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

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, 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

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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.

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:

Prof Karina Butler	Consultant Paediatrician and Infectious Diseases Specialist, Children's Health Ireland & Chair of the National Immunisation Advisory Committee
Dr Jeff Connell	Assistant Director, UCD National Virus Reference Laboratory, University College Dublin
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Dr Máirín Ryan (Chair)	Director of Health Technology Assessment & Deputy Chief Executive Officer, HIQA
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* Alternate nominee for programme and or association

\# Ad hoc member of the Expert Advisory Group for this topic

HIQA would like to thank staff from the Health Protection Surveillance Centre for providing preliminary data relating to SARS-CoV-2 reinfection notifications in Ireland.

HIQA would like to thank librarians from the Health Service Executive for their support in developing the search strategy for the evidence synthesis.

Members of HIQA's Evidence Synthesis Team:

Susan Ahern, Natasha Broderick, Paula Byrne, Karen Cardwell, Paul Carty, Barbara Clyne, Laura Comber, Christopher Fawsitt, Patricia Harrington, Karen Jordan, Kirsty O'Brien, Eamon O Murchu, Michelle O'Neill, Sinéad O'Neill, Máirín Ryan, Debra Spillane, Susan Spillane, Conor Teljeur, Barrie Tyner, Kieran Walsh.

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 five evidence summaries relating to immunity following SARS-CoV-2 infection (13 May 2020, 9 June 2020, 6 August 2020, 11 November 2020 and 8 March 2021). The 8 March 2021 update concluded that the risk of SARS-CoV-2 reinfection is low for at least six months.

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 two elements:

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

2. 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.

- Eleven observational cohort studies were identified that met the inclusion criteria. Six general population studies were identified, of which two were conducted in the United States and one each was conducted in Austria, Denmark, Israel and Qatar. Three studies that enrolled healthcare workers (HCW) and two studies that enrolled staff and residents of care homes were identified, all five were conducted in the UK.

- Across studies, the total number of PCR- or antibody-positive participants at baseline was 615,777. The median follow-up of individuals within studies was 4.4 months (range of medians: 1.8 to 7 months). Nine of the eleven included studies followed participants for ≥7 months, six for ≥8 months, five for ≥9 months and three for ≥10 months. Reinfection was a rare event (median PCR-confirmed reinfection rate: 0.27%, range: 0% to 1.1%), with no study reporting an increase in the risk of reinfection over time.

- Of the six general population studies, only one study estimated the population-level risk of reinfection based on whole genome sequencing. Sequencing was undertaken in a subset of participants with clinical evidence of reinfection from a larger cohort of 43,044 anti-SARS-CoV-2 nucleocapsid antibody positive participants at baseline. The estimated risk of reinfection was (0.1% [95% CI: 0.08 to 0.11%]), with no evidence of waning immunity for up to seven months.

- One study reported the relative risk of reinfection by age group. In individuals aged 65 years or more, the adjusted relative risk was 0.529 (95% CI: 0.372 to 0.753), compared with 0.173, 0.199 and 0.187 in individuals aged 0-34 years, 35-49 years and 50-64 years, respectively. However, one UK study that enrolled elderly residents of care homes (median age ≥84 years) reported a low relative risk of reinfection (adjusted Hazard Ratio [aHR] of 0.15).

- Three UK studies estimated the risk of reinfection based on PCR testing among HCWs (median follow-up ranged from 4.6 to 6.7 months):

    - The first study 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 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 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.

- Two UK studies were identified that investigated the risk of reinfection in staff and residents of care homes.
  - In the first study, the relative risk of reinfection in two London care homes (with median ages of 84 and 85, respectively) was very low in the seropositive group (RR=0.038; 95% CI: 0.005 to 0.273), and the protection against reinfection after four months was estimated at 96.2% (95% CI: 72.7 to 99.5%).
  - In the second study, a sample of staff and residents (N=2,111) across 100 care homes in England were followed between October 2020 and February 2021. The estimated adjusted hazard ratio for reinfection, stratified by care home, was 0.15 (95% CI: 0.05 to 0.44) in residents (with a median age of 86) and 0.39 (95% CI: 0.19 to 0.82) in staff.
- 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.
- There are limitations relating to the applicability and generalisability of identified studies. Specifically:
  - No study reported the risk or relative risk of reinfection in paediatric populations.
  - Only two studies included data from after December 2020. The first study from Israel recorded higher counts of reinfection in January 2021 compared with March-December 2020. The second study followed care home residents and staff in the UK during a period of high community prevalence of SARS-CoV-2, associated with the rapid emergence of the B.1.1.7 variant (October 2020 to February 2021). The adjusted relative hazard of infection when comparing seropositive and seronegative groups was relatively low (aHR 0.15 in residents and 0.39 in staff). Sequencing data were not available for either study. Overall, there are insufficient data

to evaluate the effectiveness of prior infection to prevent reinfection with new variants.

