National Immunisation Advisory Committee
An Coiste Comhairleach Náisiúnta um Imdhíonadh

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

Updated recommendations for post-exposure prophylaxis against rabies

Advice provided to the Minister for Health

Issued: 08 December 2025

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 Health Technology Assessment (HTA) Directorate in HIQA, provides clinical, evidence synthesis, and administrative support to NIAC.

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RECOMMENDATIONS

1. NIAC recommends that patients with potential rabies-prone exposures are assessed using the risk assessment outlined in the *Guidelines on Post-exposure Assessment and Treatment of Rabies-prone Exposures* issued by the National Health Protection Office. If post-exposure treatment is indicated, NIAC recommends the following:

For immunocompetent individuals of all ages who have not previously received rabies vaccine:

- Rabies vaccine should be administered according to the four-dose reduced Essen intramuscular (IM) regimen (one dose on: day 0, day 3, day 7 and between day 14 and 28).
- Human rabies immunoglobulin (HRIG) should be administered as soon as possible, if indicated based on the composite rabies risk.* HRIG is not indicated if more than seven days have elapsed since commencement of active immunisation.

For immunocompetent individuals of all ages who have previously received two or more doses of rabies vaccine in the context of pre-exposure prophylaxis, or post-exposure prophylaxis related to a prior exposure:

- Rabies vaccine should be administered according to the two-dose IM regimen (one dose on: day 0 and day 3). HRIG is not recommended.
- If complete rabies post-exposure prophylaxis, as indicated, was received within the preceding three months, no further rabies vaccine or HRIG is recommended.

For immunocompetent individuals of all ages who have previously received one dose of rabies vaccine in the context of pre-exposure prophylaxis, or post-exposure prophylaxis related to a prior exposure:

- Rabies vaccine should be administered according to the four-dose reduced Essen IM regimen (in other words, as if unvaccinated). HRIG is not recommended for this group regardless of the exposure type.

For immunocompromised± individuals of all ages who have experienced an amber or red rabies exposure:*

- Rabies vaccine should be administered according to the five-dose Essen IM regimen (one dose on: day 0, day 3, day 7, day 14 and 28). HRIG should be administered as soon as possible after exposure.
- Rabies virus-neutralising antibody (RVNA) serology testing should ideally be undertaken on the same day as, or a soon as possible following, receipt of the final dose of rabies vaccine. If RVNA titres are less than the WHO threshold target of 0.5 IU/mL, a further dose of rabies vaccine is recommended.

Flexibility

2. Post-exposure treatment, including receipt of the first dose of rabies vaccine and HRIG, if indicated, should be started as soon as possible following exposure.

3. Efforts should be made to administer subsequent doses on time, but if there is difficulty in achieving the specified intervals within the vaccine schedule, doses two and three may be administered within plus or minus one day of the recommended schedule and subsequent intervals should be readjusted to keep the recommended intervals between the remaining doses.

4. For high-risk exposures such as multiple bites to head and neck or bites from a confirmed rabid animal, vaccine and HRIG should be administered as soon as possible, within 12 hours of reporting.

5. Vaccination should not be delayed due to delays in accessing HRIG.

Interchangeability

6. Where post-exposure treatment has commenced outside of Ireland, vaccination should continue using a rabies vaccine authorised for use in Ireland and according to the appropriate NIAC-recommended regimen. The vaccine regimen should be restarted if the post-exposure treatment commenced outside of Ireland did not use a WHO-recommended rabies vaccine type (that is, a modern concentrated purified cell culture or embryonated egg-based rabies vaccine with a potency of at least 2.5 IU/mL per IM dose), or was not administered according to a WHO-recommended vaccine regimen (IM or ID).

[*] Amber or Red refers to the composite rabies risk, see Appendix 1.

[±] Immunocompromised individuals who may not mount an appropriate response to rabies vaccine, see Appendix 2.

Recommendations may be updated when more information becomes available.

Contents

List of abbreviations used in this report

AE	adverse event
ATAGI	Australian Technical Advisory Group on Immunisation
CCEEV	cell culture and embryonated egg-based vaccine
EMA	European Medicines Agency
EtR	evidence to recommendation
GB	Great Britain
GMC	geometric mean concentration
GMT	geometric mean titre
HAS	Haute Autorité de Santé (France)
HDCV	human diploid cell vaccine
HIQA	Health Information and Quality Authority
HPRA	Health Products Regulatory Authority
HRIG	human rabies immunoglobulin
HSE	Health Service Executive
HTA	health technology assessment
ID	intradermal
IM	intramuscular
IPC	Institute Pasteur du Cambodge
IU	international units
mAbs	monoclonal antibodies
NHPO	National Health Protection Office
NIAC	National Immunisation Advisory Committee
NITAG	National Immunisation Technical Advisory Group
PCECV	purified chick embryo cell vaccine
PEP	post-exposure prophylaxis
PET	post-exposure treatment

PrEP	pre-exposure prophylaxis
PVRV	purified Vero cell vaccine
RCT	randomised controlled trial
RIG	rabies immunoglobulin
RVNA	rabies virus-neutralising antibody
SAE	serious adverse event
SmPC	summary of product characteristics
STIKO	Ständige Impfkommission (Standing Committee on Vaccination, Germany)
UKHSA	UK Health Security Agency
WG	working group
WHO	World Health Organization

Executive Summary

- In July 2025, the Health Service Executive (HSE) regionalised rabies post-exposure prophylaxis (PEP) services, also known as post-exposure treatment (PET), prompting the need for consistent national guidance. In response, the National Health Protection Office (NHPO) published interim guidelines, adapted from UK and Scottish sources. The National Immunisation Advisory Committee (NIAC) subsequently reviewed and updated its rabies PEP recommendations to reflect the latest evidence, align with the risk assessment outlined in the NHPO guidelines, and provide additional clinical guidance related to rabies vaccine when administered as part of PET.
- PEP, or PET, involves wound care, rabies vaccination, and, where indicated, administration of human rabies immunoglobulin (HRIG). As of September 2025, the only authorised rabies vaccine available in Ireland is Verorab, a purified Vero cell rabies vaccine (PVRV) that meets World Health Organization (WHO) standards. NIAC's updated recommendations are based on a comprehensive evidence review, including 21 peer-reviewed studies and international guidance from nine countries comparable to Ireland in terms of rabies risk.
- The evidence review focused on immunogenicity, vaccine schedules, administration routes, and considerations for immunocompromised individuals. It also incorporated grey literature from national immunisation technical advisory groups (NITAGs) and public health bodies. The findings informed NIAC's updated recommendations and guidance.

Epidemiology and service use

- Rabies is a serious public health concern, mostly affecting Asia and Africa, and causing approximately 59,000 deaths annually, with 40% of these deaths in children under 15 years old. Rabies is almost 100% fatal once symptoms appear. Dog bites in endemic countries are the main source of infection.
- Ireland, the UK, most of western Europe and Australia are considered free of rabies in terrestrial mammals with the last local case of animal rabies in Ireland occurring in 1903. Ireland is considered low-risk for bat-related rabies.
- In 2025, Ireland saw a sharp rise in demand for rabies vaccines and HRIG for PEP, likely due to increased public awareness of rabies risk following a death from rabies in the UK. Between May and mid-September 2025, a total of 516 vaccines and 102 HRIG vials were distributed for this purpose, greatly exceeding the typical annual level of rabies prophylaxis product use.

Safety

- Rabies vaccines are considered safe and generally well tolerated. Minor local and mild systemic reactions may occur but are typically short lived, resolving spontaneously within one to three days.

Vaccine schedules and routes of administration

- Rabies cell culture and embryonated egg-based vaccines (CCEEVs) administered as PEP elicit a strong immune response above the WHO-established target threshold of protection regardless of administration route (intramuscular (IM) or intradermal (ID)), vaccine regimen (within WHO recommended choice of regimens) and age.
- Seroconversion typically occurs between day 7 and day 14 from initiation of the vaccine regimen, with peak antibody levels reached around day 28 to 30, followed by a decline and stabilisation above protective thresholds for up to one year.
- IM and ID routes show comparable immune responses in the first two months post vaccination, though IM schedules maintain higher antibody levels beyond day 60.
- All age groups respond adequately; however, the limited data available for individuals aged over 50 years show lower and delayed peak responses in this cohort.
- Shorter ID regimens have been shown to be non-inferior to longer schedules, supporting WHO recommendations for simplified protocols.
- In immunocompetent individuals with a rabies-prone exposure, WHO-recommended rabies vaccine regimens are widely used, with the four-dose, four-visit Essen IM regimen being the most common, followed by the four-dose, three-visit Zagreb IM regimen and the vaccine sparing, six-fractional dose, three-visit Institute Pasteur du Cambodge (IPC) regimen.
- IM regimens are typically preferred over ID ones, with the use of the latter generally limited to specific situations in countries with a similar rabies risk to Ireland (for example, vaccine shortages or continuation of treatment started abroad). For high-risk exposures, most countries recommend HRIG as well as vaccination.

