Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Evidence summary protocol:

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

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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 was developed and will form the basis of this evidence summary:

> How long does protective immunity (that is, prevention of 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. 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?
- How long can asymptomatic healthcare workers who have recovered from a prior SARS-CoV-2 infection be exempted from derogation policies if they become a close contact of a confirmed COVID-19 case?
- 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)?
- How long can asymptomatic patients who have recovered from a prior SARS-CoV-2 infection be exempted from testing prior to scheduled admission to hospital or inter institutional transfer?

Prior to this review, four evidence summaries relating to immunity following SARS-CoV-2 infection were published by HIQA (13 May 2020, 9 June 2020, 6 August 2020 and 11 November 2020).

In the November update,[1] the following research questions were addressed:

> 1) Is reinfection with SARS-CoV-2 possible following recovery?

2) What is the long-term duration of the antibody response (≥2 months)?

Due to the ongoing nature of serological studies and rapidly evolving data, the present review will also provide a scoping update on the long-term duration of antibody responses (Section 6 below).

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.
2. Screening of identified studies.
3. Data extraction and quality appraisal of included studies.
4. Summarise findings.

3. Search of relevant databases

The following databases will be searched using the search strategy defined in Appendix 1:

- PubMed
- Embase
- Europe PMC.

PubMed underwent substantial changes in early 2020, including updates to its search algorithm. This has led to searches conducted in "new" PubMed yielding different results to that of "Old PubMed". All reasonable efforts have been made to ensure that all relevant evidence from PubMed is retrieved during the searching process. The search for this research question has been conducted exclusively in "new" PubMed.

4. Screening of identified studies

All potentially eligible papers identified in the search strategy will be exported to EndNote 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 is 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 is detailed in Table 1 below.

Table 1. Population Outcome Study design

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: ▪ Health care workers ▪ Age groups (≤18 years, 18-40 years, 40-60 years, 60-70 years, ≥70 years) ▪ High risk and very high risk groups (HSE definitions**)
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 Subgroups include: ▪ symptomatic reinfection ▪ asymptomatic reinfection ▪ symptomatic initial infection ▪ asymptomatic initial infection ▪ reinfection cases identified by serial testing ▪ reinfection cases not identified by serial testing (for example, following symptoms or exposure to a confirmed case). 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.

Types of studies	**Include:** ▪ Observational studies (prospective or retrospective). **Exclude:** ▪ cohort studies that enrolled fewer than 100 participants unless the study reported comparative WGS on all reinfection cases (comparing first and second infections) ▪ 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).[2]

**Definitions used by HSE[3]

5. Data extraction and quality appraisal of included studies

For each study included, 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 is used for appraisal of observational cohort studies.[4]

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.

6. Scoping update of prior immunity evidence summaries by HIQA

The November 2020 update of HIQA's evidence summary on the duration of immunity and reinfection following SARS-CoV-2 infection[1] concluded that antibody-mediated responses can be detected in most patients beyond two months and up to six months post-symptom onset. These data were limited by the longest duration of follow-up in identified studies. Due to the evolving nature of these data, a scoping review of humoral and cell-mediated immunity will also be provided.

In line with HIQA standard operating procedure for the conduct of scoping reports, a search of the literature will be undertaken using the PubMed Clinical Queries Tool.

The results will be limited to English-language studies conducted in humans and published since October 2020. The following search terms will be used, in combination with the PubMed filters for identifying COVID-19 literature and transmission-related topics within COVID-19 literature: (SARS-CoV-2 AND immunity).

7. 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 and sent to the relevant parties in pdf format.

8. Quality assurance process

Each review question will be led by an experienced systematic reviewer. Two second reviewers will be assigned to assist and to provide cover. The second reviewer 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 a senior member of the team, to ensure processes are followed and quality maintained, this will also enable cover to be maintained.

9. References

1. HIQA. Duration of immunity and reinfection following SARS-CoV-2 infection. 11 Novemeber 2020. Available at: https://www.hiqa.ie/reports-and-publications/health-technology-assessment/evidence-summary-duration-immunity-and.
2. 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 Accessed: 22 September 2020.
3. 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.
4. 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

1. Ovid Embase

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 second or future or recur* or reactivat* or re-activat*) adj2 (infect* or disease*))).ab,ti.
10. immunity/
11. immune response/
12. mucosal immunity/
13. (immunity or immunoglobulin* or antibod*).ab,ti.
14. 7 or 8 or 9 or 10 or 11 or 12 or 13
15. 6 and 14
16. exp cohort analysis/
17. exp longitudinal study/
18. exp prospective study/
19. exp follow up/
20. exp retrospective study/
21. ((cohort or longitudinal or prospective or follow up or follow-up or retrospective) adj2 (study or analys* or design or method*)).ab,ti.
22. 16 or 17 or 18 or 19 or 20 or 21
23. 15 and 22
24. limit 23 to yr="2020 -Current"

2. Medline (Pubmed)

("cohort"[Title/Abstract] OR "longitudinal"[Title/Abstract] OR "prospective"[Title/Abstract] OR "follow-up"[Title/Abstract] OR "follow-up"[Title/Abstract] OR "retrospective"[Title/Abstract] OR "Cohort Studies"[MeSH Terms]) AND (("COVID-19"[MeSH Terms] OR "SARS-CoV-2"[MeSH Terms] OR ("2019-nCoV"[Title/Abstract] OR "2019nCoV"[Title/Abstract] OR "COVID-19"[Title/Abstract] OR "SARS-CoV-2"[Title/Abstract] OR ("wuhan"[Title/Abstract] AND ("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "coronaviruses"[All Fields])) OR "severe acute respiratory syndrome coronavirus 2"[Title/Abstract] OR "2019 novel coronavirus"[Title/Abstract] OR "2019 new coronavirus"[Title/Abstract]) OR "coronavirus"[MeSH Terms]) AND ("reinfection*"[Title/Abstract] OR "re infection*"[Title/Abstract] OR ("subsequent infect*"[Title/Abstract] OR "subsequent disease*"[Title/Abstract] OR "recurrent infect*"[Title/Abstract] OR "recurrent disease*"[Title/Abstract]) OR ("future infect*"[Title/Abstract] OR "future disease*"[Title/Abstract] OR "second infect*"[Title/Abstract] OR "second disease*"[Title/Abstract]) OR "reinfection"[MeSH Terms] OR ("immunity"[MeSH Terms] OR "adaptive immunity"[MeSH Terms] OR "immunity, mucosal"[MeSH Terms]) OR ("immunity"[Title/Abstract] OR "immunoglobulin*"[Title/Abstract])))

3. Europe PMC

(("SARS-CoV-2" OR "COVID-19") AND ("reinfection") AND (FIRST_PDATE:[2020-09-23 TO 2021-02-04])) AND (SRC:PPR)

Appendix 2

Template data extraction

Column 1	Column 2	Column 3	Column 5
Author DOI Country Study design Publication status	Population (number of participants, follow-up duration) Patient demographics	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

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