BMJ Open

Epidemiology of rabies immune globulin use in paediatric and adult patients in the USA: a cross-sectional prevalence study

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To cite: Burke RV, Russo P, Sicilia M, *et al*. Epidemiology of rabies immune globulin use in paediatric and adult patients in the USA: a cross-sectional prevalence study. *BMJ Open* 2022;**12**:e055411. doi:10.1136/bmjopen-2021-055411

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-055411).

Received 07 August 2021
Accepted 24 March 2022

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ABSTRACT

Objectives To compare the epidemiology of paediatric and adult patients receiving rabies immune globulin (RIG).
Design Cross-sectional prevalence study.
Setting Eligible participants from the Symphony Integrated Dataverse presenting between 2013 and 2019.
Participants All adult and paediatric patients with integrated claims and demographic data associated with RIG use from the Symphony Integrated Dataverse from 2013 to 2019.
Primary and secondary outcome measures Prevalence of diagnoses and procedures associated with paediatric and adult patient population based on frequency of International Classification of Diseases (ICD-9/ICD-10) and Current Procedural Terminology codes, respectively.
Methods We used mutual information to identify features that differentiate the paediatric from adult patient population. Prevalence ratios were calculated to compare adult and paediatric patients.
Results There were 79 766 adult and 20 381 paediatric patients who met the inclusion criteria. Paediatric patients had a 5.92-fold higher prevalence of 'open wounds to the head; neck; and trunk', 3.10-fold higher prevalence of 'abrasion or friction burn of face; neck; and scalp except eye; without mention of infection', 4.44-fold higher prevalence of 'open wound of scalp; without mention of complication' and 6.75-fold higher prevalence of 'laceration of skin of eyelid and periocular area | laceration of eyelid involving lacrimal passages'. Paediatric patients had a 3.83-fold higher prevalence of complex repairs compared with adult patients (n=157, 0.7% vs n=157, 0.2%, respectively).
Conclusions Paediatric patients represent a significant proportion of the patient population receiving RIG, and are associated with higher prevalence of codes reporting repair of larger, more complex wounds in highly innervated anatomical regions. Dosing and administration of RIG must be informed by animal bite wound characteristics; clinicians should understand the differences between presentations in adults and children and treat accordingly.

Strengths and limitations of this study

- Data are population- based and include both adults and children who presented with suspected rabies and received rabies prophylaxis treatment.
- Data are only applicable to the population studied and included in the data set.

INTRODUCTION

Rabies is a viral zoonotic disease with a nearly 100% case fatality rate in humans, and is the most significant public health problem following animal bite injuries.[1] Dog bites account for 99% of global rabies cases. The WHO estimates nearly 60 000 victims die each year, despite it being a vaccine-preventable disease.[2] There are no universally accepted effective treatments for rabies once clinical symptoms appear.[3] Fortunately, rabies disease is preventable with appropriate postexposure prophylaxis (PEP) that includes (in unvaccinated persons) wound washing, administration of rabies immune globulin (RIG) and vaccination.

In the USA, human rabies cases have declined significantly since the 1970s due to dog and cat vaccination programmes, stray animal control, public education campaigns and availability of PEP.[4] Following the vaccination of domestic animals against rabies, trends in animal rabies have changed; more than 90% of rabies cases now occur in wildlife.[5] Current reservoirs of concern for rabies exposure are wild animals. Annually, 30 000–60 000 people require treatment for suspected rabies exposures, and between one and three human rabies cases are reported nationally.[6] One-quarter of rabies cases between 2003 and 2014 occurred in children.[7]

