

**Australian Technical Advisory Group on Immunisation**

**Public consultation on changes to the recommended use of the rabies vaccine**

The Australian Technical Advisory Group on Immunisation (ATAGI) is consulting with stakeholders on proposed changes to rabies vaccination recommendations for inclusion in *The Australian Immunisation Handbook*, with an intention to submit the recommendations to the National Health and Medical Research Council (NHMRC) for its approval under section 14A of the *National Health and Medical Research Council Act 1992.*

This draft includes new recommendations and the rationale for the proposed changes. You are invited to make a submission on the draft recommendations by 18 November 2020. In particular, ATAGI is seeking comments on the following:

* Are there additional potential benefits, harms or unintended consequences which could arise from the proposed changes to the use of the rabies vaccine, not already outlined, and how likely are they to occur?
* Are there additional clinical or implementation considerations which need to be outlined?

Should you require additional information please contact ATAGI Secretariat on [atagi.secretaria](mailto:atagi.secretariat@health.gov.au)[t@health.gov.au.](mailto:t@health.gov.au)

Changes to the recommended use of   
rabies vaccines

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# Plain-language summary

Rabies is a disease caused by rabies virus or other lyssaviruses. The disease affects the brain and spinal cord, and is usually deadly if not treated quickly.

Rabies spreads mainly through bites or scratches from infected animals. Animals that can carry rabies include mammals such as dogs, cats, monkeys and bats.

Animals in Australia do not carry the rabies virus, but Australian bats can carry lyssavirus. Australian bat lyssavirus is a virus that is similar to rabies, and causes the same disease.

People who are at risk of rabies include:

people who have contact with wild or domestic animals in overseas countries that have rabies

people in Australia who have direct contact with bats, or who work with live lyssaviruses in a laboratory

Vaccination helps protect against rabies. Rabies vaccine can be given to people who:

might be exposed to rabies virus in the future (called pre-exposure prophylaxis)

have already potentially been exposed to rabies virus (called post-exposure prophylaxis)

Some people who may have been exposed to rabies virus may also receive HRIG (human rabies immunoglobulin) if they have not had rabies vaccine before.

The recommendations for rabies vaccination in Australia are changing. This is in line with the latest clinical studies and advice from the World Health Organization. The updated information:

allows pre-exposure rabies vaccine to be given between the layers of the skin (intradermally) or into a muscle (intramuscularly)

allows the required multiple pre-exposure doses to be given in a shorter timeframe for some travellers

recommends booster doses for people at ongoing risk of exposure to rabies virus or lyssavirus in their jobs 1 year after their 1st vaccine course, and every 3 years after that

specifies the number of vaccine doses and HRIG for people who are mildly immunocompromised and people who are severely immunocompromised

adds clarity to supporting information for several current recommendations, to help immunisation providers and public health specialists make evidence-based decisions about rabies vaccination

Rabies vaccine is not funded under the National Immunisation Program, but states and territories may fund post-exposure prophylaxis for some people.

# Summary of revised recommendations

The key changes to rabies vaccine recommendations are:

the intradermal route is accepted for pre-exposure prophylaxis, as well as the intramuscular route

an accelerated schedule is accepted for pre-exposure prophylaxis

a booster dose is recommended for people at ongoing occupational risk 1 year after the 1st pre-exposure prophylaxis dose, and every 3 years after that

a distinction is made in post-exposure prophylaxis regimens for people who are severely immunocompromised, for whom additional doses and/or testing are recommended (as a guide, people who are severely immunocompromised are those for whom live vaccines are contraindicated)

**Recommendation to be deleted**

* Rabies pre-exposure prophylaxis by the intradermal route is not routinely recommended

**New recommendation**

* People with potential category II or III rabies virus exposure are recommended to receive rabies vaccine as post-exposure prophylaxis — *Merges existing information from the following current recommendations to provide a single consolidated recommendation with specific guidance for different exposures and medical histories:*

– Immunocompetent people with potential rabies virus exposure who have not previously received rabies vaccine are recommended to receive 4 doses of rabies vaccine as post-exposure prophylaxis, with or without rabies immunoglobulin

– People who are immunocompromised with potential rabies virus exposure who have not previously received rabies vaccine are recommended to receive at least 5 doses of rabies vaccine as post-exposure prophylaxis, with or without rabies immunoglobulin

– People with potential rabies exposure who have been previously vaccinated are recommended to receive 2 doses of rabies vaccine as post-exposure prophylaxis, without rabies immunoglobulin

– Some people with a potential exposure to rabies virus or other lyssaviruses who have not previously received rabies vaccine are recommended to receive rabies immunoglobulin in addition to rabies vaccine as post-exposure prophylaxis

**Recommendations to be merged**

* Post-exposure prophylaxis for rabies must include wound management — *Merged with ‘Anyone who has potentially been exposed to rabies virus or other lyssaviruses is recommended to receive post-exposure prophylaxis with rabies vaccine and, in some cases, rabies immunoglobulin’*
* People who have received rabies vaccine and are immunocompromised; those who received the vaccine intradermally; or those who are at ongoing risk of rabies are recommended to have serological testing — *Merged into supporting information under several recommendations*

**Recommendations with updated supporting information**

* Anyone who has potentially been exposed to rabies virus or other lyssaviruses is recommended to receive post-exposure prophylaxis with rabies vaccine and, in some cases, rabies immunoglobulin
* People who work with bats, laboratory workers who work with live lyssaviruses and some people who travel to rabies-enzootic areas are recommended to receive rabies vaccine as pre-exposure prophylaxis
* People with ongoing occupational exposure to lyssaviruses are recommended to receive booster doses of rabies vaccine
* People with potential rabies exposure who started post-exposure prophylaxis overseas are recommended to complete the rabies vaccine course in Australia

**Recommendations that are not changing**

* Travellers to rabies-enzootic regions are recommended to have a risk assessment to guide vaccination decision-making, and all travellers should avoid exposure to rabies virus and other lyssaviruses
* Women who are pregnant or breastfeeding are recommended to receive rabies vaccine after potential exposure to rabies

# Background

The Australian Technical Advisory Group on Immunisation (ATAGI) advises the Australian Government on clinical recommendations for vaccinations. ATAGI is proposing changes to the recommendations for the use of rabies vaccines.

The proposed changes reflect the current best clinical practice to prevent rabies. The revised recommendations and supporting information will be published online in the [Australian Immunisation Handbook](https://immunisationhandbook.health.gov.au/).

Rabies is a zoonotic disease caused by exposure to saliva or nerve tissue of an animal infected with rabies virus or other lyssaviruses. The clinical diseases caused by classical rabies virus and other lyssaviruses are indistinguishable. The term ‘rabies’ refers to disease caused by any of the known lyssavirus species.

Australia is not a rabies-enzootic country. Exposure to classical rabies virus can occur from terrestrial mammals in rabies-enzootic countries. Bats anywhere in the world (including Australia) are a potential source of lyssaviruses and a potential risk for acquiring rabies.

The level of risk of acquiring rabies, and therefore the post-exposure treatment required, depends on the type of exposure (category I: no exposure; category II: exposure; or category III: severe exposure), the person’s vaccination history and the person’s immune status.

Rabies vaccine is recommended as post-exposure prophylaxis for anyone who has had a category II or III potential exposure.

Rabies vaccine is recommended as pre-exposure prophylaxis for the following groups at risk of exposure to rabies or other lyssaviruses:

people who have direct contact with bats

people who travel to rabies-enzootic regions, based on a risk assessment

laboratory workers who work with live lyssaviruses

Rabies vaccine is not funded under the National Immunisation Program, but states and territories may fund post-exposure prophylaxis for some people.

# Rationale

## Updated WHO position

In 2018, the World Health Organization (WHO) updated its position on rabies immunisation.1 The revised WHO position included updates to the recommended route of administration, vaccination schedules and use of rabies immunoglobulin (RIG). ATAGI has considered these changes in the Australian context, as follows.

### Intradermal vaccination

The revised WHO position advocates intradermal vaccine administration for both pre- and post-exposure prophylaxis, and for booster doses. This requires less vaccine per dose than intramuscular administration, and is therefore dose sparing and cost saving. This can have important economic advantages in rabies-enzootic areas.

The intradermal technique is not commonly used in Australia. Incorrect administration of rabies vaccine by the intradermal route may mean the person is not adequately protected, which can have fatal consequences, particularly if the person may have been exposed to rabies virus or a lyssavirus. ATAGI considers that the intradermal route should only be used by suitably qualified and experienced providers, and only for pre-exposure prophylaxis, not post-exposure prophylaxis or booster doses.

In addition, ATAGI considers that dose sparing is a lesser consideration in Australia because rabies vaccination uncommon. An opened vial of vaccine must be discarded after 8 hours; so many clinics are not likely to vaccinate enough people in one day (5 to 8 people) for dose sparing to make a substantial difference.

### Accelerated vaccination schedules

The revised WHO position allows for accelerated vaccination schedules for both pre- and post-exposure prophylaxis. These schedules reduce the number of vaccine doses and the number of clinic visits, and may increase access to and compliance with rabies vaccination schedules.

ATAGI considers that an accelerated schedule for pre-exposure prophylaxis is acceptable, but the standard schedule is preferred. The accelerated schedule may be suitable for travellers who do not have enough time before travel to complete the standard schedule. However, immunity wanes more quickly after accelerated schedules, and ATAGI considers that a booster dose is needed if the person is at ongoing risk.

