Evaluating the benefit of serology during potential Australian bat lyssavirus and rabies post-exposure prophylaxis

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Abstract

Post-exposure prophylaxis (PEP) for potential lyssavirus exposures consists of wound management, rabies vaccination and may include rabies immunoglobulin (RIG). Rabies serology is sometimes indicated if there is risk of PEP failure.

Objectives: Evaluate the benefit of serology by indication.

Methods: Chart review of potential lyssavirus exposures managed at a Public Health Unit (June 2015 – December 2022) where serology was requested was conducted. The proportion of non-therapeutic titres was compared by sex, age, Indigenous status, serology indication, and whether RIG was given.

Results: 46 notifications with serology were included. Males (5/19) and people over 40 (3/16) were more likely to demonstrate a non-therapeutic response. 2/3 of cases where vaccine doses were not given in the deltoid were non-therapeutic. The rate of non-therapeutic titres was similar for RIG given into the ipsilateral arm (2/11) and given excess RIG for weight (1/4). Although this small sample was inconclusive in isolation, it was also noted that all cases who did not receive RIG had therapeutic serology, whereas 6/35 of those receiving RIG had non-therapeutic serology.

Conclusions: This study supports broader literature questioning the utility of systemic RIG administration as likely limited and potentially detrimental considering the increased risk of immune interference.

Implications for public health: Highlights a need to review Australian national guidelines to align with World Health Organization advice recommending local RIG administration only.

Key words: rabies, lyssavirus, communicable diseases, post-exposure prophylaxis, public health

Introduction

Rabies virus, Australian bat lyssavirus (ABLV), and other lyssaviruses such as European bat lyssavirus are single-stranded, negative-sense RNA viruses that cause zoonosis rabies.[1] Lyssaviruses are transmitted following a bite or scratch from an infected animal, resulting in the deposition of virus-laden saliva in the wound. The incubation period is highly variable, but eventually, the virus infects a peripheral nerve and ascends the dorsal root ganglion.[2] Once infection enters the central nervous system, it causes acute encephalitis, for which there is no effective treatment. The disease is almost always fatal.[3] Vaccination given as pre- or post-exposure prophylaxis effectively prevents infection.[4] Vaccines stimulate virus-neutralising antibodies critical to preventing infection.[5]

Australia is free from terrestrial rabies; however, domestic bat exposures and terrestrial mammal bites in returned travellers from endemic regions are common. ABLV has been found in all species of Australian flying foxes and seven genera of insectivorous microbats, although all bats are considered potential carriers.[6] The prevalence of ABLV in the bat population is estimated to be less than 1%, but may be slightly higher among bats in urban settings.[7] Australian preventative public health management includes providing advice for travel and bat handlers to the community, advising pre-exposure prophylaxis (PrEP) for travellers visiting rabies-enzootic countries and people in high-risk occupations, and managing potential ABLV and rabies exposures.[8]

Potential rabies and ABLV exposures are managed with rabies post-exposure prophylaxis (PEP).[9] Australian guidelines recommend PEP

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involves thoroughly washing the wound and administering a rabies vaccine course. The exposure may also indicate human rabies immunoglobulin (RIG) if the person has not previously received the rabies vaccine.[8] PEP involves four vaccine doses on days 0, 3, 7, and 14, with a fifth dose on day 28 if the case is immunocompromised.[10] RIG aims to provide interim protection against the migration of the virus to the central nervous system until a protective immune response is achieved.[11] RIG doses, as per Australian guidelines, are calculated based on the patients weight.[8]

Failure of rabies PEP is rare but usually occurs due to: delayed presentation, improper vaccine or RIG dosing and administration, inadequate primary wound care, or poor-quality rabies vaccine.[12–14] Once initiated, it is important to adhere closely to PEP dosing and timing schedules.[15] Failure to give the rabies vaccine intramuscularly or intradermally is known to have resulted in PEP failure.[16] Interference can also occur between RIG and the rabies vaccine if administered together, too late, or theoretically with excess RIG.[10] Awareness of these pitfalls leads to concerns about potential PEP failure where:

- The patient is immunosuppressed or immunocompromised.
- Information about the vaccine, dose, or administration route cannot be confirmed from overseas-initiated vaccination documentation.
- A vaccine dose was given at a non-recommended site, meaning intramuscular administration is uncertain.
- RIG and rabies vaccines were given into the ipsilateral arm within three days of each other.
- Excess RIG dose for weight is administered.

