National Immunisation Advisory Committee
An Coiste Comhairleach Náisiúnta um Imdhíonadh

Health Information and Quality Authority
An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Rabies vaccines for pre-exposure and post-exposure prophylaxis: Protocol for an evidence summary to inform updated recommendations

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About the National Immunisation Advisory Committee

The National Immunisation Advisory Committee (NIAC) is Ireland's National Immunisation Technical Advisory Group (NITAG). NIAC provides independent evidence-based recommendations and advice to the Minister for Health on immunisation and related health matters to inform health policy in Ireland.

First established in 1998, NIAC has been hosted by HIQA as a statutory function under Section 8(1)(g) of the Health Act 2007 (as amended) since 31 March 2025.

NIAC membership is voluntary, and includes nominees from the Royal College of Physicians of Ireland, its Faculties and Institutes, the Royal College of Surgeons in Ireland, the Irish College of General Practitioners, the Nursing and Midwifery Board of Ireland, the Infectious Diseases Society of Ireland, the Travel Medicine Society, the National Virus Reference Laboratory, the Health Service Executive's (HSE) National Health Protection Office (NHPO) as well as members with expertise in gerontology and inclusion health, and lay members. Meetings are attended by representatives from the Department of Health and the HSE, including the HSE National Immunisation Office. Representatives of the Health Products Regulatory Authority (HPRA) attend to provide regulatory advice in relation to vaccines. Representatives of the HSE Health Protection Surveillance Centre (HPSC) attend to provide and support the interpretation of epidemiological data.

The NIAC Secretariat team, situated within the HTA Directorate in HIQA, provides clinical, evidence synthesis, and administrative support to NIAC.

Visit www.hiqa.ie for more information.

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1 Purpose and aim

Rabies is an acute encephalomyelitis caused by a lyssavirus infection. All mammals are susceptible to rabies infection, but transmission to humans is primarily through contact with the saliva of infected dogs, and less commonly through infected wildlife, such as bats or foxes.[1] Rabies is a vaccine-preventable disease, with human rabies vaccines available for use for both pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP).[1]

Ireland is free of rabies, with no indigenous cases in humans or animals reported in over 100 years.[2, 3] However, rabies is still present in a number of EU Member States (for example, Poland), and is endemic in many countries across Asia, Africa, and the Americas.[2]

The Immunisation Guidelines for Ireland describe current recommendations regarding the use of rabies vaccine in Ireland for PrEP.[3] To support the implementation of an updated regionalised pathway in Ireland for risk assessment and treatment following potential rabies exposure,[4] interim guidelines were published by the Health Service Executive's (HSE) National Health Protection Office in July 2025.[5] In this context, and in the context of global shortages of rabies vaccines and human rabies immunoglobulin (HRIG), it was considered timely and necessary for the National Immunisation Advisory Committee (NIAC) to revisit its current recommendations and the Immunisation Guidelines for Ireland, considering the most up-to-date evidence and international positions regarding the use of rabies vaccines for both PEP and PrEP. It was agreed that NIAC would prioritise updates to PEP recommendations and guidelines initially, with consideration of PrEP to follow.

This protocol outlines the methods by which the NIAC Secretariat will identify and summarise updated evidence in relation to the use of rabies vaccines in humans for PEP and PrEP. The evidence summary will support the development by NIAC of updated recommendations for rabies vaccination in Ireland, and updates to the Immunisation Guidelines for Ireland.

2 Research questions and evidence summary outline

Considering human populations specifically, the evidence summary will address the following primary research question:

RQ1. What is the optimal dosage, schedule (number of doses, interval(s) between doses, timing relative to exposure or potential exposure, requirements for booster doses), and route of administration for rabies vaccine for risk-based PEP and PrEP?

Two secondary research questions will also be addressed, as follows:

RQ2. Which rabies vaccines can safely and effectively be used interchangeably with Verorab® (Sanofi Winthrop Industrie) for PEP and PrEP?

RQ3. What populations are identified as being at risk of rabies exposure in countries with a similar rabies risk profile to Ireland?

