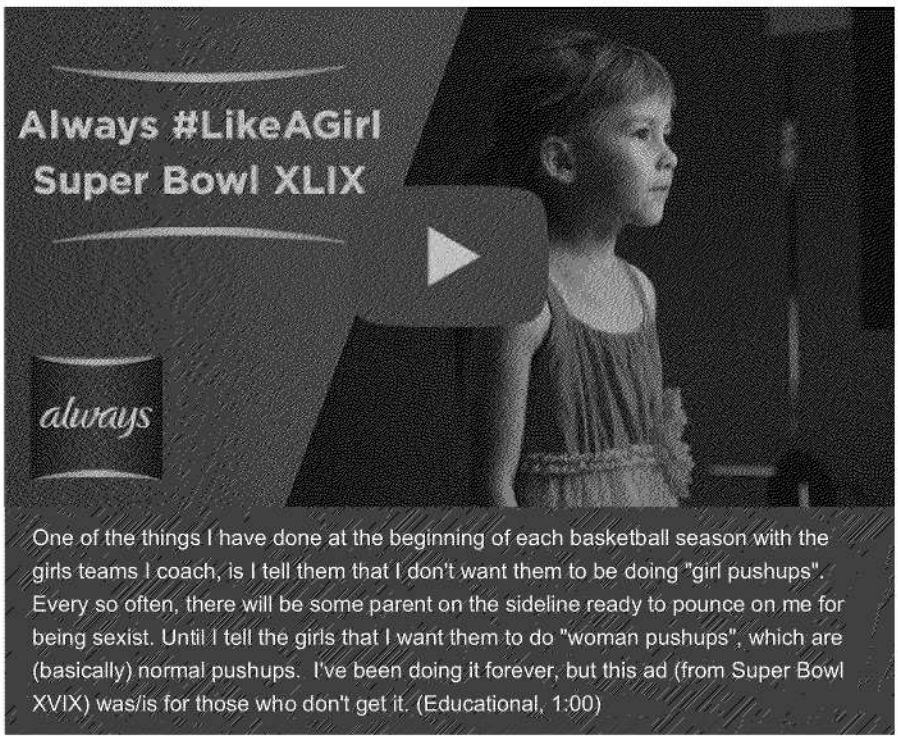


## Don't underestimate the young bench player

Back in 2000, the starting quarterback for the New England Patriots (back when I was a HUGE Patriots fan ... until they became winners and cheaters, that is), Drew Bledsoe, got knocked out late in the 4th quarter of a game early in the season. A young backup, Tom Brady, came into the game for a few plays. The game was over already, with the Patriots getting slaughtered and nobody really noticing Tom Brady. It is hard to notice

someone or something if they don't have enough exposure. But Brady would start the next few games, and the Patriots started to look like a marginally improved team. It takes a while for a star player to gather steam. But then, in Week 5 of that season, Brady led an amazing come-from-behind win and then continued to lead the Patriots to a dominant season and Super Bowl Championship. And Tom Brady—to this day—has been the single most dominant player in the NFL for the past 20 years after starting off with little notice.

As you know, I believe sports provides rich and useful analogies to our present situation. Tom Brady was just another player, until we realized he wasn't. Just like we thought those people—in the UK, Ireland, Denmark, and now across Canada—were infected with just another case of COVID-19, until we realize that they weren't. I believe the S:N501Y variant (or Nelly, or B.1.1.7, or the UK variant, or whatever) is the Tom Brady of COVID-19.

So, while we are clearly winning against COVID-19, we need to pay careful attention to B.1.1.7 because, even though we might see that early season victory, and might not think that this new player (who we haven't seen too much about yet) is worth noticing, it is very possible that this season will end up feeling longer than we'd like unless we do something about this new young player.

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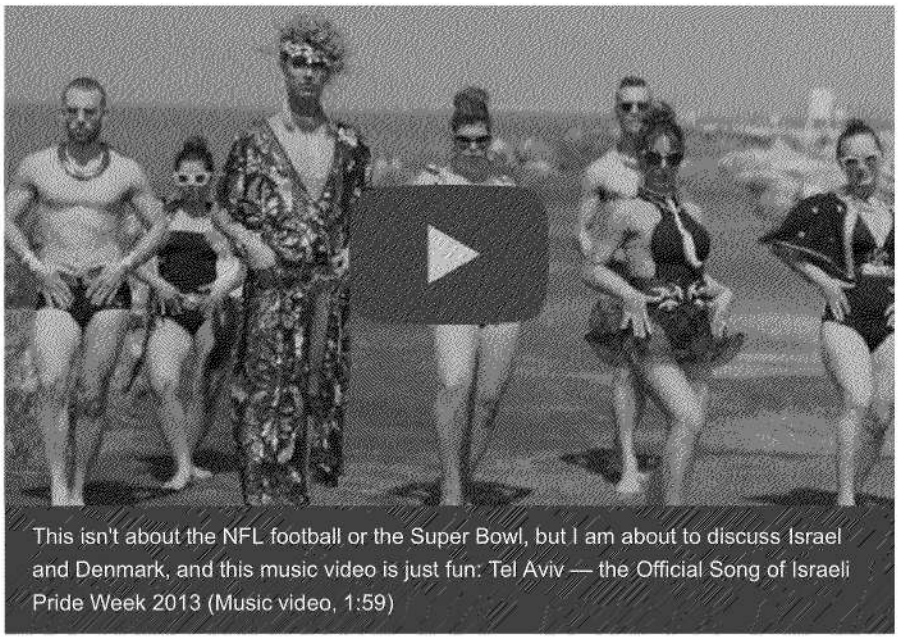


This isn't about the NFL football or the Super Bowl, but I am about to discuss Israel and Denmark, and this music video is just fun: Tel Aviv — the Official Song of Israeli Pride Week 2013 (Music video, 1:59)

## Israel vs. Denmark

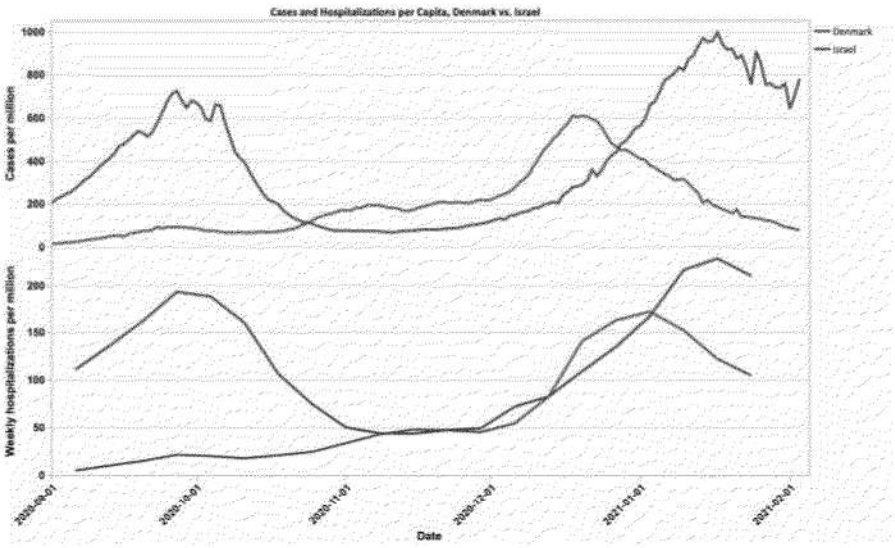
Back in October, the Israeli and Danish Women's National Football (Soccer) teams played against each other as part of the UEFA Women's Championship Qualification Round. My guess is that if I asked you to guess who won, you would say Denmark. And you would be right: Denmark won 4-0. If I now asked you to tell me who you

thought has done better battling COVID-19, Denmark or Israel, you might be tempted to say Israel. After all, they did amazingly well with their first wave and have been absolutely crushing it on the vaccine front, which has attracted worldwide attention. I explained much of this in Issue 41. (You can read even more, if you wish, at the Technical Brief from Ontario's Scientific Advisory Table. The leaders of Israel's vaccine roll out presented—it was a fascinating presentation, and is plenty instructive.) But Israel has done brutally with crushing second and third waves while Denmark, on the other hand, will be considered one of the top western nations in tackling COVID.

Israel has now immunized over 90% of people over age 60, but has immunized a relatively small percentage of its younger population. They have also had rampant and growing spread of the B.1.1.7 variant of COVID-19. What has this meant?

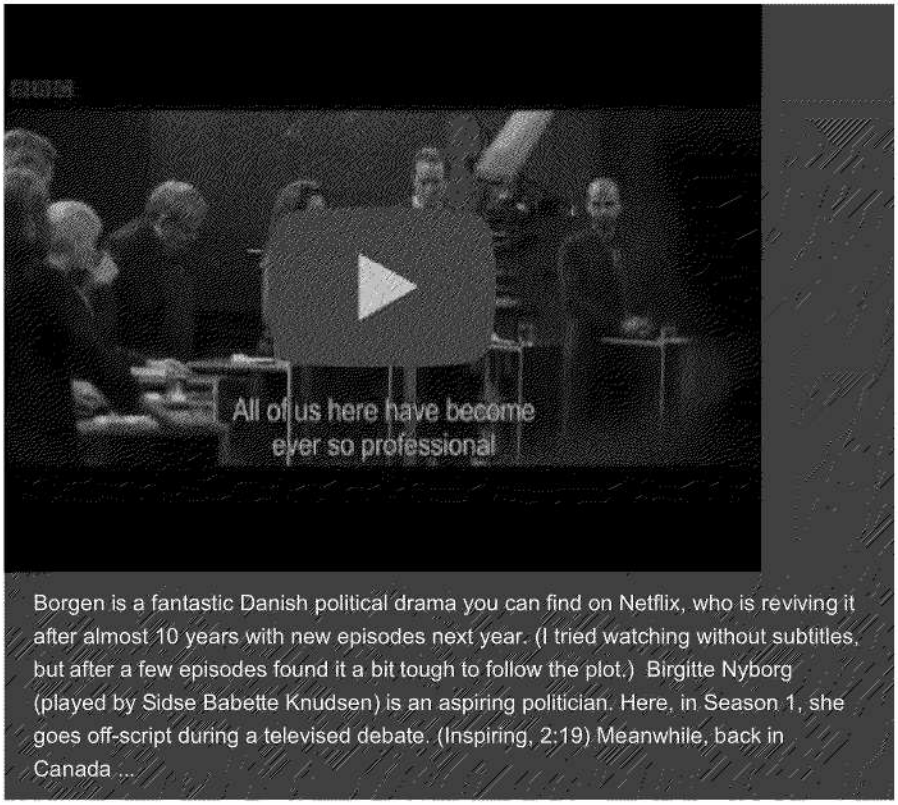
- in those Israel's who received a second dose of the Pfizer vaccine, only 0.06% (or roughly 1 out of every 1700 recipients) got infected with COVID, and none got very sick. This is absolutely a mind-boggling statistic.
- the % of cases due to people over age 60 has halved, from 14% to 7%, and there has been a 30% drop in hospitalizations in this age group
- they have stagnated to a large degree with overall cases and hospitalization despite a lockdown because their success in older adults is offset by a) poor adherence to or defiance of lockdown measures in some segments of their society (e.g. Haredim—the branch of Orthodox Jews who strictly adhere to traditional practices), b) vaccine hesitancy (esp. Haredim and Israeli Arabs), and c) the growth of B.1.1.7, which offsets some of the gains.

Without tons of vaccine, Denmark has been plodding along with a strict lockdown and tight border controls since December. They just extended their restrictions till the end of February. I will get back to Denmark shortly, but I want you to see how vaccines for older adults alone is not a panacea for COVID-19 control or hospitalizations.




As you can see, Denmark more aggressively tackled their winter wave, even though they started off at a rather similar place (especially if you look at the bottom graph, which is hospitalizations). Largely without vaccines, Denmark has had fewer cases and

fewer hospitalizations per capita. As I will show you shortly, the Danes do not feel they are out of the woods.

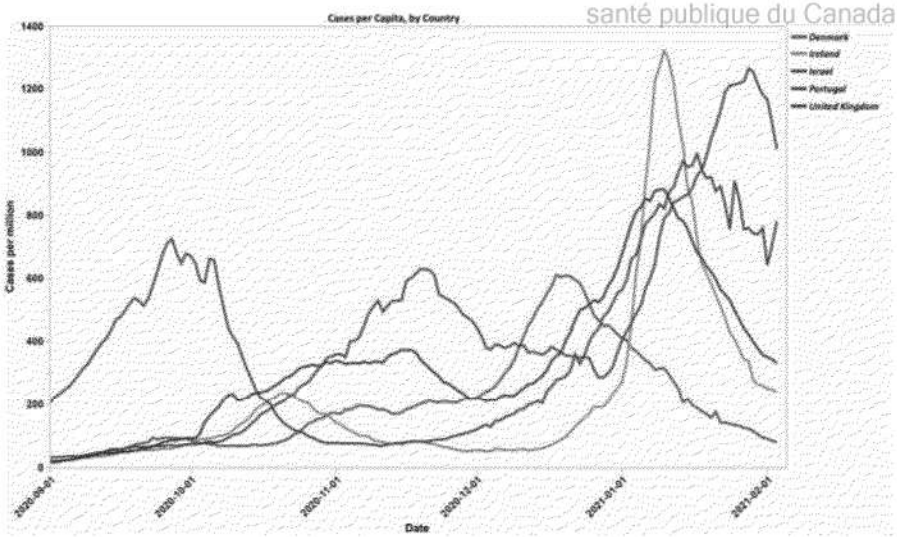



Borgen is a fantastic Danish political drama you can find on Netflix, who is reviving it after almost 10 years with new episodes next year. (I tried watching without subtitles, but after a few episodes found it a bit tough to follow the plot.) Birgitte Nyborg (played by Sidse Babette Knudsen) is an aspiring politician. Here, in Season 1, she goes off-script during a televised debate. (Inspiring, 2:19) Meanwhile, back in Canada ...

---

## Coming off the bench

As I alluded to earlier, the UK or B.1.1.7 variant insidiously appears in a country and then totally takes over in a way reminiscent of Tom Brady. Whereas most countries had pretty diverse versions, or variants, of the virus even a few months ago, once the B.1.1.7 variant appears, it not only takes over, but it replicates at an alarmingly high rate.

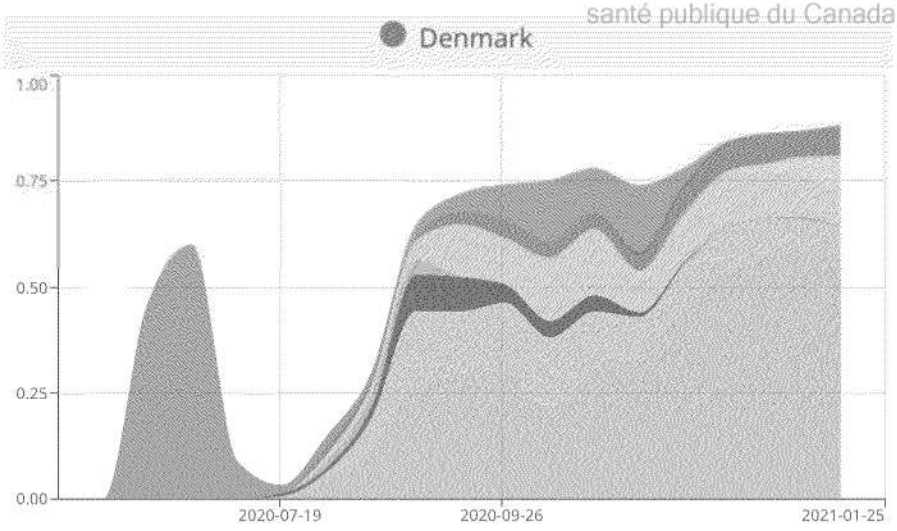


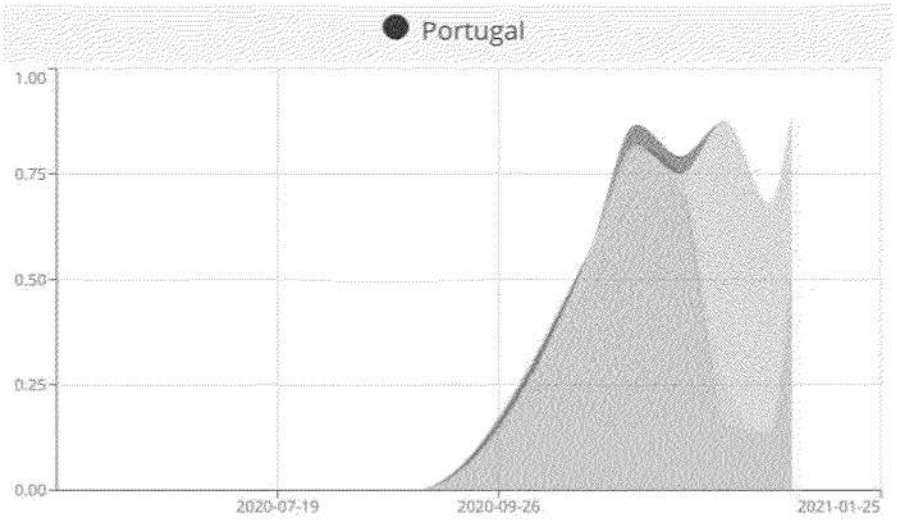

First, I want to show you above the countries that were heavily affected by variants ... and Denmark, who has aggressively kept things at bay even though they had an earlier wave than the other countries. And look where they are now. Approaching zero cases. Countries CAN AND WILL get these variants under control, but those spikes in cases —reflecting not paying attention or letting your guard down—have meaningful consequences on people's lives.

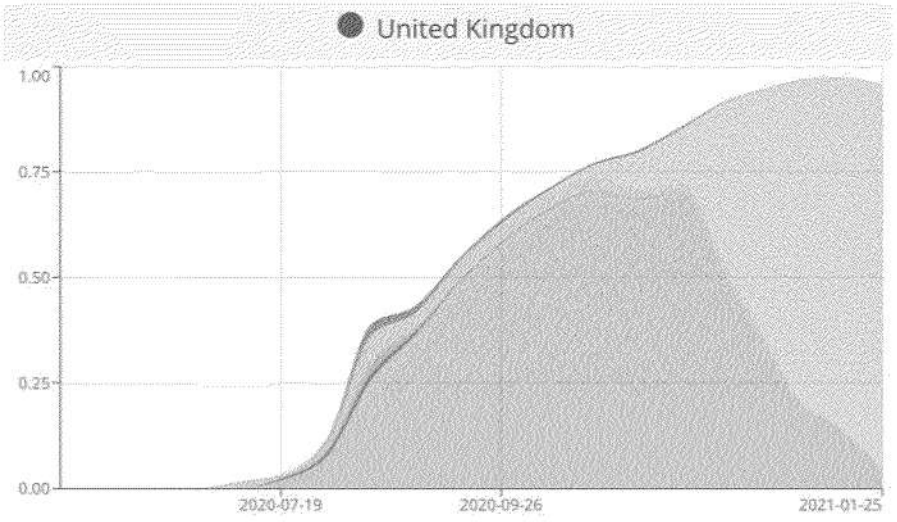
In the graphs below, grabbed from Dr. Emma Hodcroft's mind-boggling work that can be found at CoVariants.org, each variant is represented by a band of colour. If the band is thicker, it means that a larger proportion of the cases are due to that particular variant. Bands that grow thicker, therefore, become the dominant variant for one reason or another. They are "fitter" or have some kind of "selective advantage", such as replicating faster, being stickier, or beingresistant to treatment or vaccines. I want you to keep your eye on the pink band, which includes the B.1.1.7 variant. I say it "includes" the B.1.1.7 variant, because it also includes the closely related variants that originated in Brazil and South Africa.

In the first graph, you can see Denmark has a relatively thin wedge of pink. But that thin wedge shows exponential growth. As I mentioned, Denmark has been able to keep it at bay because—as you saw above—they have kept all the viral growth at bay. If you don't try and keep things under control, then you have a situation like Portugal. What happened to Portugal you asked? Portugal is just starting to get under control one of the worst waves to hit the world, correlating with a huge takeover by the S:N501 variant in a mater of weeks. As we know, in the UK, that pink band accounts for almost all cases.

These new variants do not have magical properties, and efforts to properly contain them DO work. Reports in the media attributing bizarre powers (for example, one Public Health Official speculated on their ability to penetrate personal protective equipment and another report got amplified to suggest that infection occurs "within seconds") do everyone a disservice. They might be the new Tom Brady, but they are no Black Panther or Wonder Woman.

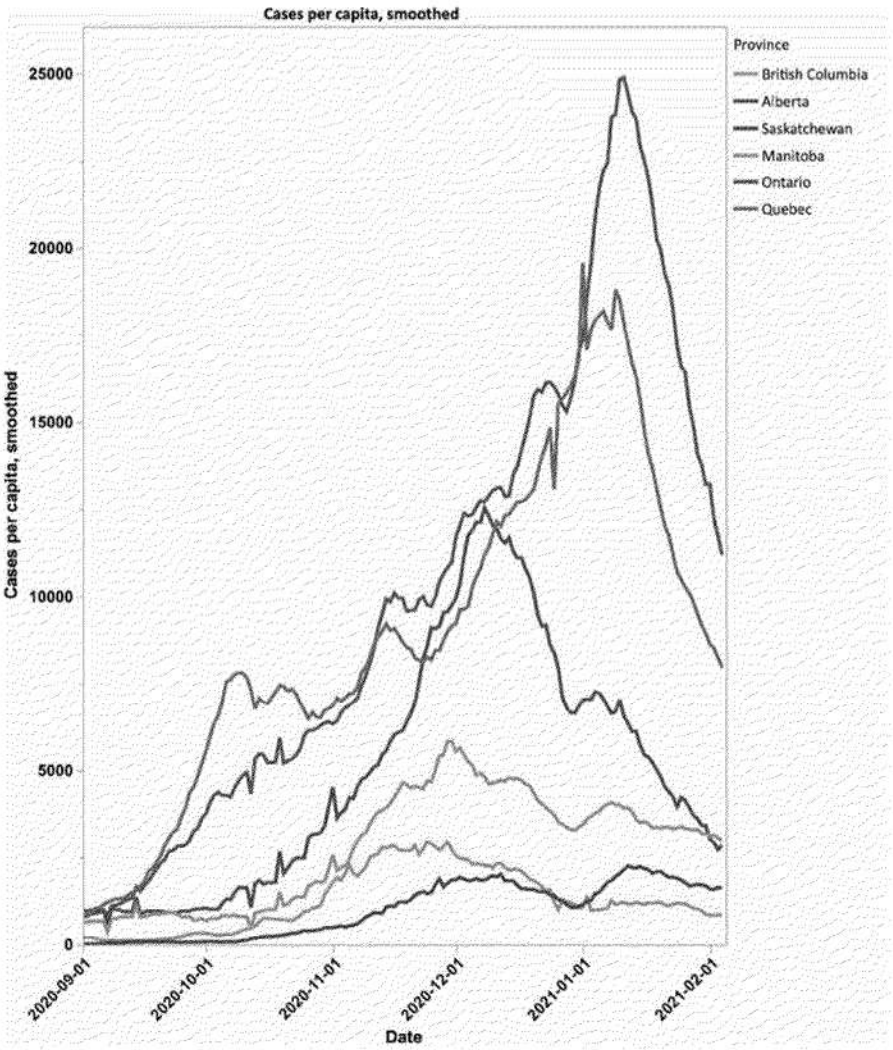



## Where does that leave Canada?

Canada is doing well as a result of the public's cooperation with public health interventions and lockdowns. But we are at a turning point. Governments, business owners, and many members of the public want things to open up. They also don't want a third wave. If you look at Portugal above, they opened things up after their second wave; their 3rd wave accompanied the appearance of S:N501. Denmark, on the other hand, is continuing its lockdown till at least the end of February. If we follow the Portuguese strategy, we have a high likelihood of a brutal third wave. Nothing is certain. But highly likely. Which strategy would YOU bet on?




As you can see, strong efforts across the country—especially in Ontario, Quebec, and Alberta, have really slayed the beast. But at a huge cost—business closures, unemployment, school closures, etc. The tendency would be to open things up. Premiers Kenney (Alberta), Ford (Ontario), and Legault (Quebec) have all indicated they will do so. Each of them is doing this against all the supportive scientific evidence. I don't blame them nor the public for wanting to open up. But with the new variants taking hold across Canada, we should be taking a Danish approach to things.

---

## Post-script on Ivermectin

- **there is no strong evidence ivermectin is more beneficial than harmful or even works**

After last week's newsletter, Dr. Pierre Kory, the peddler of ivermectin and other nonsense, contacted me to spew anger, and advise me that I would be proven wrong about ivermectin. Yesterday, Merck, the maker of ivermectin, came out to say that there is "no scientific basis for a potential therapeutic effect against COVID-19 from pre-clinical studies" and "no meaningful evidence for clinical activity or clinical efficacy in patients with COVID-19" and "a concerning lack of safety data in the majority of studies". PLEASE do not keep emailing me about ivermectin. And that includes you, dear Dr. Kory.


---

## We still have February and March

Yep. Or yup. (I have moved to yep, lately, for reasons unclear to me. I still say "yup" but type "yep". Odd.) As I have been saying for months now, this is a long, difficult winter for all. Winter ends March 22. Regardless of what our government leaders choose, the virus has "decided" that we will have a brutal winter. My advice:

1. Just think about the week or two ahead, make the most of a pretty awful situation, and avoid thinking too much about the spring or summer or a time without COVID ... because we really don't know how soon (or not) that will be. (It is very tempting for my colleagues to give you a rosy outlook, but back on December 4, I cautioned everyone about "Claiming Victory Too Soon" and I give that same advice now.)

2. Be happy that we are really doing much better.

3. Know that we WILL get vaccines, eventually, so don't fret about the minutiae about a week or month or 2 here or there

4. Get some sunlight when it is outside. There IS sunlight out there, and I am trying to get some during my day.

5. Remember that—even with these new variants—the basic principles of protecting yourself stay the same. I am putting a useful reminder for you below.

6. Eat chocolate. Preferably dark. Often.

7. I totally forgot to mention Freddy Van Vleet!!!! I am too busy.

8. Watch the video at the end.

## *Keeping Safe and Protecting Yourself and Others from COVID19*

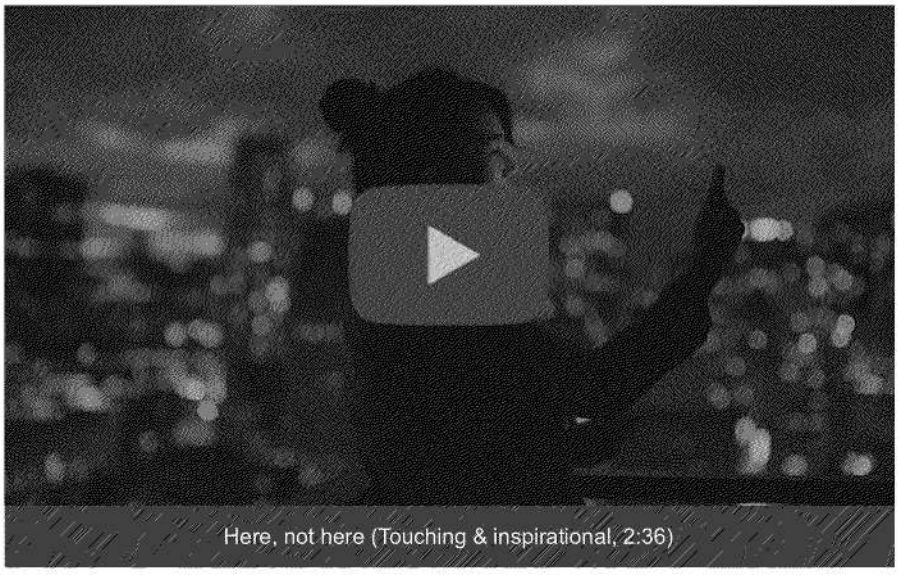
**Layer each measure on!**
The more you add to your pile of prevention, the lower your risk of COVID19 infection

| Stay Home If You Can | Wear a Mask | Stay Distant | Avoid 3'Cs: | Open Windows | Clean Hands and High Touched Surfaces |
|---|---|---|---|---|---|
| Limit contact and activities with non-household contacts<br><br>Avoid close contact with people who are sick | Select a high-quality mask with multi-layers, a good fit, and filtration<br><br>Wear a mask in indoor and outdoor settings when around other people<br><br>Wear a mask correctly (over your nose and mouth) and consistently | Stay at least 6 feet from non-household contacts but the more distance the better.<br><br>Limit duration and time spent when around others | Avoid crowded places, close contact settings, confined, enclosed spaces | Increase ventilation and airflow by opening windows and doors if possible | Clean hands often and especially after touching any high touch surfaces, contaminated items, after being in a public space and before touching your face<br><br>Clean and disinfect high touch surfaces daily or more if contaminated |

| Stay Informed | Get Tested Periodically | Get Vaccinated When Eligible | Monitor Your Health | Practice Respiratory Etiquette |
|---|---|---|---|---|
| Stay up-to-date on local COVID19 news including rate of community transmission, and public health announcements<br><br>If you get a call from a contact tracer or public health department, pick up the phone<br><br>See your local health department website among other credible sources of information | If you engage in activity requiring in-person contact outside your home or live or work in a congregate setting, you should get tested at least once a month (regardless of exposure or symptoms)<br><br>There are several types of COVID19 tests, some more reliable than others. Talk to your health care provider about which type of test is best for you based on reason for testing | Get the COVID19 vaccine when eligible and if you meet the criteria for vaccination<br><br>Ensure you follow vaccination schedule (2 dose) depending on vaccine received for full protection | Be alert for symptoms of COVID19 or any new or concerning symptoms especially if you engage in activities or settings with other people | Always practice respiratory etiquette, cover your coughs and sneezes and wash or sanitizer your hands |

**TO LEARN MORE, FOLLOW**
**@syramadad**
and
**@angie_rasmussen**

This excellent "cheat sheet" is from Drs. Syra Madad and Angie Rasmussen (who is moving to Saskatchewan very soon).



For more content from me, follow me on Twitter @ASPphysician

Share Tweet Forward Share

**From:** Gale-Rowe, Margaret (PHAC/ASPC)
**Sent:** 2021-04-26 2:32 PM
**To:** Sarwar, Elaha (PHAC/ASPC); Marinsky, Cheryl (PHAC/ASPC)
**Cc:** Cortés-Kaplan, Serena (PHAC/ASPC); Dave, Jaahnavi (PHAC/ASPC); Anna Jirovec
**Subject:** Input on therapeutics LISA AND THERAPEUTICS TEAM FOR INPUT BY APRIL 29 - 21-108019 - Vitamin D, Colcichine, Ivermectin
**Attachments:** 21-108019-10 Incoming Apr 22.pdf; 21-108019_VitD_Colchicine, Ivermectin_Response_Apr2021.doc

---

**Importance:** High

**Categories:** DO pending

Hi,

By way of this email, I am asking the technical team if they have input (short bullets/summary) and on colchicine and ivermectin or new info on Vit D.

I don't know if there are previous webmails/requests to model the response after, but suggest including wording on re-purposed drugs and authorized/off-label use. Maybe also that the practice of medicine is under PT jurisdiction, only because the writer refers to "ignoring the evidence".

Elaha/Cheryl, I know you likely have several things on your plate today. Is it possible for one of the team to look at this?

Margaret

---

**From:** Poon Young, Celisse (PHAC/ASPC) <celisse.poonyoung@canada.ca> **On Behalf Of** COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC)
**Sent:** 2021-04-26 1:54 PM
**To:** Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>; Marinsky, Cheryl (PHAC/ASPC) <cheryl.marinsky@canada.ca>; Lawuyi2, Niyi (PHAC/ASPC) <niyi.lawuyi2@canada.ca>
**Cc:** Poon Young, Celisse (PHAC/ASPC) <celisse.poonyoung@canada.ca>
**Subject:** FW: LISA AND THERAPEUTICS TEAM FOR INPUT BY APRIL 29 - 21-108019 - Vitamin D, Colcichine, Ivermectin
**Importance:** High

Hi everyone,

Please see the request that came to the Therapeutics inbox this afternoon. Sending to you all since I am not sure exactly who this should be directed to.

Thank you,

Celisse

---

**From:** Jamil, Marium (PHAC/ASPC) <marium.jamil@canada.ca>
**Sent:** 2021-04-26 12:21 PM
**To:** Waddell, Lisa (PHAC/ASPC) <lisa.waddell@canada.ca>; COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC) <phac.covid-19therapeutics-therapeutiques.aspc@canada.ca>
**Cc:** PHAC.F OCSO_ESGSecretariat / BCSC_SecrétariatGSE F.ASPC <phac.ocso_esgsecretariat-bcsc_secretariatgse.aspc@canada.ca>
**Subject:** LISA AND THERAPEUTICS TEAM FOR INPUT BY APRIL 29 - 21-108019 - Vitamin D, Colcichine, Ivermectin
**Importance:** High

Good morning Lisa and Therapeutics team,
**FOR INPUT/APPROVAL – BY APRIL 29**
**CONTEXT**

- Dr. Tam received correspondence on April 21, 2021 from a member of the public (please see attached '21-108019-10 Incoming Apr 22.pdf'), regarding the use of Vitamin D, Ivermectin and Colchicine as treatments for COVID-19.

**FOR INPUT**

- ESG Secretariat has drafted a standard response in regards to the use of Vitamin D (please see attached '21-108019-VitD_Colchicine, Ivermectin _ Response_Apr2021. doc') adapted from previous responses. The letter does not speak to Colchicine or Ivermectin however. We would be thankful if you could please provide **your input on:**
    - **Any evidence to support the use of Ivermectin and Colchicine**
    - **Any NEW evidence on the efficacy of Vitamin D**

Thank you so much for your time. We would be grateful if you could please provide us your input by April 29th.

Please let us know if you have any questions.

Regards,
Marium

*On behalf of the Office of Chief Science Officer and the PHAC Emerging Science Group Secretariat*

**Marium Jamil**
(she | elle)
Policy Analyst | Analyste des politiques
Office of the Chief Science Officer | Bureau du Conseiller scientifique en chef
Public Health Agency of Canada | Agence de la santé publique du Canada
NEW: phac.ocso_esgsecretariat-bcsc_secretariatgse.aspc@canada.ca

**From:** Azad, Mina (PHAC/ASPC)

**Sent:** 2021-06-03 7:25 PM

**To:** Forbes, Nicole (PHAC/ASPC)

**Cc:** Gale-Rowe, Margaret (PHAC/ASPC); Arthur, Jacqueline (PHAC/ASPC); Djiometio, Joseph (PHAC/ASPC)

**Subject:** Ivecmertin statment

---

**Ivermectin Overview**

Ivermectin is a broad-spectrum anti-parasitic agent authorized and approved by Health Canada for human and veterinary applications. Health Canada has not authorized its use for the treatment of COVID-19.

**Ivermectin Findings & Outcomes**

- In laboratory studies, ivermectin prevented SARS-CoV2 from replicating and has demonstrated anti-inflammatory properties, raising the possibility that ivermectin may have a role in COVID-19 prophylaxis or treatment.
- While preliminary *in vitro* and animal studies reported promising antiviral and anti-inflammatory effects of ivermectin in the context of SARS-CoV-2 infection, its use as a preventative or treatment for COVID-19 remains controversial due to mixed evidence of clinical benefit from numerous smaller, underpowered randomized trials.
- The British Medical Journal's living systematic review and network meta-analysis analysed 16 randomized trials. Based on their findings, they rated the effects of ivermectin on viral clearance, mechanical ventilation and mortality as uncertain, meaning it is uncertain whether ivermectin has an important impact on any patient-important outcome.
- Recently, a meta-analysis based on 18 randomized trials of ivermectin in COVID-19 found that ivermectin treatment reduced mortality, time to clinical recovery, and time to viral clearance.
- A powered, well-designed randomized trial is needed to clearly elucidate the appropriate role of ivermectin in the clinical management or prevention of COVID-19.

**Considerations**

***Canadian perspectives***

- The Canadian Agency for Drugs and Technologies in Health (CADTH; statement issued on February 08, 2021); Alberta Health Services (statement issued on February 02, 2021) ; as well as British Columbia's COVID-19 Therapeutics Committee/COVID-19 Therapeutics Review and Advisory Working Group (statement issued on May 25, 2021) have all concluded that there is no clear benefit associated with ivermectin treatment among patients with COVID-19. As of June 3, 2021, no statement has been issued by INESSS.
- On May 28, 2021, Ontario's COVID-19 Science Advisory Table issued a statement titled Ivermectin to Prevent Disseminated Strongyloides Infection in Patients with COVID-19. While stipulating ivermectin is currently not recommended as a treatment or preventative for COVID-19, the statement acknowledges patients with COVID-19 who receive therapies that alter immune system function may require ivermectin for the purposes of treating a pre-existing parasitic infection and to avoid severe complications of worsening parasitic infection.

***International perspectives***

- In South American countries, ivermectin is being prescribed routinely for COVID-19 infections; however, it is difficult to ascertain clinical benefit from use outside the context of randomized controlled trials.
- On March 31, 2021, the WHO issued a statement on ivermectin advising against its use outside of clinical trials, stating the current clinical evidence was inconclusive
- On March 22, 2021 the EMA issued an advisory notice against use of ivermectin for the prevention or treatment of COVID-19 outside randomised clinical trials.

- On February 11, 2021 the NIH COVID-19 Treatment Guidelines Panel issued a statement concluding there is insufficient evidence to recommend either for or against the use of ivermectin for the treatment of COVID-19.

**From:** Forbes, Nicole (PHAC/ASPC)
**Sent:** 2021-06-03 6:17 PM
**To:** Azad, Mina (PHAC/ASPC)
**Cc:** Djiometio, Joseph (PHAC/ASPC); Arthur, Jacqueline (PHAC/ASPC); Gale-Rowe, Margaret (PHAC/ASPC)
**Subject:** Ivermectin for CPHO
**Attachments:** Ivecmertin statment_NF.docx

---

**Categories:** Complete

Hi Mina,

Please see attached suggestions to your draft response. Looks good just need to add a few details and I provided some suggested text for your consideration. If you can please review and send to me *in the text of an email* as this is what CPHO wants I will send to Marina and cc you.

I think also we need to note that no new RCT has reported out… may be good to make that clear in one bullet at the top, after meta analysis bullet reporting positive benefit.

☺

Nicole

---

**Nicole Forbes, PhD**
(she | elle)
**Scientific Project Coordinator**
National Advisory Committee on Immunization Secretariat
Centre for Immunization Readiness, Public Heath Agency of Canada
Tel: (613) 447-6450
Email: nicole.forbes@canada.ca

**From:** no-reply@notifications.iloveevidence.com on behalf of I LOVE Evidence

**Sent:** 2021-06-04 1:21 AM

**To:** COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC)

**Subject:** LOVE notifications

---

**Categories:** A-2021-000129

L·OVE Powered by: Epistemonikos Foundation

Hi PHAC,

Manage L·OVE subscriptions

Your updates from 2021/06/03 to 2021/06/04

## COVID-19

**Question:** Tocilizumab for COVID-19

There are no new articles for this question

**Question:** Remdesivir for COVID-19

There are no new articles for this question

**Question:** Ivermectin for COVID-19

**Primary studies** 1

1. Abd-Elsalam S, Noor RA, Badawi R, Khalaf M, Esmail ES, Soliman S, Abd El Ghafar MS, Elbahnasawy M, Moustafa EF, Hassany SM, Medhat MA, Ramadan HK, Eldeen MAS, Alboraie M, Cordie A, Esmat G. Clinical Study Evaluating the Efficacy of Ivermectin in COVID-19 Treatment: A Randomized Controlled Study. Journal of medical virology. 2021; | Epistemonikos | DOI

**Question:** Otilimab for COVID-19

There are no new articles for this question

**Question:** Molnupiravir for COVID-19

There are no new articles for this question

**Question:** Anti-sars-cov-2 antibodies for COVID-19

There are no new articles for this question

**Question:** Colchicine for COVID-19

There are no new articles for this question

**Question:** Baricitinib for COVID-19

There are no new articles for this question

**Question:** Casirivimab and/or imdevimab for COVID-19

There are no new articles for this question

**Question:** Azd7442 for COVID-19

There are no new articles for this question

**Question:** Sarilumab for COVID-19

There are no new articles for this question

**Question:** Antiviral drugs for COVID-19

There are no new articles for this question

**Question:** Anakinra for COVID-19

There are no new articles for this question



As the identification of articles is a continuous process, including both automated and human tasks, this notification might not portray the most accurate list of evidence for this question. Go to the L·OVE platform to access it.

**From:** no-reply@notifications.iloveevidence.com on behalf of I LOVE Evidence

**Sent:** 2021-06-05 1:22 AM

**To:** COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC)

**Subject:** LOVE notifications

---

**Categories:** A-2021-000129, Shared as FYI ONLY

Hi PHAC,

Manage L·OVE subscriptions

Your updates from 2021/06/04 to 2021/06/05

## COVID-19

**Question:** Tocilizumab for COVID-19

There are no new articles for this question

**Question:** Remdesivir for COVID-19

There are no new articles for this question

**Question:** Ivermectin for COVID-19

**Primary studies** 1

1. Rizwan Faisal, Syed Furqan Ali Shah, Mazhar Hussain. Potential use of azithromycin alone and in combination with ivermectin in fighting against the symptoms of COVID-19. The Professional Medical Journal. 2021;28(5). | Epistemonikos | DOI

**Question:** Otilimab for COVID-19

There are no new articles for this question

**Question:** Molnupiravir for COVID-19

There are no new articles for this question

**Question:** Anti-sars-cov-2 antibodies for COVID-19

**Primary studies** 1

1. Cohen MS, Nirula A, Mulligan MJ, Novak RM, Marovich M, Yen C, Stemer A, Mayer SM, Wohl D, Brengle B, Montague BT, Frank I, McCulloh RJ, Fichtenbaum CJ, Lipson B, Gabra N, Ramirez JA, Thai C, Chege W, Gomez Lorenzo MM, Sista N, Farrior J, Clement ME, Brown ER, Custer KL, Van Naarden J, Adams AC, Schade AE, Dabora MC, Knorr J, Price KL, Sabo J, Tuttle JL, Klekotka P, Shen L, Skovronsky DM, BLAZE-2 Investigators. Effect of Bamlanivimab vs Placebo on Incidence of COVID-19 Among Residents and Staff of Skilled Nursing and Assisted Living Facilities: A Randomized Clinical Trial. JAMA. 2021; | Epistemonikos | DOI

**Question:** Colchicine for COVID-19

There are no new articles for this question

**Question:** Baricitinib for COVID-19

There are no new articles for this question

**Question:** Casirivimab and/or imdevimab for COVID-19

There are no new articles for this question

**Question:** Azd7442 for COVID-19

There are no new articles for this question

**Question:** Sarilumab for COVID-19

There are no new articles for this question

**Question:** Antiviral drugs for COVID-19

There are no new articles for this question

**Question:** Anakinra for COVID-19

There are no new articles for this question

**From:** Gale-Rowe, Margaret (PHAC/ASPC)
**Sent:** 2021-04-27 11:32 AM
**To:** Marinsky, Cheryl (PHAC/ASPC); Sarwar, Elaha (PHAC/ASPC); Cortés-Kaplan, Serena (PHAC/ASPC)
**Subject:** MGR comments LISA AND THERAPEUTICS TEAM FOR INPUT BY APRIL 29 - 21-108019 - Vitamin D, Colcichine, Ivermectin
**Attachments:** Correspondence on Vit. D Colchicine and Ivermectin-DRAFT mgr.docx

---

Thanks Cheryl,

I suggest some changes to simplify the first paragraph.

Elaha, I agree with your suggestions.

Perhaps you could look at the Cheryl's draft, make your changes and then route through Joseph for his review before sending to HC.

Thanks,

dMargaret

---

**From:** Marinsky, Cheryl (PHAC/ASPC) <cheryl.marinsky@canada.ca>
**Sent:** 2021-04-27 10:35 AM
**To:** Sarwar, Elaha (PHAC/ASPC) <elaha.sarwar@canada.ca>; Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>; Cortés-Kaplan, Serena (PHAC/ASPC) <serena.cortes-kaplan@canada.ca>
**Subject:** RE: LISA AND THERAPEUTICS TEAM FOR INPUT BY APRIL 29 - 21-108019 - Vitamin D, Colcichine, Ivermectin

Hi Elaha,

Yes, I agree this is in Health Canada's jurisdiction since these treatments are not authorized nor approved for use in Canada.

I think we do need to address the issue raised in the body of the letter regarding all the studies on these treatments, not sure what she is reading but it seems that publication to her, as it is for many Canadians is an endorsement of effectiveness. I have crafted some lines to address this acceptance of published results as validation of effectiveness, I think this is a valuable education opportunity as well. I have attached a very rough draft based on information from the WHO. Please have a look, it is too long, for this reply but content from the first two paragraphs could be repurposed.

Happy to keep working on this and adding content from the OCSC to what we have.

Thoughts and suggestions welcome! ☺

Cheryl

---

**From:** Sarwar, Elaha (PHAC/ASPC) <elaha.sarwar@canada.ca>
**Sent:** 2021-04-27 10:23 AM

**To:** Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>; Marinsky, Cheryl (PHAC/ASPC) <cheryl.marinsky@canada.ca>; Cortés-Kaplan, Serena (PHAC/ASPC) <serena.cortes-kaplan@canada.ca>
**Subject:** RE: LISA AND THERAPEUTICS TEAM FOR INPUT BY APRIL 29 - 21-108019 - Vitamin D, Colcichine, Ivermectin

Good morning,

Just a couple of thoughts on this request.

For drugs that are not approved in Canada for COVID-19 (ivermectin and colchicine), I think we can draft standard lines and flip to HC as it is their jurisdiction. Followed by an overarching summary of evidence on these (couple of bullets).

Something like this: The PHAC is monitoring emerging evidence of clinical efficacy and safety on novel and repurposed therapeutics for COVID-19, including ivermectin, cholchicine, and vitamin D. Health Canada, the regulator in Canada, will review clinical data once submitted from the manufacturer and determine the benefits and risks of potential therapeutics and provide regulatory approval for COVID-19 accordingly.

I don't think we need to spend too much time on it from our side.

Just my opinion ☺

Elaha

---

**From:** Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>
**Sent:** 2021-04-26 2:53 PM
**To:** COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC) <phac.covid-19therapeutics-therapeutiques.aspc@canada.ca>
**Cc:** Marinsky, Cheryl (PHAC/ASPC) <cheryl.marinsky@canada.ca>; Sarwar, Elaha (PHAC/ASPC) <elaha.sarwar@canada.ca>
**Subject:** LISA AND THERAPEUTICS TEAM FOR INPUT BY APRIL 29 - 21-108019 - Vitamin D, Colcichine, Ivermectin

Cheryl is drafting input.

Is this to be DG-approved by April 29th? We will do our best but that is a short turnaround for a request from the public that requires summarizing evidence.
I haven't been able to get to my pre-existing "to do" list today due to other time-sensitive HR things and emails.

Margaret

---

**From:** Poon Young, Celisse (PHAC/ASPC) <celisse.poonyoung@canada.ca> **On Behalf Of** COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC)
**Sent:** 2021-04-26 1:54 PM
**To:** Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>; Marinsky, Cheryl (PHAC/ASPC) <cheryl.marinsky@canada.ca>; Lawuyi2, Niyi (PHAC/ASPC) <niyi.lawuyi2@canada.ca>
**Cc:** Poon Young, Celisse (PHAC/ASPC) <celisse.poonyoung@canada.ca>

**Subject:** FW: LISA AND THERAPEUTICS TEAM FOR INPUT BY APRIL 29 - 21-108019 - Vitamin D, Colcichine, Ivermectin
**Importance:** High

Hi everyone,

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Thank you,

Celisse

---

**From:** Jamil, Marium (PHAC/ASPC) <marium.jamil@canada.ca>
**Sent:** 2021-04-26 12:21 PM
**To:** Waddell, Lisa (PHAC/ASPC) <lisa.waddell@canada.ca>; COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC) <phac.covid-19therapeutics-therapeutiques.aspc@canada.ca>
**Cc:** PHAC.F OCSO_ESGSecretariat / BCSC_SecrétariatGSE F.ASPC <phac.ocso_esgsecretariat-bcsc_secretariatgse.aspc@canada.ca>
**Subject:** LISA AND THERAPEUTICS TEAM FOR INPUT BY APRIL 29 - 21-108019 - Vitamin D, Colcichine, Ivermectin
**Importance:** High

Good morning Lisa and Therapeutics team,
**FOR INPUT/APPROVAL – BY APRIL 29**
**CONTEXT**

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**FOR INPUT**

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    - **Any evidence to support the use of Ivermectin and Colchicine**
    - **Any NEW evidence on the efficacy of Vitamin D**

Thank you so much for your time. We would be grateful if you could please provide us your input by April 29th.

Please let us know if you have any questions.

Regards,
Marium

*On behalf of the Office of Chief Science Officer and the PHAC Emerging Science Group Secretariat*

**Marium Jamil**
(she | elle)
Policy Analyst | Analyste des politiques
Office of the Chief Science Officer | Bureau du Conseiller scientifique en chef

Public Health Agency of Canada | Agence de la santé publique du Canada
NEW: phac.ocso_esgsecretariat-bcsc_secretariatgse.aspc@canada.ca

**From:** Gale-Rowe, Margaret (PHAC/ASPC)
**Sent:** 2021-06-03 10:30 AM
**To:** Djiometio, Joseph (PHAC/ASPC)
**Cc:** COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC); Arthur, Jacqueline (PHAC/ASPC)
**Subject:** MGR edits - : I-Mask+ Protocol for early treatment of Covid-19

---

**Categories:** DO pending

Hi Joe/Jackie,

I have tweaked it and think there is sufficient information in here for BE's response.

Joe, there is a question for you about describing the protocol without listing all the elements. I saw your comment about senior management needing to know more about it, but that can appear in the email sent to BE along with the response.
Also, are there any (good) trials of the protocol underway? If yes, should mention. I wouldn't worry too much about this as a number of expert tables have decided there is not good evidence for the protocol.

Margaret

**Original:**
I-MASK+ Protocol is a prevention & early outpatient treatment protocol for COVID-19Patients are treated with Ivermectin, Vitamin D3, Vitamin C, Quercetin, Zinc, Melatonin, Fluvoxamine, Nasopharyngeal, Sanitation, Melatonin and Aspirin. I-MASK+ Protocol is for COVID-19 is centered ivermectin.

**Suggested revision**: I-MASK+ Protocol is a prevention & early outpatient treatment protocol for COVID-19. While it includes a number of medications and supplements, it is centred on ivermectin, a broad-spectrum anti-parasitic agent authorized and approved by HC for human and veterinary applications to treat parasitic infections.

I-Mask+ Protocol response to J...

-----Original Message-----
From: Djiometio, Joseph (PHAC/ASPC) <joseph.djiometio@canada.ca>
Sent: 2021-06-02 12:27 PM
To: Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>
Cc: COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC) <phac.covid-19therapeutics-therapeutiques.aspc@canada.ca>; Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>
Subject: RE: I-Mask+ Protocol for early treatment of Covid-19

Hello Margaret
Here is the draft response to [redacted] about the I-Mask+ Protocol.
I used MECS#21-108019-10 as support document to draft this response.
Let me know if you have any questions

Joe

-----Original Message-----
From: COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC) <phac.covid-19therapeutics-therapeutiques.aspc@canada.ca>
Sent: 2021-06-01 11:33 AM
To: Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>; Djiometio, Joseph (PHAC/ASPC) <joseph.djiometio@canada.ca>; COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC) <phac.covid-19therapeutics-therapeutiques.aspc@canada.ca>
Cc: Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>
Subject: RE: I-Mask+ Protocol for early treatment of Covid-19

Profiled in MECS u der 21-110593-856 where I will add our final draft.

-----Original Message-----
From: Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>
Sent: 2021-05-31 4:39 PM
To: Djiometio, Joseph (PHAC/ASPC) <joseph.djiometio@canada.ca>; COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC) <phac.covid-19therapeutics-therapeutiques.aspc@canada.ca>
Cc: Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>
Subject: FW: I-Mask+ Protocol for early treatment of Covid-19

Hi Joe;
We have received the correspondence below via our Director General's office regarding the I-Mask+ Protocol that centers around the main treatment, ivermection. Follow the link provided in the incoming correspondence.
Please review and prepare a draft response for Margaret's review by Wednesday.
I've attached previous correspondence we have done on ivermectin to assist - Adéle, could you track down the final correspondence that was sent under MECS#21-108019-10? It would be helpful for Joe to have the approved version sent.

Happy to discuss.
Jackie

---
Jacqueline Arthur, BScN, RN
(she | elle)
Senior Manager, AMR Division | Gestionnaire principale, Division de la RAM
COVID-19 Therapeutics | thérapeutiques
CCDIC, PHAC | CLMTI, ASPC
t. (613) 889-8455

-----Original Message-----
From: Ephrem, Bersabel (PHAC/ASPC) <bersabel.ephrem@canada.ca>
Sent: 2021-05-31 4:07 PM
To: Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>
Cc: Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>; Hunt, Kelly (PHAC/ASPC) <kelly.hunt@canada.ca>
Subject: FW: I-Mask+ Protocol for early treatment of Covid-19

Hi Jackie,

Can we have a response? Please see below.

be

-----Original Message-----
From: McLean, Hollie (HC/SC) <hollie.mclean@canada.ca> On Behalf Of Levesque2, Kaili (HC/SC)
Sent: 2021-05-31 3:54 PM
To: [redacted]
Cc: Ephrem, Bersabel (PHAC/ASPC) <bersabel.ephrem@canada.ca>; Levesque2, Kaili (HC/SC) <kaili.levesque2@canada.ca>; McLean, Hollie (HC/SC) <hollie.mclean@canada.ca>
Subject: RE: I-Mask+ Protocol for early treatment of Covid-19

Hi [redacted]

Thank you for your email. Note that I've recently assumed the role as Vice President, COVID-19 Vaccine Rollout at the Public Health Agency. I'm connecting you with Bersabel Ephrem, the Director General responsible for the therapeutics file.

Thanks

Kaili

Kaili Levesque (she/her/elle)
613.818.0492

-----Original Message-----
From [redacted]
Sent: 2021-05-31 12:13 PM
To: Levesque2, Kaili (HC/SC) <kaili.levesque2@canada.ca>
Subject: I-Mask+ Protocol for early treatment of Covid-19

Good morning Ms. Levesque:

I am writing to ask for your assistance. I have been following a growing body of research on the use of the I-Mask Protocol for early treatment and prophylaxis for Covid-19. Early in the pandemic, this protocol was not well understood and had only anecdotal evidence of its efficacy. Recently, however, I've been encouraged to see multiple studies showing good evidence of efficacy. I am puzzled as to why this treatment is not being studied in Canada as we are still in a situation across the country where people are being hospitalized for Covid-19. I am not a medical professional, but I wonder if it is not prudent and compassionate to open the door to other treatment possibilities which could prevent further deterioration of newly diagnosed victims of this virus? I do not know if you are the right person to send this email to, but I do know that you believe that we should be doing absolutely everything to try to treat this disease. My sincere hope is that you and your Task Force are seeking to include the use of existing medicines that we know are not harmful in and of themselves, such as Ivermectin, which is one of the components in the I-Mask Protocol. While we all look forward to the day when vaccinations take effect Canada-wide, in the meantime there are still many people who are falling ill and require medical treatment for this disease.

I respectfully submit to you this link to the growing body of knowledge and research studies around the I-Mask+ Protocol and I beg you to use your considerable influence to bring it to the attention of the Covid 19 Task Force and study it with all due diligence. If there is merit in this

treatment, and your committee agrees to try it on a limited study basis, perhaps many Canadian lives could be saved and/or at the very least, saved from the longevity of hospitalizations for Covid 19 which they may be facing under the current treatment protocols. I believe that your committee has a moral and ethical obligation to fairly and diligently consider all possible treatments, irrespective of WHO or any other body who may be telling you otherwise. We are Canadians, first and foremost. We are responsible for one another.

Thank you so very much for your time. I ask you to please respectfully consider my request, and I very much look forward to your reply.

Sincerely,

[redacted]
Alberta, Canada

https://covid19criticalcare.com/covid-19-protocols/i-mask-plus-protocol/

**From:** Arthur, Jacqueline (PHAC/ASPC)
**Sent:** 2021-03-24 4:26 PM
**To:** Forbes, Nicole (PHAC/ASPC)
**Cc:** Siushansian, Jennifer (PHAC/ASPC); Lawuyi2, Niyi (PHAC/ASPC); Gale-Rowe, Margaret (PHAC/ASPC)
**Subject:** RE: ADM deck
**Attachments:** ADM DS_Emerging Therapeutics_25March2021v2.pptx; Annex_ADM DS_Emerging Therapeutics_25March2021v2.pptx

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Great job pulling this together so quickly Nicole. I've made minor tweaks. I'll present it [redacted] let me know if you plan to listen in – if so, I will turn to you for any technical questions otherwise we can follow up later.

For translation, the main deck should be sent to official translation services (I will send it to Celisse to action). Jennifer, please give Cheryl a heads up for her side by side review next week.

The second deck will have already been translated based on the FPT DS TF deck, except maybe the first page which is straight forward.

Much appreciated.
Jackie

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Jacqueline Arthur, RN, BScN
(she | elle)
Senior Manager, AMR Division | Gestionnaire principale, Division de la RAM
COVID-19 Therapeutics | thérapeutiques
CCDIC, PHAC | CLMTI, ASPC
t. (613) 889-8455

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**From:** Forbes, Nicole (PHAC/ASPC) <nicole.forbes@canada.ca>
**Sent:** 2021-03-24 3:50 PM
**To:** Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>
**Cc:** Siushansian, Jennifer (PHAC/ASPC) <jennifer.siushansian@canada.ca>; Lawuyi2, Niyi (PHAC/ASPC) <niyi.lawuyi2@canada.ca>; Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>
**Subject:** ADM deck

Hi Jackie and team,

Here is my draft deck for the ADM meeting tomorrow (and requested annex) as well as the request from Linsey for this deck:

*The ADMs are hoping PHAC can come to the ADM table tomorrow with a short presentation (5-6 slides) that covers the following:*

- *A snapshot of what's on PHAC's radar (just buckets you presented on slides 5 )*
  - *Slides 7-12 have some great info so maybe include them in an annex in case ADMs want to have a look on their own time?*

- *Plans for ongoing FPT engagement*
  - *Continued use of one-off FPT meetings that include clinical colleagues (e.g. upcoming meeting with Gilead on remdesivir)*
  - *Outreach to PTs on usage data*
- *PHAC's early thinking on how to incorporate vaccination info into the ongoing plans re emerging therapies*

I feel like the second ask is a big one provided the <1 day notice to prep this deck. I took a shot. Option to say yes to presenting the deck but to hold off on that agenda item could be considered- will leave it for you to decide Jackie!

Nicole

---

**Nicole Forbes, PhD**
(she | elle)
**Technical Lead**
COVID-19 Therapeutics | thérapeutiques
CCDIC, PHAC | CLMTI, ASPC
Tel: (613) 447-6450
Email: nicole.forbes@canada.ca

**From:** Gale-Rowe, Margaret (PHAC/ASPC)
**Sent:** 2021-06-07 5:39 PM
**To:** Djiometio, Joseph (PHAC/ASPC)
**Cc:** Azad, Mina (PHAC/ASPC)
**Subject:** RE: Also request about US position on ivermectin

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Thanks Joe

-----Original Message-----
From: Djiometio, Joseph (PHAC/ASPC) <joseph.djiometio@canada.ca>
Sent: 2021-06-07 3:29 PM
To: Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>
Cc: Azad, Mina (PHAC/ASPC) <mina.azad@canada.ca>
Subject: RE: Also request about US position on ivermectin

Hello Margaret
FDA has not approved ivermectin for use in treating or preventing COVID-19 in humans (May 03 2021).

https://www.fda.gov/consumers/consumer-updates/why-you-should-not-use-ivermectin-treat-or-prevent-covid-19

The Information is available in the following section:
Here's What You Need to Know about Ivermectin When Can Taking Ivermectin Be Unsafe?

Let me know  if there is anything else to do

Joe

-----Original Message-----
From: Djiometio, Joseph (PHAC/ASPC)
Sent: 2021-06-07 9:27 AM
To: Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>
Cc: Azad, Mina (PHAC/ASPC) <mina.azad@canada.ca>
Subject: RE: Also request about US position on ivermectin

Hello Margaret
Which request should go first? Ivermectin or Regeneron?
Joe

-----Original Message-----
From: Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>
Sent: 2021-06-07 9:15 AM
To: Djiometio, Joseph (PHAC/ASPC) <joseph.djiometio@canada.ca>
Cc: Azad, Mina (PHAC/ASPC) <mina.azad@canada.ca>
Subject: Also request about US position on ivermectin

Hi again,

She also asked about the US and what their position is / if they've issues a statement; perhaps this would be in the issue note?

Thank you,

Margaret

Medical Advisor - COVID Therapeutics Acquisitions
613-618-9266

**From:** Arthur, Jacqueline (PHAC/ASPC)
**Sent:** 2021-06-03 5:37 PM
**To:** Gale-Rowe, Margaret (PHAC/ASPC); Djiometio, Joseph (PHAC/ASPC); Azad, Mina (PHAC/ASPC)
**Cc:** Cortés-Kaplan, Serena (PHAC/ASPC)
**Subject:** RE: Call to Action on Consideration of COVID Treatment Options

---

I've spoken with Nicole and so please send her Mina's summary directly to Nicole.
Nicole will put Mina in touch with Marina for any follow up.
This needs to move quickly so that Dr. Tam has the information today.
Thanks,
Jackie

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Jacqueline Arthur, BScN, RN
(she | elle)
Senior Manager, AMR Division | Gestionnaire principale, Division de la RAM
COVID-19 Therapeutics | thérapeutiques
CCDIC, PHAC | CLMTI, ASPC
t. (613) 889-8455

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**From:** Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>
**Sent:** 2021-06-03 3:34 PM
**To:** Djiometio, Joseph (PHAC/ASPC) <joseph.djiometio@canada.ca>; Azad, Mina (PHAC/ASPC) <mina.azad@canada.ca>; Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>
**Cc:** Cortés-Kaplan, Serena (PHAC/ASPC) <serena.cortes-kaplan@canada.ca>
**Subject:** RE: Call to Action on Consideration of COVID Treatment Options

Just had a thought: Have you flagged to Nicole that we are responding to an email that came in to Kaili Levesque and was forwarded to our DG?

Margaret

**From:** Djiometio, Joseph (PHAC/ASPC) <joseph.djiometio@canada.ca>
**Sent:** 2021-06-03 3:12 PM
**To:** Azad, Mina (PHAC/ASPC) <mina.azad@canada.ca>; Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>; Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>
**Cc:** Cortés-Kaplan, Serena (PHAC/ASPC) <serena.cortes-kaplan@canada.ca>
**Subject:** RE: Call to Action on Consideration of COVID Treatment Options

Thank you Mina

**From:** Azad, Mina (PHAC/ASPC) <mina.azad@canada.ca>
**Sent:** 2021-06-03 3:10 PM
**To:** Djiometio, Joseph (PHAC/ASPC) <joseph.djiometio@canada.ca>; Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>; Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>
**Cc:** Cortés-Kaplan, Serena (PHAC/ASPC) <serena.cortes-kaplan@canada.ca>
**Subject:** RE: Call to Action on Consideration of COVID Treatment Options

Hi Joe,

Yes, I had a chat with Nicole an hour ago and am working on the summary right now. Nicole was asked by Marina and then she forwarded the email to me. I'm almost done with the first draft. I'll be sending it to Serena shortly.