RIG is indicated in unvaccinated persons, and should be infiltrated into and around wounds to neutralise virus at the inoculation site and provide passive immunity during the delay between the first vaccine dose and the immunogenic response.[4] While appropriate, PEP prevents rabies disease with near-universal efficacy, some treatment failures have been reported in the literature.[8] Dosing of RIG must provide sufficient volume to adequately infiltrate all wounds, as this is the main protective mechanism. Conversely, an upper weight-based maximum dose of 20 IU/kg must be respected in order to avoid vaccine interference, as overdosing RIG blunts the immunogenic response to vaccine. In children, this safety margin is constricted particularly in cases of severe or extensive wounds and can create clinically challenging situations where the RIG volume is insufficient to infiltrate all wounds; in such cases, RIG volume must be expanded with a compatible diluent to enable infiltration.[8] Thus, wound characteristics should inform appropriate RIG dosing and administration in order to prevent death. While the wound characteristics of paediatric patients are documented in the dog bite literature, to our knowledge, no study has comparatively evaluated the epidemiology of paediatric and adult patients receiving RIG. Given the importance of appropriate treatment and dosing of RIG, understanding the differences in distribution of cases by severity and type may help better inform clinical practice and prevent treatment errors that create risk for suboptimal care.

METHODS

Data source and study design

This was a descriptive and analytical cross-sectional prevalence study using integrated claims and demographic data associated with RIG use in adult and paediatric patients. Study data were queried from the Symphony Integrated Dataverse (IDV), an integrated healthcare database that includes claims (medical, hospital and prescription), point-of-sale prescription, non-retail invoice and demographic data, encompassing data on nearly 250 million patient lives in the USA. Records were pulled from the study period spanning from 1 October 2012 through 31 May/1 June 2020. Inclusion criteria were patients whose records included a Current Procedural Terminology (CPT) code for use of rabies immune globulin (CPT 90375 or 90376), or rabies immune globulin use combined with International Classification of Diseases (ICD-9/ICD-10) codes for contact with and (suspected) exposure to rabies (ICD-10 Z20.3), need for prophylactic vaccination and inoculation against rabies (ICD-9 V04.5), or encounter for prophylactic rabies immune globulin (ICD-10 Z29.14), or a National Drug Code for any of the marketed RIG products in the USA.

Patient and public involvement

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research. No patients were involved.

Variables and outcome of interest

The date on which RIG was administered was defined as the 'Index Date'. Variables of interest were ICD-9 and ICD-10 codes co-occurring on the index date, and CPT codes occurring 1 week before to 2 weeks after the index date.

Table 1 Characteristics of adults and children included in the study population

Characteristic	Adult n (%)	Paediatric n (%)
Gender		
Male	35 308 (44.3)	11 074 (54.3)
Female	44 457 (55.7)	9307 (45.7)
Age	79 766	
0–3	–	4101 (20.1)
4–6	–	4434 (21.8)
7–10	–	6483 (31.8)
11–15	–	4928 (24.2)
16–17	–	435 (2.1)
18–34	24 192 (30.3)	–
35–44	15 095 (18.9)	–
45–54	13 219 (16.6)	–
55–64	13 413 (16.8)	–
65+	13 847 (17.4)	–
Payer type		
Commercial	59 172 (74.9)	14 226 (70.1)
Managed care Medicare	8647 (10.8)	–
Medicaid	9989 (12.5)	5623 (27.7)
Other	1958 (2.5)	443 (2.2)

Statistical analysis

We used mutual information (MI) to identify features that differentiate the population of interest from a control population. Data variables are ranked by MI value (0–1): a high value indicates higher statistical dependence or relevance to the event or feature of interest. A value of 0 means that the two random variables are independent. Features used for MI analysis in this study included diagnostic codes (ICD-9-Clinical Modification (CM) and ICD-10-CM) and procedures performed (CPT codes).[9]

RESULTS

A total of 79 766 adult and 20 381 paediatric patients from the Symphony IDV met inclusion criteria. Table 1 depicts the demographic characteristics of the study population. The sample comprised 55.7% (44.457) adult female patients while 54.3% (11 074) of the paediatric sample was male. The most common age group in the adult category was 18–34 (30.3%) while the most common age group in the paediatric population was the 7–10 (31.8%). For both subpopulations, the majority of subjects had commercial insurance (74.9% for adult and 69.8% for paediatric subjects, respectively).

