Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

# Advice to the National Public Health Emergency Team:

# COVID-19 - Interventions and health-related factors that prevent infection or minimise progression to severe disease

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# Version History

| Version number | Date | Details |
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| **V1.0** | 23 June 2021 | |
| **V1.1** | 13 August 2021 | Addition of footnotes relating to one of the randomised controlled trials (RCTs), by Elgazzar et al., detailed in this report. This RCT has been removed from preprint publication following additional scrutiny of the reported data. However, exclusion of Elgazzar from this report's evidence base does not impact on the conclusions or the advice within this report. |

## About the Health Information and Quality Authority

The Health Information and Quality Authority (HIQA) is an independent statutory authority established to promote safety and quality in the provision of health and social care services for the benefit of the health and welfare of the public.

HIQA's mandate to date extends across a wide range of public, private and voluntary sector services. Reporting to the Minister for Health and engaging with the Minister for Children, Equality, Disability, Integration and Youth, HIQA has responsibility for the following:

- **Setting standards for health and social care services** — Developing person-centred standards and guidance, based on evidence and international best practice, for health and social care services in Ireland.
- **Regulating social care services** — The Chief Inspector within HIQA is responsible for registering and inspecting residential services for older people and people with a disability, and children's special care units.
- **Regulating health services —** Regulating medical exposure to ionising radiation.
- **Monitoring services** — Monitoring the safety and quality of health services and children's social services, and investigating as necessary serious concerns about the health and welfare of people who use these services.
- **Health technology assessment** — Evaluating the clinical and cost-effectiveness of health programmes, policies, medicines, medical equipment, diagnostic and surgical techniques, health promotion and protection activities, and providing advice to enable the best use of resources and the best outcomes for people who use our health service.
- **Health information** — Advising on the efficient and secure collection and sharing of health information, setting standards, evaluating information resources and publishing information on the delivery and performance of Ireland's health and social care services.
- **National Care Experience Programme** — Carrying out national service-user experience surveys across a range of health services, in conjunction with the Department of Health and the HSE.

## Foreword

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a highly infectious virus which has caused tens of millions of cases of COVID-19 since its emergence in 2019, with a considerable level of associated mortality. In the context of the ongoing COVID-19 pandemic, SARS-CoV-2 constitutes a significant public health concern due to its high basic reproduction rate, the absence of innate immunity in the human population, the limited evidence of effective treatment approaches, and the constrained supply of vaccines in the early stages of population-level immunisation programmes.

The National Public Health Emergency Team (NPHET) oversees and provides national direction, guidance, support and expert advice on the development and implementation of strategies to contain COVID-19 in Ireland. Since March 2020, HIQA's COVID-19 Evidence Synthesis Team has provided research evidence to support the work of NPHET and associated groups and inform the development of national public health guidance. The COVID-19 Evidence Synthesis Team which is drawn from the Health Technology Assessment Directorate in HIQA, conducts evidence synthesis incorporating the scientific literature, international public health recommendations, and existing data sources as appropriate.

From September 2020, as part of the move towards a sustainable response to the public health emergency, HIQA provides evidence based advice in response to requests from NPHET. The advice provided to NPHET is informed by research evidence developed by HIQA's COVID-19 Evidence Synthesis Team and with expert input from HIQA's COVID-19 Expert Advisory Group (EAG). Topics for consideration are outlined and prioritised by NPHET. This process helps to ensure rapid access to the best available evidence relevant to the SARS-CoV-2 outbreak to inform decision-making at each stage of the pandemic.

The purpose of this report is to outline the advice provided to NPHET by HIQA regarding interventions and health-related factors for COVID-19 that prevent infection or minimise progression to severe disease.

HIQA would like to thank its COVID-19 Evidence Synthesis Team, the members of the COVID-19 EAG and all who contributed to the preparation of this report.

**Dr Máirín Ryan**

Deputy CEO & Director of Health Technology Assessment

Health Information and Quality Authority

## Acknowledgements

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Particular thanks are due to the Library and Information Services at the Health Service Executive and the Expert Advisory Group (EAG) and the individuals within the organisations listed below who provided advice and information.

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The advice is developed by the HIQA Evidence Synthesis Team with support from the Expert Advisory Group. Not all members of the Expert Advisory Group and Evidence Synthesis Team are involved in the response to each research question. The findings set out in the advice represent the interpretation by HIQA of the available evidence and do not necessarily reflect the opinion of all members of the Expert Advisory Group.

## Conflicts of Interest

None declared.

