Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Evidence summary protocol:

Duration of immunity (protection from reinfection) following SARS-CoV-2 infection

Published: 23 September 2021

1. Purpose and aim

The purpose of this protocol is to outline the process by which the Health Information and Quality Authority (HIQA) identifies and reviews relevant SARS-CoV-2 evidence. The evidence will be used to inform advice that is provided to the National Public Health Emergency Team (NPHET) in their response to the COVID-19 pandemic. HIQA's health technology assessment (HTA) team develops evidence summaries based on specific research questions (RQs).

The following specific research question (RQ) was developed and will form the basis of this evidence summary:

How long does protective immunity (that is, prevention of RT-PCR- or antigen-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. Relevant policy questions include the following:

- 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?
    - exempted from derogation policies if they become a close contact of a confirmed COVID-19 case?
    - exempted from serial testing, for example serial testing in indoor settings where social distancing is difficult (such as food processing facilities)?
    - exempted from testing prior to scheduled admission to hospital or inter institutional transfer?
    - exempted from travel-related testing requirements?
    - considered at low risk of onward transmission in a household setting?

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.

Due to the rapidly evolving evidence base relating to SARS-CoV-2 immunity, this review updates the evidence base relating to protection from reinfection. The update will follow a similar search strategy to previous iterations. The systematic review of immune memory will not be updated in the current review.

2. Process outline

It is important that a standardised approach to the process is developed and documented, to allow for transparency and to mitigate risks, which may arise due to changes in staff delivering and or receiving the information.

Four distinct steps in the process have been identified. These are listed below and described in more detail in the following sections.

1. Search of relevant databases and search engines.
2. Screening of identified studies.
3. Data extraction and quality appraisal of included studies.
4. Summarise findings.

3. Search of relevant databases and search engines

The following databases and sites will be searched using the search strategies defined in Appendix 1:

- Medline (Ebsco)
- Embase (Ovid)

A simplified search strategy will be used to identify relevant preprints in Europe PMC https://europepmc.org , MedRxiv https://www.medrxiv.org/ and Google Scholar.

4. Screening of identified studies

All potentially eligible papers identified in the search strategy will be exported to EndNote or Covidence and single screened against the POS (population, outcome, study design) framework. No language restrictions will be applied. Non-English studies will be translated via Google translate, and this will be noted as a potential caveat. Full text papers will be single screened against the POS framework, with any uncertainty checked by a second reviewer. The POS relating to prevention of reinfection is provided in Table 1.

Table 1. Population Outcome Study design – prevention of reinfection

Population	Individuals (of any age) with evidence of prior SARS-CoV-2 infection, who subsequently recovered.* Evidence of prior infection includes diagnosis by RT-PCR or antigen testing, or evidence of an immune response through antibody detection (seropositivity). Subgroups include: ▪ healthcare workers ▪ age groups (<12 years, 12-17 years, 18-39 years, 40-59 years, 60-69 years, ≥70 years) ▪ high risk and very high risk groups (HSE definitions**) ▪ fully vaccinated (up to 15 days after completion of vaccine protocol, dependant on vaccine, as per HSE guidance**) vs. partially vaccinated (requisite time period after completion of vaccine protocol has not been achieved, as per HSE guidance**) vs. unvaccinated.
Outcomes	**Prevention of reinfection** Primary outcomes: 1. Relative risk of RT-PCR- or antigen-confirmed SARS-CoV-2 reinfection***, comparing populations with evidence of prior infection with populations with no prior evidence of infection, at specified time points. 2. Risk of RT-PCR- or antigen-confirmed SARS-CoV-2 reinfection over time. 3. Time interval between first and second infections. 4. RT-PCR cycle threshold (C_t) results, if reported. 5. Whole genome sequencing (WGS) results of reinfected cases comparing first and second infections, if reported. 6. Antibody titres in those who are reinfected vs. those with no evidence of reinfection, if reported.
Types of studies	**Include:** ▪ Observational cohort studies (prospective or retrospective) ▪ Case-control studies.