Using MI,[9] we identified the top diagnostic and procedure codes that differentiated paediatric from adult

Table 2 Top diagnoses differentiating paediatric versus adult patients

Diagnosis	Adult (n=79 766) n (%)	Paediatric (n=20 381) n (%)	Prevalence ratio (paediatric/adult)
Open wounds of head; neck; and trunk	952 (1.19)	1438 (7.05)	5.92
Dog bite	16 553 (20.73)	5417 (19.96)	0.96
Bite of other animals except arthropod	14 509 (18.19)	1797 (8.82)	0.48
Encounter for removal of sutures	74 (0.09)	36 (0.18)	2.00
Skin infections	2480 (3.11)	243 (1.19)	0.38
Open wound of hand except finger(s) alone; without mention of complication	11 593 (14.53)	1276 (6.26)	0.43
Open wound of finger(s); without mention of complication	11 114 (13.93)	1292 (6.34)	0.46
Abrasion or friction burn of face; neck; and scalp except eye; without mention of infection	490 (0.61)	386 (1.89)	3.10
Open wound of scalp; without mention of complication	196 (0.25)	226 (1.11)	4.44
Laceration of skin of eyelid and periocular area | laceration of eyelid involving lacrimal passages	126 (0.16)	220 (1.08)	6.75

patients who received RIG. The top diagnoses that distinguished the two patient populations are represented in table 2. Among the diagnoses recorded on the index date, paediatric patients had a 5.92-fold higher prevalence of 'open wounds to the head; neck; and trunk', a 3.10-fold higher prevalence of 'abrasion or friction burn of face; neck; and scalp except eye; without mention of infection', a 4.44-fold higher prevalence of 'open wound of scalp; without mention of complication' and a 6.75-fold higher prevalence of 'laceration of skin of eyelid and periocular area | laceration of eyelid involving lacrimal passages'. Notable diagnoses that were more prevalent in the adult population included a 2.61-fold higher prevalence of 'skin infections', a 2.32-fold higher prevalence of 'open wound of hand except finger(s) alone; without mention of complication' and a 2.19-fold higher prevalence of 'open wound of finger(s); without mention of complication'.

We also identified top differentiating procedures that were performed temporally associated with (1 week prior or 2 weeks after) the index date (table 3). Procedures that best differentiated paediatric from adult patients included a 161-fold higher prevalence of 'repair; intermediate wounds of face; ears; eyelids; nose; lips and/or mucous membranes; 7.6 cm to 12.5 cm' and a 15.3-fold higher prevalence of 'Injection; midazolam hydrochloride; per 1 mg'. Adult patients had a 6.58-fold higher prevalence of 'simple repair of superficial wounds of face; ears; eyelids; nose; lips; and/or mucous membranes; 2.5 cm or less'.

Wound size and severity must inform administration of RIG. Codes reporting wound severity and wound

Table 3 Top procedures differentiating paediatric versus adult patients

Procedure	Adult (n=79 766) n (%)	Paediatric (n=20 381) n (%)	Prevalence ratio (paediatric/adult)
Injection; ketorolac tromethamine; per 15 mg	135 (0.44)	3695 (2.9)	6.59
Simple repair of superficial wounds of face; ears; eyelids; nose; lips and/or mucous membranes; 2.5 cm or less	976 (3.16)	616 (0.48)	0.15
Subsequent hospital care; per day; for the evaluation and management of a patient	225 (0.73)	1887 (1.49)	2.04
Level 3 hospital emergency department visit provided in a type b emergency department	76 (0.25)	457 (0.36)	1.44
Hospital observation service; per hour	203 (0.66)	1682 (1.33)	2.02
Injection; midazolam hydrochloride; per 1 mg	378 (1.23)	1353 (18.90)	15.37
Injection; enoxaparin sodium; 10 mg	0 (0.00)	453 (1.07)	0.00
Moderate sedation services (other than those services described by codes 00100–01999); provided by a physician or other qualified healthcare professional other than the healthcare professional performing the diagnostic or therapeutic service that the sedation supports; younger than 5 years of age; first 30 min intraservice time	14 (0.04)	0 (0.00)	0.00
Topical application of fluoride varnish	32 (0.1)	0 (0.00)	0.00
Repair; intermediate; wounds of face; ears; eyelids; nose; lips and/or mucous membranes; 7.6–12.5 cm	22 (0.07)	20 (11.3)	161.43

Table 4 Simple repair wounds for adult and paediatric patients, by location and size