Best,
Mina

**From:** Djiometio, Joseph (PHAC/ASPC) <joseph.djiometio@canada.ca>
**Sent:** 2021-06-03 3:06 PM
**To:** Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>; Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>
**Cc:** Azad, Mina (PHAC/ASPC) <mina.azad@canada.ca>; Cortés-Kaplan, Serena (PHAC/ASPC) <serena.cortes-kaplan@canada.ca>
**Subject:** FW: Call to Action on Consideration of COVID Treatment Options

Hello Jacky/Margaret
We have receive another request from Nicole for Ivermectin (it looks like Dr. Tam wants the summary ASAP). The 1st request this morning was from Erika PHAC Evidence group.

Joe

**From:** Azad, Mina (PHAC/ASPC) <mina.azad@canada.ca>
**Sent:** 2021-06-03 2:19 PM
**To:** Djiometio, Joseph (PHAC/ASPC) <joseph.djiometio@canada.ca>
**Subject:** FW: Call to Action on Consideration of COVID Treatment Options

**From:** Forbes, Nicole (PHAC/ASPC) <nicole.forbes@canada.ca>
**Sent:** 2021-06-03 11:54 AM
**To:** Azad, Mina (PHAC/ASPC) <mina.azad@canada.ca>; Birdi, Harsimrat (PHAC/ASPC) <harsimrat.birdi@canada.ca>
**Subject:** FW: Call to Action on Consideration of COVID Treatment Options

See request below.

**From:** Salvadori, Marina (PHAC/ASPC) <marina.salvadori@canada.ca>
**Sent:** 2021-06-02 11:41 PM
**To:** Forbes, Nicole (PHAC/ASPC) <nicole.forbes@canada.ca>
**Subject:** Re: Call to Action on Consideration of COVID Treatment Options

It's not a specific paper she wants but a review or pointing to a definitive trial

Marina Salvadori
Sent by Mobile Device

On Jun 2, 2021, at 10:11 PM, Forbes, Nicole (PHAC/ASPC) <nicole.forbes@canada.ca> wrote:

This is the recent publication that I think has caused the recent stir of interest:

https://journals.lww.com/americantherapeutics/Fulltext/2021/06000/Review_of_the_Emerging_Evidence_Demonstrating_the.4.aspx

**Pierre et al.** Review of the Emerging Evidence Demonstrating the Efficacy of Ivermectin in the Prophylaxis and Treatment of COVID-19. American Journal of Therapeutics. May/June 2021.

## Conclusions:

Meta-analyses based on 18 randomized controlled treatment trials of ivermectin in COVID-19 have found large, statistically significant reductions in mortality, time to clinical recovery, and time to viral clearance. Furthermore, results from numerous controlled prophylaxis trials report significantly reduced risks of contracting COVID-19 with the regular use of ivermectin. Finally, the many examples of ivermectin distribution campaigns leading to rapid population-wide decreases in morbidity and mortality indicate that an oral agent effective in all phases of COVID-19 has been identified.

I can flag this to Mina in therapeutics who [redacted] can happily summarize tomorrow morning :)

Nicole

**Nicole Forbes, PhD**
**she | elle**
**Scientific Project Coordinator**
NACI Secretariat
Centre for Immunization Readiness
Public Health Agency of Canada l Agence de la santé publique du Canada

Tel: (613) 447-6450
Email: nicole.forbes@canada.ca

On Jun 2, 2021, at 10:16 PM, Salvadori, Marina (PHAC/ASPC) <marina.salvadori@canada.ca> wrote:

Any chance you can blast back to therapeutics and help me answer this? The ivermectin had a big trial...is there a review article?
Marina

**From:** Tam, Dr Theresa (PHAC/ASPC) <drtheresa.tam@canada.ca>
**Sent:** 2021-06-02 8:56 PM
**To:** Salvadori, Marina (PHAC/ASPC) <marina.salvadori@canada.ca>; Njoo, Howard (PHAC/ASPC) <howard.njoo@canada.ca>
**Subject:** Fwd: Call to Action on Consideration of COVID Treatment Options

Is there some evidence review we can point people to on the Ivermectin question?

Sent from my iPhone

Begin forwarded message:

**From:** [redacted]
**Date:** June 2, 2021 at 8:39:33 PM EDT
**To:** "Chief Public Health Officer / La chef de la santé publique (PHAC/ASPC)" <phac.cpho-acsp.aspc@canada.ca>, "Tam, Dr Theresa (PHAC/ASPC)" <drtheresa.tam@canada.ca>
**Subject: Call to Action on Consideration of COVID Treatment Options**

Good evening Dr. Tam,

Since the start of the COVID pandemic around the world, doctors and clinicians have been exploring available treatments to use to improve the outcomes of COVID patients and protect others against the disease. One medication that has been proving to be extremely effective at both of these initiatives is ivermectin. I strongly urge you and Health Canada to give serious consideration to this treatment option as it could save the lives of those who continue to succumb to this illness. There is overwhelming data and multiple studies, from around the world, that support the fact that this treatment works. Failure to consider ivermectin as a viable treatment and prophylactic option for Canadians will result in unnecessary deaths and increased cases.

I have attached numerous studies and interviews for your consideration.

https://covid19criticalcare.com/
https://www.medrxiv.org/content/medrxiv/early/2020/06/09/2020.06.06.20124461.full.pdf
https://www.medrxiv.org/content/10.1101/2021.01.28.21250706v1.full
https://www.google.com/url?sa=t&source=web&rct=j&url=https://covid19criticalcare.com/wp-content/uploads/2020/11/FLCCC-Ivermectin-in-the-prophylaxis-and-treatment-of-COVID-19.pdf&ved=2ahUKEwjrs_PXmfrwAhX0Ap0JHXFqCQkQFjABegQIBhAC&usg=AOvVaw1STL_WpJw5v358JPemoTmF
https://youtu.be/Tn_b4NRTB6k

Thank you for your time and consideration,

[redacted]

**From:** Salvadori, Marina (PHAC/ASPC)
**Sent:** 2021-06-03 8:59 PM
**To:** Tam, Dr Theresa (PHAC/ASPC); Njoo, Howard (PHAC/ASPC)
**Cc:** Ponic, Pamela (PHAC/ASPC); Killen, Marita (PHAC/ASPC)
**Subject:** RE: Call to Action on Consideration of COVID Treatment Options

---

Here is a summary, with help frim Mina Azad and Nicole Forbes.
Marina

**Ivermectin Overview**

Ivermectin is a broad-spectrum anti-parasitic agent authorized by Health Canada for human and veterinary applications. Health Canada has not authorized its use for the treatment of COVID-19.

**Ivermectin Findings & Outcomes**

- In laboratory studies, ivermectin prevented SARS-CoV2 from replicating and has demonstrated anti-inflammatory properties, raising the possibility that ivermectin may have a role in COVID-19 prophylaxis or treatment.
- While preliminary *in vitro* and animal studies reported promising antiviral and anti-inflammatory effects of ivermectin in the context of SARS-CoV-2 infection, its use as a preventative or treatment for COVID-19 remains controversial due to mixed evidence of clinical benefit from numerous smaller, underpowered randomized trials.
- The British Medical Journal's living systematic review and network meta-analysis analysed 16 randomized trials. Based on their findings, they rated the effects of ivermectin on viral clearance, mechanical ventilation and mortality as uncertain, meaning it is uncertain whether ivermectin has an important impact on any patient-important outcome.
- Recently, a meta-analysis based on 18 randomized trials of ivermectin in COVID-19 found that ivermectin treatment reduced mortality, time to clinical recovery, and time to viral clearance.
- A powered, well-designed randomized trial is needed to clearly elucidate the appropriate role of ivermectin in the clinical management or prevention of COVID-19.

**Considerations**

***Canadian perspectives***

- The Canadian Agency for Drugs and Technologies in Health (CADTH; statement issued on February 08, 2021); Alberta Health Services (statement issued on February 02, 2021) ; as well as British Columbia's COVID-19 Therapeutics Committee/COVID-19 Therapeutics Review and Advisory Working Group (statement issued on May 25, 2021) have all concluded that there is no clear benefit associated with ivermectin treatment among patients with COVID-19. As of June 3, 2021, no statement has been issued by INESSS.
- On May 28, 2021, Ontario's COVID-19 Science Advisory Table issued a statement titled Ivermectin to Prevent Disseminated Strongyloides Infection in Patients with COVID-19. While stipulating ivermectin is currently not recommended as a treatment or preventative for COVID-19, the statement acknowledges patients with COVID-19 who receive therapies that alter immune system function may require ivermectin for the purposes of treating a pre-existing parasitic infection and to avoid severe complications of worsening parasitic infection.

***International perspectives***

- In South American countries, ivermectin is being prescribed routinely for COVID-19 infections; however, it is difficult to ascertain clinical benefit from use outside the context of randomized controlled trials.
- On March 31, 2021, the WHO issued a statement on ivermectin advising against its use outside of clinical trials, stating the current clinical evidence was inconclusive
- On March 22, 2021 the EMA issued an advisory notice against use of ivermectin for the prevention or treatment of COVID-19 outside randomised clinical trials.
- On February 11, 2021 the NIH COVID-19 Treatment Guidelines Panel issued a statement concluding there is insufficient evidence to recommend either for or against the use of ivermectin for the treatment of COVID-19.

---

**From:** Tam, Dr Theresa (PHAC/ASPC)
**Sent:** 2021-06-02 8:56 PM
**To:** Salvadori, Marina (PHAC/ASPC) ; Njoo, Howard (PHAC/ASPC)
**Subject:** Fwd: Call to Action on Consideration of COVID Treatment Options

Is there some evidence review we can point people to on the Ivermectin question?

Sent from my iPhone

Begin forwarded message:

> **From:** [redacted]
> **Date:** June 2, 2021 at 8:39:33 PM EDT
> **To:** "Chief Public Health Officer / La chef de la santé publique (PHAC/ASPC)" <phac.cpho-acsp.aspc@canada.ca>, "Tam, Dr Theresa (PHAC/ASPC)" <drtheresa.tam@canada.ca>
> **Subject: Call to Action on Consideration of COVID Treatment Options**
>
> Good evening Dr. Tam,

Since the start of the COVID pandemic around the world, doctors and clinicians have been exploring available treatments to use to improve the outcomes of COVID patients and protect others against the disease. One medication that has been proving to be extremely effective at both of these initiatives is ivermectin. I strongly urge you and Health Canada to give serious consideration to this treatment option as it could save the lives of those who continue to succumb to this illness. There is overwhelming data and multiple studies, from around the world, that support the fact that this treatment works. Failure to consider ivermectin as a viable treatment and prophylactic option for Canadians will result in unnecessary deaths and increased cases.

I have attached numerous studies and interviews for your consideration.

https://covid19criticalcare.com/
https://www.medrxiv.org/content/medrxiv/early/2020/06/09/2020.06.06.20124461.full.pdf
https://www.medrxiv.org/content/10.1101/2021.01.28.21250706v1.full
https://www.google.com/url?sa=t&source=web&rct=j&url=https://covid19criticalcare.com/wp-content/uploads/2020/11/FLCCC-Ivermectin-in-the-prophylaxis-and-treatment-of-COVID-19.pdf&ved=2ahUKEwjrs_PXmfrwAhX0Ap0JHXFqCQkQFjABegQIBhAC&usg=AOvVaw1STL_WpJw5v358JPemoTmF
https://youtu.be/Tn_b4NRTB6k

Thank you for your time and consideration,

[redacted]

**From:** Arthur, Jacqueline (PHAC/ASPC)
**Sent:** 2021-01-05 3:03 PM
**To:** Mahdi, Jonathan (HC/SC)
**Cc:** Siushansian, Jennifer (PHAC/ASPC); Lawuyi2, Niyi (PHAC/ASPC); Jacqueline Arthur - PHAC|ASPC (jacqueline.arthur@canada.ca); Hollett, Linsey (HC/SC)
**Subject:** RE: Emerging Therapeutics

---

Hi Jon;
Here is the summary of our update today for the minutes:

**REGN-CoV2 (Casirivimab® and Imdevimab®; Regeneron/Roche)** - PHAC met with Roche December 17, 2020

- Monoclonal antibody cocktail targeting the SARS-CoV-2 spike protein.
- Administered by IV infusion.
- Granted EUA in US for mild to moderate COVID-19 in the outpatient setting, for those at high risk of severe disease/hospitalization.
- Ongoing clinical trial shows treatment led to reduced frequency of COVID-19-associated medical visits/hospitalizations
    - Greatest benefit in patients with high viral load/low antibody levels at baseline.

Note- Additional ongoing trials include the treatment of hospitalized patients to reduce disease severity/duration and mortality, as well as ability to prevent symptomatic infection in high-risk individuals.

**VIR-7831 (GSK) –** PHAC met with GSK December 17, 2020

- Monoclonal antibody targeting the SARS-CoV-1 and SARS-CoV-2 spike protein on a conserved protein region.
- Administered by IV infusion.
- Not authorized in any jurisdiction.
- Ongoing trials assessing extent to which the antibody treatment limits COVID-19-associated hospitalizations when administered to non-hospitalized patients at high risk for severe disease.
- Results expected early 2021 and regulatory filing anticipated for June 2021.

Note- Additional ongoing trials include the treatment of hospitalized patients to reduce disease severity/duration and mortality, as well as ability to prevent symptomatic infection in high-risk individuals.

**Baricitinib (Olumiant®, Eli Lilly)**

- Baricitinib is an orally administered Janus kinase (JAK) inhibitor.
- Approved in Canada for the treatment of rheumatoid arthritis in adults.
- Clinical evidence from a NIAID-led trial shows combination therapy of baricitinib plus remdesivir in hospitalized patients with COVID-19 receiving high flow oxygen/non-invasive ventilation led to a shortened recovery time and improved clinical status compared to remdesivir alone.
    - However, benefit was minimal and only observed in a small subset of patients based on disease severity.
- Combination therapy with remdesivir was granted EUA by the USA however is not recommended to replace dexamethasone as a standard of care.

**Otilimab (GSK)** - PHAC will meet with GSK on January 14, 2021

- Otilimab is a human monoclonal anti-granulocyte macrophage colony stimulating factor (GM-CSF) antibody.
- Administered by IV infusion.
- This investigational therapy is used to treat patients with moderate to severe rheumatoid arthritis.
- Otilimab is not currently approved in Canada for any indication.
- Clinical benefit and safety of otilimab for the treatment of severe pulmonary COVID-19 related disease is currently being investigated in late stage trials with sites including Canada, with results, including impact on reducing mortality, anticipated early to mid 2021.

**Molnupiravir (Merck/Ridgeback Pharmaceuticals) –** will present to PHAC's expert advisory COVID-19 Clinical Pharmacology Task Group January 15, 2021

- Molnupiravir (MK-4482) is an orally administered nucleoside analogue antiviral that blocks virus replication.
- Currently in clinical trials as a treatment for COVID-19 both in the ambulatory and hospitalized settings, including trial sites in Canada. Molnupiravir is being investigated for its ability to reduce disease severity/shorten the duration of disease.
- No clinical findings have been released to date however preliminary readouts are anticipated for early 2021.

**Favipiravir (Reeqonus®, Avigan®; Fujifilm/Dr.Reddy's/Appili Therapeutics) -** PHAC will meet with Appili January 21, 2021

- Favipiravir is an orally administered broad-spectrum antiviral drug that blocks viral replication of RNA viruses.
- Favipiravir is approved in Japan and China for the treatment of pandemic influenza, and in India and Russia for the treatment of mild to moderate COVID-19.
- Favipiravir is not approved in Canada for any indication but is currently being reviewed by Health Canada as a treatment for COVID-19 in adult patients with mild to moderate disease.
- Recent data from Phase 3 trial shows favirpiravir treatment of hospitalized patients with mild-to-moderate COVID-19 leads to a faster recovery time and higher probability of recovery.
- Serious concerns have been noted regarding favipiravir's safety profile, including reproductive toxicity and teratogenic effects, by PHAC's expert advisory COVID-19 Clinical Pharmacology Task Group.

**Ivermectin (Stromectol®; Merck)**

- Ivermectin is an orally administered antiparasitic-drug approved for use in Canada in both humans and animals.
- Shown to inhibit SARS-CoV-2 infection in vitro and has demonstrated anti-inflammatory effects in clinical data.
- Numerous small and likely underpowered trials on ivermectin as a treatment for COVID-19 show mixed clinical benefit.
- Numerous S. American countries have widespread off-label use of ivermectin as a treatment for COVID-19.
- PHAC continues to monitor available evidence.

**Tocilizumab (Actemra®/ RoActemra®; Roche)**

- Tocilizumab is a monoclonal antibody administered by i.v. infusion or subcutaneous injection, that targets the IL-6 receptor, leading to suppression of pro-inflammatory responses (cost approx. $3200.00/dose)

- Tocilizumab is approved in Canada for indications including rheumatoid arthritis and cytokine release syndrome.
- Numerous clinical trials have assessed its clinical benefit as a treatment for patients hospitalized with COVID-19.
- On September 18, the COVID-19 Clinical Pharmacology Task Group issued a recommendation that the use of tocilizumab and other drugs targeting the IL-6 receptor remain in clinical trials given mixed clinical evidence of efficacy and safety.
- In December 2020, the Roche-sponsored EMPACTA trial published in the New England Journal of Medicine reporting significant clinical benefits including reduced frequency of disease progression to require mechanical ventilation or death.
- Additional powered trials including the UK-led RECOVERY trial and the REMAP-CAP trial, with sites in Canada, are anticipated to read out their results in the coming months.

Thanks,
Jackie

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Jacqueline Arthur, RN, BScN
Senior Manager, AMR Division | Gestionnaire principale, Division de la RAM
COVID-19 Therapeutics | thérapeutiques
CCDIC, PHAC | CLMTI, ASPC
t. (613) 889-8455

**From:** Lingohr, Erika (PHAC/ASPC)
**Sent:** 2021-06-04 9:04 AM
**To:** Djiometio, Joseph (PHAC/ASPC)
**Subject:** RE: FOR INPUT: Seeking evidence on Ivermectin

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Wonderful – thanks for confirming.
I'll pass that information along as well.

Erika

**Erika J. Lingohr**
Erika.Lingohr@Canada.ca | Tel : (519) 400-8032 (Cell)

**From:** Djiometio, Joseph (PHAC/ASPC) <joseph.djiometio@canada.ca>
**Sent:** 2021-06-04 8:46 AM
**To:** Lingohr, Erika (PHAC/ASPC) <erika.lingohr@canada.ca>
**Subject:** RE: FOR INPUT: Seeking evidence on Ivermectin

Yes. My team can monitor

joe

**From:** Lingohr, Erika (PHAC/ASPC) <erika.lingohr@canada.ca>
**Sent:** 2021-06-04 8:44 AM
**To:** Djiometio, Joseph (PHAC/ASPC) <joseph.djiometio@canada.ca>
**Subject:** RE: FOR INPUT: Seeking evidence on Ivermectin

Thanks Joseph! This is very useful.

Will your team be monitoring these ongoing trials?

Note that our HC partners have confirmed there are no Canadian trials underway, and that HC has not received any submissions either.

Erika

**Erika J. Lingohr**
Erika.Lingohr@Canada.ca | Tel : (519) 400-8032 (Cell)

**From:** Djiometio, Joseph (PHAC/ASPC) <joseph.djiometio@canada.ca>
**Sent:** 2021-06-04 8:41 AM
**To:** Lingohr, Erika (PHAC/ASPC) <erika.lingohr@canada.ca>
**Subject:** RE: FOR INPUT: Seeking evidence on Ivermectin

Good morning Erika
We need monitor ongoing clinical trial

**Recent, high quality evidence reviews**

The British Medical Journal's living systematic review and network meta-analysis analysed 16 randomized trials and based on their findings they rated the effects of ivermectin on viral clearance, mechanical ventilation and mortality as uncertain, meaning it is uncertain ivermectin treatment has an important impact on any patient-important outcome.

A meta-analysis based on 18 randomized trials of ivermectin in COVID-19 have found that ivermectin treatment reduced mortality, time to clinical recovery, and time to viral clearance.

A recent meta-analysis that has not undergone peer-revision, evaluating 10 randomized trials found that ivermectin did not reduce all-cause mortality, length of hospital stay or viral clearance in COVID-19 patients.

**Input/thoughts on efficacy**

Evidence regarding ivermectin's efficacy remains unclear with many regulatory agencies (ie. WHO, EMA, FDA) not recommending the use of ivermectin for COVID-19 outside of clinical trials.

**Canadian perspectives**

The Canadian Agency for Drugs and Technologies in Health (CADTH; statement issued on February 08, 2021); Alberta Health Services (statement issued on February 02, 2021) ; as well as British Columbia's COVID-19 Therapeutics Committee/COVID-19 Therapeutics Review and Advisory Working Group (statement issued on May 25, 2021) have all concluded that there is no clear benefit associated with ivermectin treatment among patients with COVID-19. As of June 3, 2021, no statement has been issued by INESSS.

On May 28, 2021, Ontario's COVID-19 Science Advisory Table issued a statement titled Ivermectin to Prevent Disseminated Strongyloides Infection in Patients with COVID-19. While stipulating ivermectin is currently not recommended as a treatment or preventative for COVID-19, the statement acknowledges patients with COVID-19 who receive therapies that alter immune system function may require ivermectin for the purposes of treating a pre-existing parasitic infection and to avoid severe complications of worsening parasitic infection.

**4.International perspectives**

In South American countries, ivermectin is being prescribed routinely for COVID-19 infections; however, it is difficult to ascertain clinical benefit from use outside the context of randomized controlled trials.

On March 31, 2021, the WHO issued a statement on ivermectin advising against its use outside of clinical trials, stating the current clinical evidence was inconclusive

On March 22, 2021 the EMA issued an advisory notice against use of ivermectin for the prevention or treatment of COVID-19 outside randomised clinical trials.

On February 11, 2021 the NIH COVID-19 Treatment Guidelines Panel issued a statement concluding there is insufficient evidence to recommend either for or against the use of ivermectin for the treatment of COVID-19.

## Relevant clinical trials in progress

Most trials are currently taking place in South America, where ivermectin is routinely prescribed for COVID-19 patients.

*On-going*

- NCT04834115 Universidad Nacional de Asunción sponsored, single-centre, Phase 3, triple blind study evaluating ivermectin treatment to placebo in preventing hospitalizations in **symptomatic or asymptomatic outpatients.** Allocation concealment not specified. Estimated enrollment of 400 with 200 participants randomized to treatment. No Canadian sites. **Study end date: May 30, 2021.**
- NCT04530474 Temple University sponsored, single-centre, Phase 3, triple blind study evaluating ivermectin treatment to placebo in preventing hospitalizations in **symptomatic outpatients.** Allocation concealment not specified. Estimated enrollment of 200, with 100 participants randomized to ivermectin treatment arm. No Canadian sites. **Primary end date: June 30, 2021.**
- NCT04894721 Ministry of Public Health, Argentina sponsored, single center, Phase 2/3, triple blind study evaluating ivermectin to placebo in **post-exposure prophylaxis of close contacts of COVID-19 cases.** Allocation concealment not specified. Estimated enrollment of 750 with 500 participants randomized to treatment arm. No Canadian sites. **Primary end date: May 30, 2021.**

*Not yet recruiting*

- NCT04885530 ACTIV-6 NIH Trial, Phase 3, double-blind study evaluating ivermectin for the treatment of **symptomatic COVID-19 outpatients**. Allocation concealment not specified. Estimated enrolment of 15,000 participants with 7,500 randomized to ivermectin treatment arm. No Canadian sites. **Primary end date: December 2022.** *Not yet recruiting.*
- NCT04768179 Makerere University sponsored, Phase 2/3, Open-label study evaluating ivermectin + aspirin treatment compared to placebo in treating **hospitalized patients with moderate COVID-19.** Allocation concealment not specified. Estimated enrollment of 490, with 163 participants randomized to ivermectin+aspirin treatment arm (2 dosage groups). No Canadian sites. **Primary end date: June 30, 2021.** *Not yet recruiting.*
- NCT04886362 Ayudas Diagnosticas sponsored, Phase 2/3, quadruple blind study evaluating ivermectin treatment compared to placebo in treating **outpatients with mild COVID-19.** Allocation concealment prior to randomization. Estimated enrollment of 966, with 483 participants randomized to treatment arm. No Canadian sites. **Primary end date: September 2021.** *Not yet recruiting.*

## Significant updates to the messaging above

Nil

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**From:** Lingohr, Erika (PHAC/ASPC) <erika.lingohr@canada.ca>
**Sent:** 2021-06-04 8:36 AM
**To:** Djiometio, Joseph (PHAC/ASPC) <joseph.djiometio@canada.ca>
**Subject:** FW: FOR INPUT: Seeking evidence on Ivermectin

Good morning;
Please let me know this morning if you have anything to add to Lisa's detailed update!

**Erika J. Lingohr**
Erika.Lingohr@Canada.ca | Tel : (519) 400-8032 (Cell)

**From:** Waddell, Lisa (PHAC/ASPC) <lisa.waddell@canada.ca>
**Sent:** 2021-06-03 8:46 PM
**To:** Lingohr, Erika (PHAC/ASPC) <erika.lingohr@canada.ca>; Djiometio, Joseph (PHAC/ASPC) <joseph.djiometio@canada.ca>; COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC) <phac.covid-19therapeutics-therapeutiques.aspc@canada.ca>
**Cc:** PHAC.F OCSO_ESGSecretariat / BCSC_SecrétariatGSE F.ASPC <phac.ocso_esgsecretariat-bcsc_secretariatgse.aspc@canada.ca>
**Subject:** RE: FOR INPUT: Seeking evidence on Ivermectin

Having a quick look:
I do not think we need to change the wording, but there are a couple things to note:
1, Cochrane is doing a systematic review.
2, nothing on COVID nma (also a Cochrane product) has changed.
3, I do not see any changes to authority recommendations (WHO, NIH, FDA etc.).

To complicate the messaging though, the most recent SRs and research (summarized below) do report some potentially beneficial effects, but certainty in this evidence is still considered low:

- Data on clinical outcomes such as mortality across meta-analyses of clinical trials are conflicting where the second SR below that had the largest inclusion criteria, found a significant benefit of ivermectin on mortality which only remained significant for mild/moderate cases and not for severe/ critical cases when sub grouped. There is a lot of overlap in included studies.
- Few studies looked at severity, hospitalizations, ICU.
- The third SR reported on prevention of COVID-19 and found some reductions however the studies were considered at serious risk of bias and the certainty of the evidence is very low.
- The two new studies both reported shorter time to recovery/negative test among the Ivermectin treated groups of mild/moderate COVID-19 cases.

Ivermectin in the Canadian context, I am not sure (Perhaps therapeutics can weigh in on this). All of the trials have been conducted in Asia, S. America and Spain.

**********

Cochrane in conducting a systematic review. The protocol was published April 20. Ivermectin for preventing and treating COVID-19 (Protocol)

COVID-19 NMA on Ivermectin was last updated mid May.

- Ivemectin vs. placebo, (14 RCTs) none of the outcomes indicated a benefit of treatment.
- Ivermectin vs Lopinavir-Ritonavir - 1 RCTs none of the outcomes indicated a benefit of treatment.
- Ivermectin vs Hydroxychloroquine - 4 RCTs none of the outcomes indicated a benefit of treatment.
- Ivermectin 100 mcg/kg vs Ivermectin 200 mcg/kg - 1 RCTs none of the outcomes indicated a benefit of treatment.
- Ivermectin 12 mg vs Ivermectin 24 mg - 1 RCTs none of the outcomes indicated a benefit of treatment.
- Ivermectin 200 mcg/kg vs Ivermectin 400 mcg/kg - 1 RCTs none of the outcomes indicated a benefit of treatment.
- Ivermectin 6mg vs Ivermectin 12mg - 1 RCTs none of the outcomes indicated a benefit of treatment.
- Ivermectin+Doxycycline vs Hydroxychloroquine+Azithromycin - 1 RCTs

- Ivermectin+Doxycycline vs Standard care/Placebo - 3 RCTs, Clinical improvement at 28 days was significant in 1 RCT (RR=0.63, .44-.87)
  Ivermectin+Doxycycline vs Ivermectine - 1 RCTs none of the outcomes indicated a benefit of treatment.

**Systematic reviews that appear to have been done well, employed Cochrane RoB tools and GRADE assessments.**

Ivermectin for the treatment of COVID-19: A systematic review and meta-analysis of randomized controlled trials (MedRxiv Jun1)
Search conducted March 15, 2021 for clinical trials on Ivermectin and COVID-19.
Ten RCTs (n=1173) were included. RCTs sample size ranged from 24 to 398 patients, mean age from 26 to 56 years-old, and severity of COVID-19 disease was mild in 8 RCTs, moderate in one RCT, and mild and moderate in one RCT.

- **Ivermectin did not reduce all-cause mortality** vs. controls (RR 0.37, 95%CI 0.12 to 1.13, **very low QoE**- Quality of Evidence). Sensitivity analyses excluding RCTs with follow up <21 days showed no difference in all-cause mortality.
- **Ivermectin did not reduce LOS vs. controls** (MD 0.72 days, 95%CI -0.86 to 2.29, **very low QoE**).
- **Severe adverse effects and viral clearance were similar between Ivermectin** and controls (**low QoE** for these three outcomes).

A Meta-analysis of Mortality, Need for ICU admission, Use of Mechanical Ventilation and Adverse Effects with Ivermectin Use in COVID-19 Patients (MedRxiv preprint May 6)
A total of 15002 patients from 38 articles (Ivermectin n=6669, No Ivermectin 180 n=8333) were included in qualitative analysis , 11291 patients from 30 studies (Ivermectin 181 n=2996, No Ivermectin n=8295) were included in quantitative synthesis. All experimental and observational study designs were included.

- Mortality overall: **The odds of mortality in the Ivermectin group were significantly lower compared to control group** (OR 0.39, 95% CI 0.22-0.70, p=0.002; $I^2$=81%) but evidence was graded very low. **Mortality benefit was not observed in severe/critical cases**, thus Ivermectin was only indicated as possibly beneficial to mild/moderate cases.
- Mortality clinical trials: Subgroup analysis of 15 clinical trials (RCTs N=12, Non-RCTs N=3) and observed similar mortality benefit (OR 0.32, 95% CI 0.15-0.65, p=0.002; $I^2$ =65%) *(This SR includes more trials than the other reviews and even though there is a lot of overlap, there is not 100% overlap in studies between this analysis and the ones above.)*
- **Adverse events in the Ivermectin treatment arms were not associated with treatment in 17 studies** 273 (245/973) vs control group (234/945). We did not find an association between Ivermectin and rate of adverse events as compared to controls (OR 0.92, 95% CI 0.64- 1.33, p=0.67; I2 274 =14%).

Prophylaxis against covid-19: living systematic review and network meta-analysis (BMJ)
Search conducted Feb 20, 2021
The first iteration of this living network meta-analysis includes nine randomised trials—six of hydroxychloroquine (n=6059 participants), one **of ivermectin combined with iota-carrageenan (n=234),** and **two of ivermectin alone (n=540)**, all compared with standard care or placebo.
Owing to serious risk of bias and very serious imprecision, and thus very low certainty of evidence,

- the effects of ivermectin combined with iota-carrageenan on laboratory confirmed covid-19 (52 fewer per 1000, 58 fewer to 37 fewer),
- ivermectin alone on laboratory confirmed COVID-19 infection (50 fewer per 1000, 59 fewer to 16 fewer)
- Ivermectin alone on suspected, probable, or laboratory confirmed COVID-19 infection (159 fewer per 1000, 165 fewer to 144 fewer) remain very uncertain.

New Studies:

Ivermectin in combination with doxycycline for treating COVID-19 symptoms: a randomized trial (Journal of International Medical Research)

randomized, blinded, placebo-controlled trial conducted in Bangladesh in patients with mild-to-moderate COVID-19 symptoms (median age 40 yrs) randomly assigned to treatment (n = 200) and placebo (n = 200) groups. 363 completed follow-up. ClinicalTrials.gov Identifier: NCT04523831.

The primary outcome was duration from treatment to clinical recovery. **The median recovery time was 7 (4–10, treatment group) and 9 (5–12, placebo group) days (hazard ratio, 0.73; 95% confidence interval, 0.60–0.90). The number of patients with a ≤7-day recovery was 61% (treatment group) and 44% (placebo groups) (hazard ratio, 0.06; 95% confidence interval, 0.04–0.09).**

Secondary outcomes were disease progression and persistent COVID-19 positivity by RT-PCR.

Favorable outcome on viral load and culture viability using Ivermectin in early treatment of non-hospitalized patients with mild COVID-19, A double-blind, randomized placebo-controlled trial (preprint MedRxiv June 1)

Compared patients receiving ivermectin 0·2 mg/kg for 3 days vs. placebo in non23 hospitalized COVID-19 patients.

89 patients were eligible (47 in ivermectin and 42 in placebo arm).

Primary endpoint was reduction of viral-load on the 6th day (third day after termination of treatment) as reflected by Ct level>30 (non-infectious level). The primary outcome was supported by determination of viral culture viability.

On day 6, 34 out of 47 (72%) patients in the ivermectin arm reached the endpoint, compared to 21/ 42 (50%) in the placebo arm (OR 2·62; 95% CI: 1·09-6·31). **In a multivariable logistic-regression model, the odds of a negative test at day 6 was 2.62 time higher in the ivermectin group (95% CI: 1·06–6·45).** Cultures at days 2 to 6 were positive in 3/23 (13·0%) of ivermectin samples vs. 14/29 (48·2%) in the placebo group (p=0·008).

Cheers,
Lisa

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**From:** Lingohr, Erika (PHAC/ASPC) <erika.lingohr@canada.ca>
**Sent:** 2021-06-03 9:02 AM
**To:** Waddell, Lisa (PHAC/ASPC) <lisa.waddell@canada.ca>; Djiometio, Joseph (PHAC/ASPC) <joseph.djiometio@canada.ca>; COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC) <phac.covid-19therapeutics-therapeutiques.aspc@canada.ca>
**Cc:** PHAC.F OCSO_ESGSecretariat / BCSC_SecrétariatGSE F.ASPC <phac.ocso_esgsecretariat-bcsc_secretariatgse.aspc@canada.ca>
**Subject:** FOR INPUT: Seeking evidence on Ivermectin

Good morning;

The CPHO has received inquiry relating to the use of Ivermectin as a therapeutic for COVID-19, and is currently looking for relevant evidence.

We last engaged your input on this therapeutic late April and your input was used to inform the following response statement:

> "Ivermectin is a broad-spectrum anti-parasitic agent authorized and approved by HC for
> human and veterinary applications to treat parasitic infections. At this time, HC has

not
authorized its use for the treatment of COVID-19. On March 31, 2021, the WHO issued a
statement on ivermectin advising against its use outside of clinical trials, stating the current evidence was inconclusive. The manufacturer, Merck, also issued a
statement
against the use of ivermectin for the treatment of COVID-19."

"In summary, there is currently no robust evidence at this time to suggest that ivermectin,
colchicine, or vitamin D supplementation provides clinical benefit for the treatment or
prevention of COVID-19, particularly in the Canadian context. Please be assured that
PHAC is actively monitoring emerging evidence of clinical efficacy and safety on novel
and repurposed therapeutics for COVID-19; and makes recommendations based on findings from high quality evidence on an ongoing basis."

**Lisa (Knowledge Synthesis)/ Joseph (Therapeutics)**

- **Are you aware of any recent, high quality evidence reviews that can also be shared on this topic?** (See the early April review by COVIDEND below)
- **Any additional input/thoughts on the efficacy?**
- **Any relevant clinical trials in progress that we should be keeping our eyes on?**
- **Any significant updates to the messaging above should we subsequently be aske dot provde**

Note I will also be connecting with the Therapeutic group at HC as they have recently noted an increase in inquires RE: Ivermectin.

COVID-END summary of quality evidence summaries on the topic as ofApril 8: "What is the best-available evidence about the use of colchicine and ivermectin for COVID-19" that found:

- the effects of using ivermectin as a prophylactic treatment for COVID-19 are uncertain (McMaster/BMJ; site last checked 5 April 2021);
- the effects of ivermectin to treat COVID-19 patients are also uncertain (McMaster/BMJ; site last checked 5 April 2021);
- the effects of using ivermectin with iota-carrageenan as a prophylactic treatment for COVID-19 are uncertain (McMaster/BMJ; site last checked 5 April 2021);
- adding ivermectin to standard care may reduce all-cause mortality and may have little or no difference on clinical improvement, whereas the risk of adverse events is uncertain (COVIDNMA; site last checked 5 April 2021);
- the effects of adding ivermectin + doxycycline to standard care are uncertain (COVID-NMA; site last checked 5 April 2021);
- synthesis findings are pending for an evaluation of ivermectin + doxycycline vs hydroxychloroquine + azithromycin (COVID-NMA; site last checked 5 April 2020); and
- results from the only four RCTs classified as having a low risk of ivermectin may not significantly reduce mortality and probably does not improve time to symptom resolution (PAHC/L*VE; site last checked 8 April 2021)

Thanks in advance for your input;

Erika

*-on behalf of the OCSO and the PHAC Evidence Group*

**Erika J. Lingohr**
(she | elle)

PHAC Evidence / ASPC Données Probantes
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Erika.Lingohr@Canada.ca | Tel : (519) 400-8032 (Cell)

**From:** Marinsky, Cheryl (PHAC/ASPC)
**Sent:** 2021-04-29 3:33 PM
**To:** Gale-Rowe, Margaret (PHAC/ASPC); COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC); Lawuyi2, Niyi (PHAC/ASPC)
**Cc:** Poon Young, Celisse (PHAC/ASPC)
**Subject:** RE: For Senior Manager review: LISA AND THERAPEUTICS TEAM FOR INPUT BY APRIL 29 - 21-108019 - Vitamin D, Colcichine, Ivermectin

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Thanks Margaret.

Cheryl

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**From:** Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>
**Sent:** 2021-04-29 3:26 PM
**To:** COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC) <phac.covid-19therapeutics-therapeutiques.aspc@canada.ca>; Marinsky, Cheryl (PHAC/ASPC) <cheryl.marinsky@canada.ca>; Lawuyi2, Niyi (PHAC/ASPC) <niyi.lawuyi2@canada.ca>
**Cc:** Poon Young, Celisse (PHAC/ASPC) <celisse.poonyoung@canada.ca>
**Subject:** For Senior Manager review: LISA AND THERAPEUTICS TEAM FOR INPUT BY APRIL 29 - 21-108019 - Vitamin D, Colcichine, Ivermectin

Hi,

Additional information has been included in this response for Jackie's approval. I just realized that we/I could have kept more detail, however it was very long.

I am also including the longer version that was provided by the technical team; that could be included if Jackie thinks it appropriate.

Please note that I have also attached the incoming as well as a draft response, parts of which were edited out of my response.

Margaret

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**From:** Poon Young, Celisse (PHAC/ASPC) <celisse.poonyoung@canada.ca> **On Behalf Of** COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC)
**Sent:** 2021-04-26 1:54 PM
**To:** Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>; Marinsky, Cheryl (PHAC/ASPC) <cheryl.marinsky@canada.ca>; Lawuyi2, Niyi (PHAC/ASPC) <niyi.lawuyi2@canada.ca>
**Cc:** Poon Young, Celisse (PHAC/ASPC) <celisse.poonyoung@canada.ca>
**Subject:** FW: LISA AND THERAPEUTICS TEAM FOR INPUT BY APRIL 29 - 21-108019 - Vitamin D, Colcichine, Ivermectin
**Importance:** High

Hi everyone,

Please see the request that came to the Therapeutics inbox this afternoon. Sending to you all since I am not sure exactly who this should be directed to.

Thank you,

Celisse

---

**From:** Jamil, Marium (PHAC/ASPC) <marium.jamil@canada.ca>
**Sent:** 2021-04-26 12:21 PM
**To:** Waddell, Lisa (PHAC/ASPC) <lisa.waddell@canada.ca>; COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC) <phac.covid-19therapeutics-therapeutiques.aspc@canada.ca>
**Cc:** PHAC.F OCSO_ESGSecretariat / BCSC_SecrétariatGSE F.ASPC <phac.ocso_esgsecretariat-bcsc_secretariatgse.aspc@canada.ca>
**Subject:** LISA AND THERAPEUTICS TEAM FOR INPUT BY APRIL 29 - 21-108019 - Vitamin D, Colcichine, Ivermectin
**Importance:** High

Good morning Lisa and Therapeutics team,
**FOR INPUT/APPROVAL – BY APRIL 29**
**CONTEXT**

- Dr. Tam received correspondence on April 21, 2021 from a member of the public (please see attached '21-108019-10 Incoming Apr 22.pdf'), regarding the use of Vitamin D, Ivermectin and Colchicine as treatments for COVID-19.

**FOR INPUT**

- ESG Secretariat has drafted a standard response in regards to the use of Vitamin D (please see attached '21-108019-VitD_Colchicine, Ivermectin _ Response_Apr2021. doc') adapted from previous responses. The letter does not speak to Colchicine or Ivermectin however. We would be thankful if you could please provide **your input on:**
    - **Any evidence to support the use of Ivermectin and Colchicine**
    - **Any NEW evidence on the efficacy of Vitamin D**

Thank you so much for your time. We would be grateful if you could please provide us your input by April 29th.

Please let us know if you have any questions.

Regards,
Marium

*On behalf of the Office of Chief Science Officer and the PHAC Emerging Science Group Secretariat*

**Marium Jamil**
(she | elle)
Policy Analyst | Analyste des politiques
Office of the Chief Science Officer | Bureau du Conseiller scientifique en chef
Public Health Agency of Canada | Agence de la santé publique du Canada
NEW: phac.ocso_esgsecretariat-bcsc_secretariatgse.aspc@canada.ca

**From:** Arthur, Jacqueline (PHAC/ASPC)
**Sent:** 2021-04-30 2:51 PM
**To:** COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC)
**Cc:** Gale-Rowe, Margaret (PHAC/ASPC); Marinsky, Cheryl (PHAC/ASPC); Lawuyi2, Niyi (PHAC/ASPC)
**Subject:** RE: For Senior Manager review: LISA AND THERAPEUTICS TEAM FOR INPUT BY APRIL 30 - 21-108019 - Vitamin D, Colcichine, Ivermectin
**Attachments:** Colchicine and Ivermectin and Vitamin D_CCDIC input.docx; 21-108019-10 Incoming Apr 22.pdf

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**Categories:** DO pending

Attached, please find my approved version.
Celisse, please send to DGO for Bersabel's approval. At the same time send it over to OCSO as not yet DG approved so that they see our input and the recommendation that HC also review.
Well done team.
Jackie

---

Jacqueline Arthur, BScN, RN
(she | elle)
Senior Manager, AMR Division | Gestionnaire principale, Division de la RAM
COVID-19 Therapeutics | thérapeutiques
CCDIC, PHAC | CLMTI, ASPC
t. (613) 889-8455

---

**From:** Poon Young, Celisse (PHAC/ASPC) <celisse.poonyoung@canada.ca> **On Behalf Of** COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC)
**Sent:** 2021-04-29 3:52 PM
**To:** Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>
**Cc:** Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>; Marinsky, Cheryl (PHAC/ASPC) <cheryl.marinsky@canada.ca>; Lawuyi2, Niyi (PHAC/ASPC) <niyi.lawuyi2@canada.ca>
**Subject:** FW: For Senior Manager review: LISA AND THERAPEUTICS TEAM FOR INPUT BY APRIL 30 - 21-108019 - Vitamin D, Colcichine, Ivermectin

Thanks Margaret.

Hi Jackie, please see the response to the request below for your review before DG approval.

Note that we got an extension on this so it is due tomorrow COB.

Thank you,

Celisse

**From:** Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>
**Sent:** 2021-04-29 3:26 PM
**To:** COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC) <phac.covid-19therapeutics-therapeutiques.aspc@canada.ca>; Marinsky, Cheryl (PHAC/ASPC) <cheryl.marinsky@canada.ca>; Lawuyi2, Niyi (PHAC/ASPC) <niyi.lawuyi2@canada.ca>
**Cc:** Poon Young, Celisse (PHAC/ASPC) <celisse.poonyoung@canada.ca>
**Subject:** For Senior Manager review: LISA AND THERAPEUTICS TEAM FOR INPUT BY APRIL 29 - 21-108019 - Vitamin D, Colcichine, Ivermectin

Hi,

Additional information has been included in this response for Jackie's approval. I just realized that we/I could have kept more detail, however it was very long.

I am also including the longer version that was provided by the technical team; that could be included if Jackie thinks it appropriate.

Please note that I have also attached the incoming as well as a draft response, parts of which were edited out of my response.

Margaret

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**From:** Poon Young, Celisse (PHAC/ASPC) <celisse.poonyoung@canada.ca> **On Behalf Of** COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC)
**Sent:** 2021-04-26 1:54 PM
**To:** Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>; Marinsky, Cheryl (PHAC/ASPC) <cheryl.marinsky@canada.ca>; Lawuyi2, Niyi (PHAC/ASPC) <niyi.lawuyi2@canada.ca>
**Cc:** Poon Young, Celisse (PHAC/ASPC) <celisse.poonyoung@canada.ca>
**Subject:** FW: LISA AND THERAPEUTICS TEAM FOR INPUT BY APRIL 29 - 21-108019 - Vitamin D, Colcichine, Ivermectin
**Importance:** High

Hi everyone,

Please see the request that came to the Therapeutics inbox this afternoon. Sending to you all since I am not sure exactly who this should be directed to.

Thank you,

Celisse

---

**From:** Jamil, Marium (PHAC/ASPC) <marium.jamil@canada.ca>
**Sent:** 2021-04-26 12:21 PM
**To:** Waddell, Lisa (PHAC/ASPC) <lisa.waddell@canada.ca>; COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC) <phac.covid-19therapeutics-therapeutiques.aspc@canada.ca>
**Cc:** PHAC.F OCSO_ESGSecretariat / BCSC_SecrétariatGSE F.ASPC <phac.ocso_esgsecretariat-bcsc_secretariatgse.aspc@canada.ca>
**Subject:** LISA AND THERAPEUTICS TEAM FOR INPUT BY APRIL 29 - 21-108019 - Vitamin D, Colcichine, Ivermectin
**Importance:** High

Good morning Lisa and Therapeutics team,

**FOR INPUT/APPROVAL – BY APRIL 29**
**CONTEXT**

- Dr. Tam received correspondence on April 21, 2021 from a member of the public (please see attached '21-108019-10 Incoming Apr 22.pdf'), regarding the use of Vitamin D, Ivermectin and Colchicine as treatments for COVID-19.

**FOR INPUT**

- ESG Secretariat has drafted a standard response in regards to the use of Vitamin D (please see attached '21-108019-VitD_Colchicine, Ivermectin _ Response_Apr2021. doc') adapted from previous responses. The letter does not speak to Colchicine or Ivermectin however. We would be thankful if you could please provide **your input on:**
    - **Any evidence to support the use of Ivermectin and Colchicine**
    - **Any NEW evidence on the efficacy of Vitamin D**

Thank you so much for your time. We would be grateful if you could please provide us your input by April 29th.

Please let us know if you have any questions.

Regards,
Marium

*On behalf of the Office of Chief Science Officer and the PHAC Emerging Science Group Secretariat*

**Marium Jamil**
(she | elle)
Policy Analyst | Analyste des politiques
Office of the Chief Science Officer | Bureau du Conseiller scientifique en chef
Public Health Agency of Canada | Agence de la santé publique du Canada
NEW: phac.ocso_esgsecretariat-bcsc_secretariatgse.aspc@canada.ca

**From:** Arthur, Jacqueline (PHAC/ASPC)
**Sent:** 2021-01-14 5:39 PM
**To:** Siushansian, Jennifer (PHAC/ASPC)
**Subject:** RE: For approval: QFs for Jan. 14

---

Approved,
Thanks.
J

---

Jacqueline Arthur, RN, BScN
Senior Manager, AMR Division | Gestionnaire principale, Division de la RAM
COVID-19 Therapeutics | thérapeutiques
CCDIC, PHAC | CLMTI, ASPC
t. (613) 889-8455

---

**From:** Siushansian, Jennifer (PHAC/ASPC) <jennifer.siushansian@canada.ca>
**Sent:** 2021-01-14 5:31 PM
**To:** Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>
**Subject:** For approval: QFs for Jan. 14

Hi, Jackie. For your approval. Thanks.

January 14: US National Institutes of Health issued statement on use of ivermectin for treatment of COVID-19.

- At this time, insufficient evidence to recommend either for or against use.
- Further results needed to provide more specific, evidence-based guidance.
- FDA currently evaluating this antiparasitic drug as a potential treatment for COVID-19.

---

**From:** Sarwar, Elaha (PHAC/ASPC) <elaha.sarwar@canada.ca>
**Sent:** 2021-01-14 2:25 PM
**To:** Siushansian, Jennifer (PHAC/ASPC) <jennifer.siushansian@canada.ca>
**Cc:** Forbes, Nicole (PHAC/ASPC) <nicole.forbes@canada.ca>; Lawuyi2, Niyi (PHAC/ASPC) <niyi.lawuyi2@canada.ca>; Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>; Ha, Shalane (PHAC/ASPC) <shalane.ha@canada.ca>; Beique, Lizanne (PHAC/ASPC) <lizanne.beique@canada.ca>; Marinsky, Cheryl (PHAC/ASPC) <cheryl.marinsky@canada.ca>
**Subject:** QFs for Jan. 14

Good afternoon Jenn,

Here is one QF for today:

January 14, 2021: The National Institutes of Health guidelines issued a statement on the use of Ivermectin for the treatment of COVID-19.

- The NIH COVID-19 Treatment Guidelines Panel has determined that currently there are insufficient data to recommend either for or against the use of ivermectin for the treatment of COVID-19.
- The Panel notes that additional evidence from adequately powered and robust clinical trials are needed to provide more conclusive evidence-based guidance on the role of

ivermectin for the treatment of COVID-19.

Have a nice evening!

Elaha

**From:** Arthur, Jacqueline (PHAC/ASPC)
**Sent:** 2021-06-03 5:13 PM
**To:** Ephrem, Bersabel (PHAC/ASPC)
**Cc:** Gale-Rowe, Margaret (PHAC/ASPC); Hunt, Kelly (PHAC/ASPC); COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC)
**Subject:** RE: I-Mask+ Protocol for early treatment of Covid-19
**Attachments:** I-Mask+ Protocol response to [redacted]une 3 V2 Revised (002)_JA.docx

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**Importance:** High

**Categories:** Waiting on input, DO pending

Bersabel;
Proposed response attached and pasted here for ease of reference. We also included a short list of key trials as an annex in the attachment if you think this would be helpful.
J

Dea[redacted]

Thank you for your correspondence concerning the use of the I-Mask Protocol for early treatment and prophylaxis for COVID-19 to support Canada's response to COVID-19.

The Public Health Agency of Canada (PHAC) conducts a thorough analysis of the emerging scientific evidence regarding promising therapeutics to treat COVID-19, and Health Canada (HC) formally reviews these drugs to assess their safety, efficacy and quality before authorizing their sale in Canada. Many drugs that show promise in laboratory studies are found to be ineffective in patients.

I-MASK+ Protocol is a prevention and early outpatient treatment protocol for COVID-19. While it includes a number of medications and supplements, it is centred on ivermectin, a broad-spectrum anti-parasitic agent authorized and approved by HC for human and veterinary applications to treat parasitic infections. At this time, HC has not authorized its use for the treatment of COVID-19.

The provinces and territories are responsible for the delivery of health care and bear primary responsibility for decisions around choice and use of therapeutics - including for COVID-19 – within their jurisdictions.

Independent reviews of available clinical trial results that evaluate the effectiveness of ivermectin as a treatment for COVID-19 have been conducted by: the Canadian Agency for Drugs and Technologies in Health (CADTH); Alberta Health Services; British Columbia's COVID-19 Therapeutics Committee/COVID-19 Therapeutics Review and Advisory Working Group; and Ontario's COVID-19 Science Advisory table. These bodies of scientific experts all concluded that there is no clear benefit to ivermectin treatment among patients with COVID-19.

On March 31, 2021, the World Health Organization (WHO) issued a statement on ivermectin advising against its use outside of clinical trials, stating the current evidence was inconclusive. Further, the manufacturer - Merck - has also issued a statement against the use of ivermectin for the treatment of COVID-19.

https://www.merck.com/news/merck-statement-on-ivermectin-use-during-the-covid-19-pandemic/

In summary, there is currently no robust evidence (i.e., from high quality, well-designed clinical trials) to suggest that the I-MASK+ Protocol provides clinical benefit for the treatment or prevention of COVID-19, particularly in the Canadian context. Please be assured that PHAC continues to monitor the emerging evidence of clinical efficacy and safety from high quality trials on novel and repurposed therapeutics for COVID-19.

Thank you for writing to the Public Health Agency of Canada. I hope this information is helpful.

---

Jacqueline Arthur, BScN, RN
(she | elle)
Senior Manager, AMR Division | Gestionnaire principale, Division de la RAM
COVID-19 Therapeutics | thérapeutiques
CCDIC, PHAC | CLMTI, ASPC
t. (613) 889-8455

-----Original Message-----
From: Ephrem, Bersabel (PHAC/ASPC) <bersabel.ephrem@canada.ca>
Sent: 2021-05-31 4:07 PM
To: Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>
Cc: Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>; Hunt, Kelly (PHAC/ASPC) <kelly.hunt@canada.ca>
Subject: FW: I-Mask+ Protocol for early treatment of Covid-19

Hi Jackie,

Can we have a response? Please see below.

be

-----Original Message-----
From: McLean, Hollie (HC/SC) <hollie.mclean@canada.ca> On Behalf Of Levesque2, Kaili (HC/SC)
Sent: 2021-05-31 3:54 PM
To: [redacted]
Cc: Ephrem, Bersabel (PHAC/ASPC) <bersabel.ephrem@canada.ca>; Levesque2, Kaili (HC/SC) <kaili.levesque2@canada.ca>; McLean, Hollie (HC/SC) <hollie.mclean@canada.ca>
Subject: RE: I-Mask+ Protocol for early treatment of Covid-19

Hi [redacted]

Thank you for your email. Note that I've recently assumed the role as Vice President, COVID-19 Vaccine Rollout at the Public Health Agency. I'm connecting you with Bersabel Ephrem, the Director General responsible for the therapeutics file.

Thanks

Kaili

Kaili Levesque (she/her/elle)

613.818.0492

-----Original Message-----
From: [redacted]
Sent: 2021-05-31 12:13 PM
To: Levesque2, Kaili (HC/SC) <kaili.levesque2@canada.ca>
Subject: I-Mask+ Protocol for early treatment of Covid-19

Good morning Ms. Levesque:

I am writing to ask for your assistance. I have been following a growing body of research on the use of the I-Mask Protocol for early treatment and prophylaxis for Covid-19. Early in the pandemic, this protocol was not well understood and had only anecdotal evidence of its efficacy. Recently, however, I've been encouraged to see multiple studies showing good evidence of efficacy. I am puzzled as to why this treatment is not being studied in Canada as we are still in a situation across the country where people are being hospitalized for Covid-19. I am not a medical professional, but I wonder if it is not prudent and compassionate to open the door to other treatment possibilities which could prevent further deterioration of newly diagnosed victims of this virus? I do not know if you are the right person to send this email to, but I do know that you believe that we should be doing absolutely everything to try to treat this disease. My sincere hope is that you and your Task Force are seeking to include the use of existing medicines that we know are not harmful in and of themselves, such as Ivermectin, which is one of the components in the I-Mask Protocol. While we all look forward to the day when vaccinations take effect Canada-wide, in the meantime there are still many people who are falling ill and require medical treatment for this disease.

I respectfully submit to you this link to the growing body of knowledge and research studies around the I-Mask+ Protocol and I beg you to use your considerable influence to bring it to the attention of the Covid 19 Task Force and study it with all due diligence. If there is merit in this treatment, and your committee agrees to try it on a limited study basis, perhaps many Canadian lives could be saved and/or at the very least, saved from the longevity of hospitalizations for Covid 19 which they may be facing under the current treatment protocols. I believe that your committee has a moral and ethical obligation to fairly and diligently consider all possible treatments, irrespective of WHO or any other body who may be telling you otherwise. We are Canadians, first and foremost. We are responsible for one another.

Thank you so very much for your time. I ask you to please respectfully consider my request, and I very much look forward to your reply.

Sincerely,

[redacted]
Alberta, Canada

https://covid19criticalcare.com/covid-19-protocols/i-mask-plus-protocol/

**From:** COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC)
**Sent:** 2021-06-01 11:24 AM
**To:** Arthur, Jacqueline (PHAC/ASPC); Djiometio, Joseph (PHAC/ASPC); COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC)
**Cc:** Gale-Rowe, Margaret (PHAC/ASPC)
**Subject:** RE: I-Mask+ Protocol for early treatment of Covid-19
**Attachments:** 21-108019-10 - [redacted] - Reply sent.pdf

**Categories:** Complete

Here you go

-adele-

-----Original Message-----
From: Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>
Sent: 2021-05-31 4:39 PM
To: Djiometio, Joseph (PHAC/ASPC) <joseph.djiometio@canada.ca>; COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC) <phac.covid-19therapeutics-therapeutiques.aspc@canada.ca>
Cc: Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>
Subject: FW: I-Mask+ Protocol for early treatment of Covid-19

Hi Joe;
We have received the correspondence below via our Director General's office regarding the I-Mask+ Protocol that centers around the main treatment, ivermection. Follow the link provided in the incoming correspondence.
Please review and prepare a draft response for Margaret's review by Wednesday.
I've attached previous correspondence we have done on ivermectin to assist - Adéle, could you track down the final correspondence that was sent under MECS#21-108019-10? It would be helpful for Joe to have the approved version sent.

Happy to discuss.
Jackie

---
Jacqueline Arthur, BScN, RN
(she | elle)
Senior Manager, AMR Division | Gestionnaire principale, Division de la RAM
COVID-19 Therapeutics | thérapeutiques
CCDIC, PHAC | CLMTI, ASPC
t. (613) 889-8455

-----Original Message-----
From: Ephrem, Bersabel (PHAC/ASPC) <bersabel.ephrem@canada.ca>
Sent: 2021-05-31 4:07 PM
To: Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>

Cc: Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>; Hunt, Kelly (PHAC/ASPC) <kelly.hunt@canada.ca>
Subject: FW: I-Mask+ Protocol for early treatment of Covid-19

Hi Jackie,

Can we have a response? Please see below.

be

-----Original Message-----
From: McLean, Hollie (HC/SC) <hollie.mclean@canada.ca> On Behalf Of Levesque2, Kaili (HC/SC)
Sent: 2021-05-31 3:54 PM
To: [redacted]
Cc: Ephrem, Bersabel (PHAC/ASPC) <bersabel.ephrem@canada.ca>; Levesque2, Kaili (HC/SC) <kaili.levesque2@canada.ca>; McLean, Hollie (HC/SC) <hollie.mclean@canada.ca>
Subject: RE: I-Mask+ Protocol for early treatment of Covid-19

Hi [redacted]

Thank you for your email. Note that I've recently assumed the role as Vice President, COVID-19 Vaccine Rollout at the Public Health Agency. I'm connecting you with Bersabel Ephrem, the Director General responsible for the therapeutics file.

Thanks

Kaili

Kaili Levesque (she/her/elle)
613.818.0492

-----Original Message-----
From: [redacted]
Sent: 2021-05-31 12:13 PM
To: Levesque2, Kaili (HC/SC) <kaili.levesque2@canada.ca>
Subject: I-Mask+ Protocol for early treatment of Covid-19

Good morning Ms. Levesque:

I am writing to ask for your assistance. I have been following a growing body of research on the use of the I-Mask Protocol for early treatment and prophylaxis for Covid-19. Early in the pandemic, this protocol was not well understood and had only anecdotal evidence of its efficacy. Recently, however, I've been encouraged to see multiple studies showing good evidence of efficacy. I am puzzled as to why this treatment is not being studied in Canada as we are still in a situation across the country where people are being hospitalized for Covid-19. I am not a medical professional, but I wonder if it is not prudent and compassionate to open the door to other treatment possibilities which could prevent further deterioration of newly diagnosed victims of this virus? I do not know if you are the right person to send this email to, but I do know that you believe that we should be doing absolutely everything to try to treat this disease. My sincere hope is that you and your Task Force are seeking to include the use of existing medicines that we know are not harmful in and of themselves, such as Ivermectin, which is one of the components in the I-Mask Protocol. While we all look forward to the day when vaccinations take effect Canada-wide,

in the meantime there are still many people who are falling ill and require medical treatment for this disease.

I respectfully submit to you this link to the growing body of knowledge and research studies around the I-Mask+ Protocol and I beg you to use your considerable influence to bring it to the attention of the Covid 19 Task Force and study it with all due diligence. If there is merit in this treatment, and your committee agrees to try it on a limited study basis, perhaps many Canadian lives could be saved and/or at the very least, saved from the longevity of hospitalizations for Covid 19 which they may be facing under the current treatment protocols. I believe that your committee has a moral and ethical obligation to fairly and diligently consider all possible treatments, irrespective of WHO or any other body who may be telling you otherwise. We are Canadians, first and foremost. We are responsible for one another.

Thank you so very much for your time. I ask you to please respectfully consider my request, and I very much look forward to your reply.

Sincerely,

[redacted]
Alberta, Canada

https://covid19criticalcare.com/covid-19-protocols/i-mask-plus-protocol/

**From:** Ephrem, Bersabel (PHAC/ASPC)
**Sent:** 2021-06-04 5:00 PM
**To:** [redacted]
**Cc:** Ephrem, Bersabel (PHAC/ASPC); Arthur, Jacqueline (PHAC/ASPC); Gale-Rowe, Margaret (PHAC/ASPC)
**Subject:** RE: I-Mask+ Protocol for early treatment of Covid-19

---

Thank you [redacted] for your follow up questions. I would like to offer some points of clarification in my response.

One of the Public Health Agency of Canada's (PHAC) roles to support Canada's COVID-19 response is to acquire medications to treat COVID-19. This is to ensure that Canadians will have access to safe and effective treatments in the context of substantial global demand. PHAC monitors the emerging evidence around therapeutics to inform the decisions around procurement. Please note that PHAC does not issue recommendations as such, for or against the use of medications for COVID-19.

A manufacturer seeking market authorization will submit safety and efficacy data to Health Canada (HC). As the regulator, HC grants market authorization when it is satisfied that the benefits outweigh the potential risks. The list of applications received for drugs and vaccines for COVID-19 is available online.

The provinces and territories have primary responsibility for decisions around choice and use of therapeutics - including for COVID-19 – within their jurisdictions. In Canada, a health care professional's decision to prescribe or use a particular drug for a labelled or off-label indication is part of the practice of medicine, which falls under the jurisdiction of provincial and territorial professional regulatory authorities.

With best regards,

Bersabel
(She | Elle)

Bersabel Ephrem, BSc., MPA
Director General, Centre for Communicable Diseases and Infection Control
Infectious Disease Prevention and Control Branch
Public Health Agency of Canada
bersabel.ephrem@canada.ca / Tel: 613-948-6799 / Cell: 613-415-5897

Directrice générale, Centre de la lutte contre les maladies transmissibles et les infections
Direction générale de la prévention et du contrôle des maladies infectieuses
Agence de la santé publique du Canada
bersabel.ephrem@canada.ca / Tel: 613-948-6799 / Cell: 613-415-5897

---

**From:** [redacted]
**Sent:** 2021-06-04 10:57 AM
**To:** Ephrem, Bersabel (PHAC/ASPC) <bersabel.ephrem@canada.ca>
**Subject:** RE: I-Mask+ Protocol for early treatment of Covid-19

Good morning

Thank you for your prompt response to my inquiry. If I may, I urge you to reconsider Canada's stance on this extremely important matter. Have you, personally, read the research studies? Have you been following new developments as more and more respected scientists and researchers become convinced of the efficacy of this treatment for Covid-19? I implore you and your committee to do your own research and that you be be willing to step out of the accepted norms. Would you consider even allowing it on a person by person basis with informed consent? I know many people who are considering self treatment with veterinary quality ivermectin which concerns me greatly. I believe that it's in the best interest of Canadian for Canada to reconsider.