ATAGI does not consider that accelerated schedules for post-exposure prophylaxis are acceptable in the Australian context, as the only WHO-endorsed regimens use intradermal vaccination. However, doses given overseas as post-exposure prophylaxis, either intradermally and/or as part of an accelerated schedule, are accepted as valid doses.

### Use of rabies immunoglobulin for post-exposure prophylaxis

#### People who are immunocompromised

The UK Joint Committee on Vaccination and Immunisation (JCVI) provides 2 levels of classification of immunocompromise for the use of rabies vaccines and RIG. The JCVI specifies that people with severe immunocompromise are recommended to have a full rabies vaccine schedule and RIG for post-exposure prophylaxis after a category II or III exposure, regardless of past vaccination. Severe immunocompromise is defined as those for whom live vaccines are contraindicated.2 ATAGI considers that the JCVI recommendation and definition of severe immunocompromise are appropriate for the Australian context.

ATAGI notes that the revised WHO position recommends that people who are immunocompromised and have had a category II or III exposure should receive RIG, even if they have received pre-exposure prophylaxis. The WHO states that people with an immunocompromising condition who are monitored and well managed should not be considered immunocompromised, as they can respond adequately to rabies vaccine. However, the WHO does not further classify immunocompromising conditions. It only describes people with HIV who are not receiving antiretroviral therapy or whose CD4+ cell count is below the minimum cell count criteria as immunocompromised.

#### People who have had a category II exposure

ATAGI considers that RIG is indicated for unvaccinated people with a category II exposure to bats, but not for unvaccinated people with a category II exposure to terrestrial animals. This is because wounds from bats may be smaller, or even not apparent, which warrants a more cautious approach to potential exposure.

ATAGI notes that, in contrast, the WHO position paper recommends that RIG is not indicated for immunocompetent people who have had a category II exposure, whether or not they received pre-exposure prophylaxis and regardless of the source of animal exposure.

## Updated clinical evidence

In addition to reviewing the alignment with the revised WHO position on rabies vaccination, ATAGI also considered updated clinical evidence relating to the timing and frequency of booster vaccinations for people at ongoing occupational risk.

ATAGI therefore proposes the following changes to the Handbook recommendations and supporting information.

# Recommendation to be deleted

ATAGI currently recommends the following:

Rabies pre-exposure prophylaxis by the intradermal route is not routinely recommended

ATAGI proposes that this recommendation be deleted.

## Evidence for deleting this recommendation

Studies show that intradermal vaccination for pre-exposure prophylaxis results in rabies virus neutralising antibody (VNAb) titres >0.5 IU per mL and adequate seroconversion rates after a standard 3‑dose schedule (days 0, 7, and 21 or 28).3-6

One potential benefit of allowing intradermal pre-exposure prophylaxis is that less vaccine is used per dose than for intramuscular vaccination. This means potentially lower cost for the person being vaccinated, which may increase uptake of pre-exposure prophylaxis among travellers.

The accelerated 4-dose intradermal schedule (2 doses at each of 2 visits) provides greater flexibility than the standard schedule. In particular, it provides the option of a 7‑day-accelerated schedule for travellers, which can increase compliance with rabies pre-exposure prophylaxis in travellers who present for immunisation shortly before travel.

Several conditions should be met before administering intradermal vaccination. See ‘People who work with bats, laboratory workers who work with live lyssaviruses and some people who travel to rabies-enzootic areas are recommended to receive rabies vaccine as pre-exposure prophylaxis’.

# Updated information: vaccination before exposure to rabies virus and other lyssaviruses (pre‑exposure prophylaxis)

**People who work with bats, laboratory workers who work with live lyssaviruses and some people who travel to rabies-enzootic areas are recommended to receive rabies vaccine as pre‑exposure prophylaxis**

Pre-exposure prophylaxis with rabies vaccine is recommended for:

* people who may receive bites or scratches from bats — this includes bat handlers; veterinarians and veterinary nurses; wildlife officers, wildlife carers and zookeepers; wildlife researchers; and others who come into direct contact with bats in any country, including Australia
* research laboratory workers working with any live lyssaviruses
* people who will be travelling to, or living in, rabies-enzootic areas — give pre-exposure prophylaxis after a risk assessment that considers the likelihood that the person will interact with animals and their access to emergency medical attention

**Recommended schedule — intramuscular route**

The recommended pre-exposure prophylaxis schedule for rabies or other lyssavirus infection comprises 3 vaccine doses given by the intramuscular route:

* 1st dose on day 0
* 2nd dose on day 7
* 3rd dose on day 21–28

**Alternative route of administration — intradermal route**

The intradermal route may be used by suitably qualified and experienced providers. This route is only to be used for pre-exposure vaccination of immunocompetent people. The schedule comprises 3 doses of 0.1 mL each, given by the intradermal route:

* 1st dose on day 0
* 2nd dose on day 7
* 3rd dose on day 21–28

The intradermal route is ‘off-label’ use. If intradermal rabies pre-exposure prophylaxis is considered, it is essential that:

* it is given by immunisation providers who have expertise in, and regularly practise, the intradermal technique
* it is not given to people who are immunocompromised
* it is not given to people taking chloroquine, or other antimalarials that are structurally related to chloroquine (such as mefloquine or hydroxychloroquine), at the time of vaccination or within 1 month after vaccination
* the immunisation provider discards any remaining vaccine after 8 hours

Alternative schedule — accelerated schedules

Travellers who do not have enough time to complete the 21–28-day schedule may receive an accelerated schedule, but the standard 21–28-day schedule is preferred.

There are 2 options for administering an accelerated schedule:

* accelerated 3‑dose intramuscular schedule:

– 1st dose on day 0

– 2nd dose on day 3

– 3rd dose on day 7

* accelerated 4‑dose intradermal schedule comprising 2 vaccine doses at each visit:

– 2 × 0.1 mL injections given at different sites on day 0

– 2 × 0.1 mL injections given at different sites on day 7

These accelerated schedules provide protection for short-term travel to rabies-enzootic areas. If further travel to rabies-enzootic areas is planned after 1 year, antibody levels may no longer be adequate. A single intramuscular booster dose should be given 1 year after the 1st dose of pre-exposure prophylaxis.

**Booster doses**

Booster doses of rabies vaccine are recommended for immunised people who have ongoing occupational exposure to lyssaviruses in Australia or overseas. See ‘People with ongoing occupational exposure to lyssaviruses are recommended to receive booster doses of rabies vaccine’.

**Serological testing for people who received pre-exposure prophylaxis by the intradermal route**

If pre-exposure prophylaxis was received by the intradermal route, check the rabies antibody level 2–‍4 weeks after finishing the pre-exposure course to ensure that VNAb (rabies virus neutralising antibody) levels are ≥0.5 IU per mL. Seek expert advice from state or territory health authorities if the titre is <0.5 IU per mL.

**Serological testing for people who are immunocompromised**

People who are immunocompromised should have their VNAb titres checked 2–‍4 weeks after the 3rd intramuscular dose of vaccine in a pre-exposure prophylaxis schedule. Give a further dose if the titre is <0.5 IU per mL, and repeat serological testing. If the titre remains <0.5 IU per mL, seek advice from state or territory health authorities.

**Rationale for pre-exposure prophylaxis**

Pre-exposure prophylaxis simplifies how a potential subsequent exposure to rabies virus or Australian bat lyssavirus is managed because:

* the person needs fewer doses of rabies vaccine in the post-exposure phase
* the person does not need rabies immunoglobulin (RIG) unless they are severely immunocompromised

This is particularly important because RIG — either human (HRIG) or equine (ERIG) — can be difficult to obtain, is expensive and its safety cannot be guaranteed in many rabies-enzootic developing countries. See also ‘Vaccination after potential exposure to rabies virus or other lyssaviruses (post-exposure prophylaxis)’.

## Current recommendation

ATAGI currently recommends the following:

**People who work with bats, laboratory workers who work with live lyssaviruses and some people who travel to rabies-enzootic areas are recommended to receive rabies vaccine as pre‑exposure prophylaxis**

Pre-exposure prophylaxis with rabies vaccine is recommended for:

* people who may receive bites or scratches from bats — this includes bat handlers, veterinarians, wildlife officers and others who come into direct contact with bats in any country, including Australia
* research laboratory workers working with any live lyssaviruses
* people who will be travelling to, or living in, rabies-enzootic areas — give pre-exposure prophylaxis after a risk assessment that considers the likelihood that the person will interact with animals and their access to emergency medical attention

The recommended pre-exposure prophylaxis schedule for rabies or other lyssavirus infection comprises 3 vaccine doses given intramuscularly:

* 1st dose on day 0
* 2nd dose on day 7
* 3rd dose on day 21–28

Although the 3rd dose can be given as early as 21 days, there are no data to support the use of more accelerated schedules for people with limited time before travel to a rabies-enzootic area.

Pre-exposure prophylaxis simplifies how a potential subsequent exposure to rabies virus or Australian bat lyssavirus is managed because:

* the person needs fewer doses of rabies vaccine in the post-exposure phase
* the person does not need rabies immunoglobulin (RIG)

This is particularly important because RIG — either human (HRIG) or equine (ERIG) — can be difficult to obtain, and its safety cannot be guaranteed in many rabies-enzootic developing countries. See also Vaccination after potential exposure to rabies virus or other lyssaviruses (post-exposure prophylaxis).

