Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Evidence summary of the duration of immunity and reinfection following SARS-CoV-2 infection; protocol

11 November 2020

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).

This protocol details the process to be undertaken for the RQ, "What is the rate of reinfection/duration of immunity in individuals who recover from a laboratory-confirmed coronavirus infection?" The first report on this RQ was published on 13 May 2020 with subsequent updates on 9 June 2020 and 6 August 2020. For the present update, the scope of the review has been refined to focus on the following specific research questions:

1. Is reinfection with SARS-CoV-2 possible following recovery?
   Demonstration of reinfection must include virus isolation with whole genome sequencing that confirms the first and second SARS-CoV-2 infections were caused by different viral strains.
2. What is the long-term duration of the antibody response?
   Duration of follow-up in these studies must be ≥2 months from the time of initial infection.

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
- NHS Evidence.

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. POS framework

Population	Individuals (of any age) who were infected with a laboratory-confirmed SARS-CoV-2 infection and subsequently recovered 'Recovered' refers to molecular or clinical evidence of viral clearance following initial infection: ▪ Two consecutive negative respiratory RT-PCR tests 24 hours apart. and/or ▪ WHO clinical criteria of viral clearance (27 May 2020). For symptomatic patients, a minimum of 10 days after symptom onset, plus at least 3 additional days without symptoms (including without fever and without respiratory symptoms); for asymptomatic cases, a minimum of 10 days after positive test for SARS-CoV-2.
Outcomes	▪ Protection against reinfection ○ 'True' reinfection must include virus isolation with whole genome sequencing that confirms the first and second SARS-CoV-2 infections were caused by different viral strains ○ 'Redetection', whereby a patient tests positive by RT-PCR following recovery, is not sufficient evidence of reinfection and therefore will be excluded. ▪ Long-term duration of the antibody response

	○ Outcomes include detection of serum anti-SARS-CoV-2-specific immunoglobulin G and neutralising antibodies, and serum titres over time (typically expressed as Geometric Mean Titres [GMTs]) ○ Duration of follow-up must be ≥2 months from the time of initial infection.
Types of studies	**Include:** ▪ reinfection studies: all study designs will be considered (including case reports) ▪ duration of antibody detection: case series, cohort studies, cross-sectional studies. **Exclude:** ▪ reinfection studies: exclude studies that did not perform whole genome sequencing ▪ antibody detection studies: exclude studies that followed individuals for less than 2 months ▪ animal studies.

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

For randomised controlled trials (RCTs) the Cochrane risk of bias tool (version 1) is used, as this can be completed more rapidly than the more in-depth version 2. ROBINS-I tool (Risk of bias in non-randomised studies - of interventions) is used for quality appraisal of non-randomised studies, the AMSTAR-2 to appraise systematic reviews, and the Quality Assessment of Diagnostic Accuracy Studies version two (QUADAS-2) is used to assess explicit studies of diagnostic accuracy. The National Heart, Lung and Blood Institute (NIH) quality assessment tools is used for appraisal of observational cohort studies and for pre-post studies with no control group, for example, analytical studies. The Joanna Briggs Institute critical appraisal tools will be used for cross-sectional and case control studies. For surveys, the Center for Evidence-Based Management (CEBMa) critical appraisal of a survey tool is used. However, the majority of studies are often from case reports and case series, which have been conducted rapidly.

No universally accepted quality appraisal tool exists for assessing the methodological quality of studies based on case series. Therefore, these studies are assessed using criteria outlined in Appendix 3.

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 and sent to the relevant parties in pdf format.

7. Quality assurance process

Each review question will be led by an experienced systematic reviewer. A second reviewer will be assigned to assist and to provide cover in the event of illness. 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.

