



**Health
Information
and Quality
Authority**

An tÚdarás Um Fhaisnéis
agus Cáilíocht Sláinte

Advice to the National Public Health Emergency Team

Duration of immunity (protection from 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, 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

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a highly infectious virus which has caused hundreds of millions of cases of COVID-19 since its emergence in 2019, with a considerable level of associated mortality. Despite the high uptake rates of the COVID-19 vaccine in Ireland to-date, SARS-CoV-2 remains a significant public health concern due to its high basic reproduction rate, the limited evidence of effective treatment approaches, and emerging variants of concern.

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 to 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 the policy question: "How long does protective immunity last in individuals who were previously infected with SARS-CoV-2 and subsequently recovered?"

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

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Membership of the Expert Advisory Group involves review of evidence synthesis documents and contribution to a discussion which informs the advice from HIQA to NPHET. It does not necessarily imply agreement with all aspects of the evidence synthesis or the subsequent advice.

The membership of the EAG was as follows:

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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

Seven previous evidence summaries relating to immunity following SARS-CoV-2 infection have been published by HIQA (13 May 2020, 9 June 2020, 6 August 2020, 11 November 2020, 5 March 2021, 14 April 2021 and 3 June 2021). In the 3 June 2021 review, HIQA concluded that SARS-CoV-2 reinfection rates remain low for over ten months following initial infection. Based on a second systematic review of the long-term duration of immune responses, HIQA also found that, while there may be a waning of antibody responses over time, immune memory lasts for up to nine months post-infection. The findings of the immune memory review therefore supported the findings of the reinfection review. As a result of this, public health policies were amended to assume a period of protective immunity of nine months post-infection with SARS-CoV-2.

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

“How long does protective immunity (that is, prevention of antigen or RT-PCR confirmed reinfection) last in individuals who were previously infected with SARS-CoV-2 and subsequently recovered?”

This evidence summary is expected to inform a range of policy questions relating to the duration of protective immunity following infection with SARS-CoV-2. Potentially relevant policy questions include:

- How long can asymptomatic individuals who have recovered from a prior SARS-CoV-2 infection be:
 - exempted from:
 - restriction of movement policies if they become a close contact of a confirmed COVID-19 case?
 - derogation policies if they become a close contact of a confirmed COVID-19 case?
 - serial testing, for example serial testing in indoor settings where social distancing is difficult (such as food processing facilities)?
 - testing prior to scheduled admission to hospital or inter institutional transfer?
 - considered at low risk of onward transmission in a household setting?

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

1. a systematic search of databases to identify observational studies that estimated the risk of reinfection over time
2. input from the COVID-19 Expert Advisory Group.

The findings of the evidence synthesis were as follows:

- Sixty-five observational studies, that investigated the risk of SARS-CoV-2 reinfection, were identified that met the inclusion criteria.
- Nineteen studies exclusively included healthcare workers, seven studies included participants based on their vaccination and/or prior infection status, three studies included staff and or older residents of care homes, three studies included patients with chronic kidney disease (CKD), one study included both healthcare workers and patients with a high risk of exposure to SARS-CoV-2, one study included a broad range of essential workers, and one study included university students. The remaining 30 studies all related to general populations.
- Twenty of the 65 studies were conducted in the US; 12 were conducted in the UK; seven in Italy; three each were conducted in Iran and Switzerland; two each were conducted in France, Germany, Israel, Qatar, Sweden, and Spain; and one study each was conducted in Austria, China, Denmark, Egypt, India, Iraq, Mexico, and South Africa.
- Across all studies, the total number of PCR- or antibody-positive participants at baseline was 1,484,413 (median: 1,350; range: 88 to 378,606).
- The median follow-up of individuals within studies was 165 days (5.5 months) (range of medians: 54-300 days), with a maximum follow-up of ≥ 365 days (12 months) in 10 studies. The study with the longest maximum follow-up of over 17 months was conducted in Israel.
- Reinfection was a rare event: the median PCR- or antigen-confirmed reinfection rate was 0.6% across studies, ranging from 0% (zero reinfections in nine studies) to 5.9% (which was observed among healthcare workers in a study in the US).
- Confirmation of reinfection by whole genome sequencing (WGS) was conducted in five included studies. The rate of confirmed reinfection was low in each of these studies, ranging from 0.02% to 1.1%.
- All studies reported low relative rates of reinfection comparing prior positive (PCR and or antibody positive) and prior negative groups (no PCR positive and or antibody negative). However, between-study estimates were not directly

comparable due to varying definitions for reinfection and different outcome measures. All studies, that separately reported symptomatic and 'all' reinfection events, reported lower relative rates of symptomatic reinfections. For example, in a large sample of UK health care workers, the relative risk for 'any reinfection' was 0.16 (95% CI: 0.13–0.19), falling to 0.07 (95% CI: 0.06–0.10) for reinfections with COVID-19 symptoms.