## Key differences

The recommendation about who should receive pre-exposure prophylaxis remains unchanged. The revised and new supporting information for this recommendation includes:

options for intradermal vaccine administration

options for accelerated schedules

guidance for serological testing

added subheadings to help users find the information more easily

## Evidence for the updated information

### Intradermal vaccine administration

It is essential that intradermal vaccination is delivered by immunisation providers who have expertise in, and regularly practise, the intradermal technique.

Correct intradermal vaccine administration requires the vaccine to be delivered into the papillary dermis, which is only 100–300 µm thick.7 If the injection is too deep, the vaccine will be delivered into the underlying subcutaneous tissue. Subcutaneous injection of a 0.1 mL dose as part of a primary vaccination course is less immunogenic than intradermal administration of the same dose.8 Other factors that may contribute to inadequate vaccine delivery include failing to deliver the whole dose of vaccine and retrograde leakage of vaccine up the needle track.9

ATAGI continues to preferentially recommend a 3‑dose intramuscular regimen given over 21–‍28 days. This is because studies show that this regimen consistently leads to a higher magnitude of primary antibody response and longer duration of antibody protection than a 3‑dose intradermal regimen over 21–‍28 days, or other modified regimens.3,4,10‑12

### Accelerated vaccination schedule — intradermal

In developing its 2018 position statement, the WHO reviewed the evidence and concluded that an accelerated 4‑dose schedule for intradermal vaccination was non-inferior to the standard 3‑dose intradermal schedule and was more cost-effective.13

No randomised controlled trials have compared the immunogenicity of the accelerated 4‑dose intradermal schedule with the standard 3‑dose intramuscular schedule. One randomised open-label non-inferiority trial (n = 411) compared the accelerated 4‑dose intradermal schedule with the standard 3‑dose intradermal schedule, and reported a 100% seroconversion rate in both groups of participants at day 35.14 Also, 3 observational studies on intradermal vaccination using the accelerated 4‑dose intradermal schedule showed seroconversion rates (VNAb titre >0.5 IU per mL) of 94–100%.15‑17 This includes 2 studies in Australian travel clinics.15,16

### Accelerated vaccination schedule — intramuscular

One study examined the short-term immunogenicity of the accelerated intramuscular regimen (1 dose on each of days 0, 3 and 7), in combination with Japanese encephalitis (JE) vaccine.18 This group was compared with a standard 3‑dose intramuscular regimen in combination with JE vaccine, and a standalone standard 3‑dose intramuscular regimen. Seroconversion rates were similar (near 100%) in all 3 groups from day 14 after the 1st dose.

However, immunity appeared to wane more quickly in the accelerated rabies/JE recipients from 90 days after vaccination (85% of participants with VNAb >0.5 IU per mL, compared with 99% of standard rabies/JE recipients, and 98% of standalone standard rabies recipients).

### Booster doses

In terms of short- and long-term immune memory response, a 3‑dose intradermal regimen is as effective as a 3‑dose intramuscular regimen, provided the intradermal doses are delivered correctly.19

In people who received an accelerated or other modified pre-exposure prophylaxis regimen (1, 2 or 3 doses, either intramuscular or intradermal), revaccination or post-exposure prophylaxis up to 1 year later produces an effective immune memory response by day 7–‍14. However, there are insufficient data to assess this response for periods longer than 1 year.19

### Intradermal rabies vaccination and concurrent use of chloroquine

Chloroquine taken in the dose recommended for malaria prophylaxis can reduce the antibody response to primary immunisation with intradermal rabies vaccine. In one study among veterinary students, people who received intradermal pre-exposure prophylaxis while taking chloroquine had lower VNAb titres than people who were not taking chloroquine.20

**People with ongoing occupational exposure to lyssaviruses are recommended to receive booster doses of rabies vaccine**

Booster doses of rabies vaccine are recommended for immunised people who have ongoing occupational exposure to lyssaviruses in Australia or overseas.19 See ‘Figure. Booster algorithm for people at ongoing risk of exposure to rabies virus or other lyssaviruses’. This includes:

* **people who work with live lyssaviruses in research laboratories** — these people should have rabies virus neutralising antibody (VNAb) titres measured every 6 months. If the titre is <0.5 IU per mL, they should receive a single intramuscular booster dose. People who are immunocompromised should have their VNAb titre measured 2–‍4 weeks after the booster dose. If the titre is <0.5 IU per mL, they should receive another booster dose. Laboratory staff at ongoing risk should continue to check their VNAb titres every 6 months
* **people with exposure to bats in Australia or overseas, and people who are likely to be exposed to potentially rabid terrestrial mammals overseas** — these people should have a single intramuscular booster dose 1 year after their 1st dose of rabies vaccine pre-exposure prophylaxis. These people should have VNAb titres measured every 3 years after that, and if their VNAb titre is <0.5 IU per mL, they should have a further single intramuscular booster dose. Alternatively, after the 1st booster dose, they can have a further single intramuscular booster dose every 3 years without determining the VNAb titre

Always give booster doses of rabies vaccine by the intramuscular route. Never use the intradermal route to administer booster doses.

To determine whether a person should receive a booster dose of rabies vaccine because their antibody level falls below 0.5 IU per mL, consider:

* their anticipated risk of exposure — that is, if they are routinely handling sick animals or rabies reservoir species in rabies-enzootic areas
* their health status, such as level of immunocompromise or a history of poor vaccine response
* their timely access to vaccination for post-exposure prophylaxis if they are exposed

Figure. Booster algorithm for people at ongoing risk of exposure to rabies virus or other lyssaviruses

This flowchart helps to decide if people at ongoing occupational risk need booster doses of rabies vaccine. 
For laboratory staff at risk, perform serological testing every 6 months.
For veterinary workers, people who handle bats or may need to handle bats, and people who have ongoing exposure to potentially rabid terrestrial animals in rabies enzootic countries, give a single intramuscular booster dose 1 year after pre-exposure prophylaxis. Then perform serological testing or give a booster dose every 3 years from receipt of the 1-year booster dose.
After serological testing, for those who have a virus neutralising antibody titre of at least 0.5 IU/mL, no further action is needed until either there is further exposure (then give post-exposure prophylaxis as per rabies or bat lyssavirus post-exposure algorithms, unless exposure occurs within 3 months of receiving complete post-exposure prophylaxis, when no immediate vaccination is required) or the next serological testing period elapses (then perform serology).
For those with a virus neutralising antibody titre of <0.5 IU/mL, give a single intramuscular booster dose for immunocompetent people. For immunocompromised people, give a single intramuscular booster dose then check serology after 2–4 weeks. If the antibody titre is <0.5 IU/mL, give another booster dose. If further exposure occurs, give PEP as per rabies or bat post-exposure algorithms.

PEP = post-exposure prophylaxis; PrEP = pre-exposure prophylaxis

## Current recommendation

ATAGI currently recommends the following:

**People with ongoing occupational exposure to lyssaviruses are recommended to receive booster doses of rabies vaccine**

People do not need booster doses if they:11

* are travelling to, or living in, an area of high rabies risk, and
* have completed a primary course, either pre- or post-exposure, using either of the currently available cell culture–derived vaccines

Booster doses of rabies vaccine are recommended for immunised people who have ongoing occupational exposure to lyssaviruses in Australia or overseas. See Figure. Booster algorithm for people at ongoing risk of exposure to rabies virus or other lyssaviruses. This includes:

* people who work with live lyssaviruses in research laboratories — these people should have rabies virus neutralising antibody (VNAb) titres measured every 6 months. If the titre is inadequate (<0.5 IU per mL), they should have a booster dose
* people with exposure to bats in Australia or overseas, and people who are likely to be exposed to potentially rabid terrestrial mammals overseas — these people should have VNAb titres measured every 2 years. If the titre is inadequate (<0.5 IU per mL), they should have a booster dose. Alternatively, they can have a booster dose every 2 years without determining the antibody titre

To determine whether a person should receive a booster dose of rabies vaccine because their antibody level falls below 0.5 IU per mL, consider:

* their anticipated risk of exposure — that is, if they are routinely handling sick animals or rabies reservoir species in enzootic areas
* the length of time until the next antibody measurement
* their individual health status, such as level of immunocompromise or a history of poor vaccine response
* their timely access to vaccination if they are exposed

## Key differences

The recommendation itself has not changed. The revised supporting information for this recommendation includes:

recommending a booster dose 1 year after the last dose of the primary pre-exposure prophylaxis series for all people with ongoing occupational exposure to bats or potentially rabid animals (previously only recommended for people with VNAb titre <0.5 IU per mL)

recommending subsequent booster doses for all people with ongoing occupational exposure to bats or potentially rabid animals every 3 years (previously every 2 years), with or without measuring VNAb titre

clarifying that booster doses should only be given by the intramuscular route, not the intradermal route

## Evidence for the updated information

Studies in people at risk of occupational exposure have shown that not all people maintain protective VNAb titres (>0.5 IU per mL) 1 year after pre-exposure prophylaxis. People with ongoing occupational risk of exposure to rabies are recommended to maintain a VNAb titre >0.5 IU per mL to protect them in case of unnoticed exposure.1 This may be particularly relevant for bat handlers, who could be exposed to small amounts of virus through small wounds that may not be noticed. Indirect evidence suggests that maintaining high titres can protect against unrecognised exposures in bat handlers.21

Of people who had a 3‑dose intramuscular pre-exposure prophylaxis regimen (but not a 2‑dose regimen) followed by a booster dose at 1 year, 96–97% maintained VNAb titres >0.5 IU per mL for at least 10 years. A study in bat handlers in the UK showed that all people who had received the 3-dose intramuscular pre-exposure prophylaxis regimen and 1 or more booster doses had VNAb titres >0.5 IU per mL 2 years after the last booster dose.22

Taken together, this evidence suggests that the addition of a 1-year booster to the recommendations for those at risk of occupational exposure may increase the proportion of people with long-lasting protective titres. A repeat booster dose is unlikely to be necessary as early as 2 years after the 1st booster, and may even be harmful, because the immune memory response can be influenced by residual antibodies at the time of revaccination (known as desensitisation).23

# Updated information: vaccination after potential exposure to rabies virus or other lyssaviruses (post‑exposure prophylaxis)

**Anyone who has potentially been exposed to rabies virus or other lyssaviruses is recommended to receive post-exposure prophylaxis with rabies vaccine and, in some cases, rabies immunoglobulin**

Supporting information for this recommendation remains unchanged, except for the table of lyssavirus exposure categories. ATAGI proposes replacing the table of lyssavirus exposure categories with the following table.

