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 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, international public policy 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". The advice also reflects the findings of a discussion with the HIQA COVID-19 EAG considering key issues relating to the policy question.

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 Library and Information Services at the Health Service Executive (HSE) and the Expert Advisory Group (EAG).

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:

Dr Máirín Ryan (Chairperson)	Director of Health Technology Assessment & Deputy Chief Executive Officer, HIQA
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 Michael Power	Consultant Intensivist, Beaumont Hospital & Clinical Lead, National Clinical Programme for Critical Care, HSE
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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 six evidence summaries relating to immunity following SARS-CoV-2 infection (13 May 2020, 9 June 2020, 6 August 2020, 11 November 2020, 8 March 2021 and 14 April 2021). The 14 April 2021 update concluded that the risk of SARS-CoV-2 reinfection is low for at least ten months.

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

> "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?"

and

"What is the duration of immune memory responses (T-cell and B-cell memory and or their components' responses) following SARS-CoV-2 infection?"

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 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 health care workers who have recovered from a prior SARS-CoV-2 infection be exempted from exclusion from work policies if they become a close contact of a confirmed COVID-19 case

3. 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)?

4. 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?

5. How long can asymptomatic individuals who have recovered from a prior SARS-CoV-2 infection meet indoors without wearing face coverings or staying two metres apart:

a. with other asymptomatic individuals who have recovered from a prior SARS-CoV-2 infection or with vaccinated individuals from up to two other households

b. with people from one other household who are not vaccinated as long as no more than three other households are there.

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, in addition to a systematic search of databases to identify cohort studies that reported long-term duration of immune memory responses

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

This evidence synthesis, which informed HIQA's advice, consisted of two systematic reviews. The first identified studies that investigated the risk of SARS-CoV-2 reinfection over time, with the second identifying studies that investigated immune memory responses at least six (≥6) months post-infection.

The findings of the evidence synthesis were as follows:

Part 1 – risk of reinfection

- Nineteen observational cohort studies, that investigated the risk of SARS-CoV-2 reinfection over time, were identified that met the inclusion criteria. Five studies exclusively enrolled healthcare workers and two studies enrolled both staff and residents of elderly care homes; six of these seven studies were conducted in the UK. The remaining twelve studies were in the general population, conducted in ten different countries.
- Across studies, the total number of PCR- or antibody-positive participants at baseline was 641,911 (median: 1,899; range: 88 to 378,606).
- The median follow-up of individuals within studies was 135 days (4.5 months) (range of medians: 54-249 days), with a maximum follow-up of ≥300 days (ten months) in six studies.
- Reinfection was a rare event: the median PCR-confirmed reinfection rate was 0.6% across studies, ranging from 0% (zero reinfections in three studies) to 2.8% (which was observed among dental practitioners in the UK).
- 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. No study reported an increased relative risk of reinfection over time. 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 0.159 (95% CI: 0.13–0.19), falling to 0.074 (95% CI: 0.06–0.10) for reinfections with COVID-19 symptoms.

- Of the 11 general population studies, only one study estimated the population-level risk of reinfection based on whole genome sequencing on a representative sample. 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.
- Only one study reported the relative risk of reinfection by age group, noting higher rates in older individuals. In individuals aged 65 years or older, 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. One other study reported risk of reinfection in an older age group. This UK study reported an adjusted hazard ration of 0.15 in elderly residents of care homes (median age ≥84 years).
- One study assessed the protective effectiveness of natural infection against reinfection in both vaccinated and unvaccinated healthcare workers in the UK, and coincided with widespread transmission of the B.1.1.7 variant. This study found:
    - Compared to unvaccinated seronegative HCWs, natural immunity and two vaccination doses provided similar protection against symptomatic infection: no HCW vaccinated twice had symptomatic infection, and incidence was 98% lower in seropositive HCWs (adjusted incidence rate ratio 0.02 [95%CI <0.01-0.18]).
    - Two vaccine doses or seropositivity reduced the incidence of any PCR-positive result (with or without symptoms) by 90% (0.10 [0.02-0.38]) and 85% (0.15 [0.08-0.26]), respectively.
    - Single-dose vaccination reduced the incidence of symptomatic infection by 67% (0.33 [0.21-0.52]) and any PCR-positive result by 64% (0.36 [0.26-0.50]).

  - There was no evidence of differences in immunity induced by natural infection and vaccination for infections with B.1.1.7 and a proxy for B.1.1.7 (S-gene target failure).

- 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 9.6% in participants who were seronegative at baseline compared to 2.8% 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 four of the 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, 10 of the 19 studies are currently published as preprints.
- There are also limitations relating to the applicability and generalisability of identified studies. There is uncertainty in relation to:
  - paediatric populations
  - those with comorbidities and those who are immunocompromised
  - vaccinated populations
  - new variants.