Location (size, cm)	Adult (n=79 766) n (%)	Paediatric (n=20 381) n (%)	Prevalence ratio (paediatric/adult)
Total	3528 (4.4)	1440 (7.0)	1.59
Neck; axillae; external genitalia; trunk or extremities			
<2.5	1291 (1.6)	366 (1.8)	1.13
2.6–7.5	1288 (1.6)	261 (1.3)	0.81
7.6–12.5	254 (0.32)	44 (0.22)	0.69
12.6–20.0	86 (0.11)	23 (0.11)	1.00
20.1–30.0	19 (0.02)	3 (0.01)	0.50
>30	9 (0.01)	1 (0.0)	0
Face; ears; eyelids; nose; lips, and/or mucous membranes			
<2.5	353 (0.44)	517 (2.5)	5.68
2.6–5.0	167 (0.21)	169 (0.83)	3.95
5.1–7.5	37 (0.05)	34 (0.17)	3.4
7.6–12.5	22 (0.03)	20 (0.10)	3.33
12.6–20	2 (0.0)	2 (0.01)	0

sizes were among the top characteristics differentiating paediatric and adult patients. The CPT code set contains families of codes that report simple, intermediate and complex wound repairs of different sizes and anatomical regions. We therefore sought to evaluate wound severity by location and size for adults and children by retrieving frequencies of codes from these code sets co-occurring with RIG on the index date.

Simple wound repair requires a simple, one-layer closure and primarily involves the epidermis, dermis or subcutaneous tissues, but no deeper structures, and is reported in table 4. Paediatric patients had a 1.56-fold higher prevalence of codes reporting simple repairs compared with adults (n=1440, 6.9% vs n=3528, 4.4%, respectively). Prevalence ratios between paediatric and adult patients were largest for codes reporting simple repairs in the face, ears, eyelids, nose, lips and/or mucous membranes (3.33-fold to 5.68-fold more prevalent in paediatric patients).

Intermediate repairs require a layered closure of one or more deeper layers of subcutaneous tissue and superficial fascia, in addition to a simple repair and skin closure, and are reported in table 5. Paediatric patients had a 2.19-fold higher prevalence of intermediate repairs compared with adults (n=318, 1.5% vs n=555, 0.7%). Prevalence ratios were largest for intermediate repairs on the face, ears, eyelids, nose, lips and/or mucous membranes (threefold to sixfold more prevalent in paediatric patients).

Complex repairs require more than a layered closure, viz scar revision, debridement, extensive undermining, or stents or retention sutures, and reported in table 6. Paediatric patients had a 3.83-fold higher prevalence of complex repairs compared with adult patients (n=157, 0.7% vs n=157, 0.2%, respectively). The largest difference in prevalence was for 2.6–7.5 cm complex repairs on the forehead, cheeks, chin, mouth, neck, axillae, genitalia,

Table 5 Intermediate repair wounds for adult and paediatric patients, by location and size

Location (size, cm)	Adult n (%)	Paediatric n (%)	Prevalence ratio (paediatric/adult)
Total	555 (0.7)	318 (1.6)	2.29
Neck; axillae; trunk and/or extremities (excluding hands and feet)			
<2.5	54 (0.07)	39 (0.19)	2.71
2.6–7.5	135 (0.17)	47 (0.23)	1.35
7.6–12.5	60 (0.09)	19 (0.09)	1.00
12.6–20.0	27 (0.03)	7 (0.03)	1.00
20.1–30.0	7 (0.01)	2 (0.01)	1.00
>30	2 (0.0)	1 (0.0)	1.00
Neck; hands; feet and/or external genitalia			
<2.5	51 (0.06)	16 (0.08)	1.33
2.6–7.5	69 (0.09)	6 (0.03)	0.33
7.6–12.5	12 (0.02)	0 (0.0)	0.00
12.6–20	0 (0.00)	0 (0.0)	0.00
Face; ears; eyelids; nose; lips, and/or mucous membranes			
<2.5	50 (0.06)	73 (0.36)	6.00
2.6–5.0	49 (0.06)	69 (0.34)	5.67
5.1–7.5	19 (0.02)	13 (0.06)	3.00
7.6–12.5	16 (0.02)	13 (0.06)	3.00
12.6–20	4 (0.01)	8 (0.04)	4.00
20.1–30	0 (0)	4 (0.02)	0.00

hands and/or feet, which was 7.25-fold more prevalent in paediatric patients.