Table. Lyssavirus exposure categories

|  |  |  |
| --- | --- | --- |
| Exposure category | Description | Post-exposure prophylaxis management |
| Category I: no exposure | * Touching or feeding animals * Animal licks on intact skin * *Exposure to animal blood, urine or faeces* | * No prophylaxis required if contact history is reliable |
| Category II: exposure | * Nibbling of uncovered skin * Minor scratches or abrasions without bleeding | See the following, depending on the circumstances:   * Figure. Rabies post-exposure prophylaxis: terrestrial animal exposures * Figure. Rabies post-exposure prophylaxis: bat exposures * Table. Completing rabies post-exposure prophylaxis in Australia that started overseas |
| Category III: severe exposure | * Single or multiple transdermal bites or scratches * Contamination of mucous membrane or broken skin with saliva from animal licks * Exposures due to direct contact with bats, *including situations where bites or scratches may not be apparent* | See the following, depending on the circumstances:   * Figure. Rabies post-exposure prophylaxis: terrestrial animal exposures * Figure. Rabies post-exposure prophylaxis: bat exposures * Table. Completing rabies post-exposure prophylaxis in Australia that started overseas |

## Current recommendation

ATAGI currently recommends the following:

Table. Lyssavirus exposure categories

|  |  |  |
| --- | --- | --- |
| Type of exposure | Description | Post-exposure prophylaxis management |
| Category I: no exposure | * Touching or feeding animals * Animal licks on intact skin | No prophylaxis required if contact history is reliable |
| Category II: exposure | * Nibbling of uncovered skin * Minor scratches or abrasions without bleeding | See the following, depending on the circumstances:   * Figure. Post-exposure prophylaxis algorithm for potential exposure to lyssaviruses from a terrestrial animal in a rabies-enzootic area * Figure. Post-exposure prophylaxis algorithm for potential exposure to lyssaviruses from bats in Australia or overseas * Table. Completing post-exposure prophylaxis in Australia that started overseas |
| Category III: severe exposure | * Single or multiple transdermal bites or scratches * Contamination of mucous membrane or broken skin with saliva from animal licks * Exposures due to direct contact with bats | See the following, depending on the circumstances:   * Figure. Post-exposure prophylaxis algorithm for potential exposure to lyssaviruses from a terrestrial animal in a rabies-enzootic area * Figure. Post-exposure prophylaxis algorithm for potential exposure to lyssaviruses from bats in Australia or overseas * Table. Completing post-exposure prophylaxis in Australia that started overseas |

## Key differences

Wording in the table has been updated to align with latest updates to the Communicable Diseases Network Australia national guidelines for rabies virus and other lyssavirus exposures and infections.

**People with potential category II or III rabies virus exposure are recommended to receive rabies vaccine as post-exposure prophylaxis, with or without rabies immunoglobulin**

After managing the wound, give rabies vaccine with or without human rabies immunoglobulin (HRIG), depending on the category and source of exposure. See:

* Table. Vaccinated people: post-exposure rabies treatment based on immune status and exposure category
* Table. Unvaccinated people: post-exposure rabies treatment based on immune status and exposure category
* Figure. Rabies post-exposure prophylaxis: terrestrial animal exposures
* Figure. Rabies post-exposure prophylaxis: bat exposures

If a person’s vaccination status is uncertain because documentation showing a full course of rabies vaccine is not available, give the full post-exposure prophylaxis regimen. Pre- or post-exposure prophylaxis vaccine given intradermally can be considered previous vaccination.

Table. Vaccinated people: post-exposure rabies treatment based on immune status and exposure category

Vaccinated people have evidence of a completed recommended pre-exposure prophylaxis regimen at any time in the past, or have a documented rabies virus neutralising antibody (VNAb) titre of >0.5 IU per mL at any time in the past. For those with a history of partial immunisation, see ‘Incomplete pre-exposure prophylaxis schedule’.

| Immune status | Exposure category | HRIG | Dose 1 (day 0) | Dose 2 (day 3) | Dose 3 (day 7) | Dose 4 (day 14) | Dose 5 (day 28) |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Immunocompetent | Any category II or III | Not needed | Yes | Yes | Not needed | Not needed | Not needed |
| Mildly immunocompromised | Any category II or III | Not needed | Yes | Yes | Not needed | Not needed | Not needed |
| Severely immunocompromised | Any category II or III | Yes | Yes | Yes | Yes | Yes | Yes |

HRIG = human rabies immunoglobulin

Deviations of a few days from this schedule are not thought to be clinically relevant.1

Severely immunocompromised refers to people for whom live vaccines are contraindicated. See Vaccination for people who are immunocompromised.

Table. Unvaccinated people: post-exposure rabies treatment based on immune status and exposure category

| Immune status | Exposure | HRIG | Dose 1 (day 0) | Dose 2 (day 3) | Dose 3 (day 7) | Dose 4 (day 14) | Dose 5 (day 28) |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Immunocompetent | Category II terrestrial animals | Not needed | Yes | Yes | Yes | Yes | Not needed |
| Category II bats and any category III | Yes | Yes | Yes | Yes | Yes | Not needed |
| Mildly immunocompromised | Any category II or III | Yes | Yes | Yes | Yes | Yes | Yes |
| Severely immunocompromised | Any category II or III | Yes | Yes | Yes | Yes | Yes | Yes |

HRIG = human rabies immunoglobulin

Deviations of a few days from this schedule are probably unimportant.1

Severely immunocompromised refers to people for whom live vaccines are contraindicated. See Vaccination for people who are immunocompromised.

Administration of rabies vaccine for post-exposure prophylaxis by the intradermal route is not recommended.

No clinical trial has assessed the efficacy of rabies vaccine, but the rationale supporting a 4‑dose schedule in immunocompetent people is based on 19 studies.24-26 There have been no reported cases in Australia or internationally of vaccine failure in people who have been potentially exposed and have received a complete course of post-exposure prophylaxis.27

**Incomplete pre-exposure prophylaxis schedule**

People who are immunocompetent and have previously received an incomplete pre-exposure prophylaxis schedule of 2 doses can receive the 2‑dose post-exposure prophylaxis schedule described above. Those who have only received 1 dose previously as pre-exposure prophylaxis require 4 doses as post-exposure prophylaxis (similar to those who are unvaccinated).

People who are immunocompromised and received an incomplete pre-exposure prophylaxis schedule should receive post-exposure prophylaxis as for unvaccinated people.

**People who are immunocompromised**

Where possible, stop any immunosuppressive therapy (including corticosteroids) while giving post-exposure prophylaxis. Such treatment may interfere with the development of a protective response from the vaccine. Consult the person’s treating specialist to discuss the feasibility of this.

Measure the rabies virus neutralising antibody titre 2–4 weeks after the last dose. If the titre is <0.5 IU per mL, give another dose. Repeat the serological testing 2–4 weeks after this dose. If the titre is still <0.5 IU per mL, seek advice from state or territory health authorities.

People who are severely immunocompromised (that is, people for whom live vaccines are contraindicated) should always receive a dose of rabies immunoglobulin in addition to rabies vaccine as post-exposure prophylaxis, even if they have previously received rabies vaccine.

**Repeat rabies exposure**

People with a repeat exposure within 3 months of completing previous post-exposure prophylaxis do not need any further vaccine doses and only need wound management.

**Use of human rabies immunoglobulin**

Some people with a potential exposure to rabies virus or other lyssaviruses are recommended to receive HRIG in addition to rabies vaccine as post-exposure prophylaxis. See:

* Table. Lyssavirus exposure categories
* Table. Vaccinated people: post-exposure rabies treatment based on immune status and exposure category
* Table. Unvaccinated people: post-exposure rabies treatment based on immune status and exposure category
* Figure. Rabies post-exposure prophylaxis: terrestrial animal exposures; or
* Figure. Rabies post-exposure prophylaxis: bat exposures

Where indicated, give a dose of HRIG as soon as possible, and within 7 days (168 hours), after the 1st vaccine dose. Do not give HRIG if more than 7 days (more than 168 hours) have passed since the 1st vaccine dose.

HRIG provides localised anti-rabies antibody protection while the person responds to the rabies vaccine. For information on how to administer HRIG, see ‘Vaccines, dosage and administration’.