Where concerns about PEP failure exist, rabies serology may be requested to confirm a protective immune response. However, serology incurs additional costs for the health system and may cause anxiety.

As such, the objectives of this study were first to describe the frequency and indications for which serology is requested and serology outcomes during potential lyssavirus PEP. Second, to evaluate the benefit of serology by indication during lyssavirus PEP.

Methodology

Project Location

The project used notifiable conditions surveillance data from north Brisbane in Queensland, Australia, from 2015–2022. This study sourced data from the "Metro North" public health unit (MNPHU). MNPHU is one of sixteen statutory public health service jurisdictions covering Queensland.[17]

Data Retrieval

Bites and scratches, mucous membrane, or broken skin contact with the saliva or neural tissue of Australian bats are notifiable on clinical suspicion.[18] Notifying similar exposures from terrestrial mammals in rabies-enzootic countries is also recommended to facilitate PEP, though it is not required by law. Potential exposures are reported on the notifiable conditions register (NoCS) as either '*potential ABLV exposure*' or '*potential rabies exposure*', respectively. Rabies and lyssavirus serology are notifiable by pathology laboratories on test request.[18] Both are recorded on NoCS as '*Lyssavirus (Rabies)*', '*Lyssavirus (ABLV)*', or *'Lyssavirus (unspecified)'* notifications. Notification data for June 2015–December 2022 for the above were retrieved from NoCS. This timeframe included all cases since follow-up in MNPHU was recorded on the unit's electronic database. The data fields retrieved for each notification are listed in the Appendix.

Identifying potential ABLV and rabies exposure notifications where serology was requested

Cases, where serology was requested, were identified by cross-checking potential exposure notifications with serology request notifications. Potential exposures without a serology notification were excluded from the study.

Chart review cases where serology was requested

MNPHU case notes for identified cases were reviewed to determine serology indication and outcome. Data were extracted from case notes onto a standardised collection tool (Appendix). The serology indication(s) were coded according to the relevant category in Table 1. Cases where serology was collected before completing PEP were excluded from further study, as were cases in the following serology request categories: serology request driven by the general practitioner, serology request driven by the patient, bat lyssavirus polymerase chain reaction (PCR), routine serology, and case notes not available. Serology outcomes for the remainder were coded as therapeutic immunity (≥0.5 IU/mL) or non-therapeutic (<0.5 IU/mL). An antibody titre greater than or equal to 0.5 IU/mL was considered indicative of seroconversion, providing a therapeutic titre, in line with the World Health Organization recommendations and Australian National Guidelines.[8,9]

Data Analysis

The proportion of non-therapeutic titres was calculated for each serology indication. Where cases had multiple equally valid serology indications, they were included in the calculations for all relevant indications. Case details for non-therapeutic cases were then re-examined to identify other potentially relevant contributing factors. The proportion of non-therapeutic serology results was also compared for sex, age group, and Indigenous status.

Results

A total of one hundred and thirteen notifications for potential lyssavirus exposures for 94 individuals were identified, where the individual also had a serology request notification. There were nine individuals with multiple notifications. All were bat carers with potential ABLV exposures in Australia who had received PrEP and

Table 1: Chart review codes for requesting serology indications.