Respectfully,
[redacted]

On Thu, Jun 3, 2021 at 3:23 PM, Ephrem, Bersabel (PHAC/ASPC) <bersabel.ephrem@canada.ca> wrote:

Dear [redacted]

Thank you for your correspondence concerning the use of the I-Mask Protocol for early treatment and prophylaxis for COVID-19 to support Canada's response to COVID-19.

The Public Health Agency of Canada (PHAC) conducts a thorough analysis of the emerging scientific evidence regarding promising therapeutics to treat COVID-19, and Health Canada (HC) formally reviews these drugs to assess their safety, efficacy and quality before authorizing their sale in Canada. Many drugs that show promise in laboratory studies are found to be ineffective in patients.

I-MASK+ Protocol is a prevention and early outpatient treatment protocol for COVID-19. While it includes a number of medications and supplements, it is centred on ivermectin, a broad-spectrum anti-parasitic agent authorized and approved by HC for human and veterinary applications to treat parasitic infections. At this time, HC has not authorized its use for the treatment of COVID-19.

Independent reviews of available clinical trial results that evaluate the effectiveness of ivermectin as a treatment for COVID-19 have been conducted by: the Canadian Agency for Drugs and Technologies in Health (CADTH); Alberta Health Services; British Columbia's COVID-19 Therapeutics Committee/COVID-19 Therapeutics Review and Advisory Working Group; and Ontario's COVID-19 Science Advisory table. These bodies of scientific experts all concluded that there is no clear benefit to ivermectin treatment among patients with COVID-19.

On March 31, 2021, the World Health Organization (WHO) issued a statement on ivermectin advising against its use outside of clinical trials, stating the current evidence was inconclusive. Further, the manufacturer - Merck - has also issued a statement against the use of ivermectin for the treatment of COVID-19.

https://www.merck.com/news/merck-statement-on-ivermectin-use-during-the-covid-19-pandemic/

In summary, there is currently no robust evidence (i.e., from high quality, well-designed clinical trials) to suggest that the I-MASK+ Protocol provides clinical benefit for the treatment or prevention of COVID-19, particularly in the Canadian context. Please be assured that PHAC continues to monitor the emerging evidence of clinical efficacy and safety from high quality trials on novel and repurposed therapeutics for COVID-19. The provinces and territories have primary responsibility for decisions around choice and use of therapeutics - including for COVID-19 – within their jurisdictions.

Thank you for writing to the Public Health Agency of Canada. I hope this information is helpful.

With best regards,

Bersabel
(She | Elle)

Bersabel Ephrem, BSc., MPA
Director General, Centre for Communicable Diseases and Infection Control
Infectious Disease Prevention and Control Branch
Public Health Agency of Canada
bersabel.ephrem@canada.ca / Tel: 613-948-6799 / Cell: 613-415-5897

Directrice générale, Centre de la lutte contre les maladies transmissibles et les infections
Direction générale de la prévention et du contrôle des maladies infectieuses
Agence de la santé publique du Canada
bersabel.ephrem@canada.ca / Tel: 613-948-6799 / Cell: 613-415-5897

-----Original Message-----
From: McLean, Hollie (HC/SC) <hollie.mclean@canada.ca> On Behalf Of Levesque2, Kaili (HC/SC)
Sent: 2021-05-31 3:54 PM
To: [redacted]
Cc: Ephrem, Bersabel (PHAC/ASPC) <bersabel.ephrem@canada.ca>; Levesque2, Kaili (HC/SC) <kaili.levesque2@canada.ca>; McLean, Hollie (HC/SC) <hollie.mclean@canada.ca>
Subject: RE: I-Mask+ Protocol for early treatment of Covid-19

Hi [redacted]

Thank you for your email. Note that I've recently assumed the role as Vice President, COVID-19 Vaccine Rollout at the Public Health Agency. I'm connecting you with Bersabel Ephrem, the Director General responsible for the therapeutics file.

Thanks

Kaili

Kaili Levesque (she/her/elle)
613.818.0492

-----Original Message-----
From [redacted]
Sent: 2021-05-31 12:13 PM
To: Levesque2, Kaili (HC/SC) <kaili.levesque2@canada.ca>
Subject: I-Mask+ Protocol for early treatment of Covid-19

Good morning Ms. Levesque:

I am writing to ask for your assistance. I have been following a growing body of research on the use of the I-Mask Protocol for early treatment and prophylaxis for Covid-19. Early in the pandemic, this protocol was not well understood and had only anecdotal evidence of its efficacy. Recently, however, I've been encouraged to see multiple studies showing good evidence of efficacy. I am puzzled as to why this treatment is not being studied in Canada as we are still in a situation across the country where people are being hospitalized for Covid-19. I am not a medical professional, but I wonder if it is not prudent and compassionate to open the door to other treatment possibilities which could prevent further deterioration of newly diagnosed victims of this virus? I do not know if you are the right person to send this email to, but I do know that you believe that we should be doing absolutely everything to try to treat this disease. My sincere hope is that you and your Task Force are seeking to include the use of existing medicines that we know are not harmful in and of themselves, such as Ivermectin, which is one of the components in the I-Mask Protocol. While we all look forward to the day when vaccinations take effect Canada-wide, in the meantime there are still many people who are falling ill and require medical treatment for this disease.

I respectfully submit to you this link to the growing body of knowledge and research studies around the I-Mask+ Protocol and I beg you to use your considerable influence to bring it to the attention of the Covid 19 Task Force and study it with all due diligence. If there is merit in this treatment, and your committee agrees to try it on a limited study basis, perhaps many Canadian lives could be saved and/or at the very least, saved from the longevity of hospitalizations for Covid 19 which they may be facing under the current treatment protocols. I believe that your committee has a moral and ethical obligation to fairly and diligently consider all possible treatments, irrespective of WHO or any other body who may be telling you otherwise. We are Canadians, first and foremost. We are responsible for one another.

Thank you so very much for your time. I ask you to please respectfully consider my request, and I very much look forward to your reply.

Sincerely,

[redacted]
Alberta, Canada

https://covid19criticalcare.com/covid-19-protocols/i-mask-plus-protocol/

**From:** Gale-Rowe, Margaret (PHAC/ASPC)
**Sent:** 2021-06-07 5:47 PM
**To:** Arthur, Jacqueline (PHAC/ASPC)
**Subject:** RE: Info about US and Ivermectin for consumers - still looking

---

**Categories:** DO pending

Hi again,

The NIH COVID-19 guideline (February 11, 2021) indicates there are insufficient data to recommend for or against the use of ivermectin. The guideline notes that the FDA issued a warning letter against the use of veterinary ivermectin to treat COVID-19.

Ivermectin | COVID-19 Treatment Guidelines (nih.gov)

Margaret

Recommendation
There are insufficient data for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of ivermectin for the treatment of COVID-19. Results from adequately powered, well-designed, and well-conducted clinical trials are needed to provide more specific, evidence-based guidance on the role of ivermectin in the treatment of COVID-19.

- The FDA issued a warning in April 2020 that ivermectin intended for use in animals **should not be used** to treat COVID-19 in humans.

---

**From:** Gale-Rowe, Margaret (PHAC/ASPC)
**Sent:** 2021-06-07 5:28 PM
**To:** Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>
**Subject:** Info about US and Ivermectin for consumers - still looking

Hi Jackie,

Joe located a consumer report (advisory) about use of ivermectin, more of a caution of the dangers of using veterinary drugs. The FDA has not reviewed the evidence around ivermectin but notes "some initial research is underway."

I will see if I can find something that is for health professionals.

I copied and pasted his email (below), as I am losing hyperlinks if I try to forward or reply all. Hmmm.

Margaret

FDA has not approved ivermectin for use in treating or preventing COVID-19 in humans (May 03 2021).

https://www.fda.gov/consumers/consumer-updates/why-you-should-not-use-ivermectin-treat-or-prevent-covid-19

The Information is available in the following section:
Here's What You Need to Know about Ivermectin When Can Taking Ivermectin Be Unsafe?

Margaret Gale-Rowe MD MPH
she/elle

Medical Advisor
COVID 19 Therapeutics Acquisitions
Centre for Communicable Diseases and Infection Control
Public Health Agency of Canada / Government of Canada
Room 326-B, 130 Colonnade Road, Ottawa, Canada K1A 0K9
Margaret.gale-rowe@canada.ca 613-618-9266

Médecin-conseil
COVID 19 acquisitions thérapeutiques
Centre de la lutte contre les maladies transmissibles et les infections
Agence de la santé publique du Canada / Gouvernement du Canada
Pièce 326-B, 130 rue Colonnade, Ottawa, Canada K1A 0K9
Margaret.gale-rowe@canada.ca 613-618-9266

**From:** Gale-Rowe, Margaret (PHAC/ASPC)
**Sent:** 2021-04-26 2:48 PM
**To:** Marinsky, Cheryl (PHAC/ASPC); Sarwar, Elaha (PHAC/ASPC)
**Subject:** RE: Input on therapeutics LISA AND THERAPEUTICS TEAM FOR INPUT BY APRIL 29 - 21-108019 - Vitamin D, Colcichine, Ivermectin

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**Categories:** DO pending

I am borrowing and paraphrasing from another email re: off-label use:

If (they) are comfortable with using (it) and are comfortable with the level of evidence supporting the use in COVID-19, they can do that under the practice of medicine.

---

**From:** Gale-Rowe, Margaret (PHAC/ASPC)
**Sent:** 2021-04-26 2:43 PM
**To:** Marinsky, Cheryl (PHAC/ASPC) <cheryl.marinsky@canada.ca>; Sarwar, Elaha (PHAC/ASPC) <elaha.sarwar@canada.ca>
**Cc:** Cortés-Kaplan, Serena (PHAC/ASPC) <serena.cortes-kaplan@canada.ca>; Dave, Jaahnavi (PHAC/ASPC) <jaahnavi.dave@canada.ca>; Anna Jirovec [redacted]
**Subject:** RE: Input on therapeutics LISA AND THERAPEUTICS TEAM FOR INPUT BY APRIL 29 - 21-108019 - Vitamin D, Colcichine, Ivermectin

Thanks Cheryl,

There might be some useful content in MLs about safe and effective therapies for Canadians etc. Since we are being asked for input on the evidence, and have an extremely short turnaround time for a response, I suggest starting small and referring to WHO and other summary documents as noted.

Margaret

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**From:** Marinsky, Cheryl (PHAC/ASPC) <cheryl.marinsky@canada.ca>
**Sent:** 2021-04-26 2:38 PM
**To:** Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>; Sarwar, Elaha (PHAC/ASPC) <elaha.sarwar@canada.ca>
**Cc:** Cortés-Kaplan, Serena (PHAC/ASPC) <serena.cortes-kaplan@canada.ca>; Dave, Jaahnavi (PHAC/ASPC) <jaahnavi.dave@canada.ca>; Anna Jirovec [redacted]
**Subject:** RE: Input on therapeutics LISA AND THERAPEUTICS TEAM FOR INPUT BY APRIL 29 - 21-108019 - Vitamin D, Colcichine, Ivermectin

HI Margaret,

I have already sent a request for technical assistance to the Elaha and team, happy to help draft something.

I have searched our media lines and correspondence folders and we have nothing related to colchicine nor ivermectin, what we have on Vitamin D is not current. For GoC guidance on Colchicine we have the statement from the CPTG and with regard to ivermectin, nothing on the GoC site. I did find a statement from the WHO dated March 31st , https://www.who.int/news-

room/feature-stories/detail/who-advises-that-ivermectin-only-be-used-to-treat-covid-19-within-clinical-trials
that we could use.

Thanks,

Cheryl

---

**From:** Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>
**Sent:** 2021-04-26 2:32 PM
**To:** Sarwar, Elaha (PHAC/ASPC) <elaha.sarwar@canada.ca>; Marinsky, Cheryl (PHAC/ASPC) <cheryl.marinsky@canada.ca>
**Cc:** Cortés-Kaplan, Serena (PHAC/ASPC) <serena.cortes-kaplan@canada.ca>; Dave, Jaahnavi (PHAC/ASPC) <jaahnavi.dave@canada.ca>; Anna Jirovec[redacted]
**Subject:** Input on therapeutics LISA AND THERAPEUTICS TEAM FOR INPUT BY APRIL 29 - 21-108019 - Vitamin D, Colcichine, Ivermectin
**Importance:** High

Hi,

By way of this email, I am asking the technical team if they have input (short bullets/summary) and on colchicine and ivermectin or new info on Vit D.

I don't know if there are previous webmails/requests to model the response after, but suggest including wording on re-purposed drugs and authorized/off-label use. Maybe also that the practice of medicine is under PT jurisdiction, only because the writer refers to "ignoring the evidence".

Elaha/Cheryl, I know you likely have several things on your plate today. Is it possible for one of the team to look at this?

Margaret

---

**From:** Poon Young, Celisse (PHAC/ASPC) <celisse.poonyoung@canada.ca> **On Behalf Of** COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC)
**Sent:** 2021-04-26 1:54 PM
**To:** Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>; Marinsky, Cheryl (PHAC/ASPC) <cheryl.marinsky@canada.ca>; Lawuyi2, Niyi (PHAC/ASPC) <niyi.lawuyi2@canada.ca>
**Cc:** Poon Young, Celisse (PHAC/ASPC) <celisse.poonyoung@canada.ca>
**Subject:** FW: LISA AND THERAPEUTICS TEAM FOR INPUT BY APRIL 29 - 21-108019 - Vitamin D, Colcichine, Ivermectin
**Importance:** High

Hi everyone,

Please see the request that came to the Therapeutics inbox this afternoon. Sending to you all since I am not sure exactly who this should be directed to.

Thank you,

Celisse

---

**From:** Jamil, Marium (PHAC/ASPC) <marium.jamil@canada.ca>
**Sent:** 2021-04-26 12:21 PM
**To:** Waddell, Lisa (PHAC/ASPC) <lisa.waddell@canada.ca>; COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC) <phac.covid-19therapeutics-therapeutiques.aspc@canada.ca>
**Cc:** PHAC.F OCSO_ESGSecretariat / BCSC_SecrétariatGSE F.ASPC <phac.ocso_esgsecretariat-bcsc_secretariatgse.aspc@canada.ca>
**Subject:** LISA AND THERAPEUTICS TEAM FOR INPUT BY APRIL 29 - 21-108019 - Vitamin D, Colcichine, Ivermectin
**Importance:** High

Good morning Lisa and Therapeutics team,
**FOR INPUT/APPROVAL – BY APRIL 29**
**CONTEXT**

- Dr. Tam received correspondence on April 21, 2021 from a member of the public (please see attached '21-108019-10 Incoming Apr 22.pdf'), regarding the use of Vitamin D, Ivermectin and Colchicine as treatments for COVID-19.

**FOR INPUT**

- ESG Secretariat has drafted a standard response in regards to the use of Vitamin D (please see attached '21-108019-VitD_Colchicine, Ivermectin _ Response_Apr2021. doc') adapted from previous responses. The letter does not speak to Colchicine or Ivermectin however. We would be thankful if you could please provide **your input on:**
    - **Any evidence to support the use of Ivermectin and Colchicine**
    - **Any NEW evidence on the efficacy of Vitamin D**

Thank you so much for your time. We would be grateful if you could please provide us your input by April 29th.

Please let us know if you have any questions.

Regards,
Marium

*On behalf of the Office of Chief Science Officer and the PHAC Emerging Science Group Secretariat*

**Marium Jamil**
(she | elle)
Policy Analyst | Analyste des politiques
Office of the Chief Science Officer | Bureau du Conseiller scientifique en chef
Public Health Agency of Canada | Agence de la santé publique du Canada
NEW: phac.ocso_esgsecretariat-bcsc_secretariatgse.aspc@canada.ca

**From:** Marinsky, Cheryl (PHAC/ASPC)
**Sent:** 2021-04-27 8:24 AM
**To:** Gale-Rowe, Margaret (PHAC/ASPC); Sarwar, Elaha (PHAC/ASPC)
**Cc:** Cortés-Kaplan, Serena (PHAC/ASPC); Dave, Jaahnavi (PHAC/ASPC); Anna Jirovec
**Subject:** RE: Input on therapeutics LISA AND THERAPEUTICS TEAM FOR INPUT BY APRIL 29 - 21-108019 - Vitamin D, Colcichine, Ivermectin

---

Thanks for the update Margaret.

Cheryl

---

**From:** Gale-Rowe, Margaret (PHAC/ASPC)
**Sent:** 2021-04-27 8:23 AM
**To:** Marinsky, Cheryl (PHAC/ASPC) ; Sarwar, Elaha (PHAC/ASPC)
**Cc:** Cortés-Kaplan, Serena (PHAC/ASPC) ; Dave, Jaahnavi (PHAC/ASPC) ; Anna Jirovec
**Subject:** Re: Input on therapeutics LISA AND THERAPEUTICS TEAM FOR INPUT BY APRIL 29 - 21-108019 - Vitamin D, Colcichine, Ivermectin

FYI from Joseph:

Today noon the tech support will activate my account and set my email

Medical Advisor - COVID Therapeutics Acquisitions
[redacted]

> On Apr 27, 2021, at 7:55 AM, Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca> wrote:
>
> Hi,
>
> I have forwarded my email to him. HR is going to nudge the people responsible for getting his email set up.
> For now, I am corresponding with his personal email but that isn't ideal for sharing documents.
> Will keep you posted.
>
> Margaret
>
> ---
>
> **From:** Marinsky, Cheryl (PHAC/ASPC) <cheryl.marinsky@canada.ca>
> **Sent:** 2021-04-27 7:52 AM
> **To:** Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>; Sarwar, Elaha (PHAC/ASPC) <elaha.sarwar@canada.ca>
> **Cc:** Cortés-Kaplan, Serena (PHAC/ASPC) <serena.cortes-kaplan@canada.ca>; Dave, Jaahnavi (PHAC/ASPC) <jaahnavi.dave@canada.ca>; Anna Jirovec

[redacted]

**Subject:** RE: Input on therapeutics LISA AND THERAPEUTICS TEAM FOR INPUT BY APRIL 29 - 21-108019 - Vitamin D, Colcichine, Ivermectin

Hi Margaret,

Sure, I will. I do not have his contact information, would it be possible for you to forward me his coordinates?

Thanks,

Cheryl

---

**From:** Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>
**Sent:** 2021-04-27 7:50 AM
**To:** Marinsky, Cheryl (PHAC/ASPC) <cheryl.marinsky@canada.ca>; Sarwar, Elaha (PHAC/ASPC) <elaha.sarwar@canada.ca>
**Cc:** Cortés-Kaplan, Serena (PHAC/ASPC) <serena.cortes-kaplan@canada.ca>; Dave, Jaahnavi (PHAC/ASPC) <jaahnavi.dave@canada.ca>; Anna Jirovec
[redacted]
**Subject:** RE: Input on therapeutics LISA AND THERAPEUTICS TEAM FOR INPUT BY APRIL 29 - 21-108019 - Vitamin D, Colcichine, Ivermectin

Please don't hesitate to loop Joseph in to help. I am hoping his email will be set up soon.

Margaret

---

**From:** Marinsky, Cheryl (PHAC/ASPC) <cheryl.marinsky@canada.ca>
**Sent:** 2021-04-27 7:35 AM
**To:** Sarwar, Elaha (PHAC/ASPC) <elaha.sarwar@canada.ca>; Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>
**Cc:** Cortés-Kaplan, Serena (PHAC/ASPC) <serena.cortes-kaplan@canada.ca>; Dave, Jaahnavi (PHAC/ASPC) <jaahnavi.dave@canada.ca>; Anna Jirovec
[redacted]
**Subject:** RE: Input on therapeutics LISA AND THERAPEUTICS TEAM FOR INPUT BY APRIL 29 - 21-108019 - Vitamin D, Colcichine, Ivermectin

Hi Elaha,

My apologies for not replying to this email! We had discussed at the meeting yesterday afternoon, Wednesday would be great, I have already started working on the response and the information that you provide will help me fill in the gaps,

Thanks!

Cheryl

---

**From:** Sarwar, Elaha (PHAC/ASPC) <elaha.sarwar@canada.ca>
**Sent:** 2021-04-26 2:54 PM
**To:** Marinsky, Cheryl (PHAC/ASPC) <cheryl.marinsky@canada.ca>; Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>
**Cc:** Cortés-Kaplan, Serena (PHAC/ASPC) <serena.cortes-kaplan@canada.ca>; Dave,

Jaahnavi (PHAC/ASPC) <jaahnavi.dave@canada.ca>; Anna Jirovec [redacted]

**Subject:** RE: Input on therapeutics LISA AND THERAPEUTICS TEAM FOR INPUT BY APRIL 29 - 21-108019 - Vitamin D, Colcichine, Ivermectin

Hi all,

We previously provided input for Vitamin D. We used daily titles and a couple of other resources (e.g. COVID-NMA, the LOVE Platform) to summarize the existing evidence.

The technical team will provide a summary of evidence on Ivermectin and Colchicine and will update gaps in the summary of evidence for Vit D.

I really have my hands tied with everything else going on so I can provide something by **Wednesday** morning. Please let me know if that is okay?

Cheryl: Once we have the technical summary of evidence we can send it your way for input on suggested language/policy perspective.

Elaha

---

**From:** Marinsky, Cheryl (PHAC/ASPC) <cheryl.marinsky@canada.ca>
**Sent:** 2021-04-26 2:47 PM
**To:** Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>; Sarwar, Elaha (PHAC/ASPC) <elaha.sarwar@canada.ca>
**Cc:** Cortés-Kaplan, Serena (PHAC/ASPC) <serena.cortes-kaplan@canada.ca>; Dave, Jaahnavi (PHAC/ASPC) <jaahnavi.dave@canada.ca>; Anna Jirovec [redacted]

**Subject:** RE: Input on therapeutics LISA AND THERAPEUTICS TEAM FOR INPUT BY APRIL 29 - 21-108019 - Vitamin D, Colcichine, Ivermectin

Hi Margaret,

Working on it ☺

Elaha , any content that your team can provide will be greatly appreciated!

BTW Margaret, since Jackie is away are we still having the COVID-19 Therapeutics touch base meeting at 3 pm? I noticed that it was not cancelled.

Thanks,

Cheryl

---

**From:** Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>
**Sent:** 2021-04-26 2:43 PM
**To:** Marinsky, Cheryl (PHAC/ASPC) <cheryl.marinsky@canada.ca>; Sarwar, Elaha (PHAC/ASPC) <elaha.sarwar@canada.ca>
**Cc:** Cortés-Kaplan, Serena (PHAC/ASPC) <serena.cortes-kaplan@canada.ca>; Dave, Jaahnavi (PHAC/ASPC) <jaahnavi.dave@canada.ca>; Anna Jirovec [redacted]

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Thanks Cheryl,

There might be some useful content in MLs about safe and effective therapies for Canadians etc. Since we are being asked for input on the evidence, and have an extremely short turnaround time for a response, I suggest starting small and referring to WHO and other summary documents as noted.

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**To:** Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>; Sarwar, Elaha (PHAC/ASPC) <elaha.sarwar@canada.ca>
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Thanks,

Cheryl

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**Sent:** 2021-04-26 2:32 PM
**To:** Sarwar, Elaha (PHAC/ASPC) <elaha.sarwar@canada.ca>; Marinsky, Cheryl (PHAC/ASPC) <cheryl.marinsky@canada.ca>
**Cc:** Cortés-Kaplan, Serena (PHAC/ASPC) <serena.cortes-kaplan@canada.ca>; Dave, Jaahnavi (PHAC/ASPC) <jaahnavi.dave@canada.ca>; Anna Jirovec [redacted]
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**To:** Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>; Marinsky, Cheryl (PHAC/ASPC) <cheryl.marinsky@canada.ca>; Lawuyi2, Niyi (PHAC/ASPC) <niyi.lawuyi2@canada.ca>
**Cc:** Poon Young, Celisse (PHAC/ASPC) <celisse.poonyoung@canada.ca>
**Subject:** FW: LISA AND THERAPEUTICS TEAM FOR INPUT BY APRIL 29 - 21-108019 - Vitamin D, Colcichine, Ivermectin
**Importance:** High

Hi everyone,

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Thank you,

Celisse

---

**From:** Jamil, Marium (PHAC/ASPC) <marium.jamil@canada.ca>
**Sent:** 2021-04-26 12:21 PM
**To:** Waddell, Lisa (PHAC/ASPC) <lisa.waddell@canada.ca>; COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC) <phac.covid-19therapeutics-therapeutiques.aspc@canada.ca>
**Cc:** PHAC.F OCSO_ESGSecretariat / BCSC_SecrétariatGSE F.ASPC <phac.ocso_esgsecretariat-bcsc_secretariatgse.aspc@canada.ca>
**Subject:** LISA AND THERAPEUTICS TEAM FOR INPUT BY APRIL 29 - 21-108019 - Vitamin D, Colcichine, Ivermectin
**Importance:** High

Good morning Lisa and Therapeutics team,
**FOR INPUT/APPROVAL – BY APRIL 29**
**CONTEXT**

- Dr. Tam received correspondence on April 21, 2021 from a member of the public (please see attached '21-108019-10 Incoming Apr 22.pdf'), regarding the use of Vitamin D, Ivermectin and Colchicine as treatments for COVID-19.

**FOR INPUT**

- ESG Secretariat has drafted a standard response in regards to the use of Vitamin D (please see attached '21-108019-VitD_Colchicine, Ivermectin _ Response_Apr2021. doc') adapted from previous responses. The letter does not speak to Colchicine or Ivermectin however. We would be thankful if you could please provide **your input on:**
    - **Any evidence to support the use of Ivermectin and Colchicine**
    - **Any NEW evidence on the efficacy of Vitamin D**

Thank you so much for your time. We would be grateful if you could please provide us your input by April 29th.

Please let us know if you have any questions.

Regards,
Marium

*On behalf of the Office of Chief Science Officer and the PHAC Emerging Science Group Secretariat*

**Marium Jamil**
(she | elle)
Policy Analyst | Analyste des politiques
Office of the Chief Science Officer | Bureau du Conseiller scientifique en chef
Public Health Agency of Canada | Agence de la santé publique du Canada
NEW: phac.ocso_esgsecretariat-bcsc_secretariatgse.aspc@canada.ca

**From:** Gale-Rowe, Margaret (PHAC/ASPC)
**Sent:** 2021-04-22 7:38 PM
**To:** Arthur, Jacqueline (PHAC/ASPC); Lawuyi2, Niyi (PHAC/ASPC)
**Subject:** RE: Ivermectin and others

---

From my quick look, it is unfortunate that people are listening to a group that discounts the values of randomized control trials, basically because "we know this works."
An article I read (and their website) raise all kinds of flags.

It's also unfortunate that she didn't answer your question about a regular science/therapeutics/clinical table ☺

Margaret

---

**From:** Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>
**Sent:** 2021-04-22 5:50 PM
**To:** Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>; Lawuyi2, Niyi (PHAC/ASPC) <niyi.lawuyi2@canada.ca>
**Subject:** FW: Ivermectin and others

Looping Margaret in to have a look at the FLCCC alliance:
https://covid19criticalcare.com/ivermectin-in-covid-19/
Interesting membership, all white males…

---
Jacqueline Arthur, RN, BScN
(she | elle)
Senior Manager, AMR Division | Gestionnaire principale, Division de la RAM
COVID-19 Therapeutics | thérapeutiques
CCDIC, PHAC | CLMTI, ASPC
t. (613) 889-8455

---

**From:** [redacted]@gov.ab.ca>
**Sent:** 2021-04-22 5:43 PM
**To:** Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>; Lawuyi2, Niyi (PHAC/ASPC) <niyi.lawuyi2@canada.ca>
**Subject:** RE: Ivermectin and others

Thanks Jackie. Many callers to the government are referencing the FLCCC alliance and their evidence summaries (https://covid19criticalcare.com/ivermectin-in-covid-19/). I am sure that PHAC is aware of them but just wanted you to know who the public appears to be listening to these days!

thanks

---

**From:** Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>
**Sent:** April-22-21 3:07 PM
**To:** [redacted]@gov.ab.ca>; Lawuyi2, Niyi (PHAC/ASPC) <niyi.lawuyi2@canada.ca>
**Subject:** RE: Ivermectin and others

Thanks [redacted] for your email. PHAC does monitor the emerging evidence closely and summaries information about therapeutics showing promise. Our expert advisory group did issue public recommendations on hydroxychloroquine: Statement on hydroxychloroquine: COVID-19 Clinical Pharmacology Task Group - Canada.ca

As for ivermectin, our team continues to review the available evidence but no public recommendations are available at the federal level given the weak evidence. I know both Ontario and BC have updated guidance that includes ivermectin recommendations to not use it (attached for reference).

Our team at PHAC is working with Health Canada on the development of a new governance approach for COVID-19 therapeutics that we hope to discuss with provinces and territories soon that may be able to help in this area – for example, we think a regular therapeutics science/clinical/ table would be helpful to bring forward evidence summaries and analyses for a fulsome discussion with P/T clinical leads to help identify promising therapies. Do you think that would meet a need?
Would appreciate your thoughts.
Thanks,
Jackie

---

Jacqueline Arthur, RN, BScN
(she | elle)
Senior Manager, AMR Division | Gestionnaire principale, Division de la RAM
COVID-19 Therapeutics | thérapeutiques
CCDIC, PHAC | CLMTI, ASPC
t. (613) 889-8455

---

**From:** [redacted]@gov.ab.ca>
**Sent:** 2021-04-22 3:57 PM
**To:** Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>; Lawuyi2, Niyi (PHAC/ASPC) <niyi.lawuyi2@canada.ca>
**Subject:** Ivermectin and others

Hi Jackie and Niyi

In follow-up to the comment about evidence reviews raised in the ADM drug shortage meeting, I am wondering if Health Canada has any guidance/recommendations on any of the emerging therapies? We frequently get questions about ivermectin and hydroxychloroquine (among others) and why it is not being used for COVID. I recall a HC therapeutic committee mentioned in our meetings. Do they have public recommendations? Does HC monitor the every changing evidence based on these drugs and update recommendations as needed?

thanks very much

[redacted]

[redacted]
Alberta Health

**From:** Gale-Rowe, Margaret (PHAC/ASPC)
**Sent:** 2021-06-03 6:28 PM
**To:** Forbes, Nicole (PHAC/ASPC); Azad, Mina (PHAC/ASPC)
**Cc:** Djiometio, Joseph (PHAC/ASPC); Arthur, Jacqueline (PHAC/ASPC)
**Subject:** RE: Ivermectin for CPHO
**Attachments:** Ivecmertin statment_NF_mgr.docx

---

Some editorial changes for consideration; it shouldn't take much time to accept or not.

Thanks,

Margaret

---

**From:** Forbes, Nicole (PHAC/ASPC)
**Sent:** 2021-06-03 6:17 PM
**To:** Azad, Mina (PHAC/ASPC)
**Cc:** Djiometio, Joseph (PHAC/ASPC) ; Arthur, Jacqueline (PHAC/ASPC) ; Gale-Rowe, Margaret (PHAC/ASPC)
**Subject:** Ivermectin for CPHO

Hi Mina,

Please see attached suggestions to your draft response. Looks good just need to add a few details and I provided some suggested text for your consideration. If you can please review and send to me *in the text of an email* as this is what CPHO wants I will send to Marina and cc you.

I think also we need to note that no new RCT has reported out… may be good to make that clear in one bullet at the top, after meta analysis bullet reporting positive benefit.

☺

Nicole

---

**Nicole Forbes, PhD**
(she | elle)
**Scientific Project Coordinator**
National Advisory Committee on Immunization Secretariat
Centre for Immunization Readiness, Public Heath Agency of Canada
Tel: (613) 447-6450
Email: nicole.forbes@canada.ca

**From:** Gale-Rowe, Margaret (PHAC/ASPC)
**Sent:** 2021-06-03 6:38 PM
**To:** Djiometio, Joseph (PHAC/ASPC); Forbes, Nicole (PHAC/ASPC); Azad, Mina (PHAC/ASPC)
**Cc:** Arthur, Jacqueline (PHAC/ASPC)
**Subject:** RE: Ivermectin for CPHO
**Attachments:** Ivermectin summary_NF_mgr.docx

---

**Categories:** DO pending

Cleaner version

---

**From:** Djiometio, Joseph (PHAC/ASPC) <joseph.djiometio@canada.ca>
**Sent:** 2021-06-03 6:33 PM
**To:** Forbes, Nicole (PHAC/ASPC) <nicole.forbes@canada.ca>; Azad, Mina (PHAC/ASPC) <mina.azad@canada.ca>
**Cc:** Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>; Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>
**Subject:** RE: Ivermectin for CPHO

Thank you Nicole
Mina: CADTH information was updated **February 22, 2021**
https://cadth.ca/covid-19-update-12

Same conclusion
British Columbia COVID-19 Therapeutics Committee (CTC) and COVID-19 Therapeutics Review and Advisory Working Updated May 25th, 2021

Alberta health Service As of April 15: https://www.albertahealthservices.ca/assets/info/ppih/if-ppih-covid-19-sag-ivermectin-in-treatment-and-prevention-rapid-review.pdf

---

**From:** Forbes, Nicole (PHAC/ASPC) <nicole.forbes@canada.ca>
**Sent:** 2021-06-03 6:17 PM
**To:** Azad, Mina (PHAC/ASPC) <mina.azad@canada.ca>
**Cc:** Djiometio, Joseph (PHAC/ASPC) <joseph.djiometio@canada.ca>; Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>; Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>
**Subject:** Ivermectin for CPHO

Hi Mina,

Please see attached suggestions to your draft response. Looks good just need to add a few details and I provided some suggested text for your consideration. If you can please review and send to me *in the text of an email* as this is what CPHO wants I will send to Marina and cc you.

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Nicole

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(she | elle)
**Scientific Project Coordinator**
National Advisory Committee on Immunization Secretariat
Centre for Immunization Readiness, Public Heath Agency of Canada
Tel: (613) 447-6450
Email: nicole.forbes@canada.ca

**From:** Arthur, Jacqueline (PHAC/ASPC)

**Sent:** 2021-06-04 9:17 AM

**To:** Forbes, Nicole (PHAC/ASPC); Gale-Rowe, Margaret (PHAC/ASPC); Djiometio, Joseph (PHAC/ASPC)

**Cc:** Azad, Mina (PHAC/ASPC); Salvadori, Marina (PHAC/ASPC)

**Subject:** RE: Ivermectin summary

---

Agreed that these need to move quickly to provide Dr. Tam with the required information. Thanks Mina, Joe and Margaret for the rapid turn around.

Nicole, [redacted]

Marina, [redacted]

Jackie

---

Jacqueline Arthur, BScN, RN
(she | elle)
Senior Manager, AMR Division | Gestionnaire principale, Division de la RAM
COVID-19 Therapeutics | thérapeutiques
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**From:** Forbes, Nicole (PHAC/ASPC) <nicole.forbes@canada.ca>
**Sent:** 2021-06-03 9:00 PM
**To:** Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>; Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>; Djiometio, Joseph (PHAC/ASPC) <joseph.djiometio@canada.ca>
**Cc:** Azad, Mina (PHAC/ASPC) <mina.azad@canada.ca>
**Subject:** Fwd: Ivermectin summary

[redacted]Mina! Marina provided feedback for situational awareness of the rest of the team. This type of request is for TT's back pocket, which is nice as it doesn't need the formality of policy docs. Sounds like more requests will be headed your way :)

Nicole

---

**Nicole Forbes, PhD**

**she | elle**

**Scientific Project Coordinator**

NACI Secretariat

Centre for Immunization Readiness

Public Health Agency of Canada l Agence de la santé publique du Canada

Tel: (613) 447-6450

Email: nicole.forbes@canada.ca

Begin forwarded message:

**From:** "Salvadori, Marina (PHAC/ASPC)" <marina.salvadori@canada.ca>
**Date:** June 3, 2021 at 9:55:20 PM ADT
**To:** "Forbes, Nicole (PHAC/ASPC)" <nicole.forbes@canada.ca>
**Cc:** "Azad, Mina (PHAC/ASPC)" <mina.azad@canada.ca>
**Subject: RE: Ivermectin summary**

Thank you. Just so you know Mina, These summaries need not be approved by the whole chain and are not issue notes.

I brief Theresa on all things scientific.

Fast and right is more impt than approvals.

Welcome on board

Marina

---

**From:** Forbes, Nicole (PHAC/ASPC) <nicole.forbes@canada.ca>
**Sent:** 2021-06-03 8:20 PM
**To:** Salvadori, Marina (PHAC/ASPC) <marina.salvadori@canada.ca>
**Cc:** Azad, Mina (PHAC/ASPC) <mina.azad@canada.ca>
**Subject:** FW: Ivermectin summary

Hi Marina,

Please see summary on ivermectin below, compiled by Mina Azad, a PhD Biochemist [redacted] COVID-19 therapeutics technical team. [redacted] If Theresa needs a summary done for therapeutics in the future I suggest we route it through Mina. I am happy to review as she acquaints herself to the file. For this one it's a bit different as there was no recent trial that reported, instead a meta-analysis that suggested positive clinical benefit… see below.

Best regards,

Nicole

---

**From:** Azad, Mina (PHAC/ASPC) <mina.azad@canada.ca>
**Sent:** 2021-06-03 8:25 PM
**To:** Forbes, Nicole (PHAC/ASPC) <nicole.forbes@canada.ca>
**Cc:** Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>; Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>; Djiometio, Joseph (PHAC/ASPC) <joseph.djiometio@canada.ca>
**Subject:** Ivermectin summary

**Ivermectin Overview**

Ivermectin is a broad-spectrum anti-parasitic agent authorized by Health Canada for human and veterinary applications. Health Canada has not authorized its use for the treatment of COVID-19.

**Ivermectin Findings & Outcomes**

- In laboratory studies, ivermectin prevented SARS-CoV2 from replicating and has demonstrated anti-inflammatory properties, raising the possibility that ivermectin may have a role in COVID-19 prophylaxis or treatment.
- While preliminary *in vitro* and animal studies reported promising antiviral and anti-inflammatory effects of ivermectin in the context of SARS-CoV-2 infection, its use as a preventative or treatment for COVID-19 remains controversial due to mixed evidence of clinical benefit from numerous smaller, underpowered randomized trials.
- The British Medical Journal's living systematic review and network meta-analysis analysed 16 randomized trials. Based on their findings, they rated the effects of ivermectin on viral clearance, mechanical ventilation and mortality as uncertain, meaning it is uncertain whether ivermectin has an important impact on any patient-important outcome.
- Recently, a meta-analysis based on 18 randomized trials of ivermectin in COVID-19 found that ivermectin treatment reduced mortality, time to clinical recovery, and time to viral clearance.
- A powered, well-designed randomized trial is needed to clearly elucidate the appropriate role of ivermectin in the clinical management or prevention of COVID-19.

**Considerations**

***Canadian perspectives***

- The Canadian Agency for Drugs and Technologies in Health (CADTH; statement issued on February 08, 2021); Alberta Health Services (statement issued on February 02, 2021) ; as well as British Columbia's COVID-19 Therapeutics Committee/COVID-19 Therapeutics Review and Advisory Working Group (statement issued on May 25, 2021) have all concluded that there is no clear benefit associated with ivermectin treatment among patients with COVID-19. As of June 3, 2021, no statement has been issued by INESSS.
- On May 28, 2021, Ontario's COVID-19 Science Advisory Table issued a statement titled Ivermectin to Prevent Disseminated Strongyloides Infection in Patients with COVID-19. While stipulating ivermectin is currently not recommended as a treatment or preventative for COVID-19, the statement acknowledges patients with COVID-19 who receive therapies that alter immune system function may require ivermectin for the purposes of treating a pre-existing parasitic infection and to avoid severe complications of worsening parasitic infection.

***International perspectives***

- In South American countries, ivermectin is being prescribed routinely for COVID-19 infections; however, it is difficult to ascertain clinical benefit from use outside the context of randomized controlled trials.
- On March 31, 2021, the WHO issued a statement on ivermectin advising against its use outside of clinical trials, stating the current clinical evidence was inconclusive
- On March 22, 2021 the EMA issued an advisory notice against use of ivermectin for the prevention or treatment of COVID-19 outside randomised clinical trials.
- On February 11, 2021 the NIH COVID-19 Treatment Guidelines Panel issued a statement concluding there is insufficient evidence to recommend either for or against the use of ivermectin for the treatment of COVID-19.

Mina Azad, PhD

(She | elle)

Research Analyst | Analyste de recherche

COVID-19 Therapeutics | Thérapeutiques

CCDIC, PHAC | CLMTI, ASPC

mina.azad@canada.ca | Tel: (343) 574 4080

**From:** Arthur, Jacqueline (PHAC/ASPC)
**Sent:** 2021-01-05 9:41 AM
**To:** Forbes, Nicole (PHAC/ASPC); Ephrem, Bersabel (PHAC/ASPC)
**Cc:** Salvadori, Marina (PHAC/ASPC)
**Subject:** RE: Ivermectin

---

I agree. Bersabel, what is the next step? Will Kaili's group re-ask the TTF to look at it?

---
Jacqueline Arthur, RN, BScN
Senior Manager, AMR Division | Gestionnaire principale, Division de la RAM
COVID-19 Therapeutics | thérapeutiques
CCDIC, PHAC | CLMTI, ASPC
t. (613) 889-8455

---

**From:** Forbes, Nicole (PHAC/ASPC) <nicole.forbes@canada.ca>
**Sent:** 2021-01-05 9:17 AM
**To:** Ephrem, Bersabel (PHAC/ASPC) <bersabel.ephrem@canada.ca>
**Cc:** Salvadori, Marina (PHAC/ASPC) <marina.salvadori@canada.ca>; Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>
**Subject:** RE: Ivermectin

Good morning Bersabel,

I reviewed the document from HC and consider this sufficient to provide an overview on ivermectin and COVID-19 in anticipation of a more fulsome analysis by the CTTF.

Best regards,

Nicole

---

**Nicole Forbes, PhD**
Scientific Project Coordinator
Immunization Programs and Pandemic Preparedness Division I Division des programmes d'immunisation et de la préparation aux pandémies; Centre for Immunization and Respiratory Infectious Diseases (CIRID) I Centre de l'immunisation et des maladies respiratoires infectieuses (CIMRI)
Public Health Agency of Canada I Agence de la santé publique du Canada
130 Colonnade Road , Room 149A-05, AL 6501A

Tel: (613) 447-6450
Email: nicole.forbes@canada.ca

---

**From:** Ephrem, Bersabel (PHAC/ASPC) <bersabel.ephrem@canada.ca>
**Sent:** 2021-01-04 8:10 PM
**To:** Forbes, Nicole (PHAC/ASPC) <nicole.forbes@canada.ca>
**Cc:** Salvadori, Marina (PHAC/ASPC) <marina.salvadori@canada.ca>; Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>
**Subject:** RE: Ivermectin

Thanks Nicole.

---

**From:** Forbes, Nicole (PHAC/ASPC) <nicole.forbes@canada.ca>
**Sent:** 2021-01-04 7:38 PM

**To:** Ephrem, Bersabel (PHAC/ASPC) <bersabel.ephrem@canada.ca>
**Cc:** Salvadori, Marina (PHAC/ASPC) <marina.salvadori@canada.ca>; Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>
**Subject:** Re: Ivermectin

Hi Bersabel,

Replying back to add Jackie to this thread. I removed Clare Jackson- perhaps she may have been added accidentally?

I am happy to review the HC background doc on ivermectin and will provide feedback tomorrow.

Have a good night,

Nicole

**Nicole Forbes, PhD**
Scientific Project Coordinator
Immunization Programs and Pandemic Preparedness Division l Division des programmes d'immunisation et de la préparation aux pandémies; Centre for Immunization and Respiratory Infectious Diseases (CIRID) l Centre de l'immunisation et des maladies respiratoires infectieuses (CIMRI)
Public Health Agency of Canada l Agence de la santé publique du Canada
130 Colonnade Road , Room 149A-05, AL 6501A

Tel: (613) 447-6450
Email: nicole.forbes@canada.ca

> On Jan 4, 2021, at 6:24 PM, Ephrem, Bersabel (PHAC/ASPC) <bersabel.ephrem@canada.ca> wrote:
>
> Hi Ladies,
>
> Here is what HC prepared. Will you be able to review and let me know if you have any question or suggestion.
>
> It is very much appreciated.
>
> be
>
> **From:** Levesque2, Kaili (HC/SC) <kaili.levesque2@canada.ca>
> **Sent:** 2021-01-04 5:58 PM
> **To:** Ephrem, Bersabel (PHAC/ASPC) <bersabel.ephrem@canada.ca>
> **Cc:** Stefanis, Tasha (HC/SC) <tasha.stefanis@canada.ca>; Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>; Szumski2, Roman (PHAC/ASPC) <roman.szumski2@canada.ca>; Njoo, Howard (PHAC/ASPC) <howard.njoo@canada.ca>
> **Subject:** RE: Ivermectin
>
> Bersabel – 1-pager for your consideration. Don't think we need additional advice, but please feel free to connect with Tasha if additional information is required.
> Thanks a million!
> K
>
> **From:** Ephrem, Bersabel (PHAC/ASPC) <bersabel.ephrem@canada.ca>
> **Sent:** 2021-01-03 11:16 AM
> **To:** Rendall, Jennifer (PHAC/ASPC) <jennifer.rendall@canada.ca>
> **Cc:** Njoo, Howard (PHAC/ASPC) <howard.njoo@canada.ca>; Szumski2, Roman (PHAC/ASPC) <roman.szumski2@canada.ca>; Levesque2, Kaili (HC/SC) <kaili.levesque2@canada.ca>; Ponic, Pamela (PHAC/ASPC) <pamela.ponic@canada.ca>; Currie, Andrea (PHAC/ASPC)

<andrea.currie@canada.ca>
**Subject:** Re: Ivermectin

Thanks Jenn. We will prepare advice for their consideration, in consultation with Kaili's team.

Be

Sent from my iPhone

On Jan 2, 2021, at 6:25 PM, Rendall, Jennifer (PHAC/ASPC) <jennifer.rendall@canada.ca> wrote:

Hi Team,

Please see below correspondence into Dr. Tam.

Kaili can you please as your team/the HC team to do a roll up of what the TTF has done in this space?

Howard, Bersabel and Roman – can you please prepare advice for Dr. Tam and the President to consider in this area.

Thank you
Jen

**From:** Tam, Dr Theresa (PHAC/ASPC) <drtheresa.tam@canada.ca>
**Sent:** 2021-01-02 4:15 PM
**To:** Stewart, Iain (PHAC/ASPC) <iain.stewart@canada.ca>
**Cc:** Njoo, Howard (PHAC/ASPC) <howard.njoo@canada.ca>; Ponic, Pamela (PHAC/ASPC) <pamela.ponic@canada.ca>; Rendall, Jennifer (PHAC/ASPC) <jennifer.rendall@canada.ca>
**Subject:** Fwd: Ivermectin

There is an upsurge in emails on Ivermectin. Could we get the therapeutics task force to look at this?

Other research networks may also be able to review/summarize if this is not in line with what the therapeutic task force does.

TT
Sent from my iPad

Begin forwarded message:

**From:** [redacted]
**Date:** January 2, 2021 at 2:48:58 PM EST
**To:** "Tam, Dr Theresa (PHAC/ASPC)" <drtheresa.tam@canada.ca>
**Subject: Ivermectin**

Get Outlook for iOSI've compiled a list of the email addresses for the Federal Minister of Health, all Provincial Ministers of Health, Canada's Chief Public Health Officer (Dr. Tam), and all the Provincial Health Officers. I've also written a letter imploring

them to introduce Ivermectin as the front-line treatment to stop Covid-19 and the never-ending pandemic and it's restrictions. I will be sending it to all of them, as often as I can.

I am posting my letter below to make it easier for others to do the same. Since they are refusing to openly acknowledge it, the only way to be sure they know is for us to flood them with our demands. They are, after all, public servants, and unless we no longer live in a democratic society then they are "our" public servants, not the other way around. As I say in my closing statement, they owe it to their constituents, those they are sworn to protect, and all Canadians, to do everything in their power to stop this pandemic. This is entirely within their power to change, and they are obligated by their oath of office to do so…

---

URGENT ATTENTION:

With the Covid-19 crisis showing no signs of slowing, and current treatment options proving to have little success in the elderly and those with pre-existing life-limiting conditions, the saving of those lives is of paramount importance.

Reducing the spread of the Cov-2 virus from person to person and limiting community spread is crucial for protecting those most susceptible to the virus's respiratory effects. The WHO and manufacturers of the vaccines that are being promoted and given to Canadians have stated that there is no data showing they will reduce infection or the transmission of Cov-2, and so one must ask, "Why is this the only option being used?"

There seems to be a tunnel-vision mindset that is blinding public health authorities from considering any other alternatives, operating with single mindedness, and ignoring any information that challenges this approach. This does not follow the principles of scientific methodology and excludes any hope of discovering a control mechanism to stop Cov-2 and the devastation it is reaping on our country's health, both physical and mental, and our economy, which is in ruins.

Seeing no mention of it in any national media, or in the public health messages being provided, it is obvious you are ignoring the latest clinical research on Covid-19, that being the work done by the doctors

of the Front Line COVID-19 Critical Care Alliance (FLCCC) and their ground-breaking exploration in using Ivermectin as a phenomenally successful front-line treatment for Covid-19.

The doctors that make up the FLCCC are leaders in critical care with expertise in therapies directed at severe infections and have spent all of 2020 treating patients with an Ivermectin protocol, believing it to have vast potential as an off-label drug with anti-viral properties.

Their research, and the peer-reviewed empirical data derived from it, has proven Ivermectin to be immensely effective in both the prophylaxis and treatment of all phases of COVID-19. Here are the highlights of their findings:

1) Ivermectin inhibits the replication of many viruses, including SARS-CoV-2, influenza, and others;
2) Ivermectin has potent anti-inflammatory properties with multiple mechanisms of inhibition;
3) Ivermectin diminishes viral load and protects against organ damage in animal models;
4) Ivermectin prevents transmission of COVID-19 when taken either pre- or post-exposure;
5) Ivermectin hastens recovery and decreases hospitalization and mortality in patients with COVID-19;
6) Ivermectin leads to far lower case-fatality rates in regions with widespread use.

https://covid19criticalcare.com/wp-content/uploads/2020/11/FLCCC-Ivermectin-in-the-prophylaxis-and-treatment-of-COVID-19.pdf

Every day that this information is ignored more people die that could have been saved using the Ivermectin protocol. It could be an unknown soul dying alone, or a member of your own family. Every day, battle-weary health care workers are forced to watch helplessly in a vain attempt to save yet another casualty of Covid-19. Every day, more businesses are forced to close forever under the restrictive public health guidelines. With utmost urgency, I implore you to review the data and make this a front-line treatment in the fight against Covid-19. You owe it to your constituents, those you are sworn to protect, and all Canadians, to do everything in your power to stop this pandemic. This is entirely within your power to change, and you are obligated by your oath of office to do so…

Most Sincerely,

[redacted]

[redacted]

<Ivermectin Backgrounder Jan 4 2021.docx>

**From:** Levesque2, Kaili (HC/SC)
**Sent:** 2021-01-04 5:58 PM
**To:** Ephrem, Bersabel (PHAC/ASPC)
**Cc:** Stefanis, Tasha (HC/SC); Arthur, Jacqueline (PHAC/ASPC); Szumski2, Roman (PHAC/ASPC); Njoo, Howard (PHAC/ASPC)
**Subject:** RE: Ivermectin
**Attachments:** Ivermectin Backgrounder Jan 4 2021.docx

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Bersabel – 1-pager for your consideration. Don't think we need additional advice, but please feel free to connect with Tasha if additional information is required.
Thanks a million!
K

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**To:** Rendall, Jennifer (PHAC/ASPC) <jennifer.rendall@canada.ca>
**Cc:** Njoo, Howard (PHAC/ASPC) <howard.njoo@canada.ca>; Szumski2, Roman (PHAC/ASPC) <roman.szumski2@canada.ca>; Levesque2, Kaili (HC/SC) <kaili.levesque2@canada.ca>; Ponic, Pamela (PHAC/ASPC) <pamela.ponic@canada.ca>; Currie, Andrea (PHAC/ASPC) <andrea.currie@canada.ca>
**Subject:** Re: Ivermectin

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Sent from my iPhone

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> **Cc:** Njoo, Howard (PHAC/ASPC) <howard.njoo@canada.ca>; Ponic, Pamela (PHAC/ASPC) <pamela.ponic@canada.ca>; Rendall, Jennifer

(PHAC/ASPC) <jennifer.rendall@canada.ca>
**Subject:** Fwd: Ivermectin

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> **Subject: Ivermectin**
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> URGENT ATTENTION:

With the Covid-19 crisis showing no signs of slowing, and current treatment options proving to have little success in the elderly and those with pre-existing life-limiting conditions, the saving of those lives is of paramount importance.

Reducing the spread of the Cov-2 virus from person to person and limiting community spread is crucial for protecting those most susceptible to the virus's respiratory effects. The WHO and manufacturers of the vaccines that are being promoted and given to Canadians have stated that there is no data showing they will reduce infection or the transmission of Cov-2, and so one must ask, "Why is this the only option being used?"

There seems to be a tunnel-vision mindset that is blinding public health authorities from considering any other alternatives, operating with single mindedness, and ignoring any information that challenges this approach. This does not follow the principles of scientific methodology and excludes any hope of discovering a control mechanism to stop Cov-2 and the devastation it is reaping on our country's health, both physical and mental, and our economy, which is in ruins.

Seeing no mention of it in any national media, or in the public health messages being provided, it is obvious you are ignoring the latest clinical research on Covid-19, that being the work done by the doctors of the Front Line COVID-19 Critical Care Alliance (FLCCC) and their ground-breaking exploration in using Ivermectin as a phenomenally successful front-line treatment for Covid-19.

The doctors that make up the FLCCC are leaders in critical care with expertise in therapies directed at severe infections and have spent all of 2020 treating patients with an Ivermectin protocol, believing it to have vast potential as an off-label drug with anti-viral properties.

Their research, and the peer-reviewed empirical data derived from it, has proven Ivermectin to be immensely effective in both the prophylaxis and

treatment of all phases of COVID-19. Here are the highlights of their findings:

1) Ivermectin inhibits the replication of many viruses, including SARS-CoV-2, influenza, and others;
2) Ivermectin has potent anti-inflammatory properties with multiple mechanisms of inhibition;
3) Ivermectin diminishes viral load and protects against organ damage in animal models;
4) Ivermectin prevents transmission of COVID-19 when taken either pre- or post-exposure;
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6) Ivermectin leads to far lower case-fatality rates in regions with widespread use.

https://covid19criticalcare.com/wp-content/uploads/2020/11/FLCCC-Ivermectin-in-the-prophylaxis-and-treatment-of-COVID-19.pdf

Every day that this information is ignored more people die that could have been saved using the Ivermectin protocol. It could be an unknown soul dying alone, or a member of your own family. Every day, battle-weary health care workers are forced to watch helplessly in a vain attempt to save yet another casualty of Covid-19. Every day, more businesses are forced to close forever under the restrictive public health guidelines. With utmost urgency, I implore you to review the data and make this a front-line treatment in the fight against Covid-19. You owe it to your constituents, those you are sworn to protect, and all Canadians, to do everything in your power to stop this pandemic. This is entirely within your power to change, and you are obligated by your oath of office to do so…

Most Sincerely,

[redacted]

**From:** Arthur, Jacqueline (PHAC/ASPC)
**Sent:** 2021-01-05 5:00 PM
**To:** Forbes, Nicole (PHAC/ASPC)
**Cc:** Salvadori, Marina (PHAC/ASPC)
**Subject:** RE: Ivermectin
**Attachments:** Ivermectin Backgrounder Jan 5 2021 - clean.docx

Latest version from HC.
J

---
Jacqueline Arthur, RN, BScN
Senior Manager, AMR Division | Gestionnaire principale, Division de la RAM
COVID-19 Therapeutics | thérapeutiques
CCDIC, PHAC | CLMTI, ASPC
t. (613) 889-8455

**From:** Forbes, Nicole (PHAC/ASPC) <nicole.forbes@canada.ca>
**Sent:** 2021-01-05 9:17 AM
**To:** Ephrem, Bersabel (PHAC/ASPC) <bersabel.ephrem@canada.ca>
**Cc:** Salvadori, Marina (PHAC/ASPC) <marina.salvadori@canada.ca>; Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>
**Subject:** RE: Ivermectin

Good morning Bersabel,

I reviewed the document from HC and consider this sufficient to provide an overview on ivermectin and COVID-19 in anticipation of a more fulsome analysis by the CTTF.

Best regards,

Nicole

**Nicole Forbes, PhD**
Scientific Project Coordinator
Immunization Programs and Pandemic Preparedness Division I Division des programmes d'immunisation et de la préparation aux pandémies; Centre for Immunization and Respiratory Infectious Diseases (CIRID) I Centre de l'immunisation et des maladies respiratoires infectieuses (CIMRI)
Public Health Agency of Canada I Agence de la santé publique du Canada
130 Colonnade Road , Room 149A-05, AL 6501A

Tel: (613) 447-6450
Email: nicole.forbes@canada.ca

**From:** Ephrem, Bersabel (PHAC/ASPC) <bersabel.ephrem@canada.ca>
**Sent:** 2021-01-04 8:10 PM
**To:** Forbes, Nicole (PHAC/ASPC) <nicole.forbes@canada.ca>
**Cc:** Salvadori, Marina (PHAC/ASPC) <marina.salvadori@canada.ca>; Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>
**Subject:** RE: Ivermectin

Thanks Nicole.

**From:** Forbes, Nicole (PHAC/ASPC) <nicole.forbes@canada.ca>
**Sent:** 2021-01-04 7:38 PM
**To:** Ephrem, Bersabel (PHAC/ASPC) <bersabel.ephrem@canada.ca>
**Cc:** Salvadori, Marina (PHAC/ASPC) <marina.salvadori@canada.ca>; Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>
**Subject:** Re: Ivermectin

Hi Bersabel,

Replying back to add Jackie to this thread. I removed Clare Jackson- perhaps she may have been added accidentally?

I am happy to review the HC background doc on ivermectin and will provide feedback tomorrow.

Have a good night,

Nicole

**Nicole Forbes, PhD**
Scientific Project Coordinator
Immunization Programs and Pandemic Preparedness Division l Division des programmes d'immunisation et de la préparation aux pandémies; Centre for Immunization and Respiratory Infectious Diseases (CIRID) l Centre de l'immunisation et des maladies respiratoires infectieuses (CIMRI)
Public Health Agency of Canada l Agence de la santé publique du Canada
130 Colonnade Road , Room 149A-05, AL 6501A

Tel: (613) 447-6450
Email: nicole.forbes@canada.ca

> On Jan 4, 2021, at 6:24 PM, Ephrem, Bersabel (PHAC/ASPC) <bersabel.ephrem@canada.ca> wrote:
>
> Hi Ladies,
>
> Here is what HC prepared. Will you be able to review and let me know if you have any question or suggestion.
>
> It is very much appreciated.
>
> be
>
> **From:** Levesque2, Kaili (HC/SC) <kaili.levesque2@canada.ca>
> **Sent:** 2021-01-04 5:58 PM
> **To:** Ephrem, Bersabel (PHAC/ASPC) <bersabel.ephrem@canada.ca>
> **Cc:** Stefanis, Tasha (HC/SC) <tasha.stefanis@canada.ca>; Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>; Szumski2, Roman (PHAC/ASPC) <roman.szumski2@canada.ca>; Njoo, Howard (PHAC/ASPC) <howard.njoo@canada.ca>
> **Subject:** RE: Ivermectin
>
> Bersabel – 1-pager for your consideration. Don't think we need additional advice, but please feel free to connect with Tasha if additional information is required.
> Thanks a million!
> K
>
> **From:** Ephrem, Bersabel (PHAC/ASPC) <bersabel.ephrem@canada.ca>
> **Sent:** 2021-01-03 11:16 AM
> **To:** Rendall, Jennifer (PHAC/ASPC) <jennifer.rendall@canada.ca>
> **Cc:** Njoo, Howard (PHAC/ASPC) <howard.njoo@canada.ca>; Szumski2, Roman (PHAC/ASPC)

<roman.szumski2@canada.ca>; Levesque2, Kaili (HC/SC) <kaili.levesque2@canada.ca>; Ponic, Pamela (PHAC/ASPC) <pamela.ponic@canada.ca>; Currie, Andrea (PHAC/ASPC) <andrea.currie@canada.ca>
**Subject:** Re: Ivermectin

Thanks Jenn. We will prepare advice for their consideration, in consultation with Kaili's team.

Be

Sent from my iPhone

> On Jan 2, 2021, at 6:25 PM, Rendall, Jennifer (PHAC/ASPC) <jennifer.rendall@canada.ca> wrote:
>
> Hi Team,
>
> Please see below correspondence into Dr. Tam.
>
> Kaili can you please as your team/the HC team to do a roll up of what the TTF has done in this space?
>
> Howard, Bersabel and Roman – can you please prepare advice for Dr. Tam and the President to consider in this area.
>
> Thank you
> Jen
>
> **From:** Tam, Dr Theresa (PHAC/ASPC) <drtheresa.tam@canada.ca>
> **Sent:** 2021-01-02 4:15 PM
> **To:** Stewart, Iain (PHAC/ASPC) <iain.stewart@canada.ca>
> **Cc:** Njoo, Howard (PHAC/ASPC) <howard.njoo@canada.ca>; Ponic, Pamela (PHAC/ASPC) <pamela.ponic@canada.ca>; Rendall, Jennifer (PHAC/ASPC) <jennifer.rendall@canada.ca>
> **Subject:** Fwd: Ivermectin
>
> There is an upsurge in emails on Ivermectin. Could we get the therapeutics task force to look at this?
>
> Other research networks may also be able to review/summarize if this is not in line with what the therapeutic task force does.
>
> TT
> Sent from my iPad
>
> Begin forwarded message:
>
> **From** [redacted]
> **Date:** January 2, 2021 at 2:48:58 PM EST
> **To:** "Tam, Dr Theresa (PHAC/ASPC)" <drtheresa.tam@canada.ca>
> **Subject: Ivermectin**
>
> Get Outlook for iOSI've compiled a list of the email addresses for the Federal Minister of Health, all Provincial Ministers of Health, Canada's Chief Public

Health Officer (Dr. Tam), and all the Provincial Health Officers. I've also written a letter imploring them to introduce Ivermectin as the front-line treatment to stop Covid-19 and the never-ending pandemic and it's restrictions. I will be sending it to all of them, as often as I can.

I am posting my letter below to make it easier for others to do the same. Since they are refusing to openly acknowledge it, the only way to be sure they know is for us to flood them with our demands. They are, after all, public servants, and unless we no longer live in a democratic society then they are "our" public servants, not the other way around. As I say in my closing statement, they owe it to their constituents, those they are sworn to protect, and all Canadians, to do everything in their power to stop this pandemic. This is entirely within their power to change, and they are obligated by their oath of office to do so…

---

URGENT ATTENTION:

With the Covid-19 crisis showing no signs of slowing, and current treatment options proving to have little success in the elderly and those with pre-existing life-limiting conditions, the saving of those lives is of paramount importance.

Reducing the spread of the Cov-2 virus from person to person and limiting community spread is crucial for protecting those most susceptible to the virus's respiratory effects. The WHO and manufacturers of the vaccines that are being promoted and given to Canadians have stated that there is no data showing they will reduce infection or the transmission of Cov-2, and so one must ask, "Why is this the only option being used?"