Part 2 – immune memory

- Thirteen studies were identified that investigated immune memory responses at ≥6 months post-infection, including one study at ≥9 months post-infection. Study numbers were small, ranging from 15 to 188 participants.
- In 11 studies that considered memory B-cells, with the exception of a decline in IgM+ memory B-cells reported in two studies, memory B-cell response was found to be maintained for the duration of follow-up, which extended to nine months post infection in one study.
- In six studies that considered memory T-cells, all reported persistence over periods of six to nine months, however a number reported declining frequency over time.
- Eight studies, reporting the proportion with a response, identified that most or all of those tested developed either memory B- or memory T-cell responses.

- Two studies examined the development of neutralising antibodies from memory B-cells, and both demonstrated that memory B-cells generated neutralising antibodies. One of these studies found that, over a six month period, these antibodies increased in potency and breadth.
- The studies identified suggest that immune memory develops in most or all of those who have been infected with SARS-CoV-2 and lasts for up to nine months. There is substantial uncertainty in relation to the immune response to SARS-CoV-2 given the small study sizes and lack of clarity in relation to potential confounders.
- No studies were identified that examined mucosal immune memory or immune memory in tissues. These are likely to be key factors in preventing onward transmission of disease.
- In conclusion:
    - A large volume of data supports the likelihood that the risk and relative risk of SARS-CoV-2 reinfection is low for over ten months post-infection. While limited evidence from one study supports the hypothesis that natural infection and vaccination both result in robust immune responses, including against the variant B.1.1.7, the emerging evidence relating to new variants and vaccinated populations should be kept under review.
    - While more limited data were identified in relation to the immune memory response to SARS-CoV-2 infection, studies generally found that immune memory lasts for up to nine months post-infection and support the findings of the reinfection review.

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 24 May 2021.

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 considered robust.
- Regarding immune memory, it was noted that studies investigating serological samples may underestimate immunological memory as measures of immune memory cells in the blood are not representative of the larger proportion of these cells that may be resident in tissues.

- Extrapolating the findings regarding immune memory from laboratory studies to real-world settings should be done with caution, as assays that measure immune memory are still undergoing standardisation. Additionally, samples from patients included in studies may not be representative of the broader population.

- The included studies do not determine if natural infection prevents onward transmission of SARS-CoV-2. To date previously infected individuals have not been observed to amplify outbreaks in Ireland. Further data specifically on the presence and impact of mucosal immune memory will be required to determine the potential for onward transmission of the virus following recovery from infection.

- It was noted that post-pandemic population immunity may depend on the endemic presence of SARS-CoV-2 in conjunction with vaccination.

- Regarding the cohort studies that investigated the risk of reinfection in individuals who had knowledge of prior SARS-CoV-2 infection, the EAG noted the potential for outcome ascertainment bias and selection bias, in particular in studies where testing was voluntary and in studies with low participation in follow-up testing. Knowledge of prior infection may alter an individual's behaviour, which may result in bias in outcome measurement.

- The EAG noted a recent study by Public Health England and updated results from the SIREN study (published 23 and 24 May 2021). While not specific to reinfection, these studies provide updated evidence that vaccination is effective at preventing infection with the variants B.117 and B.1.617.2 (Indian variant).

- The potential advantages of changing the current advice (as in, extending the period of presumptive immunity from six months) were discussed. This would have a number of practical implications and would be welcomed by the health system.

    - At present, individuals are considered to have immunity for six months after their initial positive SARS-CoV-2 PCR test; therefore, a person who becomes an asymptomatic contact of a case and has had a positive test result within the previous six months does not need to restrict their movements and does not require testing.

    - The duration of presumptive immunity would be important to the implementation of 'green certificates' that provide proof of either full vaccination, recent negative test result or recovery from COVID-19.

    - Current advice from NIAC is that those with laboratory-confirmed COVID-19 within the last six months, who are under 50 years of age and who are immunocompetent, only require a single vaccine dose to be considered

fully vaccinated. Extending the period of presumptive immunity would increase the number of individuals considered fully vaccinated with a single dose. However, it was noted that implementing the one dose vaccine schedule for those previously infected was problematic as it has been difficult to ascertain previous infection status.

- The EAG acknowledged that it would be meaningful to people if the period of presumptive immunity is extended. While the impact of SARS-CoV-2 variants is uncertain, it is reassuring that to date reinfection rates have remained low. This is a positive message that is important to communicate.
- Based on the evidence review there was general agreement within the EAG that the period of presumptive immunity should be extended to nine months.

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 presumptive immunity of six months post-infection with SARS-CoV-2.
- The updated evidence summary identified 19 large cohort studies involving over 640,000 previously infected individuals, including six studies with over ten months' follow-up. Across studies, the risk of SARS-CoV-2 reinfection was consistently found to be low. No study reported an increase in reinfection risk over time. More limited data were identified in relation to the immune response to SARS-CoV-2 infection. The identified studies suggest that immune memory develops in most or all people that have been infected with SARS-CoV-2 and lasts for at least nine months.
- In light of these findings, consideration should be given to extending the period of presumptive immunity from six to nine months post-infection. Any such changes to policy should be clearly communicated and consistently applied.
- Our understanding of the impact of new variants on natural immunity is evolving rapidly 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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