These questions will be considered by NIAC according to the adapted Evidence to Recommendation (EtR) framework[6] used to develop its recommendations to the Minister for Health. Information relating to the following EtR domains will be obtained and summarised:

1. Problem
2. Benefits and harms
3. Values and preferences
4. Resource use
5. Equity
6. Acceptability
7. Feasibility.

This evidence summary will primarily focus on the first two domains, that is, the problem, and the benefits and harms of the interventions. A standardised approach to the evidence summary process has been developed and documented in this protocol to allow for transparency, to aid project management, and to mitigate risks.

Clinical considerations

Post-exposure risk assessment will be informed by updated guidelines issued by the HSE National Health Protection Office,[5] and there will be representation from the HSE National Health Protection Office on NIAC's Rabies Working Group.

NIAC will also consider additional clinical questions pertaining to rabies PEP, including but not limited to:

1. Are there scenarios where flexibility in the timing of dose two and three of rabies vaccine, when given as PEP, might be safe and acceptable?
2. Up to what time point post-exposure (and in which clinical scenarios) should rabies vaccine be considered?
3. Up to what time point post-exposure (and in which clinical scenarios) should HRIG be considered in addition to rabies vaccine?

4. What approach(es) may be taken with respect to patients who have received rabies PEP with vaccines that are not on the World Health Organization's (WHO) list of prequalified vaccines?[7]

Clinical considerations will be addressed through a review of existing recommendations, guidelines and or guidance documents issued by leading edge National Immunisation Technical Advisory Groups (NITAGs), the WHO and other reputable sources, as outlined in Section 4. Expert opinion will be sought from members of the NIAC Rabies Working Group and Committee.

3 Problem

To describe the public health importance of rabies in Ireland, an overview of the epidemiology of rabies in humans and animals in Ireland will be obtained from the Health Protection Surveillance Centre (HPSC) and the Department of Agriculture, Food and the Marine, respectively. Available data regarding health service utilisation relating to rabies PEP in Ireland, including use of and or demand for rabies vaccines and HRIG, will be obtained from the HSE, particularly through the National Health Protection Office and National Immunisation Office.

To identify populations considered to be at risk of rabies exposure in countries with comparable rabies risk to Ireland (RQ3), targeted grey literature searches will be conducted. Online searches of the websites of selected international NITAGs and other public health bodies will be carried out to identify this information, as detailed further in Section 4.

4 Benefits and harms

High-level descriptions of the following rabies vaccines will be provided:

- vaccines currently authorised for use in Ireland, either by the European Medicines Agency (EMA) or the Health Products Regulatory Authority (HPRA)
- vaccines authorised for use in other EU or European Economic Area (EEA) countries, or in the UK, either by the EMA or by national regulatory bodies.

Up-to-date evidence regarding the optimal dosages, dosing schedules, and routes of administration of rabies vaccines for PrEP and PEP, including interchangeability of vaccines within a series, will be identified using a rapid review approach. Literature for inclusion will be identified by systematically searching online databases of peer-reviewed literature and clinical trial registries, as well as targeted grey literature searches. This work will be carried out in line with the research questions and

inclusion and exclusion criteria, as outlined according to the PICOS (population, intervention, comparator, outcome and study designs) framework in Table 4.1.

Table 4.1 Population, intervention, comparator, outcomes, study designs (PICOS), settings and language of records to be included and excluded

Population	**Included:** ▪ Human participants of any age, including the following subgroups of interest, where information is available: – those who have previously received partial/incomplete pre- or post-exposure rabies vaccination regimens – those who are immunocompromised – those who are at increased risk of rabies exposure (for example, due to occupation or travel) – for post-exposure prophylaxis (PEP), those with high-risk exposures (for example, World Health Organization (WHO) category 3).
Intervention	**Included:** ▪ Rabies vaccines administered for the purposes of pre-exposure prophylaxis (PrEP) and or PEP. ▪ Rabies vaccines produced in cell culture or embryonated eggs, and authorised for use in humans in EU/EEA countries and the UK, or included on the WHO's list of prequalified vaccines. ▪ Dosing schedule (number and timing of doses) and route of administration must be described. ▪ In the context of PEP, administration of HRIG in addition to rabies vaccine. **Excluded:** ▪ Nerve tissue rabies vaccines. ▪ Rabies vaccines that are not currently authorised for use in humans by a relevant regulatory body. ▪ Rabies vaccines that are currently not marketed or not in production. ▪ Co-administration with other non-rabies vaccine(s). ▪ In the context of PEP, administration of equine rabies immunoglobulin or rabies monoclonal antibodies. ▪ For RQ1, studies in which vaccine dosage, schedule and route of administration are not described.
Comparator	**Included:** ▪ Any rabies vaccine, with or without concomitant administration of HRIG. ▪ Placebo. ▪ No vaccine. **Excluded:** ▪ Primary studies with no comparator. ▪ Studies in which vaccine schedule and route of administration are not described.

