Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

# Advice to the National Public Health Emergency Team (NPHET)

# Duration of immunity and reinfection following SARS-CoV-2 infection

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# 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 and Youth Affairs, 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 uncertainty regarding cross-protection from other coronaviruses and development of long-term immunity in those infected, and the current lack of an effective vaccination or treatment approaches.

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, with consideration of the scientific literature and input from the COVID-19 EAG regarding reinfection and the duration of immunity in individuals who recovered from a laboratory-confirmed SARS-CoV-2 infection.

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 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 Advisory Team

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

- "What is the rate of reinfection in individuals who recovered from a laboratory-confirmed SARS-CoV-2 infection?"
- "What is the duration of immunity in individuals who recover from a laboratory-confirmed SARS-C0V-2 infection?"

The response to the research questions is informed by an evidence synthesis considering two elements:

1. an evidence summary based on the findings of a rapid review of relevant literature
2. input from the COVID-19 Expert Advisory Group.

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

- With respect to reinfection:
    - In prior evidence summaries, HIQA identified studies that reported cases of re-detection of viral RNA by RT-PCR following recovery from SARS-CoV-2 infection. 'True' reinfection could not be confirmed as whole genome sequencing was not performed, and in most re-detection cases, clinical and epidemiological details were more suggestive of intermittent detection of non-viable virus remnants (RNA) from non-viable virus) than persistent shedding of infectious viral RNA.
    - In the present review, six new studies, representing seven patients, were identified that relate to reinfection following recovery from laboratory-confirmed SARS-CoV-2 infection whereby whole genome sequencing confirmed that the first and second infections were caused by different viral strains. The mean age of patients was 42 (range: 25 to 89) and the time interval between initial infection and reinfection ranged from 48 to 142 days. Disease severity ranged from asymptomatic to severe in both first and second infections. Information on antibody response in the studies was incomplete. There was no evidence of onward transmission from the re-infected individuals to any close contact.
    - In three reinfection cases, the first and second infections were caused by SARS-CoV-2 viral strains with different lineages or clades. In terms of single nucleotide polymorphisms, between nine and 23 variants were discovered comparing the first and second viruses across all patients. With an average estimated SARS-CoV-2 mutation rate of 33 nucleotides per

year (or 2-3 nucleotides per month), in all cases it is likely that the second infection was a reinfection rather than prolonged shedding of viral RNA from the first infection.

- With respect to duration of immunity:
    - Twenty-two studies were identified that examined the duration of antibody responses (IgG and or neutralising antibodies) following SARS-CoV-2 infection over 60 days or longer. Mean follow-up duration was 97 days and mean sample size was 79 (range: 3-349).
    - All studies reported 100% seropositivity for IgG and neutralising antibodies at 60-79 days post-symptom onset. At 80-99 days, detection rates were 78%-100% for IgG and 53%-100% for neutralising antibodies. In the study with the longest follow-up, over 70% of participants maintained an anti-SARS-CoV-2 and neutralising antibody response up to 182 days (six months).
    - In terms of the analysis of anti-SARS-CoV-2 IgG antibody titres over time, just over half of studies (n=7/12) found that titres were maintained, or increased, until the end of follow-up, while five studies reported a reduction in IgG titres over time. All but one study that reported neutralising antibody titres reported a substantial decline over time, in particular at the later stages of follow-up.

A meeting of the COVID-19 Expert Advisory Group (EAG) was convened for clinical and technical interpretation of the research evidence on 20 October 2020. The following points were raised in respect of the review findings:

- While rarely reported, the risk of reinfection among individuals who previously had COVID-19 is not known, however it cannot be ruled out.
- Previous evidence summaries (13 May 2020, 9 June 2020 and 6 August 2020), have documented the potential for prolonged shedding of viral material following recovery from COVID-19 infection.
- Real-time RT-PCR testing alone cannot determine if a true reinfection has occurred. While quantification of viral load through cycle threshold (Ct) could be used as an indirect measure of infectivity and or to compare infectivity at different time points, this is problematic due to differences in values obtained between different testing platforms, laboratories and sampling conditions.
- The use of whole genome sequencing is required to confirm reinfection; however, there are concerns regarding its availability.
- It was acknowledged that patients who test negative for SARS-CoV-2 by RT-PCR, but whose clinical presentations are highly suspicious for COVID-19 may benefit

from serology testing (IgA/IgM/IgG). In these instances, experience has shown many of these patients are antibody positive which can aid in the diagnosis.

- All individuals who present with symptoms of COVID-19 should be tested using rRT-PCR, irrespective of any prior diagnosis.
- Current practices in relation to serial testing and testing as part of pre-admission protocols for scheduled or unscheduled care must take consideration of the potential for reinfection in those with a history of laboratory-confirmed SARS-CoV-2 infection.
- Current understanding of the immune response to SARS-CoV-2 is limited. The presence of antibodies does not mean that the person has immunity, and cell-mediated immunity (memory B-cells, T-cell responses) are important. The relative importance of antibody versus cell-mediated responses is not known. The finding of waning neutralising antibody responses and capacity is mirrored in the natural evolution of immunity to other viral infections; the reduction of neutralising antibody titres alone does not exclude the possibility of an appropriate immune response with protection from reinfection.
- The possibility of waning natural immunity has major policy implications relating to restriction of movements, convalescent plasma donation and vaccine development. If vaccine-mediated immunity wanes, there may be requirements for vaccine booster doses. It may be the case that equilibrium can only be maintained by a certain level of circulating virus.
- The possibility of reinfection with SARS-CoV-2 must be clearly communicated to all stakeholders. This should include clear public health advice for hygiene and physical distancing measures to be maintained by those who have been previously infected.

## Advice

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

- Reinfection with SARS-CoV-2, although rarely documented, is possible. Therefore, all infection prevention and control procedures and recommendations, including hygiene and physical distancing, should apply to those who have recovered from a SARS-CoV-2 infection as immunity from reinfection cannot be assumed.
- Anti-SARS-CoV-2 IgG and neutralising antibody seropositivity is maintained in most individuals for two to six months post-infection. However, further

research is required to establish the relative importance of antibody-mediated immunity and the levels (titres) necessary to prevent reinfection. Further research is also required on cell-mediated immunity, including B- and T-cell responses.

- Clear and accessible communication regarding the potential for waning immunity and the risk of reinfection is important.

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