There seems to be a tunnel-vision mindset that is blinding public health authorities from considering any other alternatives, operating with single mindedness, and ignoring any information that challenges this approach. This does not follow the principles of scientific methodology and excludes any hope of discovering a control mechanism to stop Cov-2 and the devastation it is reaping on our country's health, both physical and mental, and our economy, which is in ruins.

Seeing no mention of it in any national media, or in the public health messages being provided, it is

obvious you are ignoring the latest clinical research on Covid-19, that being the work done by the doctors of the Front Line COVID-19 Critical Care Alliance (FLCCC) and their ground-breaking exploration in using Ivermectin as a phenomenally successful front-line treatment for Covid-19.

The doctors that make up the FLCCC are leaders in critical care with expertise in therapies directed at severe infections and have spent all of 2020 treating patients with an Ivermectin protocol, believing it to have vast potential as an off-label drug with anti-viral properties.

Their research, and the peer-reviewed empirical data derived from it, has proven Ivermectin to be immensely effective in both the prophylaxis and treatment of all phases of COVID-19. Here are the highlights of their findings:

1) Ivermectin inhibits the replication of many viruses, including SARS-CoV-2, influenza, and others;
2) Ivermectin has potent anti-inflammatory properties with multiple mechanisms of inhibition;
3) Ivermectin diminishes viral load and protects against organ damage in animal models;
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5) Ivermectin hastens recovery and decreases hospitalization and mortality in patients with COVID-19;
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https://covid19criticalcare.com/wp-content/uploads/2020/11/FLCCC-Ivermectin-in-the-prophylaxis-and-treatment-of-COVID-19.pdf

Every day that this information is ignored more people die that could have been saved using the Ivermectin protocol. It could be an unknown soul dying alone, or a member of your own family. Every day, battle-weary health care workers are forced to watch helplessly in a vain attempt to save yet another casualty of Covid-19. Every day, more businesses are forced to close forever under the restrictive public health guidelines. With utmost urgency, I implore you to review the data and make this a front-line treatment in the fight against Covid-19. You owe it to your constituents, those you are sworn to protect, and all Canadians, to do everything in your power to stop this pandemic. This is entirely within your power to change, and you are obligated by your oath of office to do so…

Most Sincerely,

[redacted]

<Ivermectin Backgrounder Jan 4 2021.docx>

**From:** Gale-Rowe, Margaret (PHAC/ASPC)
**Sent:** 2021-04-26 2:35 PM
**To:** Marinsky, Cheryl (PHAC/ASPC); COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC); Lawuyi2, Niyi (PHAC/ASPC)
**Cc:** Poon Young, Celisse (PHAC/ASPC)
**Subject:** RE: LISA AND THERAPEUTICS TEAM FOR INPUT BY APRIL 29 - 21-108019 - Vitamin D, Colcichine, Ivermectin

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Yes please, Cheryl!

I don't think we can reference the colchicine statement itself, since it will be removed but we can indicate the CPTG reviewed the evidence and mention what trials are ongoing.
We aren't doing anything to prevent the use of Vit D, as far as I know.

Margaret

---

**From:** Marinsky, Cheryl (PHAC/ASPC) <cheryl.marinsky@canada.ca>
**Sent:** 2021-04-26 2:21 PM
**To:** COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC) <phac.covid-19therapeutics-therapeutiques.aspc@canada.ca>; Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>; Lawuyi2, Niyi (PHAC/ASPC) <niyi.lawuyi2@canada.ca>
**Cc:** Poon Young, Celisse (PHAC/ASPC) <celisse.poonyoung@canada.ca>
**Subject:** RE: LISA AND THERAPEUTICS TEAM FOR INPUT BY APRIL 29 - 21-108019 - Vitamin D, Colcichine, Ivermectin

Hi Celisse,

I have not been tasked with replies to correspondence, I am not sure who these requests went to, it might have been Jennifer who is no longer with us.

Margaret, did you want me to take a stab at this? I had a look in the correspondence folder and there is no content related to standard lines for colchicine nor for ivermectin and nothing in the media lines folder for either of these therapeutics. On our GoC PHAC site we have the statement from the CPTG on colchicine, nothing on ivermectin.

Thanks,

Cheryl

---

**From:** Poon Young, Celisse (PHAC/ASPC) <celisse.poonyoung@canada.ca> **On Behalf Of** COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC)
**Sent:** 2021-04-26 1:54 PM
**To:** Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>; Marinsky, Cheryl (PHAC/ASPC) <cheryl.marinsky@canada.ca>; Lawuyi2, Niyi (PHAC/ASPC) <niyi.lawuyi2@canada.ca>
**Cc:** Poon Young, Celisse (PHAC/ASPC) <celisse.poonyoung@canada.ca>
**Subject:** FW: LISA AND THERAPEUTICS TEAM FOR INPUT BY APRIL 29 - 21-108019 - Vitamin D, Colcichine, Ivermectin
**Importance:** High

Hi everyone,

Please see the request that came to the Therapeutics inbox this afternoon. Sending to you all since I am not sure exactly who this should be directed to.

Thank you,

Celisse

---

**From:** Jamil, Marium (PHAC/ASPC) <marium.jamil@canada.ca>
**Sent:** 2021-04-26 12:21 PM
**To:** Waddell, Lisa (PHAC/ASPC) <lisa.waddell@canada.ca>; COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC) <phac.covid-19therapeutics-therapeutiques.aspc@canada.ca>
**Cc:** PHAC.F OCSO_ESGSecretariat / BCSC_SecrétariatGSE F.ASPC <phac.ocso_esgsecretariat-bcsc_secretariatgse.aspc@canada.ca>
**Subject:** LISA AND THERAPEUTICS TEAM FOR INPUT BY APRIL 29 - 21-108019 - Vitamin D, Colcichine, Ivermectin
**Importance:** High

Good morning Lisa and Therapeutics team,
**FOR INPUT/APPROVAL – BY APRIL 29**
**CONTEXT**

- Dr. Tam received correspondence on April 21, 2021 from a member of the public (please see attached '21-108019-10 Incoming Apr 22.pdf'), regarding the use of Vitamin D, Ivermectin and Colchicine as treatments for COVID-19.

**FOR INPUT**

- ESG Secretariat has drafted a standard response in regards to the use of Vitamin D (please see attached '21-108019-VitD_Colchicine, Ivermectin _ Response_Apr2021. doc') adapted from previous responses. The letter does not speak to Colchicine or Ivermectin however. We would be thankful if you could please provide **your input on:**
    - **Any evidence to support the use of Ivermectin and Colchicine**
    - **Any NEW evidence on the efficacy of Vitamin D**

Thank you so much for your time. We would be grateful if you could please provide us your input by April 29th.

Please let us know if you have any questions.

Regards,
Marium

*On behalf of the Office of Chief Science Officer and the PHAC Emerging Science Group Secretariat*

**Marium Jamil**
(she | elle)
Policy Analyst | Analyste des politiques
Office of the Chief Science Officer | Bureau du Conseiller scientifique en chef
Public Health Agency of Canada | Agence de la santé publique du Canada
NEW: phac.ocso_esgsecretariat-bcsc_secretariatgse.aspc@canada.ca

**From:** Marinsky, Cheryl (PHAC/ASPC)
**Sent:** 2021-04-27 10:35 AM
**To:** Sarwar, Elaha (PHAC/ASPC); Gale-Rowe, Margaret (PHAC/ASPC); Cortés-Kaplan, Serena (PHAC/ASPC)
**Subject:** RE: LISA AND THERAPEUTICS TEAM FOR INPUT BY APRIL 29 - 21-108019 - Vitamin D, Colcichine, Ivermectin
**Attachments:** Correspondence on Vit. D Colchicine and Ivermectin-DRAFT.docx

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Hi Elaha,

Yes, I agree this is in Health Canada's jurisdiction since these treatments are not authorized nor approved for use in Canada.

I think we do need to address the issue raised in the body of the letter regarding all the studies on these treatments, not sure what she is reading but it seems that publication to her, as it is for many Canadians is an endorsement of effectiveness. I have crafted some lines to address this acceptance of published results as validation of effectiveness, I think this is a valuable education opportunity as well. I have attached a very rough draft based on information from the WHO. Please have a look, it is too long, for this reply but content from the first two paragraphs could be repurposed.

Happy to keep working on this and adding content from the OCSC to what we have.

Thoughts and suggestions welcome! ☺

Cheryl

---

**From:** Sarwar, Elaha (PHAC/ASPC)
**Sent:** 2021-04-27 10:23 AM
**To:** Gale-Rowe, Margaret (PHAC/ASPC) ; Marinsky, Cheryl (PHAC/ASPC) ; Cortés-Kaplan, Serena (PHAC/ASPC)
**Subject:** RE: LISA AND THERAPEUTICS TEAM FOR INPUT BY APRIL 29 - 21-108019 - Vitamin D, Colcichine, Ivermectin

Good morning,

Just a couple of thoughts on this request.

For drugs that are not approved in Canada for COVID-19 (ivermectin and colchicine), I think we can draft standard lines and flip to HC as it is their jurisdiction. Followed by an overarching summary of evidence on these (couple of bullets).

Something like this: The PHAC is monitoring emerging evidence of clinical efficacy and safety on novel and repurposed therapeutics for COVID-19, including ivermectin, cholchicine, and vitamin D. Health Canada, the regulator in Canada, will review clinical data once submitted from the manufacturer and determine the benefits and risks of potential therapeutics and provide regulatory approval for COVID-19 accordingly.

I don't think we need to spend too much time on it from our side.

Just my opinion ☺

Elaha

---

**From:** Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>
**Sent:** 2021-04-26 2:53 PM
**To:** COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC) <phac.covid-19therapeutics-therapeutiques.aspc@canada.ca>
**Cc:** Marinsky, Cheryl (PHAC/ASPC) <cheryl.marinsky@canada.ca>; Sarwar, Elaha (PHAC/ASPC) <elaha.sarwar@canada.ca>
**Subject:** LISA AND THERAPEUTICS TEAM FOR INPUT BY APRIL 29 - 21-108019 - Vitamin D, Colcichine, Ivermectin

Cheryl is drafting input.

Is this to be DG-approved by April 29th? We will do our best but that is a short turnaround for a request from the public that requires summarizing evidence.
I haven't been able to get to my pre-existing "to do" list today due to other time-sensitive HR things and emails.

Margaret

---

**From:** Poon Young, Celisse (PHAC/ASPC) <celisse.poonyoung@canada.ca> **On Behalf Of** COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC)
**Sent:** 2021-04-26 1:54 PM
**To:** Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>; Marinsky, Cheryl (PHAC/ASPC) <cheryl.marinsky@canada.ca>; Lawuyi2, Niyi (PHAC/ASPC) <niyi.lawuyi2@canada.ca>
**Cc:** Poon Young, Celisse (PHAC/ASPC) <celisse.poonyoung@canada.ca>
**Subject:** FW: LISA AND THERAPEUTICS TEAM FOR INPUT BY APRIL 29 - 21-108019 - Vitamin D, Colcichine, Ivermectin
**Importance:** High

Hi everyone,

Please see the request that came to the Therapeutics inbox this afternoon. Sending to you all since I am not sure exactly who this should be directed to.

Thank you,

Celisse

---

**From:** Jamil, Marium (PHAC/ASPC) <marium.jamil@canada.ca>
**Sent:** 2021-04-26 12:21 PM
**To:** Waddell, Lisa (PHAC/ASPC) <lisa.waddell@canada.ca>; COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC) <phac.covid-19therapeutics-therapeutiques.aspc@canada.ca>
**Cc:** PHAC.F OCSO_ESGSecretariat / BCSC_SecrétariatGSE F.ASPC <phac.ocso_esgsecretariat-bcsc_secretariatgse.aspc@canada.ca>
**Subject:** LISA AND THERAPEUTICS TEAM FOR INPUT BY APRIL 29 - 21-108019 - Vitamin D,

Colcichine, Ivermectin
**Importance:** High

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    - **Any NEW evidence on the efficacy of Vitamin D**

Thank you so much for your time. We would be grateful if you could please provide us your input by April 29th.

Please let us know if you have any questions.

Regards,
Marium

*On behalf of the Office of Chief Science Officer and the PHAC Emerging Science Group Secretariat*

**Marium Jamil**
(she | elle)
Policy Analyst | Analyste des politiques
Office of the Chief Science Officer | Bureau du Conseiller scientifique en chef
Public Health Agency of Canada | Agence de la santé publique du Canada
NEW: phac.ocso_esgsecretariat-bcsc_secretariatgse.aspc@canada.ca

**From:** Djiometio, Joseph (PHAC/ASPC)
**Sent:** 2021-06-03 4:45 PM
**To:** Arthur, Jacqueline (PHAC/ASPC); Gale-Rowe, Margaret (PHAC/ASPC)
**Cc:** COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC)
**Subject:** RE: MGR edits - : I-Mask+ Protocol for early treatment of Covid-19

---

I-Mask+ Protocol response to J...

Hello Jacky/Margaret
Please find attached the revision of the letter

Joe

---

**From:** Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>
**Sent:** 2021-06-03 4:20 PM
**To:** Djiometio, Joseph (PHAC/ASPC) <joseph.djiometio@canada.ca>; Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>
**Cc:** COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC) <phac.covid-19therapeutics-therapeutiques.aspc@canada.ca>
**Subject:** RE: MGR edits - : I-Mask+ Protocol for early treatment of Covid-19

Is the letter good to go?
Bersabel is asking for it.
Please let me know.
Jackie

---

Jacqueline Arthur, BScN, RN
(she | elle)
Senior Manager, AMR Division | Gestionnaire principale, Division de la RAM
COVID-19 Therapeutics | thérapeutiques
CCDIC, PHAC | CLMTI, ASPC
t. (613) 889-8455

---

**From:** Djiometio, Joseph (PHAC/ASPC) <joseph.djiometio@canada.ca>
**Sent:** 2021-06-03 11:30 AM
**To:** Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>
**Cc:** COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC) <phac.covid-19therapeutics-therapeutiques.aspc@canada.ca>; Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>
**Subject:** RE: MGR edits - : I-Mask+ Protocol for early treatment of Covid-19

Thank you Margaret

I will review your comments

Joe

---

**From:** Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>
**Sent:** 2021-06-03 10:30 AM
**To:** Djiometio, Joseph (PHAC/ASPC) <joseph.djiometio@canada.ca>
**Cc:** COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC) <phac.covid-19therapeutics-therapeutiques.aspc@canada.ca>; Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>
**Subject:** MGR edits - : I-Mask+ Protocol for early treatment of Covid-19

Hi Joe/Jackie,

I have tweaked it and think there is sufficient information in here for BE's response.

Joe, there is a question for you about describing the protocol without listing all the elements. I saw your comment about senior management needing to know more about it, but that can appear in the email sent to BE along with the response.
Also, are there any (good) trials of the protocol underway? If yes, should mention. I wouldn't worry too much about this as a number of expert tables have decided there is not good evidence for the protocol.

Margaret

**Original:**
I-MASK+ Protocol is a prevention & early outpatient treatment protocol for COVID-19Patients are treated with Ivermectin, Vitamin D3, Vitamin C, Quercetin, Zinc, Melatonin, Fluvoxamine, Nasopharyngeal, Sanitation, Melatonin and Aspirin. I-MASK+ Protocol is for COVID-19 is centered ivermectin.

**Suggested revision**: I-MASK+ Protocol is a prevention & early outpatient treatment protocol for COVID-19. While it includes a number of medications and supplements, it is centred on ivermectin, a broad-spectrum anti-parasitic agent authorized and approved by HC for human and veterinary applications to treat parasitic infections.

<< File: I-Mask+ Protocol response to J Schultz mgr.docx >>
-----Original Message-----
From: Djiometio, Joseph (PHAC/ASPC) <joseph.djiometio@canada.ca>
Sent: 2021-06-02 12:27 PM
To: Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>
Cc: COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC) <phac.covid-19therapeutics-therapeutiques.aspc@canada.ca>; Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>
Subject: RE: I-Mask+ Protocol for early treatment of Covid-19

Hello Margaret
Here is the draft response to [redacted] bout the I-Mask+ Protocol.
I used MECS#21-108019-10 as support document to draft this response.
Let me know if you have any questions

Joe

-----Original Message-----
From: COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC) <phac.covid-19therapeutics-therapeutiques.aspc@canada.ca>
Sent: 2021-06-01 11:33 AM
To: Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>; Djiometio, Joseph (PHAC/ASPC) <joseph.djiometio@canada.ca>; COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC) <phac.covid-19therapeutics-therapeutiques.aspc@canada.ca>
Cc: Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>
Subject: RE: I-Mask+ Protocol for early treatment of Covid-19

Profiled in MECS u der 21-110593-856 where I will add our final draft.

-----Original Message-----
From: Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>
Sent: 2021-05-31 4:39 PM
To: Djiometio, Joseph (PHAC/ASPC) <joseph.djiometio@canada.ca>; COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC) <phac.covid-19therapeutics-therapeutiques.aspc@canada.ca>
Cc: Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>
Subject: FW: I-Mask+ Protocol for early treatment of Covid-19

Hi Joe;
We have received the correspondence below via our Director General's office regarding the I-Mask+ Protocol that centers around the main treatment, ivermection. Follow the link provided in the incoming correspondence.
Please review and prepare a draft response for Margaret's review by Wednesday.
I've attached previous correspondence we have done on ivermectin to assist - Adéle, could you track down the final correspondence that was sent under MECS#21-108019-10? It would be helpful for Joe to have the approved version sent.

Happy to discuss.
Jackie

---
Jacqueline Arthur, BScN, RN
(she | elle)
Senior Manager, AMR Division | Gestionnaire principale, Division de la RAM
COVID-19 Therapeutics | thérapeutiques
CCDIC, PHAC | CLMTI, ASPC
t. (613) 889-8455

-----Original Message-----
From: Ephrem, Bersabel (PHAC/ASPC) <bersabel.ephrem@canada.ca>
Sent: 2021-05-31 4:07 PM
To: Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>
Cc: Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>; Hunt, Kelly (PHAC/ASPC) <kelly.hunt@canada.ca>
Subject: FW: I-Mask+ Protocol for early treatment of Covid-19

Hi Jackie,

Can we have a response? Please see below.

be

-----Original Message-----
From: McLean, Hollie (HC/SC) <hollie.mclean@canada.ca> On Behalf Of Levesque2, Kaili (HC/SC)
Sent: 2021-05-31 3:54 PM
To: [redacted]
Cc: Ephrem, Bersabel (PHAC/ASPC) <bersabel.ephrem@canada.ca>; Levesque2, Kaili (HC/SC) <kaili.levesque2@canada.ca>; McLean, Hollie (HC/SC) <hollie.mclean@canada.ca>
Subject: RE: I-Mask+ Protocol for early treatment of Covid-19

Hi [redacted]

Thank you for your email. Note that I've recently assumed the role as Vice President, COVID-19 Vaccine Rollout at the Public Health Agency. I'm connecting you with Bersabel Ephrem, the Director General responsible for the therapeutics file.

Thanks

Kaili

Kaili Levesque (she/her/elle)
613.818.0492

-----Original Message-----
From [redacted]
Sent: 2021-05-31 12:13 PM
To: Levesque2, Kaili (HC/SC) <kaili.levesque2@canada.ca>
Subject: I-Mask+ Protocol for early treatment of Covid-19

Good morning Ms. Levesque:

I am writing to ask for your assistance. I have been following a growing body of research on the use of the I-Mask Protocol for early treatment and prophylaxis for Covid-19. Early in the pandemic, this protocol was not well understood and had only anecdotal evidence of its efficacy. Recently, however, I've been encouraged to see multiple studies showing good evidence of efficacy. I am puzzled as to why this treatment is not being studied in Canada as we are still in a situation across the country where people are being hospitalized for Covid-19. I am not a medical professional, but I wonder if it is not prudent and compassionate to open the door to other treatment possibilities which could prevent further deterioration of newly diagnosed victims of this virus? I do not know if you are the right person to send this email to, but I do know that you believe that we should be doing absolutely everything to try to treat this disease. My sincere hope is that you and your Task Force are seeking to include the use of existing medicines that we know are not harmful in and of themselves, such as Ivermectin, which is one of the components in the I-Mask Protocol. While we all look forward to the day when vaccinations take effect Canada-wide, in the meantime there are still many people who are falling ill and require medical treatment for this disease.

I respectfully submit to you this link to the growing body of knowledge and research studies around the I-Mask+ Protocol and I beg you to use your considerable influence to bring it to the attention of the Covid 19 Task Force and study it with all due diligence. If there is merit in this treatment, and your committee agrees to try it on a limited study basis, perhaps many Canadian lives could be saved and/or at the very least, saved from the longevity of hospitalizations for Covid 19 which they may be facing under the current treatment protocols. I believe that your committee

has a moral and ethical obligation to fairly and diligently consider all possible treatments, irrespective of WHO or any other body who may be telling you otherwise. We are Canadians, first and foremost. We are responsible for one another.

Thank you so very much for your time. I ask you to please respectfully consider my request, and I very much look forward to your reply.

Sincerely,

[redacted]
Alberta, Canada

https://covid19criticalcare.com/covid-19-protocols/i-mask-plus-protocol/

**From:** Gale-Rowe, Margaret (PHAC/ASPC)
**Sent:** 2021-02-12 1:52 PM
**To:** Forbes, Nicole (PHAC/ASPC); Lawuyi2, Niyi (PHAC/ASPC)
**Cc:** Siushansian, Jennifer (PHAC/ASPC)
**Subject:** RE: Seeking guidance on therapeutics update for President and DM - scientific "news"

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Thank you Nicole.

I am hoping there isn't too much to add from the science side for this list except for Bamlanivimab which is missing and a summary of evidence for colchicine.

Margaret

**From:** Forbes, Nicole (PHAC/ASPC) <nicole.forbes@canada.ca>
**Sent:** 2021-02-12 12:33 PM
**To:** Lawuyi2, Niyi (PHAC/ASPC) <niyi.lawuyi2@canada.ca>; Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>
**Cc:** Siushansian, Jennifer (PHAC/ASPC) <jennifer.siushansian@canada.ca>
**Subject:** RE: Seeking guidance on therapeutics update for President and DM - scientific "news"

Ok sounds good. I wrote this up (see below) for Jackie a month ago. ***@Niyi- if I update with new content as needed, and add a line speaking to PHAC status (e.g. in discussions w supplier, discussing procurement, planning to meet x month ect) would this do the trick?***

REGN-CoV2 (Casirivimab® and Imdevimab®; Regeneron/Roche) - Monoclonal antibody cocktail targeting the SARS-CoV-2 spike protein. This therapeutic was granted EUA in the USA for the indication of mild to moderate COVID-19 in the outpatient setting, for those at high risk of severe disease/hospitalization. Ph1/2 trial shows treatment led to reduced frequency of COVID-19 associated medical visits/hospitalizations with greatest benefit in patients with high viral load/low antibody levels at baseline. REGN-COV2 is administered by i.v. infusion.

Note- Additional ongoing trials include the treatment of hospitalized patients to reduce disease severity/duration and mortality, as well as ability to prevent symptomatic infection in high-risk individuals.

VIR-7831 (GSK) – Monoclonal antibody targeting the SARS-CoV-1 and SARS-CoV-2 spike protein on a conserved protein region. VIR-7831 is not authorized in any jurisdiction. Ongoing trials are assessing the extent to which the antibody treatment limits COVID-19-associated hospitalizations when administered to non-hospitalized patients at high risk for severe disease, with results expected early 2021 and regulatory filing anticipated for

[redacted]

Note- Additional ongoing trials include the treatment of hospitalized patients to reduce disease severity/duration and mortality, as well as ability to prevent symptomatic infection in high-risk individuals.

Baricitinib (Olumiant®, Eli Lilly)- Baricitinib is an orally administered Janus kinase (JAK) inhibitor that has been approved in Canada for the treatment of rheumatoid arthritis in adults. Clinical evidence from a NIAID-led trial shows combination therapy of Baricitinib plus remdesivir in hospitalized patients with COVID-19 receiving high flow oxygen/non-invasive ventilation led to a shortened recovery time and improved clinical status compared to remdesivir alone. However clinical benefit was minimal and only observed in a small subset of patients based on disease severity. Combination therapy with remdesivir was granted EUA by the USA however is not recommended to replace dexamethasone as a standard of care.

Otilimab (GSK)- Otilimab is a human monoclonal anti-granulocyte macrophage colony stimulating factor (GM-CSF) antibody. This investigational therapy is used to treat patients with moderate to severe rheumatoid arthritis. Otilimab is not currently approved in Canada for any indication. Clinical benefit and safety of otilimab for the treatment of severe pulmonary COVID-19 related disease is currently being investigated in late stage trials with sites including Canada, with results, including impact on reducing mortality, anticipated early to mid 2021. Otilimab is administered by i.v. infusion.

[redacted]

Molnupiravir (Merck/Ridgeback Pharmaceuticals) – Molnupiravir (MK-4482) is an orally administered nucleoside analogue antiviral that blocks virus replication currently in clinical trials as a treatment for COVID-19 both in the ambulatory and hospitalized settings, including trial sites in Canada. Molnupiravir is being investigated for its ability to reduce disease severity/shorten the duration of disease. No clinical finidings have been released to date however preliminary readouts are anticipated for early 2021.

Favipiravir (Reeqonus®, Avigan®; Fujifilm/Dr.Reddy's/Appili Therapeutics)- Favipiravir is an orally administered broad-spectrum antiviral drug that blocks viral replication of RNA viruses. Favipiravir is approved in Japan and China for the treatment of pandemic influenza, and in India and Russia for the treatment of mild to moderate COVID-19. Favipiravir is not approved in Canada for any indication but is currently being reviewed by Health Canada as a treatment for COVID-19 in adult patients with mild to moderate disease. Recent data from Phase 3 trial shows favirpiravir treatment of hospitalized patients with mild-to-moderate COVID-19 leads to a faster recovery time and higher probability of recovery. [redacted]

Ivermectin (Stromectol®; Merck)- Ivermectin is an orally administered antiparasitic-drug approved for use in Canada in both humans and animals. Ivermectin has been shown to inhibit SARS-CoV-2 infection in vitro and has demonstrated anti-inflammatory effects in clinical data. Numerous small and likely underpowered trials on ivermectin as a treatment for COVID-19 show mixed clinical benefit. Numerous S. American countries have widespread off-label use of ivermectin as a treatment for COVID-19.

Tocilizumab (Actemra®/ RoActemra®; Roche) – Tocilizumab is a monoclonal antibody administered by i.v. infusion or subcutaneous injection, that targets the IL-6 receptor, leading to suppression of pro-inflammatory responses. Tocilizumab is approved in Canada for the indication of rheumatoid arthritis, other autoimmune diseases, and cytokine release syndrome. Tocilizumab is currently under clinical investigation as a repurposed drug for the treatment of hospitalized patients with COVID-19. Numerous clinical trials have assessed its clinical benefit as a treatment for COVID-19 including reduction in mortality and reduction in disease severity/progression to mechanical ventilation however given the heterogeneity of patient populations and mixed evidence, it is unclear whether the drug has a positive benefit to risk ratio. On September 18, the COVID-19 Clinical Pharmacology Task Group issued a recommendation that the use of tocilizumab and other drugs targeting the IL-6 receptor remain in clinical trials. Recently the Roche-sponsored EMPACTA trial published in the New England Journal of Medicine reporting significant clinical benefits including reduced frequency of disease progression to require mechanical ventilation or death. Additional powered trials including the UK-led RECOVERY trial and the REMAP-CAP trial, with sites in Canada, are anticipated to read out their results in the coming months.

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Nicole Forbes, PhD
Scientific Project Coordinator
Immunization Programs and Pandemic Preparedness Division I Division des programmes d'immunisation et de la préparation aux pandémies; Centre for Immunization and Respiratory Infectious Diseases (CIRID) I Centre de l'immunisation et des maladies respiratoires infectieuses (CIMRI)
Public Health Agency of Canada I Agence de la santé publique du Canada
130 Colonnade Road , Room 149A-05, AL 6501A

Tel: (613) 447-6450
Email: nicole.forbes@canada.ca

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**From:** Lawuyi2, Niyi (PHAC/ASPC) <niyi.lawuyi2@canada.ca>
**Sent:** 2021-02-12 12:28 PM
**To:** Forbes, Nicole (PHAC/ASPC) <nicole.forbes@canada.ca>; Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>
**Cc:** Siushansian, Jennifer (PHAC/ASPC) <jennifer.siushansian@canada.ca>
**Subject:** RE: Seeking guidance on therapeutics update for President and DM - scientific "news"

Thank you Margaret and Nicole,

This is intended to be an update on the status of the various therapeutics for the President and DM Lucas, so we will have to format the wording typical with an official For Information Briefing Note as that is how it is going to be sent.

To answer your question Nicole, Yes, I think that we should include those respective updates, as Jackie did provide those updates to Roman last week.

Thanks,

Niyi

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**From:** Forbes, Nicole (PHAC/ASPC) <nicole.forbes@canada.ca>
**Sent:** 2021-02-12 12:15 PM
**To:** Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>
**Cc:** Lawuyi2, Niyi (PHAC/ASPC) <niyi.lawuyi2@canada.ca>; Siushansian, Jennifer (PHAC/ASPC) <jennifer.siushansian@canada.ca>
**Subject:** RE: Seeking guidance on therapeutics update for President and DM - scientific "news"

Hi Margaret,

Thanks for this- I think this is a good start to populate the update.
@Niyi/Jen, should we also provide updates on drugs for we are currently in correspondence with suppliers (Molnupiravir, VIR-7831, Otilimab, AZ LAAB (I forget acronym ☺)?
Also is this the level of detail you want? Happy to provide additional context but am seeking a bit more direction ☺

PS please note I will have limited time to work on this before CPTG (2-3pm today).

Nicole

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**From:** Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>
**Sent:** 2021-02-12 12:10 PM
**To:** Forbes, Nicole (PHAC/ASPC) <nicole.forbes@canada.ca>
**Cc:** Lawuyi2, Niyi (PHAC/ASPC) <niyi.lawuyi2@canada.ca>; Siushansian, Jennifer (PHAC/ASPC) <jennifer.siushansian@canada.ca>
**Subject:** Seeking guidance on therapeutics update for President and DM - scientific "news"

Hi Nicole,

I have drawn from this week's Quick Facts and upcoming statements as updates (Niyi, I am not sure but hope that this is what is needed – in addition, I don't know the best format to present info about CPTG statements if appropriate to include here).

Could you please let me know if there are other things I should include for the update? I believe the last one was sent a week ago.

Thank you so much,

Margaret

**Tocilizumab:**

- Clinical findings from the RECOVERY trial have been released in a pre-print (not peer reviewed). Tocilizumab was found to reduce the risk of death in hospitalised patients with severe COVID-19: for every 25 patients treated with tocilizumab, one additional life would be saved. The study also showed that treatment reduced duration of hospitalization and need for mechanical ventilation.
- Tocilizumab is not currently approved, or under review, by Health Canada as a treatment for COVD-19.

**Bamlanivimab (LY-CoV555)**

- US FDA has issued an EUA for bamlanivimab and etesevimab combination therapy for treatment of mild-to-moderate COVID-19 in patients aged ≥ 12 years, at high risk of severe illness/hospitalization. While HC has authorized use of bamlanivimab for non-hospitalized patients with mild-to-moderate COVID-19, the combination therapy is not currently authorized nor under review by HC.
- BC is undertaking a clinical trial on the use of bamlanivimab in non-hospitalized COVID-19 patients at risk of severe illness. [redacted] All participants will be tested for UK, SA and BRA variants to see if variants impact bamlanivimab's performance.

**REGN-COV2:**

- The CPTG will issue an updated recommendation for REGN-COV2 recommending against the implementation of casirivimab and imdevimab as outpatient intravenous (IV) infusion treatment, given the limited clinical evidence on the safety and efficacy in non-hospitalized adults with mild to moderate COVID-19. There are concerns about the resources required to provide outpatient infusion therapy and the CPTG has recommended that CADTH be consulted on the implementation, should its use be authorized in Canada.

**Colchicine:**

- The CPTG has drafted a statement recommending that off-label use of colchicine as a treatment for non-hospitalized patients with COVID-19 be limited to randomized controlled trials. Additional clinical evidence is required to determine whether potential benefits of colchicine outweigh known and potential risks.

Margaret Gale-Rowe MD MPH
she/elle

Medical Advisor, COVID 19 therapeutics
Centre for Communicable Diseases and Infection Control
Public Health Agency of Canada / Government of Canada
Room 326-B, 130 Colonnade Road, Ottawa, Canada K1A 0K9
Margaret.gale-rowe@canada.ca 613-618-9266

Médecin-conseil, COVID 19 thérapeutiques
Centre de la lutte contre les maladies transmissibles et les infections
Agence de la santé publique du Canada / Gouvernement du Canada
Pièce 326-B, 130 rue Colonnade, Ottawa, Canada K1A 0K9
Margaret.gale-rowe@canada.ca 613-618-9266

**From:** Djiometio, Joseph (PHAC/ASPC)
**Sent:** 2021-06-06 12:45 PM
**To:** Gale-Rowe, Margaret (PHAC/ASPC); Arthur, Jacqueline (PHAC/ASPC); Azad, Mina (PHAC/ASPC)
**Subject:** RE: Transcript of another interview w Dr. McCullough

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**Follow Up Flag:** Follow up
**Flag Status:** Completed

Thank you Margaret
The team will review the transcript and publications from Dr. McCullough

Joe

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**From:** Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>
**Sent:** 2021-06-06 9:51 AM
**To:** Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>; Djiometio, Joseph (PHAC/ASPC) <joseph.djiometio@canada.ca>; Azad, Mina (PHAC/ASPC) <mina.azad@canada.ca>
**Subject:** Transcript of another interview w Dr. McCullough

In favour of ivermectin, HCQ and favipiravir

https://childrenshealthdefense.org/transcripts/truth-with-rfk-jr-and-dr-peter-mccullough-the-age-of-covid-and-abrogation-of-hippocratic-oath/

Medical Advisor - COVID Therapeutics Acquisitions
[redacted]

**From:** Arthur, Jacqueline (PHAC/ASPC)
**Sent:** 2021-01-05 10:38 AM
**To:** Forbes, Nicole (PHAC/ASPC); Siushansian, Jennifer (PHAC/ASPC)
**Cc:** Lawuyi2, Niyi (PHAC/ASPC)
**Subject:** RE: short update for the FPT DS meeting today

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Thank you!

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Jacqueline Arthur, RN, BScN
Senior Manager, AMR Division | Gestionnaire principale, Division de la RAM
COVID-19 Therapeutics | thérapeutiques
CCDIC, PHAC | CLMTI, ASPC
t. (613) 889-8455

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**From:** Forbes, Nicole (PHAC/ASPC) <nicole.forbes@canada.ca>
**Sent:** 2021-01-05 10:26 AM
**To:** Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>; Siushansian, Jennifer (PHAC/ASPC) <jennifer.siushansian@canada.ca>
**Cc:** Lawuyi2, Niyi (PHAC/ASPC) <niyi.lawuyi2@canada.ca>
**Subject:** RE: short update for the FPT DS meeting today

Hi Jackie,

I will work with tech team to draft up short summaries of each for Jen to review by 1230ish.

Best,

Nicole

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**From:** Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>
**Sent:** 2021-01-05 10:19 AM
**To:** Forbes, Nicole (PHAC/ASPC) <nicole.forbes@canada.ca>; Siushansian, Jennifer (PHAC/ASPC) <jennifer.siushansian@canada.ca>
**Cc:** Lawuyi2, Niyi (PHAC/ASPC) <niyi.lawuyi2@canada.ca>
**Subject:** short update for the FPT DS meeting today

Nicole and Jennifer;
I want to give the PTs a short summary of therapeutics on the horizon and need your help.
These are the products I think we should cover:
REGN-CoV2
VIR7831
Favipiravir
Otilimab
Baricitinib
Molnupiravir
Ivermectin
Tocilizumab

Have I missed anything?

Could you pull together a short description of each for me by 1:30? What it is, what it could potential do for COVID-19 patients, what we know as of today (not details about studies but very short summary of the state of things).
I only have 10 minutes so it is just to flag these for the group today.
We can chat more at 11 to see what is feasible.
Thanks,
J

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Jacqueline Arthur, RN, BScN
Senior Manager, Policy Development, AMR Division | Gestionnaire principale, elaboration de politiques, Division de la RAM
COVID-19 Therapeutics | thérapeutiques
Centre for Communicable Diseases and Infection Control | Centre de la lutte contre les maladies transmissibles et les infections
Public Health Agency of Canada | Agence de la santé publique du Canada
t. (613) 889-8455

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**From:** Gale-Rowe, Margaret (PHAC/ASPC)
**Sent:** 2021-05-07 8:11 PM
**To:** Arthur, Jacqueline (PHAC/ASPC)
**Cc:** Sarwar, Elaha (PHAC/ASPC); Cortés-Kaplan, Serena (PHAC/ASPC); Djiometio, Joseph (PHAC/ASPC); Lawuyi2, Niyi (PHAC/ASPC)
**Subject:** Re: Daily Therapeutics Titles for Friday, May 7th

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Note that I wasn't intending to indicate we should follow ivermectin, just sharing something that I thought might be interesting to others.

I don't think we need to have issue sheets on everything, though it has seemed that we have been asked for details / briefs on almost anything that turns up.

Margaret

Medical Advisor - COVID Therapeutics Acquisitions
613-618-9266

On May 7, 2021, at 5:03 PM, Arthur, Jacqueline (PHAC/ASPC) wrote:

Agree Elaha. Bring this to our next management meeting to discuss both points.
Thanks,
J

---
Jacqueline Arthur, BScN, RN
(she | elle)
Senior Manager, AMR Division | Gestionnaire principale, Division de la RAM
COVID-19 Therapeutics | thérapeutiques
CCDIC, PHAC | CLMTI, ASPC
t. (613) 889-8455

**From:** Sarwar, Elaha (PHAC/ASPC) <elaha.sarwar@canada.ca>
**Sent:** 2021-05-07 2:40 PM
**To:** Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>; Cortés-Kaplan, Serena (PHAC/ASPC) <serena.cortes-kaplan@canada.ca>
**Cc:** Djiometio, Joseph (PHAC/ASPC) <joseph.djiometio@canada.ca>; Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>; Lawuyi2, Niyi (PHAC/ASPC) <niyi.lawuyi2@canada.ca>
**Subject:** RE: Daily Therapeutics Titles for Friday, May 7th

[redacted]

We do not have an issue sheet on lenzilumab yet, perhaps it's worth discuss some criteria for starting an issue sheet for a therapeutics.

**From:** Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>
**Sent:** 2021-05-07 2:20 PM
**To:** Cortés-Kaplan, Serena (PHAC/ASPC) <serena.cortes-kaplan@canada.ca>
**Cc:** Djiometio, Joseph (PHAC/ASPC) <joseph.djiometio@canada.ca>; Sarwar, Elaha (PHAC/ASPC) <elaha.sarwar@canada.ca>; Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>; Lawuyi2, Niyi (PHAC/ASPC) <niyi.lawuyi2@canada.ca>
**Subject:** RE: Daily Therapeutics Titles for Friday, May 7th

While ivermectin may not be useful for treatment of COVID-19, there is still a connection due to the potential for parasitic "hyperinfection" secondary to the use of immunosuppressive therapies for COVID, in areas of the world where parasitic infections are endemic (S. America/SE Asia).

Do we have an issue sheet on lenzilumab? (how many anti-inflammatory mAbs are there?!)

Margaret

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**From:** Cortés-Kaplan, Serena (PHAC/ASPC) <serena.cortes-kaplan@canada.ca>
**Sent:** 2021-05-07 1:48 PM
**To:** COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC) <phac.covid-19therapeutics-therapeutiques.aspc@canada.ca>; Szumski2, Roman (PHAC/ASPC) <roman.szumski2@canada.ca>; Salvadori, Marina (PHAC/ASPC) <marina.salvadori@canada.ca>; Baclic, Oliver (PHAC/ASPC) <oliver.baclic@canada.ca>; Patel, Milan (PHAC/ASPC) <milan.patel@canada.ca>; Killikelly, April (PHAC/ASPC) <april.killikelly@canada.ca>; Abraham, Natalia k (PHAC/ASPC) <nataliak.abraham@canada.ca>; Chung, Yung-En (PHAC/ASPC) <yung-en.chung@canada.ca>; Lehman, Kelly (HC/SC) <kelly.lehman@canada.ca>; Frappier2, Fiona (HC/SC) <fiona.frappier2@canada.ca>; Chigrinova, Mariya (HC/SC) <mariya.chigrinova@canada.ca>; Uhthoff, Peter (SAC/ISC) <peter.uhthoff@canada.ca>; Beaulieu, Marc-Andre (PHAC/ASPC) <marc-andre.beaulieu@canada.ca>; Mitchelmore, Bradley (PHAC/ASPC) <bradley.mitchelmore@canada.ca>; Blanchard, Bradley (PHAC/ASPC) <bradley.blanchard@canada.ca>; Kamkar, Maryam (PHAC/ASPC) <maryam.kamkar@canada.ca>; Forbes, Nicole (PHAC/ASPC) <nicole.forbes@canada.ca>; Murthy, Srinivas [CWBC <Srinivas.Murthy@cw.bc.ca>; Lordkipanidze Marie <marie.lordkipanidze@umontreal.ca>; R.I.Hall@Dal.Ca; mrieder@uwo.ca; Collier, Abby <Abby.Collier@ubc.ca>; Goldhawk, Michael (PHAC/ASPC) <michael.goldhawk@canada.ca>; m.piquette.miller@utoronto.ca; Levesque2, Kaili (HC/SC) <kaili.levesque2@canada.ca>; Groeneweg, Sheryl (IC) <sheryl.groeneweg@canada.ca>; Arancibia, Rodrigo (IC) <rodrigo.arancibia@canada.ca>; Taha, Zaid (PHAC/ASPC) <zaid.taha@canada.ca>; Courtemanche, Jocelyne (PHAC/ASPC) <jocelyne.courtemanche@canada.ca>; Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>; Lawuyi2, Niyi (PHAC/ASPC) <niyi.lawuyi2@canada.ca>; Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>; Krishnan, Ramya (PHAC/ASPC) <ramya.krishnan@canada.ca>; Beique, Lizanne (PHAC/ASPC) <lizanne.beique@canada.ca>; Marinsky, Cheryl (PHAC/ASPC) <cheryl.marinsky@canada.ca>; Ephrem, Bersabel (PHAC/ASPC) <bersabel.ephrem@canada.ca>; PHAC.F Emerging Science Secretariat / Secrétariat des sciences émergentes F.ASPC <phac.emergingsciencesecretariat-secretariatdessciencesemergentes.aspc@canada.ca>; Garcia Carrasco, Alexandra

(HC/SC) <alexandra.garciacarrasco@canada.ca>; Farrah, Kelly (PHAC/ASPC) <kelly.farrah@canada.ca>; Jaahnavi Dave <jdave@ohri.ca>; Dave, Jaahnavi (PHAC/ASPC) <jaahnavi.dave@canada.ca>; Jirovec, Anna (PHAC/ASPC) <anna.jirovec@canada.ca>; Stephens-Rennie2, Ericka (HC/SC) <ericka.stephens-rennie2@canada.ca>; Sigouin, Ryan (HC/SC) <ryan.sigouin@canada.ca>; Cortés-Kaplan, Serena (PHAC/ASPC) <serena.cortes-kaplan@canada.ca>; Hanson Pastran, Sasha (HC/SC) <sasha.hansonpastran@canada.ca>; Rajendra, Kanya (HC/SC) <kanya.rajendra@canada.ca>; Djiometio, Joseph (PHAC/ASPC) <joseph.djiometio@canada.ca>; Cassista, Caroline (PHAC/ASPC) <caroline.cassista@canada.ca>; Mitchell, Stephanie (CFIA/ACIA) <stephanie.mitchell@canada.ca>
**Cc:** COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC) <phac.covid-19therapeutics-therapeutiques.aspc@canada.ca>
**Subject:** Daily Therapeutics Titles for Friday, May 7th

**Good afternoon,**

**Here are the Daily COVID-19 Therapeutics Titles for Friday, May 7th, 2021:**
***Please note this email and any assessments contained within are intended for your situational awareness of emerging clinical evidence of COVID-19 therapeutics; it is not intended as a complete systematic review.***

**Monoclonal Antibodies**

- **PREPRINT:** Temesgen et al., Lenzilumab Efficacy And Safety In Newly Hospitalized Covid-19 Subjects: Results From The Live-Air Phase 3 Randomized Double-Blind Placebo-Controlled Trial MedRxiv. May 5, 2021.
  *Taken directly from the abstract:*
  **Background**: Severe COVID19 pneumonia results from a hyperinflammatory immune response (cytokine storm, CS), characterized by GM CSF mediated activation and trafficking of myeloid cells, leading to elevation of downstream inflammatory chemokines (MCP1, IL8, IP10), cytokines (IL6, IL1), and other markers of systemic inflammation (CRP, D dimer, ferritin). CS leads to fever, hypotension, coagulopathy, respiratory failure, ARDS, and death. Lenzilumab is a novel Humaneered anti-human GM CSF monoclonal antibody that directly binds GM CSF and prevents signaling through its receptor. The LIVE AIR Phase 3 randomized, double blind, placebo controlled trial investigated the efficacy and safety of lenzilumab to assess the potential for lenzilumab to improve the likelihood of ventilator free survival (referred to herein as survival without ventilation, SWOV), beyond standard supportive care, in hospitalized subjects with severe COVID-19.
  **Methods**: Subjects with COVID-19 (n=520), >18 years <94% oxygen saturation on room air and/or requiring supplemental oxygen, but not invasive mechanical ventilation, were randomized to receive lenzilumab (600 mg, n=261) or placebo (n=259) via three intravenous infusions administered 8 hours apart. Subjects were followed through Day 28 following treatment.
  **Results**: Baseline demographics were comparable between the two treatment groups: male, 64.7%; mean age, 60.5 years; mean BMI, 32.5 kg/m2; mean CRP, 98.36 mg/L; CRP was <150 mg/L in 77.9% of subjects. The most common comorbidities were obesity (55.1%), diabetes (53.4%), chronic kidney disease (14.0%), and coronary artery disease (13.6%). Subjects received steroids (93.7%), remdesivir (72.4%), or both (69.1%). Lenzilumab improved the likelihood of SWOV by 54% in the mITT population (HR: 1.54; 95% CI: 1.02 to 2.31, p=0.041) and by 90% in the ITT population (HR: 1.90; 1.02 to 3.52, nominal p=0.043)

compared to placebo. SWOV also relatively improved by 92% in subjects who received both corticosteroids and remdesivir (1.92; 1.20 to 3.07, nominal p=0.0067); by 2.96-fold in subjects with CRP<150 mg/L and age <85 years (2.96; 1.63 to 5.37, nominal p=0.0003); and by 88% in subjects hospitalized <2 days prior to randomization (1.88; 1.13 to 3.12, nominal p=0.015). Survival was improved by 2.17-fold in subjects with CRP<150 mg/L and age <85 years (2.17; 1.04 to 4.54, nominal p=0.040).

**Conclusions**: Lenzilumab significantly improved SWOV in hospitalized, hypoxic subjects with COVID-19 pneumonia over and above treatment with remdesivir and/or corticosteroids. Subjects with CRP<150 mg/L and age <85 years demonstrated an improvement in survival and had the greatest benefit from lenzilumab. NCT04351152

SUMMARY+ CONTEXT: **This multi-center, Phase 3, double-blind, randomized, placebo-controlled study evaluated the use of lenzilumab, a GM-CSF monoclonal antibody, in the early treatment of newly hospitalized COVID-19 patients that require supplemental oxygen and have not progressed to invasive mechanical ventilation. 520 participants were randomized 1:1 to receive lenzilumab or placebo in addition to standard of care, including steroids and remdesivir. The primary outcome, likelihood of survival without ventilation through day 28, was met in the lenzilumab group: 54% improvement in the mITT population (HR: 1.54; 95% CI: 1.02 to 2.31, p=0.041) and by 90% in the ITT population (HR: 1.90; 1.02 to 3.52, nominal p=0.043) compared to placebo. Reported adverse events were similar between the lenzilumab and placebo group and no drug-related adverse events were observed.**

- *Caution should be taken in the interpretation of this study as this has not been peer reviewed.*

**Antivirals – Molnupiravir**

- **PREPRINT:** Khoo et al., Optimal dose and safety of molnupiravir in patients with early SARS-CoV-2: a phase 1, dose-escalating, randomised controlled study. MedRxiv. May 5, 2021.

  *Taken directly from the abstract:*

  **Background**: AGILE is a phase Ib/IIa platform for rapidly evaluating COVID-19 treatments. In this trial (NCT04746183) we evaluated the safety and optimal dose of molnupiravir in participants with early symptomatic infection.

  **Methods**: We undertook a dose-escalating, open-label, randomised-controlled (standard-of-care) Bayesian adaptive phase I trial at the Royal Liverpool and Broadgreen Clinical Research Facility. Participants (adult outpatients with PCR-confirmed SARS-CoV-2 infection within 5 days of symptom onset) were randomised 2:1 in groups of 6 participants to 300mg, 600mg and 800mg doses of molnupiravir orally, twice daily for 5 days or control. A dose was judged unsafe if the probability of 30% or greater dose-limiting toxicity (the primary outcome) over controls was higher than 25%. Secondary outcomes included safety, clinical progression, pharmacokinetics and virologic responses.

  **Results**: Of 103 volunteers screened, 18 participants were enrolled between 17 July and 30 October 2020. Molnupiravir was well tolerated at 400, 600 or 800mg doses with no serious or severe adverse events. Overall, 4 of 4 (100%), 4 of 4 (100%) and 1 of 4 (25%) of the participants receiving 300, 600 and 800mg molnupiravir respectively, and 5 of 6 (83%) controls, had at least one adverse event, all of which were mild (≤grade 2). The probability of ≥30% excess toxicity over controls at 800mg was estimated at 0.9%.

  **Conclusions**: Molnupiravir was safe and well tolerated; a dose of 800mg twice-daily for 5 days was recommended for Phase II evaluation.

SUMMARY+ CONTEXT: **This Phase 1b, multi-center, open-label, randomized-controlled trial evaluated the safety and tolerability of multiple ascending doses of molnupiravir in participants with symptomatic COVID-19 to recommend a dose for Phase 2 of the study. At total of 18 participants were randomized, n=4 allocated to each dosage group (300, 600 or 800 mg) and n=6 allocated to the control group (standard of care). Molnupiravir was well tolerated at all doses, with no serious adverse events. The dose of 800 mg of molnupiravir was recommended for further investigation in Phase 2 of the trial.**

- *Caution should be taken in the interpretation of this study as this has not been peer reviewed.*

**Systematic review and meta-analysis Studies**

- **PREPRINT:** Karale et al., A Meta-analysis of Mortality, Need for ICU admission, Use of Mechanical Ventilation and Adverse Effects with Ivermectin Use in COVID-19 Patients. medRxiv. May 4th 2021.

  *Taken directly from the abstract:*

  **Background**: Despite the global healthcare's exhaustive efforts to treat COVID-19, we still do not have an effective cure for it. Repurposing Ivermectin, a known antiparasitic agent, for treating COVID-19 has demonstrated positive results in several studies. We aim to evaluate the benefit and risk of Ivermectin in COVID-19.

  **Methods**: We conducted a systematic search for full-text manuscripts published from February 1, 2020 to March 27, 2021 that focused on efficacy and safety of Ivermectin therapy against COVID-19. The primary outcomes were overall mortality, need for intensive care unit (ICU) admission; secondary outcomes were - adverse effects, need for mechanical ventilation. Random-effects models were used for all analysis.

  **Results:** We included a total of 38 studies (n=15,002) in the qualitative analysis (Mortality N=28, ICU admission= 8, Mechanical Ventilation= 10, Adverse events=28) and out of these, 30 studies (n=11,291) were included in the quantitative analysis (Mortality N=22, ICU admission= 5, Mechanical Ventilation= 9, Adverse events=17). In the mortality meta-analysis, odds of death were lower in the Ivermectin-arm compared to the non-Ivermectin arm. (OR 0.39, 95% CI 0.22-0.70; I2=81%). Subgroup analysis of 12 randomized controlled trials with severity-based data showed mortality benefit overall (OR 0.33, 95% CI 0.15-0.72; I2=53%) and in the mild/moderate sub-group (OR 0.10, 95% CI 0.03-0.33; I2=0%). Benefit of Ivermectin in decreasing; the need for ICU admission (OR 0.48, 95% CI 0.17-1.37; I2=59%) and mechanical ventilation (OR 0.64, 95% CI 0.40-1.04; I2=17%) was not significant. The quantitative analysis of adverse effects with Ivermectin use was inconclusive (OR 0.92, 95% CI 0.64-1.33; I2=14%).

  **Conclusions**: Our meta-analysis suggests that Ivermectin could be an effective adjuvant therapy in reducing mortality, particularly in patients with mild-moderate clinical presentation of COVID-19. Trends of decreased need for ICU admissions and mechanical ventilation were observed but were not significant. The analysis for adverse effects was inconclusive.

  SUMMARY+ CONTEXT: **This systematic review and meta-analysis of RCTs (n=24), observational studies (n=8) and case series (n=6), available up to March 27 2021, aimed to evaluate the efficacy and safety of Ivermectin use for COVID-19 patients. Analysis of primary outcomes indicated that odds of death were lower in the Ivermectin-arm compared to the control arm (OR 0.39, 95% CI**

**0.22-0.70; I2=81%). However, no significant benefits were observed in reduction of ICU admission or mechanical ventilation (a secondary outcome). Further, analysis of adverse effects was inconclusive. Based on AMSTAR 2 criteria the overall confidence in the results of this study was rated as low, indicating that it may not provide an accurate summary of the data included in analysis.**

- *Caution should be taken in the interpretation of this study as this has not been peer reviewed.*

***Notes:***
***As of January 28, 2021, systematic review and meta-analysis studies of low/very low quality (based on AMSTAR 2 criteria) and those on therapeutics that the CPTG has approved statements will be included in the daily titles as an abstract with a rapid critical appraisal.***

***As of October 23, 2020, clinical data on lopinavir/ritonavir and hydroxychloroquine/chloroquine are no longer included in this listing due to overwhelming evidence of little to no clinical benefit. However, these titles are still being retained in our cloud based database.***
***Feedback and discussion on this daily email is always welcome.***

***Have a good evening,***

**The Daily COVID-19 Therapeutics Titles Team**
**(Yung-En Chung, Jaahnavi Dave, Ramya Krishnan, Elaha Sarwar, and Serena Cortés-Kaplan)**

**From:** Gale-Rowe, Margaret (PHAC/ASPC)
**Sent:** 2021-05-31 9:26 PM
**To:** Djiometio, Joseph (PHAC/ASPC)
**Cc:** Arthur, Jacqueline (PHAC/ASPC); COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC)
**Subject:** Re: I-Mask+ Protocol for early treatment of Covid-19

---

**Categories:** Complete, DO pending

Hi,

I don't think we need to summarize PT recommendations. We aren't responsible for answering for practices throughout Canada, nor are we making recommendations for or against the use of specific products. We do follow the evidence and can speak to that.

Margaret

Medical Advisor - COVID Therapeutics Acquisitions
613-618-9266

> On May 31, 2021, at 7:52 PM, Djiometio, Joseph (PHAC/ASPC) <joseph.djiometio@canada.ca> wrote:
>
> In addition, we have to clarify the state of evidence about Ivermectin and recommendations from PT experts in Canada (BC, Alberta, CADTH?, WHO, FDA.
> But I can't see any letter prepared by the COVID-19 Therapeutics Task Force on ivermectin.
>
>
>
> -----Original Message-----
> From: Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>
> Sent: 2021-05-31 5:53 PM
> To: Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>;
> Djiometio, Joseph (PHAC/ASPC) <joseph.djiometio@canada.ca>; COVID-19
> Therapeutics / Thérapeutiques (PHAC/ASPC)
> <phac.covid-19therapeutics-therapeutiques.aspc@canada.ca>
> Subject: RE: I-Mask+ Protocol for early treatment of Covid-19
>
> Part of the response could be around our role in procurement versus decisions within jurisdictions around choice and use of therapeutics.
> We aren't making recommendations for clinical practice but there are several bodies developing guidance around management of COVID (BC, ON, QC and AB to a lesser degree).
>
> Margaret
>
> -----Original Message-----
> From: Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>
> Sent: 2021-05-31 4:42 PM
> To: Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>;
> Djiometio, Joseph (PHAC/ASPC) <joseph.djiometio@canada.ca>; COVID-19
> Therapeutics / Thérapeutiques (PHAC/ASPC)

> <phac.covid-19therapeutics-therapeutiques.aspc@canada.ca>
> Subject: RE: I-Mask+ Protocol for early treatment of Covid-19
>
> I am assuming it is referring to the COVID-19 Therapeutics Task Force so we will need to pull out any letters that they prepared on ivermectin (if any).
> J
>
>
> ----------
> Jacqueline Arthur, BScN, RN
> (she | elle)
> Senior Manager, AMR Division | Gestionnaire principale, Division de la
> RAM
> COVID-19 Therapeutics | thérapeutiques CCDIC, PHAC | CLMTI, ASPC t.
> (613) 889-8455
>
>
> -----Original Message-----
> From: Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>
> Sent: 2021-05-31 4:40 PM
> To: Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>;
> Djiometio, Joseph (PHAC/ASPC) <joseph.djiometio@canada.ca>; COVID-19
> Therapeutics / Thérapeutiques (PHAC/ASPC)
> <phac.covid-19therapeutics-therapeutiques.aspc@canada.ca>
> Subject: RE: I-Mask+ Protocol for early treatment of Covid-19
>
> Jackie,
>
> Could you please give some guidance re: the COVID-19 TF? Is that the Therapeutics Task Force?
>
> Thanks for the background materials to get Joe started.
>
> Margaret
>
> -----Original Message-----
> From: Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>
> Sent: 2021-05-31 4:39 PM
> To: Djiometio, Joseph (PHAC/ASPC) <joseph.djiometio@canada.ca>;
> COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC)
> <phac.covid-19therapeutics-therapeutiques.aspc@canada.ca>
> Cc: Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>
> Subject: FW: I-Mask+ Protocol for early treatment of Covid-19
>
> Hi Joe;
> We have received the correspondence below via our Director General's office regarding the I-Mask+ Protocol that centers around the main treatment, ivermection. Follow the link provided in the incoming correspondence.
> Please review and prepare a draft response for Margaret's review by Wednesday.
> I've attached previous correspondence we have done on ivermectin to assist - Adèle, could you track down the final correspondence that was sent under MECS#21-108019-10? It would be helpful for Joe to have the approved version sent.
>
> Happy to discuss.
> Jackie

>
> ----------
> Jacqueline Arthur, BScN, RN
> (she | elle)
> Senior Manager, AMR Division | Gestionnaire principale, Division de la
> RAM
> COVID-19 Therapeutics | thérapeutiques CCDIC, PHAC | CLMTI, ASPC t.
> (613) 889-8455
>
>
> -----Original Message-----
> From: Ephrem, Bersabel (PHAC/ASPC) <bersabel.ephrem@canada.ca>
> Sent: 2021-05-31 4:07 PM
> To: Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>
> Cc: Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>;
> Hunt, Kelly (PHAC/ASPC) <kelly.hunt@canada.ca>
> Subject: FW: I-Mask+ Protocol for early treatment of Covid-19
>
> Hi Jackie,
>
> Can we have a response? Please see below.
>
> be
>
> -----Original Message-----
> From: McLean, Hollie (HC/SC) <hollie.mclean@canada.ca> On Behalf Of
> Levesque2, Kaili (HC/SC)
> Sent: 2021-05-31 3:54 PM
> To: [redacted]
> Cc: Ephrem, Bersabel (PHAC/ASPC) <bersabel.ephrem@canada.ca>;
> Levesque2, Kaili (HC/SC) <kaili.levesque2@canada.ca>; McLean, Hollie
> (HC/SC) <hollie.mclean@canada.ca>
> Subject: RE: I-Mask+ Protocol for early treatment of Covid-19
>
> Hi [redacted]
>
> Thank you for your email. Note that I've recently assumed the role as Vice President, COVID-19 Vaccine Rollout at the Public Health Agency. I'm connecting you with Bersabel Ephrem, the Director General responsible for the therapeutics file.
>
> Thanks
>
> Kaili
>
> Kaili Levesque (she/her/elle)
> 613.818.0492
>
>
> -----Original Message-----
> From: [redacted]
> Sent: 2021-05-31 12:13 PM
> To: Levesque2, Kaili (HC/SC) <kaili.levesque2@canada.ca>
> Subject: I-Mask+ Protocol for early treatment of Covid-19
>

> Good morning Ms. Levesque:
>
> I am writing to ask for your assistance. I have been following a growing body of research on the use of the I-Mask Protocol for early treatment and prophylaxis for Covid-19. Early in the pandemic, this protocol was not well understood and had only anecdotal evidence of its efficacy. Recently, however, I've been encouraged to see multiple studies showing good evidence of efficacy. I am puzzled as to why this treatment is not being studied in Canada as we are still in a situation across the country where people are being hospitalized for Covid-19. I am not a medical professional, but I wonder if it is not prudent and compassionate to open the door to other treatment possibilities which could prevent further deterioration of newly diagnosed victims of this virus? I do not know if you are the right person to send this email to, but I do know that you believe that we should be doing absolutely everything to try to treat this disease. My sincere hope is that you and your Task Force are seeking to include the use of existing medicines that we know are not harmful in and of themselves, such as Ivermectin, which is one of the components in the I-Mask Protocol. While we all look forward to the day when vaccinations take effect Canada-wide, in the meantime there are still many people who are falling ill and require medical treatment for this disease.
>
> I respectfully submit to you this link to the growing body of knowledge and research studies around the I-Mask+ Protocol and I beg you to use your considerable influence to bring it to the attention of the Covid 19 Task Force and study it with all due diligence. If there is merit in this treatment, and your committee agrees to try it on a limited study basis, perhaps many Canadian lives could be saved and/or at the very least, saved from the longevity of hospitalizations for Covid 19 which they may be facing under the current treatment protocols. I believe that your committee has a moral and ethical obligation to fairly and diligently consider all possible treatments, irrespective of WHO or any other body who may be telling you otherwise. We are Canadians, first and foremost. We are responsible for one another.
>
> Thank you so very much for your time. I ask you to please respectfully consider my request, and I very much look forward to your reply.
>
> Sincerely,
>
[redacted]
> Alberta, Canada
>
> https://covid19criticalcare.com/covid-19-protocols/i-mask-plus-protoco
> l/
>
>

**From:** Gale-Rowe, Margaret (PHAC/ASPC)
**Sent:** 2021-04-29 4:35 PM
**To:** Arthur, Jacqueline (PHAC/ASPC); COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC)
**Cc:** Marinsky, Cheryl (PHAC/ASPC); Lawuyi2, Niyi (PHAC/ASPC)
**Subject:** Short cut: For Senior Manager review: LISA AND THERAPEUTICS TEAM FOR INPUT BY APRIL 30 - 21-108019 - Vitamin D, Colcichine, Ivermectin

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Here is wording from the website that could be used/substituted:

Before drug products are authorized for sale in Canada, Health Canada reviews them to assess their safety, efficacy and quality. ~~Drug products include prescription and non-prescription pharmaceuticals, disinfectants and sanitizers with disinfectant claims.~~ Prior to being given market authorization, a manufacturer must present substantive scientific evidence of a product's safety, efficacy and quality as required by the Food and Drugs Act and Regulations.