Immunosuppression or immunosuppressive use
Overseas-initiated rabies PEP where the vaccine type, dose site, or administration route cannot be confirmed.
One or more PEP doses administered to a non-recommended site.
RIG is given into the ipsilateral arm as a rabies vaccine within three days of each other.
Excess RIG was administered for the case's weight.
Other
Serology request driven by the general practitioner
Serology request driven by the patient
Bat lyssavirus PCR
Routine serology; no serology associated with an exposure event
Case notes are not available.

underwent regular serology. Only one exposure in an individual with multiple presentations had serology requested by MNPHU.

Sixty-eight notifications where MNPHU did not request serology were excluded. These included: serology driven by the general practitioner (11), serology driven by the patient (5), routine serology not associated with an exposure event (26), notifications where case notes were not available (3), where the notification was for lyssavirus PCR on a bat specimen (22), and where serology was collected before completing PEP (1). Lyssavirus PCRs on bat specimens were flagged as a notification as an artefact of a historical information systems issue, where bat specimens linked to notifications in humans were erroneously linked to an individual rather than a notification incident.

After exclusion, 45 potential exposure notifications where MNPHU requested serology were included in the analysis (Table 2). Participants ranged from 1 to 79 years of age, and 24/45 (53%) were male. There was some suggestion that males and people over 40 were more likely to demonstrate a non-therapeutic response. There was no apparent relationship between Indigenous status and non-therapeutic serology.

All non-therapeutic titres in this study were identified in patients administered RIG as a component of their PEP. Male exposures in this sample were slightly more likely to receive RIG as compared to females (83% *vs*. 71%). RIG administration in younger age groups ranged from 72–83% of presentations receiving RIG, but was slightly less likely in people 61–80 (60%).

Table 3 compares the proportion of non-therapeutic and therapeutic serologies by indication for requesting serology. All immunosuppressed or immunocompromised cases had therapeutic titres after five PEP doses. PEP for one overseas exposure resulted in a non-therapeutic titre. PEP was initiated in the Middle East, and documentation regarding the vaccine, administration site and route, and RIG was unclear. Notably, this serology was collected relatively early, 15 days after the last PEP dose, and was only marginally non-therapeutic at 0.48 IU/mL. No other risk factors for poor response were identified. All other cases of overseas-initiated PEP where there was uncertainty as to what had been administered and how had therapeutic titres including cases from Bhutan, China, India, and Thailand.

Two of the three doses administered to non-recommended sites resulted in a non-therapeutic response. All three cases had vaccine administered into the thigh, and no other contributing factors for poor serological response (e.g. medical comorbidities, older age, serology timing) were identified. However, given the small sample size, conclusions from this result should be circumspect.

In most cases, RIG and rabies vaccine administration into the ipsilateral arm resulted in therapeutic serology. In both instances with non-therapeutic titres, RIG was given to distal arm wounds on the hands and wrists. Both cases were male and in older age groups (40-80 years). No other potential contributing factors were identified, and neither case had a significant medical co-morbidity.

Only one of the four cases given excess RIG had non-therapeutic results. It is noteworthy that one case had therapeutic results despite being immunosuppressed and receiving RIG in the ipsilateral arm. Excess doses ranged from 5–16% of the indicated dose. Although the non-therapeutic case received an additional 12% dose, another case receiving a larger excess dose (16%) had a therapeutic response. The case with a non-therapeutic titre was therapeutic after a booster dose and serology recollection two months later. No medical risk factors were identified as potentially contributing to the poor antibody response; however, the case was a male over 40 years of age.

Discussion

This study aimed to describe the indications for which MNPHU requests serology and the benefits of doing so. However, conclusions must be drawn cautiously due to the small sample size and rely substantially on the broader literature. Further study is needed to validate the trends suggested in this study. Older individuals and male sex were possibly associated with the poorer immune response. RIG was administered in all the non-therapeutic serological responses examined. Findings suggest that administering rabies vaccines at non-recommended sites may increase the risk of a non-therapeutic serologic response. There were also instances where RIG given within three days of a rabies vaccine in the ipsilateral arm and administration of excess RIG for weight resulted in non-therapeutic titres.