For adults, the most common wound location was hand/feet (33.2%), followed by arms (19.1%) and legs (14.1%). For paediatric patients, the most common wound location was hand/feet (15.1%), followed by head/neck (13.7%) and legs (11.2%). The prevalence ratio was largest for wounds in the head/neck, with a 4.72-fold greater prevalence in paediatric patients relative to adults (table 7). For both adult and paediatric cases, dogs were the most common type of animal encounter (table 8).

DISCUSSION

Several characteristics distinguished paediatric from adult patients who received RIG. The location and severity of wounds were among the top characteristics identified by MI, particularly higher prevalence of hand wounds in adults versus higher prevalence of head wounds in children. We observed distinct differences in wound severity between adults and children. Our results are consistent with other studies that have found that children were more likely to sustain bites on the head and face due to their smaller size.[1 10 11]

In this study, we found that more instances of paediatric RIG use occurred in males (54.3%) compared with more adult use in females (55.7%), which may be partially due

Table 6 Complex repair wounds for adult and paediatric patients, by location and size

	Adult n (%)	Paediatric n (%)	Prevalence ratio (paediatric/adult)
Total (excluding supplementary codes)	157 (0.2)	157 (0.77)	3.85
Location (size, cm)			
Trunk			
1.1–2.5	1 (0)	0 (0)	0.00
2.6–7.5	2 (0)	5 (0.02)	0.00
Each additional 5	2 (0)	1 (0)	0.00
Scalp; arms; and/or legs			
1.1–2.5	4 (0.01)	2 (0.01)	1.00
2.6–7.5	51 (0.06)	21 (0.1)	1.67
Each additional 5	20 (0.03)	13 (0.06)	2.00
Forehead; cheeks; chin; mouth; neck; axillae; genitalia; hands and/or feet			
1.1–2.5	12 (0.02)	8 (0.04)	2.00
2.6–7.5	34 (0.04)	59 (0.29)	7.25
Each additional 5	13 (0.11)	23 (0.11)	1.00
Eyelids; nose; ears and/or lips			
<1	0 (0)	0 (0)	0.00
1.1–2.5	17 (0.02)	16 (0.08)	4.00
2.6–7.5	36 (0.05)	46 (0.23)	4.60
Each additional 5	8 (0.01)	11 (0.05)	5.00

to previously reported risk-taking behaviours of male children towards dogs. We also found a slightly higher prevalence of dog bites in paediatric compared with adult patients. This finding is consistent with other reports where children were found to be the major targets and more vulnerable to dog bites because of lack of awareness of the dangers of rabies, dogs viewing them as easier targets due to their small size[12] and children's natural curiosity.[13 14] Additional studies have also reported higher bite frequencies among boys compared with girls which can partially be explained by gender differences in behaviour towards dogs.[12] Shetty *et al* have observed that more than half of animal bite victims were children aged <14 years.[15] Male children were found to be twice as likely as females to be bit which is also consistent with the findings in previous studies.[13 16]

Dogs may be more likely to bite the face, especially the 'central target area', which includes the lips, nose and cheeks.[17] Between 50% and 80% of paediatric bite injuries involve the head and neck.[17] This results in 44 000 paediatric facial injuries in the USA per year.[17] About one-third of these are categorised as severe, and most occur in younger children under the age of 10.[17]

Table 7 Wound location by adult versus paediatric patients

Wound location	Adult n (%)	Paediatric n (%)	Prevalence ratio (paediatric/adult)
Head/neck	2357 (2.9)	2783 (13.65)	4.71
Body	2474 (3.1)	846 (4.15)	1.34
Arms	15 267 (19.1)	1645 (8.07)	0.42
Legs	11 208 (14.1)	2274 (11.16)	0.79
Hand/feet	26 470 (33.2)	3086 (15.14)	0.46