- There was limited evidence of waning protection from natural immunity observed across the 11 included studies that examined reinfections over time (within the time frame of these studies). However, one included study found some evidence of reduced (but still high) protection from reinfection against the Delta variant, in the context of longer follow-up (maximum 17 months).
- Studies consistently demonstrated high levels of protection following infection, similar to vaccine-mediated effectiveness. In total, five studies separately reported protective effectiveness in previously infected and vaccinated groups; four of these studies found comparable or greater effectiveness associated with natural immunity; one study found lower effectiveness associated with natural immunity specifically in an older population.
- The risk of reinfection was found to be highest among older adults (≥ 65 years) in three studies, however no significant difference was found in one study and another study found a very small decreasing risk of reinfection with increasing age. In three studies reporting paediatric data, the risk and/or rates of reinfection were consistently lower in children (< 18 years) with two of these studies reporting no cases of reinfection in children. Another study found higher counts of reinfections in the 10-19 age group than in other age categories, however a risk or relative risk was not reported.
- Six included studies assessed the risk of reinfection in subgroups with comorbid or immunocompromising conditions. Five of these studies found that individuals with chronic kidney disease or who were immunocompromised had a higher risk of reinfection, or were at high risk of mortality in the case of reinfection. The sixth study found no significant association between any covariate for comorbidity or an immunocompromising condition and risk of reinfection/breakthrough infection.
- One study directly assessed the relationship between serological antibody levels and reinfection risk among a cohort of dental practitioners in the UK. In this study, the risk of infection was 9.7% in participants who were seronegative at baseline compared to 2.9% in individuals who were seropositive ($p=0.001$). However, there were no PCR-proven infections among 64 individuals with a baseline anti-SARS-CoV-2 IgG level greater than 147.6 IU/ml (with respect to the WHO international standard NIBSC 20/136).

- Only 12 of the 65 included studies were considered of high methodological quality, with a number of issues identified across studies. Apart from the inherent biases associated with observational study designs, many studies were downgraded due to poor quality of reporting and for inadequate control of confounders. A recognised limitation of a number of studies was the risk of outcome ascertainment bias. In addition, 15 of the 65 studies are currently published as preprints.
- Importantly, the findings from these observational studies which were largely conducted in the context of stringent public health measures and less transmissible variants, may have limited generalisability to the current context of easing public health measures and a more transmissible Delta variant.
- There is still uncertainty on a range of issues, including the:
 - durability of protective immunity over time
 - protective immunity in paediatric populations
 - the potential for additional protection from vaccination in those with a history of prior infection
 - duration and extent of protective immunity in populations with comorbidities and in those with immunocompromising conditions
 - impact of new variants on protective immunity.
- In conclusion, the evidence suggests that the risk and relative risk of SARS-CoV-2 reinfection is low for over 12 months post-infection. However, there is also some evidence that the duration and or extent of protective immunity following infection may be lower in older adults, in patients with CKD and those with immunocompromising conditions.

COVID-19 Expert Advisory Group

A meeting of the COVID-19 Expert Advisory Group (EAG) was convened for clinical and technical interpretation of the research evidence on 13 October 2021.

In respect of the findings of the Evidence Summary, the following points were raised by members of the Expert Advisory Group:

- Communication around messaging of the report was felt to be particularly important. A point was raised that vaccination should still be advocated for regardless of any advice regarding the duration of presumed protective immunity post-infection. People should be encouraged to get vaccinated instead of deferring until the end of the period of presumed protective immunity.