HRIG is **not** recommended in people who:

* received the 1st dose of vaccine more than 7 days (more than 168 hours) before presenting for HRIG — that is, more than 7 days (more than 168 hours) have passed since they received the 1st dose of vaccine
* present for medical care more than 12 months after the potential exposure
* have a documented history of at least 2 doses of rabies vaccine from either pre- or post-exposure prophylaxis, as this may suppress the memory response and circulating VNAb (this excludes people who are severely immunocompromised, who always need HRIG. See ‘Table. Vaccinated people: post-exposure rabies treatment based on immune status and exposure category’, and ‘Table. Unvaccinated people: post-exposure rabies treatment based on immune status and exposure category’)
* have documented evidence of rabies virus neutralising antibody titres >0.5 IU per mL at any time in the past

These people should receive rabies vaccine only.

Data are limited on the effectiveness of rabies vaccine and HRIG as post-exposure prophylaxis against infection with lyssaviruses other than classical rabies virus. However, the available animal data and clinical experience support their use.28‑33

## Current recommendation

ATAGI currently recommends the following:

**Immunocompetent people with potential rabies virus exposure who have not previously received rabies vaccine are recommended to receive 4 doses of rabies vaccine as post-exposure prophylaxis, with or without rabies immunoglobulin**

**People who are immunocompromised with potential rabies virus exposure who have not previously received rabies vaccine are recommended to receive at least 5 doses of rabies vaccine as post-exposure prophylaxis, with or without rabies immunoglobulin**

**Some people with a potential exposure to rabies virus or other lyssaviruses who have not previously received rabies vaccine are recommended to receive rabies immunoglobulin in addition to rabies vaccine as post-exposure prophylaxis**

**People with potential rabies exposure who have been previously vaccinated are recommended to receive 2 doses of rabies vaccine as post-exposure prophylaxis, without rabies immunoglobulin**

## Key differences

The nature of the recommendation remains unchanged, but several previous standalone recommendations have been consolidated into a single overarching recommendation, with more detailed guidance provided as supporting information.

The updated information clarifies that:

post-exposure prophylaxis should only be given by the intramuscular route, not the intradermal route

people with potential rabies exposure who are immunocompromised and unvaccinated should receive HRIG for post-exposure prophylaxis

people who are severely immunocompromised — that is, people for whom live vaccines are contraindicated — should always receive HRIG along with 5 doses of rabies vaccine as post-exposure prophylaxis, even if they have previously received rabies vaccine

HRIG is not recommended for people who present for medical care more than 12 months after the potential exposure, or for people who have a documented history of at least 2 doses of rabies vaccine from either pre- or post-exposure prophylaxis (excluding people who are severely immunocompromised)

immunocompetent people who have evidence of receiving at least 2 doses of pre- or post-exposure prophylaxis any time in the past (that is, not necessarily the full course) can receive 2 doses of rabies vaccine as post-exposure prophylaxis

people with a repeat exposure within 3 months of completing previous post-exposure prophylaxis do not require any further vaccine doses and only require wound management

pre- or post-exposure prophylaxis vaccine doses given intradermally can be considered previous vaccination

## Evidence for the updated information

### Post-exposure prophylaxis in people who are immunocompromised

Immunocompromise is not a contraindication to receiving rabies vaccination as post-exposure prophylaxis. Most studies show the immune response is adequate in the majority of people who are immunocompromised, for both primary and booster vaccinations.34-37 However, in some people — typically those who are severely immunocompromised — the immune response to rabies vaccination may be suboptimal.

Immunogenicity was assessed in a group of 13 HIV-positive children who received 3 doses of rabies cell culture vaccine intramuscularly, compared with immunogenicity in 9 healthy children. While geometric mean titres rose to >0.5 IU per mL in both groups, titres in HIV-positive children with <15% CD4+ cells were significantly lower than those in HIV-positive children with >15% CD4+ cells.35 In another study, HIV-positive people with CD4+ cell counts of <200 per μL had a poor antibody response after 4‑site intradermal vaccinations (doubling the WHO-approved regimen; doses of 4‑4‑4‑0-2‑2 on days 0, 3, 7, 30 and 90) using rabies cell culture vaccine. By day 14 after vaccination, 3 of 7 individuals with CD4+ cell counts of <200 per μL had not reached a VNAb titre of 0.5 IU per mL. In comparison, all people (3 of 3) with CD4+ cell counts of ≥200 per μL had VNAb titres >0.5 IU per mL by day 14 after vaccination.38

The WHO 2018 guidance specifies that people who are immunocompromised should receive 5 doses of rabies vaccine plus RIG, regardless of whether they have been previously vaccinated.1 It specifies immunocompromise with regard to HIV-positive people with CD4+ cell counts of <200 per μL, but does not do this for other types of immunocompromise. The JCVI provides further guidance, specifying this recommendation for those who are severely immunocompromised (defined as those for whom live vaccines are contraindicated).2

### Post-exposure prophylaxis in previously vaccinated people who are immunocompromised

Some rabies studies use simulated post-exposure prophylaxis, where rabies vaccine is given in a post-exposure prophylaxis schedule to participants who have not been exposed to rabies. Sibunruang et al. examined the anamnestic response to simulated post-exposure prophylaxis in 29 HIV-positive people who had previously received a primary rabies vaccination course.36 All individuals received simulated intramuscular post-exposure prophylaxis with vaccine doses on days 0 and 3. All individuals elicited rapid and satisfactory anamnestic responses by day 7, except 1 person with a CD4+ cell count of <100 per mm3. People with CD4+ cell counts of ≥200 per mm3 had statistically significantly higher geometric mean titres on day 7 than those with CD4+ cell counts of <200 per mm3.

These data demonstrate that people who are mildly immunocompromised and have been previously primed with rabies vaccine can mount an immune response after only 2 doses of post-exposure prophylaxis. However, people who are more severely immunocompromised mounted a lower immune response. This suggests that a more cautious approach to reducing post-exposure risk may be warranted in people who are severely immunocompromised, such as a full post-exposure prophylaxis regimen.

### Repeat exposure

Data from numerous clinical studies (2795 subjects in 66 vaccine cohorts) of both intramuscular and intradermal pre- and post-exposure prophylaxis regimens were analysed by Sudarshan et al,39 to describe VNAb titres on days 28, 90, 180 and 365 after primary vaccinations. All people who had received post-exposure prophylaxis by the intramuscular route had VNAb titres >0.5 IU per mL on days 28 and 90 (1051 subjects). Antibody levels did not fall below 0.5 IU per mL until day 180. All people who received pre-exposure prophylaxis had VNAb titres >0.5 IU per mL on days 28 and 90, irrespective of whether the vaccination course was given intramuscularly or intradermally.

These data demonstrate that people who receive a rabies pre- or post-exposure prophylaxis regimen do not require revaccination if they are exposed again within 3 months.

**People with potential rabies exposure who started post-exposure prophylaxis overseas are recommended to complete the rabies vaccine course in Australia**

Australians travelling overseas who are exposed to a potentially rabid animal (including bats from any country) may receive post-exposure prophylaxis using cell culture–derived vaccines and schedules that are not used in Australia.

If the person received an older nerve tissue–derived rabies vaccine, do not regard these doses as valid. This is a very rare circumstance. See ‘Table. Completing rabies post-exposure prophylaxis in Australia that started overseas’.

If a person received either a chick embryo–derived or a cell culture–derived vaccine overseas, they are recommended to continue the standard post-exposure prophylaxis regimen in Australia with either human diploid cell vaccine or purified chick embryo cell vaccine. See ‘Interchangeability of rabies vaccines’.

In general, cell culture–derived vaccines are acceptable if they contain at least 2.5 IU of rabies virus per dose and there is scientific literature demonstrating an acceptable post-exposure antibody response (rabies virus neutralising antibody ≥0.5 IU per mL). See ‘Table. Rabies vaccines available globally and compatibility with vaccines registered in Australia’.

Intramuscular dosing schedules for post-exposure rabies vaccination that are approved by the World Health Organization include:

* Zagreb regimen — 2 doses on day 0, doses on days 7 and 21 (annotated as 2‑0‑1-0‑1)
* Essen regimen — doses on days 0, 3, 7, 14, and 28 or 30 (annotated as 1‑1-1‑1-1)
* Modified Essen regimen — doses on days 0, 3, 7 and 14 (annotated as 1‑1-1‑1-0)

Intradermal dosing regimens for post-exposure rabies vaccination that are approved by the World Health Organization include:

* Institut Pasteur du Cambodge (IPC) regimen — 2 doses on days 0, 3 and 7 (annotated as 2‑2‑2‑0‑0)
* Updated Thai Red Cross (TRC) regimen — 2 doses on days 0, 3, 7 and 28 (annotated as 2‑2‑2‑0‑2)

A person is recommended to receive human rabies immunoglobulin (HRIG) in Australia if:

* it is indicated for the type of exposure and the person’s immune status (see ‘Figure. Rabies post-exposure prophylaxis: terrestrial animal exposures’ or ‘Figure. Rabies post-exposure prophylaxis: bat exposures’) **and**
* the potential exposure was within the past 12 months **and**
* they started post-exposure prophylaxis overseas but HRIG or equine rabies immunoglobulin (ERIG) was not given **and**
* they received the 1st post-exposure prophylaxis vaccine dose within the past 7 days (168 hours)

If the person in Australia had their 1st post-exposure prophylaxis dose more than 7 days ago, they should not receive HRIG. However, they should still complete the appropriate number of remaining rabies vaccine doses.