**From:** Arthur, Jacqueline (PHAC/ASPC)
**Sent:** 2021-04-29 4:34 PM
**To:** Gale-Rowe, Margaret (PHAC/ASPC) ; COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC)
**Cc:** Marinsky, Cheryl (PHAC/ASPC) ; Lawuyi2, Niyi (PHAC/ASPC)
**Subject:** RE: For Senior Manager review: LISA AND THERAPEUTICS TEAM FOR INPUT BY APRIL 30 - 21-108019 - Vitamin D, Colcichine, Ivermectin

Thanks. I'll send it over to Megan for input and flag this to OCSO as it may be late.
J

---
Jacqueline Arthur, BScN, RN
(she | elle)
Senior Manager, AMR Division | Gestionnaire principale, Division de la RAM
COVID-19 Therapeutics | thérapeutiques
CCDIC, PHAC | CLMTI, ASPC
t. (613) 889-8455

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**From:** Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>
**Sent:** 2021-04-29 4:30 PM
**To:** Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>; COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC) <phac.covid-19therapeutics-therapeutiques.aspc@canada.ca>
**Cc:** Marinsky, Cheryl (PHAC/ASPC) <cheryl.marinsky@canada.ca>; Lawuyi2, Niyi (PHAC/ASPC) <niyi.lawuyi2@canada.ca>
**Subject:** RE: For Senior Manager review: LISA AND THERAPEUTICS TEAM FOR INPUT BY APRIL 30 - 21-108019 - Vitamin D, Colcichine, Ivermectin

Hi Jackie,

No it hasn't and we did edge over a bit into their territory. I hadn't thought about that.

Two options – have them review or flag for OCSO, as we were asked to provide input on the evidence.
The details around authorization are the type of context that typically goes into a webmail response.

Margaret

---

**From:** Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>
**Sent:** 2021-04-29 4:28 PM
**To:** COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC) <phac.covid-19therapeutics-therapeutiques.aspc@canada.ca>
**Cc:** Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>; Marinsky, Cheryl (PHAC/ASPC) <cheryl.marinsky@canada.ca>; Lawuyi2, Niyi (PHAC/ASPC) <niyi.lawuyi2@canada.ca>
**Subject:** RE: For Senior Manager review: LISA AND THERAPEUTICS TEAM FOR INPUT BY APRIL 30 - 21-108019 - Vitamin D, Colcichine, Ivermectin

Margaret;
Has this request been shared with Health Canada for review and input?

---
Jacqueline Arthur, BScN, RN
(she | elle)
Senior Manager, AMR Division | Gestionnaire principale, Division de la RAM
COVID-19 Therapeutics | thérapeutiques
CCDIC, PHAC | CLMTI, ASPC
t. (613) 889-8455

---

**From:** Poon Young, Celisse (PHAC/ASPC) <celisse.poonyoung@canada.ca> **On Behalf Of** COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC)
**Sent:** 2021-04-29 3:52 PM
**To:** Arthur, Jacqueline (PHAC/ASPC) <jacqueline.arthur@canada.ca>
**Cc:** Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>; Marinsky, Cheryl (PHAC/ASPC) <cheryl.marinsky@canada.ca>; Lawuyi2, Niyi (PHAC/ASPC) <niyi.lawuyi2@canada.ca>
**Subject:** FW: For Senior Manager review: LISA AND THERAPEUTICS TEAM FOR INPUT BY APRIL 30 - 21-108019 - Vitamin D, Colcichine, Ivermectin

Thanks Margaret.

Hi Jackie, please see the response to the request below for your review before DG approval.

Note that we got an extension on this so it is due tomorrow COB.

Thank you,

Celisse

---

**From:** Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>
**Sent:** 2021-04-29 3:26 PM
**To:** COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC) <phac.covid-19therapeutics-therapeutiques.aspc@canada.ca>; Marinsky, Cheryl (PHAC/ASPC) <cheryl.marinsky@canada.ca>;

Lawuyi2, Niyi (PHAC/ASPC) <niyi.lawuyi2@canada.ca>
**Cc:** Poon Young, Celisse (PHAC/ASPC) <celisse.poonyoung@canada.ca>
**Subject:** For Senior Manager review: LISA AND THERAPEUTICS TEAM FOR INPUT BY APRIL 29 - 21-108019 - Vitamin D, Colcichine, Ivermectin

Hi,

Additional information has been included in this response for Jackie's approval. I just realized that we/I could have kept more detail, however it was very long.

I am also including the longer version that was provided by the technical team; that could be included if Jackie thinks it appropriate.

Please note that I have also attached the incoming as well as a draft response, parts of which were edited out of my response.

Margaret

---

**From:** Poon Young, Celisse (PHAC/ASPC) <celisse.poonyoung@canada.ca> **On Behalf Of** COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC)
**Sent:** 2021-04-26 1:54 PM
**To:** Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>; Marinsky, Cheryl (PHAC/ASPC) <cheryl.marinsky@canada.ca>; Lawuyi2, Niyi (PHAC/ASPC) <niyi.lawuyi2@canada.ca>
**Cc:** Poon Young, Celisse (PHAC/ASPC) <celisse.poonyoung@canada.ca>
**Subject:** FW: LISA AND THERAPEUTICS TEAM FOR INPUT BY APRIL 29 - 21-108019 - Vitamin D, Colcichine, Ivermectin
**Importance:** High

Hi everyone,

Please see the request that came to the Therapeutics inbox this afternoon. Sending to you all since I am not sure exactly who this should be directed to.

Thank you,

Celisse

---

**From:** Jamil, Marium (PHAC/ASPC) <marium.jamil@canada.ca>
**Sent:** 2021-04-26 12:21 PM
**To:** Waddell, Lisa (PHAC/ASPC) <lisa.waddell@canada.ca>; COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC) <phac.covid-19therapeutics-therapeutiques.aspc@canada.ca>
**Cc:** PHAC.F OCSO_ESGSecretariat / BCSC_SecrétariatGSE F.ASPC <phac.ocso_esgsecretariat-bcsc_secretariatgse.aspc@canada.ca>
**Subject:** LISA AND THERAPEUTICS TEAM FOR INPUT BY APRIL 29 - 21-108019 - Vitamin D, Colcichine, Ivermectin
**Importance:** High

Good morning Lisa and Therapeutics team,
**FOR INPUT/APPROVAL – BY APRIL 29**
**CONTEXT**

- Dr. Tam received correspondence on April 21, 2021 from a member of the public (please see attached '21-108019-10 Incoming Apr 22.pdf'), regarding the use of Vitamin D, Ivermectin and Colchicine as treatments for COVID-19.

**FOR INPUT**

- ESG Secretariat has drafted a standard response in regards to the use of Vitamin D (please see attached '21-108019-VitD_Colchicine, Ivermectin _ Response_Apr2021. doc') adapted from previous responses. The letter does not speak to Colchicine or Ivermectin however. We would be thankful if you could please provide **your input on:**
    - **Any evidence to support the use of Ivermectin and Colchicine**
    - **Any NEW evidence on the efficacy of Vitamin D**

Thank you so much for your time. We would be grateful if you could please provide us your input by April 29th.

Please let us know if you have any questions.

Regards,
Marium

*On behalf of the Office of Chief Science Officer and the PHAC Emerging Science Group Secretariat*

**Marium Jamil**
(she | elle)
Policy Analyst | Analyste des politiques
Office of the Chief Science Officer | Bureau du Conseiller scientifique en chef
Public Health Agency of Canada | Agence de la santé publique du Canada
NEW: phac.ocso_esgsecretariat-bcsc_secretariatgse.aspc@canada.ca

**From:** [redacted]@mcmaster.ca

**Sent:** 2021-05-18 10:05 AM

**To:** COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC); Chung, Yung-En (PHAC/ASPC); Farrah, Kelly (PHAC/ASPC); Alluqmani, Nouf (PHAC/ASPC); Gadient, Stephan (PHAC/ASPC); Lim, Su Hyun (PHAC/ASPC)

**Cc:** [redacted]@mcmaster.ca

**Subject:** Updated/Updated COVID-19 articles from McMaster University

---

**Categories:** A-2021-000129

Hello from McMaster COVID-19+,

The following articles we previously alerted you to have PASSED our criteria

- Ivermectin in combination with doxycycline for treating COVID-19 symptoms: a randomized trial. (View on COVID-19 EA)
- Quality and consistency of clinical practice guidelines for treating children with COVID-19. (View on COVID-19 EA)

The following articles we previously alerted you to are now fully rated

- Mortality Benefit of Convalescent Plasma in COVID-19: A Systematic Review and Meta-Analysis. (View on COVID-19 EA)
- The link between COVID-19 and VItamin D (VIVID): A systematic review and meta-analysis. (View on COVID-19 EA)
- Favipiravir in the treatment of patients with SARS-CoV-2 RNA recurrent positive after discharge: A multicenter, open-label, randomized trial. (View on COVID-19 EA)

**From:** Forbes, Nicole (PHAC/ASPC)
**Sent:** 2021-03-24 2:40 PM
**To:** Lawuyi2, Niyi (PHAC/ASPC)
**Cc:** Arthur, Jacqueline (PHAC/ASPC)
**Subject:** to send to FPT DSTF members
**Attachments:** FTP DSTF Emerging Therapeutics March 23 2021_mAbs.pptx

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Good afternoon,

Please see the attached slide deck that was presented to the FPT DSTF on March 23, 2021 on emerging COVID-19 therapeutics with special focus on neutralizing monclonal antibodies.

Best regards,

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Bonjour,

Veuillez consulter les diapositives ci-jointes qui ont été présentées au groupe de travail FPT sur les pénuries de médicaments le 23 mars 2021. Ces diapositives portent sur les nouvelles thérapies du COVID-19 et plus particulièrement sur les anticorps monoclonaux neutralisants.

Salutations distinguées,

---

**Nicole Forbes, PhD**
(she | elle)
**Technical Lead**
COVID-19 Therapeutics | thérapeutiques
CCDIC, PHAC | CLMTI, ASPC
Tel: (613) 447-6450
Email: nicole.forbes@canada.ca

# Context - Drug approval and guidance: Comparison of selected countries

| Function | Canada | USA | UK | Australia | Germany |
|---|---|---|---|---|---|
| Drug Approval (safety, efficacy, quality) | √ | √ | √ | √ | √ |
| Health Technology Assessment (cost/benefit to health systems) | √ | √ | √ | √ | √ |
| National Guidelines for Clinical Use (guidance on care paths) | X Provincial/Territorial Ministries of Health AMMI | X State/Territorial Departments of Health IDSA | √ | √ | √ |

UK, AU, and Germany have national level entities that produce clinical guidelines. These entities are part of the national-level government infrastructure or the guidance is produced arm's length but is endorsed/funded by the national-level government. Canada and US do not have the equivalent to these entities. For clinical guidance specific to COVID-19 therapeutics, US is using NIH; Canada has set up the CPTG in order to have the same function fulfilled in Canada.

WITHHELD / RETENUE

Is(Are) exempted and/or excluded pursuant to section(s)
est(sont) exemptée(s) et/ou exclus en vertu de(s)(l')article(s)

20(1)(b)
Subject to this section, the head of a government institution shall refuse to disclose any record requested under this Act that contains (b) financial, commercial, scientific or technical information that is confidential information supplied to a
Le responsable d'une institution fédérale est tenu, sous réserve des autres dispositions du présent article, de refuser la communication de documents contenant : b) des renseignements financiers, commerciaux, scientifiques ou techniques fournis à

20(1)(d)
Subject to this section, the head of a government institution shall refuse to disclose any record requested under this Act that contains (d) information the disclosure of which could reasonably be expected to interfere with contractual or other n
Le responsable d'une institution fédérale est tenu, sous réserve des autres dispositions du présent article, de refuser la communication de documents contenant : d) des renseignements dont la divulgation risquerait vraisemblablement d'entraver de

21(1)(a)
The head of a government institution may refuse to disclose, if the record came into existence less than twenty years prior to the request, any record requested under this Act that contains (a) advice or recommendations developed by or for a gove
Le responsable d'une institution fédérale peut refuser la communication de documents datés de moins de vingt ans lors de la demande et contenant : a) des avis ou recommandations élaborés par ou pour une institution fédérale ou un ministre

14(a)
The head of a government institution may refuse to disclose any record requested under this Act that contains information the disclosure of which could reasonably be expected to be injurious to the conduct by the Government of Canada of federal-p
Le responsable d'une institution fédérale peut refuser la communication de documents contenant des renseignements dont la divulgation risquerait vraisemblablement de porter préjudice à la conduite par le gouvernement du Canada des affaires fédéro

WITHHELD / RETENUE

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# Emerging COVID-19 Therapeutics

*FPT Drug Shortages Task Force*

*23 March 2021*

# Purpose

- To provide an update to the FPT Drug Shortages Task Force on emerging therapeutics for COVID-19
  - *Ongoing clinical trials*
  - *Recently reported clinical findings*
- Special focus on neutralizing monoclonal antibody treatments
  - *Emerging evidence on activity against SARS-CoV-2 variants of concern (VOC)*

# Emerging and Authorized COVID-19 Therapeutics

***Antivirals***

- Remdesivir*
- Molnupiravir

***Neutralizing Monoclonals***

- Bamlanivimab monotherapy*
- Bamlanivmab + Etesevimab
- Casirivimab + Imdevimab
- VIR-7831
- AZD-7442
- CT-P59

***Immunomodulating drugs***

- Dexamethasone/ Glucocorticoids
- Tocilizumab
- Sarilumab
- Anakinra
- Baricitinib
- Otilimab
- Colchicine

***Other***

- Aspirin
- Ivermectin
- Fluvoxamine
- SaNOtize

**Authorized by Health Canada*

# Emerging and Authorized COVID-19 Therapeutics: *Focus on Neutralizing Monoclonal Antibodies*

***Antivirals***

- Remdesivir*
- Molnupiravir

***Neutralizing Monoclonals***

- Bamlanivimab monotherapy*
- Bamlanivmab + Etesevimab
- Casirivimab + Imdevimab
- VIR-7831
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***Immunomodulating drugs***

- Dexamethasone/ Glucocorticoids
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- Sarilumab
- Anakinra
- Baricitinib
- Otilimab
- Colchicine

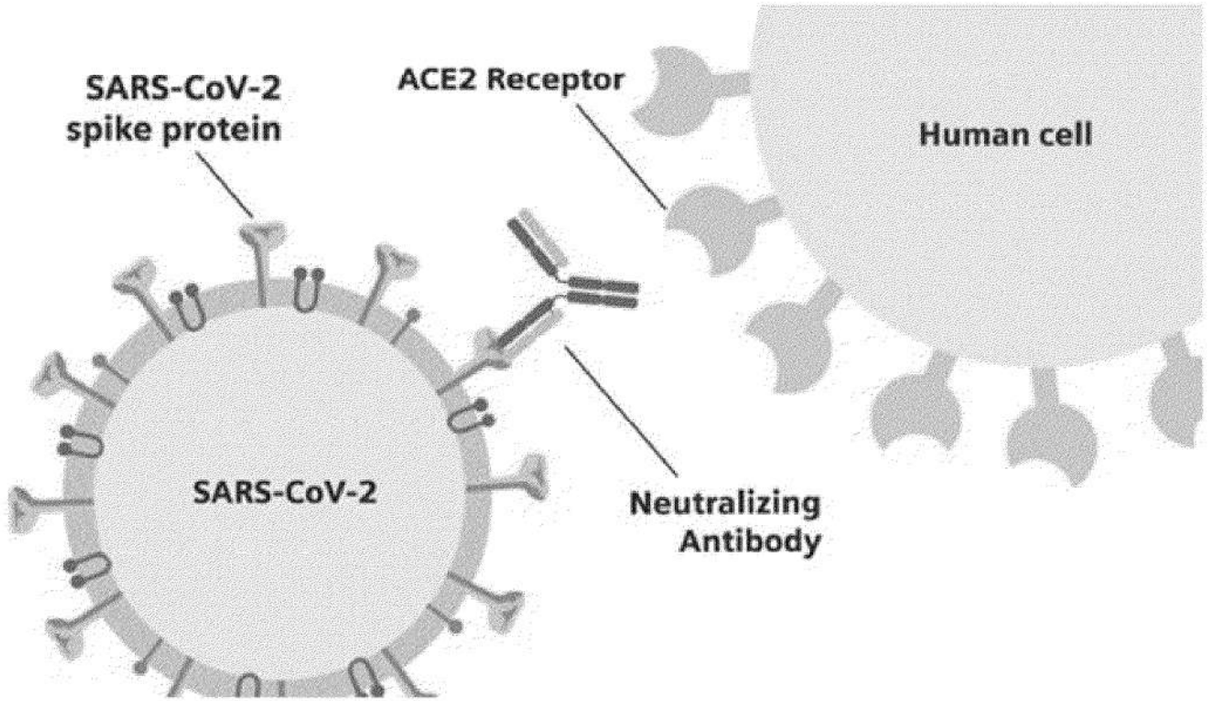
***Other***

- Aspirin
- Ivermectin
- Fluvoxamine
- SaNOtize

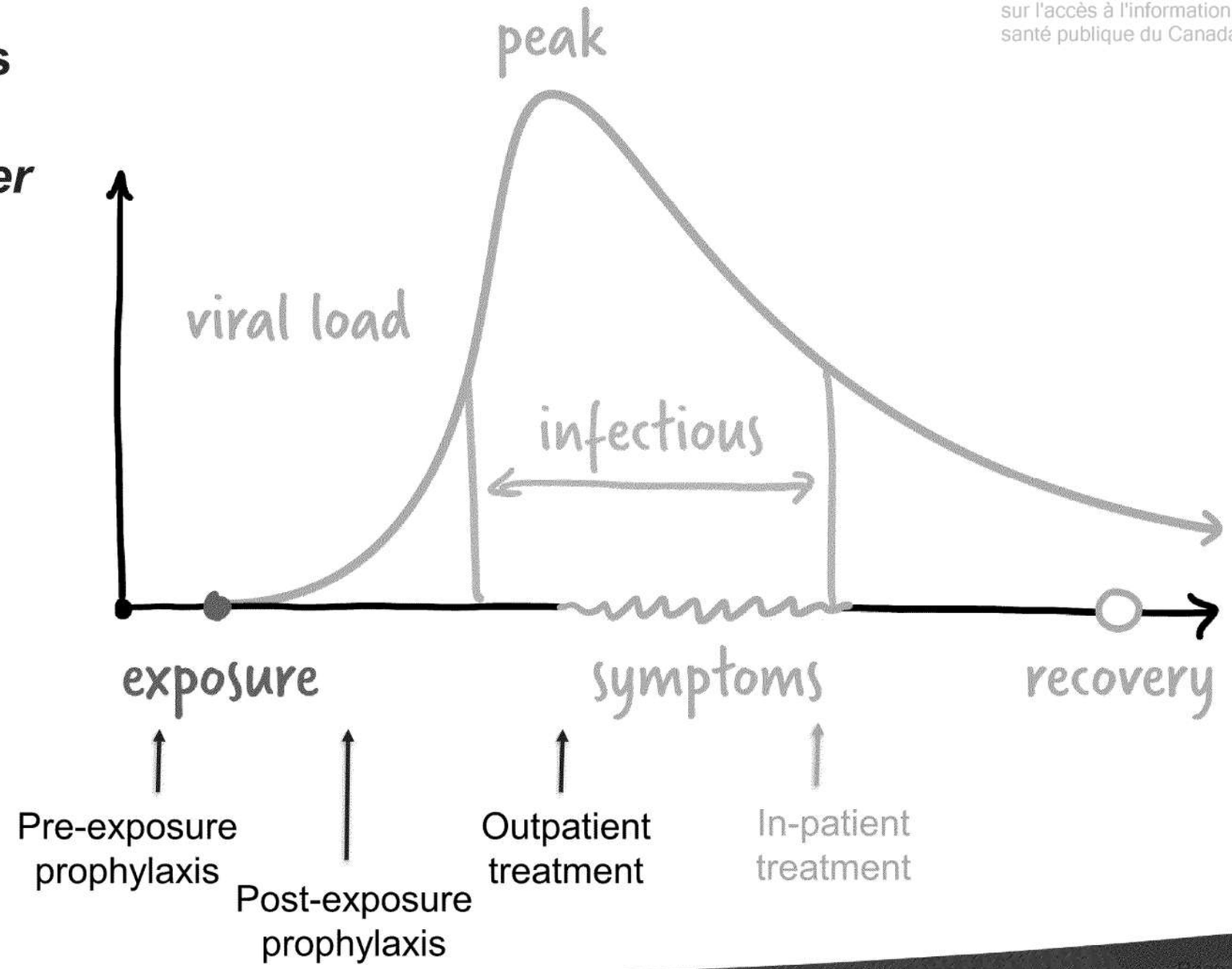
**Authorized by Health Canada*

# Neutralizing monoclonal antibodies targeted against SARS-CoV-2

- Numerous neutralizing monoclonal antibodies (neutralizing mAbs) are in clinical development for the treatment or prevention of SARS-CoV-2 infection
- Target a single region on the SARS-CoV-2 spike protein and prevent binding to the ACE-2 receptor, which neutralizes the virus
- Administered as a monotherapy or with other monoclonal antibodies (combination therapy, aka cocktail)



# Neutralizing mAbs for COVID-19: *Clinical uses under investigation*




Adapted from the New York Times

# Neutralizing mAbs versus SARS-CoV-2 Vaccine

| | Neutralizing mAb(s) | Vaccine |
|---|---|---|
| ***What is it?*** | Molecule that binds and neutralizes the virus | Non-infectious virus and/or piece of virus your immune system will recognize |
| ***What is the goal?*** | Directly treat someone infected with SARS-CoV-2 or to prevent infection (prophylaxis) | Train immune system to protect from future SARS-CoV-2 infections |
| ***How quickly does it work?*** | Immediately | Immunity progressively builds starting 1-2 weeks after vaccination (maximum immunity) |
| ***How long will it last?*** | Weeks to months | Years to lifetime |

*Adapted from Vanderbilt Vaccine Center*

# Neutralizing mAbs: Comparison of design/properties

| | Bamlanivimab *(authorized)* | Bamlanivimab + Etesevimab | Casirivimab + Imdevimab | VIR-7831 | CT-P59 | AZD-4552 |
|---|---|---|---|---|---|---|
| **Manufacturer** | Eli Lilly (AbCellera) | Eli Lilly (AbCellera/ Junshi Biosci.) | Roche (Regeneron) | Vir Biosciences/GSK | Celltrion | Astra-Zeneca |
| **Composition** | Single mAb | Two mAbs | Two mAbs | Single mAb | Single mAb | Two mAbs |
| **Target(s)** | SARS-CoV-2 spike | Distinct regions on SARS-CoV-2 spike RBD | Distinct regions on SARS-CoV-2 spike RBD | Conserved region on SARS-CoV-2 spike protein (shared with SARS-CoV-1) | SARS-CoV-2 spike RBD | SARS-CoV-2 spike |
| **Durability of response (half life)** | T 1/2 ~17 days | T 1/2 ~17 days | ~17 day half life | Extended half-life (proprietary Fc modification) | T 1/2 ~17 days | Extended T 1/2 → durability up to 6-12 months |
| **Route of admin.** | IV | IV | IV; SC in clinical trials | IV; IM in clinical trials | IV | IM |
| **Other attributes** | | Etesevimab – ablated effector function | | Designed to achieve high lung concentration<br>In tact effector function → can neutralize virus AND flag infected cells for destruction | | Reduced Fc receptor binding (reduced effector activity) |

RBD- receptor binding domain

# Neutralizing mAbs: Comparison of clinical treatment effects

| | Bamlanivimab | Bamlanivimab + Etesevimab | Casirivimab + Imdevimab | VIR-7831 | CT-P59 |
|---|---|---|---|---|---|
| **Population** | - | N=769 outpatients at high risk for severe disease/ hospitalization | N=4180 outpatients at high risk for severe disease/ hospitalization | N=583 outpatients at high risk for severe disease/ hospitalization | |
| **Reduced hospitalization or death** | - | 87% reduction in hospitalizations or deaths by day 29<br><br>(Press release; not peer reviewed) | 70% reduction<br><br>(Press release issued on March 23, not included in original presentation) | 85% reduction* in hospitalizations >24h or deaths by day 29 | |
| **Population** | N=613 adult non-hospitalized patients | N=577 adult non-hospitalized patients | N=665 adult non-hospitalized patients | - | N=327 adult non-hospitalized patients |
| **COVID-19 related hospitalizations /ER visits** | 70% reduction in hospitalizations or ER visits by day 29<br><br>(Press release; not peer reviewed) | 84% reduction in hospitalizations or ER visits by day 29 | 57% reduction in medically-attended visits for COVID-19 *(primary care to hospitalization; data from pre-submission filing)* | - | 49% reduction*** in hospitalizations or requirement for oxygen therapy<br><br>(Preprint- not peer reviewed) |

# Susceptibility/resistance of viral variants to neutralizing mAbs

| | Bamlanivimab | Bamlanivimab + Etesevimab | Casirivimab + Imdevimab | VIR-7831 | AZD-7442 | CT-P59 |
|---|---|---|---|---|---|---|
| **B.1.1.7 (UK variant)** | Susceptible | Susceptible | Susceptible | Susceptible | Susceptible | Susceptible |
| **B.1.351 (SA variant)** | Resistant | Resistant | Susceptible | Susceptible | Susceptible | Susceptible |
| **P.1 (Brazil variant)** | Resistant | Resistant | Conflicting evidence | Susceptible | Susceptible | Susceptible |
| **P.2 (Brazil variant)** | Resistant | Not tested | Not tested | Susceptible | Not tested | Susceptible |

*Note: Above table based on non-clinical evidence (in vitro pseudovirus/whole virus neutralization assays)*

# Additional post-market analysis data from the United States

**PREPRINT:** Webb et al., Real-World Effectiveness and Tolerability of Monoclonal Antibodies for Ambulatory Patients with Early COVID-19. medRxiv. March 17, 2021.

- Population: 13,534 symptomatic high-risk outpatients with symptomatic, lab-confirmed COVID-19 treated at infusion centers and urgent care clinics in the USA within 7 days of symptom onset.
- Intervention: bamlanivimab 700 mg or casirivimab/imdevimab 1200 mg/1200 mg (n=594 given a mAb; 80.6% receiving bamlanivimab)
- Patients who received mAb infusion were compared to contemporaneous controls and a pre-implementation cohort (n=5536 and 7404 respectively).
- The primary outcome was emergency department visit or hospitalization within 14 days of positive test.
- MAb treatment was associated with fewer subsequent ER visits and hospitalizations (31% reduction).
- Overall, 7 (1.2%) mAb patients experienced an adverse event; two (0.3%) were considered serious.
- No statistically significant difference between effect of casirivimab/imdevimab and bamlanivimab treatment.

# Neutralizing mAbs: Ongoing randomized trials for COVID-19 indications

| | Bamlanivimab | Bamlanivimab + Etesevimab | Casirivimab + Imdevimab | VIR-7831 | CT-P59 | AZD-4552 |
|---|---|---|---|---|---|---|
| **Outpatient** | Ph2/3 trial N=2000; Jul 2021 (ACTIV-2; NIAID)<br>Ph2 trial N=700; March 2021<br>Ph2/3 trial N=3300; May 2021 | Ph2 trial N=700; March 2021<br>Ph2/3 trial N=3300; May 2021 | Symptomatic; Ph2/3 trial N=6420; April 2021 | Ph2 trial N=700; March 2021 (BLAZE-4; VIR-7831 + bamlanivimab)<br>Ph2/3 trial N=1360; July 2021 | Ph2/3 trial N=1020; Sept 2021 | Ph3 trial N=1700; June 2021 |
| **Outpatient subpopulation** | 65y+ symptomatic Ph4 trial N=576; June 2021 (BC) | | Asymptomatic/ low risk; Ph2 trial N=1400; Mar 2021 | | | |
| **Inpatient** | | | Ph1/2 trial N=6900; April 2021<br>Ph3 trial N= 2000 (enrollment to treatment arm; RECOVERY trial); March 2021 | Ph3 NIAID sponsored (n=10,000; 344 to VIR arm*); Aug 2021 (ACTIV-3; NIAID)<br>*Halted by NIH for futility* | | Ph3 NIAID sponsored (n=10,000; 950 to AZD arm); Aug 2021 (ACTIV-3; NIAID) |
| **Pre-exp. prophylaxis** | Ph3 trial N=5000; March 2021 (LTC residents/staff) | Ph3 trial N=5000; March 2021 LTC residents/staff) | | | | Ph3 trial N=5000; June 2021 |
| **Post-exp. prophylaxis** | | | Ph3 trial N=2450; June 2021 | | | Ph3 trial; N=1125; Jan 2022 |

# Additional neutralizing monoclonal antibodies for COVID-19

- Numerous neutralizing mAbs for SARS-CoV-2 in early and late stage clinical trials including:

- *VIR-7832 (Vir Biosciences/GSK)*
- *STI-1499 (COVI-GUARD; Sorrento)*
- *SCTA01 (Sinocelltech Ltd and Chinese Academy of Sciences)*
- *BRII-198/196 (Brii Bioscience)*
- *ADM03820 (Ology Bioservices)*
- *TAXT-03 (ImmunoPrecise)*
- *DZIF/DZIF10c (University of Cologne and Boehringer Ingelheim)*
- *ABBV-47D11 (AbbVie)*
- *ABBV-2B04 (AbbVie)*
- *HFB30132A (HiFiBiO Therapeutics)*
- *TY027 (Tychan/SingHealth)*
- *BI 767551 (Cologne University Hospital (UKK), University of Marburg (UMR), the German Center for Infection* Research (DZIF) and Boehringer Ingelheim)

## Considerations

- All neutralizing monoclonal antibodies targeting SARS-CoV-2 spike protein share the same mechanism of action.
- Differentiating factors include:
  - Single monoclonal antibody (most at risk for resistance by viral variants) or combination of >1 mAbs ( >1 target therefore less risk for resistance by variants)
  - Resistance/susceptibility profile for emerging variants of concern
  - Route of administration (intravenous versus subcutaneous versus intra-muscular)
  - Proprietary modifications to increase durability of treatment (Fc modifications, ect)
- On March 18, the FDA has issued updated fact sheets for bamlanvimab, bamlanivimab + etesevimab and casirivimab + imdevimab noting antiviral resistance for a panel of viral variants.
- A healthcare provider's decision to treat a patient with a neutralizing mAb for COVID-19 should consider prevalence of viral variants in their area.

# Sources – clinical data

- https://investor.lilly.com/news-releases/news-release-details/lillys-bamlanivimab-and-etesevimab-together-reduced
- https://newsroom.regeneron.com/news-releases/news-release-details/independent-data-monitoring-committee-finds-clear-efficacy-regen
- https://www.gsk.com/en-gb/media/press-releases/vir-biotechnology-and-gsk-announce-vir-7831-reduces-hospitalisation-and-risk-of-death-in-early-treatment-of-adults-with-covid-19/
- https://jamanetwork.com/journals/jama/fullarticle/2775647
- Efficacy and safety of CT-P59 plus standard of care: a phase 2/3 randomized, double-blind, placebo-controlled trial in outpatients with mild-to-moderate SARS-CoV-2 infection
- https://www.roche.com/media/releases/med-cor-2021-03-23.htm

# Sources- in vitro data on variants of concern

Wang et al, Nature, 2021
Yao et al, preprint, 2021
Hoffman et al, preprint, 2021
Liu et al, preprint, 2021
Wibmer et al, preprint, 2021
Tada et al, preprint, 2021
Widera et al, preprint, 2021
Reuschl et al, preprint, 2021
Rothenberger et al, preprint, 2021
Wang P et al, preprint, 2021
Vir Biotechnology, press release, 2021
Kim et al, Nature Communications, 2021
Starr et al, preprint, 2021
Cathcart et al, preprint, 2021
Wang R et al, preprint, 2021
Copin et al, preprint, 2021
Dejnirattisai et al, preprint, 2021

# Contacts at the Public Health Agency of Canada

COVID-19 Therapeutics | thérapeutiques

**Jacqueline Arthur, RN, BScN**
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Email: niyi.lawuyi2@Canada.ca

**Nicole Forbes, PhD**
Technical Lead
t. (613) 447-6450
Email: nicole.forbes@canada.ca

# Produits thérapeutiques émergentes pour la COVID-19

*Groupe de travail FPT sur les pénuries de médicaments*

*6 avril 2021*

PROTECTING AND EMPOWERING CANADIANS
TO IMPROVE THEIR HEALTH

# Objectif

- Présenter au groupe de travail FPT sur les pénuries de médicaments une mise à jour sur les thérapies émergentes pour la COVID-19 :
  - *Essais cliniques en cours;*
  - *Résultats cliniques récemment rapportés.*
- Une attention particulière est accordée aux médicaments antiviraux et à certains médicaments actuellement à l'étude à Santé Canada

# Produits thérapeutiques émergentes et autorisées pour la COVID-19

***Médicaments Antiviraux***

- **Remdesivir***
- **Favipiravir****
- **Molnupiravir**
- **PF-07321332**

***Monoclonaux neutralisants***

- Bamlanivimab en monothérapie*
- Bamlanivmab + Etesevimab**
- Casirivimab + Imdevimab**
- VIR-7831
- AZD-7442
- CT-P59

***Médicaments immunomodulateurs***

- Dexaméthasone/ Glucocorticoïdes
- Tocilizumab
- Sarilumab
- Anakinra
- Baricitinib
- Otilimab
- **Colchicine****
- **Leronlimab****
- Fumarate de diméthyle (DMF)

***Autre***

- Aspirine
- Ivermectine
- Fluvoxamine
- Oxyde nitrique

**Homologué par Santé Canada*
***En cours d'examen à Santé Canada*

# Cibles pharmacologiques pour la COVID-19

**Médicaments anti-inflammatoires à cibles multiples**

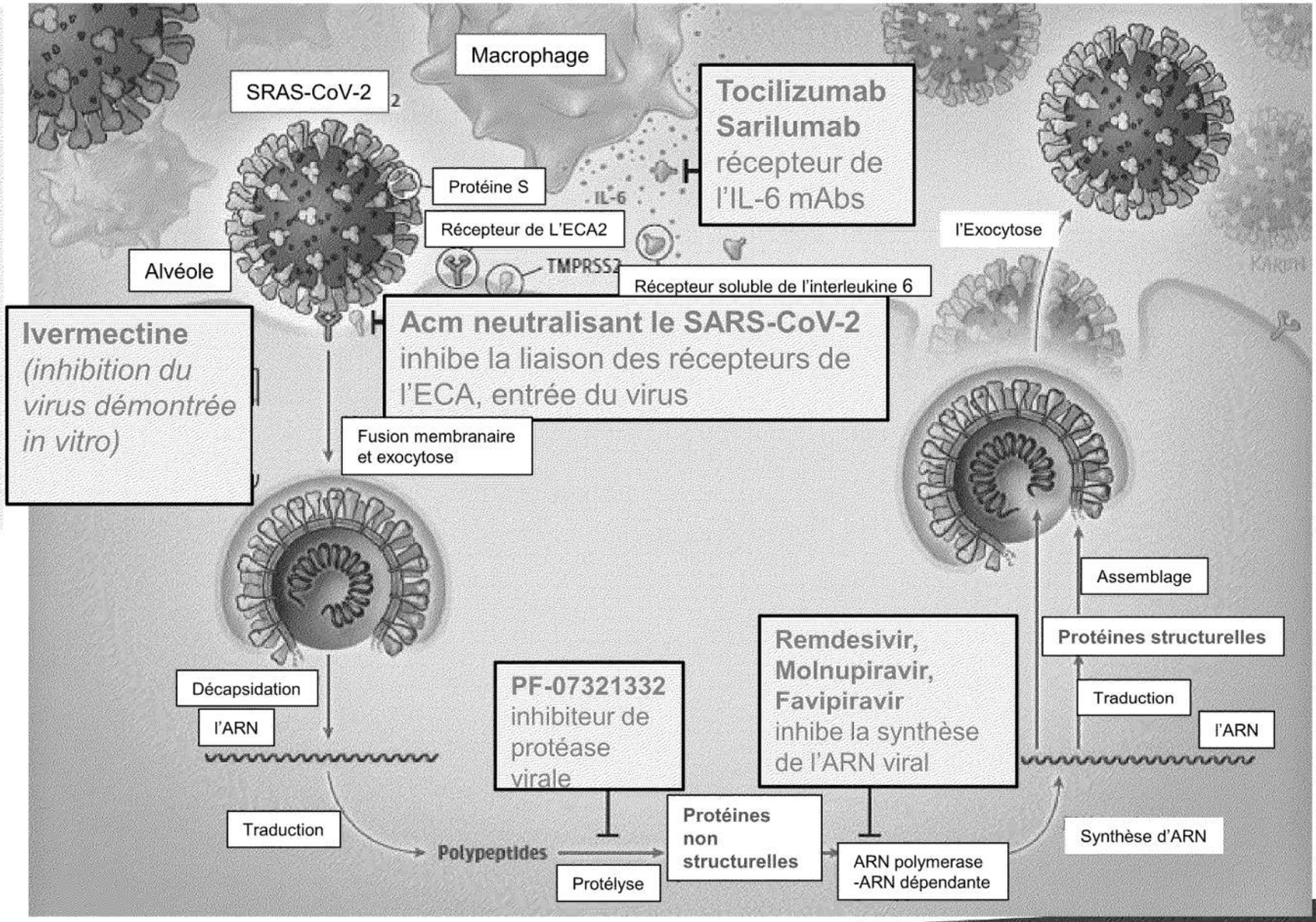
**Dexaméthasone/ glucocorticoïdes de** nombreux effets; antagoniste du NFkB

**Colchicine, DMF** de nombreux effets; inhibe l'inflammasome NLRP3

**Autres thérapeutiques**

**Aspirine** antiplaquettaire

**Oxyde nitrique** antiviral, immunomodulateur




**Autres médicaments anti-inflammatoires ayant des cibles cellulaires spécifiques**

**Anakinra**
Antagoniste de l'IL-1

**Leronlimab**
(*AcM* anti-CCR5)

**Baricitinib**
(inhibiteur de JAK1/2)

**Otilimab**
*AcM* anti-GM-CSF

**Fluvoxamine**
Active le récepteur sigma-1

*AcM = anticorps monoclonal*

Adapté de Sanders, JM, et coll. *Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19)*. Examen, JAMA, 2020, vol.18, nº 323, p.1824-1836

# Médicaments antiviraux du SRAS-CoV-2

- Potentiels pour les thérapies combinées (par exemple le régime antiviral combiné du VIH);
- Ciblent la reproduction active du virus;
- Phase aiguë (avant ou début de la phase symptomatique);
- COVID de longue durée (excrétion virale prolongée).

# Médicaments antiviraux autorisés et expérimentaux contre le SRAS-CoV-2

| | Remdesivir *(Veklury®)* | Favipiravir *(Avigan®, Reeqonus®)* | Molnupiravir *(MK-4482)* | PF-07321332 |
|---|---|---|---|---|
| **Fabricant** (Cible originale) | Gilead (Ebola; médicament expérimental) | Appili; Dr Reddy; Global Response Aid; FujiFilm (grippe pandémique). | Merck; Ridgeback Pharmaceuticals (grippe). | Pfizer (SRAS-CoV-1) |
| **Cible** | analogue de nucléotide. | enzyme virale (ARN polymérase ARN dépendante) | prodrogue d'analogue nucléosidique. | Protéase virale (3CL) |
| **Mécanisme d' action** | Inhibe la synthèse de l'ARN viral. | Inhibe la synthèse de l'ARN viral. | Inhibe la synthèse de l'ARN viral. | Inhibe la réplication viral |
| **Administration** | IV (forme inhalée dans les essais). | Oral | Oral | Oral |
| **Statut** | Autorisé par Santé Canada dans le cadre d'une ordonnance provisoire pour les adultes et les adolescents âgés de 12 ans et plus souffrant d'une COVID-19 grave et nécessitant un supplément d'O2. | Examen en cours par Santé Canada pour la COVID-19 légère à modérée chez les adultes | Essais de phase 2 et de phase 2 et 3 adaptatifs en cours, tant en milieu hospitalier qu'en milieu ambulatoire. | Début des essais de phas 1 en mars 2021 |
| **Essais en cours** | Essai de phase 1/2 sous **par voie inhalée** (traitement ambulatoire | Autorisé en Russie, en Indonésie et en Inde pour la COVID-19. | Données de phase 2 positives pour la réduction de la charge virale. | |

# Favipiravir c. soins standard pour la gravité légère/modérée/non spécifiée de la COVID-19 : *Méta-analyse de réseau à partir de 7 essais contrôlés randomisés*

| Résultats | Effets absolus anticipés (IC 95 %) | | Risque relatif (IC 95 %) | Nombre de participants (études) | Certitude de la preuve (GRADE) | Commentaires |
|---|---|---|---|---|---|---|
| | Risque avec les soins standard/le placebo | Risque avec Favipiravir | | | | |
| Conversion virale négative D7 | 668 per 1,000 | **735 per 1,000** (641 to 848) | **RR 1.10** (0.96 to 1.27) | 696 (6 RCTs) [b] | ⨁⨁◯◯ LOW [c,d] | |
| Amélioration clinique D28 | 552 per 1,000 | **563 per 1,000** (524 to 601) | **RR 1.02** (0.95 to 1.09) | 579 (5 RCTs) [e] | ⨁⨁◯◯ LOW [f,g] | |
| Amélioration clinique D60 ou plus - non signalé | | - | - | - | - | Résultat non encore mesuré ou rapporté |
| Score de progression de l'OMS (niveau 7 ou supérieur) D28 | 0 per 1,000 | **0 per 1,000** (0 to 0) | not estimable | 370 (3 RCTs) [h] | ⨁◯◯◯ VERY LOW [i,j] | Aucun événement dans les deux groupes |
| Score de progression de l'OMS (niveau 7 ou supérieur) D60 ou plus - non signalé | - | - | - | - | - | Résultat non encore mesuré ou rapporté |
| Mortalité toutes causes confondues D28 | 9 per 1,000 | **3 per 1,000** (0 to 27) | **RR 0.33** (0.04 to 3.16) | 470 (4 RCTs) [k] | ⨁◯◯◯ VERY LOW [i,l] | |
| Mortalité toutes causes confondues D60 ou plus - non rapporté | | - | - | - | - | Résultat non encore mesuré ou rapporté |
| Événements indésirables | 287 per 1,000 | **442 per 1,000** (250 to 789) | **RR 1.54** (0.87 to 2.75) | 578 (4 RCTs) [m] | ⨁◯◯◯ VERY LOW [n,o,p] | |
| Événements indésirables graves | 21 per 1,000 | **25 per 1,000** (10 to 62) | **RR 1.20** (0.48 to 3.00) | 538 (4 RCTs) [q] | ⨁◯◯◯ VERY LOW [l,n] | |

Le risque dans le groupe d<intervention (et son intervalle de confiance à 95%) est fondé sur le risque présumé dans le groupe de comparaison et l'effet relatif de l'intervention (et son IC à 95%) RCT-ECR RR- Risque relatif (RR) CI-IC

**+ Très faible** **++ Faible** **+++ Modérée**

# Remdesivir c. soins standard pour la COVID-19 légère/modérée/grave/critique : *Méta-analyse en réseau à partir de 5 essais contrôlés randomisés*

| Résultats | Effets absolus anticipés (IC 95 %) | | Risque relatif (IC 95 %) | Nombre de participants (études) | Certitude de la preuve (GRADE) | Commentaires |
|---|---|---|---|---|---|---|
| | Risque avec les soins standard /le placebo | Risque avec Remdesivir | | | | |
| Conversion virale négative D3 | 292 per 1,000 | **284 per 1,000** (178 to 450) | **RR 0.97** (0.61 to 1.54) | 196 (1 RCT) [b] | ⊕◯◯◯ VERY LOW [c,d,e] | |
| Conversion virale négative D7 | 492 per 1,000 | **502 per 1,000** (374 to 679) | **RR 1.02** (0.76 to 1.38) | 196 (1 RCT) [b] | ⊕◯◯◯ VERY LOW [c,d,f] | |
| Amélioration clinique D7 | 345 per 1,000 | **366 per 1,000** (307 to 439) | **RR 1.06** (0.89 to 1.27) | 832 (2 RCTs) [g] | ⊕⊕⊕◯ MODERATE [f] | |
| Amélioration clinique D14-D28 | 759 per 1,000 | **805 per 1,000** (751 to 858) | **RR 1.06** (0.99 to 1.13) | 832 (2 RCTs) [g] | ⊕⊕⊕◯ MODERATE [h] | |
| Score de progression de l'OMS (niveau 6 ou supérieur) D7 | 451 per 1,000 | **419 per 1,000** (243 to 717) | **RR 0.93** (0.54 to 1.59) | 1298 (2 RCTs) [i] | ⊕⊕◯◯ LOW [f,j] | |
| Score de progression de l'OMS (niveau 6 ou supérieur) D14-D28 | 193 per 1,000 | **131 per 1,000** (106 to 164) | **RR 0.68** (0.55 to 0.85) | 1894 (3 RCTs) [k] | ⊕⊕⊕◯ MODERATE [l] | |
| Score de progression de l'OMS (niveau 7 ou supérieur) D7 | 359 per 1,000 | **251 per 1,000** (212 to 294) | **RR 0.70** (0.59 to 0.82) | 1298 (2 RCTs) [i] | ⊕⊕⊕◯ MODERATE [h] | |
| Score de progression de l'OMS (niveau 7 ou supérieur) D14-D28 | 178 per 1,000 | **124 per 1,000** (100 to 156) | **RR 0.70** (0.56 to 0.88) | 1894 (3 RCTs) [k] | ⊕⊕⊕⊕ HIGH | |
| Mortalité toutes causes confondues D7 | 63 per 1,000 | **43 per 1,000** (18 to 104) | **RR 0.68** (0.28 to 1.64) | 1298 (2 RCTs) [i] | ⊕◯◯◯ VERY LOW [e,m] | |
| Mortalité toutes causes confondues D14-D28 | 112 per 1,000 | **101 per 1,000** (82 to 125) | **RR 0.90** (0.73 to 1.11) | 7345 (4 RCTs) [n] | ⊕⊕⊕◯ MODERATE [f] | |
| Événements indésirables | 583 per 1,000 | **583 per 1,000** (507 to 671) | **RR 1.00** (0.87 to 1.15) | 1894 (3 RCTs) [k] | ⊕⊕⊕◯ MODERATE [l,o] | |
| Événements indésirables graves | 252 per 1,000 | **186 per 1,000** (156 to 221) | **RR 0.74** (0.62 to 0.88) | 1894 (3 RCTs) [k] | ⊕⊕⊕◯ MODERATE [o,p] | |

Le risque dans le groupe d<intervention (et son intervalle de confiance à 95%) est fondé sur le risque présumé dans le groupe de comparaison et l'effet relatif de l'intervention (et son IC à 95%) RCT-ECR RR- Risque relatif (RR) CI-IC

**+ Très faible** **++ Faible** **+++ Modérée**

https://covid-nma.com/living_data

# COLCHICINE -
# *EMPLOI NON CONFORME POUR LA COVID-19*

# *Colchicine : Preuves cliniques de premier ordre*

Essai RECOVERY (communiqué de presse; *non évalué par les pairs*) *:*

- Essai randomisé ouvert basé au Royaume-Uni chez des patients hospitalisés pour la COVID-19.
- Décision du Comité indépendant de surveillance de données, rendue le 4 mars, de fermer le volet de traitement à la colchicine en raison de la futilité
- Analyse préliminaire fondée sur 2 178 décès signalés parmi 11 162 patients randomisés (94 % également traités par un corticostéroïde).
- Aucune différence significative dans le critère principal de mortalité à 28 jours
  - 20 % colchicine contre 19 % soins habituels seuls; (p=0,63)
- Le suivi des patients est en cours; la publication de l'analyse finale est prévue prochainement.

  https://www.recoverytrial.net/news/recovery-trial-closes-recruitment-to-colchicine-treatment-for-patients-hospitalised-with-covid-19
- Preuves diverses de l'avantage clinique provenant de nombreux petits essais insuffisamment puissants chez les patients hospitalisés atteints de COVID-19

# COVID-19 directives de traitement pour la colchicine dans les provinces et territoires

- Comité thérapeutique du BC COVID-19 : Le CTC ne recommande pas l'utilisation systématique de la colchicine à en ce moment. Chez les patients âgés de 40 ans ou plus atteints de COVID-19 confirmé par ACR, qui présentent au moins un facteur de risque (selon l'essai COLCORONA) et aucune contre-indication [spécifiée dans les directives], l'administration de colchicine à raison de 0,6 mg PO BID x 3 jours, puis 0,6 mg par jour x 27 jours peut être envisagée au cas par cas en discussion avec le patient en soulignant clairement l'incertitude quant au bénéfice du traitement, ainsi que les risques et les effets indésirables potentiels. Le consentement éclairé doit être obtenu et le traitement doit être initié dès que possible. La colchicine pour le traitement des patients gravement ou gravement malades atteints de COVID-19 n'est pas recommandée en dehors des essais cliniques approuvés.

- Groupe consultatif scientifique COVID-19 des services de santé de l'Alberta : Pour l'instant, la colchicine ne doit pas être prescrite ou administrée pour traiter la COVID-19. Les cliniciens et les chercheurs de l'Alberta devraient soutenir des essais cliniques de haute qualité en Alberta ou dans le cadre d'une étude multicentrique bien conçue pour aider à découvrir si la colchicine présente un avantage pour le traitement de la COVID-19.

- INESSS : L'état actuel des connaissances scientifiques et l'incertitude sur les avantages et les risques potentiels de l'administration de colchicine chez les personnes non hospitalisées ayant un diagnostic de COVID-19 confirmé ou non par un test RT-PCR, et qui répondent aux critères de sélection de l'étude COLCORONA (plus de 40 ans avec au moins un facteur de risque), ne permettent pas de soutenir l'utilisation de la colchicine pour cette population en dehors d'un protocole de recherche. SRAS-CoV-2 confirmé, traitement en milieu hospitalier.

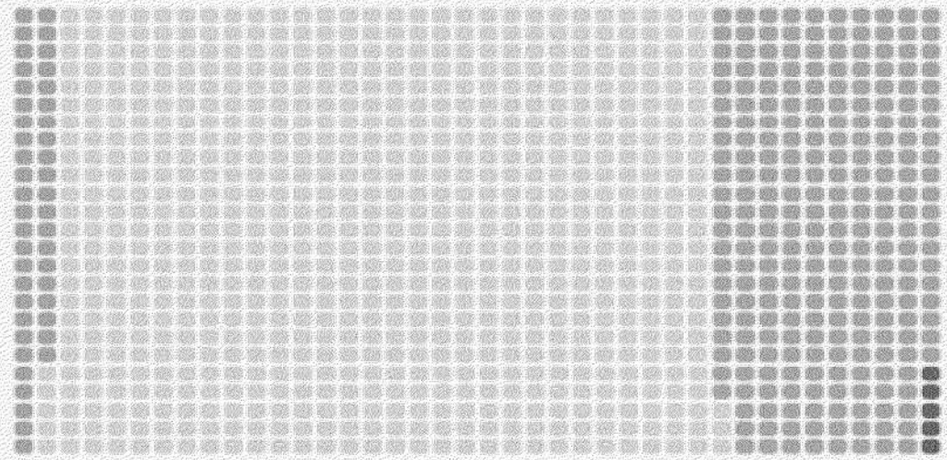
# REPRÉSENTATION GRAPHIQUE DES EFFETS POTENTIELS DU TRAITEMENT

La figure ci-dessous illustre les effets potentiels de la colchicine sur les hospitalisations et les évènements indésirables chez des personnes qui correspondent aux critères de l'étude et qui ont un obtenu un test RT-PCR positif.

⚠ Les causes qui ont mené aux hospitalisations, la durée réelle du séjour au-delà des 24 heures prédéfinies et la nécessité d'un transfert aux soins intensifs sont non documentées dans la prépublication.

## Traitement de 30 jours avec colchicine

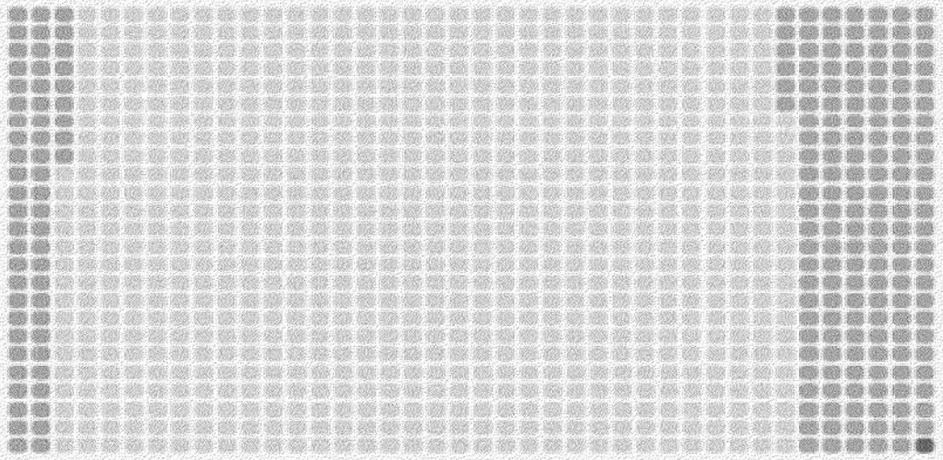
**1000 personnes** ayant résultat par RT-PCR positif pour la COVID-19
Non hospitalisées | 40 ans et plus | ≥ 1 Facteur de risque



- **45** auraient été hospitalisées en raison de la COVID-19
- **242** auraient subi des événements indésirables (surtout gastro-intestinal)
- **5** auraient subi une embolie pulmonaire

## Traitement de 30 jours avec placébo

**1000 personnes** ayant résultat par RT-PCR positif pour la COVID-19
Non hospitalisées | 40 ans et plus | ≥ 1 Facteur de risque



- **59** auraient été hospitalisées en raison de la COVID-19
- **155** auraient subi des événements indésirables (surtout gastro-intestinal)
- **1** aurait subi une embolie pulmonaire

# LERONLIMAB - *MÉDICAMENT EXPÉRIMENTAL POUR LES PATIENTS ATTEINTS DE COVID-19 CRITIQUE*

# *Leronlimab : Profil du médicament*

- Anticorps monoclonal humanisé anti-CCR5 (récepteur de la chimiokine C-C de type 5); bloque le co-récepteur CCR5 présent sur les cellules T et d'autres cellules immunitaires.

- L'activation de CCR5 par l'intermédiaire de ligands immuno-stimulateurs (CCL5 (RANTES), CCL3 (MIP-1α) et CCL4 (MIP-1β)) entraîne une infiltration des cellules immunitaires.

- L'état hyper-inflammatoire caractérisé par la COVID-19 grave et critique peut être en partie attribuable à une infiltration accrue de cellules immunitaires.

# *Leronlimab : Statut de l'autorisation*

- Non approuvé pour utilisation au Canada pour toute indication.

- Le 23 mars 2021, Santé Canada a reçu une demande dans le cadre de l'ordinance provisoire pour le leronlimab (CytoDyn, Inc.; Amarex) comme traitement de la COVID-19 légère à modérée (examen en cours).

- L'Administration des États-Unis chargée des aliments et des médicaments a accordé à **CytoDyn Inc.** le statut de médicament nouveau expérimental d'urgence (EIND) pour le leronlimab dans le cadre de la COVID-19.

# *Leronlimab : Preuves cliniques de premier ordre*

- Un communiqué de presse portant sur une étude multicentre, randomisée, à double insu, contrôlée par placebo, de phase IIb/III, parrainée par une société pharmaceutique, à deux volets, randomisée, à double insu, contrôlée par placebo, chez des patients adultes hospitalisés atteints de la COVID-19 grave ou critique.

- Les patients ont été randomisés pour recevoir soit des doses hebdomadaires de 700 mg de leronlimab, soit un placebo, par voie sous-cutanée.

- Le critère de jugement principal est la mortalité toutes causes confondues à 28 jours.

- Les résultats basés sur 309 patients de la population en intention de traiter modifiée, rapportés dans un communiqué de presse le 30 mars 2021, ont indiqué une réduction du risque absolu de décès le 28$^{e}$ jour de 6,5 % pour les patients ayant reçu le leronlimab par rapport au placebo, en plus des autres traitements de la COVID-19 (P = 0,0319).

- Aucune étude ou prépublication par les pairs n'a été effectuée sur des études contrôlées randomisées démontrant l'efficacité et l'innocuité clinique  en tant que traitement pour la COVID-19

# Contacts à l'Agence de la santé publique du Canada

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# Emerging COVID-19 Therapeutics

*FPT Drug Shortages Task Force*

*6 April 2021*

## Purpose

- To provide an update to the FPT Drug Shortages Task Force on emerging therapeutics for COVID-19
  - *Ongoing clinical trials*
  - *Recently reported clinical findings*
- Special focus on antivirals and select drugs currently under review at Health Canada

# Emerging and Authorized COVID-19 Therapeutics

***Antivirals***

- **Remdesivir***
- **Favipiravir****
- **Molnupiravir**
- **PF-07321332**

***Neutralizing Monoclonals***

- Bamlanivimab monotherapy*
- Bamlanivmab + Etesevimab**
- Casirivimab + Imdevimab**
- VIR-7831
- AZD-7442
- CT-P59

***Immunomodulating drugs***

- Dexamethasone/ Glucocorticoids
- Tocilizumab
- Sarilumab
- Anakinra
- Baricitinib
- Otilimab
- **Colchicine****
- **Leronlimab****
- Dimethyl Fumarate (DMF)

***Other***

- Aspirin
- Ivermectin
- Fluvoxamine
- Nitric Oxide

**Authorized by Health Canada*
***Under review by Health Canada*

# Pharmacologic Targets for COVID-19

**Anti-inflammatory drugs with multiple targets**

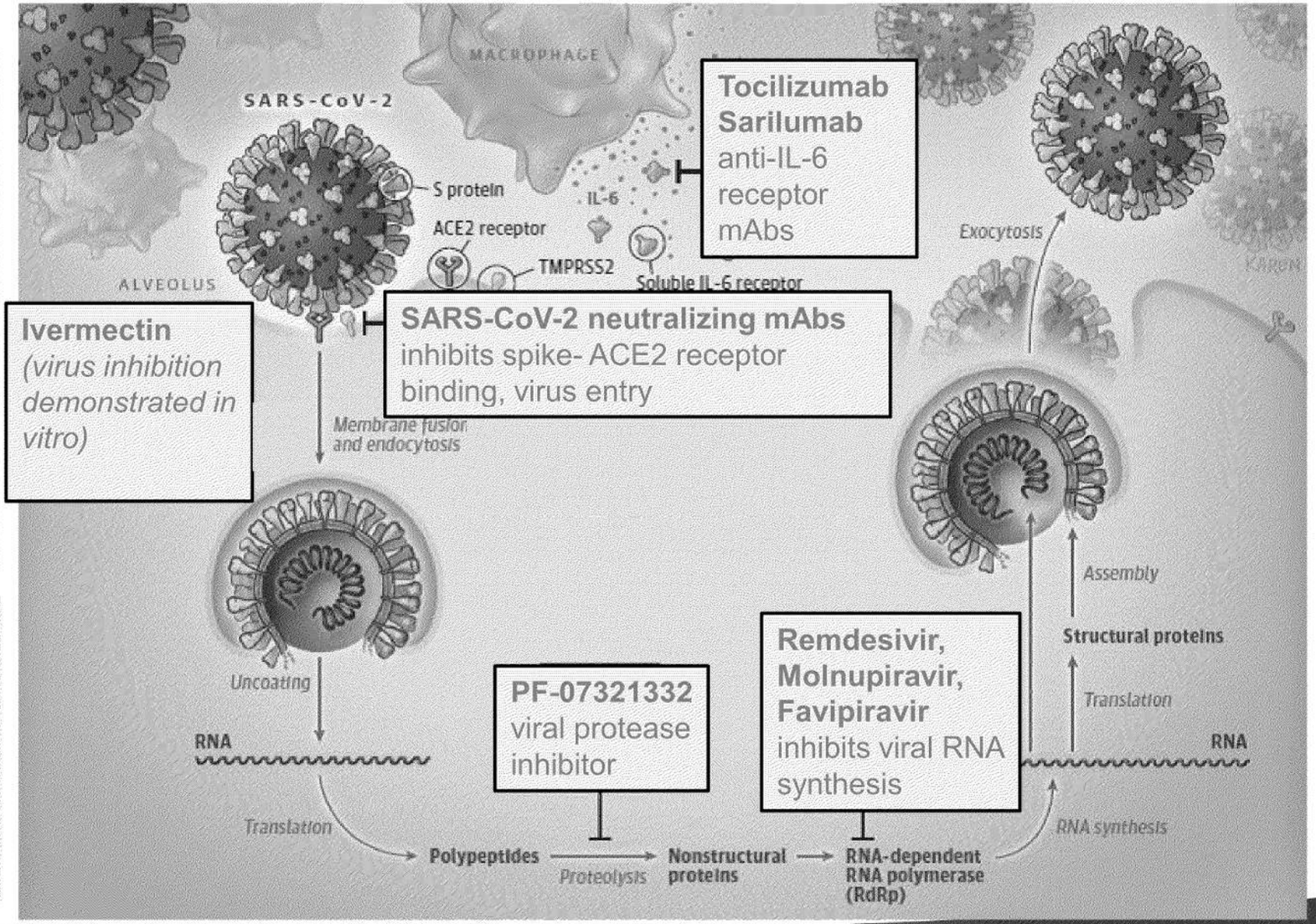
**Dexamethasone/ glucocorticoids**
numerous effects; NFkB antagonist

**Colchicine, DMF**
numerous effects; inhibits NLRP3 inflammasome

**Other therapeutics**

**Aspirin**
anti-platelet

**Nitric Oxide**
anti-viral, immunomodulatory




**Other anti-inflammatory drugs with specific cellular targets**

**Anakinra**
IL-1 antagonist

**Leronlimab**
(anti-CCR5 mAb

**Baricitinib**
(JAK1/2 inhibitor

**Otilimab**
anti-GM-CSF mAb

**Fluvoxamine**
Activates sigma-1 receptor

*mAb = monoclonal antibody*

Adapted from Sanders, JM, et al, Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19). A Review. JAMA, 2020; 323(18):1824-1836).

