



**Health
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An tÚdarás Um Fhaisnéis
agus Cáilíocht Sláinte

Protocol for evidence synthesis for duration of restriction of movements for those exposed, or potentially exposed, to SARS-CoV-2

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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 (NPHE) in their response to the COVID-19 pandemic. HIQA's health technology assessment team develops evidence summaries based on specific research questions (RQs). This protocol details the process to be undertaken to inform the policy question relating to the duration of restricted movements for individuals exposed, or potentially exposed, to SARS-CoV-2. This protocol includes two specific review questions:

1. RQ1: What is incubation period of COVID-19, or time to first positive test, in individuals exposed to SARS-CoV-2?
2. RQ2: What is the international guidance for the duration of restriction of movements for individuals exposed, or potentially exposed, to SARS-CoV-2?

1.0 Protocol for RQ1

RQ1: What is incubation period of COVID-19, or time to first positive test, in individuals exposed to SARS-CoV-2?

Five distinct steps in the process have been identified for the first review question. These are listed below and described in more detail in sections 1.1-1.5.

1. search relevant databases
2. screen identified studies to match relevant clinical question
3. data extraction and quality appraisal of included studies
4. data analysis
5. summarise findings.

1.1 Search 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.

1.2 Screen identified studies to match relevant clinical question

All potentially eligible papers identified in the search strategy will be exported to Covidence, a software to review documents and single screened against the PEO (population, exposure, outcome) 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 PEO framework, with any uncertainty checked by a second reviewer. The PEO is detailed in Table 1 below.

Table 1. PEO for "What is the incubation period of COVID-19, or time to first positive test, in individuals exposed to SARS-CoV-2?"

Population	<p>Individuals of any age diagnosed with COVID-19 and for whom time from exposure to onset of symptoms or a positive molecular test (e.g. RT-PCR test) for SARS-CoV-2 can be ascertained.</p> <ul style="list-style-type: none"> ▪ Potential subgroups of interest: <ul style="list-style-type: none"> ○ exposure: travel (movement history) vs close contact ○ close contact exposure: household vs non-household ○ age range: adults vs children.
Exposure	<ul style="list-style-type: none"> ▪ confirmed or suspected case of COVID-19 OR ▪ travel/movement history from a high-risk area (as defined by study authors) where both the time of likely exposure and time since leaving area are known.
Outcomes	<ul style="list-style-type: none"> ▪ Time (in days) from exposure to symptom onset, and associated measures of uncertainty (e.g. error, 95% CI). ▪ In symptomatic and asymptomatic cases, time (in days) from exposure to first positive test, as identified through serial molecular testing, and associated measures of uncertainty (e.g. error, 95% CI)
Types of studies	<p>Include:</p> <ul style="list-style-type: none"> ▪ Observational studies that present estimates (including the level of uncertainty) of the above outcomes in human

	<p>populations.</p> <p>Exclude:</p> <ul style="list-style-type: none">▪ animal studies▪ mathematical modelling studies that are not based on novel empirical data▪ non-primary research (for example editorials/opinion pieces/guidance documents/reviews, or pooled datasets from unspecified sources)▪ case reports (due to the availability of higher quality study designs)▪ if a sufficient number of large case series are identified, small cases series which focus on a limited number of cases, clusters, or households will be excluded▪ studies that do not report a point estimate and associated level of uncertainty.
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1.3 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. This will be conducted in a predefined Microsoft Excel file under the the following headings, as highlighted in Appendix 2:

- study descriptors
- participant demographics
- incubation period estimates (typically defined as time from exposure to symptom onset)
- asymptomatic populations.

From scoping work conducted, the expected scale of the returned search, and potentially relevant studies, are expected to be large. For efficiency, an abridged quality appraisal will be conducted considering the following key domains:

- appropriateness of participant selection criteria
- appropriateness of statistical analysis
- definition of incubation period
- peer-review.

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 this 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.