For these and other scenarios, ‘Table. Completing rabies post-exposure prophylaxis in Australia that started overseas’ outlines the most common post-exposure prophylaxis regimens that may be started overseas and the recommended schedule to complete post-exposure prophylaxis in Australia.

Advise travellers that, if they start post-exposure prophylaxis while overseas, they must request a post-exposure prophylaxis certificate from the vaccination centre, and obtain or record the following information (preferably in English):

* the contact details for the clinic attended (telephone and email address)
* the batch and source of rabies immunoglobulin (RIG) used (some countries may use ERIG rather than HRIG)
* the volume of RIG administered
* the type of cell culture vaccine used
* the vaccine batch number
* the number of vials used
* the route of vaccine administration
* the date and time of administration of RIG and/or vaccine

These details help inform decisions about how to complete post-exposure prophylaxis when the traveller returns home.

Table. Rabies vaccines available globally, and compatibility with vaccines registered in Australia

|  |  |  |
| --- | --- | --- |
| Rabies vaccine | Vaccine information | Compatible |
| Human diploid cell vaccine (HDCV) | Imovax, Sanofi Pasteur SA  Kanghua Rabies, Chengdu Kanghua Biological Products China | Yes |
| Purified chick embryo cell vaccine (PCECV) | RabAvert, GSK  Vaxirab-N, Cadila Healthcare India | Yes |
| Purified Vero cell vaccine (PVCV) | Rabivax, Serum Institute India  SPEEDA, Chengda Bio China  Verorab, Sanofi Pasteur  Abhayrab, Human Biologicals Institute India  Indirab, Bharat Biotech India | Yes |
| Purified duck embryo vaccine (PDEV) | Lyssavac, Cadila Healthcare India  Vaxirab, Cadila Healthcare India | Yes |
| Primary Syrian hamster kidney cell (PHKCV) | Local producers in China | Yes |
| Baby hamster kidney cells (BHKV) | Kokav, Russia | Yes |
| Suckling mouse brain vaccine (SMBV) | Used in South America | No |
| Nervous tissue vaccine (sheep, goat) | Used in Asia, Ethiopia and Argentina | No |

Table. Completing rabies post-exposure prophylaxis in Australia that started overseas

These scenarios assume the person had not received pre-exposure prophylaxis before the exposure. For more details, see ‘Figure. Rabies post-exposure prophylaxis: terrestrial animal exposures’ or ‘Figure. Rabies post-exposure prophylaxis: bat exposures’.

|  |  |
| --- | --- |
| Overseas scenario | Rabies vaccine schedule (with or without HRIG) in Australia |
| Person received nerve tissue–derived vaccine. | * Restart schedule, starting from day 0 * Give HRIG immediately if indicated |
| Use of vaccine or RIG is uncertain or unknown, or documentation is poor. | * Restart schedule, starting from day 0 * Assume that RIG has not been given. If HRIG is indicated, give immediately if still within 7 days (168 hours) of receiving 1st dose of vaccine (even if uncertain) |
| Person is immunocompromised, and vaccines were administered intradermally. | * Regardless of number of previous doses, give a 5-dose schedule intramuscularly. Check serology 2–4 weeks after final dose * Give HRIG immediately if still within 7 days (168 hours) of receiving 1st intradermal dose of vaccine while overseas |
| Scenario is well documented. Person received 2 vaccine doses given intradermally on day 0 (IPC/TRC regimens). RIG (equine or human) may or may not have been administered at same time as 1st dose of vaccine. | * Give a further dose intramuscularly on day 3, day 7 and day 14 * If HRIG is indicated, give immediately if still within 7 days (168 hours) of receiving 1st dose of vaccine |
| Scenario is well documented. Person received 2 vaccine doses given intradermally on day 0 and again on day 3 (IPC/TRC regimens). RIG (equine or human) may or may not have been administered at same time as 1st dose of vaccine. | * Give a further single dose intramuscularly on day 7 and another dose on day 14 * If HRIG is indicated, give immediately if still within 7 days (168 hours) of receiving 1st dose of vaccine |
| Scenario is well documented. Person received 2 vaccine doses given intradermally on each of day 0, day 3 and day 7 (IPC/TRC regimens). RIG (equine or human) may or may not have been administered at same time as 1st dose of vaccine. | * Give a further single dose intramuscularly on day 14 |
| Scenario is well documented. Person received a vaccine dose given intramuscularly on day 0 and again on day 3 (Essen/modified Essen regimen). RIG (equine or human) may or may not have been administered at same time as 1st dose of vaccine. | * Give a further dose on day 7 and day 14 (modified Essen regimen). If the person is immunocompromised, give an additional dose at day 28 * If HRIG is indicated, give immediately if still within 7 days (168 hours) of receiving 1st dose of vaccine |
| Person received 2 vaccine doses given intramuscularly on day 0 (Zagreb regimen). RIG (equine or human) may or may not have been administered at same time as 1st dose of vaccine. | * Give a further dose on day 7 and day 21 (Zagreb regimen). If the person is immunocompromised, give an additional dose at day 28 * If HRIG is indicated, give immediately if still within 7 days (168 hours) of receiving 1st dose of vaccine |

HRIG = human rabies immunoglobulin; IPC/TRC = Institut Pasteur du Cambodge/Updated Thai Red Cross; PEP = post-exposure prophylaxis; RIG = rabies immunoglobulin

## Current recommendation

ATAGI currently recommends the following:

**People with potential rabies exposure who started post-exposure prophylaxis overseas are recommended to complete the rabies vaccine course in Australia**

Australians travelling overseas who are exposed to a potentially rabid animal (including bats from any country) may receive post-exposure prophylaxis using vaccines and schedules that are not used in Australia.

If the person received an older nerve tissue–derived rabies vaccine, do not regard these doses as valid. This is a very rare circumstance. See Table. Completing post-exposure prophylaxis in Australia that started overseas.

If a person received either a chick embryo–derived or a cell culture–derived vaccine overseas, they are recommended to continue the standard post-exposure prophylaxis regimen in Australia with either human diploid cell vaccine or purified chick embryo cell vaccine. See Interchangeability of rabies vaccines.

World Health Organization–approved post-exposure rabies vaccination dosing regimens include:

* Zagreb regimen — 2 doses on day 0, doses on days 7 and 21 (annotated as 2‑0‑1-1)
* Essen regimen — doses given on days 0, 3, 7, 14 and 28 (or 30) (annotated as 1‑1‑1‑1‑1)
* Modified Essen regimen — doses given on days 0, 3, 7 and 14 (annotated as 1‑1‑1‑1)

A person is recommended to receive human rabies immunoglobulin (HRIG) in Australia if:

* they started post-exposure prophylaxis overseas but HRIG or equine rabies immunoglobulin (ERIG) was not given, and
* they received the 1st post-exposure prophylaxis vaccine dose within the past 7 days

If the person in Australia had their 1st post-exposure prophylaxis dose more than 7 days ago, they should not receive HRIG. Instead, they should receive the appropriate number of remaining rabies vaccine doses.

For these and other scenarios, Table. Completing post-exposure prophylaxis in Australia that started overseas outlines the most common post-exposure prophylaxis regimens that may be started overseas and the recommended schedule to complete post-exposure prophylaxis in Australia.

**Documentation required from travellers receiving rabies vaccine overseas**

Advise travellers that, if they start post-exposure prophylaxis while overseas, they need to request a post-exposure prophylaxis certificate from the vaccination centre and obtain or record the following information (preferably in English):

* the contact details for the clinic attended (telephone and email address)
* the batch and source of rabies immunoglobulin (RIG) used (some countries may use ERIG rather than HRIG)
* the volume of RIG administered
* the type of cell culture vaccine used
* the vaccine batch number
* the number of vials used
* the route of vaccine administration
* the date of RIG and/or vaccine administration

These details help inform decisions about how to complete post-exposure prophylaxis when the traveller returns home.

## Key differences

The recommendation itself remains unchanged. The revised supporting information:

defines acceptable cell culture–derived vaccines

specifies the intradermal dosing regimens approved by WHO

clarifies that people are recommended to receive HRIG if it is indicated for the type of exposure and their immune status

clarifies, using a table, the rabies vaccines that are available globally and their compatibility with vaccines registered in Australia

## Evidence for the updated recommendation

The 2018 WHO position paper states that changing the vaccine or the route of administration during a course of pre- or post-exposure prophylaxis is safe and immunogenic. A retrospective study conducted in India identified 47 people who had completed a course of post-exposure prophylaxis, including RIG, following a category III exposure to a dog bite, where the route of administration had changed during the course from intradermal to intramuscular (n = 23) or from intramuscular to intradermal (n = 24).40 All study participants had VNAb titres >0.5 IU per mL on day 14. Participants had no prior history of rabies vaccinations, and all were alive at the end of the 6-month follow-up period.

Another study in small sample of 20 healthy adult volunteers demonstrated that changing the route of vaccine administration from intramuscular to intradermal or vice versa for booster doses, compared with the route of administration used for the primary vaccination course, did not affect the antibody response.41 A 15-fold increase in antibody response was elicited by booster doses administered via either route.

