COVID-19 Evidence Synthesis: Protocol for an international review of the epidemiology of long COVID

16 January

Version	1.0

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.

1   Purpose and Aim

The Health Service Executive requested the Health Information and Quality Authority (HIQA) to undertake an international review of the epidemiology (including prevalence, incidence, risk factors and mitigating factors) of long COVID. Long COVID is known by several names (for example, post-acute COVID-19, post-acute sequelae of SARS-CoV-2 infection, long-term effects of COVID, and chronic COVID). Typically, it refers to a range of post-COVID conditions that people experience after first being infected with SARS-CoV-2. This protocol aims to outline the process by which the COVID-19 Evidence Synthesis Team will undertake this review.

2   Process outline

It is vital that a standardised approach to the process is developed and documented to allow for transparency, aid project management, and mitigate risks that may arise during the project. Five distinct steps in the process have been identified and will be completed. These are listed below and described in more detail in sections 3.1-3.5.

1. Identify document types of interest.

2. Search relevant sources.

3. Screen identified documents.

4. Data extraction and quality appraisal of included documents.

5. Summarise findings.

3   Review process

This review will address the following two research questions (RQs):

RQ1. What is the epidemiology and clinical burden of long COVID internationally?

RQ2. Among those who have had a SARS-CoV-2 infection, what are the associations between risk/mitigation factors and development of long COVID?

For the purpose of the review and to facilitate international comparisons, the following definition of long COVID, used in the NICE guidelines,[1] will be applied:

"long COVID" is commonly used to describe signs and symptoms that continue or develop after acute COVID-19. It includes both ongoing symptomatic COVID-19 (from 4 to 12 weeks) and post-COVID-19 syndrome (12 weeks or more).

Ongoing symptomatic COVID-19: signs and symptoms of COVID-19 from 4 weeks up to 12 weeks post infection with SARS-CoV-2.

Post-COVID-19 syndrome: signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis. It usually presents with clusters of symptoms, often overlapping, which can fluctuate and change over time and can affect any system in the body. Post COVID-19 syndrome may be considered before 12 weeks while the possibility of an alternative underlying disease is also being assessed.

RQ1 and RQ2 were formulated using the POS (population, outcome, study type) and PECOS (population, exposure, comparator, outcome, study type) framework as detailed in Table 1 and Table 2.

Table 1. Population, outcome and study type (POS) for RQ1.

Population	Individuals of any age:
	• with a history of probable or confirmed SARS-CoV-2.
	Subgroups:
	▪ age (subgroups such as those aged <18 years, those aged ≥ 65 years)
	▪ those aged < 65 years who are extremely vulnerable (as outlined by the HSE) (Appendix 1)[2]
	▪ those with a history of severe COVID-19 illness (defined as those hospitalised or admitted to intensive care due to COVID-19).
Outcomes	Epidemiology and clinical burden in those who meet the criteria for long COVID (as defined in the NICE guidelines),[1] for the following outcomes:
	▪ prevalence (prevalence estimate/rate)
	▪ incidence (per 100,000 population)
	▪ all-cause mortality (%)
	▪ persistent[†] signs and symptoms (such as, but not limited to, chest pain, fatigue, cognitive impairment, anxiety, dyspnoea and cough and sputum production)
	▪ impact on daily living (such as, but not limited to, quality of life, health-related quality of life, employment status and level of care dependency).

Study type	**Include:** ▪ prospective / retrospective community-, population- and hospital-based original research studies with ≥ 10,000 participants ▪ prospective / retrospective community-, population- and hospital-based original research studies, focused on a previously outlined subgroup, with ≥ 300 participants ▪ epidemiological and clinical burden data reported within public health guidance and policy documents identified as relevant within the international review of clinical guidelines and models of care for long COVID currently being conducted by HIQA ▪ national and international disease registries containing data on those with a history of probable or confirmed SARS-CoV-2. **Exclude:** ▪ reviews ▪ original research studies with <10,000 participants not focused on a previously outlined subgroup ▪ original research studies that do not include community / population and hospital-based settings ▪ original research studies that do not specify a history of probable or confirmed SARS-CoV-2 ▪ original research studies that do not include those who meet the criteria for long COVID (as defined in the NICE guidelines) ▪ original research studies with outcomes not associated with a previous SARS-CoV-2 infection ▪ original research studies that include animals.

