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

Published: 8 March 2021
Submitted to NPHET: 24 February 2021

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 Office of 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 established 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, with consideration of the scientific literature and input from the COVID-19 EAG regarding the rate of reinfection and the duration of immunity in individuals with evidence of prior SARS-CoV-2 infection. The advice also reflects the findings of a facilitated discussion with the HIQA COVID-19 EAG considering key issues regarding the related policy questions.

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

HIQA would like to thank all of the individuals and organisations who provided their time, advice and information in support of this health technology assessment.

Particular thanks are due to the Expert Advisory Group (EAG) and the individuals within the organisations listed below who provided advice and information.

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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Dr Máirín Ryan (Chair)	Director of Health Technology Assessment & Deputy Chief Executive Officer, HIQA
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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

HIQA has previously conducted four evidence summaries relating to immunity following SARS-CoV-2 infection (13 May 2020, 9 June 2020, 6 August 2020 and 11 November 2020). The November 2020 update concluded that SARS-CoV-2 reinfection is possible, although a rarely reported event, and that antibody-mediated immune responses can be detected in most patients beyond two months and up to six months post-symptom onset.

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:

1. How long can asymptomatic individuals (including healthcare workers) 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?

2. How long can asymptomatic individuals who have recovered from a prior SARS-CoV-2 infection be exempted from serial testing, for example serial testing in indoor settings where social distancing is difficult (such as food processing facilities)?

3. How long can asymptomatic patients who have recovered from a prior SARS-CoV-2 infection be exempted from the requirement for testing prior to scheduled admission to hospital or inter institutional transfer?

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

1. a systematic search of databases to identify cohort studies that estimated the risk of reinfection over time

2. a scoping review of the long-term duration of humoral and cellular responses following SARS-CoV-2 infection

3. input from the COVID-19 Expert Advisory Group.

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

- A systematic search was conducted to identify studies that investigated the risk of SARS-CoV-2 reinfection in previously infected individuals over time.
- Five studies were identified that met the inclusion criteria. Three studies were conducted in the UK, and one each in Qatar and the US. All were observational cohort studies, of which two were prospective and three were retrospective.
- Across studies, the median number of PCR- or antibody-positive participants at baseline was 6,614 (range: 1,038 to 378,606) and the median duration of follow-up was 4.6 months (range: 1.8 to 6.7 months). Maximum follow-up in individual studies ranged from 3.1 to 8.1 months.
- The estimated risk of reinfection was low (0.1% [95% CI: 0.08 to 0.11%]) in the Qatar study comprising a large cohort of 43,044 anti-SARS-CoV-2 nucleocapsid antibody positive participants with over seven months of follow-up. No evidence of waning immunity over time was seen. Reinfection events were confirmed by whole genome sequencing in a subset of study participants.
- Three UK studies estimated the risk of reinfection based on PCR testing among healthcare workers (HCWs) (median follow-up ranged from 4.6 to 6.7 months):
    - The first study (Hanrath et al.) detected no symptomatic infections out of 1,038 HCWs with evidence of previous infection (0%, 95% CI: 0–0.4%), compared with 290 out of 10,137 HCWs without evidence of prior infection (2.9%, 95% CI: 2.6–3.2%, p<0.0001).
    - The second study (Lumley et al.) detected two asymptomatic infections (and no symptomatic infections) out of 1,265 seropositive HCWs, compared with 223 infections (100 asymptomatic and 123 symptomatic) out of 11,364 seronegative HCWs; the adjusted incidence rate ratio in HCWs who were seropositive at baseline was 0.11 (95% CI: 0.03 to 0.44) (adjusted for age, gender and month of testing).
    - The third study (Hall et al.) reported 44 reinfections (15 of which were symptomatic) out of 6,614 seropositive HCWs, compared with 318 new PCR positive infections (249 of which were symptomatic) and 94 antibody seroconversions in the seronegative cohort of 14,173 individuals. The adjusted odds ratio was 0.17 in HCWs who were seropositive at baseline for all reinfections (95% CI: 0.13 to 0.24) and 0.08 (95% CI 0.05-0.13) for symptomatic reinfections.

- One large retrospective database analysis of 3,257,478 unique patients in the US (Harvey et al.) found that patients who display positive antibody tests are initially more likely to have a positive nucleic acid amplification test (NAAT), consistent with prolonged RNA shedding. However, over time, patients became less likely to test positive by NAAT when followed for three months. There were concerns regarding bias in this study ('poor quality') and the outcome measure used (NAAT) was a proxy measure for both reinfection and redetection.
- When only the four studies of 'good' or 'fair' methodological quality were considered, the evidence suggests that the reinfection risk is low for at least seven months following primary infection (maximum duration of follow-up was ≥7 months in all four studies).
- There are a number of limitations associated with this review. As all studies were observational in nature, they cannot be used to demonstrate causality. Therefore, only longitudinal associations between prior infection and protective immunity can be measured.
- The applicability of included studies may be limited due the completion of all studies before December 2020, preceding the widespread identification and spread of a number of new variants of international concern since December 2020 and preceding vaccine roll-out. Thus, the applicability of the findings to recent variants of concern and vaccinated populations is unknown. Separately, as all studies provided estimates in the general population or HCWs, it is unclear how generalisable the findings are to other populations such as the elderly, those with comorbidities and immunocompromised individuals.
- A scoping review was conducted to evaluate the long-term duration of immune responses following SARS-CoV-2 infection. Five studies were identified that investigated immune responses at ≥6 months post-infection, including two studies at ≥8 months post-infection. In general, studies reported a waning of antibody responses in the late convalescent period (3-6 months post-infection). However, T-cell and memory B-cell responses were still present, and in many cases increased, up to eight months post-infection in all study participants.
- In conclusion, five studies were identified that reported low rates of SARS-CoV-2 reinfection up to seven months following initial infection. Additionally, a scoping review of the long-term duration of immune responses found that while there may be a waning of antibody responses over time, T- and B-cell responses persist for up to eight months post-infection.