1.4 Data analysis

The outcome of incubation period (in days) will be pooled across studies. As the outcome may be reported in a variety of ways (such as using the mean and standard deviation, median and interquartile range), the outcome values may need to be transformed to ensure a common format of central tendency and variance. If appropriate, the study estimates will be pooled using random effects meta-analysis. Heterogeneity will be assessed using the I^2 statistic. In the event of substantial statistical heterogeneity ($I^2 > 50\%$), study-level characteristics (e.g., mean age of participants, study timing, nature of exposure to COVID-19) will be included in a meta-analysis as covariates to determine if they explain the heterogeneity. Subgroup analysis will also be considered based on study design if applicable.

Data preparation

The analysis will include studies that report the parameters for statistical distributions fit to incubation period data, as well as studies reporting data on central tendency and dispersion in the observed distribution of incubation period data.

For studies reporting distribution parameters, our focus will be on data relating to log-normal, Weibull and Gamma distributions. Reported mean parameter values and their associated precision (as standard errors) will be used for main analysis.

Studies that do not report fitted distribution parameters will not be used in the main analysis, but will be used to determine whether those used in the main analysis may be biased or in some way systematically different from the remaining studies.

For studies reporting central tendency and dispersion, data on mean, median, standard deviation, interquartile range and any percentiles will be used to determine the parameters for the associated log-normal, Weibull and Gamma distributions. The fitting process will involve finding candidate parameter values from a wide range of potential values. After an initial wide range search, a more targeted search will be conducted to improve precision. Fit will be optimised by the minimising the absolute difference between the known and estimated data points (e.g., mean and standard deviation, median and 25th and 75th percentiles). A fit where the error on any one of the estimated data points is greater than 0.5 days will be considered inaccurate and not used in the meta-analysis.

For the data to be included in a meta-analysis, estimates of both the distribution parameters and their standard errors will be required. Where standard errors are not provided, they will need to be estimated using sample size. This will be done by Monte Carlo simulation. Briefly, a dataset will be simulated using the mean parameter values for the distributions. From this, the mean and standard deviation can be computed. Combined with the sample size for a given study, the standard

errors for the mean and standard deviation will be estimated. Using repeated sampling of the mean and standard deviation, the log-normal, Weibull and Gamma distributions will be refitted to the data. In doing so, it will be possible to estimate precision for the distribution parameters.

Meta-analysis

Each of the three distributions require two parameters to be specified. In each case, the two parameters will be pooled independently across studies. It will be assumed that the parameters follow a normal distribution. A random-effects model will be used using a restricted maximum-likelihood estimator for heterogeneity. As the precision as outputted from the meta-analysis will reflect uncertainty in the mean, we will also extract the prediction intervals, which better encompass the uncertainty of what might be observed in a future study.

A range of influence diagnostics will be used to explore whether any individual studies might be very influential or might be considered as outliers. Where a study is considered to be potentially distorting the results, we will investigate whether a reason for the difference can be explained (i.e., a different definition of exposure was used to other studies). If there are ten or more studies available for meta-analysis, funnel plot asymmetry will be explored using Egger's test. Funnel plot asymmetry identifies small study bias which may be indicative of publication bias.

Meta-regression will be used to explore covariates that may explain the anticipated heterogeneity across studies. Potential covariates include country or region, date of last data collection, mean patient age, percentage male, study design, and type of data provided in the study (e.g., distribution parameters, mean and standard deviation). Contingent on available data, we will consider a subgroup analysis to investigate evidence of differences in incubation period length by age.

Summary statistics

The pooled distribution parameters will be used to generate curves of cumulative proportion of cases that are symptomatic by days since exposure. The confidence intervals and prediction intervals will also be computed. The analysis will consider both the number of days to achieve a certain level of coverage of cases (e.g., 95%) and the cumulative percentage cases that have become symptomatic a given number of days after exposure (e.g., 14 days).

While the parameters for each distribution will be analysed separately, and hence treated as independent, this may ignore important covariance in parameter values. As a sensitivity analysis, we will calculate the correlation between parameter values across studies and then generate correlated pairs using the pooled estimates.

1.5 Summarise findings

A descriptive overview and meta-analysis (where appropriate) of the identified evidence to date for this review question will be compiled and sent to the relevant parties in PDF format. A PRISMA flow chart will be presented where appropriate.

2.0 Protocol for RQ2

RQ2: What is the international guidance for the duration of restriction of movements for individuals exposed, or potentially exposed, to SARS-CoV-2?