- The public's understanding of immunity is important to consider. It was emphasised that there should be clear messaging that prior infection does not provide absolute protection from reinfection. While there is a risk people can get reinfected following recovery from prior infection, they may not experience clinically impactful symptoms.
- Based on what is seen in practice, concerns were raised about extending the duration of presumed protective immunity post-infection to longer than nine months. Unpublished Irish data from the HPSC would appear to suggest that reinfections, while still uncommon in absolute terms, are becoming relatively more frequent.
- National and international data indicate that healthcare workers (HCW) are disproportionately affected by reinfections due to the increased risk of exposure. Thus, the most significant impact of a policy decision to increase the presumed period of protective immunity from nine to 12 months would likely be in healthcare settings. While HCW at the tail-end of their period of presumed protective immunity may get reinfected, they may only develop mild or asymptomatic COVID-19. However, the concern remains that they can transmit the virus to colleagues and patients. This potential for the spread of virus amongst HCWs with waning immunity, and to their patients, should be to the fore of any decision to extend the duration of presumed protective immunity.
- An extension of the duration of presumed protective immunity may also have unintended negative implications at a population level.
- With regards to the studies included in the review, it was noted that the follow-up is less than nine months in a large number of studies. Concerns were also raised regarding the [US study](#) which found that almost 6% of HCWs were reinfected, and also with regard to the limited data on the impact of the Delta variant on the reinfection risk.
- The observational nature of all included studies was noted and thus the potential for residual confounding. The context of the included studies was also highlighted: the majority of the evidence is based on time periods when restrictive public health measures were in place, and so when the risk of infection was likely lower. For example, reinfection rates could have been artificially lowered by people wearing masks and socially distancing. It is therefore unclear how generalisable the evidence would be to situations where all measures are relaxed.

- UK seroprevalence (antibody) studies show high seroprevalence rates across the UK. Despite this, the current force of infection is contributing to the ongoing spread of SARS-CoV-2 in the community.
- While the research evidence regarding the low risk of reinfection was found to be encouraging, concerns were raised regarding the timing of a change in policy. Given the current high prevalence of infection and hence a greater level of exposure to the virus, extending the duration of presumed protective immunity from nine months may raise the risk of reinfection.
- There was support to take a cautious approach and to leave the advice unchanged at nine months duration of presumed protective immunity. It was noted that for other seasonal coronaviruses, the duration of protective immunity is usually around 12 months. The Delta variant is currently dominant in Ireland, leading to a high viral load in those infected and an abnormally high burden of infection in the population. The risk of reinfection needs to be considered under the current conditions of a significant amount of circulating virus in the population. Therefore, extrapolating evidence from studies - which were predominantly conducted prior to the dominance of the Delta variant - to the current setting of high community prevalence was not felt to be appropriate.
- There was agreement that any advice regarding natural immunity (that is, immunity due to prior infection) should not be nuanced around any particular subgroups, as to do so would not be practical. Advice needs to be applied equally to everyone who has been previously infected, but other advice around booster or additional vaccine doses may be offered, where appropriate.
- It was suggested that the question should be kept under review as further evidence may provide greater certainty regarding the presumed duration of protective immunity post-infection.
- Due to the wider context of significant changes to public health restrictions, along with increasing levels of international travel and the high levels of virus currently circulating in the community, there was consensus that due to these factors, that the presumed duration of protective immunity post-infection should not be extended.

Advice

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

- Current public health policies assume a period of protective immunity of nine months post-infection with SARS-CoV-2.
- The updated evidence summary identified 65 large observational studies involving over 1.4 million previously infected individuals, including 10 studies with over 12 months' maximum follow-up. Across studies, the risk of SARS-CoV-2 reinfection was consistently found to be low, with natural immunity found to provide protection similar to that provided by vaccine-mediated immunity. There was also some real-world evidence that vaccination provides additional protection to those previously infected with SARS-CoV-2.
- There was limited evidence of waning protection from natural immunity (that is, immunity due to prior infection) observed within the time frame of these studies. However, one included study found some evidence of reduced protection from reinfection against the Delta variant, in the context of a longer follow-up of 17 months.
- Importantly, the findings from these observational studies, which were largely conducted in the context of stringent public health measures and less transmissible variants, may have limited generalisability to the current context of easing public health measures and a more transmissible Delta variant. Given the uncertainty regarding current epidemiological trends in Ireland, there are concerns regarding the potential negative impact of extending the period of protective immunity post-infection.
- In light of these issues, it is advised that the current period of presumptive protective immunity should remain at nine months post-infection. This advice should be kept under review and should be informed by national surveillance data and research evidence.
- Communication campaigns should continue to encourage people to come forward for vaccination, including those who have been previously infected. The additional protection provided by vaccination to those previously infected should be clearly communicated to the public. In addition, there should be clear messaging that natural immunity does not provide absolute protection from reinfection.

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