†Persistent outcomes must be identified as outcomes that are ongoing or continuous (for example, daily cough), outcomes that come and go (for example, periods of fatigue) and or outcomes that have occurred more than once (for example, episodic chest pain). In the event of a new occurrence of an outcome, this must be identified as being associated with a previous SARS-CoV-2 infection.

Table 2. Population, exposure, comparator, outcome and study type (PECOS) for RQ2.

Population	Individuals of any age with: ▪ a history of probable or confirmed SARS-CoV-2. Subgroups: ▪ age (subgroups such as those aged <18 years, those aged ≥ 65 years) ▪ those aged <65 years who are extremely vulnerable (as outlined by the HSE) (Appendix 1)[2] ▪ those with a history of severe COVID-19 illness (defined as those hospitalised or admitted to intensive care due to COVID-19).
Exposure	**Risk factors**

	Pre-existing
	- being unvaccinated - female sex - older age (≥ 65 years of age) - belonging to an ethnic minority - socioeconomic deprivation - smoking - obesity - pre-existing medical condition(s) - pregnancy (at time of COVID-19 diagnosis). Clinical (during the acute phase of COVID-19) - number of symptoms - COVID-19 severity (defined as those hospitalised or admitted to intensive care due to COVID-19) - variant type. **Mitigating factors** - vaccination status - medication use during the acute phase management, specifically use of corticosteroids and or pharmaceuticals licensed for the treatment of COVID-19 (such as monoclonal antibodies, antivirals and immunosuppressants) - physical activity level (prior to COVID-19 onset).
Comparator	Those without the exposure (this may include those with or without a history of probable or confirmed SARS-CoV-2).
Outcomes	Relative risk, hazard/odds ratios, in those who meet the criteria for long COVID (as defined in the NICE guidelines),[1] related to the following outcomes, adapted from Pillay et al.,[3] will be extracted. For community-, population- and hospital-based studies the baseline risk will also be extracted, if reported. - non-recovery/persistent† symptoms - major cardiovascular event or organ impairment - experiencing moderate/severe* or persistent† fatigue - experiencing moderate/severe* or persistent† breathlessness/dyspnoea - experiencing important impact on quality of life - experiencing clinical/pathological levels of psychopathology such as anxiety and depression - experiencing moderate/severe* or persistent† impairment in functional capacity - experiencing moderate/severe* or persistent† cognitive impairment - experiencing moderate/severe* or persistent† sleep disturbances - experiencing moderate/severe* or persistent† pain including headaches and chest pain

	▪ unable to return to full-time work/school/education or caring role (as applicable).
Study type	**Include:** ▪ prospective / retrospective community-, population- and hospital-based original research studies with ≥ 10,000 participants ▪ prospective / retrospective community / population and hospital-based original research studies, focused on a previously outlined subgroup, with ≥ 300 participants ▪ epidemiological and clinical burden data reported within public health guidance and policy documents identified as relevant within the international review of clinical guidelines and models of care for long COVID currently being conducted by HIQA ▪ national and international disease registries containing data on those with a history of probable or confirmed SARS-CoV-2. **Exclude:** ▪ reviews ▪ original research studies with <10,000 participants not focused on a previously outlined subgroup ▪ original research studies that do not include community / population and hospital-based settings. ▪ original research studies that do not specify a history of probable or confirmed SARS-CoV-2. ▪ original research studies that do not include those who meet the criteria for long COVID (as defined in the NICE guidelines). ▪ original research studies with outcomes not associated with a previous SARS-CoV-2 infection ▪ original research studies that include animals.

*Moderate/severe as reported by the study author. †Persistent outcomes must be identified as outcomes that are ongoing or continuous (for example, daily cough), outcomes that come and go (for example, periods of fatigue) and or outcomes that have occurred more than once (for example, episodic chest pain). In the event of a new occurrence of an outcome, this must be identified as being associated with a previous SARS-CoV-2 infection.

3.1 Identify document types of interest

The evidence describing the epidemiology of long COVID will be identified from the following document categories:

a)   original research studies

b)   public health guidance and policy documents

c)   national and international disease registries.

3.2   Search relevant sources

A systematic literature search will be conducted in Medline (EBSCO), Embase (Elsevier), and the Cochrane Library to identify evidence of the epidemiology (including prevalence, incidence, risk factors and mitigating factors) of long COVID internationally; a grey literature search for the same will also be conducted. The detailed search strategies are presented in Appendix 2.