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 22 February 2021. The following points were raised in respect of the review findings:

- A review of protective immunity has been also undertaken by the National Immunisation Advisory Committee (NIAC). While there is some overlap in terms of the evidence reviewed, the aim of the NIAC work is to inform vaccine policy.
- It was noted that observed trends in the waning of antibodies and persistence of immunity for SARS-CoV-2 is in line with that of other infectious diseases. However, cellular immunity and production of neutralising antibodies has not been extensively examined in clinical settings. Study data suggest that a small proportion of individuals do not mount an antibody response; however, this may be due to inadequate follow-up or test performance. Failure to detect an immune response is more common in asymptomatic infections.
- The studies identified in the review included both symptomatic and asymptomatic reinfection; evidence of initial infection could be based on RT-PCR positivity or detection of an immune response. It was clarified that it was not possible to determine if there was a higher risk of reinfection in those with asymptomatic infection.
- It was noted that the immune trajectory of SARS-CoV-2 appears to be similar to the original SARS-CoV with respect to humoral and cellular immune responses. It was acknowledged that some other respiratory viruses, such as seasonal coronaviruses, have not been investigated as thoroughly as SARS-CoV-2.
- A concern was raised that a small proportion of cases could be false positives. Secondary evidence of infection (for example, clinical findings, evidence of an immune response) and clinical judgment may be needed when implementing policies that take consideration of risk of reinfection.
- It is not possible to undertake randomised controlled trials in this area, nor would such trials typically be ethical. The highest quality evidence will therefore come from robust well designed cohort studies such as those included in this review. While noting these studies represent good quality evidence, they were all conducted prior to December 2020, that is, before the detection of a number of variants of concern and prior to the widespread roll-out of population level vaccination programmes.

- The large knowledge gaps with respect to SARS-CoV-2 were noted. The serial PCR screening of staff in nursing homes and other settings, was suggested as a potential data source that could be audited to evaluate the risk of reinfection and infection in the context of a vaccinated population. These data could then potentially inform policy decisions related to this area.

- It was acknowledged that the immune trajectory and viral evolution associated with SARS-CoV-2 is unlikely to differ from other viral infections, such as SARS-CoV, so the population-level response to natural infection and vaccination will inevitably lead to the emergence of variants including immune escape variants. Restricting the movements of healthcare workers can negatively impact on the delivery of quality care as staffing shortages can reduce the ability of healthcare workers to comply with infection prevention and control measures. Any change to policies that address the exemption from close contact status should always consider the balance of risk. If risk of reinfection is low, extending the duration of exemption from close contact status would not lead to an overall increase in risk of transmission.

- The EAG were in agreement that the studies included in the review provided good evidence that the risk of reinfection is low for at least six months post-infection. On balance the EAG reasoned that exemption from close contact status could be extended to six months. However, it was acknowledged that uncertainty exists relating to reinfection potential with emerging variants. Any policy decision relating to this should be kept under review and informed by the international evidence and national surveillance data.

Advice

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

- Evidence from five large cohort studies, including three studies that enrolled healthcare workers, demonstrated that the risk of reinfection with SARS-CoV-2 is very low up to seven months post-infection. These findings were supported by evidence of long-term duration of T- and B-cell responses up to eight months post-infection.
    - The included studies provided estimates in the general population and in healthcare workers. It is unclear if the findings are generalisable to other populations such as the elderly, those with comorbidities and immunocompromised individuals.

- The applicability of included studies may be limited as all were completed before December 2020, preceding vaccine roll-out and the widespread identification and reporting of emerging variants of international concern.

- On the basis of this evidence, consideration could be given to extending the period of presumptive immunity (lower risk of reinfection) from 12 weeks to six months post-infection. This would have implications for a range of policy areas including current policies for serial testing, testing prior to admission or transfer to a healthcare facility and policies regarding possible exemption from close contact status. However, given the uncertainty that exists relating to reinfection potential with emerging variants, any policy changes:
  - may not be applicable to possible exposure to emerging immune escape variants of concern
  - should be kept under review and informed by the international evidence and national surveillance data.

Published by the Health Information and Quality Authority (HIQA).

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