## Advice to the National Public Health Emergency Team

The purpose of this evidence synthesis is to provide advice to the National Public Health Emergency Team (NPHET) on the following policy questions:

- "What is the emerging evidence in relation to (i) pharmaceutical interventions, and (ii) lifestyle interventions prior to diagnosis of COVID-19 in the community aimed at preventing or minimising progression to severe disease?"
- "With respect to COVID-19, what potentially modifiable lifestyle factors are associated with a reduction in risk of infection and or progression to severe disease?"

The following research questions were developed to address these policy questions:

- RQ1. What is the evidence on the effectiveness of pharmacological interventions in the community, prior to a diagnosis of COVID-19, aimed at preventing or minimising progression to severe disease?
- RQ2. What is the evidence on the effectiveness of non-pharmacological interventions in the community, prior to a diagnosis of COVID-19, aimed at preventing or minimising progression to severe disease?
- RQ3. What is the evidence of association between modifiable health-related factors and risk of COVID-19 or progression to severe COVID-19?

The key points of this evidence synthesis, which informed HIQA's advice, are as follows:

### Evidence summary: COVID-19 - Interventions and health-related factors that prevent infection or minimise progression to severe disease

- Fifty-one studies (four randomised controlled trials [RCTs][1], one non-RCT [nRCT] and 46 cohort studies) were identified and included in this evidence summary. The five controlled trials were relevant to RQ1 (pharmacological interventions), and 46 cohort studies were relevant to RQ3 (modifiable health-related risk factors); none of the studies identified were relevant to RQ2 (non-pharmacological interventions).
- Four of the five controlled trials considered ivermectin:
    - The studies examined the use of oral ivermectin alone or in combination with carrageenan or iota carrageen nasal spray; some also controlled for

[1] It has come to the attention of the evaluation team that one of the RCTs (Elgazzar et al.) detailed in this report has been removed from preprint publication following additional scrutiny of the reported data.

the use of PPE. Dosing regimens differed between the trials and length of follow-up was short or not reported.

- One RCT was conducted in healthcare workers and administration staff, one in household and healthcare close contacts of COVID-19 cases and the other in household contacts of COVID-19 cases. The nRCT was conducted in asymptomatic healthcare workers involved in the care of COVID-19 patients.

- Safety outcomes were either poorly reported or not reported at all; where reported, it was suggested that adverse events were mild, and did not warrant treatment discontinuation.

- All four studies[2] reported that ivermectin, alone or in combination with carrageenan or iota carrageen nasal spray, had a protective effect; however, all were deemed to be of 'very low' certainty. This designation indicates that the estimate of effect is very uncertain and should not be relied upon to inform decision-making.

- Ivermectin medicines are not authorised for use in COVID-19 in the EU. The European Medicines Agency (EMA) has not received any application for such use, and currently advises against the use of ivermectin for the prevention or treatment of COVID-19 outside RCTs.

- The fifth controlled trial[3] was a double-blind, RCT of bamlanivimab versus placebo for the prevention of COVID-19 infection in residents and staff of 74 skilled nursing and assisted living facilities in the US with at least one confirmed SARS-CoV-2 index case. While bamlanivimab significantly reduced the incidence of COVID-19 in the overall population compared with placebo; disaggregated results showed that this was only significant in the residents' subgroup, not the staff. This evidence from this trial was deemed to be of 'low' certainty and should not be relied upon to inform decision-making.

- Forty-six cohort studies reported the association between various modifiable health-related risk factors and COVID-19 outcomes. Across the 46 cohort studies, the risk factors identified were:

  - Being overweight and or obese (34 studies)

  - smoking (25 studies)

[2] It has come to the attention of the evaluation team that one of the RCTs (Elgazzar et al.) detailed in this report has been removed from preprint publication following additional scrutiny of the reported data.
[3] This RCT was identified after the COVID-19 Expert Advisory Group (EAG) meeting had been convened.

  - vitamin D status (10 studies)
  - level of physical activity (seven studies)
  - alcohol consumption (five studies)
  - processed meat consumption (one study).

- Associations between being overweight and or obese and COVID-19 outcomes, including diagnosis, hospitalisation, severity of COVID-19 and mortality were estimated in 34 included studies. All eight studies that analysed BMI as a continuous variable (for example, 1kg/$m^2$, 5kg/$m^2$ or 1-standard deviation increments) reported a positive association between higher BMI and poorer outcomes. Strengthening the findings from studies that measured BMI as a continuous variable, studies that reported across multiple BMI categories reported worsening outcomes with higher categories of obesity.