HIQA has published an evidence synthesis titled 'International review of clinical guidelines and models of care for long COVID' (here). Where appropriate, information related to the epidemiology of long COVID provided within the documents in this review will be identified and included. Similarly, information related to the epidemiology of long COVID provided by international disease registries will also be included. Where epidemiological and clinical burden data cannot be identified within public health guidance documents and disease registries, forward citation searching of these documents will be undertaken. Additionally, forward citation searching of all included original research studies, will be undertaken.

The November 2021 update of the NICE "COVID-19 rapid guidelines: managing the long term effects of COVID-19" included updates to evidence reviews on signs, symptoms and prevalence; and risk factors.[1] Therefore, only documents published from November 2021 onward will be included.

3.3   Screen identified documents

All potentially eligible documents identified will be exported to Covidence. For title and abstract screening, all documents will be screened against the eligibility criteria (see Tables 1 and 2) by one reviewer. For full text screening, all documents will be screened against the eligibility criteria (see Tables 1 and 2) by two reviewers, with any disputes resolved by a third reviewer. Documents will only be included where full texts are available. No language restrictions will be applied. Where websites or documents are not readily available in English, titles will be screened for relevant keywords using the language of the document; full page translations will not be performed at the screening stage. Where documents are considered for inclusion in the evidence summary, they will be translated via Google Translate; this translation will be noted as a potential caveat.

3.4   Data extraction and quality appraisal of included documents

For each RQ, data extraction will be completed by one reviewer and checked for accuracy and omissions by a second reviewer. Where disagreements occur,

discussions will be held to reach consensus and where necessary, a third reviewer will be involved. Data extraction templates will be used to aid in the identification and storage of relevant data, and are detailed in Appendix 3 and 4.

Briefly, the data collected for each document category are:

1. Original research studies: study descriptors, population demographics, outcomes related to RQ1 (epidemiology and clinical burden) and RQ2 (risk / mitigating factors), author conclusions.
2. National and international disease registries: registry name, disease name (RQ2 only as long COVID and or long COVID factors may appear in specific disease registries), country, population demographics, outcomes reported (related to long COVID).
3. Public health guidance and policy documents: country or organisation, guidance/document title, URL, date, outcomes related to RQ1 (epidemiology and clinical burden) and RQ2 (risk / mitigating factors), evidence source.

The Newcastle-Ottawa Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies will be used for the appraisal of observational cohort studies.[5] The criteria outlined in a cross sectional survey of multicentre clinical databases in the UK,[6] will be used for assessing the attributes of included registries.

3.5 Summarise findings

A PRISMA flow chart of the identified documents will be presented and a summary of the evidence of the epidemiology of long COVID internationally will be compiled.

4   Quality assurance process

The review question will be undertaken in accordance with HIQA's Quality Assurance Framework and led by an experienced member of staff. The report will be reviewed by two senior members of the team, to ensure processes are followed and quality maintained. Additionally, draft outputs from the evidence synthesis will be circulated to HIQA's COVID-19 Expert Advisory Group (EAG) for review and will be presented and discussed at a meeting of the COVID-19 EAG.

5   Review and update

Given the rapidly changing environment, this protocol will be regarded as a live document and amended when required to ensure it reflects any changes made to the outlined processes. Amendments will be captured in the version history.

References

1. National Institute for Health and Care Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN), Royal College of Genereal Practitioners (RCGP). COVID-19 rapid guideline: managing the long term effects of COVID-19. 2022.

2. Health Service Executive (HSE). People at higher risk from COVID-19 2022. Available from:https://www2.hse.ie/conditions/covid19/people-at-higher-risk/overview/

3. Pillay J, Rahman S, Guitard S, Wingert A, Hartling L. Risk factors and preventive interventions for post Covid-19 condition: systematic reviews. medRxiv. 2022.

4. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017;358:j4008.

5. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Oxford; 2000.

6. Black N, Barker M, Payne M. Cross sectional survey of multicentre clinical databases in the United Kingdom. Bmj. 2004;328(7454):1478.

7. Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. AGREE II: advancing guideline development, reporting and evaluation in health care. Cmaj. 2010;182(18):E839-E42.

8. National Health Library and Knowledge Service (NHLKS), Leen B, McCarthy S, Quinn E, Helen C. [Evidence summary:] What is the latest national and international evidence about the existence of long COVID or post-COVID and its persistence for COVID-19 survivors? [v2.0]. Health Service Executive, 2022.