# Antivirals for SARS-CoV-2

- Potential for combination therapies (e.g. HIV combination antiviral regimen)
- Target active virus replication
- Acute phase (prior to/early symptomatic stage)
- Long COVID (extended viral shedding)

# SARS-CoV-2 Authorized and Investigational Antivirals

| | Remdesivir *(Veklury®)* | Favipiravir *(Avigan®, Reeqonus®)* | Molnupiravir *(MK-4482)* | PF-07321332 |
|---|---|---|---|---|
| **Manufacturer** (Original target) | Gilead (Ebola; investigational drug) | Appili; Dr. Reddy's; Global Response Aid; FujiFilm (pandemic influenza) | Merck; Ridgeback Pharmaceuticals (influenza) | Pfizer (SARS-CoV-1) |
| **Target** | nucleotide analogue | viral enzyme (RNA dependent RNA polymerase) | nucleoside analogue prodrug | Viral protease (3CL) |
| **Mechanism of action** | Inhibits viral RNA synthesis | Inhibits viral RNA synthesis | Inhibits viral RNA synthesis | Inhibits viral replication |
| **Administration** | IV (inhaled form in trials) | Oral | Oral | Oral |
| **Status** | Authorized by Health Canada under the Interim Order for adults and adolescents aged 12 and up with severe COVID-19 requiring supplemental O2 | Ongoing Health Canada review for mild to moderate COVID-19 in adults | Ongoing Phase 2 and adaptive Phase 2/3 trials, both in the inpatient and outpatient setting | Phase 1 trials initiated in March 2021 |
| **Ongoing trials** | Ph1/2 trial on **inhaled form** (outpatient treatment; April 2021)<br>Ongoing outpatient, pediatric trials | Authorized in Russia, Indonesia, and India for COVID-19<br>Phase 3 outpatient treatment trial expected to report out later this spring. | Positive Phase 2 data for reducing viral load<br>Phase 2 efficacy and safety data anticipated Spring 2021 | |

# Favipiravir vs Standard Care for Mild/Moderate/Unspecified COVID-19 disease severity: *Network meta-analysis from 7 randomized controlled trials*

| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | № of participants (studies) | Certainty of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Risk with Standard care | Risk with Favipiravir | | | | |
| Viral negative conversion D7 | 668 per 1,000 | **735 per 1,000** (641 to 848) | **RR 1.10** (0.96 to 1.27) | 696 (6 RCTs) [b] | ⨁⨁◯◯ LOW [c,d] | |
| Clinical improvement D28 | 552 per 1,000 | **563 per 1,000** (524 to 601) | **RR 1.02** (0.95 to 1.09) | 579 (5 RCTs) [e] | ⨁⨁◯◯ LOW [f,g] | |
| Clinical improvement D60 or more - not reported | - | - | - | - | - | outcome not yet measured or reported |
| WHO progression score (level 7 or above) D28 | 0 per 1,000 | **0 per 1,000** (0 to 0) | not estimable | 370 (3 RCTs) [h] | ⨁◯◯◯ VERY LOW [i,j] | zero events in both groups |
| WHO progression score (level 7 or above) D60 or more - not reported | - | - | - | - | - | outcome not yet measured or reported |
| All-cause mortality D28 | 9 per 1,000 | **3 per 1,000** (0 to 27) | **RR 0.33** (0.04 to 3.16) | 470 (4 RCTs) [k] | ⨁◯◯◯ VERY LOW [i,l] | |
| All-cause mortality D60 or more - not reported | - | - | - | - | - | outcome not yet measured or reported |
| Adverse events | 287 per 1,000 | **442 per 1,000** (250 to 789) | **RR 1.54** (0.87 to 2.75) | 578 (4 RCTs) [m] | ⨁◯◯◯ VERY LOW [n,o,p] | |
| Serious adverse events | 21 per 1,000 | **25 per 1,000** (10 to 62) | **RR 1.20** (0.48 to 3.00) | 538 (4 RCTs) [q] | ⨁◯◯◯ VERY LOW [l,n] | |

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio

# Remdesivir vs Standard Care for Mild/Moderate/Severe/Critical COVID-19:
## *Network meta-analysis from 5 randomized controlled trials*

| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | № of participants (studies) | Certainty of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Risk with Standard Care/Placebo | Risk with Remdesivir | | | | |
| Viral negative conversion D3 | 292 per 1,000 | **284 per 1,000** (178 to 450) | **RR 0.97** (0.61 to 1.54) | 196 (1 RCT) [b] | ⨁◯◯◯ VERY LOW [c,d,e] | |
| Viral negative conversion D7 | 492 per 1,000 | **502 per 1,000** (374 to 679) | **RR 1.02** (0.76 to 1.38) | 196 (1 RCT) [b] | ⨁◯◯◯ VERY LOW [c,d,f] | |
| Clinical improvement D7 | 345 per 1,000 | **366 per 1,000** (307 to 439) | **RR 1.06** (0.89 to 1.27) | 832 (2 RCTs) [g] | ⨁⨁⨁◯ MODERATE [f] | |
| Clinical improvement D14-D28 | 759 per 1,000 | **805 per 1,000** (751 to 858) | **RR 1.06** (0.99 to 1.13) | 832 (2 RCTs) [g] | ⨁⨁⨁◯ MODERATE [h] | |
| WHO progression score (level 6 or above) D7 | 451 per 1,000 | **419 per 1,000** (243 to 717) | **RR 0.93** (0.54 to 1.59) | 1298 (2 RCTs) [i] | ⨁⨁◯◯ LOW [f,j] | |
| WHO progression score (level 6 or above) D14-D28 | 193 per 1,000 | **131 per 1,000** (106 to 164) | **RR 0.68** (0.55 to 0.85) | 1894 (3 RCTs) [k] | ⨁⨁⨁◯ MODERATE [l] | |
| WHO progression score (level 7 or above) D7 | 359 per 1,000 | **251 per 1,000** (212 to 294) | **RR 0.70** (0.59 to 0.82) | 1298 (2 RCTs) [i] | ⨁⨁⨁◯ MODERATE [h] | |
| WHO progression score level 7 or above D14-28 | 178 per 1,000 | **124 per 1,000** (100 to 156) | **RR 0.70** (0.56 to 0.88) | 1894 (3 RCTs) [k] | ⨁⨁⨁⨁ HIGH | |
| All-cause mortality D7 | 63 per 1,000 | **43 per 1,000** (18 to 104) | **RR 0.68** (0.28 to 1.64) | 1298 (2 RCTs) [i] | ⨁◯◯◯ VERY LOW [e,m] | |
| All-cause mortality D14-D28 | 112 per 1,000 | **101 per 1,000** (82 to 125) | **RR 0.90** (0.73 to 1.11) | 7345 (4 RCTs) [n] | ⨁⨁⨁◯ MODERATE [f] | |
| Adverse events | 583 per 1,000 | **583 per 1,000** (507 to 671) | **RR 1.00** (0.87 to 1.15) | 1894 (3 RCTs) [k] | ⨁⨁⨁◯ MODERATE [l,o] | |
| Serious adverse events | 252 per 1,000 | **186 per 1,000** (156 to 221) | **RR 0.74** (0.62 to 0.88) | 1894 (3 RCTs) [k] | ⨁⨁⨁◯ MODERATE [o,p] | |

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio

https://covid-nma.com/living_data

# COLCHICINE – *OFF-LABEL USE FOR COVID-19*

# *Colchicine: Drug Profile and Authorization Status*

- Authorized by Health Canada for the treatment of acute gout, prophylaxis of recurrent gout attacks, and prevention of acute attacks of Familial Mediterranean Fever (FMF); its use is not authorized for any indication in patients under 16 years of age.
- Marketed as 0.6mg tablets from multiple suppliers (Generic).
- Common off-label uses: prevention of acute or recurrent pericarditis, treatment of Behçet's syndrome, prophylaxis/treatment of calcium pyrophosphate crystal deposition disease.
- Not approved for use in Canada for the prevention or treatment of COVID-19.
- A submission under the Interim Order pathway was received by Health Canada on January 25, 2021 for 0.5mg colchicine tablets (PendoPharm; PharmaScience) as a treatment for mild to moderate COVID-19 (ongoing review).

# *Colchicine: Top line clinical evidence*

COLCORONA Trial (preprint; *not peer reviewed*):

- Investigators issued a preprint of their multinational, contact-free, randomized double blind trial on January 27, 2021.
- Trial prematurely terminated; preprint analyzed clinical data from 4,488 adults aged 40 and older diagnosed with probable or confirmed COVID-19 within the 24 hours prior to enrolment, with at least one risk factor for COVID-19 complications.
- Risk factors included age (≥ 70 years), obesity (BMI ≥ 30), cardiovascular comorbidities, diabetes mellitus, uncontrolled hypertension, bicytopenia/pancytopenia, as well as COVID-19 symptoms (Fever ≥ 38.4 within past 48h and/or combination of high neutrophil count/ low lymphocyte count and/or dyspnea).
- Colchicine 0.5mg twice a day for three days then once a day for 27 days (tablets; PharmaScience, Quebec; n=2,235); or placebo (n=2,253), initiated within 48h of positive COVID-19 test results/diagnosis.

https://www.medrxiv.org/content/10.1101/2021.01.26.21250494v1

# *Colchicine: Top line clinical evidence*

COLCORONA Trial (preprint; *not peer reviewed*):

- Trial failed to meet its primary composite endpoint of reduction of hospitalizations or mortality at 30 days (4.7% for colchicine vs. 5.8% for placebo).
- No significant differences between the two groups for incidence of death or hospitalization nor for mechanical ventilation, which was assessed as a secondary outcome
- In a subgroup analysis on PCR-confirmed patients (n=4159): Reduced incidence of hospitalizations or mortality at 30 days COVID-19, (4.6% colchicine [n=2075] vs. 6.0% placebo [n=2084]; OR 0.75; 95% CI 0.57 to 0.99).
- Within this subgroup, the odds ratio for reduction in hospitalizations was OR 0.75; (95% CI, 0.57 to 0.99), but no difference was observed for death alone (0.56; 95% CI, 0.19 to 1.66) or mechanical ventilation (0.50; 95% CI, 0.23 to 1.07).
- Serious AEs were reported in 4.9% of participants in the colchicine group [n=2,195] vs. 6.3% in the placebo group [n=2,217] groups (p=0.05), including pneumonia 2.9% vs. 4.1% (p=0.02), pulmonary embolism 0.5% vs. 0.1% (p=0.01), and diarrhea 13.7% vs. 7.3% (p<0.0001), respectively.

https://www.medrxiv.org/content/10.1101/2021.01.26.21250494v1

# *Colchicine: Top line clinical evidence*

RECOVERY trial (press release; *not peer reviewed*):

- UK-based open label randomized trial in hospitalized patients with COVID-19
- Independent Data Monitoring Committee decision issued on March 4th to close colchicine treatment arm due to futility
- Preliminary analysis based on 2178 reported deaths among 11,162 randomised patients (94% also treated with a corticosteroid)
- No significant difference in the primary endpoint of 28-day mortality
  - 20% colchicine vs. 19% usual care alone; (p=0.63)
- Follow-up of patients is ongoing; publication of final analysis anticipated soon.
- https://www.recoverytrial.net/news/recovery-trial-closes-recruitment-to-colchicine-treatment-for-patients-hospitalised-with-covid-19
- Mixed evidence of clinical benefit from numerous smaller underpowered trials in hospitalized patients with COVID-19

# Colchicine for COVID-19: *EXPERT OPINIONS*

***Ad hoc* Clinical Pharmacology Task Group (CPTG):** *February 10, 2021 Recommendation*

The Clinical Pharmacology Task Group recommends that use of colchicine (0.6mg) as a treatment for non-hospitalized patients with COVID-19 – which is off-label - be limited to randomized controlled trials. Additional clinical evidence is required to determine whether potential benefits of colchicine (0.6mg) outweigh known and potential risks. This guidance/recommendation will be updated as peer-reviewed evidence emerges, specifically from adequately powered clinical trials that can provide additional evidence of risks and benefits in specific patient subgroups (comorbidities, elderly/pediatric populations, ethnicity, or sex).

https://www.canada.ca/en/public-health/corporate/mandate/about-agency/external-advisory-bodies/list/covid-19-clinical-pharmacology-task-group/statement-colchicine.html

# COVID-19 treatment guidelines for colchicine across provinces and territories

- BC COVID-19 Therapeutics Committee: The CTC does not recommend the routine use of colchicine at this time. In patients aged 40 years or older with PCR-confirmed COVID-19 who have at least one risk factor (as per COLCORONA trial) and no contraindications [specified in guidance], colchicine 0.6 mg PO BID x 3 days, then 0.6 mg daily x 27 days may be considered on a case-by-case basis in discussion with the patient by clearly highlighting the uncertainty in the benefit of treatment, and the risks and potential adverse effects. Informed consent should be obtained and treatment initiated as soon as possible. Colchicine for the treatment of severe to critically ill patients with COVID-19 is not recommended outside of approved clinical trials.

- Alberta Health Services COVID-19 Scientific Advisory Group: At this time, colchicine should not be prescribed or taken to treat COVID-19. Clinicians and researchers in Alberta should support high quality clinical trials in Alberta or in the context of a well designed multicentre study to help find out if colchicine has a benefit in treating COVID-19.

- INESSS: The current state of scientific knowledge and the uncertainty about potential benefits and risks of taking colchicine in people out of hospital with a diagnosis of COVID-19 confirmed or not by an RT-PCR test, and which meet the criteria of selection of the COLCORONA study (over 40 years with at least one risk factor), do not support the use of colchicine for this population outside of a research protocol. SARS-CoV-2 confirmed, inpatient treatment.

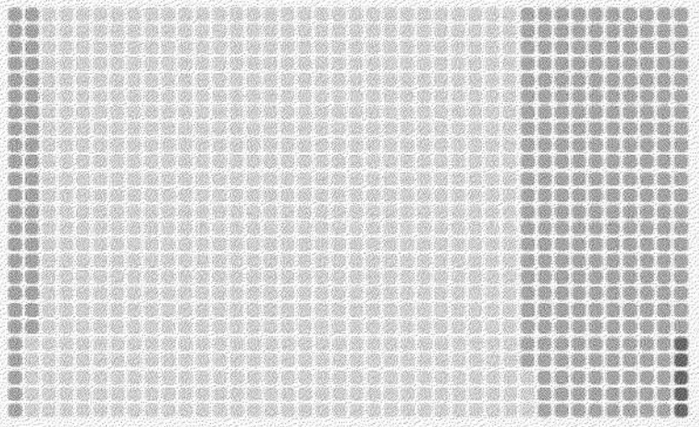
## VISUAL REPRESENTATION OF THE POTENTIAL IMPACT OF THE TREATMENT

The figure below shows the potential impact of colchicine on hospitalizations and adverse events in RT-PCR-positive individuals who meet the study criteria.

⚠The causes that led to the hospitalizations, the actual length of hospital stay beyond the predefined 24 hours, and the need for a transfer to intensive care are not reported in the preprint.

### 30-day treatment with colchicine

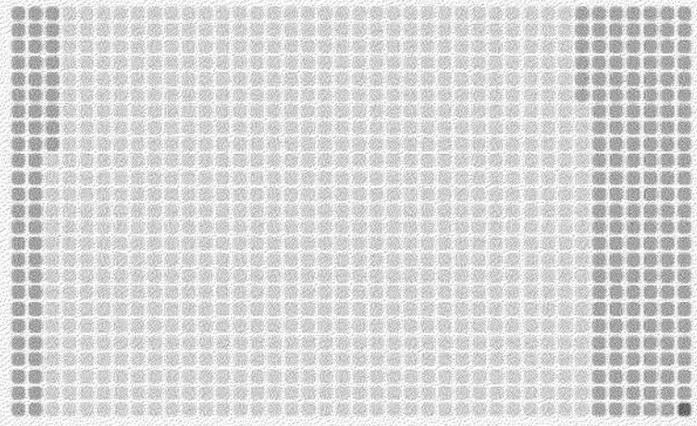
**Of 1,000 individuals** who tested positive for COVID-19 on RT-PCR
Not hospitalized | 40 years or older | ≥ 1 Risk factor



- **45** would be hospitalized for COVID-19 disease
- **242** would experience adverse events (mainly gastrointestinal)
- **5** would experience a pulmonary embolism

### 30-day treatment with placebo

**Of 1,000 individuals** who tested positive for COVID-19 on RT-PCR
Not hospitalized | 40 years or older | ≥ 1 Risk factor



- **59** would be hospitalized for COVID-19 disease
- **155** would experience adverse events (mainly gastrointestinal)
- **1** would experience a pulmonary embolism



https://www.inesss.qc.ca/fileadmin/doc/INESSS/COVID-19/INESSS_COVID-19_Colcorona_date_analysis_tool.pdf

# LERONLIMAB – *INVESTIGATIONAL DRUG FOR PATIENTS WITH CRITICAL COVID-19*

# *Leronlimab: Drug Profile*

- Anti-CCR5 (C-C chemokine receptor type 5) humanized monoclonal antibody; blocks CCR5 co-receptor found on T cell and other immune cells.

- CCR5 activation via immunostimulatory ligands (CCL5 (RANTES), CCL3 (MIP-1α), and CCL4 (MIP-1β)) leads to immune cell infiltration.

- Hyperinflammatory state characterized by severe/critical COVID-19 may be in part due to increased immune cell infiltration.

# *Leronlimab: Authorization status*

- Not approved for use in Canada for any indication.

- A submission under the Interim Order pathway was received by Health Canada on March 23, 2021 for leronlimab (CytoDyn, Inc.; Amarex) as a treatment for mild to moderate COVID-19 (ongoing review).

- The US FDA granted **CytoDyn Inc.** Emergency Investigational New Drug (EIND) status for leronlimab for COVID-19.

# *Leronlimab: Top line clinical evidence*

- One press release on a pharma-sponsored phase IIb/III, two-arm, randomized, double blind, placebo-controlled, multi-centre study in hospitalized adult patients with severe or critical COVID-19.
- Patients were randomized to receive either weekly doses of 700 mg leronlimab or placebo, subcutaneously.
- The primary end point is all-cause mortality at 28 days.
- Results based on 309 patients in the modified intention-to-treat population reported in a press release on March 30, 2021 indicated a 6.5% absolute risk reduction in death at day 28 for patients administered leronlimab compared to placebo, in addition to other COVID-19 treatments (P = 0.0319).
- No peer reviewed studies/preprints on randomized controlled studies demonstrating clinical efficacy/safety as a treatment for COVID-19.

# Contacts at the Public Health Agency of Canada

COVID-19 Therapeutics | thérapeutiques

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# *Immunomodulatory Drugs*

## Anakinra (IL-1 antagonist; Orphan Biovitrum)

- NCT04443881 Fundacion Miguel Serviet sponsored, Multi-Centre, Phase 2/3, Open label study investigating anakinra in **severe hospitalized patients.** Allocation concealment not specified. Estimated enrollment of 180 with 90 participants to be randomized to the treatment arm. No Canadian sites. **Study end date: March 2021.**
- NCT04330638 University of Ghent sponsored, Multi-Centre, Phase 3, Open label study investigating anakinra in **hospitalized patients in ICU COVID-19 ward.** Allocation concealment not specified. Estimated enrollment of 342 (multiple treatment arms, with 60 participants to be randomized to receive anakinra). No Canadian sites. **Study end date: April 12 2021.**
- NCT04412291 Karolinska University sponsored, Single Centre, Phase 2, Open label study investigating in **severe hospitalized patients.** Allocation concealment not specified. Estimated enrollment of 120 (multiple treatment arms, estimated 40 participants to be randomized to anakinra). No Canadian sites. **Study end date: June 2021.**
- NCT04680949 Hellenic Institute sponsored, Multi-Centre, Phase 3, quadruple blind study investigating anakinra in **hospitalized patients with LRI.** Allocation concealment not specified. Estimated enrollment of 600 with 300 participants for the treatment arm. No Canadian sites. **Primary end date: March 31, 2021.**

## Baricitinib (Olumiant, JAK1/2 Inhibitor; Eli Lilly)

- NCT04390464 Cambridge University sponsored, Single centre, Phase 4, Open-label study evaluating baricitinib+SOC, ravulizumab+SOC to SOC alone in **severe hospitalized patients.** Allocation concealment not specified. Estimated enrollment of 1167 with 389 participants randomized to baricitinib +SOC treatment arm. No Canadian sites. **Primary End date: May 7, 2021.**
- NCT04421027 Eli Lilly sponsored, Single centre, Phase 3, Double-blinded study evaluating baricitinib compared to placebo in **moderate-severe hospitalized patients requiring oxygen .** Allocation concealment not specified. Estimated enrollment of 1400, with 700 participants for baricitinib treatment arm. No Canadian sites. **Primary end date: May 19, 2021.**
- NCT04381936 University of Oxford sponsored, Multi-Centre, Phase 3, Open-label study evaluating baricitinib in **hospitalized patients.** Allocation concealment not specified. Estimated enrollment of 40,000 with 2500 patient planned enrollment for the baricitinib treatment arm. No Canadian sites. **Estimated primary end date: August 18, 2021.** ***RECOVERY TRIAL.***

## Colchicine

- NCT04328480 Estudios Clínicos Latino América sponsored, Single Centre, Phase 3, Open-Label study evaluating colchicine to SOC treatment in **moderate/severe hospitalized patients.** Allocation concealment not specified. Estimated enrollment of 1200, with 600 participants randomized to colchicine treatment arm. No Canadian sites. **Study End date: March 30, 2021.**
- NCT04359095 University of Columbia sponsored, multi-centre, Phase 2/3, Open-Label study evaluating colchicine+rosuvatanine, emtricitabine+tenofovir, Emtricitabine+tenofobir +colchicine+rosuvastatin treatment to SOC in **mild/moderate/severe/critical hospitalized patients.** Allocation concealment not specified. Estimated enrollment of 1200, with 300 participants randomized to each treatment arm. No Canadian sites. **Study end date: May 21, 2021.**
- NCT04818489 ClinAmygate sponsored, single-centre, Phase 4, single-blind study evaluating colchicine treatment to SOC in the clinical outcome of COVID-19 and post-COVID-19 pulmonary fibrosis in adults with COVID-19. Allocation concealment not specified. Estimated enrollment of 250, with 125 participants randomized to each treatment arm. No Canadian sites. **Primary end date: May 25, 2021**.
- NCT04375202 University of Perugia sponsored, multi-centre, Phase 2, Open-Label study evaluating colchicine treatment to SOC in **critical hospitalized patients.** Allocation concealment not specified. Estimated enrollment of 308, with 154 participants randomized to colchicine treatment arm. No Canadian sites. **Primary end date: June 30, 2021.**

# *Immunomodulatory Drugs*

## Tocilizumab (Hoffman La Roche, Sanofi, anti-IL-6 receptor monoclonal antibody)

- NCT04479358 University of Chicago sponsored, Single Centre, Phase 2, Open-Label study evaluating the efficacy of tocilizumab vs SOC in **hospitalized patients.** Allocation concealment not specified. Estimated enrollment of 332 with 166 participants randomized to four tocilizumab treatment arms. No Canadian sites. **Study end date: March 21, 2021.**
- NCT04330638 University Hospital, Ghent sponsored, Multi-Centre, Phase 3, Open-Label study evaluating the efficacy of tocilizumab, tocilizumab+anakinra, anakinra, siltuximab, anakinra+siltuximab to usual care on blood oxygenation and systemic cytokine release syndrome in **severe/critical hospitalized patients.** Allocation concealment not specified. Estimated enrollment of 342, with 57 participants randomized to tocilizumab treatment arm. No Canadian sites. **Study end date: April 12, 2021.**
- NCT04331808 Assistance Publique - Hôpitaux de Paris sponsored, Multi-Centre, Phase 2, Open-Label study evaluating the efficacy of tocilizumab to SOC in **moderate/severe/critical hospitalized patients.** Allocation concealment not specified. Estimated enrollment of 228, with 114 participants randomized to tocilizumab treatment arm. No Canadian sites. **Primary end date: March 31, 2021.**
- NCT04377750 Hadassah Medical Organization sponsored, Multi-Centre, Phase 4, Open-Label study evaluating the efficacy of tocilizumab to placebo in **severe hospitalized patients.** Allocation concealment not specified. Estimated enrollment of 500, with 333 participants randomized to tocilizumab treatment arm. No Canadian sites. **End date: May 8, 2021.**
- NCT04412291 Karolinska University sponsored, Single Centre, Phase 2, Open label study investigating in **severe hospitalized patients.** Allocation concealment not specified. Estimated enrollment of 120 (multiple treatment arms, estimated 40 participants to be randomized to tocilizumab). No Canadian sites. **Study end date: June 2021.**

## Otililimab (GSK, anti-GM-CSF antibody)

- NCT04376684 GSK sponsored, Multi-Centre, Phase 2, Double-blinded study investigating the efficacy of otilimab+SOC to placebo+SOC in **severe hospitalized patients requiring oxygen or mechanical ventilation.** Allocation concealment not specified. Estimated enrollment of 1150, with 575 participants randomized between two otilimab treatment arms. Canadian sites. **Study end date: August 23, 2021.**

## Sarilumab (Hoffman La Roche, Sanofi, anti-IL-6 receptor monoclonal antibody)

- NCT04324073 Assistance Publique - Hôpitaux de Paris sponsored, Multi-Centre, Phase 2/3, Open-Label study evaluating the efficacy of sarilumab to SOC in **moderate/severe/critical hospitalized patients.** Allocation concealment not specified. Estimated enrollment of 239, with 119 participants randomized to sarilumab treatment. No Canadian sites. **Primary end date: March 27, 2021.**

## Leronlimab (CytoDyn, CCR5 antagonist monoclonal antibody)

- NCT04347239 CytoDyn sponsored, Multi-Centre, Phase 2b/3, quadruple-blind study evaluating the efficacy of leronlimab in hospitalized patients with severe or critical COVID-19. Allocation concealment not specified. Estimated enrollment of 394, with 197 participants randomized to leronlimab treatment. No Canadian sites. **Primary end date: June 15, 2021**

# *SARS-CoV-2 Antivirals*



## Remdesivir (Veklury, RNA-Dependent RNA polymerase inhibitor (induces delayed chain termination); Gilead)

- NCT04501952 Gilead Sciences sponsored, Multi-Centre, Phase 3, Double-blinded study evaluating the efficacy of remdesivir to placebo in reducing hospitalizations in **adult and pediatric outpatients.** Allocation concealment not specified. Estimated enrollment of 585, with 292 participants randomized to remdesivir treatment arm. No Canadian sites. **Study end date: May 2021**.

## Molnupiravir (RNA-Dependent RNA polymerase inhibitor (induces mutagenesis); Merck)

- NCT04575597 Merck sponsored, Multi-Centre, Phase 2/3, Double-blinded study evaluating the combination of molnupiravir to placebo **in symptomatic outpatients**. Allocation concealment not specified. Estimated enrollment of 1450, with 240 participants randomized to each molnupiravir treatment arm (3 doses). Canadian sites. **Primary end date: June 23 2021**

# Other Therapeutics

## Ivermectin

- NCT04529525 Instituto de Cardiología de Corrientes sponsored, Single Centre, Phase 2/3, Quadruple-blinded study evaluating ivermectin treatment to placebo in preventing hospitalizations in **outpatients.** Allocation concealment not specified. Estimated enrollment of 500, with 250 participants randomized to treatment arm. No Canadian sites. **Study end date: March 15, 2021.**
- NCT04712279 Corpometria Institute sponsored, single-centre, Phase 2/3, triple blind study evaluating ivermectin+hydroxychloquine treatment to placebo+hydroxychloroquine in preventing hospitalizations in **outpatients.** Allocation concealment not specified. Estimated enrollment of 294 with 98 participants randomized to each treatment arm (two ivermectin dosages). No Canadian sites. **Study end date: April 20, 2021.**
- NCT04834115 Universidad Nacional de Asunción sponsored, single-centre, Phase 3, triple blind study evaluating ivermectin treatment to placebo in preventing hospitalizations in **symptomatic or asymptomatic outpatients.** Allocation concealment not specified. Estimated enrollment of 400 with 200 participants randomized to treatment. No Canadian sites. **Study end date: May 30, 2021.**
- NCT04530474 Temple University sponsored, single-centre, Phase 3, triple blind study evaluating ivermectin treatment to placebo in preventing hospitalizations in **symptomatic outpatients.** Allocation concealment not specified. Estimated enrollment of 200, with 100 participants randomized to ivermectin treatment arm. No Canadian sites. **Primary end date: June 30, 2021.**

## Fluvoxamine

- NCT04668950 Washington University sponsored, multi centre , Phase 3, triple blind study evaluating the efficacy of fluvoxamine treatment to placebo in **symptomatic outpatients.** Allocation concealment not specified. Estimated enrollment of 1100, with 550 participants randomized to treatment arm. Canadian sites. **Primary end date: July 2021.**
- NCT04718480 SigmaDrugs Research sponsored, multi centre , Phase 2, double blind study evaluating the efficacy of fluvoxamine treatment to placebo in **moderate hospitalized patients.** Allocation concealment not specified. Estimated enrollment of 100, with 50 participants randomized to treatment arm. No Canadian sites. **Primary end date: August 2021.**

## Aspirin (acetylsalicylic acid NSAID, antiplatelet; Generic)

- NCT04381936 University of Oxford sponsored, Multi-Centre, Phase 3, Open-label study evaluating the efficacy of aspirin in **hospitalized patients.** Allocation concealment not specified. Estimated enrollment of 40,000 with 9800 patient planned enrollment for the aspirin treatment arm. No Canadian sites. **Estimated primary end date: May 2021. RECOVERY TRIAL**
- NCT04324463 Population Health Research Institute sponsored, Multi-Centre, Phase 3, Open-Label study evaluating the efficacy of aspirin in **symptomatic outpatients and hospitalized patients.** Allocation concealment not specified. Estimated enrollment of 4000 with 1000 participants to be randomized to aspirin. Canadian sites. **Primary end date: June 30, 2021.**
- NCT04808895 Azienda Ospedaliera Universitaria Integrata Verona sponsored, Phase 3, double-blind study evaluating the efficacy of aspirin compared to placebo in **hospitalized patients with moderate disease.** Allocation concealment not specified. Estimated enrollment of 204 with 102 participants to be randomized to aspirin. Not yet recruiting. No Canadian sites. **Primary end date: July 1, 2021.**
- NCT04498273 National Lung and Blood Institute sponsored, Multi-Centre, Phase 3, Quadruple-blinded study evaluating the efficacy of aspirin in **outpatients.** Allocation concealment not specified. Estimated enrollment of 7000 with 1750 participants for treatment arm. No Canadian sites. **Primary end date: September 2021.**

Correspondence on Colchicine and Ivermectin and Vitamin D

Dea [redacted]

I am writing in response to your correspondence of April 21, 2021, addressed to Dr. Tam, alerting us to the use of ivermectin, vitamin D, and colchicine, to support Canada's response to COVID-19. The honourable Minister of Health, Patty Hajdu, has asked that I reply on her behalf. I sincerely regret the delay in responding.

The Public Health Agency of Canada (PHAC) conducts a thorough analysis of the emerging evidence regarding promising therapeutics to treat COVID-19. This work informs decisions around procurement of therapeutics proven to be safe and effective for COVID-19.

Before drug products are authorized for sale in Canada, Health Canada reviews them to assess their safety, efficacy and quality. Prior to being given market authorization, a manufacturer must present substantive scientific evidence of a product's safety, efficacy and quality as required by the Food and Drugs Act and Regulations.

**Commented [JA1]:** Health Canada should review.

The provinces and territories, rather than the Government of Canada, are primarily responsible for the administration and delivery of healthcare services. A health care provider may – at their discretion - use a medication for other conditions ("off-label") as part of the practice of medicine. For any therapeutic, the decision to use it must balance expected benefit against potential harms.

Currently there is no clear evidence from any clinical trial to suggest that vitamin D supplementation has any clinical benefit for the treatment or prevention of COVID-19. Although some studies observed an association between vitamin D deficiency and higher COVID-19 incidence, this does not establish causation that vitamin D supplements could treat or prevent COVID-19.

Ivermectin is a broad-spectrum anti-parasitic agent authorized and approved by Health Canada for human and veterinary applications to treat parasitic infections, Health Canada has not authorized its use for the treatment of COVID-19.

Ivermectin has been shown in laboratory studies to prevent the replication of SARS-CoV2; however, many drugs that show promise in laboratory studies are not found to be effective in patients. Given the interest in ivermectin as a potential treatment for COVID-19, the World Health Organization (WHO) convened an independent, international panel of clinical care experts from multiple specialties, patient partners and ethicists to review the evidence. On March 31, 2021, the WHO issued a statement on ivermectin advising against its use outside of clinical trials, stating the current evidence was inconclusive: https://www.who.int/news-room/feature-stories/detail/who-advises-that-ivermectin-only-be-used-to-treat-covid-19-within-clinical-trials.

The manufacturer, Merck, also issued a statement against the use of ivermectin for the treatment of COVID-19: https://www.merck.com/news/merck-statement-on-ivermectin-use-during-the-covid-19-pandemic/

Colchicine is an anti-inflammatory drug authorized by Health Canada for the treatment of gout, and other inflammatory diseases, raising interest in its potential to prevent the "cytokine storm" characteristic of severe COVID-19. Independent reviews of available clinical trial results that

evaluate the effectiveness of colchicine as a treatment for COVID-19 were conducted by PHAC, the Canadian Agency for Drugs and Technologies in Health (CADTH), l'Institut national d'excellence en santé et services sociaux (INESS) and Alberta Health Services, all of whom concluded that there was no clear benefit to colchicine treatment and some concerning harms (e.g. blood clots in the lungs, a potentially fatal complication). At this time, Canadian expert groups do not recommend prescribing colchicine to treat COVID-19.

In summary there is currently no robust evidence at this time to suggest that ivermectin, colchicine, or vitamin D supplementation provides clinical benefit for the treatment or prevention of COVID-19, particularly in the Canadian context. Please be assured that PHAC is actively monitoring emerging evidence of clinical efficacy and safety on novel and repurposed therapeutics for COVID-19; and makes recommendations based on findings from high quality evidence on an ongoing basis.

## Manuel, Suzzanne (PHAC/ASPC)

**From:** Cassidy, Vicki-Lynn (PHAC/ASPC) on behalf of Chief Public Health Officer / La chef de la santé publique (PHAC/ASPC)
**Sent:** 2021-04-21 12:31 PM
**To:** Executive Correspondence (PHAC/ASPC)
**Cc:** McLeod, Robyn (PHAC/ASPC)
**Subject:** 21-108019-10 FW: Ivermectin

Good afternoon Exec Correspondence,

Please see the below questions for a direct reply.

-----Original Message-----
From: [redacted]
Sent: 2021-04-21 12:14 PM
To: Chief Public Health Officer / La chef de la santé publique (PHAC/ASPC) <phac.cpho-acsp.aspc@canada.ca>
Subject: Ivermectin

Dear Dr. Tam,
First, thank you for your service during this trying time of Covid. During this time I have been doing a lot of research on Covid and on many treatments. [redacted] I am distressed that three things that dramatically impact Covid are being ignored, Ivermectin, Vitamin D(with adequate dosing) and Colchicine. WHY are these are not being allowed! Please do not write back and say that there is not enough evidence as that is simply not true! These are medications that have been studied and used for a very long time. People are losing their lives, livelihoods are being destroyed, families are being stressed beyond their ability to cope and here we sit ignoring treatments that would dramatically impact all of these. These kinds of treatments along with the vaccines are needed. It is not enough to simply mask and distance . It is beyond time for the powers that be to open up their minds and stop ignoring the evidence!
Thank you for your time.
Sincerely, [redacted]

Sent from my iPad

[redacted]

Dear [redacted]

I am writing in response to your correspondence of April 21, 2021, addressed to Dr. Tam, alerting us to the use of Ivermectin, vitamin D, and Colchicine, to support Canada's response to COVID-19. The honourable Minister of Health, Patty Hajdu, has asked that I reply on her behalf. I sincerely regret the delay in responding.

The Government of Canada is closely tracking all potential therapeutic treatments, vaccines, diagnostic tests, medical devices, and disinfectants currently available and in development in Canada and abroad. We are aware of the many health benefits of Vitamin D and the rapidly evolving science examining its potential effect to reduce the risk, severity or duration of COVID-19 infections in various populations.

Evidence from well designed studies is needed to determine whether vitamin D might be helpful in preventing or treating COVID-19. In this context, we are very attentive to the progress of various clinical trials on the potential effect of vitamin D on COVID-19 outcomes conducted in Canada and abroad. The Public Health Agency of Canada has recently conducted a current state of evidence that can be found in the attachment entitled "Evidence Brief of vitamin D and zinc supplementation for therapeutic use on COVID-19 cases".

As of now, there is no definitive evidence to determine that vitamin D supplementation would help to enhance resistance or prevent COVID-19 infection in the Canadian context, but as we get more information, our understanding on this may change.

I hope that this information is helpful, and I thank you for writing to share your views on vitamin D, Colchicine and Ivermectin.

Sincerely,

SIGNATURE
Dr. Pascal Michel
Chief Science Officer
Public Health Agency of Canada

Attachment –
Evidence Brief of vitamin D and zinc supplementation for therapeutic use on COVID-19 cases

Correspondence on Colchicine and Ivermectin and Vitamin D

Dear [redacted]

I am writing in response to your correspondence of April 21, 2021, addressed to Dr. Tam, alerting us to the use of Ivermectin, vitamin D, and Colchicine, to support Canada's response to COVID-19. The honourable Minister of Health, Patty Hajdu, has asked that I reply on her behalf. I sincerely regret the delay in responding.

The Public Health Agency of Canada (PHAC) conducts a thorough analysis and synthesis of the emerging evidence regarding promising therapeutics to treat COVID-19. This work informs decisions around procurement of therapeutics proven to be safe and effective for COVID-19 indication by Health Canada.

Therapeutics that are authorized by Health Canada (marketed for a particular use/condition) have been proven safe and effective for a given indication on the basis of high quality evidence from well-designed clinical trials. The provinces and territories, rather than the Government of Canada, are primarily responsible for the administration and delivery of healthcare services. A health care provider may – at their discretion - use a medication for other conditions ("off-label") as part of the practice of medicine. For any therapeutic, the decision to use it must balance expected benefit against potential harms.

Currently there is no clear evidence from any clinical trial to suggest that Vitamin D supplementation has any clinical benefit for the treatment or prevention of COVID-19. Although some studies observed an association between vitamin D deficiency and higher COVID-19 incidence, this does not establish a causal that vitamin D supplements could treat or prevent COVID-19.

Ivermectin is a broad-spectrum anti-parasitic agent authorized and approved by Health Canada for human and veterinary applications to treat parasitic infections, Health Canada has not authorized its use for the treatment of COVID-19.

Ivermectin has been shown in laboratory studies to prevent the replication of SARS-CoV2;;; however, many drugs that show promise in laboratory studies are not found to be effective in patients. Given the interest in ivermectin as a potential treatment for COVID-19, the World Health Organization (WHO) convened an independent, international panel of clinical care experts from multiple specialties, patient partners and ethicists to review the evidence. On March 31st 2021, the WHO issued a statement on ivermectin advising against its use outside of clinical trials, stating the current evidence was inconclusive. The manufacturer also issued the following statement against the use of ivermectin for the treatment of COVID-19:

https://www.merck.com/news/merck-statement-on-ivermectin-use-during-the-covid-19-pandemic/

Colchicine is an anti-inflammatory drug authorized by Health Canada for the treatment of gout, and other inflammatory diseases, raising interest in its potential to prevent the "cytokine storm" characteristic of severe COVID-19. Independent reviews of available clinical trial results that evaluate the effectiveness of colchicine as a treatment for COVID-19 were conducted by PHAC, the Canadian Agency for Drugs and Technologies in Health (CADTH), l'Institut national

d'excellence en santé et services sociaux (INESS) and Alberta Health Services, all of whom concluded that there was no clear benefit to colchicine treatment and some concerning harms (e.g. blood clots in the lungs, a potentially fatal complication). There are a number of ongoing clinical trials of colchicine; as results become available [redacted] At this time, Canadian expert groups do not recommend prescribing colchicine to treat COVID-19.

Commented [MG1] [redacted]

In summary there is currently no clear evidence to suggest that any of ivermectin, colchicine, or Vitamin D supplementation provides clinical benefit for the treatment or prevention of COVID-19, particularly in the Canadian context. Please be assured that PHAC is actively monitoring emerging evidence of clinical efficacy and safety on novel and repurposed therapeutics for COVID-19, including ivermectin, colchicine, and vitamin D; and makes recommendation based on findings from emerging high quality evidence on an ongoing basis.

You may find additional information at the following links:

[redacted]

Commented [CM2] [redacted]

Correspondence on Colchicine and Ivermectin and Vitamin D

Publication of a study's findings does not necessarily indicate that the studied treatment is effective, nor that the study's conclusions are valid. The certainty (or quality) of the evidence refers to how confident we can be that the research provides an accurate picture of the effect of a particular treatment and can be trusted to inform decision-making about theorizationon, procurement and recommendations for use to treat Canadian patients with COVID-19. The Public Health Agency of Canada (PHAC) conducts a thorough analysis and synthesis of the emerging evidence of promising therapeutics to treat COVID-19. This work informs decisions around procurement of therapeutics that have been proven safe and effective, and authorized for COVID-19 indication by Health Canada.

Commented [MG1]: Not sure if this stays true to the meaning, but trying to simplify

Commented [MG2]: Add in text around PHAC work, i.e., analysis and synthesis of the emerging evidence of promising therapeutics to treat COVID-19. This work informs decisions around procurement of therapeutics that have been proven safe and effective.

Although many studies have been conducted on vitamin D, ivermectin and colchicine for the treatment of COVID-19, the certainty of the evidence has ranged from inconclusive to poor due to flaws in the methods (such as the wrong study design, small sample size, no plan to limit confounding and bias, and insufficient follow-up). Consequently, additional studies, which are larger are providing more data with better methods and designs, are required to ensure confidence in the usefulness of the evidence regarding the use of vitamin D, ivermectin and colchicine as treatments for COVID-19.

Ivermectin is a broad-spectrum anti-parasitic agent authorized and approved by Health Canada for human and veterinary applications. Although ivermectin is used in humans to treat parasitic infections such as intestinal strongyloidiasis, onchocerciasis, scabies and possible use to treat rosacea. Health Canada has **not** authorized its use for the treatment of COVID-19. The first of many steps in the authorization process includes the provision of promising results documented and obtained from high quality study designs followed by submission of an application by the manufacturer to Health Canada, which follows a well-defined channel to qualify for approval for a particular indication.

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In laboratory studies ivermectin has been shown to inhibit the virus causing COVID-19 from replicating raising the possibility that ivermectin may have a role in COVID-19 prophylaxis or treatment; however, many drugs that show promise in laboratory studies are not found to be effective in patients. To address the increased international attention on ivermectin as a potential treatment for COVID-19, the World Health Organization (WHO) convened an independent, international panel of clinical care experts from multiple specialties, patient partners and ethicists. Following a review of the existing data reviewing both inpatient and outpatient trial results, the panel concluded that the existing evidence regarding ivermectin's effectiveness in reducing mortality, need for mechanical ventilation, need for hospital admission and time to clinical improvement was of very low certainty. Consequently, on March 31st 2021, The WHOorld Health Organization issued a statement on ivermectin advising against its use outside of clinical trials, stating the current evidence was inconclusive.

Prior to the statement issued by the WHO, Merck and Co. Inc., the manufacturer of ivermectin, issued a statement February 4th, 2021 against the use of this drug for the purposes of treating COVID-19. The announcement ensued its own analysis of the preclinical and clinical trials indicating that the data did not support the efficacy of this drug to treat COVID-19. Furthermore, Merck stated concerns over the lack of safety data in studies evaluating ivermectin use in patients with COVID-19 and has not applied to Health Canada for authorization of this drug to treat COVID-19.

Colchicine is an anti-inflammatory drug authorized by Health Canada for the treatment of gout, and other inflammatory diseases, for short courses of treatment and is used off-label for the prevention of acute or recurrent pericarditis, and other conditions at the discretion of the primary heath care provider. Use of this drug for therapeutic purposes is limited by side effects such as fatigue, nausea, vomiting, and diarrhea. Interest in this drug, which has been marketed in Canada for at least 40 years with known side effects, is derived from its anti-inflammatory activity and potential use to prevent the "cytokine storm" characteristic of severe COVID-19. A review of available clinical trial results, evaluating the effectiveness of colchicine as a treatment for COVID-19 was independently conducted by various Canadian expert groups (PHAC, the Canadian Agency for Drugs and Technologies in Health, l'Institut national d'excellence en santé et services sociaux and Alberta Health Services). All of whom concluded that the available studies were of low quality. The only exception was the trial conducted by a Canadian research team at the Montreal Heart Institute, which was of moderate quality; however all the studies evaluated had several weaknesses limiting the certainty placed on the results. Canadian expert groups therefore concluded that there was no clear benefit to colchicine treatment and some concerning harms (e.g. a small number of patients colchicine treatment led to the development of blood clots in the lungs, a serious complication that could lead to death). There are a number of ongoing clinical trials of colchicine, as these results become available, they will be evaluated to assess if there is a benefit to treating COVID-19 patients with this re-purposed drug. At this time, Canadian expert groups do not recommend prescribing colchicine to treat COVID-19.

In summary, to date, there is no definitive evidence to suggest that either ivermectin, colchicine, or Vitamin D supplementation has potential clinical benefit for the treatment or prevention of COVID-19, particularly in the Canadian context. Health Canada, the regulator in Canada, will review clinical data once submitted from the manufacturer and determine the benefits and risks of potential therapeutics and provide regulatory approval for COVID-19 accordingly. PHAC is actively monitoring emerging evidence of clinical efficacy and safety on novel and repurposed therapeutics for COVID-19, including ivermectin, cholchicine, and vitamin D; and makes recommendation based on findings from emerging high quality evidence on an ongoing basis.

(We could add the links to the CADTH, INESS and Alberta Health Services here, thoughts?)

For more information, the following link provides a statement from Merck and Co. Inc. issuing a statement against the use of ivermectin for the treatment of COVID-19:

https://www.merck.com/news/merck-statement-on-ivermectin-use-during-the-covid-19-pandemic/

For more information, the following link provides the World Health Organization's guidance on the use to ivermectin to treat COVID-19:

https://www.who.int/news-room/feature-stories/detail/who-advises-that-ivermectin-only-be-used-to-treat-covid-19-within-clinical-trials

Ivermectin

- Most randomized, placebo-controlled clinical trials for ivermectin are evaluating its efficacy in non-hospitalized patients with COVID-19.
- Clinical evidence in patients with mild COVID-19: hospitalized and non-hospitalized patients with mild COVID-19, showed that a 5-day course of ivermectin vs placebo initiated in the first 7 days after evidence of infection did not significantly improve the time to resolution of symptom.
- In its recent iteration Drug treatments for COVID-19: living systematic review and network meta-analysis found that pooled results for ivermectin suggests a possible reduction in mortality but the data are limited by serious risk of bias.

Regulatory authorities:

- WHO advises that ivermectin only be used to treat COVID-19 within clinical trials.
- NIH states there is insufficient data to recommend for or against the use of ivermectin for the treatment of COVID-19.

Field Code Changed

Colchcine

- On-going randomized, placebo-controlled clinical trials for colchicine are evaluating its efficacy in hospitalized and non-hospitalized patients with COVID-19.
- Clinical evidence in hospitalized patients with COVID-19: RECOVERY trial stopped enrolling patients to the trial's colchicine treatment arm as preliminary analysis found that treatment was not associated with a reduction in death. Results not published.
- Clinical evidence in outpatients with COVID-19: COLCORONA trial found that colchicine treatment modestly reduced death or hospitalization or hospitalization only in a sub-group analysis but this was not significant when the whole study population was analyzed. Results published but not peer-reviewed.
- In its recent iteration Drug treatments for COVID-19: living systematic review and network meta-analysis found that in patients with non-severe disease, colchicine may reduce mortality and mechanical ventilation, although the certainty was stated as low certainty.

Regulatory authorities:

- The NIH recommends against the use of colchicine in hospitalized patients for treatment of COVID-19 except in clinical trials.

Vitamin D

- As of now, there is no definitive evidence to suggest that Vitamin D supplementation has potential clinical benefit for the treatment or prevention of COVID-19, particularly in the Canadian context.

- Some studies observed an association between vitamin D deficiency and higher COVID-19 incidence, however this does not establish a cause between low vitamin D and COVID-19 infection and can be due to other demographic factors found in these populations.
- In its recent iteration Drug treatments for COVID-19: living systematic review and network meta-analysis found little evidence to support the use of vitamin D in COVID-19 treatment.
- Clinical evidence in hospitalized patients: Among hospitalized patients with COVID-19, a single high dose of vitamin D3, compared with placebo, did not significantly reduce hospital length of stay.

Regulatory Authorities:

- NIH states there is insufficient data to recommend for or against the use of vitamin D for the prevention or treatment of COVID-19.

**Ivermectin Overview**

Ivermectin is a broad-spectrum anti-parasitic agent authorized and approved by Health Canada for human and veterinary applications. Although ivermectin is used in humans to treat parasitic infections, Health Canada has not authorized its use for the treatment of COVID-19.

**Ivermectin Findings & Outcomes**

- In laboratory studies, ivermectin prevented the virus causing COVID-19 from replicating and has demonstrated anti-inflammatory properties, raising the possibility that ivermectin may have a role in COVID-19 prophylaxis or treatment.
- While preliminary *in vitro* and animal studies reported promising antiviral and anti-inflammatory effects of ivermectin in the context of SARS-CoV-2 infection, its use as a preventative or treatment for COVID-19 remains controversial due to mixed evidence of clinical benefit from numerous smaller, underpowered randomized trials.
- The British Medical Journal's living systematic review and network meta-analysis analysed 16 randomized trials and based on their findings they rated the effects of ivermectin on viral clearance, mechanical ventilation and mortality as uncertain, meaning it is uncertain ivermectin treatment has an important impact on any patient-important outcome.
- Recently~~Contrarily~~, a meta-analysis based on 18 randomized trials of ivermectin in COVID-19 have found that ivermectin treatment reduced mortality, time to clinical recovery, and time to viral clearance.
- A powered, well-designed randomized trial is needed to clearly elucidate the appropriate role of ivermectin in the clinical management or prevention of COVID-19.

**Considerations**

***Canadian perspectives***

- Canadian Agency for Drugs and Technologies in Health (CADTH; statement issued on X date); Alberta Health Services (statement issued on x date) ; as well as British Columbia's COVID-19 Therapeutics Committee/COVID-19 Therapeutics Review and Advisory Working Group (statement issued on x date)~~; and Ontario's COVID-19 Science Advisory Table~~ have all concluded that there is no clear benefit for ivermectin treatment among patients with COVID-19. No statement has been issued by INESSS as of June 3, 2021.
- On May 28, 2021, Ontario's COVID-19 Science Advisory Table issued a statement titled Ivermectin to Prevent Disseminated Strongyloides Infection in Patients with COVID-19. While stipulating ivermectin is currently not recommended as a treatment or preventative for COVID-19, the statement acknowledges patients with COVID-19 who receive therapies that alter immune system function may require ivermectin for the purposes of treating a pre-existing parasitic infection and to avoid severe complications of worsening parasitic infection.

***International perspectives***

- In South American countries, ivermectin is being routinely prescribed for COVID-19 infections; however, it is difficult to ascertain clinical benefit from use outside the context of randomized controlled trials.

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**Commented [NF1]:** Would be important to know when these were last updated.

**Commented [NF2R1]:**

- On X date, The WHO issued a statement on ivermectin advising against its use outside of clinical trials, stating the current clinical evidence was inconclusive.
- On X date, ~~T~~the EMA issued an advisory notice~~s~~ against use of ivermectin for the prevention or treatment of COVID-19 outside randomised clinical trials.

[redacted]

- On X date, t~~T~~he NIH COVID-19 Treatment Guidelines Panel ~~states~~ issued a statement concluding there is insufficient evidence to recommend either for or against the use of ivermectin for the treatment of COVID-19.

[redacted]

Commented [NF3]:

Commented [NF4]: [redacted]

~~The quality of scientific studies and evidence varies and is not equal~~. Publication of a study's findings ~~is not a validation of the~~does not necessarily indicate that ~~effectiveness of~~ the studied treatment is effective, nor that ~~nor the certainty that can be placed in~~ the study's conclusions are valid. ~~The results from clinical trials and studies are graded on a hierarchy based on the certainty of the evidence from low to high.~~ The certainty (or quality) of the evidence ~~is the extent to which we can be~~refers to how confident we can be that ~~what~~ the research ~~tells us about a~~ provides an accurate picture of the effect of a particular treatment~~. effect is likely to be accurate~~ and can be trusted to inform decision-making about procurement and recommendations for use to treat Canadian patients with COVID-19.

Although many studies have been conducted on vitamin D, ivermectin and colchicine for the treatment of COVID-19, the certainty of the evidence has ranged from inconclusive to poor due to flaws in the methods (such as the wrong study design, small sample size, no plan to limit confounding and bias, and insufficient follow-up). Consequently, additional studies, which are larger providing more data with better methods and designs, are required to ensure confidence in the usefulness of the evidence regarding the use of vitamin D, ivermectin and colchicine as treatments for COVID-19.

Ivermectin is a broad-spectrum anti-parasitic agent authorized and approved by Health Canada for human and veterinary applications. Although ivermectin is used to treat parasitic infections such as intestinal strongyloidiasis, onchocerciasis, scabies and possible use to treat rosacea. Health Canada has not authorized its use for the treatment of COVID-19. The first of many steps includes promising results documented and obtained from high quality study designs followed by submission of an application to Health Canada, which follows a well-defined process to qualify for approval for a particular indication.

In laboratory studies ivermectin has been shown to inhibit the virus causing COVID-19 from replicating in the lab raising the possibility that ivermectin may have a role in COVID-19 prophylaxis or treatment; however, many drugs that show promise in laboratory studies are not found to be effective in patients. To address the increased international attention on ivermectin as a potential treatment for COVID-19, the World Health Organization convened an independent, international panel of clinical care experts from multiple specialties, patient partners and ethicists. Following a review of the existing data reviewing both inpatient and outpatient trial results, the panel concluded that the existing evidence regarding ivermectin's effectiveness in reducing mortality, need for mechanical ventilation, need for hospital admission and time to clinical improvement was of very low certainty. Consequently, on March 31st 2021, The World Health Organization issued a statement on

**Commented [MG1]:** Not sure if this stays true to the meaning, but trying to simplify.

**Commented [MG2]:** Meaning how outsiders judge them? Suggest removing as it may not be necessary to include this detail for context.

**Commented [MG3]:** Add in text around PHAC work, i.e., analysis and synthesis of the emerging evidence of promising therapeutics to treat COVID-19. This work informs decisions around procurement of therapeutics that have been proven safe and effective.

ivermectin advising against its use outside of clinical trials, stating the current evidence was inconclusive.

Merck statement about not using ivermectin for COVID, not authorized by Health Canada for COVID 19 treatment.

https://www.who.int/news-room/feature-stories/detail/who-advises-that-ivermectin-only-be-used-to-treat-covid-19-within-clinical-trials

**Commented [MG4]:** Need to be rephrased to fit with webmail style "the following link provides (or other wording) ... etc"

Dear [redacted]

Thank you for~~I am writing in response to~~ your correspondence ~~of 2021-05-31, addressed to our Director General, Bersabel Ephrem alerting us to consider~~concerning the use of the I-Mask Protocol for early treatment and prophylaxis for Covid-19 to support Canada's response to COVID-19. ~~Our Director General, Bersabel Ephrem has asked that I reply on her behalf.~~

The Public Health Agency of Canada (PHAC) conducts a thorough analysis of the emerging scientific evidence regarding promising therapeutics to treat COVID-19, and Health Canada (HC) formally reviews these drugs to assess their safety, efficacy and quality before authorizing their sale in Canada. ~~The provinces and territories are primarily responsible to make decisions around choice and use of therapeutics.~~ Many drugs that show promise in laboratory studies are not found to be effective in patients.

I-MASK+ Protocol is a prevention & early outpatient treatment protocol for COVID-19. While it includes a number of medications and supplements, it is centred on ivermectin, ~~is~~ a broad-spectrum anti-parasitic agent authorized and approved by HC for human and veterinary applications to treat parasitic infections.~~Patients are treated with Ivermectin, Vitamin D3, Vitamin C, Quercetin, Zinc, Melatonin, Fluvoxamine, Nasopharyngeal, Sanitation, Melatonin and Aspirin. I-MASK+ Protocol is for COVID-19 is centered ivermectin. Ivermectin is a broad-spectrum anti-parasitic agent authorized and approved by HC for human and veterinary applications to treat parasitic infections.~~ At this time, HC has not authorized its use for the treatment of COVID-19.

The provinces and territories are responsible for the delivery of health care and bear primary responsibility for decisions around choice and use of therapeutics - including for COVID-19 – within their jurisdictions.

Independent reviews of available clinical trial results that evaluate the effectiveness of ivermectin as a treatment for COVID-19 ~~were~~ have been conducted by~~,~~ the Canadian Agency for Drugs and Technologies in Health (CADTH)~~,~~ Alberta Health Services~~,~~ ~~and~~ British Columbia's COVID-19 Therapeutics Committee/COVID-19 Therapeutics Review and Advisory Working Group~~,~~/ and Ontario's COVID-19 Science Advisory table.~~,~~ These bodies of scientific experts all ~~of whom~~ concluded that there ~~was~~ is no clear benefit to ivermectin treatment.

~~-~~On March 31, 2021, the World Health Organization (WHO) issued a statement on ivermectin advising against its use outside of clinical trials, stating the current evidence was inconclusive. Further, ~~T~~the manufacturer~~,~~ ~~-~~ ~~-~~Merck~~,~~ ~~-~~ ~~-~~has also issued a statement against the use of ivermectin for the treatment of COVID-19.

https://www.merck.com/news/merck-statement-on-ivermectin-use-during-the-covid-19-pandemic/

**Commented [MG1]:** I think BE will send the response directly.

**Commented [MG2]:** Added reference to "high quality well-designed clinical trials" in the last paragraph. I think the "growing body" of evidence the writer refers to doesn't include such trials. Also, are there any trials underway? Would be good to mention that if there are/aren't.

**Commented [MG3]:** Could we summarize like this? The writer knows what is in it, so just wanted to shorten.

**Commented [JD4]:** I think senior management needs to know more about mask

**Commented [MG5R4]:** We can put that in the email that goes to BE for her approval.

**Commented [MG6]:** I played around with the placement of this and suggest putting it before the PT positions/guidance as it ties in to the lack of uptake/use.

**Commented [JD7]:** I am sure if we all this info about ivermectin assessment from different partners?

**Commented [MG8R7]:** A word missing above.

In summary, there is currently no robust evidence (i.e., from high quality, well-designed clinical trials) ~~at this time~~ to suggest that the I-MASK+ Protocol provides clinical benefit for the treatment or prevention of COVID-19, particularly in the Canadian context. Please be assured that PHAC ~~is actively~~continues to monitor~~ing~~ the emerging evidence of clinical efficacy and safety from high quality trials on novel and repurposed therapeutics for COVID-19.

Thank you for writing to the Public Health Agency of Canada. I hope this information is helpful. ~~; and makes recommendations based on findings from high-quality evidence on an ongoing basis.~~

**Commented [MG9]:** We aren't making recommendations so maybe this could be "to inform decisions around procurement" or just delete.

# Emerging COVID-19 Therapeutics

*FPT ADM Drug Shortages Table*

*25 March 2021*

# Purpose

- To provide an update to the FPT ADM Drug Shortages Table on COVID-19 Therapeutics
  - Emerging therapeutics
  - PHAC's plans for ongoing FPT engagement
  - Implications of vaccine rollout, increased prevalence of immunized population on forward plan for emerging therapies for COVID-19

# Emerging and authorized COVID-19 therapeutics

***Antivirals***

- Remdesivir*
- Molnupiravir

***Neutralizing Monoclonals***

- Bamlanivimab monotherapy*
- Bamlanivmab + Etesevimab
- Casirivimab + Imdevimab
- VIR-7831
- AZD-7442
- CT-P59

***Immunomodulating drugs***

- Dexamethasone/ Glucocorticoids
- Tocilizumab
- Sarilumab
- Anakinra
- Baricitinib
- Otilimab
- Colchicine

***Other***

- Aspirin
- Ivermectin
- Fluvoxamine
- SaNOtize

**Authorized by Health Canada*

# Plans for Ongoing FPT Engagement

- Ad-hoc FPT Clinical meetings
  - April meeting planning with Gilead on Veklury (Remdesivir)
  - Subsequent meetings anticipated with Merck (Molnupiravir) and with GSK (Vir-7831)

- Outreach to PTs on usage data for authorized COVID-19 therapeutics
  - Informs approach for future planning and procurement decisions

# Implications of vaccine roll-out and COVID-19 therapeutics

- The target population for COVID-19 therapeutics is characterized by those at high risk of severe disease/hospitalization (elderly, co-morbidities)
  - This target population can be estimated by anticipated incidences of hospitalizations
    - Anticipated number of hospitalization events each month will be estimated based on best and worse case scenarios

- Collaboration with PHAC modelling group
  - Plan to use modeling projections to inform current and future COVID-19 therapeutic needs
    - Considerations:
      - Anticipated vaccination deliveries
      - Vaccine efficacy
      - Variants of concern
    - For future modeling scenarios: vaccine hesitancy based on age groups

# Contacts at the Public Health Agency of Canada

COVID-19 Therapeutics | thérapeutiques

**Jacqueline Arthur, RN, BScN**
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**Nicole Forbes, PhD**
Technical Lead
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Email: nicole.forbes@canada.ca

# *ANNEX*: Emerging COVID-19 Therapeutics

*ADM Drug Shortages Table*

*25 March 2021*

# Neutralizing mAbs: Comparison of design/properties

| | Bamlanivimab *(authorized)* | Bamlanivimab + Etesevimab | Casirivimab + Imdevimab | VIR-7831 | CT-P59 | AZD-4552 |
|---|---|---|---|---|---|---|
| **Manufacturer** | Eli Lilly (AbCellera) | Eli Lilly (AbCellera/ Junshi Biosci.) | Roche (Regeneron) | Vir Biosciences/GSK | Celltrion | Astra-Zeneca |
| **Composition** | Single mAb | Two mAbs | Two mAbs | Single mAb | Single mAb | Two mAbs |
| **Target(s)** | SARS-CoV-2 spike | Distinct regions on SARS-CoV-2 spike RBD | Distinct regions on SARS-CoV-2 spike RBD | Conserved region on SARS-CoV-2 spike protein (shared with SARS-CoV-1) | SARS-CoV-2 spike RBD | SARS-CoV-2 spike |
| **Durability of response (half life)** | T 1/2 ~17 days | T 1/2 ~17 days | ~17 day half life | Extended half-life (proprietary Fc modification) | T 1/2 ~17 days | Extended T 1/2 → durability up to 6-12 months |
| **Route of admin.** | IV | IV | IV; SC in clinical trials | IV; IM in clinical trials | IV | IM |
| **Other attributes** | | Etesevimab – ablated effector function | | Designed to achieve high lung concentration<br>In tact effector function → can neutralize virus AND flag infected cells for destruction | | Reduced Fc receptor binding (reduced effector activity) |

RBD- receptor binding domain

# Neutralizing mAbs: Comparison of clinical treatment effects

| | Bamlanivimab | Bamlanivimab + Etesevimab | Casirivimab + Imdevimab | VIR-7831 | CT-P59 |
|---|---|---|---|---|---|
| **Population** | - | N=769 outpatients at high risk for severe disease/ hospitalization | N=4180 outpatients at high risk for severe disease/ hospitalization | N=583 outpatients at high risk for severe disease/ hospitalization | |
| **Reduced hospitalization or death** | - | 87% reduction in hospitalizations or deaths by day 29<br><br>(Press release; not peer reviewed) | 70% reduction<br><br>(Press release issued on March 23, not included in original presentation) | 85% reduction* in hospitalizations >24h or deaths by day 29 | |
| **Population** | N=613 adult non-hospitalized patients | N=577 adult non-hospitalized patients | N=665 adult non-hospitalized patients | - | N=327 adult non-hospitalized patients |
| **COVID-19 related hospitalizations /ER visits** | 70% reduction in hospitalizations or ER visits by day 29<br><br>(Press release; not peer reviewed) | 84% reduction in hospitalizations or ER visits by day 29 | 57% reduction in medically-attended visits for COVID-19 *(primary care to hospitalization; data from pre-submission filing)* | - | 49% reduction*** in hospitalizations or requirement for oxygen therapy<br><br>(Preprint- not peer reviewed) |

# Susceptibility/resistance of viral variants to neutralizing mAbs

| | Bamlanivimab | Bamlanivimab + Etesevimab | Casirivimab + Imdevimab | VIR-7831 | AZD-7442 | CT-P59 |
|---|---|---|---|---|---|---|
| **B.1.1.7 (UK variant)** | Susceptible | Susceptible | Susceptible | Susceptible | Susceptible | Susceptible |
| **B.1.351 (SA variant)** | Resistant | Resistant | Susceptible | Susceptible | Susceptible | Susceptible |
| **P.1 (Brazil variant)** | Resistant | Resistant | Conflicting evidence | Susceptible | Susceptible | Susceptible |
| **P.2 (Brazil variant)** | Resistant | Not tested | Not tested | Susceptible | Not tested | Susceptible |

*Note: Above table based on non-clinical evidence (in vitro pseudovirus/whole virus neutralization assays)*

# Additional post-market analysis data from the United States

**PREPRINT:** Webb et al., Real-World Effectiveness and Tolerability of Monoclonal Antibodies for Ambulatory Patients with Early COVID-19. medRxiv. March 17, 2021.