- Twenty-five studies estimated the association between smoking status (current, never, ever and non-smoker) and COVID-19 outcomes. Six studies reported that smoking was significantly associated with negative COVID-19 outcomes, eight studies reported mixed findings, seven studies reported no association between smoking and COVID-19 outcomes.

- While four studies reported that smoking was protective, this finding should be viewed with extreme caution due to the limitations reported by the study authors. Moreover, there are likely confounders mediating this effect. For example, adjusting for comorbidities such as chronic obstructive pulmonary disease (COPD) and use of inhaled corticosteroids in COPD.

- Ten included studies estimated the association between vitamin D status (25(OH)D concentration) or vitamin D use and COVID-19 outcomes. Four studies reported no association between 25(OH)D concentration and COVID-19 outcomes, three studies reported that 25(OH)D deficiency was significantly associated with negative COVID-19 outcomes, two studies reported a protective effect of habitual vitamin D supplement use and increased vitamin D concentration and one study reported mixed findings between 25(OH)D concentration and increased risk of COVID-19 outcomes.

- Seven included studies estimated the association between physical activity and COVID-19 outcomes. Four studies reported mixed findings between physical activity and risk of COVID-19 outcomes, two studies reported that decreased physical activity was significantly associated with negative COVID-19 outcomes, one study reported a protective effective of physical activity.

- Five included studies estimated the associations between alcohol use and COVID-19 outcomes. Two studies reported mixed findings between alcohol use and COVID-19 outcomes, while one study reported a significant association between alcohol use and negative COVID-19 outcomes. One study used the US Veteran Affairs (VA) database and reported a protective effective of alcohol use disorder and a COVID-19 diagnosis. However, it should be noted that the US VA population, in general, has a high relative alcohol consumption and is therefore a very skewed population. Furthermore, this study was conducted in May 2020, before there was widespread testing for COVID-19. One study reported no association between alcohol use and COVID-19 outcomes.

- One included study estimated the association between processed meat intake and COVID-19 diagnosis; this study reported no association.

- Twenty-nine of the 46 cohort studies were rated as good quality. However, eighteen of these 46 cohort studies used data from the UK Biobank, as such, it is likely that there is considerable overlap in the populations included in these studies. They are also subject to the following limitations of UK Biobank data:

    - the UK Biobank is a prospective cohort study of over 500,000 men and women aged 40–69 years at the time of recruitment, from urban and rural settings across the UK.

    - exposure data were collected at baseline (between 2006-2010) therefore, participants' self-reported exposures may have changed.

    - the cohort is not representative of the general UK population. The response rate to the baseline survey was 5.5%; it may be the case that this self-selected cohort is healthier and has a higher education level relative to the general population.

- The COVID-19 pandemic has disproportionately affected those from lower socioeconomic status. However, this review does not consider socioeconomic factors as these are largely non-modifiable and these were typically not appropriately adjusted for within the analysis of included studies.

- In addition to the 51 studies included in this evidence summary, 60 planned or ongoing trials of interventions for the prevention of COVID-19 were identified; none had formally published results at the time of writing.

- At the time of writing there is a lack of high-quality evidence of benefit to support pharmacological or non-pharmacological interventions (including use of Vitamin D

supplements) to prevent COVID-19 or to minimise risk of progression to severe disease.

- While there are mixed results reported from the included cohort studies, in general those who are overweight or obese, who smoke, who have inadequate levels of Vitamin D, are physically inactive and consume excessive amounts of alcohol are more likely to contract COVID-19 or have poorer outcomes.

- This information can be used to inform clinical decision making around risk reduction. In general, maintaining a healthy weight, not smoking, engaging in physical activity, moderating alcohol consumption, good nutrition and being Vitamin D sufficient have beneficial effects on general health and should continue to be encouraged.

**COVID-19 Expert Advisory Group**

- A meeting of the COVID-19 Expert Advisory Group (EAG) was convened for clinical and technical interpretation of the evidence provided.

- The EAG agreed that availing of the COVID-19 vaccine when offered it, continues to be the most effective measure to prevent serious illness due to COVID-19.

- The EAG agreed that evidence regarding the effectiveness of therapeutic interventions, particularly for pharmaceutical treatments, must be subject to the highest standards of rigour. It was noted that trials included in the present review are severely limited with respect to the certainty, quantity, and applicability of the evidence and are insufficient to inform decision-making on treatment options for COVID-19 in Ireland. If evidence of effectiveness should emerge in the future, due process would apply in decision-making regarding recommendation of a treatment and the reimbursement of any medicine.