Appendix 1: Very high risk groups (extremely vulnerable) as defined by the HSE.[2]

The list of people in very high risk groups (extremely vulnerable) include people who:

- have Down syndrome
- have cancer and are being treated with (or within six weeks of) chemotherapy or targeted therapy, monoclonal antibodies or immunotherapies
- have lung or head and neck cancer and are having (or within six weeks of) radical surgery or radiotherapy
- are having certain complex cancer surgery, for example, surgery for lung cancer, head and neck cancer or oesophageal cancer
- getting treatment or pending treatment for a cancer of blood or bone marrow
- have advanced cancer or cancer that has spread to another part of the body
- are on dialysis or have end-stage kidney disease and an estimated glomerular filtration rate less than 15 ml/min
- have a condition affecting the brains or nerves that has significantly affected your ability to breathe, meaning you require non-invasive ventilation (such as motor neurone disease or spinal muscular atrophy)
- have unstable or severe cystic fibrosis, including people waiting for a transplant
- have severe respiratory conditions including Alpha-1 antitrypsin deficiency, pulmonary fibrosis, lung fibrosis, interstitial lung disease and severe chronic obstructive pulmonary disease
- have uncontrolled diabetes
- have had an organ transplant or are waiting for a transplant
- have had a bone marrow or stem cell transplant in the last 12 months, or are waiting for a transplant
- have a rare genetic condition that means you have a very high risk of getting infections (such as APECED or errors in the interferon pathway)
- sickle cell disease
- have been treated with drugs such as rituximab, cyclophosphamide, alemtuzumab, cladribine or ocrelizumab in the last six months
- have certain inherited metabolic disorders (such as Maple Syrup Urine Disease)
- have obesity with a body mass index greater than 40 kg/m^2.

Appendix 2: Search Strategies

Database search[*]

Database: Medline (EBSCO)		
#	Query	Limiters/Expanders
S28	S19 OR S27	Limiters - Date of Publication: 20211101- Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S27	S10 AND S22 AND S26	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S26	S23 OR S24 OR S25	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S25	MH "Cohort Studies" OR MH "Longitudinal Studies" OR MH "Prospective Studies" OR MH "Follow Up Studies" OR MH "Retrospective Studies" OR TI (cohort OR longitudinal OR prospective OR "follow up" OR retrospective) N1 (study OR analys* OR design OR method*) OR AB (cohort OR longitudinal OR prospective OR "follow up" OR retrospective) N1 (study OR analys* OR design OR method*)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S24	MH "Cross Sectional Studies" OR TI ("cross sectional" OR transverse OR prevalence) N1 (study OR analys* OR design OR method*) OR (AB ("cross sectional" OR transverse OR prevalence) N1 (study OR analys* OR design OR method*)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S23	MH "Systematic Review" OR MH "Meta Analysis" OR PT "Meta-Analysis" OR TI systematic* N1 (review* OR overview*) OR AB systematic* N1 (review* OR overview*) OR TI "meta analys*" OR TI "meta analyz*" OR AB "meta analys*" OR AB "meta analyz* OR TI literature N2 (review* OR overview*) OR AB literature N2 (review* OR overview*)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S22	S20 OR S21	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase

S21	AB (risk* or prevalence* or incidence* or predict* or associat*) OR TI (risk* or prevalence* or incidence* or predict* or associat*)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S20	(MH "Risk Factors+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S19	S10 AND S17	Limiters - Date of Publication: 20211101- Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S18	S10 AND S17	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S17	S11 OR S12 OR S13 OR S14 OR S15 OR S16	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S16	AB (prevalence or incidence or epidemiol* or survey or cohort or surveillance or screening) OR TI (prevalence or incidence or epidemiol* or survey or cohort or surveillance or screening)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S15	(MH "Epidemiologic Methods+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S14	(MH "Cross-Sectional Studies") OR (MH "Longitudinal Studies+") OR (MH "Follow-Up Studies") OR (MH "Prospective Studies") OR (MH "Epidemiologic Studies+") OR (MH "Retrospective Studies")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S13	(MH "Cohort Studies+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S12	(MH "Prevalence")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S11	(MH "Incidence")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S10	S1 OR S4 OR S5 OR S6 OR S9	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase

S9	S7 AND S8	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S8	S2 OR S3	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S7	AB ((Ongoing or long* or endur* or legacy* or slow* or gradual* or protract* or lengthy or chronic* or persist* or remission or residual* or prolong* or extend* or linger* or permanent or nonrecover* or "non recover*" or lasting or continuous* or continual* or continuing* or postacute* or "post acute*" or "long* term*" or "long duration*" or "long last*" or "long standing*" or postinfect* or "post infect*" or postviral* or "post viral*" or postvirus* or "post virus*") N2 (sequela* or illness or symptom* or sign* or indicat* or syndrom*)) OR TI ((Ongoing or long* or endur* or legacy* or slow* or gradual* or protract* or lengthy or chronic* or persist* or remission or residual* or prolong* or extend* or linger* or permanent or nonrecover* or "non recover*" or lasting or continuous* or continual* or continuing* or postacute* or "post acute*" or "long* term*" or "long duration*" or "long last*" or "long standing*" or postinfect* or "post infect*" or postviral* or "post viral*" or postvirus* or "post virus*") N2 (sequela* or illness or symptom* or sign* or indicat* or syndrom*))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S6	AB ((Ongoing or long* or endur* or legacy* or slow* or gradual* or protract* or lengthy or chronic* or persist* or remission or residual* or prolong* or extend* or linger* or permanent or nonrecover* or "non recover*" or lasting or continuous* or continual* or continuing* or postacute* or "post acute*" or "long* term*" or "long duration*" or "long last*" or "long standing*" or postinfect* or "post infect*" or postviral* or "post viral*" or postvirus* or "post virus*") N2 (sequela* or illness or symptom* or sign* or indicat* or syndrom*)) N10 (covid* or coronavirus* or corona* virus* or Cov or "SARS-CoV-2*" or "SARSCoV-2*" or "SARSCoV2*" or "SARS-CoV2*" or "severe acute respiratory syndrome*" or Ncov* or "n-cov")) OR TI ((Ongoing or long* or endur* or legacy* or slow* or gradual* or protract* or lengthy or chronic* or persist* or remission or residual* or prolong* or extend* or linger* or permanent or nonrecover* or "non recover*" or lasting or continuous* or continual* or continuing* or postacute* or "post acute*" or "long* term*" or "long duration*" or "long last*" or "long standing*" or postinfect* or "post infect*" or postviral* or "post viral*" or postvirus* or "post virus*") N2 (sequela* or illness or symptom* or sign* or indicat* or syndrom*)) N10 (covid* or coronavirus* or corona* virus* or Cov or "SARS-CoV-2*" or "SARSCoV-2*" or "SARSCoV2*" or "SARS-CoV2*" or "severe acute respiratory syndrome*" or Ncov* or "n-cov"))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S5	AB (("long haul*" OR longhaul* OR postacute OR "post acute" OR post-acute) N2 (covid19 OR covid-19 OR "sars-cov-2*" OR "sarscov-2*" OR "sarscov2*" OR "sars-cov2*" OR "severe acute respiratory syndrome*" OR ncov* OR "n-cov")) OR TI (("long haul*" OR longhaul* OR postacute OR "post acute"	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase

	OR post-acute) N2 (covid19 OR covid-19 OR "sars-cov-2*" OR "sarscov-2*" OR "sarscov2*" OR "sars-cov2*" OR "severe acute respiratory syndrome*" OR ncov* OR "n-cov"))	
S4	AB (("post covid" or postcovid or "post coronavirus" or postcoronavirus or "post coronovirus" or postcoronovirus or "post sars cov 2" or "post-sars-CoV-2") N2 (syndrome* OR disorder* OR illness* OR sickness* OR disease* OR condition* OR symptom* OR sign* OR feature*)) OR TI (("post covid" or postcovid or "post coronavirus" or postcoronavirus or "post coronovirus" or postcoronovirus or "post sars cov 2" or "post-sars-CoV-2") N2 (syndrome* OR disorder* OR illness* OR sickness* OR disease* OR condition* OR symptom* OR sign* OR feature*))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S3	(MH "SARS-CoV-2")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S2	(MH "COVID-19")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S1	AB ((longcovid* or long covid* or longcoronavirus* or "longcorona* virus*" or "long coronavirus*" or "long corona* virus*" or longcoronovirus* or "longcorono* virus*" or "long coronovirus*" or "long corono* virus*" or longcoronavirinae* or "longcorona* virinae*" or "long coronavirinae*" or "long corona* virinae*" or longCov or "long Cov" or longsars* or "long sars*" or "long severe acute respiratory syndrome*" or longncov* or "long ncov*" or longhcov* or "long hcov*" or "chronic covid*" or "post covid-19 condition*")) OR TI ((longcovid* or long covid* or longcoronavirus* or "longcorona* virus*" or "long coronavirus*" or "long corona* virus*" or longcoronovirus* or "longcorono* virus*" or "long coronovirus*" or "long corono* virus*" or longcoronavirinae* or "longcorona* virinae*" or "long coronavirinae*" or "long corona* virinae*" or longCov or "long Cov" or longsars* or "long sars*" or "long severe acute respiratory syndrome*" or longncov* or "long ncov*" or longhcov* or "long hcov*" or "chronic covid*" or "post covid-19 condition*"))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase

Database: Embase 1974 to 2022 September 02	
#	**Searches**
1	(longcovid* or 'long covid*' or longcoronavirus* or 'longcorona* virus*' or 'long coronavirus*' or 'long corona* virus*' or longcoronovirus* or 'longcorono* virus*' or 'long coronovirus*' or 'long corono* virus*' or longcoronavirinae* or 'longcorona* virinae*' or 'long coronavirinae*' or

	'long corona* virinae*' or longcov or 'long cov' or longsars* or 'long sars*' or 'long severe acute respiratory syndrome*' or longncov* or 'long ncov*' or longhcov* or 'long hcov*').ab,ti.
2	((postcovid* or 'post covid*' or postcoronavirus* or 'postcorona* virus*' or 'post coronavirus*' or 'post corona* virus*' or postcoronovirus* or 'postcorono* virus*' or 'post coronovirus*' or 'post corono* virus*' or postcoronavirinae* or 'postcorona* virinae*' or 'post coronavirinae*' or 'post corona* virinae*' or postcov or 'post cov' or postsars* or 'post sars*' or 'post severe acute respiratory syndrome*' or postncov* or 'post ncov*' or posthcov* or 'post hcov*') adj3 (syndrome* or disorder* or illness* or sickness* or disease* or condition* or symptom* or sign* or feature*)).ab,ti.
3	(('long haul*' or longhaul* or 'long haul*') adj3 (covid* or coronavirus* or 'corona* virus*' or cov or 'sars-cov-2*' or 'sarscov-2*' or 'sarscov2*' or 'sars-cov2*' or 'severe acute respiratory syndrome*' or ncov* or 'n-cov')).ti,ab.
4	((ongoing or long* or endur* or legacy* or slow* or gradual* or protract* or lengthy or chronic* or persist* or remission or residual* or prolong* or extend* or linger* or permanent or nonrecover* or 'non recover*' or lasting or continuous* or continual* or continuing* or postacute* or 'post acute*' or 'long* term*' or 'long duration*' or 'long last*' or 'long standing*' or postinfect* or 'post infect*' or postviral* or 'post viral*' or postvirus* or 'post virus*') adj2 (sequela* or illness or symptom* or sign* or indicat* or syndrom*) adj10 (covid* or coronavirus* or 'corona* virus*' or cov or 'sars-cov-2*' or 'sarscov-2*' or 'sarscov2*' or 'sars-cov2*' or 'severe acute respiratory syndrome*' or ncov* or 'n-cov')).ti,ab.
5	('chronic covid*' or 'post covid-condition*').ti,ab.
6	exp long COVID/
7	((ongoing or long* or endur* or legacy* or slow* or gradual* or protract* or lengthy or chronic* or persist* or remission or residual* or prolong* or extend* or linger* or permanent or nonrecover* or 'non recover*' or lasting or continuous* or continual* or continuing* or postacute* or 'post acute*' or 'long* term*' or 'long duration*' or 'long last*' or 'long standing*' or postinfect* or 'post infect*' or postviral* or 'post viral*' or postvirus* or 'post virus*') adj2 (sequela* or illness or symptom* or sign* or indicat* or syndrom*)).ti,ab.
8	6 and 7
9	1 or 2 or 3 or 4 or 5 or 8
10	exp incidence/
11	exp prevalence/
12	exp cohort analysis/
13	exp longitudinal study/