	Exclude: ▪ Cohort studies that enrolled fewer than 100 participants ▪ Case studies ▪ Studies with durations of follow-up of less than 3 months ▪ Animal studies.

*'Recovered' refers to molecular or clinical evidence of viral clearance following initial infection; definitions of recovery in primary studies will be used. Common definitions include two consecutive negative respiratory RT-PCR tests 24 hours apart and WHO clinical criteria of viral clearance (27 May 2020).[1]

**Definitions used by HSE.[2,3]

*** A gold-standard confirmation of SARS-CoV-2 reinfection will require confirmation of initial infection and virus detection across two distinct time periods with genetic sequencing data needed to support a conclusion of high probability that reinfection has occurred. Possible SARS-CoV-2 reinfection could be differentiated from persistent viral carriage through a variety of laboratory-based parameters, patient symptomology, and/or epidemiologic links. Definitions of reinfection in primary studies will be used. Common definitions include persons with detected SARS-CoV-2 RNA ≥90 days after the first detection of SARS-CoV-2 RNA, whether or not symptoms were present (US Centers for Disease Control and Prevention, 27 Oct 2020).[4]

5. Data extraction and quality appraisal of included studies

For each included study, data on the study design, participant demographics and clinically relevant data will be extracted by one reviewer and cross-checked by a second reviewer (Appendix 2). If the paper has not been peer reviewed, this is noted.

The National Heart, Lung and Blood Institute (NIH) quality assessment tools for cohort and cross sectional studies will be used for appraisal of included studies.[5]

Data from pre-print publications may contain errors and or older data, which may be corrected and or updated when the final published version becomes available in a peer-reviewed journal. Prior to the final version of an evidence summary being published on the HIQA website, pre-print publications will be checked to identify if final published versions have become available since the original search was conducted. Any discrepancies identified will be corrected. In addition, prior to publication, all included studies will be checked for any errata or retractions.

6. Summarise findings and send to relevant contact

A descriptive overview of the identified evidence to date for each research question will be compiled and or a meta-analysis where appropriate. A PRISMA flow chart will be presented.

7. Quality assurance process

The review question will be led by an experienced systematic reviewer. Four additional reviewers will be assigned to assist and to provide cover. The additional reviewers will be required to read all the key studies and check that the summary accurately reflects the body of literature. All summaries will be reviewed by two senior members of the team, to ensure processes are followed and quality maintained, this will also enable cover to be maintained.

8. Timelines

This evidence summary will be conducted in line with the processes and timelines outlined for Phase 2 of HIQA's COVID-19 response. Work will commence on 8 September 2021 and a final draft will be completed by 1 October 2021. Draft outputs from the rapid evidence synthesis will be circulated to HIQA's COVID-19 Expert Advisory Group for review, with a view to providing advice to NPHET on 8 October 2021.

8. References

1. World Health Organization (WHO). Criteria for releasing COVID-19 patients from isolation. Scientific Brief. 17 June 2020. Available at: https://www.who.int/news-room/commentaries/detail/criteria-for-releasing-covid-19-patients-from-isolation
2. HSE. People at higher risk from COVID-19. Available at: https://www2.hse.ie/conditions/coronavirus/people-at-higher-risk.html#:~:text=have%20a%20condition%20that%20means%20you%20have%20a%20high%20risk,and%20other%20long%2Dstay%20settings. 2020.
3. HSE. COVID-19 vaccination. Available at:

   https://www2.hse.ie/screening-and-vaccinations/covid-19-vaccine/
4. US Centers for Disease Control and Prevention. Common Investigation Protocol for Investigating Suspected SARS-CoV-2 Reinfection. Available at:

   https://www.cdc.gov/coronavirus/2019-ncov/php/reinfection.html
5. National Heart Lung and Blood Institute (NIH). Study Quality Assessment Tools. Available at: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools.