- It was noted that to be recommended as a prophylactic treatment for individuals without COVID-19 in the community setting, such treatment would have to adhere to the usual requirements for robust clinical governance with strong evidence of effectiveness and safety.

- Ivermectin is not currently licensed for the treatment of COVID-19. From this evidence summary, there is currently insufficient information on whether it can be safely used to prevent or reduce the severity of COVID-19. Ivermectin should therefore not be used as prophylaxis outside well-designed, regulated clinical trials as the benefits and harms are not yet clear when taken in the context of COVID-19 treatment.With respect to Vitamin D supplementation, there needs to be a clear distinction between population-level and individual-level advice. There

is currently no evidence to show that the use of Vitamin D supplementation prevents COVID-19 or reduces the severity of the disease.

- It was highlighted that there is still much debate on the reference range for Vitamin D sufficiency, insufficiency and deficiency. Studies that have assessed the association between Vitamin D status and COVID-19 outcomes are subject to bias and confounding.

- For those who are Vitamin D deficient, current national guidance on supplementation in this population should be followed and considered on a case-by-case basis, as there is a small proportion of the population who may be harmed by hypercalcaemia associated with vitamin D supplementation. However, it was noted that low Vitamin D levels can be improved by going outside, for example, to engage in physical activity such as walking. This poses no additional risk to the individual and may incur additional benefits such as the physical and mental benefits of exercise that are widely acknowledged.

- There should be very clear communication that, based on the current evidence, there are no medicines that should be prescribed outside of a well-designed and regulated clinical trials for the prevention of COVID-19.

- The EAG agreed that the findings from the review, in relation to health-related risk factors, provide an opportunity to remind individuals of the impact of such risk factors on general health as well as the potential to mitigate risk of poorer COVID-19 outcomes by maintaining a healthy weight, avoiding smoking, engaging in physical activity, moderating alcohol consumption and good nutrition.

- As restrictions begin to ease and individuals are vaccinated, it is important to empower individuals to take ownership of their health, and to highlight that small steps can lead to benefits in health status.

- The EAG emphasised the role health inequalities play in people's current health status; for many people, they have not had the opportunity or ability to maintain their health. For example, healthy inequality, which already existed before the COVID-19 pandemic, has been exacerbated by the pandemic and disproportionately affects those from lower socioeconomic positions. This highlights the need for efforts to be focused on addressing such inequalities.

## Advice

Arising from the findings above, HIQA's advice to the National Public Health Emergency Team is as follows:

- With respect to interventions prior to a diagnosis of COVID-19 aimed at the prevention or reduction of progression to severe disease:
    - The evidence identified and included in this review does not currently support the use of any pharmaceutical intervention outside of well conducted, well regulated clinical trials.
        - In particular, prophylactic use of ivermectin or bamlanivimab[4] should not be recommended outside of well-designed, regulated clinical trials as the benefits and harms are not yet clear when taken prior to a diagnosis of COVID-19 to prevent or reduce progression to severe disease.
    - No evidence was identified for non–pharmaceutical interventions.
- There is currently insufficient evidence to support the use of Vitamin D supplementation aimed at preventing or reducing the severity of COVID-19. However, national guidance on Vitamin D supplementation should continue to be followed, particularly for those who are housebound with limited and or no sunlight exposure.
- A large number of COVID-19 clinical trials are ongoing. Additional evidence will therefore continue to be reported both for novel interventions and those identified in this review. Consistent with current requirements:
    - As there are potential harms associated with all interventions, including non-pharmaceutical interventions, they must have a robust safety profile, and be subject to appropriate governance, before they can be recommended for widespread use in the community setting. This is important given the serious risk of harm associated with unproven interventions.
    - If effectiveness evidence does emerge, all current due processes will be required, including with respect to potential reimbursement of drugs provided within the publicly funded healthcare system.
- Availing of the COVID-19 vaccine, when offered it, continues to be the most effective measure to prevent serious illness due to COVID-19.
- Public health messaging on the benefits of engaging in healthy behaviours should continue. In general, maintaining a healthy weight, not smoking, engaging in physical activity, moderating alcohol consumption, good nutrition and being Vitamin D sufficient have beneficial effects on general health and may reduce the risk of poor outcomes from COVID-19.

[4] This RCT was identified after the COVID-19 Expert Advisory Group (EAG) meeting had been convened.

- Public health messaging should endeavour to empower individuals to take ownership of their own health, while recognising that due to health inequalities not everyone has the same opportunity or capacity to be healthy. Public health initiatives should therefore continue to focus on addressing any such inequalities.

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