Outcomes	**Included:** ▪ Measures of clinical effectiveness against rabies infection (including breakthrough infection), hospitalisation and or death following PEP or PrEP, including duration of protection. ▪ Measures of immunogenicity during and or after PEP, including duration of immunity. ▪ Measures of immunogenicity during and or after PrEP, including duration of immunity. ▪ Safety outcomes relating to PEP or PrEP regimens.
Study designs	**Included:** ▪ High-quality systematic reviews* (with or without meta-analysis). ▪ Randomised controlled trials (RCTs). ▪ Non-randomised studies of interventions (NRSIs) with one or more comparator arms. **Excluded:** ▪ Animal model studies. ▪ Preclinical studies. ▪ Modelling studies. ▪ Narrative reviews. ▪ Rapid reviews. ▪ Case reports. ▪ Case series. ▪ Editorials. ▪ Commentaries. ▪ Correspondence. ▪ Qualitative studies. ▪ Conference abstracts. ▪ Review or trial protocols. **Grey literature to be included:** ▪ Recommendations, guidelines and or guidance documents issued by NITAGs and or other relevant national public health bodies. ▪ Position papers, guidelines and or supporting reports issued by the WHO.
Settings	**Peer-reviewed literature:** ▪ Any geographical region or setting. **Grey literature:** ▪ Selected NITAGs or other relevant national public health bodies in countries with similar rabies risk levels to Ireland. ▪ Documents issued by the WHO and applicable to Ireland.
Language	**Peer-reviewed literature:** Studies available in English only. **Grey literature:** Documents available in any language.

Key: NITAG – National Immunisation Technical Advisory Group; NRSI – non-randomised study of intervention; PEP – post-exposure prophylaxis; PrEP – pre-exposure prophylaxis; RCT – randomised controlled trial; RQ – research question; WHO – World Health Organization.

*For the purpose of this evidence summary, a high-quality systematic review will be considered as a review that reports on at least one outcome of interest and includes all of the following: i) a clearly stated set of objectives with an explicit, reproducible methodology, ii) a systematic search of at least two databases, which attempts to identify all studies that would meet the eligibility criteria, iii) a systematic presentation and synthesis of the characteristics and findings of the included studies, iv) a critical appraisal of the available evidence, v) ideally, the systematic review will have evaluated the certainty of the evidence using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.[8]

Online databases and clinical trial registries will be searched from 1 January 2015 as, based on preliminary scoping, the most up-to-date recommendations and supporting evidence syntheses regarding rabies vaccination have been published within the past 10 years. Search strategies will be developed in consultation with a librarian (see Appendix 1). Forward citation searching of studies included after full text screening will be conducted using citationchaser.[9]

The results of the searches will be exported to Covidence (www.covidence.org). Following removal of duplicates, single screening of titles and abstracts of records retrieved will be conducted by two reviewers, in line with the inclusion and exclusion criteria outlined in Table 4.1. Full texts of potentially eligible studies will subsequently be reviewed by one of two reviewers in line with the inclusion and exclusion criteria. To minimise overlap, primary studies included in systematic reviews deemed eligible for inclusion will be excluded following full text review. To characterise the degree of overlap between included systematic reviews, the corrected covered area will be calculated and reported. For both title and abstract screening, and full text review, a minimum of 10% of records will be dual screened to ensure agreement between reviewers. For each included study, data extraction will be carried out by one reviewer with a standard template using Microsoft Excel software. Cross-checking by a second reviewer will be conducted for any critical data that may affect the results or conclusions (for example, definitions and or outcomes data).