14	exp prospective study/
15	exp cross-sectional study/
16	exp follow up/
17	exp epidemiology/
18	(prevalence or incidence or epidemiol* or survey or cohort or surveillance or screening).ab,ti.
19	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20	9 and 19
21	limit 20 to dc=20211101-20221231
22	exp risk factor/
23	(risk* or prevalence* or incidence* or predict* or associat*).ab,ti.
24	22 or 23
25	exp Systematic Review/ or exp Meta Analysis/ or ((systematic* adj2 (review* or overview*)) or (meta analys* or meta analyz*) or (literature adj3 (review* or overview*))).ti,ab.
26	exp Cross Sectional Study/ or ((cross sectional or transverse or prevalence) adj2 (study or analys* or design or method*)).ti,ab.
27	exp Cohort Analysis/ or exp Longitudinal Study/ or exp Prospective Study/ or exp Follow Up/ or exp Retrospective Study/ or ((cohort or longitudinal or prospective or follow up or retrospective) adj2 (study or analys* or design or method*)).ti,ab.
28	25 or 26 or 27
29	9 and 24 and 28
30	20 or 29
31	limit 30 to dc=20211101-20221231
32	limit 31 to (conference abstract or conference paper or "conference review" or editorial or letter)

33	31 not 32

Database: The Cochrane Library	
#	**Query**
1	(("post covid" or postcovid or "post coronavirus" or postcoronavirus or "post coronovirus" or postcoronovirus or "post sars cov 2" or "post-sars-CoV-2") NEAR/2 (syndrome* OR disorder* OR illness* OR sickness* OR disease* OR condition* OR symptom* OR sign* OR feature*)):ti,ab,kw (Word variations have been searched)
2	("chronic covid*" or "post covid-19 condition*"):ti,ab,kw (Word variations have been searched)
3	(longcovid* or longcoronavirus* or longcoronovirus* or longcoronavirinae* or longCov or "long Cov" or longsars* or "long severe acute respiratory syndrome" or "long severe acute respiratory syndromes" or longncov* or longhcov*):ti,ab,kw (Word variations have been searched)
4	((long NEXT covid*) or (longcorona* NEXT virus*) or (long NEXT coronavirus*) or (long NEXT corona* NEXT virus*) or (longcorono* NEXT virus*) or (long NEXT coronovirus*) or (long NEXT corono* NEXT virus*) or (longcorona* NEXT virinae*) or (long NEXT coronavirinae*) or (long NEXT corona* NEXT virinae*) or (long NEXT Cov) or (long NEXT sars*) or (long NEXT ncov*) or (long NEXT hcov*)):ti,ab,kw (Word variations have been searched)
5	(("long haul" OR longhaul* OR long-haul* OR postacute OR "post acute" OR post-acute) NEAR/2 (covid19 OR covid-19 OR "sars-cov-2" OR "sarscov-2*" OR "sarscov2*" OR "sars-cov2" OR "severe acute respiratory syndrome" OR ncov* OR "n-cov")):ti,ab,kw (Word variations have been searched)
6	((Ongoing or long* or endur* or legacy* or slow* or gradual* or protract* or lengthy or chronic* or persist* or remission or residual* or prolong* or extend* or linger* or permanent or nonrecover* or "non recover" or lasting or continuous* or continual* or continuing* or postacute* or "post acute" or "long term*" or "long duration" or "long last" or "long standing" or postinfect* or "post infect" or postviral* or "post viral" or postvirus* or "post virus") NEAR/2 (sequela* or illness or symptom* or sign* or indicat* or syndrom*) NEAR/10 (covid* or coronavirus* or corona* virus* or Cov or "SARS-CoV-2" or "SARSCoV-2*" or "SARSCoV2*" or "SARS-CoV2" or "severe acute respiratory syndrome" or Ncov* or "n-cov")):ti,ab,kw (Word variations have been searched)
	((Ongoing or long* or endur* or legacy* or slow* or gradual* or protract* or lengthy or chronic* or persist* or remission or residual* or prolong* or extend* or linger* or permanent or nonrecover* or "non recover" or lasting or continuous* or continual* or continuing* or postacute* or "post acute" or "long term*" or "long duration" or "long last" or "long standing" or postinfect* or "post infect" or postviral* or