Interchangeability

- Rabies CCEEVs are considered interchangeable in clinical practice, both in terms of product and administration route. Evidence from small studies supports their safe use and the achievement of an immune response above the WHO target threshold of rabies virus-neutralising antibody (RVNA) titres when switching between vaccine types or routes of administration.

- The WHO recommends rabies vaccines with a potency of at least 2.5 IU per IM dose and allows switching of vaccine products or administration routes during PEP without restarting the series, as long as the vaccine type is a CCEEV and not an older nerve tissue formulation.
- Five of the countries whose recommendations were reviewed (Australia, Denmark, France, Netherlands, UK) follow this WHO guidance on interchangeability. Furthermore, Denmark and Germany permit interchangeable use of nationally-authorised vaccines only, while Australia, Netherlands, and the UK advise continuing PEP started abroad using WHO-approved vaccines according to their national schedules.

Boosting of RVNA titres in previously vaccinated individuals

- Rabies vaccine booster doses reliably produce antibody levels above the WHO target threshold within 7 to 14 days, regardless of the route of administration or vaccine regimen (within WHO approved regimens) of the primary series. Two-dose IM booster schedules given over a year after initial IM pre-exposure prophylaxis (PrEP) are effective for previously vaccinated individuals. While both IM and ID primary schedules have been shown to be boostable above the WHO target RVNA titre level, IM priming has been shown to lead to higher antibody levels post-booster.
- Internationally, many countries recommend a two-dose IM regimen for PEP and no rabies immunoglobulin (RIG) in previously vaccinated individuals (that is, those who have been vaccinated more than three months prior to the current exposure). No additional vaccine is recommended for those who have received PEP within three months of the current exposure.
- With respect to defining previously vaccinated, including partially vaccinated, individuals, most countries and the WHO consider individuals who have received at least two doses of PrEP or previous PEP to be previously vaccinated. The UK is more stringent, requiring at least three doses for someone to be considered vaccinated, or RVNA titres above 0.5 IU/mL.

Immunocompromised populations

- Immunocompromised patients may have a weaker or less predictable response to rabies vaccination. Shortened regimens, such as the four-dose IM reduced Essen regimen, may not always produce adequate antibody levels. Serological testing and additional doses may be needed to ensure effective protection.
- Internationally, the WHO recommends serological testing for immunocompromised individuals after completing PEP, with additional vaccine doses given if antibody

levels are insufficient. Several countries, including the UK, France, Germany, Denmark, Australia, and the Netherlands, generally align with this approach. Many such countries also recommend administering RIG to immunocompromised individuals for moderate to high-risk exposures.

Breakthrough rabies infection

- While rare, breakthrough rabies infection (which is when rabies infection occurs despite receipt of PEP) can occur, highlighting the critical importance of timely and correct wound care and PEP administration.
- In a 2023 study of breakthrough rabies infections, most cases involved severe wounds, however deviations from recommended wound care and vaccine administration practices were also reported in over half of the cases.

Acceptability, feasibility, values and preferences

- Implementation factors such as number of doses, vaccine volume, timing of visits, and the total duration of a vaccination regimen influence feasibility, cost, adherence, and patient preferences in rabies PEP delivery. WHO guidance recommends choosing PEP schedules based on practical considerations, including healthcare provider experience with IM and ID administration and the clinical setting.
- Acceptability and feasibility are key to deciding whether to recommend one or multiple regimens, especially in systems where rabies PEP is infrequently administered and expert support may be limited.
- Six countries (Belgium, Denmark, France, Germany, Netherlands, Portugal) recommend multiple alternative PEP regimens for unvaccinated, immunocompetent individuals, with national expert advice services available to support the provision of PEP in four of these countries. Three countries (Australia, UK, and separately, Scotland) recommend only the reduced Essen regimen, with expert contact points outlined in the separate UK and Scottish guidelines.
- UK guidelines allow flexibility in PEP vaccine timing for travellers, prioritising delivery of the first three doses (days 0, 3, and 7) within ±1 day. Missed or delayed doses in the UK and Portugal are managed by adjusting the schedule rather than restarting it, in line with WHO recommendations.

NIAC Considerations

- Informed by the review of the above evidence and the input of the Rabies Working Group (WG) and according to NIAC's Evidence to Recommendation (EtR) framework, NIAC agreed revised recommendations for rabies PEP.

- NIAC agreed that eligibility for rabies PEP should be guided by the risk assessment set out in NHPO guidelines.
- NIAC's updated rabies PEP recommendations reflect a strong focus on practical implementation, particularly in light of the move from a centralised to a regionalised service delivery model.
- NIAC discussions reflected a preference for clarity and consistency in approach and messaging, especially where multiple internationally accepted options exist. The preference for a single IM regimen was driven by feasibility and training considerations, not efficacy concerns.
- Flexibility in scheduling and administration was considered important in terms of feasibility. NIAC supports flexibility of plus or minus one day for doses two and three of the five-dose Essen and four-dose reduced Essen regimens to accommodate varied clinical settings. Operational challenges, particularly around HRIG access out-of-hours, were discussed, with emphasis on not delaying vaccine initiation in the absence of HRIG.
- NIAC highlighted the need for clear, actionable guidance for healthcare professionals, including definitions of immunocompromised status in the context of rabies PEP and recommendations for partially-vaccinated individuals. The importance of accommodating patients who begin PEP abroad was also addressed, with support for WHO-recommended vaccine types and interchangeability of administration routes.
- NIAC's approach reflects a balance between evidence-based practice and the practicalities of clinical delivery, and aims to support safe, consistent, and accessible rabies PEP.

1 Introduction

In July 2025, each HSE Health Region assumed responsibility for the provision of risk assessment and post-exposure treatment (PET) services for individuals with rabies-prone exposures. This regionalisation resulted in a need for clear and consistent national guidance for healthcare professionals to whom individuals with rabies-prone exposures may present. In response to this need, the National Health Protection Office (NHPO) published interim guidelines on post-exposure assessment and treatment of rabies-prone exposures in July 2025,[1] adapted from existing guidelines issued by the UK Health Security Agency (UKHSA)[2] and Public Health Scotland.[3]

NIAC's recommendations in relation to rabies PEP are outlined in Chapter 18 of the Immunisation Guidelines for Ireland.[4] In light of the interim guidelines published by the NHPO, NIAC considered it necessary to review its existing recommendations without delay and, where necessary, update these recommendations with respect to new evidence and to ensure alignment with NHPO guidelines.

In this context, NIAC considered the most up-to-date information available regarding rabies post-exposure prophylaxis (PEP) as of September 2025 and developed updated recommendations for this population in Ireland. This report outlines the evidence summarised by the NIAC Secretariat to inform NIAC's recommendations and the considerations of the Committee and the Rabies Working Group (WG), presented with respect to the Evidence to Recommendation (EtR) framework used by NIAC.[5]

2 Methods

The methods used by the NIAC Secretariat to identify and summarise the evidence that informed the Committee's and WG's considerations are described in the protocol, *Rabies vaccines for pre-exposure and post-exposure prophylaxis: Protocol for an evidence summary to inform updated recommendations*, available at www.hiqa.ie. As outlined in the protocol, aspects of the evidence summary relating to PEP were prioritised, with the relevant findings and considerations described in this report.

The evidence summary was presented to NIAC's Rabies WG on 18 September 2025, and the Rabies WG's considerations were documented. The evidence summary and WG considerations were subsequently presented to NIAC at a full Committee meeting on 29 September 2025. NIAC considered the information presented and developed its recommendations in line with its Terms of Reference and Standard Operating Procedures.[6]

3 Rabies post-exposure prophylaxis

Rabies PEP, also referred to as PET in national and international literature, consists of thorough wound washing, prompt administration of rabies vaccine and, where indicated, infiltration of the wound(s) with rabies immunoglobulin (RIG).[7] Throughout the current report, the terms 'PEP' and 'PET' are used interchangeably, in accordance with the terminology used in the cited literature.