Appendix 1

Search strategy – prevention of reinfection

1. Ovid Embase

Embase Ovid
Embase <1974 to 2021 September 08>

1 exp Coronavirus infection/
2 (COVID-19 or CORONAVIRUS or "corona virus" or "2019-ncov" or "2019 ncov").ab,ti.
3 (wuhan adj3 virus).ab,ti.
4 "severe acute respiratory syndrome coronavirus 2".ab,ti.
5 ("2019" and (new or novel) and coronavirus).ab,ti.
6 1 or 2 or 3 or 4 or 5
7 reinfection/
8 exp recurrent disease/
9 (reinfect* or re-infect* or ((subsequent or future or recur* or reactivat* or re-activat*) adj2 (infect* or disease*))).ab,ti.
10 immunity/
11 immune response/
12 immunity/ or mucosal immunity/
13 (immunity or immunoglobulin*).ab,ti.
14 (antibod* adj2 (positive or neutral*)).ab,ti.
15 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16 7 or 9 or 10 or 11 or 12 or 13
17 6 and 15
18 6 and 16
19 17 not 18
20 exp cohort analysis/
21 exp longitudinal study/
22 exp prospective study/
23 exp follow up/
24 exp retrospective study/
25 ((cohort or longitudinal or prospective or follow up or follow-up or retrospective) adj2 (study or analys* or design or method*)).ab,ti.
26 20 or 21 or 22 or 23 or 24 or 25
27 17 and 26
28 ("202118" or "202119" or "202120" or "202121" or "202122" or "202123" or "202124" or "202125" or "202126" or "202127" or "202128" or "202129" or "202130" or "202131" or "202132" or "202133" or "202134" or "202135" or "202136").em.
29 27 and 28

2. Medline (Ebsco)

#	Query
S1	AB (reinfection* or re-infection*) OR TI (reinfection* or re-infection*)
S2	AB ((subsequent* or recur* or reactivate* or re-activate* or future or second) N2 (infect* or disease*)) OR TI ((subsequent* or recur* or reactivate* or re-activate*or future or second) N2 (infect* or disease*))
S3	(MH "Reinfection")
S4	AB (immunity or antibod* or immunoglobulin) OR TI (immunity or antibod* or immunoglobulin)
S5	(MH "Immunity") OR (MH "Immunity, Mucosal") OR (MH "Adaptive Immunity+")
S6	S1 OR S2 OR S3
S7	S4 OR S5
S8	S6 OR S7
S9	AB (COVID-19 or coronavirus or corona virus or Wuhan N2 virus or "2019 n-cov" or "2019 ncov" or "severe acute respiratory syndrome coronavirus 2" OR SARS-CoV-2 or (2019 and (new or novel) and coronavirus)) OR TI (COVID-19 or coronavirus or corona virus or Wuhan N2 virus or "2019 n-cov" or "2019 ncov" or "severe acute respiratory syndrome coronavirus 2" OR SARS-CoV-2 or (2019 and (new or novel) and coronavirus))
S10	(MH "Coronavirus+")
S11	(MH "COVID-19") OR (MH "SARS-CoV-2")
S12	S9 OR S10 OR S11
S13	S8 AND S12
S14	(MH "Cohort Studies+")
S15	TI ((cohort or longitudinal or prospective or follow up or follow-up or retrospective) W1 (study or studies or analys* or design or method*)) OR AB ((cohort or longitudinal or prospective or follow up or follow-up or retrospective) W1 (study or studies or analys* or design or method*))

S16	S14 OR S15
S17	S13 AND S16
S18	S13 AND S16

3. Databases/search engines

A search for preprints using a simplified search strategy will be conducted in the following:

- Europe PMC https://europepmc.org/
- MedRxiv https://www.medrxiv.org/
- Google Scholar https://scholar.google.com/

Appendix 2

Template data extraction for reinfection

Column 1	Column 2	Column 3	Column 4
Author DOI Country Study design Publication status	Population (number of participants, follow-up duration) Patient demographics Predominant variant in circulation Incidence of SARS-CoV-2	Test parameters: SARS-CoV-2 confirmation Serological confirmation Additional testing, e.g., whole genome sequencing Clinical description (symptomatic/asymptomatic)	Relative risk of reinfection (or Odds Ratio) Risk or relative risk over time Adjusted estimates (for covariates) Absolute (/crude) reinfection events Antibody titres

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