For grey literature, online searches of the websites of selected NITAGs and other national public health bodies will be carried out to identify national recommendations, guidelines and or guidance documents relating to rabies vaccine use for PEP and or PrEP, including target populations. Countries will be selected to include a combination of EU and non-EU countries, with established NITAGs that meet all six WHO criteria,[10] and categorised as having 'no risk' of rabies by the UK Health Security Agency (UKHSA).[11] Consideration will also be given to the availability of recommendations, guidelines and or guidance documents issued by relevant bodies. Targeted searches will include the following countries:

- Australia

- Belgium
- Denmark
- France
- Germany
- Netherlands
- Portugal
- UK.

Documents published by the WHO will also be included, as outlined in Table 4.1. Google Translate, Deepl Pro or similar will be used to translate non-English language documents, where appropriate. Data extraction will be completed by one reviewer with a standard template using Microsoft Excel software. Cross-checking by a second reviewer will be conducted for any critical data that may affect the results or conclusions (for example, dosing schedules and definitions of risk groups).

For peer-reviewed and grey literature, any disagreements regarding eligibility for inclusion or data extraction will be resolved through discussion, and using a third reviewer where necessary. Due to the rapid nature of this review and the diverse range of document types to be included, quality appraisal of included literature will not be undertaken. Summaries of any quality appraisal or risk of bias assessments reported by the authors of included systematic reviews will be outlined. Data will be synthesised narratively.

5 Other domains

The following domains will be primarily informed by the shared expertise and experiences of NIAC members and members of the Rabies Working Group: values and preferences, resource use, equity, acceptability, and feasibility. Where relevant information regarding these domains is identified through evidence relating to the problem, and benefits and harms domains, it will be summarised narratively and presented to the Working Group and Committee.

6 Quality assurance process

The work will be undertaken in accordance with HIQA's HTA Directorate Quality Assurance Framework and led by an experienced member of the NIAC Secretariat team. The outputs will be reviewed by at least two senior members of the team to ensure processes are followed and quality is maintained. A draft of the protocol will be circulated to the Rabies Working Group for review. To further ensure quality, accurate interpretation of the evidence, and accurate representation of their considerations, feedback on draft outputs will be sought from the Rabies Working Group and Committee.

7 Recommendations and publication

The evidence gathered, as outlined above, will be compiled for presentation to the NIAC Rabies Working Group, and for consideration at full NIAC meetings. The evidence summary regarding PEP will be prioritised and presented initially, with evidence relating to PrEP summarised and presented at a subsequent NIAC meeting. The evidence summaries will be presented in accordance with the adapted EtR framework[6] used by NIAC to develop its recommendations to the Minister for Health. The evidence summary findings will then be synthesised in reports for submission to the Minister for Health and publication on the HIQA website together with the opinion, discussion points and recommendations of NIAC. The relevant chapter of the Immunisation Guidelines for Ireland will be updated in line with the recommendations and published on the HIQA website.

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Appendix 1. Outline of planned search strategy

Databases to be searched:

- Embase via Elsevier
- Medline via EBSCOhost
- The Cochrane Library
- ClinicalTrials.gov.

Searches will be conducted in July 2025. The search periods will be from 1 January 2015 to the date on which the search is run. A sample search strategy for a single database is shown in Tables A1.1.

Table A1.1 Sample search strategy, to be run in Embase via Elsevier

#	Searches
#18	#15 NOT #16 AND [english]/lim
#17	#15 NOT #16
#16	#15 AND ('Conference Abstract'/it OR 'Conference Paper'/it)
#15	#9 AND #13 AND [2015-2025]/py
#14	#9 AND #13
#13	#10 OR #11 OR #12
#12	exposure:ab,ti OR 'pre exposure':ab,ti OR preexposure:ab,ti OR 'post exposure':ab,ti OR postexposure:ab,ti
#11	'pre-exposure prophylaxis'/exp
#10	'post exposure prophylaxis'/exp
#9	#7 OR #8
#8	'rabies vaccine'/exp
#7	#3 AND #6
#6	#4 OR #5
#5	vaccin*:ab,ti OR immuni*:ab,ti OR verorab:ab,ti
#4	'vaccination'/exp
#3	#1 OR #2
#2	rabies:ab,ti OR lyssa:ab,ti OR hydrophobia:ab,ti
#1	'rabies'/exp

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For further information please contact:

National Immunisation Advisory Committee

Health Information and Quality Authority

George's Court

George's Lane

Smithfield

Dublin 7

D07 E98Y

+353 (0)1 8147400

www.hiqa.ie