PEP is indicated for those who may have been exposed to rabies virus, based on assessment of the risk associated with the exposure. Guidelines in relation to risk assessment of individuals with rabies-prone exposures are published by the HSE's NHPO.[1]

For the purposes of PEP, the World Health Organization (WHO) recommends the use of concentrated, purified cell culture or embryonated egg-based rabies vaccines (CCEEVs) with a potency of at least 2.5 international units (IU) per dose for intramuscular (IM) injection.[7] Vaccines of these types that have been authorised for use in humans in several European countries include purified Vero cell vaccines (PVRV), purified chick embryo cell vaccines (PCECV) and human diploid cell vaccines (HDCV).[8] Although still in use in certain parts of Asia, Africa and South America,[2] the WHO strongly recommends against the production and use of nerve tissue rabies vaccines.[7] In Ireland, the only rabies vaccine authorised for use in humans as of 29 September 2025 is Verorab (Sanofi Winthrop Industrie), a PVRV which contains inactivated rabies virus of the WISTAR Rabies PM/WI38 1503-3M strain.[9] No rabies vaccines are authorised by the European Medicines Agency (EMA) through the centralised procedure. Verorab is included on the WHO List of Prequalified Rabies Vaccines.[10]

In the context of PEP, several well-established and widely used rabies vaccine regimens are recommended by the WHO. The recommended regimens vary depending on the immune status of the individual and their history of rabies vaccination and, in addition, multiple options are recommended for certain populations. For example, the three WHO-recommended regimens for previously unvaccinated, immunocompetent individuals are outlined in Table 1, including their corresponding routes of administration, dosing schedules, and total number of days required to complete each regimen.[7]

Table 1. Overview of WHO-recommended rabies vaccine regimens for PEP in previously unvaccinated, immunocompetent individuals[7]

Regimen	Route	Doses	Total volume (mL)	Schedule	Visits	Duration
Reduced Essen	IM	4	2.0	D0, D3, D7, D14-28	4	14-28 days
Zagreb	IM	4	2.0	D0 (x2), D7, D21	3	21 days
IPC	ID	6	0.6	D0, D3, D7 (x2 each)	3	7 days

Key: D – day; ID – intradermal; IM – intramuscular; IPC – Institut Pasteur du Cambodge.

In addition to wound washing and active immunisation with rabies vaccine, passive immunisation with RIG may be indicated for certain individuals with high-risk exposures. In Ireland, human rabies immunoglobulin (HRIG) is used in such cases.[1] Internationally, equine RIG is used in some settings in place of HRIG. Rabies monoclonal antibody products are also recommended by the WHO as an alternative to RIG, where available (for example, in India).[7]

4 Overview of included literature

4.1 Peer-reviewed literature

Twenty-one peer-reviewed studies on rabies PEP met the inclusion criteria for this review. These were 10 systematic reviews and 11 additional primary studies which were not also included in any of the systematic reviews. Included studies primarily focused on immunogenicity outcomes, and covered rabies vaccination schedules, routes of administration, rabies breakthrough infections and factors influencing seroconversion in primarily immunocompetent children and adults with and without receipt of pre-exposure prophylaxis (PrEP). A small number of included studies detailed evidence on rabies vaccination in immunocompromised populations. Across systematic reviews there was minimal overlap in included primary studies with a corrected covered area of 4.1%. Further details of all studies, including details related to quality of included evidence for systematic reviews, if assessed, key limitations of primary studies and funding sources are included in Appendix 3. Overview of included literature Tables A3 and A4. These tables indicate which studies were presented in detail to the Rabies WG and which studies were provided as supplementary material.

4.2 Grey literature

Recommendations, guidelines and or guidance documents issued by NITAGs and other national public health bodies in nine selected high-income countries with rabies risk

profiles similar to Ireland (Australia, Belgium, Denmark, France, Germany, the Netherlands, Portugal, Scotland, and the UK) were included in this review. Scotland was addressed separately to the UK as distinct guidelines were identified for Scotland. The WHO's 2018 position paper on rabies vaccines[7] and Ireland's NHPO Interim Guidelines on Post-exposure Assessment and Treatment of Rabies Prone Exposures were also included.[1] All included grey literature was published or updated between 2018 and 2025. The full list of included grey literature is provided in Appendix 3. Overview of included literature Table A5.

5 Evidence to Recommendation framework

5.1 Domain 1: The problem

Rabies is a serious public health problem in over 150 countries and territories, mainly in Asia and Africa. It is estimated to cause 59,000 human deaths annually, with 40% of these deaths occurring in children aged under 15 years. Rabies infects mammals, including humans, dogs, cats, livestock, and wildlife and is almost 100% fatal in humans once clinical symptoms appear. Up to 99% of human rabies cases are caused by dog bites or scratches, predominantly in countries where rabies is endemic.[7, 11] Ireland, the UK, most of western Europe and Australia are considered free of rabies in terrestrial mammals.[12] The last known indigenous case of animal rabies in Ireland occurred in 1903.[13] Bat lyssaviruses can cause rabies in humans. Ireland and the UK are considered low risk for rabies infection contracted from contact with bats. All other countries are considered high-risk for rabies exposure from bats.[12]

In 1996, European bat 2 lyssavirus (EBLV-2) was first identified in Daubenton's bats in Great Britain (GB). Since then, authorities in GB have identified approximately two Daubenton's bats infected with EBLV-2 each year. EBVL-2 is, therefore, considered endemic in GB's Daubenton's bat population. In 2002, an unvaccinated bat handler died of rabies following unprotected exposure to a Daubenton's bat in Scotland. While EBLV-2 has not been identified in bats on the island of Ireland, Daubenton's bats are native to Ireland and, given the potential for movement between GB and Ireland, it is assumed that Daubenton's bats in Ireland may be infected with EBLV-2. As there is not enough information about the likelihood of pipistrelle bats, the most common bat species in Ireland, being infected with EBLV-2 in the UK or Ireland, the NHPO have determined that this species must also be assumed to pose a risk of rabies and that all bats in Ireland regardless of species must be assumed to pose a potential risk of rabies.[1]

In Ireland, there was a marked increase in demand for rabies vaccine and HRIG from May to September 2025. Between May and mid-September 2025, 516 vaccines and 102 vials of HRIG were distributed in Ireland. This surge in demand contrasted with typical annual usage, which ranged from 200 to 300 vaccines and 10 to 40 HRIG vials.[14] This was likely driven primarily by increased awareness of rabies risk resulting from a high-profile death from rabies in the UK related to an exposure abroad.

Prior to the regionalisation of rabies PEP services, rabies PEP was primarily managed through the designated Senior Medical Officer in Cherry Orchard Hospital. In 2024, 106 individuals were treated in Cherry Orchard Hospital for rabies exposure, comprising 50 males and 56 females. The median age of those treated was 27 years old, ranging from 2 to 82 years; 22.6% of patients were children aged under 15 years. Most exposures (102) occurred outside of Ireland, with only four exposures occurring within Ireland. Of those exposed internationally, 18 individuals (17.6%) did not begin treatment abroad, requiring initiation of care upon return.[15]

5.2 Domain 2: Benefits and harms

5.2.1 Safety

Cell culture and embryonated egg-based rabies vaccines have consistently been shown to be safe and generally well tolerated.[7] Minor local reactions such as erythema, pain, and swelling occur in 35 to 45% of recipients, especially with intradermal (ID) administration during repeat vaccinations.[7, 16, 17] Mild systemic adverse events (AEs), including transient fever, headache, dizziness, and gastrointestinal symptoms, are reported in 5 to 15% of cases. Serious AEs are rare, and no causal link with vaccines has been established for neurological symptoms.[7] A systematic review and meta-analysis published in 2022, including 27 articles and a total of 18,630 participants, comparing safety across rabies vaccines using the five-dose intramuscular (IM) Essen regimen found pooled local and systemic adverse reaction rates of 3.2% for HDCVs, 11.7% for PVRVs, and 26.0% for PCECVs.[18]

Verorab, the rabies vaccine authorised for use in Ireland, has been administered to over 13,000 individuals in clinical studies, including 1,000 children aged under 18 years.[9] Adverse events were typically moderate, occurred within three days post-vaccination, and resolved spontaneously within one to three days. No serious adverse events were attributed to the vaccine and no serious adverse events are noted in the Verorab Summary of Product Characteristics (SmPC) as of 29 September 2025.[9]