	"post viral" or postvirus* or "post virus") NEAR/2 (sequela* or illness or symptom* or sign* or indicat* or syndrom*)):ti,ab,kw (Word variations have been searched)
	MeSH descriptor: [COVID-19] explode all trees
	#7 AND #8
	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #9
	MeSH descriptor: [Prevalence] explode all trees
	MeSH descriptor: [Cohort Studies] explode all trees
	MeSH descriptor: [Incidence] explode all trees
	(prevalence or incidence or epidemiol* or survey or cohort or surveillance or screening):ti,ab,kw (Word variations have been searched)
	MeSH descriptor: [Epidemiologic Studies] explode all trees
	#11 OR #12 OR #13 OR #14 OR #15
	#10 AND #16 with Cochrane Library publication date Between Nov 2021 and Dec 2022

Database search adapted from National Health Library and Knoweldge Service et al.[8]

Grey literature search

A search of unpublished (grey) literature will be conducted. Resources searched will include: McMaster Health Forum https://www.mcmasterforum.org, Turning Research into Practice (TRIP) database https://www.tripdatabase.com/, and a search of Google/Google Scholar.

Search Strategy used for https://www.google.com/

Search 1 ("long covid" OR "post COVID conditions" OR post COVID-19 syndrome") AND epidemiology

Search 2: Search 1 ("long covid" OR "post COVID conditions" OR post COVID-19 syndrome") AND risk factors

Sort by relevance, limit by date: Since 2022, and search first 10 pages (100 results)

Appendix 3: Data extraction templates for RQ1

Original research studies

Document identification	Population demographics	Outcomes
First author (date): Country: DOI: Study type: Setting: Date range of study:	Sample size: Age (Mean/Median, SD/range): Sex distribution: Ethnicity: Groups considered (where applicable): Hospitalisation Status	Outcomes: ▪ prevalence (prevalence estimate/rate) ▪ incidence (per 100,000 population) ▪ all-cause mortality (%) ▪ signs and symptoms ▪ impact on daily living Author conclusions:

International disease registries

Document identification	Population demographics	Outcomes
Registry name: Disease name: Country:	Sample Size: Age (Mean/Median, SD/Range): Sex Distribution: Ethnicity: Groups considered (where applicable): Hospitalisation status:	Outcomes: ▪ any related to long COVID

Public health guidance and policy documents

Document identification	Population demographics	Outcomes
Country or organisation: Guidance/document title: URL: Date:	Sample Size: Age (Mean/Median, SD/Range): Sex Distribution: Ethnicity: Groups considered (where applicable):	Evidence source: Outcomes: ▪ prevalence (prevalence estimate/rate) ▪ incidence (per 100,000 population) ▪ all-cause mortality (%) ▪ signs and symptoms ▪ impact on daily living

	Hospitalisation Status:	

Appendix 4: Data extraction templates for RQ2

Reviews

Document identification	Population demographics	Outcomes
First author (date): *Country:* *Review type:* *DOI:* *Number of included studies:*	*Sample size:* *Age (Mean/Median, SD/range):* *Sex distribution:* *Ethnicity:* *Groups considered (where applicable):* *Vaccination Status*	*Hazard/odds ratio or relative risk results for risk/mitigating factors related to the outcomes outlined in Table 2.* *Author conclusions:*

Original research studies

Document identification	Population demographics	Outcomes
First author (date): *Country:* *DOI:* *Study type:* *Setting:* *Date range of study:*	*Sample size:* *Age (Mean/Median, SD/range):* *Sex distribution:* *Ethnicity:* *Groups considered (where applicable):* *Vaccination status:*	*Hazard/odds ratio or relative risk results for risk/mitigating factors related to the outcomes outlined in Table 2.* *Author conclusions:*

International disease registries

Document identification	Population demographics	Outcomes
Registry name: *Disease name:* *Country:*	*Sample Size:* *Age (Mean/Median, SD/Range):* *Sex Distribution:* *Ethnicity:* *Groups considered (where applicable):* *Vaccination Status:*	*Outcomes:* ▪ *any related to long COVID*

Public health guidance and policy documents

Document identification	Population demographics	Outcomes
Country or organisation: *Guidance/document title:* *URL:* *Date:*	*Sample Size:* *Age (Mean/Median, SD/Range):* *Sex Distribution:* *Ethnicity:* *Groups considered (where applicable):* *Vaccination Status:*	*Evidence source:* *Hazard/odds ratio or relative risk results for risk/mitigating factors related to the outcomes outlined in Table 2.*