Older age and males were identified as potentially associated with a less robust response to rabies vaccination. Several previous studies have suggested males demonstrate a lower rabies virus antibody titre after vaccination.[19,20] Older age was also reported as a risk factor for

Table 2: Demographic data of potential lyssavirus exposures where Metro North public health unit requested serology.

	Non-therapeutic	Therapeutic	Non-therapeutic %
Sex			
Male	5	19	21%
Female	1	20	9%
Age			
1-20	-	5	-
21-40	3	21	14%
41-60	2	9	22%
61-80	1	4	25%
Indigenous status			
Neither Aboriginal nor Torres Strait Islander	6	35	15%
Aboriginal or Torres Strait Islander	-	3	-
Not stated	-	1	-
Total	6	39	13%

Table 3: Comparison of non-therapeutic vs. therapeutic serology results by the indication for serology collection.

Serology Indication	Non-therapeutic	Therapeutic	Percentage non-therapeutic
Immunosuppression or immunosuppressive use	-	6 (7)[a]	-
Overseas-initiated rabies PEP where the vaccine type, administration site, or route cannot be confirmed.	1	15	6%
One or more PEP doses administered to a non-recommended site.	2	1	67%
RIG is given into the ipsilateral arm as a rabies vaccine within three days of each other.	2	8 (9)[a]	18%
Excess RIG was administered for the case's weight.	1	2 (3)[a]	25%
Other	-	6	-
Combined	-	1	-

[a]Number in parentheses used for calculation, accounting for cases with multiple equally valid indications for serology.

reduced rabies vaccine response in two studies of 260 and 136 individuals receiving PEP,[21,22] and the WHO has recognised extremes of age as a risk factor for a poorer serological response to rabies vaccination.[23] Analogously, older age and males have also been associated with a poorer vaccine response to the hepatitis B vaccine.[24–27] Although there remains uncertainty as the literature is limited and heterogeneous, findings in the present study add to the weight of evidence suggesting older age and male sex are risk factors for poorer rabies vaccine response.

In the present study, older individuals were slightly less likely to receive RIG. This observation is most likely due to variability in a small sample, as management of lyssavirus exposures in Australia is guideline-driven without consideration for patient demographics. It may also reflect that older individuals are more likely to have had previous vaccinations, and therefore do not need RIG. However, sub-conscious bias impacting clinician decision-making and social factors cannot be excluded.

Administration of the rabies vaccine into sites other than the deltoid was suggested to be associated with potential PEP failure in this study. The latest WHO rabies position paper (2018) and Australian national guidelines recommend deltoid intramuscular administration of the rabies vaccine for everyone except young children, where the anterolateral thigh is acceptable.[8,9] Among several reasons, administration to non-recommended sites may increase the risk of injection into or around adipose tissue, which may degrade or delay absorption and attenuate immunogenicity.[16,28,29] Several PEP failures have been reported in cases where the rabies vaccine was administered to the gluteal muscle.[30,31] A small serosurvey on 19 individuals administered the rabies vaccine in the gluteal region has also subsequently shown a reduced immune response as compared to those receiving vaccines in the deltoid.[32] A similar reduced immunogenicity for doses outside the deltoid has been described in vaccine responses for hepatitis B.[33] Though the sample size in the present study is small, the trend appears consistent with previous studies. Although further study is needed to validate this finding, in the interim, it may be safest to regard doses at non-recommended sites as invalid and to repeat without serology.