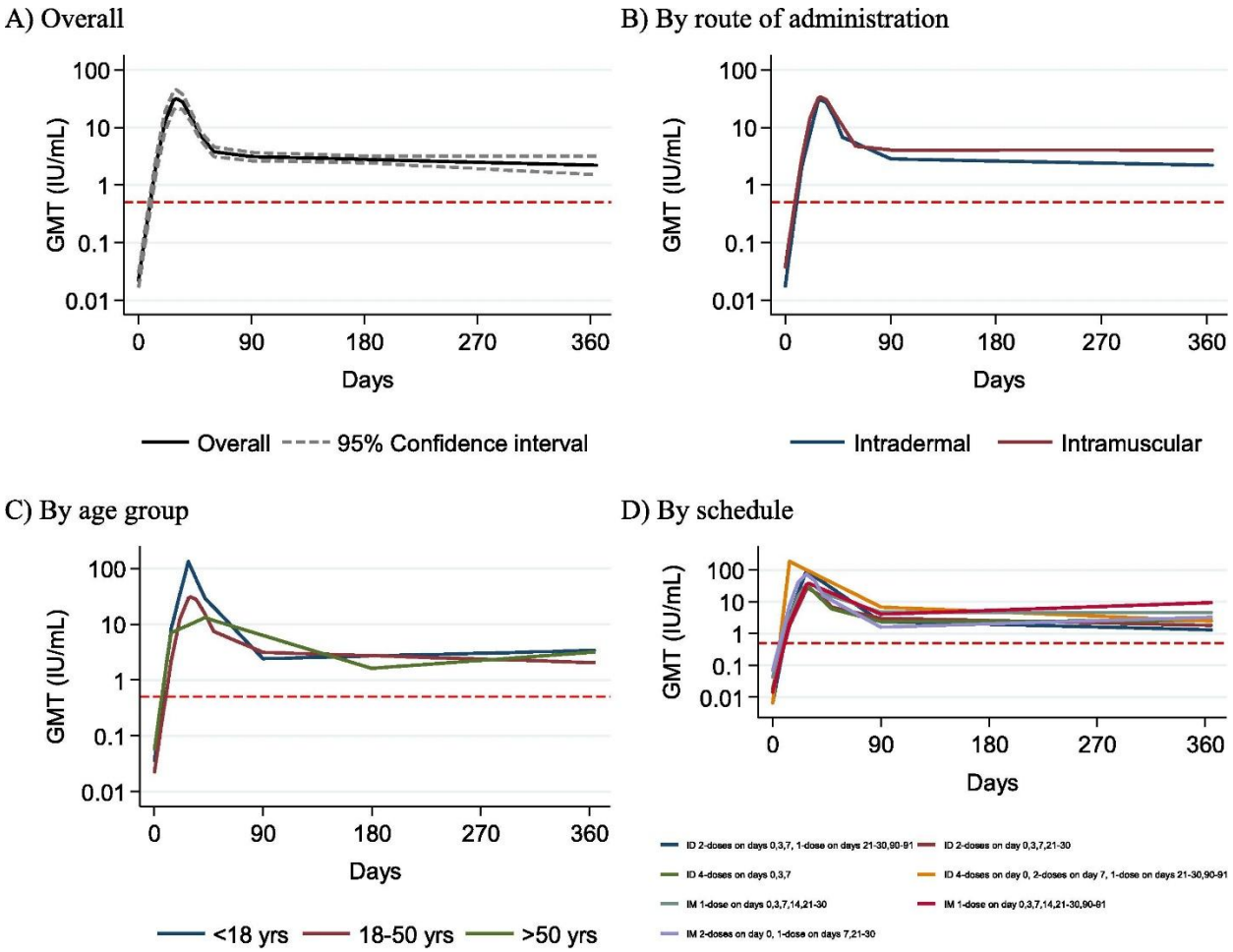
5.2.2 Vaccine schedules and routes of administration

Immunogenicity

The immune response to rabies vaccines in humans was described by Xu et al.[19] in a 2021 systematic review and dose-response meta-analysis. The authors' analyses focused on PEP included 96 datasets from 41 unique studies, comprising clinical trials and observational studies. Participants were seronegative healthy volunteers (59 datasets; 61.5%) and seronegative patients with category I or II exposures (37 datasets; 38.5%). The reported median age of participants was 28.1 years (interquartile range 21.4 to 31.6 years), with mean ages in the included datasets ranging from 8.9 to 62.1 years. Geometric mean titres (GMTs), measured from the first day of a vaccine schedule (day 0, reported in 41 studies) and at various time points up to one year following initiation of vaccination (reported in 11 studies), were pooled overall, with separate analyses reported by route of administration, vaccine schedule and age group. Findings, as reported by the authors, are presented in Figure 1.

Overall, GMT levels were reported to rise above the threshold of 0.5 IU/mL approximately 7 to 14 days after initiating PEP, with peak GMTs of 30.9 IU/mL reached at approximately day 28 to 30. Subsequently, GMTs declined until day 60, then stabilised at approximately 3.0 IU/mL for up to one year. When separated by route of administration, similar findings to the overall analysis were reported for IM and ID vaccine schedules up to day 30. GMTs were reported to stabilise at statistically significantly higher levels from day 60 onwards in those who received IM schedules compared with ID schedules, although titres exceeded threshold levels for both routes. Pooled analyses of seven distinct vaccine schedules (three IM and four ID schedules) also indicated similar patterns within the first 30 days of vaccination, with GMTs maintained above threshold levels for up to one year (the maximum length of follow-up in the included studies).

Figure 1. Pooled geometric mean titre levels over time after rabies post-exposure prophylaxis[19]



Note: Y-axes are presented as log scales. The horizontal red dotted lines represent a geometric mean titre level of 0.5 IU/mL.
Source: Reproduced from Xu et al.[19]

Adequate immune responses were also reported for all age groups (that is, those aged under 18 years, 18 to 50 years, and over 50 years), although it was noted that peak GMT levels (13.2 IU/mL) were lower and occurred at a later point following vaccination (at day 42) in those aged over 50 years (median age 62 years) compared with those aged under 50 years. Datasets relating to adults aged over 50 years were obtained from two of the 41 primary studies included. The total number of participants aged 65 years or older was not reported in the included systematic review.

The findings of Xu et al.[19] regarding seroconversion occurring in the majority of participants by day 14 was supported by the findings of another included systematic review and meta-analysis by Wang et al.[18] These authors reported pooled

immunogenicity data in terms of seroconversion rates (that is, the proportion of participants who reached GMT levels greater than 0.5 IU/mL) measured on day 7 and day 14 in participants aged two years and older who received PVRV according to a five-dose Essen regimen. Pooled data from six studies (n=605) indicated that seroconversion had occurred in 56% of participants (95% CI: 23% to 86%) by day 7, and in 99% (95% CI: 95% to 100%) of participants (n=1,595; 7 studies) by day 14.

Similar findings in relation to adequate GMT levels achieved by day 14 regardless of administration route were reported in an industry-funded systematic review by Preiss et al.[16] The authors reported on five studies that directly compared immunogenicity between groups (including children and adults) who received Rabipur (a PCECV) according to IM or ID PEP regimens. GMTs below the 0.5 IU/mL threshold were reported in most groups at day 7, but GMTs had surpassed threshold levels by day 14 and day 28/30 in all groups regardless of route of administration.

The immune response elicited by rabies vaccines administered IM or ID in the context of PEP was reported to be comparable in a further systematic review by Schnyder et al.[17] The authors included five studies that reported this finding as part of a broad systematic review and meta-analysis comparing fractional dose of ID with IM administration for a number of vaccine preventable diseases. These comprised two studies in relation to PCECV, which were also reported in Preiss et al.'s systematic review,[16] and three studies relating to PVRV.

Finally, a systematic review by Kessels et al.[20] noted that the immunogenicity of one-week ID vaccine regimens (administered at four sites or two sites on each of day 0, day 3 and day 7) was non-inferior to that of the longer ID regimen previously recommended by the WHO in 2010. The findings of this review informed the WHO's recommendation of the IPC regimen in its 2018 position paper on rabies vaccines.

International positions

An overview of rabies PEP recommendations in the selected countries and by the WHO for individuals who are immunocompetent and have not previously received rabies PEP or PrEP is provided in Table 2.

WHO-recommended vaccine regimens were the most frequently recommended regimens across the selected countries. Seven out of nine countries' recommendations included the four-dose reduced Essen IM regimen, six out of nine included the Zagreb IM regimen, and four out of nine included the IPC ID regimen. Overall, IM vaccine regimens were more frequently recommended than ID regimens. Aside from France,

where IM and ID regimens were equally recommended, other selected countries' recommendations made provision for the use of ID vaccination in certain circumstances; for example, if in line with the relevant vaccine's SmPC (Germany), in case of vaccine shortage (Portugal), or if PEP was started according to an ID regimen and was required to be completed on return from abroad (Denmark). For those with high-risk exposures, the type of RIG recommended was not specified in two countries (France and Portugal), whereas for all other selected countries, HRIG was recommended.

