Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Evidence summary protocol:

Duration of protective immunity following COVID-19 vaccination (efficacy and effectiveness)

Published: 3 September 2021

1. Purpose and aim

The purpose of this protocol is to outline the process by which the Health Technology Assessment (HTA) directorate in the Health Information and Quality Authority (HIQA) identifies and reviews relevant SARS-CoV-2 evidence. This review will inform advice that is provided to the National Public Health Emergency Team (NPHET), in their response to the COVID-19 pandemic. The advice will take account of expert interpretation of the evidence by HIQA's COVID-19 Expert Advisory Group.

This protocol details the process to be undertaken to inform the following policy question requested by NPHET:

"What is the evidence relating to the duration of protective immunity (vaccine efficacy and effectiveness) following COVID-19 vaccination?"

Given there is no defined threshold of efficacy or effectiveness where efficacy or effectiveness would be classified as lost and given the limited follow-up expected (less than 15 months follow-up data), the following specific research question was developed and will form the basis of this evidence summary:

"To what extent and over what period of time does the efficacy and effectiveness of COVID-19 vaccination change?"

2. Process outline

A standardised approach to the process has been 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.

Five distinct steps in the process have been identified. These are listed below and described in more detail in the Sections 2.1-2.5.

1. Develop research question and formulate PICOS framework.
2. Search relevant databases.
3. Screen identified studies to match relevant clinical question.
4. Data extraction and quality appraisal of included studies.
5. Summarise findings.

2.1. Research question and PICOS

Table 1 outlines the Population, Intervention, Comparator, Outcomes, and Study Design (PICOS) criteria for the research question.

"To what extent and over what period of time does the efficacy and effectiveness of COVID-19 vaccination change?"

Table 1. PICOS criteria

Population	▪ any persons aged ≥12 years ▪ persons from special populations (to include, immunocompromised, people with cancer or severe respiratory disease, older adults (70 years or older), health care workers, and residents and staff of long term care facilities). Depending on data availability, results from relevant subgroups (for example age group, or immunocompromised) will also be presented.
Intervention	**Include:** Vaccines against COVID-19 which are licensed and distributed in Ireland: ▪ ChAdOx1 (AstraZeneca)[#] ▪ Ad26.COV2.S (Janssen) ▪ mRNA-1273 (Moderna) ▪ BNT162b2 (Pfizer/BioNTech). Studies which include vaccine regimens with extended intervals between first and second doses or heterologous vaccine regimens will also be included. **Exclude:** Studies which only include a single dose regimens (of what are routinely 2-dose vaccine schedules) for those previously infected or which include booster doses.
Comparators	▪ alternative COVID-19 vaccine licensed in Ireland ▪ placebo (or alternative vaccine given as placebo) ▪ no vaccination ▪ vaccination at a different time point.
Outcomes*	**Primary Outcomes** ▪ severe disease as measured by hospitalisations and /or ICU admissions for COVID-19 ▪ COVID-19 mortality and/or all-cause mortality. **Secondary Outcomes** ▪ SARS-CoV-2 infection (RT-PCR or antigen-confirmed) by disease severity as defined by study authors

	(asymptomatic/mild/moderate) and duration (<12 weeks and ≥12 weeks (chronic COVID-19)).[1] Outcomes will be extracted for study-defined time points since vaccination. Changes in absolute and relative efficacy or effectiveness will be noted. Disaggregated data by variant will be extracted if reported. **Exclude**: Outcomes relating to time points in the period when individuals are waiting for the second dose of a two-dose schedule and in the period immediately after full vaccination, but before immunity is expected to occur.
Types of studies	**Include:** ▪ randomised controlled trials ▪ non-randomised controlled trials ▪ quasi-experimental studies ▪ prospective and retrospective cohort studies ▪ case-control studies ▪ test-negative case control studies ▪ analytical cross sectional studies. ▪ Studies where the median time from administration of the final regimen dose to outcome ascertainment is ≥ eight weeks~ or studies which report outcomes eight weeks after administration of the final regimen dose. **Exclude:** ▪ Studies that enrolled fewer than 1,000 participants from the general population. ▪ Studies that enrolled fewer than 100 participants of special populations, as defined above. ▪ Animal studies. However, if a subgroup analysis from a study meeting the exclusion criteria above, would have been eligible for inclusion if reported as a study in its own right, data from the relevant subgroups will be included and extracted.

*Safety outcomes are considered beyond the scope of this review. Outcomes related to immunogenicity (where there is no long-term efficacy/effectiveness data) and transmission will not be included in the review.

#Brands of ChAdOx1 which are not licensed in Ireland (for example Covishield) will be included.

~Where median is not reported, the mean time will be used to assess eligibility.

2.2. Search of relevant databases

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

- PubMed
- Embase
- Europe PMC and MedRxiv.org (for the retrieval of preprints).

The relevant product European public assessment reports (EPAR) from the European Medicines Agency (EMA) and their equivalent from the US Food and Drug Administration (FDA) will also be searched for relevant clinical information.

2.3. Screening of identified studies to match relevant clinical questions

All potentially eligible papers identified in the search strategy will be exported to Covidence systematic review software (available at www.covidence.org) and single screened against the PICOS framework (Table 1). Full text papers will be single screened, with any uncertainty checked by a second reviewer. No language restrictions will be applied. Non-English studies will be translated via Google translate, and this is will be noted as a potential caveat.