Study data on the impact of giving RIG in the ipsilateral arm as a rabies vaccine and excess RIG dose by weight are unclear in isolation. However, all cases not receiving RIG had therapeutic results, whereas 17% of those receiving RIG had non-therapeutic results. Taken together, these findings support a broader literature that suggests RIG may interfere with timely active immunity development. Although the exact mechanism is not well understood and reports are variable, the potential for interference between RIG and rabies vaccines is recognised in human and animal models.[34] It is thought that RIG binding to rabies antigens may sequester vaccine epitopes and lessen immune antigen exposure.[35] This effect appears transient, in keeping with the antibody's biological half-life.[36,37] A study comparing immunogenicity in hamsters found significant transient interference with antibody production in hamsters concomitantly injected with weight-based RIG at a different anatomical location until day 7 after administration.[35] The difference was insignificant by day 14, but only reached parity on day 28. Similarly in human studies, a randomised clinical study in the Philippines with 45 healthy subjects aged 18–40 found a delayed response and higher seroconversion failure rate (40–43% *vs.* 7%) by day 21 in subjects co-administered RIG as compared to vaccine alone.[38] The WHO reports that in most individuals, seroconversion is achieved by days 7–14 of PEP, irrespective of whether RIG was given.[9] However, commentators have argued that observational studies demonstrate seroconversion varying from 93–100% as late as day 28, compared to 80-100% by day 14 in clinical trials.[39] Using weight-based dosing results in high dose injection volumes in obese patients, potentially further increasing the risk of interference.[19,40] The administration errors discussed in the present study may potentiate this interference effect, contributing to the overall risk profile for a poor immune response coupled with other individual and vaccine factors.

These findings give reason to further question the benefit of systemic RIG administration. Australian guidelines have not been updated to align with the latest WHO rabies position paper, which recommends maximum local infiltration of RIG only.[9] RIG injected intramuscularly has been shown to remain relatively localised, and does not produce therapeutic titres in the circulation.[41,42] A study in mice exposed to the rabies virus showed 100% survival with 1% of their weight-based RIG dose infiltrated at the site of exposure.[39] The vital role of local RIG administration has been further stressed in case studies where not administering RIG, not injecting into wounds, or not all wounds where there are multiple was identified as a factor in PEP failure.[29,43,44] More recently, clinical studies using only local RIG administration in India showed effective rabies prevention with samples of 269, 26, and 7,506 exposures, which included high-risk bites and scratches from animals with laboratory-confirmed rabies.[45–47] These studies highlight that RIG's benefit to rabies PEP is obtained by local administration and that the utility of systemic RIG administration is likely limited and may even be detrimental considering the increased risk of immune interference.

This study's main limitation is the small sample size. Conclusions have therefore been drawn cautiously, and interpretation relies on supporting evidence from the literature. It is plausible, given the low true exposure rate in this cohort where serology was requested on a case-by-case basis only, that there may be other non-protective serological responses among those notified that were missed. Studies with greater statistical power are needed to better understand if RIG administration errors potentiate interference with the immune response to vaccination.

Conclusion

This study suggests older age groups and male sex are factors contributing to the overall risk profile and impacting individual-response variation. Given that there may be a risk of reduced immunogenicity when rabies vaccine doses are not given in the deltoid, repeating the dose may ensure more efficient and timely immunity than waiting for serology. This approach is consistent with the management of other vaccine administration errors. Although not a definitive finding in this study, rabies immunoglobulin (RIG) administration errors may increase the risk of RIG interference in developing active immunity. This highlights the need to review Australian national guidelines to align with the World Health Organization advice recommending local RIG administration only. This is supported by increasing evidence that the benefit of RIG is mostly attributable to what is given locally and that systemic RIG provides limited function and may interfere with a timely, active immune response. There is a risk of adverse events when administering blood products, and minimising unnecessary exposure should be considered in reviewing guidelines. Finally, RIG is an expensive, scarce resource that needs responsible stewardship for its use. There is an economic and ethical argument that more judicious use may have beneficial downstream impacts on both Australian

healthcare costs and equitable access in lower- and middle-income countries where rabies prevalence and need are greater.

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Ethics approval

This study was granted ethics exemption as a quality assurance study.

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Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.anzjph.2023.100091.