- Population: 13,534 symptomatic high-risk outpatients with symptomatic, lab-confirmed COVID-19 treated at infusion centers and urgent care clinics in the USA within 7 days of symptom onset.
- Intervention: bamlanivimab 700 mg or casirivimab/imdevimab 1200 mg/1200 mg (n=594 given a mAb; 80.6% receiving bamlanivimab)
- Patients who received mAb infusion were compared to contemporaneous controls and a pre-implementation cohort (n=5536 and 7404 respectively).
- The primary outcome was emergency department visit or hospitalization within 14 days of positive test.
- MAb treatment was associated with fewer subsequent ER visits and hospitalizations (31% reduction).
- Overall, 7 (1.2%) mAb patients experienced an adverse event; two (0.3%) were considered serious.
- No statistically significant difference between effect of casirivimab/imdevimab and bamlanivimab treatment.

# Neutralizing mAbs: Ongoing randomized trials for COVID-19 indications

| | Bamlanivimab | Bamlanivimab + Etesevimab | Casirivimab + Imdevimab | VIR-7831 | CT-P59 | AZD-4552 |
|---|---|---|---|---|---|---|
| **Outpatient** | Ph2/3 trial N=2000; Jul 2021 (ACTIV-2; NIAID)<br>Ph2 trial N=700; March 2021<br>Ph2/3 trial N=3300; May 2021 | Ph2 trial N=700; March 2021<br>Ph2/3 trial N=3300; May 2021 | Symptomatic; Ph2/3 trial N=6420; April 2021 | Ph2 trial N=700; March 2021 (BLAZE-4; VIR-7831 + bamlanivimab)<br>Ph2/3 trial N=1360; July 2021 | Ph2/3 trial N=1020; Sept 2021 | Ph3 trial N=1700; June 2021 |
| **Outpatient subpopulation** | 65y+ symptomatic Ph4 trial N=576; June 2021 (BC) | | Asymptomatic/ low risk; Ph2 trial N=1400; Mar 2021 | | | |
| **Inpatient** | | | Ph1/2 trial N=6900; April 2021<br>Ph3 trial N= 2000 (enrollment to treatment arm; RECOVERY trial); March 2021 | Ph3 NIAID sponsored (n=10,000; 344 to VIR arm*); Aug 2021 (ACTIV-3; NIAID)<br>*Halted by NIH for futility* | | Ph3 NIAID sponsored (n=10,000; 950 to AZD arm); Aug 2021 (ACTIV-3; NIAID) |
| **Pre-exp. prophylaxis** | Ph3 trial N=5000; March 2021 (LTC residents/staff) | Ph3 trial N=5000; March 2021 LTC residents/staff) | | | | Ph3 trial N=5000; June 2021 |
| **Post-exp. prophylaxis** | | | Ph3 trial N=2450; June 2021 | | | Ph3 trial; N=1125; Jan 2022 |

# Additional neutralizing monoclonal antibodies for COVID-19

- Numerous neutralizing mAbs for SARS-CoV-2 in early and late stage clinical trials including:

- *VIR-7832 (Vir Biosciences/GSK)*
- *STI-1499 (COVI-GUARD; Sorrento)*
- *SCTA01 (Sinocelltech Ltd and Chinese Academy of Sciences)*
- *BRII-198/196 (Brii Bioscience)*
- *ADM03820 (Ology Bioservices)*
- *TAXT-03 (ImmunoPrecise)*
- *DZIF/DZIF10c (University of Cologne and Boehringer Ingelheim)*
- *ABBV-47D11 (AbbVie)*
- *ABBV-2B04 (AbbVie)*
- *HFB30132A (HiFiBiO Therapeutics)*
- *TY027 (Tychan/SingHealth)*
- *BI 767551 (Cologne University Hospital (UKK), University of Marburg (UMR), the German Center for Infection* Research (DZIF) and Boehringer Ingelheim)

Correspondence on Colchicine and Ivermectin and Vitamin D

Dear [redacted]

I am writing in response to your correspondence of April 21, 2021, addressed to Dr. Tam, alerting us to the use of ivermectin, vitamin D, and colchicine, to support Canada's response to COVID-19. The honourable Minister of Health, Patty Hajdu, has asked that I reply on her behalf. I sincerely regret the delay in responding.

The Public Health Agency of Canada (PHAC) conducts a thorough analysis of the emerging evidence regarding promising therapeutics to treat COVID-19. This work informs decisions around procurement of therapeutics proven to be safe and effective for COVID-19.

Before drug products are authorized for sale in Canada, Health Canada reviews them to assess their safety, efficacy and quality. Prior to being given market authorization, a manufacturer must present substantive scientific evidence of a product's safety, efficacy and quality as required by the Food and Drugs Act and Regulations.

**Commented [JA1]:** Health Canada should review.

The provinces and territories, rather than the Government of Canada, are primarily responsible for the administration and delivery of healthcare services. A health care provider may – at their discretion - use a medication for other conditions ("off-label") as part of the practice of medicine. For any therapeutic, the decision to use it must balance expected benefit against potential harms.

Currently there is no clear evidence from any clinical trial to suggest that vitamin D supplementation has any clinical benefit for the treatment or prevention of COVID-19. Although some studies observed an association between vitamin D deficiency and higher COVID-19 incidence, this does not establish causation that vitamin D supplements could treat or prevent COVID-19.

Ivermectin is a broad-spectrum anti-parasitic agent authorized and approved by Health Canada for human and veterinary applications to treat parasitic infections, Health Canada has not authorized its use for the treatment of COVID-19.

Ivermectin has been shown in laboratory studies to prevent the replication of SARS-CoV2; however, many drugs that show promise in laboratory studies are not found to be effective in patients. Given the interest in ivermectin as a potential treatment for COVID-19, the World Health Organization (WHO) convened an independent, international panel of clinical care experts from multiple specialties, patient partners and ethicists to review the evidence. On March 31, 2021, the WHO issued a statement on ivermectin advising against its use outside of clinical trials, stating the current evidence was inconclusive: https://www.who.int/news-room/feature-stories/detail/who-advises-that-ivermectin-only-be-used-to-treat-covid-19-within-clinical-trials.

The manufacturer, Merck, also issued a statement against the use of ivermectin for the treatment of COVID-19: https://www.merck.com/news/merck-statement-on-ivermectin-use-during-the-covid-19-pandemic/

Colchicine is an anti-inflammatory drug authorized by Health Canada for the treatment of gout, and other inflammatory diseases, raising interest in its potential to prevent the "cytokine storm" characteristic of severe COVID-19. Independent reviews of available clinical trial results that

evaluate the effectiveness of colchicine as a treatment for COVID-19 were conducted by PHAC, the Canadian Agency for Drugs and Technologies in Health (CADTH), l'Institut national d'excellence en santé et services sociaux (INESS) and Alberta Health Services, all of whom concluded that there was no clear benefit to colchicine treatment and some concerning harms (e.g. blood clots in the lungs, a potentially fatal complication). At this time, Canadian expert groups do not recommend prescribing colchicine to treat COVID-19.

In summary there is currently no robust evidence at this time to suggest that ivermectin, colchicine, or vitamin D supplementation provides clinical benefit for the treatment or prevention of COVID-19, particularly in the Canadian context. Please be assured that PHAC is actively monitoring emerging evidence of clinical efficacy and safety on novel and repurposed therapeutics for COVID-19; and makes recommendations based on findings from high quality evidence on an ongoing basis.

**Forrest, Jean (PHAC/ASPC)**

**From:** PHAC Correspondence / Correspondance ASPC (PHAC/ASPC)
**Sent:** 2021-05-10 10:37 AM
**To:** [redacted]
**Subject:** Response from the Public Health Agency of Canada
**Attachments:** COVID-19_VitD_Zinc_EvidenceBrief.pdf

Dear [redacted]

I am writing in response to your correspondence of April 21, 2021, addressed to Dr. Tam, alerting us to the use of vitamin D, colcichine, and ivermectin to support Canada's response to COVID-19. Dr. Tam has asked that I reply on her behalf.

The Public Health Agency of Canada (PHAC) conducts a thorough analysis of the emerging scientific evidence regarding promising therapeutics to treat COVID-19, and Health Canada (HC) formally reviews these drugs to assess their safety, efficacy and quality before authorizing their sale in Canada. Many drugs that show promise in laboratory studies are not found to be effective in patients.

Ivermectin is a broad-spectrum anti-parasitic agent authorized and approved by HC for human and veterinary applications to treat parasitic infections. At this time, HC has not authorized its use for the treatment of COVID-19. On March 31, 2021, the World Health Organization (WHO) issued a statement on ivermectin advising against its use outside of clinical trials, stating the current evidence was inconclusive. The manufacturer, Merck, also issued a statement against the use of ivermectin for the treatment of COVID-19.

Colchicine is an anti-inflammatory drug authorized by HC for the treatment of gout and other inflammatory diseases. Colchicine was submitted to HC for priority review in February 2021, and the submission is currently under expedited review. In the meanwhile, independent reviews of available clinical trial results were also conducted by PHAC, the Canadian Agency for Drugs and Technologies in Health, l'Institut national d'excellence en santé et services sociaux (Quebec) and Alberta Health Services, all of whom concluded that there was no clear benefit to colchicine treatment and potential concerning side-effects (e.g., blood clots in the lungs, a potentially fatal complication).

We are aware of the many health benefits of vitamin D and the rapidly evolving science examining its potential effect to reduce the risk, severity or duration of COVID-19 infections in various populations. We are very attentive to the progress of various clinical trials on the potential effect of vitamin D on COVID-19 outcomes conducted in Canada and abroad. PHAC has recently conducted a current state of evidence that can be found in the attachment entitled "Evidence Brief of vitamin D and zinc supplementation for therapeutic use on COVID-19 cases". As of now, there is no clear evidence from any clinical trial to suggest that vitamin D supplementation has any clinical benefit for the treatment or prevention of COVID-19.

In summary, there is currently no robust evidence at this time to suggest that ivermectin, colchicine, or vitamin D supplementation provides clinical benefit for the treatment or prevention of COVID-19, particularly in the Canadian context. Please be assured that PHAC is actively monitoring emerging evidence of clinical efficacy and safety on novel and repurposed therapeutics for COVID-19; and makes recommendations based on findings from high quality evidence on an ongoing basis.

I hope that this information is helpful, and I thank you for writing to share your views.

Sincerely,

Dr. Pascal Michel
Chief Science Officer
Public Health Agency of Canada

**Ivermectin Overview**

Ivermectin is a broad-spectrum anti-parasitic agent authorized and approved by Health Canada for human and veterinary applications. ~~Although ivermectin is used in humans to treat parasitic infections,~~ Health Canada has not authorized its use for the treatment of COVID-19.

**Ivermectin Findings & Outcomes**

- In laboratory studies, ivermectin prevented the virus causing COVID-19 from replicating and has demonstrated anti-inflammatory properties, raising the possibility that ivermectin may have a role in COVID-19 prophylaxis or treatment.
- While preliminary *in vitro* and animal studies reported promising antiviral and anti-inflammatory effects of ivermectin in the context of SARS-CoV-2 infection, its use as a preventative or treatment for COVID-19 remains controversial due to mixed evidence of clinical benefit from numerous smaller, underpowered randomized trials.
- The British Medical Journal's living systematic review and network meta-analysis analysed 16 randomized trials, ~~and b~~Based on their findings, they rated the effects of ivermectin on viral clearance, mechanical ventilation and mortality as uncertain, meaning it is uncertain whether ivermectin ~~treatment~~ has an important impact on any patient-important outcome.
- Recently~~Contrarily~~, a meta-analysis based on 18 randomized trials of ivermectin in COVID-19 ~~have~~ found that ivermectin treatment reduced mortality, time to clinical recovery, and time to viral clearance.
- A powered, well-designed randomized trial is needed to clearly elucidate the appropriate role of ivermectin in the clinical management or prevention of COVID-19.

**Considerations**

***Canadian perspectives***

- The Canadian Agency for Drugs and Technologies in Health (CADTH; statement issued on X date); Alberta Health Services (statement issued on x date) ; as well as British Columbia's COVID-19 Therapeutics Committee/COVID-19 Therapeutics Review and Advisory Working Group (statement issued on x date)~~; and Ontario's COVID-19 Science Advisory Table~~ have all concluded that there is no clear benefit ~~for~~ associated with ivermectin treatment among patients with COVID-19. As of June 3, 2021, ~~N~~no statement has been issued by INESSS ~~as of June 3, 2021~~.
- On May 28, 2021, Ontario's COVID-19 Science Advisory Table issued a statement titled Ivermectin to Prevent Disseminated Strongyloides Infection in Patients with COVID-19. While stipulating ivermectin is currently not recommended as a treatment or preventative for COVID-19, the statement acknowledges patients with COVID-19 who receive therapies that alter immune system function may require ivermectin for the purposes of treating a pre-existing parasitic infection and to avoid severe complications of worsening parasitic infection.

***International perspectives***

- In South American countries, ivermectin is being prescribed routinely ~~prescribed~~ for COVID-19 infections; however, it is difficult to ascertain clinical benefit from use outside the context of randomized controlled trials.

**Commented [MG1]:** Already indicated by first sentence so can delete.

**Commented [MG2]:** Consider SARS-CoV2 instead?

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**Commented [NF3]:** Would be important to know when these were last updated.

**Commented [NF4R3]:**

**Commented [MG5]:** Suggest italicizing or using quotation marks.

- On X date, ~~T~~the WHO issued a statement on ivermectin advising against its use outside of clinical trials, stating the current clinical evidence was inconclusive.
- On X date, ~~T~~the EMA issued an advisory notice~~s~~ against use of ivermectin for the prevention or treatment of COVID-19 outside randomised clinical trials.
- The FDA has not reviewed data to support use of ivermectin in COVID-19 patients to treat or to prevent COVID-19.
- On X date, t~~T~~he NIH COVID-19 Treatment Guidelines Panel ~~states~~ issued a statement concluding there is insufficient evidence to recommend either for or against the use of ivermectin for the treatment of COVID-19.
- ~~In South American countries, ivermectin is being routinely prescribed for COVID-19 infections.~~

**Commented [NF6]:**

**Commented [NF7]:** Suggest to delete. It's already authorized in the states so would be up to manufacturer to file with regulator for a new indication (think tocilizumab). This isn't really an issue as drugs are used off label all the time and it costs manufacturers $$ to file for new indications. Colchicine and corticosteroids are great examples- old drugs being used for tons of stuff mainly off label.

**Ivermectin Overview**

Ivermectin is a broad-spectrum anti-parasitic agent authorized and approved by Health Canada for human and veterinary applications. Health Canada has not authorized its use for the treatment of COVID-19.

**Ivermectin Findings & Outcomes**

- In laboratory studies, ivermectin prevented SARS-CoV2 from replicating and has demonstrated anti-inflammatory properties, raising the possibility that ivermectin may have a role in COVID-19 prophylaxis or treatment.
- While preliminary *in vitro* and animal studies reported promising antiviral and anti-inflammatory effects of ivermectin in the context of SARS-CoV-2 infection, its use as a preventative or treatment for COVID-19 remains controversial due to mixed evidence of clinical benefit from numerous smaller, underpowered randomized trials.
- The British Medical Journal's living systematic review and network meta-analysis analysed 16 randomized trials. Based on their findings, they rated the effects of ivermectin on viral clearance, mechanical ventilation and mortality as uncertain, meaning it is uncertain whether ivermectin has an important impact on any patient-important outcome.
- Recently, a meta-analysis based on 18 randomized trials of ivermectin in COVID-19 found that ivermectin treatment reduced mortality, time to clinical recovery, and time to viral clearance.
- A powered, well-designed randomized trial is needed to clearly elucidate the appropriate role of ivermectin in the clinical management or prevention of COVID-19.

**Considerations**

***Canadian perspectives***

- The Canadian Agency for Drugs and Technologies in Health (CADTH; statement issued on X date); Alberta Health Services (statement issued on x date) ; as well as British Columbia's COVID-19 Therapeutics Committee/COVID-19 Therapeutics Review and Advisory Working Group (statement issued on x date) have all concluded that there is no clear benefit ~~for~~ associated with ivermectin treatment among patients with COVID-19. As of June 3, 2021, no statement has been issued by INESSS.
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***International perspectives***

- In South American countries, ivermectin is being prescribed routinely for COVID-19 infections; however, it is difficult to ascertain clinical benefit from use outside the context of randomized controlled trials.
- On X date, the WHO issued a statement on ivermectin advising against its use outside of clinical trials, stating the current clinical evidence was inconclusive.

**Commented [MG1]:** Suggest "clarify"

**Commented [NF2]:** Would be important to know when these were last updated.

**Commented [NF3R2]:**

**Commented [NF4]:**

- On X date, ~~T~~the EMA issued an advisory noticees ~~against~~ against use of ivermectin for the prevention or treatment of COVID-19 outside randomised clinical trials.
- On X date, t~~T~~he NIH COVID-19 Treatment Guidelines Panel ~~states~~ issued a statement concluding there is insufficient evidence to recommend either for or against the use of ivermectin for the treatment of COVID-19.

# IVERMECTIN
# BACKGROUNDER (January 4, 2021)

Ivermectin

- Ivermectin is an antiparasitic-drug approved for use in Canada in both people and animals.
- The Merck manufactured drug stromectol (ivermectin) was authorized by Health Canada in September 2018 to treat intestinal strongyloidiasis and onchocerciasis (parasitic worms), and proven or suspected microfilaremia in patients with lymphatic filariasis caused by Wuchereria bancrofti.
- Ivermectin is widely available due to its inclusion on the WHO model list of essential medicines.
- Before the 2018 Notice of Compliance, the drug was only accessible in Canada through the Special Access Program.

COVID-19 and Clinical Trials

- Ivermectin is not approved for use in Canada or in the USA for the prevention or treatment of COVID-19. In April 2020, the USA FDA issued guidance not to use it to prevent or treat COVID-19.
- Completed clinical trials to test the use of ivermectin as a therapy to treat COVID-19 to date have had negative results (Camprubi et al, Public Library of Science, November 11, 2020). Several additional clinical trials are underway.
- A recent Australian article in Antiviral Research noted the positive impacts ivermectin had as an inhibitor of COVID-19 in vitro. It notes that more research is needed, and their work does not mean it should be used in humans.
- In Latin America, countries such as Peru, Bolivia, and Guatemala, ivermectin is over-the-counter, and has been been popularly used as a preventative against COVID-19. Its use there is so widespread that it may make clinical trials in those countries difficult.
- There are currently no authorized COVID-19 ivermectin clinical trials in Canada.

Therapeutics Task Force

- At the last TTF meeting (December 11, 2020), the TTF was asked to investigate ivermectin given recent attention to its potential utility in COVID-19 treatment.

- TTF members had a brief discussion about ivermectin, including both research studies and clinical trials, as well as its use in practice. Members found that its use as either a prophylactic or treatment lacked evidence of effectiveness. They concluded that it was not a promising therapy and that it required further investigation.
- Health Canada and Public Health Agency of Canada officials continue to be in dialogue with the TTF about further evidence, if additional clinical data emerges.

# IVERMECTIN
# BACKGROUNDER (January 5, 2021)

Ivermectin

- Ivermectin is an antiparasitic-drug approved for use in Canada in both people and animals.
- The Merck manufactured drug stromectol (ivermectin) was authorized by Health Canada in September 2018 to treat intestinal strongyloidiasis and onchocerciasis (parasitic worms), and proven or suspected microfilaremia in patients with lymphatic filariasis caused by Wuchereria bancrofti.
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COVID-19 and Clinical Trials

- Ivermectin is not approved for use in Canada or in the USA for the prevention or treatment of COVID-19. In April 2020, the USA FDA issued guidance not to use it to prevent or treat COVID-19.
- Completed clinical trials to test the use of ivermectin as a therapy to treat COVID-19 to date have had negative results (Camprubi et al, Public Library of Science, November 11, 2020). Globally, there are 46 clinical trials are underway (source: clinicaltrials.gov), none of which are in Canada.
    - Three of the studies are in the USA, and all are currently in the recruitment stage.
    - The vast majority of the studies are in South America, Africa, and Asia.
- A recent Australian article in Antiviral Research noted the positive impacts ivermectin had as an inhibitor of COVID-19 in vitro. It notes that more research is needed, and their work does not mean it should be used in humans.
- In Latin America, countries such as Peru, Bolivia, and Guatemala, ivermectin is over-the-counter, and has been popularly used as a preventative against COVID-19. Its use there is so widespread that it may make clinical trials in those countries difficult.
- There are currently no authorized COVID-19 ivermectin clinical trials in Canada.

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- TTF members had a brief discussion about ivermectin, including both research studies and clinical trials, as well as its use in practice. Members found that its use as either a prophylactic or treatment lacked evidence of effectiveness. They concluded, that it was not a promising therapy, and there is no indication at this time that the TTF intends to investigate further.
- The TTF mandate expires at the end of February 2021.

Next Steps

Health Canada and Public Health Agency of Canada officials (PHAC's COVID-19 Therapeutics team) will continue to monitor ivermectin evidence (e.g. additional clinical and/or research data, including outcomes from clinical trials underway) in the coming months.

The quality of scientific studies and evidence varies and is not equal. Publication of study findings is not a validation of the effectiveness of the studied treatment nor the certainty that can be placed in the study's conclusions. The results from clinical trials and studies are graded on a hierarchy based on the certainty of the evidence from low to high. The certainty or quality of the evidence is the extent to which we can be confident that what the research tells us about a particular treatment effect is likely to be accurate and can be trusted to inform decision-making about procurement and recommendations for use to treat Canadian patients with COVID-19.

Although many studies have been conducted on vitamin D, ivermectin and colchicine for the treatment of COVID-19, the certainty of the evidence has ranged from inconclusive to poor due to flaws in the methods (such as the wrong study design, small sample size, no plan to limit confounding and bias, and insufficient follow-up). Consequently, additional studies, which are larger providing more data with better methods and designs, are required to ensure confidence in the usefulness of the evidence regarding the use of vitamin D, ivermectin and colchicine as treatments for COVID-19.

Ivermectin is a broad-spectrum anti-parasitic agent authorized and approved by Health Canada for human and veterinary applications. Although ivermectin is used to treat parasitic infections such as intestinal strongyloidiasis, onchocerciasis, scabies and possible use to treat rosacea. Health Canada has not authorized its use for the treatment of COVID-19. The first of many steps includes promising results documented and obtained from high quality study designs followed by submission of an application to Health Canada, which follows a well-defined process to qualify for approval for a particular indication.

In laboratory studies ivermectin has been shown to inhibit the virus causing COVID-19 from replicating in the lab raising the possibility that ivermectin may have a role in COVID-19 prophylaxis or treatment; however, many drugs that show promise in laboratory studies are not found to be effective in patients. To address the increased international attention on ivermectin as a potential treatment for COVID-19, the World Health Organization convened an independent, international panel of clinical care experts from multiple specialties, patient partners and ethicists. Following a review of the existing data reviewing both inpatient and outpatient trial results, the panel concluded that the existing evidence regarding ivermectin's effectiveness in reducing mortality, need for mechanical ventilation, need for hospital admission and time to clinical improvement was of very low certainty. Consequently, on March 31st 2021, The World Health Organization issued a statement on ivermectin advising against its use outside of clinical trials, stating the current evidence was inconclusive.

Merck statement about not using ivermectin for COVID, not authorized by Health Canada for COVID 19 treatment.

https://www.who.int/news-room/feature-stories/detail/who-advises-that-ivermectin-only-be-used-to-treat-covid-19-within-clinical-trials

Correspondence on Colchicine and Ivermectin and Vitamin D

Dea [redacted]

I am writing in response to your correspondence of April 21, 2021, addressed to Dr. Tam, alerting us to the use of Ivermectin, vitamin D, and Colchicine, to support Canada's response to COVID-19. The honourable Minister of Health, Patty Hajdu, has asked that I reply on her behalf. I sincerely regret the delay in responding.

The Government of Canada is closely tracking all potential therapeutic treatments, vaccines, diagnostic tests, medical devices, and disinfectants currently available and in development in Canada and abroad. The Public Health Agency of Canada (PHAC) conducts a thorough analysis and synthesis of the emerging evidence of promising therapeutics to treat COVID-19. This work informs decisions around procurement of therapeutics ~~that have been~~ proven to be safe~~, and~~ effective, and authorized for COVID-19 indication by Health Canada.

~~Although many studies have been conducted on vitamin D, ivermectin and colchicine for the treatment of COVID-19, the certainty of the evidence has ranged from inconclusive to poor due to flaws in the methods (such as the wrong study design, small sample size, no plan to limit confounding and bias, and insufficient follow-up). Consequently, additional studies, which are larger providing more data with better methods and designs, are required to ensure confidence in the usefulness of the evidence regarding the use of vitamin D, ivermectin and colchicine as treatments for COVID-19.~~

Currently there is no clear ~~definitive~~ evidence from any clinical trial to suggest that Vitamin D supplementation has any clinical benefit for the treatment or prevention of COVID-19, particularly in the Canadian context. ~~For instance, studies among hospitalized patients treated with a single high dose of vitamin D did not have shorter hospital stays than placebo treated patients.~~ Although some studies observed an association between vitamin D deficiency and higher COVID-19 incidence, this does not establish a causal linke between low vitamin D levels and COVID-19 infection, nor does it serve as proof that supplementing with vitamin D could treat or prevent COVID-19.

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Ivermectin is a broad-spectrum anti-parasitic agent authorized and approved by Health Canada for human and veterinary applications. Although ivermectin is used in humans to **treat** parasitic infections ~~such as intestinal strongyloidiasis, onchocerciasis, scabies and possible use to treat rosacea.~~, Health Canada has **not** authorized its use for the treatment of COVID-19. The first of many steps in the authorization process includes the provision of promising results documented and obtained from high quality study designs and clinical trials demonstrating safety and efficacy followed by submission of an application by the manufacturer to Health Canada, which follows a well-defined channel to qualify for approval for a particular indication.

In laboratory studies ivermectin prevented ~~has been shown to inhibit~~ the virus causing COVID-19 from replicating, raising the possibility that ivermectin may have a role in COVID-19 prophylaxis or treatment; however, many drugs that show promise in laboratory studies are not found to be effective in patients. To address the increased international attention on ivermectin as a potential treatment for COVID-19, the World Health Organization (WHO) convened an independent, international panel of clinical care experts from multiple specialties, patient partners and ethicists to review the evidence. ~~-~~Following a review of the existing data ~~reviewing both inpatient and outpatient trial results,~~ , the panel concluded that there was little proof of

ivermectin's effectiveness on several important clinical measures such as reducing mortality, need for mechanical ventilation and time to clinical improvement. ~~the existing evidence regarding ivermectin's effectiveness in reducing mortality, need for mechanical ventilation, need for hospital admission and time to clinical improvement was of very low certainty.~~ Consequently, on March 31st 2021, The WHO issued a statement on ivermectin advising against its use outside of clinical trials, stating the current evidence was inconclusive.

[redacted]

Commented [CM2]: Could remove all this content too.

Colchicine is an anti-inflammatory drug authorized by Health Canada for the treatment of gout, and other inflammatory diseases, for short courses of treatment and is used off-label for ~~the prevention of acute or recurrent pericarditis, and~~ other conditions at the discretion of the primary heath care provider. Use of this drug for therapeutic purposes is limited by side effects such as fatigue, nausea, vomiting, and diarrhea. Interest in this drug~~, which has been marketed in Canada for at least 40 years with known side effects,~~ originatesis ~~derived~~ from its anti-inflammatory activity and potential use to prevent the "cytokine storm" characteristic of severe COVID-19. A review of available clinical trial results, evaluating the effectiveness of colchicine as a treatment for COVID-19 was independently conducted by ~~various Canadian expert groups~~ (PHAC, the Canadian Agency for Drugs and Technologies in Health, l'Institut national d'excellence en santé et services sociaux and Alberta Health Services~~)~~. All of whom concluded that ~~the available studies were of low quality. The only exception was the trial conducted by a Canadian research team at the Montreal Heart Institute, which was of moderate quality; however all the studies evaluated had several weaknesses limiting the certainty placed on the results. Canadian expert groups therefore concluded that~~ there was no clear benefit to colchicine treatment and some concerning harms (e.g. a small number of patients treated with colchicine in the trials developed blood clots in the lungs, a serious complication that could lead to death). There are a number of ongoing clinical trials of colchicine, as these results become ~~available,~~available; ~~they will be evaluated~~ PHAC will to ~~assess~~ if there is a benefit to treating COVID-19 patients with this repurposed drug. At this time, Canadian expert groups do not recommend prescribing colchicine to treat COVID-19.

In summary, currently~~to date,~~ there is no clear~~definitive~~ evidence to suggest that either ivermectin, colchicine, or Vitamin D supplementation provides ~~has potential~~ clinical benefit for the treatment or prevention of COVID-19, particularly in the Canadian context. Health Canada, the regulator in Canada, will review clinical data once submitted from the manufacturer and determine the benefits and risks of potential therapeutics and provide regulatory approval for COVID-19 accordingly. PHAC is actively monitoring emerging evidence of clinical efficacy and safety on novel and repurposed therapeutics for COVID-19, including ivermectin, colchicine, and vitamin D; and makes recommendation based on findings from emerging high quality evidence on an ongoing basis.

For information, the following link provides an update from l'Institut national d'excellence en santé et services sociaux on colchicine:

https://www.inesss.qc.ca/en/covid-19/traitements-specifiques-a-la-covid-19/colchicine.html

For more information, the following link provides a statement from Merck and Co. Inc. issuing a statement against the use of ivermectin for the treatment of COVID-19:

https://www.merck.com/news/merck-statement-on-ivermectin-use-during-the-covid-19-pandemic/

For more information, the following link provides the World Health Organization's guidance on the use to ivermectin to treat COVID-19:

https://www.who.int/news-room/feature-stories/detail/who-advises-that-ivermectin-only-be-used-to-treat-covid-19-within-clinical-trials

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# Emerging COVID-19 Therapeutics

*FPT ADM Drug Shortages Table*

*8 April 2021*

# Purpose

- To provide an update to the FPT ADM Drug Shortages Table on COVID-19 Therapeutics
  - Emerging therapeutics

# Emerging and Authorized COVID-19 Therapeutics

***Antivirals***

- Remdesivir*
- Favipiravir**
- Molnupiravir
- PF-07321332

***Neutralizing Monoclonals***

- Bamlanivimab monotherapy*
- Bamlanivmab + Etesevimab**
- Casirivimab + Imdevimab**
- VIR-7831 (Sotrovimab)**
- AZD-7442
- CT-P59

***Immunomodulating drugs***

- Dexamethasone/ Glucocorticoids
- Tocilizumab
- Sarilumab
- Anakinra
- Baricitinib
- Otilimab
- Colchicine**
- Leronlimab**
- Dimethyl Fumarate (DMF)

***Other***

- Aspirin
- Ivermectin
- Fluvoxamine
- Nitric Oxide

**Authorized by Health Canada*
***Under review by Health Canada*

# Emerging and Authorized COVID-19 Therapeutics

## ***Antivirals***

- One authorized antiviral (remdesivir); limited efficacy (shortened time to clinical improvement)
- Other antivirals in ongoing trials
- Combination antiviral therapies may offer greater effectiveness
- No clinical trials of combination antiviral therapies currently underway

## ***Neutralizing Monoclonals***

- Emerging evidence of efficacy for high risk outpatients
- PTs recommend use be limited to clinical trials
- Ongoing trials (pre-/post-exposure prophylaxis; inpatients)
- VOCs have varied resistance to specific monoclonal antibiodies; implications in efficacy (e.g. bamlanivimab and P1 strain)

## ***Immunomodulating drugs***

- Dexamethasone/ glucocorticoids and tocilizumab both considered standard of care across provinces and territories
- Numerous additional candidates in ongoing trials; limited evidence of clear clinical benefit
- No clear promising candidates

# Emerging COVID-19 Therapeutics

*FPT ADM Drug Shortages Table*

*25 March 2021*

# Purpose

- To provide an update to the FPT ADM Drug Shortages Table on COVID-19 Therapeutics
  - Emerging therapeutics
  - PHAC's plans for ongoing FPT engagement
  - Implications of vaccine rollout, increased prevalence of immunized population on forward plan for emerging therapies for COVID-19

# Emerging and authorized COVID-19 therapeutics

***Antivirals***

- Remdesivir*
- Molnupiravir

***Neutralizing Monoclonals***

- Bamlanivimab monotherapy*
- Bamlanivmab + Etesevimab
- Casirivimab + Imdevimab
- VIR-7831
- AZD-7442
- CT-P59

***Immunomodulating drugs***

- Dexamethasone/ Glucocorticoids
- Tocilizumab
- Sarilumab
- Anakinra
- Baricitinib
- Otilimab
- Colchicine

***Other***

- Aspirin
- Ivermectin
- Fluvoxamine
- SaNOtize

**Authorized by Health Canada*

# Plans for Ongoing FPT Engagement

- Ad-hoc FPT Clinical meetings
  - April meeting planning with Gilead on Veklury (Remdesivir)
  - Subsequent meetings anticipated with Merck (Molnupiravir) and with GSK (Vir-7831)

- Outreach to PTs on usage data for authorized COVID-19 therapeutics
  - Informs approach for future planning and procurement decisions

# Implications of vaccine roll-out and COVID-19 therapeutics

- The target population for COVID-19 therapeutics is characterized by those at high risk of severe disease/hospitalization (elderly, co-morbidities)
  - This target population can be estimated by anticipated incidences of hospitalizations
    - Anticipated number of hospitalization events each month will be estimated based on best and worse case scenarios

- Collaboration with PHAC modelling group
  - Plan to use modeling projections to inform current and future COVID-19 therapeutic needs
    - Considerations:
      - Anticipated vaccination deliveries
      - Vaccine efficacy
      - Variants of concern
    - For future modeling scenarios: vaccine hesitancy based on age groups

# Contacts at the Public Health Agency of Canada

COVID-19 Therapeutics | thérapeutiques

**Jacqueline Arthur, RN, BScN**
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t. (613) 889-8455
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Technical Lead
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Email: nicole.forbes@canada.ca

**DRAFT**

**F/P/T ADM Drug Shortages Table Meeting**

3:00 p.m. – 4:00 p.m. EST

May 6, 2021

**Record of Discussions**

Participating jurisdictions:

Co-chairs: Ontario & Health Canada

Members in attendance: BC, AB, SK, NB, NS, NL, PEI, NT, PHAC

Documents shared: Agenda, Record of Discussion from April 22.

**Drug Shortages – Emerging Signals**

[redacted]

[redacted]

**Commented [JA1]:** I need to correct what I said at the meeting; it is still blinded and we have seen interim data analysis of the COMET-ICE study.

ATIA - 21(1)(a)
ATIA - 21(1)(b)
ATIA - 21(1)(c)

[redacted]

Formatted: Line spacing: single

Commented [BR(2)]: For PHAC to confirm, not sure if I got this correct

Commented [JA3R2]: Yes correct.

**From:** Ha, Shalane (PHAC/ASPC)
**Sent:** 2021-01-13 10:50 AM
**To:** Timmerman, Karen (PHAC/ASPC); Sarwar, Elaha (PHAC/ASPC); Marinsky, Cheryl (PHAC/ASPC)
**Subject:** Daily Titles for Jan. 13

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**Follow Up Flag:** Follow up
**Flag Status:** Flagged

Hello everyone!

Here are the titles for today:

| | |
|---|---|
| Lizanne | Absent |
| Cheryl | Abstract<br>**Ahmed, S, Karim, et al(2021). A five-day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness *International Journal of Infectious Diseases*,** https://www.sciencedirect.com/science/article/pii/S1201971220325066?via%3Dihub<br><br>Abstract<br>**Castelnovo, L, Tamburello, et al(2021). Anti-IL6 treatment of serious COVID-19 disease: A monocentric retrospective *Medicine (Baltimore)*,** https://pubmed.ncbi.nlm.nih.gov/33429732/ |
| Elaha | Potential SR<br>**Kinobe, RT, Owens, et al(2021). A systematic review of experimental evidence for antiviral effects of ivermectin and an in-silico analysis of ivermectin's possible mode of action against SARS-CoV-2 *Fundam Clin Pharmacol*,** https://onlinelibrary.wiley.com/doi/abs/10.1111/fcp.12644<br><br>Potential SR<br>**Million, M, Roussel, et al(2021). Effect of hydroxychloroquine and azithromycin on SARS-CoV-2 clearance in COVID-19 patients, a meta-analysis *International journal of antimicrobial agents*,** https://www.sciencedirect.com/science/article/pii/S0924857920304593?via%3Dihub<br><br>Potential SR<br>**Walz, L, Cohen, et al(2021). JAK-inhibitor and type I interferon ability to produce favorable clinical outcomes in COVID-19 patients: a systematic review and meta-analysis *BMC Infect Dis*,** https://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-020-05730-z<br><br>Potential SR<br>**Zaffanello, M, Piacentini, et al(2021). The use of convalescent plasma for pediatric patients with SARS-CoV-2: A systematic literature review *Transfusion and Apheresis Science*,** https://www.sciencedirect.com/science/article/pii/S1473050220303761?via%3Dihub |
| Shalane | Abstract |

| | |
|---|---|
| | **Rajter, JC, Sherman, et al(2021). Use of Ivermectin Is Associated With Lower Mortality in Hospitalized Patients With Coronavirus Disease 2019: The Ivermectin in COVID Nineteen Study *Chest*,** https://www.sciencedirect.com/science/article/pii/S0012369220348984?via%3Dihub<br><br>Abstract<br>**Salazar, E, Christensen, et al(2021). Significantly Decreased Mortality in a Large Cohort of Coronavirus Disease 2019 (COVID-19) Patients Transfused Early with Convalescent Plasma Containing High-Titer Anti–Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Spike Protein IgG *American Journal of Pathology*,** https://www.sciencedirect.com/science/article/pii/S0002944020304892?via%3Dihub |
| Karen | **Triage all titles**<br><br>**Send titles to review team**<br><br>**Review all summaries/abstracts**<br><br>**Email prep and send out to MCM group** |

Have a nice day ☺

Shalane

**From:** Ha, Shalane (PHAC/ASPC)
**Sent:** 2021-01-28 10:57 AM
**To:** Sarwar, Elaha (PHAC/ASPC); Marinsky, Cheryl (PHAC/ASPC)
**Cc:** Timmerman, Karen (PHAC/ASPC)
**Subject:** Daily titles for Jan. 28

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Good morning everyone,

Here are the daily titles for today. If you could please save your summaries/abstracts in the shared folder by 3PM EST, that would be great. I've included some carry over titles from yesterday so we don't have to dig through our e-mails.

Thank you!

Shalane

| | |
|---|---|
| Cheryl | **Abstract**<br>Shouman, et al. Use of Ivermectin as a potential chemoprophylaxis for COVID-19 in Egypt : A Randomised clinical trial. Journal of Clinical and Diagnostic Research. 2021; \| Epistemonikos \| DOI<br><br>**Abstract**<br>Chachar et al. Effectiveness of ivermectin in SARSCoV-2/COVID-19 patients. International Journal of Sciences. 2020;09(12):31-35. \| Epistemonikos \| DOI |
| Elaha | **Potential SR**<br>Remdesivir therapy in patients with COVID-19: A systematic review and meta-analysis of randomized controlled trials. (View on PubMed)<br><br>**Potential SR**<br>Hill et al. Meta-analysis of randomized trials of ivermectin to treat SARS-CoV-2 infection. ResearchSquare. 2021; \| Epistemonikos \| DOI<br><br>**Potential Appraisal of Rapid Review + MA**<br>Lawrie. Ivermectin reduces the risk of death from COVID-19 -a rapid review and meta-analysis in support of the recommendation of the Front Line COVID-19 Critical Care Alliance. ResearchGate - Evidence-based Medicine Consultancy Ltd. 2021; \| Epistemonikos \| DOI<br><br>**QF/few bullets for titles if there is data**<br>Eli Lilly and Company. Lilly, Vir Biotechnology and GSK announce first patient dosed in expanded BLAZE-4 trial evaluating bamlanivimab (LY-CoV555) with VIR-7831 (GSK4182136) for COVID-19. Press release - PR Newswire - 27 January 2021. 2021; \| Epistemonikos |
| Shalane | **Triage titles**<br><br>**Abstract**<br>The effect of early treatment with ivermectin on viral load, symptoms and humoral response in patients with non-severe COVID-19: A pilot, double-blind, placebo-controlled, randomized clinical trial. (View on PubMed) |

| | |
|---|---|
| | **Abstract**<br>Spoorthi V, Sasank S. Utility of Ivermectin and Doxycycline combination for the treatment of SARSCoV-2. International Archives of Integrated Medicine. 2021;7(10):177-182. \| Epistemonikos<br><br>**Summary (completed)**<br>Tardif et al. Efficacy of Colchicine in Non-Hospitalized Patients with COVID-19. medRxiv. 2021; \| Epistemonikos \| DOI |
| Karen | **Triage all titles**<br><br>**Send titles to review team**<br><br>**Review all summaries/abstracts**<br><br>**Email prep and send out to MCM group** |

**From:** Timmerman, Karen (PHAC/ASPC)
**Sent:** 2021-02-04 10:58 AM
**To:** Marinsky, Cheryl (PHAC/ASPC); Sarwar, Elaha (PHAC/ASPC); Ha, Shalane (PHAC/ASPC)
**Subject:** Titles for Thursday February 4th, 2021

---

**Importance:** High

Hi Everyone,

Here are the daily titles. Some have already been sent to you through Teams.

| | |
|---|---|
| Cheryl | **Abstract**<br>Mohan, et al(2021). **Ivermectin in mild and moderate COVID-19 (RIVET-COV): a randomized, placebo-controlled trial.** *Research Square prepub.* https://www.researchsquare.com/article/rs-191648/v1 |
| Elaha | **Potential SR/MA**<br>Klassen, StephenA, Senefeld, et al(2021). The Effect of Convalescent Plasma Therapy on COVID-19 Patient Mortality: Systematic Review and Meta-analysis *medRxiv*, *https://www.medrxiv.org/content/10.1101/2020.07.29.20162917v4*<br><br>**Potential SR/MA**<br>**Kow, CS, Hasan, et al(2021). The effect of tocilizumab on mortality in hospitalized patients with COVID-19: a meta-analysis of randomized controlled trials *Eur J Clin Pharmacol*,** https://link.springer.com/article/10.1007/s00228-021-03087-z<br><br>**Potential SR/MA**<br>Manuel Lago. Survival of adults hospitalized with COVID-19 and remdesivir: Bayesian re-analysis and meta-analysis of two clinical trials. 2020;12. \| Epistemonikos<br><br>**Potential SR/MA**<br>Muhammad Ardi Munir, Hendra Kuganda, Amirah Basry. The efficacy and safety of antivirus drugs for COVID-19: A systematic review. Systematic Reviews in Pharmacy. 2020;11(7). \| Epistemonikos |
| Shalane | **Summary**<br>Abaleke, et al(#year#). **Azithromycin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial.** *The **Lancet**.* https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00149-5/fulltext |
| Karen | **Scan LOVE and McMaster Titles from platforms**<br><br>**Triage all titles** |

| | |
|---|---|
| | **Send titles to review team**<br>**Review all summaries/abstracts**<br>**Email prep and send out to MCM group** |

Have a great day,
Karen

**From:** Timmerman, Karen (PHAC/ASPC)
**Sent:** 2021-02-09 12:14 PM
**To:** Marinsky, Cheryl (PHAC/ASPC); Sarwar, Elaha (PHAC/ASPC); Ha, Shalane (PHAC/ASPC); Dave, Jaahnavi (PHAC/ASPC)
**Subject:** Daily Titles for Tuesday February 9th, 2021

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**Importance:** High

Hi everyone,

Here are the titles for today. Please let me know when they are in today's folder.

| | |
|---|---|
| Cheryl | **Abstract**<br>Shah Bukhari et al., Efficacy of Ivermectin in COVID-19 Patients with Mild to Moderate Disease<br>https://www.medrxiv.org/content/10.1101/2021.02.02.21250840v1 |
| Elaha | **Potential SR/MA**<br>Rezagholizadeh, A, Khiali, et al(2021). Remdesivir for treatment of COVID-19; an updated systematic review and meta-analysis *Eur J Pharmacol*, **https://www.sciencedirect.com/science/article/pii/S0014299921000790?via%3Dihub**<br><br>**Potential SR/MA**<br>**Vegivinti, CTR, Pederson, et al(2021). Efficacy of convalescent plasma therapy for COVID-19: A systematic review and meta-analysis *J Clin Apher*, https://onlinelibrary.wiley.com/doi/10.1002/jca.21881**<br><br>**Potential SR/MA**<br>Robinson, et al(2021). **Impact of systemic corticosteroids on hospitalized patients with COVID-19: January 2021 Meta-analysis of randomized controlled trials.***medRxiv.*<br>*https://www.medrxiv.org/content/10.1101/2021.02.03.21251065v1*<br><br>**Potential SR/MA**<br>Wang, et al(2021). **Effect of antiplatelet treatments on patients with COVID-19 infection: A systematic review and meta-analysis.** *Am J Emerg Med.*<br>*https://www.sciencedirect.com/science/article/pii/S0735675721000188?via%3Dihub*<br><br>**Potential SR/MA**<br>**Li, P, Li, et al(2021). Effect of antitumor therapy on cancer patients infected by SARS-CoV-2: A systematic review and meta-analysis *Cancer Med*,**<br>https://onlinelibrary.wiley.com/doi/10.1002/cam4.3754<br><br>**Potential SR/MA** |

| | |
|---|---|
| | **Koeckerling, D, Pan, et al(2021). Re: 'Efficacy and safety of tocilizumab in COVID-19 patients: A living systematic review and meta-analysis' by Tleyjeh et al *Clin Microbiol Infect*,** https://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(21)00052-5/pdf |
| Jaahnav | 1) Working on retrospective cohort antidepressants study from last week; will review draft with Elaha before submitting summary in Y:drive folder (Y:\PHAC\IDPCB\CCDIC\CCDIC-SHARED\X_REFERENCE\Therapeutics\Daily Titles\4. February 2021) for Karen's review. Due for Monday/Tuesday<br><br>2) Will assist Elaha with backlog of SR/MA Titles from last week once finished retro cohort summaary |
| Shalane | |
| Karen | **Scan LOVE and McMaster Titles from platforms**<br><br>**Triage all titles**<br><br>**Send titles to review team**<br><br>**Review all summaries/abstracts**<br><br>**Email prep and send out to MCM group** |

Have a great day!
Karen

Correspondence on Colchicine and Ivermectin

https://www.canada.ca/en/public-health/corporate/mandate/about-agency/external-advisory-bodies/list/covid-19-clinical-pharmacology-task-group/statement-colchicine.html

The certainty (or quality) of evidence is the extent to which evaluators/scientists/PHAC can be confident that what the research tells us about a particular treatment effect is likely to be accurate. Concerns about factors such as bias can reduce the certainty of the evidence.

The quality of scientific stuides and evidence varies and is not equal. Publication of study findings is not a validation of the effectiveness of the studied treatment nor the certainty that be placed in the study's conclusions. The results from clinical trials and studies are graded on a hierarchy based on the certainty of the evidence from low to high.(and is graded on a hierarchy based on the certainty of the evidence from low to high). The certainty or quality of the evidence is the extent to which we can be confident that what the research tells us about a particular treatment effect is likely to be accurate and can be trusted to inform decision-making about procurement and recommendations for use to treat Canadian patients with COVID-19. Although many studies have been conducted on both ivermectin and colchicine for the treatment of COVID-19, the certainty of the evidence has ranged from being inconclusive to poor.

**WHO advises that ivermectin be used to treat COVID-19 within clinical trials**

31 March, 2021WHO advises that

The current evidence on the use of ivermectin to treat COVID-19 patients is inconclusive. Until more data is available, WHO recommends that the drug only be used within clinical trials.

This recommendation, which applies to patients with COVID-19 of any disease severity, is now part of WHO's guidelines on COVID-19 treatments.

Ivermectin is a broad spectrum anti-parasitic agent, included in WHO essential medicines list for several parasitic diseases. It is used in the treatment of onchocerciasis (river blindness), strongyloidiasis and other diseases caused by soil transmitted helminthiasis. It is also used to treat scabies.

A guideline development group was convened in response to the increased international attention on ivermectin as a potential treatment for COVID-19. This group is an independent, international panel of experts, which includes clinical care experts in multiple specialties and also include an ethicist and patient-partners.

The group reviewed pooled data from 16 randomized controlled trials (total enrolled 2407), including both inpatients and outpatients with COVID-19. They determined that the evidence on whether ivermectin reduces mortality, need for mechanical ventilation, need for hospital admission and time to clinical improvement in COVID-19 patients is of "very low certainty," due to the small sizes and methodological limitations of available trial data, including small number of events.

The panel did not look at the use of ivermectin to prevent COVID-19, which is outside of scope of the current guidelines.

**From:** Timmerman, Karen (PHAC/ASPC)
**Sent:** 2020-12-08 10:26 AM
**To:** Marinsky, Cheryl (PHAC/ASPC)
**Subject:** Two Summaries to start on

---

**Importance:** High

Hi Cheryl,

There are a lot of titles this morning so I am sending you two titles to start summaries on while I'm still going through everything.

Thanks,
Karen Timmerman

Summary

Ahmed, S, Karim, et al(2020). PMC7709596; A five day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness *Int J Infect Dis*, https://www.sciencedirect.com/science/article/pii/S1201971220325066?via%3Dihub

Summary

Butt, JH, Gerds, et al(2020). Association between statin use and outcomes in patients with coronavirus disease 2019 (COVID-19): a nationwide cohort study *BMJ Open*, https://bmjopen.bmj.com/content/10/12/e044421

# Global Clinical Trials for COVID-19 Tx Development

Source: Clinicaltrials.gov and WHO clinical trial registry as of 1/14/2021

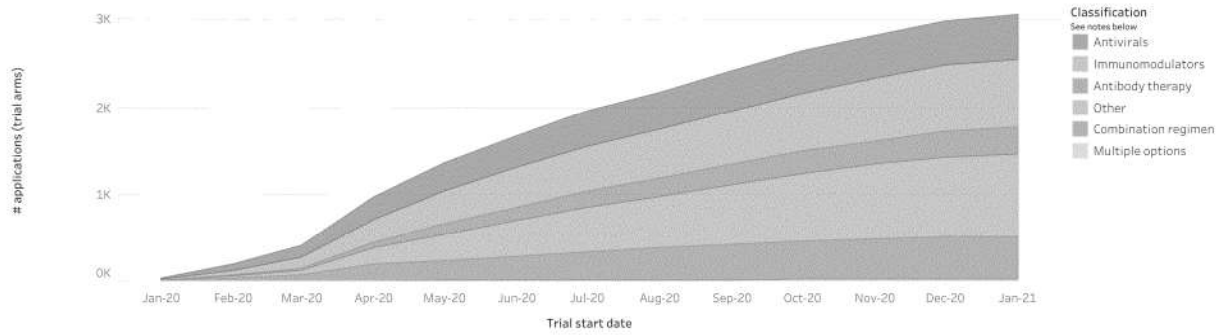
**JANUARY 26, 2021**

## Global overview of COVID-19 clinical trials landscape

The therapies below are in development and are being tested in clinical trials.

### Distribution of launched COVID-19 trial arms by therapy class # trial arms by class, cumulative

See notes below



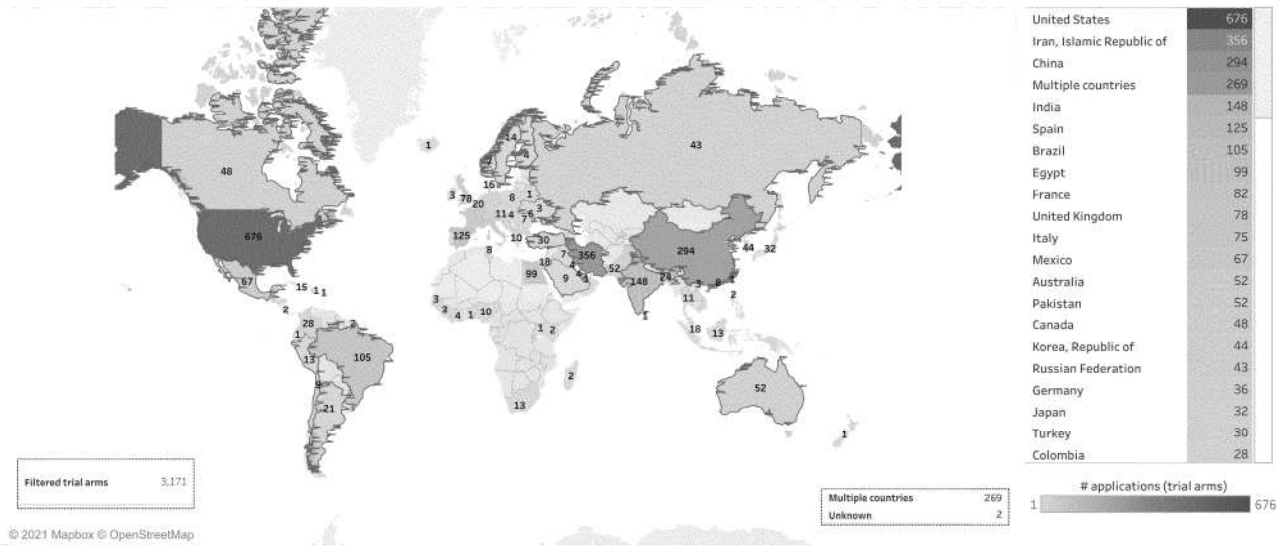

**Filters** (apply to all charts that follow)

| Randomized, adequately powered? | Start date (month) | US involved? | USG agency involved? |
|---|---|---|---|
| All | All | All | All |

Reset filters (this bar)

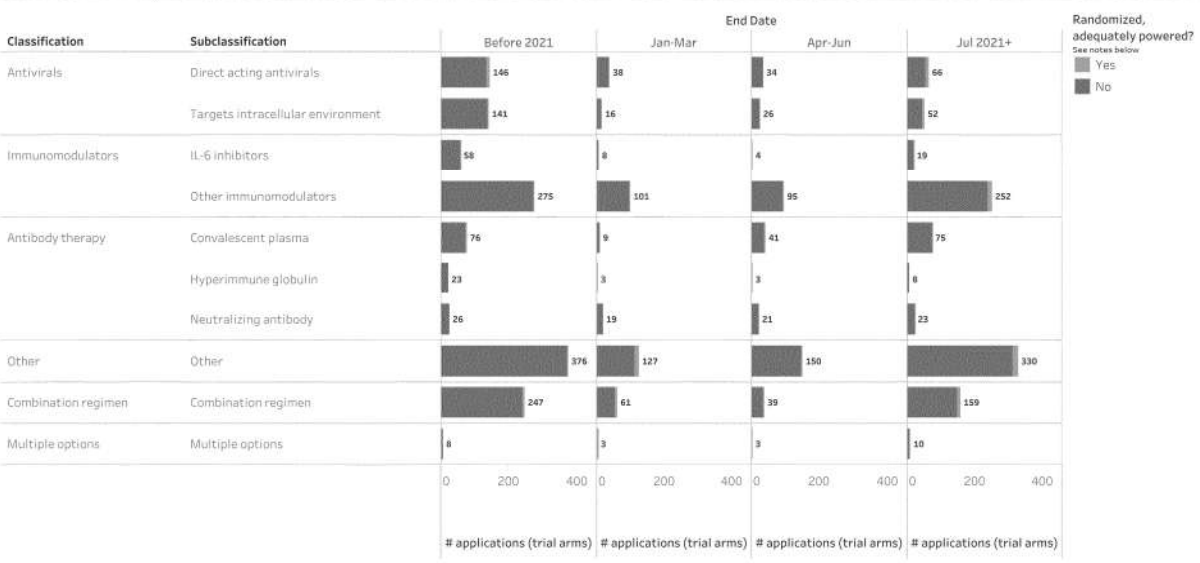
### Global COVID-19 clinical trial arms by country (underway and completed) (filtered)

See notes below



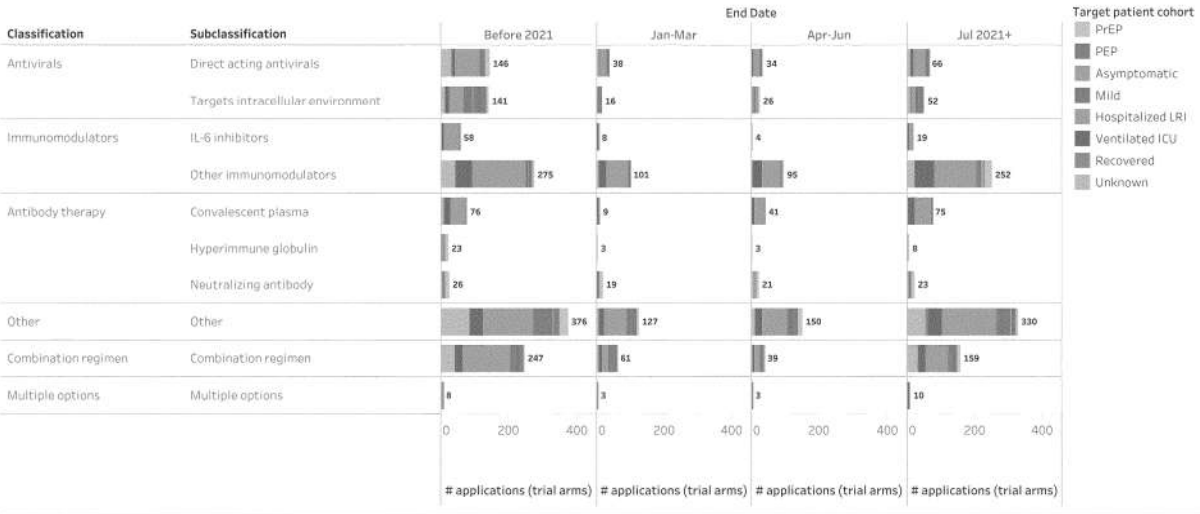

### Clinical trial arms, breakdown by potential readout dates (filtered)

See notes below



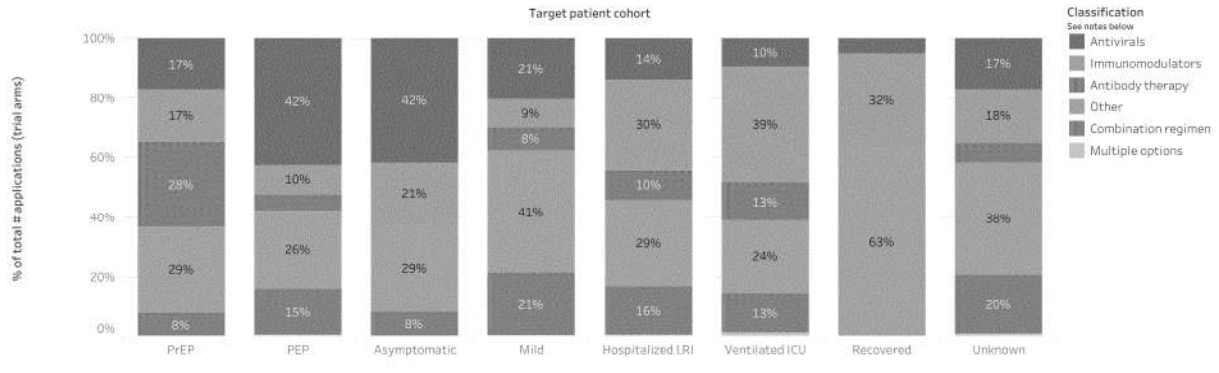

### Target patient cohorts of clinical trial arms, breakdown by potential readout dates (filtered)

See notes below




### Distribution of drug classes tested by patient severity % of total trial arms (filtered)

See notes below




All data in this output is subject to inherent uncertainty, limits, and variability and is shared to provide one of multiple contributions to informing discussions on COVID response, not as a stand-alone basis for recommendations or decision-making. The recipient is solely responsible for its decisions (including policy decisions), use of the materials, and compliance with applicable laws, rules and regulations.

**Global trial arms** corresponds to number of global investigational trials recruiting or completed. Excludes trials that have been terminated (or equivalent). Separates out multi-arm trials into distinct counts, including arms testing the same intervention in different doses or durations. May not be fully comprehensive. Excludes Traditional Chinese Medicine and vaccine trials. For trials without country information in registries, location is assigned as possible based on sponsor location.
**US involved** filter selects for trials in the United States, with at least one US site, or with USG agency involvement. **USG agency involved** filter selects for trial arms involving a USG agency.
**Multiple countries** indicates trial arms with sites in multiple countries.
**Randomized, adequately powered trials** are defined as randomized controlled trials in Phase 2 or beyond with expected enrollment of 250+ per arm for ventilated ICU, 500+ for hospitalized LRI, 1,000+ for early mild or asymptomatic, and 5,000+ for post-exposure prophylaxis (PEP) or pre-exposure prophylaxis (PrEP).
**Planned enrollment** is defined as enrollment per arm estimated from total enrollment by assuming even distribution of patients across all arms. It is not reflective of actual enrollment. Trial arms without planned enrollment information may represent expanded access programs.
**Counts for intervention classification** represent trial arms that involve single agents with that classification. Trial arms testing interventions as part of a regimen are included under "Combination regimen" and are indicated as "[Intervention] ++ [Intervention]". Trial arms testing interventions through multiple options (e.g., HCQ or CQ) are included under "Multiple options" and are indicated as "[Intervention]<or>[Intervention]".
**Hyperimmune globulin** includes non-human polyclonal antibody. **Other** category includes (not exhaustive) ACE inhibitors, ARBs, NSAIDs, other anti-infectives, other anti-hypertensives, oncolytics, and supplements.
**End date** represents primary readout for CT.gov trials and final completion dates for EU trials. **Date range 2021+** includes trials with unknown primary end dates.
**Primary endpoints** use the following grouping classification: mortality = mortality; markers of clinical status = index / composite score, time to recovery, organ failure, oxygenation requirements, imaging data, and other lab data; setting of care = ICU utilization and hospitalization status; viral load = viral load or clearance; adverse events = adverse events (caused by intervention); infection prevention = rate of COVID-19 infection; seroconversion = COVID-19 seroconversion; Other = endpoints not mentioned above including those with unknown endpoints.

Source: Clinicaltrials.gov accessed 12/11/2020 and WHO clinical trial registry accessed 12/11/2020

## Overview of COVID-19 clinical trials landscape by treatment approach

The therapies below are in development and are being tested in clinical trials.