2.4. Data extraction and appraisal of included studies

Data extraction and quality appraisal will be performed by one reviewer, and double checked by a second reviewer. For each study included, data on the study design, participant demographics and clinically relevant data will be extracted as required. A template for the data extraction table is provided in Appendix 2.

For randomised controlled trials (RCTs) the Cochrane risk of bias tool (version 1) will be used.[2] The National Heart, Lung and Blood Institute (NIH) quality assessment tools will be used for appraisal of observational cohort studies and case-control studies.[3]

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

2.5. Summarise findings

A descriptive overview of the identified evidence to date for the research question will be compiled and or a meta-analysis where appropriate. A PRISMA flow chart will be presented.

3. Quality assurance process

The review will be led by an experienced systematic reviewer. A minimum of four team members will conduct the evidence summary. This will permit confirmation that the report accurately reflects the body of literature, and will help expedite the process given the short turnaround time. Each key study will be read by a minimum of two reviewers who will check that the summary accurately reflects the body of literature. The report will be further reviewed by two members of the senior management team, to ensure processes are followed and quality maintained.

4. 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 09 August 2021 and a final draft will be completed in September 2021, dependent on the amount and complexity of literature retrieved. Draft outputs from the evidence summary will be circulated to the COVID-19 Expert Advisory Group for review, with a view to providing advice to NPHET.

5. References

1. ECDC. Clinical characteristics of COVID-19 2021 [1 September 2021]. Available from: https://www.ecdc.europa.eu/en/covid-19/latest-evidence/clinical.
2. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.
3. National Heart Lung and Blood Institute (NIH). Study Quality Assessment Tools 2021 [20 August 2021]. Available from: https://www.nhlbi.nih.gov/health-topics/studyquality-assessment-tools.

Appendix 1

Embase Search strategy

1	exp Coronavirus infection/	158995
2	(COVID-19 or CORONAVIRUS or "corona virus" or "2019-ncov" or "2019 ncov").ab,ti.	162810
3	(wuhan adj3 virus).ab,ti.	126
4	"severe acute respiratory syndrome coronavirus 2".ab,ti.	14868
5	("2019" and (new or novel) and coronavirus).ab,ti.	11116
6	1 or 2 or 3 or 4 or 5	189485
7	vaccin*.ab,ti.	389211
8	vaccination/	154368
9	vaccine immunogenicity/	3855
10	7 or 8 or 9	417587
11	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.	842424
12	exp Randomized Controlled Trial/ or randomized controlled trial.pt. or ((random* adj3 trial) or (placebo* or single blind* or double blind* or triple blind*)).ti,ab.	994785
13	exp Cross Sectional Study/ or ((cross sectional or transverse or prevalence) adj2 (study or analys* or design or method*)).ti,ab.	538978
14	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.	3827309
15	(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.) and (inception adj2 cohort).ti,ab.	3107
16	exp Cohort Analysis/ or exp Longitudinal Study/ or exp Prospective Study/ or exp Follow Up/ or exp Retrospective Study/ or exp Case Control Study/ or exp Case Study/ or ((cohort or longitudinal or prospective or follow up or retrospective or case control or case referent or case comparison or case series) adj2 (study or analys* or design or method*)).ti,ab.	4043145

17	11 or 12 or 13 or 14 or 15 or 16	5830803
18	mortality/ or hospital mortality/ or mortality rate/	902565
19	death/	276310
20	clinical outcome/	191285
21	hospitalization/	419592
22	reinfection/	10083
23	(mortality or death or hospitali*).ab,kw,ti.	2418584
24	((treatment or patient or disease) adj1 outcomes).ab,kw,ti.	124620
25	(severe adj1 (disease or illness)).ab,kw,ti.	38732
26	((ICU or "intensive care" or "critical care") adj2 (admitted or admission*)).ab,kw,ti.	44603
27	((confirmed or positive) adj3 ("RT-PCR" or "SARS-CoV-2")).ab,kw,ti.	14677
28	(reinfect* or re-infect*).ab,kw,ti.	15805
29	(subsequent* adj2 infect*).ab,kw,ti.	8593
30	(("post vaccination" or "post-vaccination") adj2 (infect* or reinfect* or re-infect*)).ab,kw,ti.	79
31	18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30	3135122
32	((effective* or protection) adj2 vaccin*).ab,kw,ti.	25931
33	31 or 32	3155513
34	6 and 10 and 17 and 33	1151
35	limit 34 to yr="2020 -Current"	1093
36	epidemiology/	220295
38	17 or 36	6000487
39	6 and 10 and 33 and 38	1234
40	limit 39 to yr="2020 -Current"	1169

Appendix 2

Template Data Extraction

Study characteristics	Intervention and Comparators	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author: *Country:* *DOI:* *Setting:* *Time Period:* *Study Design:* *Publication status:*	*Intervention(s):* *Comparator(s)* Follow-up/Time since vaccination	Population description: Participants = N Mean age = X Male = X%	▪ Severe disease as measured by hospitalisations and /or ICU admissions for SARS-CoV-2 infection. ▪ COVID-19 mortality. Outcomes will be extracted for each defined time point since vaccination reported in the study. Absolute and relative changes in vaccines efficacy and effectiveness over time since vaccination (after full planned vaccination. Variants of Concern (as reported by the study authors).	▪ Confirmed RT-PCR or antigen-confirmed SARS-CoV-2 infection (mild, moderate or asymptomatic). Outcomes will be extracted for each defined time point since vaccination reported in the study. Absolute and relative changes in vaccines efficacy and effectiveness over time since vaccination. Variants of Concern in circulation (as reported by the study authors).

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