Evidence summary protocol:

Duration of protective immunity 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 questions were developed and will form the basis of this evidence summary:

Research question 1: 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?

Research question 2: What is the duration and composition 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. 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?

   - derogation policies if they become a close contact of a confirmed COVID-19 case?

   - serial testing, for example serial testing in indoor settings where social distancing is difficult (such as food processing facilities)?

   - testing prior to scheduled admission to hospital or inter institutional transfer?

Prior to this review, six evidence summaries relating to immunity following SARS-CoV-2 infection were published by HIQA (13 May 2020, 9 June 2020, 6 August 2020, 11 November 2020, 5 March 2021 and 14 April 2021). In the 14 April 2021 review, HIQA concluded that SARS-CoV-2 reinfection rates remain low for 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.

Due to the rapidly evolving evidence base relating to SARS-CoV-2 immunity, this review updates the evidence base relating to protection from reinfection (following a similar search strategy). Additionally, a de novo systematic search of long-term immune memory responses was conducted.

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 Appendices 1 and 2:

- Medline (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 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 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 relating to prevention of reinfection is provided in Table 1 and immune memory in Table 2.

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:
	▪ 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.
	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 cohort 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)
	▪ 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]

Table 2.   Population Outcome Study design – immune memory

Population	▪ Individuals (of any age) with evidence of prior SARS-CoV-2 infection; evidence of prior infection includes diagnosis by RT-PCR or antigen testing, or evidence of an immune response through antibody detection (seropositivity).
Outcomes	▪ Development of immune memory B and or T cells or their components.
Types of studies	**Include:** ▪ Observational studies (prospective or retrospective) with follow-up ≥6 months post-infection or post-symptom onset. **Exclude:** ▪ modelling studies ▪ studies of cross-protection from immune memory development from a prior infection with a virus other than SARS-CoV-2 ▪ systematic or narrative reviews ▪ case series ▪ case reports ▪ studies that describe precursors to immune memory cells ▪ studies of deceased patients ▪ studies in animals ▪ studies of populations vaccinated against SARS-CoV-2.

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 3). If the paper has not been peer reviewed, this is noted.

The National Heart, Lung and Blood Institute (NIH) quality assessment tools and Joanna Briggs Institute (JBI) checklist for cohort studies will be used for appraisal of observational cohort studies.[3, 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. 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 where appropriate.

7. 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.

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 4 May 2021 and a final draft will be completed by 20 May 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 27 May 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.   National Heart Lung and Blood Institute (NIH). Study Quality Assessment Tools. Available at: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools.

4.   Joanna Briggs Institute. Critical Appraisal Checklist for Cohort Studies 2017 [cited 2021 Apr 26]. Available from: https://jbi.global/sites/default/files/2019-05/JBI_Critical_Appraisal-Checklist_for_Cohort_Studies2017_0.pdf

Appendix 1.

Search strategy – prevention of reinfection

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. 23 and [19-3-2021]/sd NOT [4-5-2021]/sd

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])))

Filter: from 19/3/2021 until 04/05/2021

3.   Europe PMC

(("SARS-CoV-2" OR "COVID-19") AND ("reinfection") AND (FIRST_PDATE:[2020-03-19 TO 2021-04-05])) AND (SRC:PPR)

Appendix 2.

Search strategy – immune memory

Medline

1. AB (COVID-19 OR coronavir* OR "corona virus") OR TI (COVID-19 OR coronavir* OR "corona virus")
2. AB ((Wuhan AND virus) OR "2019 nCoV" OR "2019-nCoV" OR "severe acute respiratory syndrome 2" OR SARS-CoV-2) OR TI ((Wuhan AND virus) OR "2019 nCoV" OR "2019-nCoV" OR "severe acute respiratory syndrome 2" OR SARS-CoV-2)
3. AB (2019 AND (new OR novel) AND coronavirus) OR TI (2019 AND (new OR novel) AND coronavirus)
4. (MH "COVID-19")
5. (MH "SARS-CoV-2")
6. S1 OR S2 OR S3 OR S4 OR S5
7. (MH "Immunologic Memory")
8. (MH "CD8-Positive T-Lymphocytes+")
9. AB (immunological AND (memory or memories)) OR TI (immunological AND (memory or memories))
10. AB (immunologic AND (memory or memories)) OR TI (immunologic AND (memory or memories))
11. AB "immune memor*" OR TI "immune memor*"
12. AB "Memory B cell" OR TI "Memory B cell"
13. AB "Memory T Cell" OR TI "Memory T Cell"
14. AB (CD4+ AND (memory or memories)) OR TI (CD4+ AND (memory or memories))
15. AB (CD8+ AND (memory or memories)) OR TI (CD8+ AND (memory or memories))
16. AB (CD8+ AND (memory or memories)) OR TI (CD8+ AND (memory or memories))
17. AB ("T Lymphocytes" AND (memory or memories)) OR TI ("T Lymphocytes" AND (memory or memories))
18. AB ("B lymphocytes" AND (memory or memories)) OR TI ("B lymphocytes" AND (memory or memories))
19. AB "cellular immun*" OR TI "cellular immun*"
20. S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19
21. S6 AND S20

Embase Ovid

1. exp coronavirus disease 2019/
2. COVID-19.ab,ti.
3. coronavirus.ab,ti.
4. "corona virus".ab,ti.
5. (Wuhan adj3 virus).ab,ti.
6. ("2019-nCoV" or "2019 ncov").ab,ti.
7. ("severe acute respiratory syndrome coronavirus 2" or SARS-CoV-2).ab,ti.
8. ("2019" and (new or novel) and coronavirus).ab,ti.

9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. exp immunological memory/
11. cellular immunity/
12. exp memory cell/
13. ((immune or immunity or immunologic or immunological) and (memory or memories)).ab,ti.
14. ((memory or memories) and ("T cell" or T-cell or "B cell" or B-cell or "T lymphocytes" or "B lymphocytes")).ab,ti.
15. ((memory or memories) and ("CD4+" or "CD8+")).ab,ti.
16. "cellular immun*".ab,ti.
17. response.ab,ti.
18. 16 and 17
19. 10 or 11 or 12 or 13 or 14 or 15 or 18
20. 9 and 19

Appendix 3

Template data extraction for reinfection

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

Template data extraction for immune memory

Study characteristics	Patient demographics Clinical characteristics Test parameters	Primary outcome results
Author: *Country:* *DOI:* *Study design:* *Setting:* *Publication status:*	*Patient demographics:* Participants = X Mean age = X Male = X% Type of test: Follow-up duration/range/intervals:	*Immune memory component reported:* *Results:* *Author conclusions:*