**Filters** (apply to all charts)

| Randomized, adequately powered? | Start date (month) | US involved? | USG agency involved? |
|---|---|---|---|
| All | All | All | All |

**Reset filters** (this bar)

### Number of clinical trial arms by treatment approach (underway and completed) (filtered)

See notes below

| Classification | Subclassification | |
|---|---|---|
| Antivirals | Direct acting antivirals | 284 |
| | Targets intracellular environment | 235 |
| Immunomodulators | IL-6 inhibitors | 89 |
| | Other immunomodulators | 723 |
| Antibody therapy | Convalescent plasma | 201 |
| | Hyperimmune globulin | 37 |
| | Neutralizing antibody | 89 |
| Other | Other | 983 |
| Combination regimen | Combination regimen | 506 |
| Multiple options | Multiple options | 24 |

**Filtered trial arms** 3,171

0 100 200 300 400 500 600 700 800 900 1000

# applications (trial arms)

| | |
|---|---|
| Convalescent plasma | 201 |
| Hydroxychloroquine | 184 |
| MSCs | 75 |
| ivermectin | 67 |
| Favipiravir | 60 |
| Lopinavir/Ritonavir | 58 |
| tocilizumab | 57 |
| remdesivir | 53 |
| Chloroquine | 49 |
| Dexamethasone | 39 |
| Azithromycin ++ Hydroxychloroqui.. | 34 |
| Enoxaparin | 34 |
| Vitamin D | 33 |
| Methylprednisolone | 29 |
| povidone-iodine | 29 |
| niclosamide | 28 |
| Vitamin C | 26 |

# applications (trial arms)

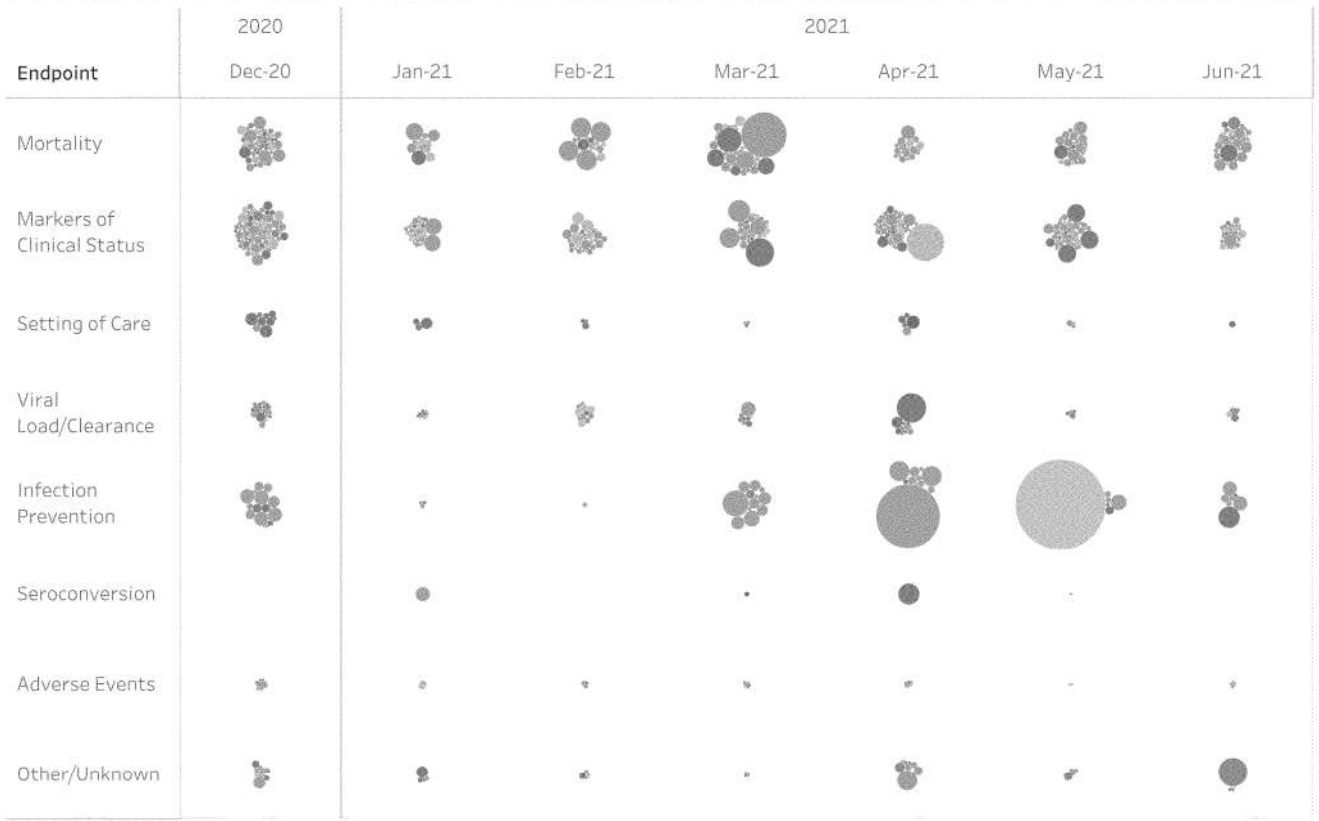
1 201

### Upcoming readouts by primary endpoints, target enrollment, and patient severity (filtered)

See notes below

**Intervention**

- ✔ 5-ALA/Sodium ferrous citrate
- ✔ Abatacept
- ✔ Abatacept ++ Remdesivir
- ✔ Abivertinib
- ✔ ABX-464
- ✔ ACEi
- ✔ Acetaminophen
- ✔ Acetaminophen ++ Azithromycin ++ Iverme..
- ✔ Acetyl-(L)-Carnitine hydrochloride
- ✔ Acetylcysteine
- ✔ Acetylcysteine ++ Bromelain
- ✔ adalimumab ++ IFN-b1A ++ Lopinavir/Riton..
- ✔ agenT-797
- ✔ AK-119
- ✔ AKS-452
- ✔ Aliskiren
- ✔ Alisporivir
- ✔ Allocetra-OTS
- ✔ almitrine dimesylate
- ✔ Alpha-1 proteinase inhibitor (human)
- ✔ alteplase
- ✔ Ambrisentan ++ Dapagliflozin
- ✔ Amiodarone
- ✔ Amlodipine
- ✔ Amniotic fluid
- ✔ Ampion
- ✔ AMX-101




**Target patient cohort**

- PrEP
- PEP
- Asymptomatic
- Mild
- Hospitalized LRI
- Ventilated ICU
- Recovered
- Unknown

All data in this output is subject to inherent uncertainty, limits, and variability and is shared to provide one of multiple contributions to informing discussions on COVID response, not as a stand-alone basis for recommendations or decision-making. The recipient is solely responsible for its decisions (including policy decisions), use of the materials, and compliance with applicable laws, rules and regulations.

**Global trial arms** corresponds to number of global investigational trials recruiting or completed. Excludes trials that have been terminated (or equivalent). Separates out multi-arm trials into distinct counts, including arms testing the same intervention in different doses or durations. May not be fully comprehensive. Excludes Traditional Chinese Medicine and vaccine trials. For trials without country information in registries, location is assigned as possible based on sponsor location.
**US involved** filter selects for trials in the United States, with at least one US site, or with USG agency involvement. **USG agency involved** filter selects for trial arms involving a USG agency.
**Multiple countries** indicates trial arms with sites in multiple countries.
**Randomized, adequately powered trials** are defined as randomized controlled trials in Phase 2 or beyond with expected enrollment of 250+ per arm for ventilated ICU, 500+ for hospitalized LRI, 1,000+ for early mild or asymptomatic, and 5,000+ for post-exposure prophylaxis (PEP) or pre-exposure prophylaxis (PrEP).
**Planned enrollment** is defined as enrollment per arm estimated from total enrollment by assuming even distribution of patients across all arms. It is not reflective of actual enrollment. Trial arms without planned enrollment information may represent expanded access programs.
**Counts for intervention classification** represent trial arms that involve single agents with that classification. Trial arms testing interventions as part of a regimen are included under "Combination regimen" and are indicated as "[Intervention] ++ [Intervention]". Trial arms testing interventions through multiple options (e.g., HCQ or CQ) are included under "Multiple options" and are indicated as "[Intervention]<or>[Intervention]".
**Hyperimmune globulin** includes non-human polyclonal antibody. **Other** category includes (not exhaustive) ACE inhibitors, ARBs, NSAIDs, other anti-infectives, other anti-hypertensives, oncolytics, and supplements.
**End date** represents primary readout for CT.gov trials and final completion dates for EU trials. **Date range 2021+** includes trials with unknown primary end dates.
**Primary endpoints** use the following grouping classification: mortality = mortality; markers of clinical status = index / composite score, time to recovery, organ failure, oxygenation requirements, imaging data, and other lab data; setting of care = ICU utilization and hospitalization status; viral load = viral load or clearance; adverse events = adverse events (caused by intervention); infection prevention = rate of COVID-19 infection; seroconversion = COVID-19 seroconversion; Other = endpoints not mentioned above including those with unknown endpoints.

Source: Clinicaltrials.gov accessed 12/11/2020 and WHO clinical trial registry accessed 12/11/2020

**From:** Sarwar, Elaha (PHAC/ASPC)
**Sent:** 2021-02-26 10:41 AM
**To:** Ha, Shalane (PHAC/ASPC); Marinsky, Cheryl (PHAC/ASPC); Dave, Jaahnavi (PHAC/ASPC); Cortés-Kaplan, Serena (PHAC/ASPC)
**Cc:** Forbes, Nicole (PHAC/ASPC)
**Subject:** Daily Titles for Feb. 26

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Good morning,

Here is the one title for today. We are still waiting for the McMaster email for the day, so I may have a follow-up email coming your way!

If you could please add your completed work to the shared folder by 2PM EST, that would be great!

| | |
|---|---|
| **Cheryl** | Abstract<br>**Okumuş, Nurullah, Demirtürk, et al(2021). Evaluation of the Effectiveness and Safety of Adding Ivermectin to Treatment in Severe COVID-19 Patients *Research Square prepub*,** https://www.researchsquare.com/article/rs-224203/v1 |
| **Shalana** | Nil |
| **Jaahnavi** | Carried-over SR abstract |
| **Serena** | Nil |
| **Elaha** | Scan LOVE and McMaster platforms for relevant titles<br>Triage all titles<br>Send titles to review team<br>Review all summaries/abstracts<br>Email prep and send out to MCM group |

Thank you,
Elaha

**From:** Sarwar, Elaha (PHAC/ASPC)
**Sent:** 2021-03-10 1:06 PM
**To:** Marinsky, Cheryl (PHAC/ASPC); Dave, Jaahnavi (PHAC/ASPC); Cortés-Kaplan, Serena (PHAC/ASPC)
**Cc:** Forbes, Nicole (PHAC/ASPC)
**Subject:** UPDATE Daily Titles for March 10

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Good afternoon,

I was too quick to celebrate today's workload, please see additional titles that were flagged for today!

| | |
|---|---|
| Cheryl | **Abstract**<br>**Use of ivermectin in the treatment of Covid-19: a pilot trial**<br>https://www.sciencedirect.com/science/article/pii/S2214750021000445 |
| Jaahnavi | **Abstract**<br>**Robinson, Robert, Prakash, et al(2021). Impact of remdesivir on 28 day mortality in hospitalized patients with COVID-19: February 2021 Meta-analysis *medRxiv*,**<br>https://www.medrxiv.org/content/10.1101/2021.03.04.21252903v1 |
| Serena | **Nil** |
| **Elaha** | **Summary**<br>**Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial**<br>https://www.medrxiv.org/content/10.1101/2021.03.09.21252736v1<br><br>**Scan ESG, LOVE and McMaster platforms for relevant titles**<br>**Triage all titles**<br>**Send titles to review team**<br>**Review all summaries/abstracts**<br>**Email prep and send out to MCM group** |

Thank you,
Elaha

Correspondence on Colchicine and Ivermectin and Vitamin D

Publication of a study's findings does not necessarily indicate that the studied treatment is effective, nor that the study's conclusions are valid. The certainty (or quality) of the evidence refers to how confident we can be that the research provides an accurate picture of the effect of a particular treatment and can be trusted to inform decision-making about procurement and recommendations for use to treat Canadian patients with COVID-19. The Public Health Agency of Canada (PHAC) conducts a thorough analysis and synthesis of the emerging evidence of promising therapeutics to treat COVID-19. This work informs decisions around procurement of therapeutics that have been proven safe and effective.

Commented [MG1]: Not sure if this stays true to the meaning, but trying to simplify

Commented [MG2]: Add in text around PHAC work, i.e., analysis and synthesis of the emerging evidence of promising therapeutics to treat COVID-19. This work informs decisions around procurement of therapeutics that have been proven safe and effective.

Although many studies have been conducted on vitamin D, ivermectin and colchicine for the treatment of COVID-19, the certainty of the evidence has ranged from inconclusive to poor due to flaws in the methods (such as the wrong study design, small sample size, no plan to limit confounding and bias, and insufficient follow-up). Consequently, additional studies, which are larger providing more data with better methods and designs, are required to ensure confidence in the usefulness of the evidence regarding the use of vitamin D, ivermectin and colchicine as treatments for COVID-19.

Ivermectin is a broad-spectrum anti-parasitic agent authorized and approved by Health Canada for human and veterinary applications. Although ivermectin is used in humans to treat parasitic infections such as intestinal strongyloidiasis, onchocerciasis, scabies and possible use to treat rosacea. Health Canada has **not** authorized its use for the treatment of COVID-19. The first of many steps in the authorization process includes the provision of promising results documented and obtained from high quality study designs followed by submission of an application by the manufacturer to Health Canada, which follows a well-defined channel to qualify for approval for a particular indication.

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In laboratory studies ivermectin has been shown to inhibit the virus causing COVID-19 from replicating raising the possibility that ivermectin may have a role in COVID-19 prophylaxis or treatment; however, many drugs that show promise in laboratory studies are not found to be effective in patients. To address the increased international attention on ivermectin as a potential treatment for COVID-19, the World Health Organization (WHO) convened an independent, international panel of clinical care experts from multiple specialties, patient partners and ethicists. Following a review of the existing data reviewing both inpatient and outpatient trial results, the panel concluded that the existing evidence regarding ivermectin's effectiveness in reducing mortality, need for mechanical ventilation, need for hospital admission and time to clinical improvement was of very low certainty. Consequently, on March 31st 2021, The World Health Organization issued a statement on ivermectin advising against its use outside of clinical trials, stating the current evidence was inconclusive.

Prior to the statement issued by the WHO, Merck and Co. Inc., the manufacturer of ivermectin, issued a statement February 4th, 2021 against the use of this drug for the purposes of treating COVID-19. The announcement ensued its own analysis of the preclinical and clinical trials indicating that the data did not support the efficacy of this drug to treat COVID-19. Furthermore, Merck stated concerns over the lack of safety data in studies evaluating ivermectin use in patients with COVID-19 and has not applied to Health Canada for authorization of this drug to treat COVID-19.

Colchicine is an anti-inflammatory drug authorized by Health Canada for the treatment of gout, and other inflammatory diseases, for short courses of treatment and is used off-label for the prevention of acute or recurrent pericarditis, and other conditions at the discretion of the primary heath care provider. Use of this drug for therapeutic purposes is limited by side effects such as fatigue, nausea, vomiting, and diarrhea. Interest in this drug, which has been marketed in Canada for at least 40 years with known side effects, is derived from its anti-inflammatory activity and potential use to prevent the "cytokine storm" characteristic of severe COVID-19. A review of available clinical trial results, evaluating the effectiveness of colchicine as a treatment for COVID-19 was independently conducted by various Canadian expert groups (PHAC, the Canadian Agency for Drugs and Technologies in Health, l'Institut national d'excellence en santé et services sociaux and Alberta Health Services). All of whom concluded that the available studies were of low quality. The only exception was the trial conducted by a Canadian research team at the Montreal Heart Institute, which was of moderate quality; however all the studies evaluated had several weaknesses limiting the certainty placed on the results. Canadian expert groups therefore concluded that there was no clear benefit to colchicine treatment and some concerning harms (e.g. a small number of patients colchicine treatment led to the development of blood clots in the lungs, a serious complication that could lead to death). There are a number of ongoing clinical trials of colchicine, as these results become available, they will be evaluated to assess if there is a benefit to treating COVID-19 patients with this re-purposed drug. At this time, Canadian expert groups do not recommend prescribing colchicine to treat COVID-19.

(We could add the links to the CADTH, INESS and Alberta Health Services here, thoughts?)

For more information, the following link provides a statement from Merck and Co. Inc. issuing a statement against the use of ivermectin for the treatment of COVID-19:

https://www.merck.com/news/merck-statement-on-ivermectin-use-during-the-covid-19-pandemic/

For more information, the following link provides the World Health Organization's guidance on the use to ivermectin to treat COVID-19:

https://www.who.int/news-room/feature-stories/detail/who-advises-that-ivermectin-only-be-used-to-treat-covid-19-within-clinical-trials

**From:** Timmerman, Karen (PHAC/ASPC)
**Sent:** 2020-12-08 11:18 AM
**To:** Marinsky, Cheryl (PHAC/ASPC); Sarwar, Elaha (PHAC/ASPC); Ha, Shalane (PHAC/ASPC)
**Subject:** Daily Titles for Tuesday December 8th

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**Importance:** High

Hi Everyone,

Lots of titles today.

Here they are:

| | |
|---|---|
| Cheryl | **Summary**<br>**Ahmed, S, Karim, et al(2020). PMC7709596; A five day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness *Int J Infect Dis*,**<br>https://www.sciencedirect.com/science/article/pii/S1201971220325066?via%3Dihub<br><br>**Summary**<br>**Butt, JH, Gerds, et al(2020). Association between statin use and outcomes in patients with coronavirus disease 2019 (COVID-19): a nationwide cohort study *BMJ Open*,**<br>https://bmjopen.bmj.com/content/10/12/e044421 |
| Elaha | **Potential SR**<br>**Kalfas, Stefanie, Visvanathan, et al(2020). THE THERAPEUTIC POTENTIAL OF IVERMECTIN FOR COVID-19: A SYSTEMATIC REVIEW OF MECHANISMS AND EVIDENCE *medRxiv*,**<br>https://www.medrxiv.org/content/10.1101/2020.11.30.20236570v1<br><br>**Abstract**<br>**Vu, Christine, Deronde, et al(2020). Effects of Tocilizumab in COVID-19 patients: a cohort study *Research Square prepub*,**<br>https://www.researchsquare.com/article/rs-49532/v3<br><br>**Abstract**<br>**Yoon, Hyun ah, Bartash, et al(2020). Treatment of Severe COVID-19 with Convalescent Plasma in the Bronx, NYC *medRxiv*,**<br>https://www.medrxiv.org/content/10.1101/2020.12.02.20242909v1<br><br>**Abstract**<br>**Zhao, H, Zhu, et al(2021). Tocilizumab combined with favipiravir in the treatment of COVID-19: A multicenter trial in a small sample size *Biomedicine and Pharmacotherapy*,**<br>https://www.sciencedirect.com/science/article/pii/S0753332220310180?via%3Dihub |

| | |
|---|---|
| Shalane | **Abstract**<br>Choi, MJ, Kang, et al(2021). Comparison of antiviral effect for mild-to-moderate COVID-19 cases between lopinavir/ritonavir versus hydroxychloroquine: A nationwide propensity score-matched cohort study *International Journal of Infectious Diseases*, https://www.sciencedirect.com/science/article/pii/S1201971220322669?via%3Dihub<br><br>**Abstract**<br>Górgolas Hernández-Mora, M, Cabello Úbeda, et al(2021). Compassionate use of tocilizumab in severe SARS-CoV2 pneumonia *International Journal of Infectious Diseases*, https://www.sciencedirect.com/science/article/pii/S1201971220322499?via%3Dihub<br><br>**Abstract**<br>Ji, J, Wu, et al(2020). Early, low-dose, short-term methylprednisolone decreased the mortality in critical COVID-19 patients: A multicenter retrospective cohort study *Journal of Infection*, https://www.sciencedirect.com/science/article/pii/S0163445320306964?via%3Dihub<br><br>**Abstract**<br>Li, G, Yuan, et al(2020). Safety and efficacy of artemisinin-piperaquine for treatment of COVID-19: an open-label, non-randomised and controlled trial *International journal of antimicrobial agents*, https://www.sciencedirect.com/science/article/pii/S0924857920304271?via%3Dihub<br><br>**Abstract**<br>Shi, N, Guo, et al(2021). Efficacy and safety of Chinese herbal medicine versus Lopinavir-Ritonavir in adult patients with coronavirus disease 2019: A non-randomized controlled trial *Phytomedicine*, https://www.sciencedirect.com/science/article/pii/S0944711320301987?via%3Dihub |
| Karen | **Citation**<br>(2020). 32749474; Erratum: Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: a randomized clinical trial (JAMA (2020) DOI: 10.1001/jama.2020.10044) *JAMA - Journal of the American Medical Association*, https://jamanetwork.com/journals/jama/fullarticle/2768954<br><br>**Citation**<br>(2020). Erratum: Hydroxychloroquine with or without azithromycin in mild-to-moderate covid-19 (The New England Journal of Medicine DOI: 10.1056/nejmoa2019014) *New England Journal of Medicine*, https://www.nejm.org/doi/10.1056/NEJMx200021<br><br>**Triage all titles** |

| | |
|---|---|
| | **Send titles to review team**<br><br>**Review all summaries/abstracts**<br><br>**Email prep and send out to MCM group** |

## Manuel, Suzzanne (PHAC/ASPC)

**From:** Cassidy, Vicki-Lynn (PHAC/ASPC) on behalf of Chief Public Health Officer / La chef de la santé publique (PHAC/ASPC)
**Sent:** 2021-04-21 12:31 PM
**To:** Executive Correspondence (PHAC/ASPC)
**Cc:** McLeod, Robyn (PHAC/ASPC)
**Subject:** 21-108019-10 FW: Ivermectin

Good afternoon Exec Correspondence,

Please see the below questions for a direct reply.

-----Original Message-----
From [redacted]
Sent: 2021-04-21 12:14 PM
To: Chief Public Health Officer / La chef de la santé publique (PHAC/ASPC) <phac.cpho-acsp.aspc@canada.ca>
Subject: Ivermectin

Dear Dr. Tam,
First, thank you for your service during this trying time of Covid. During this time I have been doing a lot of research on Covid and on many treatments [redacted] I am distressed that three things that dramatically impact Covid are being ignored, Ivermectin, Vitamin D(with adequate dosing) and Colchicine. WHY are these are not being allowed! Please do not write back and say that there is not enough evidence as that is simply not true! These are medications that have been studied and used for a very long time. People are losing their lives, livelihoods are being destroyed, families are being stressed beyond their ability to cope and here we sit ignoring treatments that would dramatically impact all of these. These kinds of treatments along with the vaccines are needed. It is not enough to simply mask and distance . It is beyond time for the powers that be to open up their minds and stop ignoring the evidence!
Thank you for your time.
Sincerely, [redacted]

Sent from my iPad

**From:** Gale-Rowe, Margaret (PHAC/ASPC)
**Sent:** 2021-04-26 3:36 PM
**To:** COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC)
**Cc:** Marinsky, Cheryl (PHAC/ASPC); Sarwar, Elaha (PHAC/ASPC)
**Subject:** Re: LISA AND THERAPEUTICS TEAM FOR INPUT BY APRIL 29 - 21-108019 - Vitamin D, Colcichine, Ivermectin

---

It wasn't clear to me if they wanted our approval of the draft input (could be that) or approval of our input on our end.

Would appreciate a 2 day extension.

Thanks,

Margaret

Medical Advisor - COVID Therapeutics Acquisitions
613-618-9266

> On Apr 26, 2021, at 3:12 PM, COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC) <phac.covid-19therapeutics-therapeutiques.aspc@canada.ca> wrote:
>
> Thanks everyone.
>
> I assume it must be DG approved by the 29th. No, it doesn't seem like a feasible amount of time. Would it be appropriate for me to request an extension?
>
> Celisse
>
> ---
>
> **From:** Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>
> **Sent:** 2021-04-26 2:53 PM
> **To:** COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC) <phac.covid-19therapeutics-therapeutiques.aspc@canada.ca>
> **Cc:** Marinsky, Cheryl (PHAC/ASPC) <cheryl.marinsky@canada.ca>; Sarwar, Elaha (PHAC/ASPC) <elaha.sarwar@canada.ca>
> **Subject:** LISA AND THERAPEUTICS TEAM FOR INPUT BY APRIL 29 - 21-108019 - Vitamin D, Colcichine, Ivermectin
>
> Cheryl is drafting input.
>
> Is this to be DG-approved by April 29th? We will do our best but that is a short turnaround for a request from the public that requires summarizing evidence. I haven't been able to get to my pre-existing "to do" list today due to other time-sensitive HR things and emails.
>
> Margaret

**From:** Poon Young, Celisse (PHAC/ASPC) <celisse.poonyoung@canada.ca> **On Behalf Of** COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC)
**Sent:** 2021-04-26 1:54 PM
**To:** Gale-Rowe, Margaret (PHAC/ASPC) <margaret.gale-rowe@canada.ca>; Marinsky, Cheryl (PHAC/ASPC) <cheryl.marinsky@canada.ca>; Lawuyi2, Niyi (PHAC/ASPC) <niyi.lawuyi2@canada.ca>
**Cc:** Poon Young, Celisse (PHAC/ASPC) <celisse.poonyoung@canada.ca>
**Subject:** FW: LISA AND THERAPEUTICS TEAM FOR INPUT BY APRIL 29 - 21-108019 - Vitamin D, Colcichine, Ivermectin
**Importance:** High

Hi everyone,

Please see the request that came to the Therapeutics inbox this afternoon. Sending to you all since I am not sure exactly who this should be directed to.

Thank you,

Celisse

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**From:** Jamil, Marium (PHAC/ASPC) <marium.jamil@canada.ca>
**Sent:** 2021-04-26 12:21 PM
**To:** Waddell, Lisa (PHAC/ASPC) <lisa.waddell@canada.ca>; COVID-19 Therapeutics / Thérapeutiques (PHAC/ASPC) <phac.covid-19therapeutics-therapeutiques.aspc@canada.ca>
**Cc:** PHAC.F OCSO_ESGSecretariat / BCSC_SecrétariatGSE F.ASPC <phac.ocso_esgsecretariat-bcsc_secretariatgse.aspc@canada.ca>
**Subject:** LISA AND THERAPEUTICS TEAM FOR INPUT BY APRIL 29 - 21-108019 - Vitamin D, Colcichine, Ivermectin
**Importance:** High

Good morning Lisa and Therapeutics team,
**FOR INPUT/APPROVAL – BY APRIL 29**
**CONTEXT**

- Dr. Tam received correspondence on April 21, 2021 from a member of the public (please see attached '21-108019-10 Incoming Apr 22.pdf'), regarding the use of Vitamin D, Ivermectin and Colchicine as treatments for COVID-19.

**FOR INPUT**

- ESG Secretariat has drafted a standard response in regards to the use of Vitamin D (please see attached '21-108019-VitD_Colchicine, Ivermectin _ Response_Apr2021. doc') adapted from previous responses. The letter does not speak to Colchicine or Ivermectin however. We would be thankful if you could please provide **your input on:**
    - **Any evidence to support the use of Ivermectin and Colchicine**
    - **Any NEW evidence on the efficacy of Vitamin D**

Thank you so much for your time. We would be grateful if you could please provide us your input by April 29th.

Please let us know if you have any questions.

Regards,
Marium

*On behalf of the Office of Chief Science Officer and the PHAC Emerging Science Group Secretariat*

**Marium Jamil**
(she | elle)
Policy Analyst | Analyste des politiques
Office of the Chief Science Officer | Bureau du Conseiller scientifique en chef
Public Health Agency of Canada | Agence de la santé publique du Canada
NEW: phac.ocso_esgsecretariat-bcsc_secretariatgse.aspc@canada.ca

**From:** Timmerman, Karen (PHAC/ASPC)
**Sent:** 2020-12-09 10:54 AM
**To:** Marinsky, Cheryl (PHAC/ASPC); Sarwar, Elaha (PHAC/ASPC); Ha, Shalane (PHAC/ASPC)
**Subject:** Daily Titles for Wednesday December 9th

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**Importance:** High

Hi Everyone,

Here are the titles for today:

| | |
|---|---|
| **Cheryl** | **Summary**<br>Gonzalez Ochoa, et al(2020). **Sulodexide in the treatment of patients with early stages of COVID-19: a randomised controlled trial.** *medRxiv*<br>https://www.medrxiv.org/content/10.1101/2020.12.04.20242073v1<br><br>**Abstract**<br>Chaccour, Carlos, Casellas, et al(2020). The effect of early treatment with ivermectin on viral load, symptoms and humoral response in patients with mild COVID-19: a pilot, double-blind, placebo-controlled, randomized clinical trial *Research Square prepub*,<br>https://www.researchsquare.com/article/rs-116547/v1 |
| **Elaha** | **Abstract**<br>Xiang, Yong, Wong, et al(2020). Exploring drugs and vaccines associated with altered risks and severity of COVID-19: a UK Biobank cohort study of all ATC level-4 drug categories *medRxiv*,<br>https://www.medrxiv.org/content/10.1101/2020.12.05.20244426v1<br><br>**Abstract**<br>Dai, W, Wu, et al(2020). Clinical outcomes for COVID-19 patients with diabetes mellitus treated with convalescent plasma transfusion in Wuhan, China *J Med Virol*,<br>https://onlinelibrary.wiley.com/doi/10.1002/jmv.26712 |
| **Shalane** | **Summary**<br>Frost, MT, Jimenez-Solem, et al(2020). The Adaptive COVID-19 Treatment Trial-1 (ACTT-1) in a real-world population: a comparative observational study *Crit Care*,<br>https://ccforum.biomedcentral.com/articles/10.1186/s13054-020-03406-3<br><br>**Abstract**<br>Alsharidah, S, Ayed, et al(2020). COVID-19 Convalescent Plasma Treatment of Moderate and Severe Cases of SARS-CoV-2 Infection: A Multicenter Interventional Study *Int J Infect Dis*, |

| | |
|---|---|
| | https://www.sciencedirect.com/science/article/pii/S1201971220325133?via%3Dihub |
| **Karen** | **Triage all titles**<br>**Send titles to review team**<br>**Review all summaries/abstracts**<br>**Email prep and send out to MCM group** |

- Ahmed et al, 2021. A five-day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness. Journal of Infectious Diseases, February, 2021.
- *Taken directly from Abstract:*

  **Background:** Ivermectin, a US Food and Drug Administration-approved anti-parasitic agent, was found to inhibit severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) replication in vitro.

  **Methods:** A randomized, double-blind, placebo-controlled trial was conducted to determine the rapidity of viral clearance and safety of ivermectin among adult SARS-CoV-2 patients. The trial included 72 hospitalized patients in Dhaka, Bangladesh, who were assigned to one of three groups: oral ivermectin alone (12 mg once daily for 5 days), oral ivermectin in combination with doxycycline (12 mg ivermectin single dose and 200 mg doxycycline on day 1, followed by 100 mg every 12 h for the next 4 days), and a placebo control group. Clinical symptoms of fever, cough, and sore throat were comparable among the three groups.

  **Results:** Virological clearance was earlier in the 5-day ivermectin treatment arm when compared to the placebo group (9.7 days vs 12.7 days; p = 0.02), but this was not the case for the ivermectin + doxycycline arm (11.5 days; p = 0.27). There were no severe adverse drug events recorded in the study.

  **Conclusions:** A 5-day course of ivermectin was found to be safe and effective in treating adult patients with mild COVID-19. Larger trials will be needed to confirm these preliminary findings

- SUMMARY + CONTEXT: **This randomized, double-blind, placebo-controlled trial in a single centre assessed the safety of ivermectin treatment and rapidity of viral clearance in a sample of 72 hospitalized, adult patients with mild COVID-19 assigned to one of three arms (oral ivermectin monotherapy, oral ivermectin + doxycycline combination therapy or a placebo control). The mean duration to viral clearance was reported to be significantly lower in the 5-day oral ivermectin monotherapy group compared with the placebo treated group on day 7 and 14 follow-up a similar non-significant trend was reported in the combination therapy group versus the placebo treated group. No severe adverse events were reported.**

- **PREPRINT** Bukhari et al, 2021. Efficacy of Ivermectin in COVID-19 Patients with Mild to Moderate Disease medRxiv, February 5,2020
- *Taken directly from Abstract:*

  **Objective:** To evaluate the efficacy of ivermectin (IVM) as an addition to the standard of care (SOC) treatment in COVID-19 patients with mild and moderate disease

  **Methods:** A randomized clinical trial (Trial registration # NCT04392713) was carried out at Combined Military Hospital Lahore from March 15, 2020, to June 15, 2020. Eighty-six patients with reverse transcriptase-polymerase chain reaction (RT-PCR) proven SARS-CoV-2 infection completed the trial protocol. Patients were stratified via the lottery method into two groups. Group A was administered standard of care (SOC) treatment as per existing hospital guidelines whereas group B was given ivermectin (single dose of 12 milligrams) along with SOC treatment. PCR was repeated at 72 hours, 7th day, and at 14th day of admission for both the groups and the point at which the PCR became negative was noted. Complete blood counts, liver function tests and renal function tests were done at recruitment, 7th day, and 14th day. The primary outcome was the viral clearance, measured as days to achieve PCR negativity. The secondary outcome was the development of any adverse side effects pertinent to ivermectin or derangement in baseline laboratory parameters.

  **Results:** In group A, 36 (80%) participants were males, and 9 (20%) were females, whereas in group B, 37 (90.2%) were males and 4 (9.8%) were females. Mean age was 39.0± 12.6 and 42.2 ± 12.0 years for groups A and B, respectively (p= 0.394). There was early viral clearance in group B as compared to group A (p=0.001). No adverse reaction or derangements in laboratory parameters was noted in the intervention arm during the trial period.

  **Conclusions:** In the intervention arm, early viral clearance was observed and no side effects were documented. Therefore ivermectin is a potential addition to the standard care of treatment in COVID-19 patients.
- SUMMARY + CONTEXT**: This single centre, non-blinded, randomized clinical trial assessed the safety and efficacy of ivermectin treatment + standard of care (SOC) to achieve viral clearance (time to RT-PCR negativity) compared with SOC alone among 86 hospitalized, adult patients with mild to moderate COVID-19 disease. The ivermectin +SOC treatment arm reported early viral clearance with more patients achieving a negative RT-PCR in fewer days compared with the SOC alone treated group (p=0.001). No adverse events reported in either group over the 14-day follow-up period.**

- Chaccour et al, 2020, The effect of early treatment with ivermectin on viral load, symptoms and humoral response in patients with mild COVID-19: a pilot, double-blind, placebo-controlled, randomized clinical trial Research Square, December 7, 2020
- *Taken directly from Abstract:*

  **Background:** Ivermectin inhibits the replication of SARS-CoV-2 in vitro at concentrations not readily achievable with currently approved doses. There is limited evidence to support its clinical use in COVID-19 patients.

  **Methods:** A pilot, randomized, double-blind, placebo-controlled trial to determine the efficacy of a single dose of ivermectin to reduce the proportion of PCR positives, viral load at day 7 post treatment. Consecutive patients with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and mild COVID-19 (no pneumonia) and no risk factors for complicated disease attending the emergency room of the Clínica Universidad de Navarra. Patients were randomized 1:1 to receive ivermectin, 400 mcg/kg, single dose (n = 12) or placebo (n = 12).

  **Results:** The primary outcome measure was the proportion of patients with detectable SARS-CoV-2 RNA by PCR from nasopharyngeal swab at day 7 post-treatment. The primary outcome was supported by determination of the viral load and infectivity of each sample. The differences between ivermectin and placebo were calculated using Fisher's exact test and presented as a relative risk ratio. All patients recruited completed the trial (median age, 26 [range, 18-54] years; 12 [50%] women; 100% had symptoms at recruitment, 70% reported headache, 62% reported fever, 50% reported general malaise and 25% reported cough). At day 7, there was no difference in the proportion of PCR positive patients (RR 0.92, 95% CI: 0.77-1.09, p = 1.0). The ivermectin group had lower median viral loads at days 4 and 7 post treatment as well as lower median IgG titers at day 21 post treatment. Hyposmia/anosmia (76 vs 158 patient-days) and cough (68 vs 97 patient-days) were less frequent in the ivermectin group.

  **Conclusions:** Among patients with mild COVID-19 and no risk factors for severe disease receiving a single 400 mcg/kg dose of ivermectin within 48 hours of fever or cough onset there was no difference in the proportion of PCR positives. There was however a marked reduction of anosmia/hyposmia, a reduction of cough and a tendency to lower viral loads and lower IgG titers which warrants assessment in larger trials.
- SUMMARY + CONTEXT: **This pilot, randomized, double-blind, placebo controlled trial of adult outpatients at low risk, with mild COVID-19 disease treated with a single dose of ivermectin reported lower median viral loads, lower IgG titers 21 days post treatment than the placebo arm. A reduction in cough and anosmia/hyposmia was also reported in the invermectin treated group compared with the placebo arm at 21 days post treatment. Fifteen adverse events were reported at 28 day follow up, 7 in the ivermectin arm and 8 in the placebo arm, which included confusion, drowsiness, and pruritus. Ten patients experienced adverse events, five of whom were in the ivermectin treated arm reported more patient-days of dizziness and blurred vision.**

- Chachar et al, 2020. Effectiveness of ivermectin in SARSCoV-2/COVID-19 patients. International Journal of Sciences, September 2020.
- *Taken directly from Abstract:*

  **Background:** The first case of Infection with severe acute respiratory syndrome coronavirus 2 (SARSCoV-2) were diagnosed in Wuhan, China in 2019. In the first half of 2020, this disease has already converted into a global pandemic. Objectives, to assess the efficacy of Ivermectin in mild cases of COVID-19 patients on the basis of predefined assessment criteria.

  **Methods:** Study setting Fatima Memorial Hospital, Lahore open label randomized control trial. Duration of study, from 1st May, 2020 to 30th June, 2020. Sample size and technique: Sample size was 50 patients; 25 patients were kept in control group and 25 patients were kept in experimental group.

  **Results:** There were total 50 patients, divided into two groups case and control group. The mean age of the participants was 40.60 ± 17 and out of those 31 (62%) were male and 19 (38%) were females. Cough was observed more in case group (p= 0.049). Fever, myalgias and dyspnea were the commonest symptoms in both the groups (p= 1.000). Diarrhea and vomiting were more common in control group (p=0.0001, p= 0.042 respectively). On follow up at day 7, patients were stratified as asymptomatic and symptomatic. Amongst the case group, out of 25 patients, 16 (64%) patients were asymptomatic and rest of the 9 (36%) patients were asymptomatic. In control group, out of 25 patients, 15 (60%) patients were asymptomatic and rest of the 10 (40%) patients was asymptomatic p-value (0.500). Statistically there was no significant difference between case group who were given ivermectin along with symptomatic treatment and control group who were only given symptomatic treatment without ivermectin, being asymptomatic on day 7 at follow up. p-value (0.500)

  **Conclusions:** Our study didn't show statistically any significant difference between case and control group. In Ivermectin's (case group) recovery was almost equal to control group who received only conventional symptomatic treatment, so this is the need of the day that we need to conduct more randomized controlled trials across our country involving major tertiary care health care facilities with larger sample size to assess its efficacy for validating the use of Ivermectin against SARS-CoV-2.

- SUMMARY + CONTEXT: **This open label randomized controlled trial in a single centre of 50 adult outpatients with mild COVID-19 disease compared the efficacy of ivermectin treatment + symptomatic care versus symptomatic care alone in symptom resolution. No difference was reported between groups on symptom resolution by day 7 follow-up. Eight patients in the ivermectin treated arm reported experiencing heartburn.**

- **Preprint** Mohan et al, 2021. Ivermectin in mild and moderate COVID-19 (RIVET-COV): a randomized, placebo-controlled trial. Research Square, February 2,2021
- *Taken directly from Abstract:*

  **Background:** Till date, no drug has shown definite benefit in non-severe COVID-19. Ivermectin is an antiparasitic drug which has in-vitro efficacy in reducing coronavirus-2 (SARS-CoV-2) load in severe disease. To determine if a single oral administration of Ivermectin to patients with mild and moderate COVID-19 is effective in converting SARS-CoV-2 RT-PCR to negative result and in reducing viral load.

  **Methods:** In this double-blind trial, patients were randomized to elixir formulation of Ivermectin in 24 mg, 12 mg or placebo in 1:1:1 ratio. The co-primary outcomes were conversion of RT-PCR to negative result and the decline of viral load at day 5 of enrolment and were assessed in patients with positive RT-PCR at enrolment (modified intention-to-treat population). Safety outcomes included total and serious adverse events and were assessed in all patients who received the trial drug (intention-to-treat population).

  **Results:** Among 157 patients randomized, 125 patients were included in mITT analysis. Forty patients each were assigned to Ivermectin 24 mg and 12 mg, and 45 patients to placebo. The RT-PCR negativity at day 5 was higher in the two Ivermectin arms but failed to attain statistical significance (Ivermectin 24 mg, 47.5%; 12 mg, 35.0%; and placebo, 31.1%; p= 0.30). The decline of viral load at day 5 was similar in the three arms. No serious adverse events were encountered.

  **Conclusions:** In patients with mild and moderate COVID-19, a single administration of Ivermectin elixir (either 24 mg or 12 mg) demonstrated a trend towards higher proportion of RT-PCR negativity at day 5 of enrolment.
- SUMMARY + CONTEXT: **This single centre, multi-arm, double-blind randomized controlled trial, assessed the efficacy of two different doses of oral ivermectin (single treatment) in reducing the viral load and conversion of RT-PCR test result from positive to negative in 157 adult patients with mild to moderate COVID-19. Both of the ivermectin treatment arms reported a higher proportion of negative RT-PCR results by day 5 than the placebo group; the result was not statistically significant (p=0.30). No difference in reduction of viral load between groups at 5-day follow-up, nor on any of the secondary outcome measures (i.e. mean duration of symptom resolution, duration of hospital free days at day 28 and measure of clinical worsening by WHO ordinal scale). All arms experienced adverse events; the most commonly reported side effect was the sensation of epigastric burning in 17 patients.**

- **Preprint** Okumus et al, 2021. Evaluation of the Effectiveness and Safety of Adding Ivermectin to Treatment in Severe COVID-19 Patients. BMC Infectious Diseases, February 24,2021.
- *Taken directly from Abstract:*

  **Background:** An effective treatment option is not yet available for SARS-CoV2, which causes the COVID-19 pandemic and whose effects are felt more and more every day. Ivermectin is among the drugs whose effectiveness in treatment has been investigated. In this study; it was aimed to investigate the presence of gene mutations that alter ivermectin metabolism and cause toxic effects in patients with severe COVID-19 pneumonia, and to evaluate the effectiveness and safety of ivermectin use in the treatment of patients without mutation.

  **Methods:** Patients with severe COVID19 pneumonia were included in the study, which was planned as a prospective, randomized, controlled, single-blind phase 3 study. Two groups, the study group and the control group, took part in the study. Ivermectin 200 mcg/kg/day for five days in the form of a solution prepared for enteral use added to the reference treatment protocol -hydroxychloroquine + favipiravir + azithromycin- of patients included in the study group. Patients in the control group were given only reference treatment with 3 other drugs without ivermectin. The presence of mutations was investigated by performing sequence analysis in the mdr1/abcab1 gene with the Sanger method in patients included in the study group according to randomization. Patients with mutations were excluded from the study and ivermectin treatment was not continued. Patients were followed for 5 days after treatment. At the end of the treatment and follow-up period, clinical response and changes in laboratory parameters were evaluated.

  **Results:** A total of 66 patients, 36 in the study group and 30 in the control group were included in the study. Mutations affecting ivermectin metabolism was detected in genetic tests of six (16.7%) patients in the study group and they were excluded from the study. At the end of the 5-day follow-up period, the clinical improvement rate was higher in the study group [22/30 (73.3%)] compared to the control group [16/30 (53.3%)] (p=0.10). At the end of the study, mortality developed in 6 patients (20%) in the study group and in 9 (30%) patients in the control group (p=0.37). At the end of the follow-up period, the average peripheral capillary oxygen saturation (SpO2) values of the study and control groups were found to be 93.5% and 93.0%, respectively. Partial pressure of oxygen (PaO2)/FiO2 ratios were determined as 236.3 ± 85.7 and 220.8 ± 127.3 in the study and control groups, respectively. While the blood lymphocyte count was higher in the study group compared to the control group (1698±1438 and 1256±710, respectively) at the end of the follow-up period (p=0.24); reduction in serum C-reactive protein (CRP), ferritin and D-dimer levels was more pronounced in the study group (p=0.02, p=0.005 and p=0.03, respectively).

  **Conclusions:** According to the findings obtained, ivermectin can provide an increase in clinical recovery, improvement in prognostic laboratory parameters and a decrease in mortality rates even when used in patients with severe COVID-19. Consequently, ivermectin should be considered as an important alternative to the treatment of COVID-19 disease or as an additional option to existing protocols.

- SUMMARY + CONTEXT: **This prospective, randomized, controlled, single-blind multicenter clinical trial assessed the effectiveness of ivermectin treatment compared with standard of care (hydroxychloroquine + favipiravir + azithromycin) among 66 hospitalized, adult male patients with severe COVID-19 pneumonia. No difference between groups on rate of clinical improvement and**

**SOFA scores at 5-day follow-up. Improved peripheral capillary oxygen saturations and reductions in various blood markers (C - reactive protein, ferritin and D-dimer) were reported for the ivermectin group vs the standard of care group by the end of the follow-up period. Six patients randomized to the ivermectin arm were excluded due to a mutation affecting ivermectin metabolism. No difference in mortality between groups by the end of the study period. No side effects were reported in the ivermectin arm.**

- Pott-Junior et al, 2021. Use of ivermectin in the treatment of Covid-19: a pilot trial. Toxicology Reports, March 9, 2021.
- *Taken directly from Abstract:*
  **Background:** In this randomized open-label trial pilot study we assessed the antiviral effects and safety of various doses of ivermectin in patients with mild clinical symptoms of COVID-19.
  **Methods:** Patients were randomly assigned to receive standard of care (SOC) treatment at hospital admission; SOC plus ivermectin 100 mcg/kg; SOC plus ivermectin 200 mcg/kg; or SOC plus ivermectin 400 mcg/kg. The primary assessed endpoint was the proportion of patients who achieved two consecutive negative SARS-CoV-2 RT PCR tests within 7 days of the start of the dosing period. This study was registered at ClinicalTrials.gov (NCT04431466).
  **Results:** A total of 32 patients were enrolled and randomized to treatment. SOC treatment together with ivermectin did not result in any serious adverse events. All patients exhibited a reduction in SARS-CoV-2 viral load within 7 days; however, those who received ivermectin had a more consistent decrease as compared to the SOC alone group, characterized by a shorter time for obtaining two consecutive negative SARS-CoV-2 RT PCR tests.
  **Conclusions:** Ivermectin is safe in patients with SARS-CoV-2, reducing symptomatology and the SARS-CoV-2 viral load. This antiviral effect appears to depend on the dose used, and if confirmed in future studies, it suggests that ivermectin may be a useful adjuvant to the SOC treatment in patients with mild COVID-19 symptoms.
- SUMMARY + CONTEXT: **This single-centre, randomized open-label pilot study assessed the antiviral effect and safety of various doses of ivermectin + standard of care (SOC) compared with SOC alone among 32 hospitalized, adult patients with mild COVID-19. The proportion of patients with a reported decline in viral load by day 7 varied by dose, with the greatest proportion, 71.4% among the 200mcg/kg group, vs 66.7% in the group provided with SOC alone (57.1% in the 400 mcg/kg group, 50% in the 100mcg/kg group). Ivermectin +SOC treated patients reported a shorter time to two consecutive negative SARS-CoV-2 RT PCR tests compared with the SOC group and reported a higher median change in cycle threshold values, with the greatest change at 200mcg/kg dose of ivermectin compared with SOC alone. Both groups reported adverse events such as abdominal pain, muscle pain, dizziness, dyspnoea, and cough. A higher relative frequency of occurrence was reported in the SOC group (50%) vs 37.5% in the 200mcg/kg ivermectin +SOC group and the pooled ivermectin group (25.9%).**

- **Preprint** Ravikirti et al, 2021. Ivermectin as a potential treatment for mild to moderate COVID-19: A double blind randomized placebo-controlled trial. medRxiv, January 9 ,2021.
- *Taken directly from Abstract:*

  **Background:** Ivermectin has been suggested as a treatment for COVID-19.This randomized control trial was conducted to test the efficacy of Ivermectin in the treatment of mild and moderate COVID-19.

  **Methods:** Parallel, double blind, randomised, placebo controlled trial in a tertiary care dedicated COVID-19 hospital in Bihar, India. Adult patients (> 18 years) admitted with mild to moderate COVID 19 disease (saturation > 90% on room air, respiratory rate < 30 and no features of shock) with no contraindications to ivermectin and willing to participate in the study. Patients in the intervention arm were given ivermectin 12 mg on day 1 and day 2 of admission. Patients in the placebo arm were given identical looking placebo tablets. Rest of the treatment was continued as per the existing protocol and the clinical judgment of the treating teams. The primary outcome measure was a negative RT-PCR test for SARS-CoV-2 on day 6 of admission. The secondary outcome measures were symptom status on day 6, discharge status on day 10, admission to ICU, need for invasive mechanical ventilation and in-hospital mortality.

  **Results:** A total of 115 patients were enrolled for the study of which 112 were included in the final analysis. Of them, 55 were randomized to the intervention arm while 57 were randomized to the placebo arm. There was no significant difference in the baseline characteristics of the two arms. There was no significant difference in the primary outcome, i.e. negative RT-PCR status on day 6 between the two groups. Similarly, there was no significant difference between the two groups in most of the secondary outcome measures, viz. symptom status on day 6, discharge status on day 10, admission to ICU, and need for invasive mechanical ventilation. However, while there was no in-hospital mortality in the intervention arm, there were 4 deaths in the placebo arm. As a result, all patients in the intervention arm (n=56) were successfully discharged as compared to 93.1% (n=54/58) in the placebo arm (RR 1.1, 95% CI 1.0 to 1.2, p=0.019).

  **Conclusions:** There was no difference in the primary outcome i.e. negative RT-PCR status on day 6 of admission with the use of ivermectin. However, a significantly higher proportion of patients were discharged alive from the hospital when they received ivermectin.
- SUMMARY + CONTEXT: **This parallel, double blind, randomized placebo controlled trial in a single center of 112 adult, hospitalized patients evaluated the efficacy of ivermectin in the management of mild to moderate COVID-19. No difference reported between the ivermectin + standard care group compared with the placebo + standard of care group for negative RT-PCR test on day 6 of admissions, symptom status on day 6, discharge by day 10, admission to ICU, and need for mechanical ventilation. A higher proportion of ivermectin treated patients were reported to be discharged from the hospital than the placebo + standard of care treated group.**

- Shouman et al, 2021. Use of Ivermectin as a potential chemoprophylaxis for COVID-19 in Egypt: A Randomised clinical trial. Journal of Clinical and Diagnostic Research, January 2021.
- *Taken directly from Abstract:*

  **Background:** The rate of secondary attacks of SARS-COV-2 is high among household close contacts. Social distancing, isolation and infection control measures are important for preventing exposure to infection, but insufficient. The study aimed to evaluate possible role of oral ivermectin as a chemoprophylaxis in asymptomatic family close contacts with COVID-19 patients.

  **Methods:** A prospective interventional randomised open label-controlled study was conducted (registered at clinicaltrials.gov; NCT04422561) during June and July 2020. Two arms were designed according to use of ivermectin. In ivermectin arm, contacts received ivermectin according to Body Weight (BW) on day of the diagnosis of their index case. The non-intervention group received no treatment. Both groups were followed-up for two weeks for development of symptoms suggestive of COVID-19.

  **Results:** Ivermectin group included 203 contacts (to 52 index cases) aged 39.75±14.94 years; 52.2% were males. Nonintervention group included 101 contacts (to a total of 24 index cases) aged 37.69±16.96 years, 49.5% were males. Fifteen contacts (7.4%) developed COVID-19 in the ivermectin arm compared to 59 (58.4%) in the nonintervention arm (P <0.001). The protection rate for ivermectin was more prominent in contacts aged less than 60-year-old (6.2% infected compared to 58.7% if no treatment). Ivermectin in the protection against SARS-CoV-2 infection had an OR of 12.533 and 11.445 (compared to non-treatment) in both univariate and multivariate models, respectively. Side effects of ivermectin were reported in 5.4%; they were mild.

  **Conclusions:** Ivermectin is suggested to be a promising, effective and safe chemoprophylactic drug in management of COVID-19.
- SUMMARY + CONTEXT: **This community based, open label randomized controlled study of 304 adult, asymptomatic, close family contacts of RT-PCR confirmed COVID-19 patients reported that the ivermectin treated group had significantly lower odds of developing COVID-19 disease than the no treatment group in the 14-day follow-up period (multivariate analysis, p<0.001). Similarly, a significantly lower proportion of ivermectin treated contacts developed COVID 19 than the no-treatment close contacts (p<0.001).The protective benefit of treatment was reportedly more pronounced in ivermectin treated participants <60 years of age, with fewer progressing to COVID-19 disease than participants over 60 years of age (6.2% and 16% respectively). Mild side effects (gastrointestinal, reports of tingling and burning sensations, fatigue and sleepiness) were reported in 5.4% of the ivermectin treated group.**

Ontario COVID-19 Drugs and Biologics Clinical Practice Guidelines Working Group

# Antimicrobial and Immunomodulatory Therapy in Adult Patients with COVID-19

SCIENCE TABLE
COVID-19 ADVISORY FOR ONTARIO

Recommendations in this document apply to patients >18 years of age. Click the medication names in the table to view the associated **science briefs**.

Recommendations are based on the best available data and may change as additional data becomes available.

Infectious diseases consultation (where available) is recommended before any investigational treatment is offered to a patient with COVID-19 outside of a clinical trial.

Click for **dosing and pharmacologic considerations** for medications approved or under investigation for management of COVID-19.

| SEVERITY OF ILLNESS | RECOMMENDATIONS | |
|---|---|---|
| **Critically Ill Patients**<br>Patients requiring ventilatory and/or circulatory support, including high-flow nasal oxygen, non-invasive ventilation, invasive mechanical ventilation, or ECMO. These patients are usually managed in an intensive care setting. | ● **Dexamethasone** 6 mg PO/IV daily for 10 days (or until discharge if sooner) **is recommended** for critically ill patients.<br>● **Tocilizumab is recommended** for patients who are critically ill with suspected or confirmed COVID-19, who: are on optimal dexamethasone therapy; AND are within 14 days of hospital admission (or within 14 days of a new COVID-19 diagnosis if nosocomially acquired).<br>• In light of ongoing drug shortages, a fixed dose of 400 mg should be used for all eligible patients.<br>• In light of ongoing drug shortages, a second dose of tocilizumab should not be given to any patient.<br>■ **Remdesivir** is **not recommended** for critically ill patients with COVID-19 receiving mechanical ventilation.<br>▲ In patients with suspected or confirmed COVID-19 requiring high-flow oxygen (i.e., oxygen by mask, oxygen by high-flow nasal cannula, or non-invasive ventilation), **remdesivir** 200 mg IV on day 1, then 100 mg IV daily for 4 days **may be considered**.<br>◆ **Bamlanivimab** is **not recommended outside of clinical trials.** | ◆ **Ivermectin:** There is **insufficient evidence** to support the use of ivermectin in the treatment of critically ill patients with COVID-19 outside of clinical trials or where other indications would justify its use. Individuals who require ivermectin for other established non-COVID indications may use it if they develop COVID-19.<br>◆ **Vitamin D:** There is **insufficient evidence** to support the use of vitamin D in the treatment of critically ill patients with COVID-19 outside of clinical trials. Individuals who are taking vitamin D for other established, non-COVID indications may continue using it if they develop COVID-19.<br>◆ **COVID-19 convalescent plasma** is currently **unavailable** in Canada in critically ill patients and is unavailable outside of clinical trials.<br>◆ **Interferon** (with or without combination of lopinavir-ritonavir and ribavirin) is **not recommended outside of clinical trials**.<br>■ Bacterial co-infection is uncommon in COVID-19 pneumonia at presentation. **Do not add empiric antibiotics for bacterial pneumonia** unless bacterial infection is strongly suspected. Continue empiric antibiotics for no more than 5 days, and de-escalate on the basis of microbiology results and clinical judgment. |
| **Moderately Ill Patients**<br>Patients newly requiring low-flow supplemental oxygen. These patients are usually managed in hospital wards. | ● **Dexamethasone** 6 mg PO/IV daily for 10 days (or until discharge if sooner) **is recommended** for moderately ill patients.<br>● **Tocilizumab is recommended** for patients who are moderately ill with suspected or confirmed COVID-19, who: have evidence of systemic inflammation, defined as a CRP 75 mg/L or higher; AND have evidence of disease progression (i.e., increasing oxygen or ventilatory requirements) despite 24-48 hours of optimal dexamethasone therapy; AND are within 14 days of hospital admission (or within 14 days of a new COVID-19 diagnosis if nosocomially acquired).<br>• In light of ongoing drug shortages, a fixed dose of 400 mg should be used for all eligible patients.<br>• In light of ongoing drug shortages, a second dose of tocilizumab should not be given to any patient.<br>● **Remdesivir** 200 mg IV on day 1, then 100 mg IV daily for 4 days **is recommended** for patients who are moderately ill with suspected or confirmed COVID-19.<br>◆ **Bamlanivimab** is **not recommended outside of clinical trials.** | ◆ **Ivermectin:** There is **insufficient evidence** to support the use of ivermectin in the treatment of moderately ill patients with COVID-19 outside of clinical trials or where other indications would justify its use. Individuals who require ivermectin for other established non-COVID indications may use it if they develop COVID-19.<br>◆ **Vitamin D:** There is **insufficient evidence** to support the use of vitamin D in the treatment of moderately ill patients with COVID-19 outside of clinical trials. Individuals who are taking vitamin D for other established, non-COVID indications may continue using it if they develop COVID-19.<br>◆ **COVID-19 convalescent plasma** is **not recommended outside of clinical trials** (unavailable outside of clinical trials).<br>◆ **Interferon** (with or without combination of lopinavir-ritonavir and ribavirin) is **not recommended outside of clinical trials**.<br>◆ **Antibacterial therapy** is **not routinely recommended outside of clinical trials** or where other indications would justify its use. |
| **Mildly Ill Patients**<br>Patients who do not require new or additional supplemental oxygen from their baseline status, intravenous fluids, or other physiological support. These patients are usually managed in an ambulatory/outpatient setting. | ■ **Dexamethasone** is **not recommended** for mildly ill patients.<br>■ **Tocilizumab** is **not recommended outside of clinical trials** for patients who are mildly ill with suspected or confirmed COVID-19.<br>■ **Remdesivir** is **not recommended** for patients who are mildly ill patients with suspected or confirmed COVID-19.<br>◆ **Bamlanivimab** is **not recommended outside of clinical trials**. | ◆ **Ivermectin:** There is **insufficient evidence** to support the use of ivermectin in the treatment of mildly ill patients with COVID-19 outside of clinical trials or where other indications would justify its use. Individuals who require ivermectin for other established non-COVID indications may use it if they develop COVID-19.<br>◆ **Vitamin D:** There is **insufficient evidence** to support the use of vitamin D in the treatment of mildly ill patients with COVID-19 outside of clinical trials. Individuals who are taking vitamin D for other established, non-COVID indications may continue using it if they develop COVID-19.<br>◆ **COVID-19 convalescent plasma** is **not recommended outside of clinical trials** (unavailable outside of clinical trials).<br>◆ **Interferon** (with or without combination of lopinavir-ritonavir and ribavirin) is **not recommended outside of clinical trials**.<br>◆ **Antibacterial therapy** is **not routinely recommended outside of clinical trials** or where other indications would justify its use. |

**NOT RECOMMENDED for any patient severity:** ■ **Hydroxychloroquine** or **chloroquine** ■ **Lopinavir/ritonavir**

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- Ahmed et al, 2020., A five day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness, International Journal of Infectious Diseases, December 2, 2020
- DESCRIPTION: A randomized, double blind, placebo controlled study of hospitalized adult patients with mild COVID-19 in a single centre in Bangladesh. This multi-armed study aims to assess the time required for virological clearance and safety of ivermectin.
- ***Population***: Hospitalized adults (admitted within last 7 days) (N=72) with either fever ≥ 37.5 ° C, cough or sore throat and a RT-PCR confirmed SARS-CoV-2 infection.
- Patients in both groups were monitored for SARS-CoV-2 infection on days 3, 7, and 14 and followed weekly thereafter until a negative test was found. Various blood parameters were monitored on enrolment and day 4 (CBC, creatinine, SGPT, RBS); chest x-ray and ECG assessed on enrolment and day 3, and blood biomarkers (C-reactive protein (CRP), ferritin, lactose dehydrogenase (LDH) and procalcitonin) were measured on enrolment and day 7.
- ***Intervention***: Patients in the ivermectin alone arm (n=24) received a 12 mg dose of ivermectin once daily for 5 days. Patients in the combination (n=24) received the following combination 12 mg ivermectin single dose and 200 mg stat doxycycline day-1 followed by 100 mg 12hrly for next 4 days.
- ***Comparator***: Patients (n=24) received a placebo
- ***Key Results:***
- Primary outcomes:
    - The mean duration to viral clearance was 9.7 days (CI = 7.8 - 11.8) for the 5-day ivermectin arm (P = 0.02), 11.5 days (CI = 9.8 - 13.2) ivermectin + doxycycline (P = 0.27) arm and 12.7 days (CI = 11.3 - 14.2) for the placebo group
    - At day 7 and 14 virological clearance in the 5-day ivermectin group was significantly earlier compared to placebo [Hazard Ratio (HR) = 4.1; Confidence Interval (CI) = 1.1 - 14.7; p = 0.03 versus HR = 2.7; CI = 1.2 - 6.0; p = 0.02]. A similar trend was reported for the ivermectin + doxycycline group on day 7 and 14 but not statistically significant (HR = 2.3; CI = 0.6 - 9.0; p = 0.22 versus HR = 1.7; CI = 0.8 - 4.0; p = 0.19).
    - Remission of fever, cough and sore throat occurred in all groups to varying proportions within 7 days; however these changes were not statistically significant for fever (p = 0.35 and 0.09), cough (p = 0.18 and 0.23) or sore throat (p = 0.35 and 0.09) in the ivermectin + doxycycline and the 5-day ivermectin groups when compared with placebo.
- Secondary outcomes:
    - None of the patients enrolled required oxygen
    - The mean duration of hospitalization after treatment was 9.6 days (CI = 7.7 - 11.7) for ivermectin alone 9.7 (CI = 8.1 - 11.0), 10.1days (CI = 8.5 - 11.8) in the ivermectin +doxycycline arm and 9.7 days (CI = 8.1 - 11.0 in the placebo arm(P=0.93).
    - The mean values of the blood-biomarkers (CRP, LDH, Procalcitonin and Ferritin) dropped from base-line to day 7 in all three groups and these changes were significant for CRP (P = 0.02) and LDH (P = 0.01) in the 5-day ivermectin arm and for LDH in the placebo group (P = 0.01).
    - All cause mortality
- ***Safety Signals:*** No serious adverse events reported
- SUMMARY + CONTEXT: **In this double blind, placebo controlled multi-armed study of 72 mild COVID patients randomized to receive ivermectin alone, ivermectin+doxycycline, or placebo reported faster viral clearance in the ivermectin alone group compared with the placebo arm, no difference between groups for symptom resolution within 7 days, nor a difference between groups on mean duration of hospitalization stay. The mean values of blood**

**biomarkers declined in all three groups from baseline to day 7, only c-reactive protein and lactase dehydrogenase level changes were significant in the ivermectin alone group an LDH in the placebo arm. No serious adverse events or mortality were reported.**

- Considerations:
  - Small size of the current study makes it difficult to conclude if ivermectin alone provides any benefit.
  - Four patients withdrew consent after being allocated to the various treatment arms, two from the ivermectin alone arm, and one from each of the ivermectin +doxycycline and placebo arms.
  - Results need to confirmed and validated with larger randomized controlled trials