Appendix 1

Search strategy

	PubMed
A	((coronavirus [MeSH]) OR ("coronavirus infections"[MeSH Terms]) OR (coronavirus [All Fields]) OR ("covid 2019") OR ("SARS2") OR ("SARS-CoV-2") OR ("SARS-CoV-19") OR ("severe acute respiratory syndrome coronavirus 2" [supplementary concept]) OR (coronavirus infection) OR ("severe acute respiratory" pneumonia outbreak) OR ("novel cov") OR (2019ncov) OR (sars cov2) OR (cov2) OR (ncov) OR (covid-19) OR (covid19) OR (coronaviridae) OR ("corona virus"))
B	Immunity[Mesh] OR immunity[All Fields] OR antibodies[Mesh] OR antibodies[All Fields] OR antibody[All Fields] OR "Immunoglobulin G"[All Fields] OR "IgG"[All Fields] OR "IgG3"[All Fields] OR "IgG4"[All Fields] OR "neutralizing antibody"[All Fields] OR "neutralising antibody"[All Fields] OR "neutralizing antibodies"[All Fields] OR "neutralising antibodies"[All Fields] OR NAbs[All Fields] OR reinfection[All Fields] OR reinfections[All Fields] OR "Recurrence"[MeSH] OR "recurrence"[All Fields]
C	A AND B, limit humans, 6/7/2020 to 23/9/2020
	EMBASE
A	'coronavirinae'/exp OR 'coronavirinae' OR 'coronaviridae infection'/exp OR 'coronaviridae infection':ti,ab,kw OR 'coronavirus'/exp OR coronavirus:ti,ab,de,kw OR 'coronavirus infection'/de OR SARS-VoV-2:ti,ab,kw OR covid-19:ti,ab,kw OR covid19:ti,ab,kw
B	Immunity:ti,ab,de,kw OR 'immunity'/exp OR 'antibody'/exp OR antibody:ti,ab,de,kw OR antibodies:ti,ab,de,kw OR 'immunoglobulin'/exp OR immunoglobulin:ti,ab,de,kw OR immunoglobulins ti,ab,de,kw OR IgG OR IgG3 OR IgG4 OR "neutralizing antibody":ti,ab,de,kw OR "neutralising antibody":ti,ab,de,kw OR "neutralizing antibodies":ti,ab,de,kw OR "neutralising antibodies":ti,ab,de,kw OR NAbs:ti,ab,de,kw OR "neutralizing antibody"/exp OR "neutralising antibody"/exp OR "neutralizing antibodies"/exp OR "neutralising antibodies"/exp OR NAbs/exp OR 'reinfection'/exp OR reinfection:ti,ab,de,kw OR reinfections:ti,ab,de,kw OR 'recurrent disease'/exp OR recurrence :ti,ab,de,kw
C	A AND B; limit human, 6/7/2020 to 23/9/2020
	EuropePMC
A	(coronavirus OR covid-19 OR "covid 19" OR "SARS-CoV-2") AND (immunity OR antibody OR antibodies OR immunoglobulin OR immunoglobulins OR IgG OR IgG3 OR IgG4 OR "neutralizing antibody" OR "neutralising antibody" OR "neutralizing antibodies" OR "neutralising antibodies" OR Nabs OR reinfection OR reinfections OR recurrence) AND (SRC:PPR); limit human, 6/7/2020 to 23/9/2020

Appendix 2

Template data extraction

Column 1	Column 2	Column 3	Column 4	Column 5	Column 6	Column 7
Author DOI Country Study design	Population Patient demographics	Test parameters	Clinical description	Whole genome sequencing	Antibody testing	Peer review status

Appendix 3

Questions to assist with the critical appraisal case report/series for COVID-19

Question	Response
Relevance to Irish system	
Was the study question or objective clearly stated?	
Are the study patients described in sufficient demographically?	
Is the context applicable?	
Study design	
Were there clear criteria for inclusion of the case(s)?	
Was the condition measured in a standard, reliable way for all participants included in the case series?	
Was the outcome measured in a standard, reliable way for all participants included in the case series?	
Was the statistical analysis appropriate?	
Peer-review status	
Has this study been formally peer-reviewed?	

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