Table 2. Recommendations in relation to rabies PEP for previously unvaccinated immunocompetent individuals

Country/ Organisation	IM regimens			ID regimen	IM or ID regimens	RIG/mAbs
	Essen	Reduced Essen	Zagreb	IPC	Other	High-risk exposures
Australia[21]	-	✓	-	-	-	HRIG
Belgium[22]	✓	-	✓	-	-	HRIG
Denmark[23]	-	✓	*	*	-	HRIG
France[24]	✓	-	✓	✓	-	RIG
Germany[25, 26]	✓	✓#	✓	✓#	✓#	HRIG
Netherlands[27]	-	✓	✓	-	-	HRIG
Portugal[28]	-	✓	✓	✓^	-	RIG
Scotland[3]	-	✓¥	-	-	-	HRIG
UK[2]	-	✓¥	-	-	-	HRIG
WHO[7]	-	✓	✓	✓	-	RIG or mAbs

Key: ID – intradermal; IM – intramuscular; IPC – Institut Pasteur du Cambodge; mAbs – monoclonal antibodies; RIG – rabies immunoglobulin.

Notes:

* If started on such a regimen abroad with cell-culture or embryonated egg-based rabies vaccine, PEP to be completed in line with the same regimen on return to Denmark.

If in line with relevant SmPC.

^ Can be used if there is a vaccine shortage, for example, during an outbreak.

¥ Dose four must not be given before day 21; if given before day 21, a fifth dose should be given two weeks later.

5.2.3 Interchangeability

Rabies CCEEVs are considered interchangeable in clinical practice with respect to vaccine product and route of administration. Two small studies[29, 30] demonstrating the safe and immunogenic interchangeability of rabies CCEEVs were summarised in an included systematic review.[20] In a prospective study of 90 animal bite cases presenting to two Bangalore hospitals, for whom a change of vaccine product or route of administration had occurred, immunogenicity at 14 days post-vaccination and self-reported adverse events were assessed.[29] Change of vaccine product (Rabipur, Verorab, Indirab, Abhayrab) occurred for 43 participants and change of route of administration occurred for 47 participants (n=24 from ID to IM and n=23 from ID to IM). None of the study subjects reported adverse reactions and the RVNA titres of all vaccinees were ≥0.5 IU/mL on day 14. Geometric mean concentration (GMC) of 11.84 IU/mL (95% CI: 10.83 to 12.94) with a range of 7.5 to 15.5IU/mL was reported for those with a change in vaccine product and 14.83 IU/mL (95% CI: 13.83 to 12.94) with a range of 7.5 to 15.5IU/mL with a change in administration route.[29]

In the second of those two studies, 20 healthy volunteers who had received a primary series of PCECV rabies vaccination either by IM (n=10) or ID (n=10) route received a booster vaccination with the same vaccine by the alternative route.[30] No adverse events were observed after vaccination with either of the routes. RVNA titres of all participants were ≥0.5 IU/mL on day 14 post vaccination.

International positions

As noted in Section 3, the WHO has recommended concentrated, purified cell culture and embryonated egg-based rabies vaccines with a potency of at least 2.5 IU per IM dose. The WHO stated that, if unavoidable, a change in vaccine product or route of administration during PEP is acceptable. The WHO also advised that, in such cases, it is not necessary to restart the vaccine series; rather, vaccination should continue in line with the schedule for the new route of administration.[7]

Five of the selected countries (Australia, Denmark, France, Netherlands, UK) aligned with the WHO's position, recommending that it is not necessary to restart the vaccine series if changing route of administration or if changing to another WHO-recommended vaccine type.[2, 21, 23, 24, 27] Recommendations in two countries (Denmark and Germany) specified that nationally-authorised vaccines may be used interchangeably within a series, if required.[23, 25, 26] Three of the selected countries (Australia, Netherlands, UK) recommended that PEP started abroad using a WHO-recommended vaccine type should be continued according to a nationally-recommended vaccine regimen on return from

travel.[2, 21, 27] The UKHSA further specified that, where two doses have been delivered on the same day abroad, these should be considered as one dose when converting to the UK regimen.[2] In Denmark, if PEP has started aboard according to either the Zagreb or IPC regimen, it is recommended that it should be continued according the same regimen on return to Denmark.[23]

5.2.4 Boosting of RVNA titres in previously vaccinated individuals

Immunogenicity

RNVA induced from primary rabies vaccination or previous rabies PEP can be easily boosted with subsequent vaccine doses. A 2018 systematic review of rabies antibody response to booster vaccination included 36 studies, 19 of which were eligible for inclusion in meta-analyses.[31] Across studies, RVNA geometric mean titres ≥0.5IU/mL were reported by day 7 or day 14 post booster administration, regardless of the route of administration of the primary schedule or booster vaccines. Included in these results were six studies which reported on the immune response induced by two-dose IM schedules administered >350 days post IM PrEP. These two-dose IM schedules are comparable to the current two-dose IM post-exposure schedule recommended by NIAC for previously vaccinated individuals. While all IM and ID routes of primary schedule administration were boostable to WHO target threshold titre levels, post-booster geometric mean titres were higher following primary schedules with IM route of administration compared with ID administration.

These findings were supported in a 2022 multicentre, open-label, controlled trial of 570 healthy participants aged 2 to 64 years who were randomised to one of five different PrEP regimens and followed up one year later with simulated PEP vaccination (two IM or ID doses of HDCV or PVRV three days apart).[32] RVNA titres and seroconversion (titres ≥ 0.5 IU/mL) rates were assessed 14 days and up to one year post-PrEP, and pre- and post-PEP. After simulated PEP, all groups showed rapid and robust immune responses, with all but one participant achieving seroconversion (titres ≥ 0.5 IU/mL) by day 14.

International positions

Table 3 provides a summary of rabies PEP recommendations in the selected countries and by the WHO for individuals who are immunocompetent and have previously received rabies vaccine in the context of PEP or PrEP. A two-dose IM regimen, with doses administered on day 0 and day 3, was most frequently recommended. RIG was not recommended for this population in any selected country, nor by the WHO.

Table 3. Recommendations in relation to rabies PEP for previously vaccinated immunocompetent individuals

Country/ Organisation	IM regimens		ID regimens		Other	RIG/mAbs
	2-dose (D0, D3)	Other	2-site, 2 visits	4-site, 1 visit	If previous PEP <3 months ago	All exposures
Australia[21]	✓	-	-	-	No PEP	No HRIG
Belgium[22]	✓	-	-	✓	-	No HRIG
Denmark[23]	✓	-	-	-	No PEP	No HRIG
France[24]	#	#	✓	✓	-	No RIG
Germany[25, 26]	✓*	-	✓*	-	-	No HRIG
Netherlands[27]	✓	-	-	-	No PEP	No HRIG
Portugal[28]	✓	-	✓^	✓^	No PEP	No RIG
Scotland[3]	✓¥	*	-	-	No PEP	No HRIG¥
UK[2]	✓¥	*	-	-	No PEP	No HRIG¥
WHO[7]	✓	-	✓	✓	No PEP	No RIG or mAbs

Key: D0 – day zero; D3 – day three; ID – intradermal; IM – intramuscular; mAbs – monoclonal antibodies; PEP – post-exposure prophylaxis; RIG – rabies immunoglobulin; UK – United Kingdom; WHO – World Health Organization.

Notes:

As per relevant SmPC.

* For Verorab, if it has been more than one year since two-dose pre-exposure prophylaxis, a third dose of PEP is required.

^ Can be used if there is a vaccine shortage, for example, during an outbreak.

¥ Dose two may be give between day three and day seven. If inadvertently given HRIG, a complete four-dose schedule of vaccine should be given.

In three of the selected countries (Australia, Denmark, France)[21, 23, 24] and for the WHO,[7] the recommendations outlined in Table 3 were deemed to apply to individuals who have received at least two doses of rabies vaccine. UKHSA guidelines stated that recommendations for unvaccinated individuals (excluding the use of HRIG) should be followed for those who have had an incomplete or inadequate primary vaccination course. Specifically, this was defined as receiving less than three doses of IM rabies PrEP, or less than three doses of ID rabies vaccine over two separate days.[2] In Australia and the UK, including Scotland, the recommendations in Table 3 were noted to apply to individuals with RVNA titres greater than 0.5 IU/mL.[2, 3, 21] In Germany and

the Netherlands, recommendations for vaccinated individuals were noted to apply to those who have received a complete PrEP vaccine series.[25-27]

For those who have previously received PEP, the WHO-recommended regimens outlined in Table 3 apply for further exposures that occur more than three months after the last PEP. If a repeat exposure occurs less than three months after a previous exposure for which an individual received complete PEP, the WHO recommends that only wound treatment is required. Neither vaccine nor RIG is recommended in such cases.[7] Six of the selected countries included recommendations that aligned with the WHO in this regard (Australia, Denmark, the Netherlands, Portugal, and the UK, including Scotland).