Three distinct steps in the process have been identified for the second review question. These are listed below and described in more detail in sections 2.1 to 2.3.

1. Perform a rapid review by searching relevant international resources.
2. Review and extract relevant information on restriction of movements for individuals exposed, or potentially exposed, to SARS-CoV-2.
3. Summarise findings.

2.1 Perform a rapid review by searching relevant international resources

The international resources included in this rapid review are from a range of ministries of health and public health agencies. These were chosen based on them being in a similar phase of pandemic response, widespread use of the organisation's advice, and or the working constraints of the HTA team. In addition to including information from the World Health Organization (WHO), European Centre for Disease Control and Prevention (ECDC), US Centers for Disease Control and Prevention (CDC) and European Commission, guidance from 24 countries will be sought. Where guidance could not be found or is unavailable, this will not be reported.

Guidance from the following national or international public health bodies, ministries of health and associated governmental departments will be sought for this rapid review:

International public health bodies

- World Health Organization
<https://www.who.int>
- European Centre for Disease Prevention and Control
<https://www.ecdc.europa.eu>
- Centres for Disease Control and Prevention
<https://www.cdc.gov>

- European Commission

<https://ec.europa.eu>

United Kingdom

- England

<https://www.gov.uk>

- Scotland

<https://www.gov.scot>

- Northern Ireland

<https://www.publichealth.hscni.net>

- Wales

<https://gov.wales>

Other European countries

- Austria

<https://www.sozialministerium.at>

- Belgium

<https://www.info-coronavirus.be>

- Bulgaria

<https://coronavirus.bg/bg>

- Denmark

<https://www.sst.dk>

- France

<https://www.gouvernement.fr>

- Germany

<https://www.bundesgesundheitsministerium.de>

- Iceland

<https://www.landlaeknir.is>

- Ireland

<https://www.hpsc.ie>

<https://www.gov.ie>

- Italy

<http://www.salute.gov.it>

- Norway

<https://www.fhi.no/en/id/infectious-diseases/coronavirus/>

- Portugal

<https://covid19.min-saude.pt>

- Spain

<https://www.lamoncloa.gob.es>

- Sweden
<https://www.folkhalsomyndigheten.se>
- Switzerland
<https://www.bag.admin.ch>
- The Netherlands (Ministry of Health)
<https://www.government.nl>

North America

- Canada
<https://www.canada.ca>

Australasia

- Australia
<https://www.health.gov.au/>
- New Zealand
<https://www.health.govt.nz>

Asia

- Hong Kong
<https://www.coronavirus.gov.hk>
- Singapore (Ministry of Health)
<https://www.moh.gov.sg>

2.2 Review and extract relevant information on restriction of movements for individuals exposed, or potentially exposed, to SARS-CoV-2

All identified data relating to duration of restriction of movements, for close contacts and travel-related exposure, will be extracted by one reviewer. A second reviewer will verify all extracted data and ensure no information is missing; see Appendix 2.

The following information will be extracted:

- country or organisation
- URL
- date released or updated
- duration of quarantine recommended.

2.3 Summarise findings

A summary of the findings will be drafted with all extracted data presented in the report.

3.0 Evidence to Advice framework

Following completion of this evidence synthesis, and in conjunction with advice from the expert advisory group, findings will be applied to HIQA's 'Evidence to Advice' framework. The development of advice is a key component of HIQA's evidence synthesis process.

4.0 Quality assurance process

The review questions will be led by experienced systematic reviewers. A number of second reviewers will be assigned to assist and to provide cover in the event of illness. The second reviewers will be required to read all the key studies and check that the evidence reports accurately reflect the body of literature. The summary 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 for "What is incubation period of COVID-19, or time to first positive test, in individuals exposed to SARS-CoV-2?"