Figure. Rabies post-exposure prophylaxis: terrestrial animal exposures

This algorithm gives guidance on post-exposure prophylaxis after potential exposure to lyssaviruses from a terrestrial animal in a rabies-enzootic area

There are 3 categories of rabies exposure: 1) Touching or feeding animals, animal licks on intact skin, or exposure to animal blood, urine or faeces. 2) Animal nibbling of uncovered skin, or minor scratches or abrasions without bleeding. 3) Single or multiple transdermal bites or scratches; contamination of mucous membrane or broken skin with saliva from animal licks; or exposures due to direct contact with bats, including situations where bites or scratches may not be apparent. 
Category 1 exposure does not require any prophylaxis if the contact history is reliable. 
Category II exposure in a non-immune person (see note a). For immunocompetent people, HRIG is not indicated; give 4 vaccine doses intramuscularly on days 0, 3, 7 and 14. For all immunocompromised people with a category II exposure, give HRIG if 7 days (168 hours) or less since the 1st vaccine dose on day 0; give 5 vaccine doses intramuscularly on days 0, 3, 7, 14 and 28; check serology 2–4 weeks after dose 5; give another dose if VNAb titre is <0.5 IU/mL and recheck serology. 
Category II or III exposure in a person who has been previously immunised (see note b; if in doubt, treat as non-immune). If exposure is <3 months after complete post-exposure prophylaxis, no vaccine or HRIG is needed. If exposure is 3 months or longer after complete post-exposure prophylaxis, vaccination is required. For immunocompetent people, HRIG is not indicated; give 2 vaccine doses intramuscularly on days 0 and 3. For mildly immunocompromised people, HRIG is not indicated; give 2 vaccine doses intramuscularly on days 0 and 3; check serology 2–4 weeks after dose 2; if VNAb titre is <0.5 IU/mL, seek expert advice for total number of doses. For severely immunocompromised people, give HRIG if 7 days (168 hours) or less since the 1st vaccine dose on day 0; give 5 vaccine doses intramuscularly on days 0, 3, 7, 14 and 28; check serology 2–4 weeks after dose 5; give another dose if VNAb titre is <0.5 IU/mL and recheck serology.
Category III exposure in a non-immune person (see note a). For immunocompetent people, give HRIG if 7 days (168 hours) or less since the 1st vaccine dose on day 0; give 4 vaccine doses intramuscularly on days 0, 3, 7 and 14. For all immunocompromised people, give HRIG if 7 days (168 hours) or less since the 1st vaccine dose on day 0; give 5 vaccine doses intramuscularly on days 0, 3, 7, 14 and 28; check serology 2–4 weeks after dose 5; give another dose if VNAb titre is <0.5 IU/mL and recheck serology.
For all exposure groups, there are further exposures in the future, treat as previously immunised and follow the algorithm as above. If there is ongoing occupational exposure risk, see Figure: Booster algorithm for people at ongoing risk of exposure to rabies virus or other lyssaviruses.

HRIG = human rabies immunoglobulin; IM = intramuscularly; PEP = post-exposure prophylaxis; VNAb = virus neutralising antibody

a Non-immune — person who has never received pre- or post-exposure prophylaxis with rabies vaccine, or has had an incomplete (<2 doses) primary vaccination course.

b Previously immunised — documentation of at least 2 doses of pre- or post-exposure prophylaxis rabies vaccine, regardless of the time since the last dose was given. It may be either a completed primary pre-exposure course or post-exposure course. It includes people who had subsequent boosters, or who have documented rabies VNAb titres ≥0.5 IU per mL.

Figure. Rabies post-exposure prophylaxis: bat exposures

This algorithm gives guidance on post-exposure prophylaxis after potential exposure to lyssaviruses from bats in Australia or overseas

There are 3 categories of exposure to lyssaviruses from bats: 1) Touching or feeding animals, animal licks on intact skin, or exposure to animal blood, urine or faeces. 2) Animal nibbling of uncovered skin, or minor scratches or abrasions without bleeding. 3) Single or multiple transdermal bites or scratches; contamination of mucous membrane or broken skin with saliva from animal licks; or exposures due to direct contact with bats, including situations where bites or scratches may not be apparent.
Category 1 does not require any prophylaxis if the contact history is reliable. 
Category II or III exposure in people who have been previously immunised (see note b; if in doubt, treat as non-immune). If exposure is <3 months after complete post-exposure prophylaxis, no vaccine or HRIG is needed. If exposure is 3 months or longer after complete post-exposure prophylaxis, vaccination is required. For immunocompetent people, HRIG is not indicated; give 2 vaccine doses intramuscularly on days 0 and 3. For mildly immunocompromised people, HRIG is not indicated; give 2 vaccine doses intramuscularly on days 0 and 3; check serology 2–4 weeks after dose 2; if VNAb titre is <0.5 IU/mL, seek expert advice for total number of doses. For severely immunocompromised people, give HRIG if 7 days (168 hours) or less since the 1st vaccine dose on day 0; give 5 vaccine doses intramuscularly on days 0, 3, 7, 14 and 28; check serology 2–4 weeks after dose 5; give another dose if VNAb titre is <0.5 IU/mL and recheck serology.
Category II or III exposure in a non-immune person (see note c). For immunocompetent people, give HRIG if 7 days (168 hours) or less since the 1st vaccine dose on day 0; give 4 vaccine doses intramuscularly on days 0, 3, 7 and 14. For all immunocompromised people, give HRIG if 7 days (168 hours) or less since the 1st vaccine dose on day 0; give 5 vaccine doses intramuscularly on days 0, 3, 7, 14 and 28; check serology 2–4 weeks after dose 5; give another dose if VNAb titre is <0.5 IU/mL and recheck serology.
For all exposure groups, there are further exposures in the future, treat as previously immunised and follow the algorithm as above. If there is ongoing occupational exposure risk, see Figure: Booster algorithm for people at ongoing risk of exposure to rabies virus or other lyssaviruses.

HRIG = human rabies immunoglobulin; IM = intramuscularly; PEP = post-exposure prophylaxis; VNAb = virus neutralising antibody

a Includes direct contact with bats, and situations where the exposure may be difficult to categorise because a person does not know or cannot communicate if or how an exposure to a bat has occurred. Some bats have small teeth and claws, so bites or scratches may not be apparent.

b Previously immunised — documentation of at least 2 doses of pre- or post-exposure prophylaxis rabies vaccine, regardless of the time since the last dose was given. It may be either a completed primary pre-exposure course or post-exposure course. It includes people who had subsequent boosters, or who have documented rabies VNAb titres ≥0.5 IU per mL.

c Non-immune — person who has never received pre- or post-exposure rabies vaccine, or has had an incomplete (<2 doses) primary vaccination course.

# Recommendations that are not changing

There are no proposed changes to the following current recommendations or their supporting information:

**Travellers to rabies-enzootic regions are recommended to have a risk assessment to guide vaccination decision-making, and all travellers should avoid exposure to rabies virus and other lyssaviruses**

**Women who are pregnant or breastfeeding are recommended to receive rabies vaccine after potential exposure to rabies**

# Benefits

The potential benefits of the updated information include the following:

The option for intradermal vaccination for pre-exposure prophylaxis gives greater choice to immunisation providers about the route of administration for rabies vaccines.

The option for accelerated vaccination schedules may reduce the cost, the lead time required before travel and the number of clinic visits required to complete pre-exposure prophylaxis. This may increase access to and compliance with acceptable rabies vaccination schedules for some travellers.

The updated information about the timing and frequency of booster doses ensures optimal protection against rabies for people at ongoing occupational risk of exposure, and avoids frequent boosting that may be unnecessary or harmful.

The updated information about vaccination in people who are severely immunocompromised will help optimise protection for these people against rabies.

The updated information about the use of HRIG in people who have had an incomplete pre-exposure prophylaxis regimen means that HRIG will not be given to these people (because there are no additional benefits) and will be spared for those who need it.

The updated information about post-exposure prophylaxis for people who have received rabies vaccine in the previous 3 months means that people with frequent and recent exposures will not receive doses of vaccine that show no additional benefits.

The consolidation of several recommendations simplifies the rabies chapter of the Handbook and reduces the need for providers to look for information in several sections of the Handbook.

The updated supporting information in several recommendations adds clarity to help immunisation providers and public health specialists make evidence-based decisions about rabies vaccination.

# Potential risks

The potential risks that may arise from the updated information include the following:

Intradermal vaccination may be provided by healthcare professionals who are not experienced in the intradermal technique. This risk is mitigated by specifying that intradermal vaccination should only be provided by suitably qualified practitioners who are experienced in and regularly practise the intradermal technique.

Intradermal vaccination may inadvertently be provided as post-exposure prophylaxis; if the vaccine is not administered correctly, the person may not be adequately protected against this otherwise invariably fatal disease. This risk is mitigated by specifying that the intradermal route may be used for pre-exposure prophylaxis only, not post-exposure prophylaxis or booster doses.

Clinicians may find it difficult to ascertain whether an intradermal dose administered overseas as part of a WHO-approved post-exposure prophylaxis regimen has been administered correctly.

# Preference and values

The proposed changes to the use of rabies vaccines are in line with best clinical advice. It is expected that the changes will expand the options available to immunisation providers and consumers for rabies vaccines. This may also improve affordability and therefore uptake of rabies vaccines by consumers, which will help to optimise protection for people at risk of exposure to rabies or other lyssaviruses.