5.2.5 Immunocompromised populations

Immunogenicity

A small number of studies identified in the evidence review supporting these recommendations included immunocompromised individuals. Evidence from these studies suggests that not all immunocompromised patients are likely to reach the WHO target threshold RVNA titre level of 0.5 IU/mL with shortened vaccine regimens including the four-dose reduced Essen IM regimen.[33] Immunocompetent and immunocompromised patients may respond similarly to the five-dose Essen IM regimen, although average antibody titres are likely to be higher in immunocompetent populations.[34] Some severely immunocompromised patients, for example those who have recently undergone chemotherapy, may require a further dose to the five-dose Essen IM regimen.[35] In a 2020 retrospective review of medical records of 28 individuals with secondary acquired immunodeficiencies from French anti-rabies clinics between 2013 and 2018, inadequate response was unpredictable and not explained by the characteristics of the patients. These findings support WHO recommendations to systematically test serology in immunocompromised patients and administer further doses if required to meet target RVNA titres.[33]

International positions

International recommendations in relation to rabies vaccination and subsequent serological testing, where relevant, for individuals who are immunocompromised are summarised in Table 4. In addition to these recommendations, all of the selected countries and the WHO recommended administration of RIG for Category II or III exposures or, in the UK and Scotland, Amber or Red exposures.

Table 4. Recommendations in relation to rabies PEP for immunocompromised individuals

Country/ Organisation	IM regimens			ID regimen	IM or ID	Serology	
	Essen	Reduced Essen	Zagreb	IPC	Other	Timing	If titre <0.5 IU/ml
Australia[21]	✓*	-	-	-	-	2-4 weeks after last dose	Further dose & retest
Belgium[22]	✓	-	-	-	-	10-14 days after last dose	Aim for >5.0 IU/mL
Denmark[23]	✓	-	-	-	-	NR	NR
France[24]	✓	-	-	-	-	#	Further dose
Germany[25, 26]	✓	-	-	-	-	2-4 weeks after last dose	Further dose
Netherlands[27]	✓	-	-	-	-	Seek advice	NR
Portugal[28]	-	✓	✓	✓^	-	At the time of the last dose	Further dose
Scotland[3]	✓¥	-	-	-	-	On day 30	NR
UK[2]	✓¥	-	-	-	-	On day 30	NR
WHO[7]	-	-	-	-	✓	2-4 weeks after first dose	Further dose

Key: ID – intradermal; IM – intramuscular; IPC – Institut Pasteur du Cambodge; mAbs – monoclonal antibodies; NR – not reported; RIG – rabies immunoglobulin.

Notes:

* For unvaccinated individuals categorised as mildly, moderately or severely immunocompromised.

See relevant SmPC.

^ Can be used if there is a vaccine shortage, for example, during an outbreak.

¥ Dose five given on day 30, rather than day 28.

In five of the selected countries (Denmark, France, Germany, Scotland and the UK),[2, 3, 23-26] and for the WHO, PEP for immunocompromised individuals was recommended as outlined in Table 4 regardless of the individual's rabies vaccination history. In Australia and Belgium, PEP was recommended for specific groups considered to have mild or moderate immunocompromise comprised two doses of vaccine (day 0 and day 3) with follow-up serological testing, and no administration of HRIG.[21, 36] For all other immunocompromised individuals in these countries, recommendations were as outlined in Table 4. In the Netherlands, the two-dose vaccine regimen plus HRIG and potentially serology (depending on expert advice) was recommended for those who were

vaccinated when immunocompetent; otherwise, treatment as per Table 4 was recommended.[27]

5.2.6 Breakthrough infections

Breakthrough rabies infections, while uncommon, offer important insights into the limitations and challenges of PEP. Such cases reaffirm that PEP is effective when administered correctly and promptly, but its success depends on strict adherence to recommended protocols. A 2023 systematic review of rabies breakthrough infections identified 52 articles describing 122 breakthrough infections between 1980 and 2022.[37] While severe wounds involving multiple wound sites or bites to the head, face, or neck were common in breakthrough infection cases, deviations from core wound cleaning and vaccination practices were reported in 68 (56%) of the 122 cases. With respect to vaccination, issues identified by researchers included administration of the vaccine into the gluteal muscle in seven cases (10%), incomplete vaccine series in 17 cases (25%) and incorrect regimen in two cases (3%). In five cases (7%) details on vaccine completion and regimen were unknown and in 32 cases (47%) rabies symptoms developed before the vaccine series could be completed. Although not counted as a core practice by researchers, RIG was not administered in 60 out of 117 documented cases (51%), and was potentially administered inappropriately (intramuscularly only, wounds sutured before administering, not all wounds infiltrated) in a further 25 out of 117 cases (21%).

Immunosuppressive conditions including liver cirrhosis secondary to alcoholism, chronic lymphoproliferative leukaemia and uncontrolled diabetes were present in five cases with deviations from core practices and in three cases without deviations from core practices. Additional reasons outside of PEP practices proposed by case study authors for breakthrough infection included inoculation of the virus into highly innervated tissue or nerves, which occurred in 18% of documented cases and the severity of the bites, particularly those involving the head or neck. Concurrent medications such as anti-malarials or ketamine were highlighted in two cases, while possible systemic failures in PEP administration were highlighted in a further two cases, as two fatal infections occurred in rapid succession at the same clinic. These findings highlight the importance of timely and appropriate PEP care, and that in rare cases with high-risk exposure, infection can occur despite appropriate PEP.

5.3 Domains 3 to 7: Implementation considerations

Evidence and discussion relating to values and preferences of the target population, equity, resource use, acceptability and feasibility are highly interconnected in the context of the implementation of rabies PEP.

As outlined previously in Table 1, the number of vaccine doses, volume of vaccine, visits and their timings, and total number of days required to complete PEP are determined by the choice of vaccine schedule and route of administration. The WHO has stated that the choice of PEP schedule should consider feasibility, for example, with respect to cost, number of doses, time, and adherence.[7] The choice may also depend on the clinical settings in which PEP may be administered and patient preferences; for example, the training and experience levels of healthcare professionals in IM and or ID administration of vaccines, and the timing and number of visits required by patients to complete PEP. Such factors relating to implementation may be considered to be of particular importance to decision-making in the context of the comparable immunogenicity between WHO-recommended vaccine regimens, as outlined in section 5.2.2.

Acceptability and feasibility considerations, and particularly the organisational contexts in which rabies PEP is implemented, are relevant to a decision to recommend one or more than one vaccine regimen for a specific target population. For example, a single recommended regimen may facilitate clear messaging to and consistent practice among healthcare professionals who administer rabies PEP infrequently and may not have a dedicated contact point for expert advice. For unvaccinated, immunocompetent individuals, more than one rabies vaccine regimen was recommended in six of the nine selected countries (Belgium, Denmark, France, Germany, Netherlands, and Portugal).[22-28] Expert advice regarding rabies PEP was available at national level in four of these countries (Belgium, Denmark, Netherlands, and Portugal) while in France, PEP was reported to be provided in specific anti-rabies centres. Information regarding the availability of expert advice was not identified for Germany.[25, 26] In three countries (Australia, Scotland, and the UK),[2, 3, 21] only one regimen was recommended for this population, the reduced Essen regimen. Specific contact points for expert advice were outlined in guidelines applicable in the UK and Scotland, whereas no such information was identified for Australia.

In one of the selected countries (the UK), guidelines made provision for flexibility in the timing of doses within a recommended vaccine schedule. Specifically, UKHSA guidelines stated:

> If a person is travelling and has difficulty in achieving the specified interval for PET [post-exposure treatment], it is most important to deliver the first three vaccines within plus or minus one day.[2]

In the UKHSA-recommended four-dose reduced Essen IM regimen, this refers to the vaccine doses due on day 0, day 3, and day 7. No other selected country or the WHO specified similar recommendations regarding flexibility in the reduced Essen regimen.