- The applicability of the findings to vaccinated populations is unknown. All studies preceded vaccine roll-out, apart from one study that removed vaccinated individuals from the study 12 days after vaccination.

- While the clinical characteristics of reinfected cases were poorly reported across studies, reinfection events were generally not associated with severe disease.

- 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, eleven studies were identified that reported low rates of SARS-CoV-2 reinfection up to ten 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 30 March 2021.

- The HPSC provided preliminary data relating to suspected reinfection cases in Ireland. Of 232,738 confirmed cases of COVID-19 notified between 2 March 2020 and 23 March 2021, 514 (0.2%) were potentially reinfections, based on the criteria of more than 84 days between notification or specimen dates.

In respect of the findings of the Evidence Summary, the following points were raised:

- The evidence regarding immunity up to 10 months post-infection was felt to be reasonably robust. HIQA clarified that nine of the eleven included studies followed participants for ≥7 months, six for ≥8 months, five for ≥9 months and three for ≥10 months. While the maximum follow up extended beyond 10 months, median follow-up ranged from 1.8 to 7 months across studies. The certainty of the findings will improve with studies with longer durations of follow-up.

- The current advice is to assume immunity up to six months post-infection. The impact of changing this assumption on protocols for testing, definition of close contacts, and other areas of policy should be considered, as well as how changes could introduce confusion into established policies.

- The findings of the review were felt to strengthen the recommendation of an assumption of immunity for six months. It was acknowledged that extending the duration of presumptive immunity from six to nine months at this point in time may have a limited impact as it would mostly apply to those infected after the first wave at the beginning of the pandemic, and before the widespread transmission during the third wave. While incremental increases in this timescale could be made, for practical reasons, and for reasons of clarity, the advice should be to retain the current six month cut-off.

- The next version of this report should be scheduled before June 2021 so as to inform any changes before the large cohort infected during the third wave, are considered to no longer have protective immunity. Subsequent reviews may consider protective immunity in both unvaccinated and vaccinated populations

- It was acknowledged that there is limited data on elderly people, children, populations with comorbidities, the immunocompromised, as well as for new variants of concern. It was suggested that in the next update, more information will have accrued which will result in stronger recommendations for policy changes relating to the duration of presumptive immunity.

- It was clarified that none of the included studies were confounded by inclusion of vaccinated participants. Only one included study, conducted among a population of elderly UK care home residents, coincided with vaccination roll-out. However, this study explicitly excluded vaccinated individuals from their analyses. It was acknowledged that this confounding with vaccine rollout will likely be problematic in future studies.

Advice

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

- The updated evidence summary identified eleven cohort studies on the risk and relative risk of SARS-CoV-2 reinfection over time. Across studies, the total number of PCR- or antibody-positive participants at baseline was 615,777. The median follow-up of individuals within studies was 4.4 months (range of medians: 1.8 to 7 months). Nine of the eleven included studies followed participants for ≥7 months, six for ≥8 months, five for ≥9 months and three for ≥10 months. Reinfection was a rare event (median PCR-confirmed reinfection rate: 0.27%, range: 0% to 1.1%), with no study reporting an increase in the risk of reinfection over time.
- The data remain limited in certain populations, such as in children, the elderly, individuals with comorbidities, the immunocompromised and vaccinated populations. In addition, there is considerable uncertainty surrounding protective immunity against new variants of concern.
- Current policies assume a period of presumptive immunity of six months post-infection. No specific changes to policies regarding the duration of presumptive immunity following natural infection are advised at this time.
- Consideration must be given to the practicalities and feasibility of any changes to policy arising out of amendments to the duration of presumptive immunity.
- The body of evidence relating to protective immunity is emerging at a fast pace and should be kept under review. Future policy changes should be informed by the international evidence in addition to national surveillance data.

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