# Additional information to be included in the Australian Immunisation Handbook

## Vaccines, dosage and administration

Updates will be made to this section of the Handbook chapter, including changes to the text describing dose and route, and clarifying that intradermal administration is off-label use.

# Practical considerations

ATAGI emphasises the importance of intradermal vaccination only being provided by suitably qualified and experienced practitioners who regularly practise the intradermal technique.

# Glossary

A [glossary of technical terms](https://immunisationhandbook.health.gov.au/technical-terms) is available on the Australian Immunisation Handbook website.

# References

1. World Health Organization. Rabies vaccines: WHO position paper – April 2018. Weekly Epidemiological Record 2018;16:201–20.

2. Public Health England. Guidelines on managing rabies post-exposure. London: Public Health England; 2019.

3. Bernard K, Fishbein D, Miller K, et al. Pre-exposure rabies immunization with human diploid cell vaccine: decreased antibody response in persons immunized in developing countries. American Journal of Tropical Medicine and Hygiene 1985;34:633–47.

4. Lemon S, Pang L, Miller R, Prier R, Bernard K. Failure to achieve predicted antibody response with intradermal and intramuscular human diploid cell rabies vaccine. Lancet 1984;323:1098–100.

5. Gherardin A, Lau S. Intradermal rabies vaccine. Medical Journal of Australia 2007;187:58–9.

6. Lau C, Sisson J. The effectiveness of intradermal pre-exposure rabies vaccination in an Australian travel medicine clinic. Journal of Travel Medicine 2002;9:285–8.

7. Nicolas J-F, Guy B. Intradermal, epidermal and transcutaneous vaccination: from immunology to clinical practice. Expert Review of Vaccines 2008;7:1201–14.

8. Bernard KW, Roberts MA, Sumner J, et al. Human diploid cell rabies vaccine: effectiveness of immunization with small intradermal or subcutaneous doses. JAMA 1982;247:1138–42.

9. Fishbein DB, Pacer RE, Holmes DF, et al. Rabies preexposure prophylaxis with human diploid cell rabies vaccine: a dose–response study. Journal of Infectious Diseases 1987;156:50–5.

10. Nicholson KG, Farrow PR, Bijok U, Barth R. Pre-exposure studies with purified chick embryo cell culture rabies vaccine and human diploid cell vaccine: serological and clinical responses in man. Vaccine 1987;5:208–10.

11. Dreesen DW, Fishbein DB, Kemp DT, Brown J. Two-year comparative trial on the immunogenicity and adverse effects of purified chick embryo cell rabies vaccine for pre-exposure immunization. Vaccine 1989;7:397–400.

12. Rosa FW. Pre-exposure prophylaxis in Peace Corps volunteers with intradermal human diploid cell rabies vaccine. Journal of Tropical Medicine and Hygiene 1983;86:81–4.

13. SAGE working group on rabies vaccines and immunoglobulins and the World Health Organization (WHO) Secretariat. Background paper: proposed revision of the policy on rabies vaccines and rabies immunoglobulins. Geneva: WHO; 2017.

14. Soentjens P, Andries P, Aerssens A, et al. Preexposure intradermal rabies vaccination: a noninferiority trial in healthy adults on shortening the vaccination schedule from 28 to 7 days. Clinical Infectious Diseases 2019;68:607–14.

15. Lau C, Hohl N. Immunogenicity of a modified intradermal pre-exposure rabies vaccination schedule using a purified chick embryo cell vaccine: an observational study. Travel Medicine and Infectious Disease 2013;11:427–30.

16. Mills DJ, Lau CL, Fearnley EJ, Weinstein P. The immunogenicity of a modified intradermal pre-exposure rabies vaccination schedule – a case series of 420 travelers. Journal of Travel Medicine 2011;18:327–32.

17. De Pijper CA, Boersma J, Terryn S, et al. Rabies antibody response after two intradermal pre-exposure prophylaxis immunizations: an observational cohort study. Travel Med Infect Dis 2018;22:36–9.

18. Jelinek T, Cramer JP, Dieckmann S, et al. Evaluation of rabies immunogenicity and tolerability following a purified chick embryo cell rabies vaccine administered concomitantly with a Japanese encephalitis vaccine. Travel Med Infect Dis 2015;13:241–50.

19. Langedijk AC, De Pijper CA, Spijker R, et al. Rabies antibody response after booster immunization: a systematic review and meta-analysis. Clinical Infectious Diseases 2018;67:1932–47.

20. Pappaioanou M, Fishbein DB, Dreesen DW, et al. Antibody response to preexposure human diploid-cell rabies vaccine given concurrently with chloroquine. New England Journal of Medicine 1986;314:280–4.

21. Plotkin S, Orenstein W, Offit P, Edwards K. Chapter 50: Rabies vaccines. In: Plotkin's Vaccines. 7th ed.: Elsevier; 2018.

22. Morris J, Crowcroft N, Fooks A, Brookes S, Andrews N. Rabies antibody levels in bat handlers in the United Kingdom: immune response before and after purified chick embryo cell rabies booster vaccination. Human Vaccines 2007;3:165–70.

23. Suwansrinon K, Wilde H, Benjavongkulchai M, et al. Survival of neutralizing antibody in previously rabies vaccinated subjects: a prospective study showing long lasting immunity. Vaccine 2006;24:3878–80.

24. Jones RL, Froeschle JE, Atmar RL, et al. Immunogenicity, safety and lot consistency in adults of a chromatographically purified Vero-cell rabies vaccine: a randomized, double-blind trial with human diploid cell rabies vaccine. Vaccine 2001;19:4635–43.

25. Wang XJ, Lang J, Tao XR, et al. Immunogenicity and safety of purified Vero-cell rabies vaccine in severely rabies-exposed patients in China. Southeast Asian Journal of Tropical Medicine and Public Health 2000;31:287–94.

26. Wang C, Zhang X, Song Q, Tang K. Promising rabies vaccine for postexposure prophylaxis in developing countries, a purified Vero cell vaccine produced in China. Clinical and Vaccine Immunology 2010;17:688–90.

27. Wilde H. Failures of post-exposure rabies prophylaxis. Vaccine 2007;25:7605–9.

28. Nel LH. Vaccines for lyssaviruses other than rabies. Expert Review of Vaccines 2005;4:533–40.

29. Brookes SM, Parsons G, Johnson N, McElhinney LM, Fooks AR. Rabies human diploid cell vaccine elicits cross-neutralising and cross-protecting immune responses against European and Australian bat lyssaviruses. Vaccine 2005;23:4101–9.

30. Sampath G, Madhusudana SN, Sudarshan MK, et al. Immunogenicity and safety study of Indirab: a Vero cell based chromatographically purified human rabies vaccine. Vaccine 2010;28:4086–90.

31. Vodopija I, Sureau P, Smerdel S, et al. Interaction of rabies vaccine with human rabies immunoglobulin and reliability of a 2‑1‑1 schedule application for postexposure treatment. Vaccine 1988;6:283–6.

32. Lang J, Simanjuntak GH, Soerjosembodo S, Koesharyono C. Suppressant effect of human or equine rabies immunoglobulins on the immunogenicity of post-exposure rabies vaccination under the 2‑1‑1 regimen: a field trial in Indonesia. Bulletin of the World Health Organization 1998;76:491–5.

33. Bose A, Munshi R, Tripathy RM, et al. A randomized non-inferiority clinical study to assess post-exposure prophylaxis by a new purified Vero cell rabies vaccine (Rabivax-S) administered by intramuscular and intradermal routes. Vaccine 2016;34:4820–6.

34. Azzoni L, Foulkes AS, Firnhaber C, et al. ART interruptions result in loss of protective humoral immunity to neoantigens in HIV-infected individuals. AIDS 2012;26:1355–62.

35. Thisyakorn U, Pancharoen C, Ruxrungtham K, et al. Safety and immunogenicity of preexposure rabies vaccination in children infected with human immunodeficiency virus type 1. Clinical Infectious Diseases 2000;20:218.

36. Sibunruang S, Jaijaroensup W, Khawplod P, et al. Immune response after booster vaccination in HIV-infected patients who had previously received primary rabies immunisation. Clinical Microbiology and Infection Conference: 22nd European Congress of Clinical Microbiology and Infectious Diseases; London.

37. Cramer CH, 2nd, Shieck V, Thomas SE, et al. Immune response to rabies vaccination in pediatric transplant patients. Pediatric Transplantation 2008;12:874–7.

38. Tantawichien T, Jaijaroensup W, Khawplod P, Sitprija V. Failure of multiple-site intradermal postexposure rabies vaccination in patients with human immunodeficiency virus with low CD4+ T lymphocyte counts. Clinical Infectious Diseases 2001;33:E122–4.

39. Sudarshan MK, Ravish HH, Narayana DH. Time interval for booster vaccination following reexposure to rabies in previously vaccinated subjects. Asian Biomedicine 2011;5:589–93.

40. Ravish HS, Sudarshan MK, Madhusudana SN, et al. Assessing safety and immunogenicity of post-exposure prophylaxis following interchangeability of rabies vaccines in humans. Human Vaccines and Immunotherapy 2014;10:1354–8.

41. Sudarshan MK, Madhusudana SN, Mahendra BJ, et al. Boosting effect of purified chick embryo cell rabies vaccine using the intradermal route in persons previously immunized by the intramuscular route or vice versa. National Medical Journal of India 2006;19:192–4.