The UKHSA also recommended that, in cases where a dose has been missed or the timing of a dose has been compromised, the next dose should be considered as the missed dose, and subsequent intervals between doses should be readjusted accordingly.[2] Similar recommendations were in place in Portugal, including the recommendations to maintain minimum intervals between subsequent vaccine doses in the schedule.[28] The recommendations in the UK and Portugal to resume vaccination in the case of delayed doses, rather than restarting the schedule, are in line with WHO recommendations.[7]

6 Working Group and Committee considerations

The Rabies WG and the Committee agreed that risk assessment of patients presenting with potential rabies exposures should be carried out in accordance with the relevant guidelines issued by the NHPO. Therefore, NIAC's updated recommendations relate only to PEP, where indicated based on risk assessment.

Overall, NIAC members highlighted the importance of implementation considerations in the development of updated recommendations, specifically in the context of the regionalisation of rabies PEP services in Ireland and the absence of a formalised national contact point for expert advice on rabies PEP. Where published data and international recommendations supported several potential options, NIAC had a preference for those that aimed to maximise clarity and consistency in messaging, and ease of implementation.

In line with the WG's proposals, NIAC agreed to continue to issue a preferential recommendation for IM rabies vaccine regimens over ID regimens for PEP, and to recommend a single IM PEP regimen, the reduced Essen regimen (that is, four doses of rabies vaccine, one dose administered on each of day 0, 3, and 7, and one dose administered between days 14 to 28). It was noted that the recommendation of a single IM regimen is based on feasibility rather than concerns about efficacy or safety. Similarly, the preference to recommend IM over ID administration was based on the wide range of potential rabies PEP providers in Ireland and the associated extensive

training requirements needed to safely implement ID vaccination for PEP. NIAC noted that the available evidence demonstrates comparable immunogenicity, regardless of route of administration, and acknowledged that other established vaccine regimens recommended by the WHO and used internationally are also acceptable if started abroad. The WG and Committee noted the equity considerations associated with using IM regimens, which involve greater volumes of rabies vaccine than ID regimens, in the context of global shortages of rabies vaccines.

NIAC agreed to recommend the five-dose Essen regimen (one dose administered on each of days 0, 3, 7, 14, and 28) for immunocompromised patients, plus administration of HRIG. This recommendation is based on published immunogenicity data, and in line with international recommendations in several countries, including the UK. In light of evidence suggesting that the immune response to rabies vaccines may be somewhat unpredictable in immunocompromised patients, the WG and Committee agreed that RVNA testing is advisable in this population to confirm that an adequate response has been mounted. Considering the likely time to receive test results and administer a further vaccine dose, if required, the Committee agreed that testing should ideally take place on the same day as the final dose of the recommended schedule, or as soon as possible after the final dose. The Committee noted that a degree of flexibility around the recommended timing of testing would be important as rabies PEP may be administered in a variety of clinical settings with varied arrangements for access to phlebotomy.

The need for flexibility to facilitate implementation across clinical settings informed NIAC's recommendation that doses two and three of the reduced Essen or Essen regimens may be administered within plus or minus one day of the recommended schedule. The Committee emphasised the importance of administering the first dose of rabies vaccine as soon as possible after exposure. The Committee agreed that adherence to the recommended vaccine schedule is strongly advised, yet acknowledged that, for operational reasons, strict adherence may be challenging to achieve in all cases. The Committee noted that the approach outlined in UKHSA and Public Health Scotland guidelines, providing for limited flexibility in the timings of dose two and or dose three of the schedule, could offer a reasonable level of flexibility in the current Irish context.

Regarding HRIG administration, operational challenges with respect to delivery out of hours were also highlighted. It is broadly accepted that for very high-risk exposures (such as severe and multiple bites to the neck or bites from a confirmed rabid animal) HRIG should be administered as soon as possible and within 12 hours of reporting.

However, it was proposed that for other exposures, if presenting out of hours, HRIG may be deferred until the following day. The Committee emphasised that delays in obtaining access to HRIG should not result in delayed administration of the first dose of rabies vaccine.

The need for clear guidance for healthcare professionals across diverse clinical settings, including out-of-hours services, informed NIAC's decision to include a list of sample patient groups considered to be immunocompromised, in addition to specifying that immunocompromised status in some cases may be based on the opinion of the patient's treating specialist. Similarly, NIAC's decision to issue a recommendation regarding PEP for partially vaccinated individuals (that is, those who have received less than two doses of rabies vaccine previously) was also informed by the preference for clear and unambiguous guidance. The Committee noted that limited data were available regarding immune response to rabies vaccination in older adults (that is, those aged 65 years and older).

The majority of patients presenting for PEP in Ireland are likely to have started their vaccine course abroad. NIAC agreed that it is acceptable to use WHO-recommended vaccine types (that is, cell culture and embryonated egg-based rabies vaccines) and regimens (including IM and ID regimens) interchangeably, if required, noting that available data and WHO recommendations support interchangeability between routes of administration (IM and ID). For those who have commenced PEP abroad, the Committee noted that it is only necessary to restart the rabies vaccine schedule if the vaccine administered abroad was not of a WHO-recommended type (for example, nerve tissue rabies vaccine) or if it is not possible to identify the type of rabies vaccine administered abroad (for example, if no documentation, packaging or patient-reported information regarding vaccine type is available).

7 Conclusion

The delivery of appropriate and timely rabies PEP is effective at preventing death from rabies, an almost universally fatal illness. Clinical considerations can be complex, and clinicians managing rabies-prone exposures should be supported by clear, practicable and safe guidance. This has become particularly important in Ireland where there is no longer one central expert providing rabies advice to clinicians. These updated recommendations, which aim to support the delivery of rabies PEP in a safe and timely manner, are based on the available evidence, international recommendations and context-specific implementation issues.

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Declarations of Interest

These recommendations have been developed by NIAC (list of Committee members), with support provided by the Rabies Working Group (list of members) and the NIAC Secretariat (list of members).

Declarations of Interest were reviewed by the NIAC Chair and by the Director of HTA as per NIAC's Terms of Reference and Standard Operating Procedures. No relevant conflicts of interest were identified.

It is noted that general practices may derive a small portion of their income from administration of vaccines.

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Appendices

Appendix 1. NHPO INTERIM Guidelines on Post-exposure Assessment and and Treatment of Rabies-Prone Exposures (August 2025)[1]

Category of exposure is determined separately depending on whether the exposure was to a:

1. terrestrial animal overseas (or to an imported terrestrial animal in Ireland/UK) or
2. bat, given differences in the way risk is assessed for terrestrial animals and bats (see **Table A**).

Table A1. Category of exposure

Category	Terrestrial Mammals	Bats
1	No physical contact with saliva **Examples:** - Touching, stroking, or feeding animals - Animal licks on intact skin - Exposure to animal blood, urine or faeces	No direct physical contact with bat's saliva or urine (when there is a reliable exposure history) **Examples:** - Touching a dead bat - Touching a bat while protected by a barrier (e.g. boot, shoe, protective clothing)
2	Minimal contact with saliva, no evidence of transdermal inoculation or mucosal exposure **Examples:** - Bruising or abrasions/scratches without bleeding - Nibbling uncovered skin - Licks to broken skin (e.g. insect bites or scratches) - Bites that do not break the skin	Uncertain or potentially unrecognised physical contact **Examples:** - Handling a live bat without protective clothing (e.g. gloves) - Bat tangled in hair - Waking to find a bat in the room (Ireland/UK/elsewhere) - Potential contact with a bat in Ireland/UK in someone unable to give accurate history (e.g. intoxicated, young child, mentally impaired)
3	Direct contact with saliva **Examples:** - Cuts/lacerations - Bites that break the skin - Contamination of mucous membranes with saliva (e.g. licks)	Direct physical contact with bat's saliva or urine **Examples:** - All bites and scratches - Contamination of mucous membranes with saliva or urine

The composite rabies risk is estimated using the exposure category estimated above (Table A1) along with a combined country/animal risk (Table A2), estimated by using information on the country in which the potential rabies prone exposure occurred and the mammal species using the UKHSA's rabies risk levels in terrestrial animals by country.[12]

Table A2. Estimation of composite rabies risk (adapted from NHPO)[1]

Combined country/animal risk	Category 1 exposure	Category 2 exposure	Category 3 exposure
No risk§	Green	Green	Green
Low risk	Green	Amber	Amber
High risk	Green	Amber	Red
Confirmed rabid animal*	Green or amber	Red	Red

Notes: § **NB**: no risk refers to countries that have no risk for terrestrial rabies – all countries are at least **low risk** for bat rabies.
* Urgent advice should be sought form Public Health who will work with DAFM in assessing and managing the incidents.