	PubMed
1	"coronavirus"[MeSH Terms] OR "coronavirus infections"[MeSH Terms] OR "coronavirus"[All Fields] OR "covid 2019"[All Fields] OR "SARS2"[All Fields] OR "SARS-CoV-2"[All Fields] OR "SARS-CoV-19"[All Fields] OR "coronavirus infection"[All Fields] OR "severe acute respiratory"[All Fields] OR "pneumonia outbreak"[All Fields] OR "novel cov"[All Fields] OR "2019ncov"[All Fields] OR "sars cov2"[All Fields] OR "cov2"[All Fields] OR "ncov"[All Fields] OR "covid-19"[All Fields] OR "covid19"[All Fields] OR "coronaviridae"[All Fields] OR "corona virus"[All Fields] OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept]
2	"incubate"[All Fields] OR "incubated"[All Fields] OR "incubates"[All Fields] OR "incubating"[All Fields] OR "incubation"[All Fields] OR "incubations"[All Fields] OR "incubators"[MeSH Terms] OR "incubators"[All Fields] OR "incubator"[All Fields] OR "Incubation period"[All Fields] OR "Incubation time"[All Fields] OR "Latency period"[All Fields] OR "Latent period"[All Fields] OR ("quarantine"[Title/Abstract] AND "asymptomatic"[Title/Abstract]) OR ("serial testing"[Title/Abstract] AND "asymptomatic"[Title/Abstract]) OR ("surveillance"[Title/Abstract] AND "asymptomatic"[Title/Abstract]) OR ("serial laboratory testing"[Title/Abstract] AND "asymptomatic"[Title/Abstract]) OR ("mass testing"[Title/Abstract] AND "asymptomatic"[Title/Abstract])
3	#1 AND #2
4	"animals"[MeSH Terms] NOT "humans"[MeSH Terms]
5	#3 NOT #4
6	Limit to 2020
	EMBASE
1	'coronavirus'/exp OR coronavirus:ti,ab,de,kw OR 'coronavirus infection'/exp OR covid19:ti,ab,de,kw OR 'covid 19':ti,ab,kw OR 'covid-19' OR 'covid 2019' OR 'sars cov 2':ti,ab,kw OR '2019 ncov':ti,ab) OR 'novel coronavirus':ti,ab,kw
2	incubation OR 'incubation period' OR 'latent period' OR 'latency period' OR 'incubation time' OR (quarantine:ti,ab,kw AND asymptomatic:ti,ab,kw) OR (surveillance:ti,ab,kw AND asymptomatic:ti,ab,kw) OR ('serial testing':ti,ab,kw AND asymptomatic:ti,ab,kw) OR ('mass testing':ti,ab,kw AND asymptomatic:ti,ab,kw) OR ('serial laboratory testing':ti,ab,kw AND asymptomatic:ti,ab,kw)
3	#1 AND #2
4	Limit to 2020
5	'animal'/exp NOT 'human'/exp
6	#4 NOT #5
	Europe PubMed Central
1	(coronavirus OR covid-19 OR "covid 19" OR "SARS-CoV-2") AND ("incubation period" OR "incubation time" OR "Latency period" OR "Latent period" OR (quarantine AND

	asymptomatic) OR ("serial testing" AND asymptomatic) OR ("Mass testing" AND asymptomatic) OR ("serial laboratory testing" AND asymptomatic) OR (surveillance AND asymptomatic)) AND (SRC:PPR) AND (FIRST_PDATE:2020)
	NHS Evidence
	(coronavirus OR covid-19 OR "covid 19" OR "SARS-CoV-2") AND ("incubation period" OR "incubation time" OR "Latency period" OR "Latent period" OR (quarantine AND asymptomatic) OR ("serial testing" AND asymptomatic) OR ("Mass testing" AND asymptomatic) OR ("serial laboratory testing" AND asymptomatic) OR (surveillance AND asymptomatic))
	Limit to 2020

Appendix 2

Template data extraction for RQ1

Study descriptors	Population characteristics	Incubation period estimates	Asymptomatic populations
Author	Setting	Primary outcome results as presented by study (may be in form of mean, standard deviation, Median, interquartile range, distribution etc)	Sample size
Country	Patient demographics		Participant demographics
DOI	Exposure type		Exposure type
Study design	Incubation period criteria		Duration from exposure to positive test (through serial sampling only)
Sample size	Disease Severity		
Last month of data collection			

Template data extraction tables for RQ2

Country or organisation URL Date released or updated	Duration of restriction of movement recommended for close-contact of confirmed case
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