Appendix 2. Immunocompromised patients

Immunocompromised includes patients in the following categories:

- Patients living with primary immunodeficiency (as described in Chapter 3 of the Immunisation Guidelines of Ireland).[38]
- Patients living with HIV with a CD4+ count <200 (Adults) or CD4+ percentage <15% (Children).
- Patients post solid organ transplant or haematopoietic stem cell transplant.
- Patients who have recently received or are currently receiving immunomodulatory therapy, including immunosuppressive dosing of steroids as outlined in Table 3.7 (Immunomodulatory and immunosuppressing treatment requiring deferral of live vaccination) of Chapter 3 of the Immunisation Guidelines of Ireland.[38]

This list is not exhaustive; there may be patients outside of these groups who should be considered immunocompromised for the purpose of rabies PEP. Where there is doubt about a patient's ability to mount an adequate rabies vaccine response, advice from the relevant treating specialist should be sought.

Appendix 3. Overview of included literature

Table A3. List of included systematic reviews

First author, year	Type	PEP studies included (n)	Safety	Immunogenicity	Breakthrough infections	Quality of included studies	Funding
Xu, 2021[19]	SR & MA	49	-	✓	-	39% external validity; 36% <3 measurements during follow-up	Non-industry
Schnyder, 2020[17]	SR & MA	12	-	✓	-	NRSIs: median 4 (3-6) out of 7; 30% high RoB for blinding	None
Langedijk, 2018[31]	SR & MA	10	-	✓	-	NRSIs: majority 3-4 out of 7; RoB: 53% high risk for attrition bias	Non-industry
Preiss, 2018[16]	SR & MA	48	✓	✓	-	Unclear; large number low quality	Industry
Kessels, 2019[20]	SR	14	-	✓	-	Not assessed	Non-industry
Whitehouse, 2023[37]	SR	52	-	-	✓	Not assessed	Non-industry
Wang, 2022a[18]	SR & MA	27	✓	✓	-	19% high RoB on 4 domains	Non-industry
Ahmad, 2022[39]	SR	11	✓	✓	-	No studies excluded on quality	None
Moulenat, 2020[40]	SR	26	-	✓	-	Not assessed	Industry
Wang, 2022b[41]	SR & MA	32	✓	✓	-	Unclear; most studies low RoB	Industry

Key: MA – meta-analysis; NRSIs – non-randomised studies of interventions; PEP – post-exposure prophylaxis; RoB – risk of bias; SR – systematic review.

Note: Reviews shaded in grey were not presented to the Working Group, as they were deemed to be less relevant and/or comprehensive than the reviews presented; the review shaded in light blue was provided to the Working Group as supplementary material.

Table A4. List of included primary studies

First author, year	Type	(n)	Population	Relevant study objectives	Outcomes	Main Limitations	Funding
Parize, 2020[33]	RR	28	IC patients	Factors influencing seroconversion by dose 4 (Essen)	RVNA titres	Small sample size	None
Banović, 2024[35]	RR	601	PEP recipients Serbia	Factors influencing seroconversion by dose 4 (Essen)	RVNA titres	No Day 0 titre assessment	Industry
Quiambao, 2022[32]	RT	570	2-64 yr olds Philippines	Comparison: PEP regimens, administration routes	RVNA titres, AEs	Timing of titre assessment	Industry
Hens, 2024[42]	RR	317	PEP recipients Belgium	Comparison: delayed 2, 4 or 5 dose PEP ±RIG regimens	RVNA titres	Inclusion bias with respect to RIG	None
Auerswald, 2023[43]	RT	210	PEP recipients Cambodia	Comparison: IPC ID vs reduced Essen IM regimens	RVNA titres	No long-term follow-up	Industry
Quiambao, 2020[44]	RT	397	≤50 yr olds Philippines	Comparison: 1 week, 4 site vs TRC ID regimens at 5yrs	RVNA titres, AEs	ID regimens only	Industry
Matson, 2020[45]	RT	118	18-75 yr olds USA	Comparison: 2 different HRIG products plus Rabipur	RVNA titres, AEs	Unlicensed HRIG product	Industry
Pineda-Peña, 2024[46]	RT	638	≥18 yr olds France	Comparison: new PVRV vs Verorab or Imovax ±RIG	RVNA titres, AEs	New unlicensed vaccine	Industry
Soentjens, 2019[47]	RT	303	18-54 yr olds Belgium	Comparison: single visit 2 dose vs single visit 4 dose PEP	RVNA titres, AEs	ID regimens only	NIF
Haradanahalli, 2021[48]	NRCC	70	PEP recipients India	Comparison: 4 dose vs 5 dose IM Essen regimen	RVNA titres, AEs	Small sample size, ERIG	None

Key: AEs = adverse events; ERIG = equine rabies immunoglobulin; HRIG = human rabies immunoglobulin; IC = immunocompromised; ID = intradermal; IPC = Institute Pasteur du Cambodge; IM = intramuscular; NIF = non-industry-funded; NRCC = non-randomised comparative controlled study; PC = prospective cohort study; PEP = post-exposure prophylaxis; RIG = rabies immunoglobulin; RR = retrospective review; RT = randomised trial; RVNA = rabies virus-neutralising antibodies; TRC = Thai Red Cross.

Note: Studies shaded in grey were not presented to the Working Group, as they either aligned with systematic review findings or were less relevant to research questions; the studies shaded in light blue were provided to the Working Group as supplementary material.

Table A5. List of included grey literature

Country	Author	Year	Title
Australia	ATAGI	2025	Australian Immunisation Handbook: Rabies and other lyssaviruses[21]
Belgium	SHC	2019	Vaccination against rabies CSS 9499 (revision 8818) - February 2019[22]
	SHC	2019	Vaccination of immunocompromised or chronically ill children and/or adults[36]
Denmark	SSI	2025	Rabies: Post-exposure prophylaxis[23]
	SSI	2023	Rabies[49]
	SSI	2025	Rabies vaccine (Rabipur)[50]
	SSI	2025	Rabies vaccine (Verorab)[51]
France	HAS	2018	Rabies vaccination for post-exposure prophylaxis[24]
	HCSP	2013	Rabies vaccinations and post-exposure prophylaxis. Recommendations. Notice and Report. [52]
Germany	STIKO	2025	Recommendations of the Standing Committee on Vaccination at the Robert Koch Institute 2025[25]
	STIKO	2024	Recommendations of the German Standing Committee on Vaccination (STIKO) and the German Society for Tropical Medicine, Travel Medicine and Global Health (DTG) on travel vaccinations[26]
Netherlands	RIVM	2016 (last updated 2025)	Rabies | LCI guideline[27]
Portugal	DGS	2025	Regulation 001/2025: Pre- and post-exposure prophylaxis of the rabies virus. Procedures for accessing the National Strategic Reserve of Rabies Immunoglobulin[28]
UK	UKHSA	2023	Guidelines on managing rabies post exposure (January 2023)[2]
	UKHSA	2025	Interim recommendations for human rabies immunoglobulin (HRIG) use[53]
	UKHSA	2023	The Green Book – Chapter 27: Rabies[54]
Scotland	PHS	2023	Rabies: guidance on pre-exposure and post-exposure measures for humans in Scotland Version 2.1[3]
N/A	WHO	2018	Rabies vaccines: WHO position paper – April 2018[7]

Ireland	NIAC	2025	Immunisation Guidelines for Ireland: Chapter 18 – Rabies[4]
	HSE: NHPO	2025	INTERIM Guidelines on Post-exposure Assessment and Treatment of Rabies prone Exposures (August 2025)[1]
	HSE: NHPO	2025	Risk Assessment for Patients who have commenced Rabies PET in Another Country[55]
	HSE: NHPO	2025	Post-exposure Pathway for Human Rabies Immune globulin (HRIG) administration if HRIG is indicated following Risk Assessment[56]

Key: ATAGI – Australian Technical Advisory Group on Immunisation; DGS – Direção-Geral da Saúde; HAS – Haute Autorité de Santé; HCSP – Haut Conseil de la Santé Publique; HSE – Health Service Executive; LCI – Landelijke Coördinatie Infectieziektebestrijding; NHPO – National Health Protection Office; NIAC – National Immunisation Advisory Committee; PHS – Public Health Scotland; RIVM – Rijksinstituut voor Volksgezondheid en Milieu; SHC – Superior Health Council; SSI – Statens Serum Institut; STIKO – Ständige Impfkommission; UKHSA – UK Health Security Agency; WHO – World Health Organization.

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