Table 8 Type of animal encounter by adult versus paediatric patients

Wound location	Adult n (%)	Paediatric n (%)
Dog	12 188 (15.28)	3924 (19.25)
Squirrel	228 (0.29)	55 (0.27)
Other rodent	237 (0.30)	53 (0.26)
Raccoon	1689 (2.12)	115 (0.56)
Insect/non-venomous arthropods	102 (0.13)	24 (0.12)
Animate mechanical forces	689 (0.86)	106 (0.52)

Prevention of infections that affect the central nervous system is of the highest research priority; complete prevention of infection reduces the risk of nervous system sequelae. Prevention and treatment of infections that affect the central nervous system requires the identification of the pathogens responsible, the pathogen reservoirs and the potential points at which the pathogen life cycle can be disrupted.[18] The development of a human rabies vaccine has a distinguished history dating back more than 120 years to Louis Pasteur. Since then, innumerable lives have been saved and human morbidity decreased through pre-exposure prophylaxis and PEP. However, despite the availability of effective rabies vaccines for humans and intensive efforts to control rabies in animals worldwide, every year, people continue to suffer and die from rabies virus infections.[1] Up to 60% of these cases are in children,[1] making rabies the seventh leading infectious disease in terms of years of life lost.[19] Despite the high disease burden in paediatric patients, no registered clinical studies for any human RIG (HRIG) had been conducted in this population until recently.[20] In certain areas, the overall number of rabid animals detected has increased by almost 20%,[21] illustrating the challenge in containing epizootic viral reservoirs and emphasising the need to have animal bites evaluated for possible exposure to rabies. Although human rabies is rare in the USA, viral reservoirs persist in wildlife and a significant number of persons receive PEP treatment annually.[22 23] Educating clinicians about appropriate PEP protocol is key to the prevention of rabies infection, but educational gaps, particularly related to RIG, remain.[24] The challenge lies in rabies cases being rare and maintaining clinician's knowledge and skills to treat a patient who has presented for possible rabies exposure.

Timeliness and sufficiency of care are key determinants of treatment effectiveness following a rabies virus exposure. Delayed and incomplete care, particularly in infiltration of RIG and paediatric patients, are documented in literature as primary contributors to cases of PEP failure leading to rabies disease and patient death.[8 25] Our present findings further emphasise the particular importance of prompt and adequate care in paediatric patients.

Animal bites to the head and face are especially risky due to proximity to the central nervous system, reducing the time window for effective preventive intervention and thereby increasing the risk of clinical progression to rabies if the bite occurs from a rabid animal.[1] In addition, lower body bites are associated with a longer rabies incubation period, therefore, resulting in a longer period for rabies to manifest and providing a false sense of security.[12] Unvaccinated patients should receive immediate PEP that includes RIG as soon as possible to neutralise the viral inoculum, as the immunogenic response to vaccination may be delayed by 7–10 days.[1 4]

RIG neutralises virus at the bite site to prevent migration of the virus to the nervous system. Cases of PEP failure, despite vaccination, have been reported in children with extensive wounds in whom RIG treatment was insufficient.[8] Insufficiency of RIG comprised omission, delayed administration or incomplete infiltration due to lack of volume to enable infiltration of all wounds (particularly when old recommendations to use only 50% of the RIG volume for infiltration were followed). Indeed, these seminal findings in children prompted revision in the Centers for Disease Control and Prevention (CDC) guidelines in 1999 to instead recommend infiltration of the full dose of RIG.[26] In cases of volume insufficiency, increasing the dose of RIG is prohibited as dosing higher than 20 IU/kg interferes with vaccine immunogenicity.[27] Instead, WHO recommends dilution with a compatible diluent (normal saline for most standard-volume HRIGs; 1:1 dilution with 5% dextrose for low-volume concentrated HRIGs).[8 28] Our findings demonstrate that children more frequently sustain larger, more complex wounds compared with adults, increasing the minimum volume of RIG necessary to fully infiltrate; in contrast, their low bodyweight restricts the volume of RIG available. This constricted safety margin creates risk for underdosing and overdosing treatment errors in these patients, compounded by deficient provider awareness and adherence to practice standards.[6 24 29] CDC guidelines use standardised weight-based dosing that do not distinguish between adult and paediatric patients.[4] Weight-based dosing of RIG is based on evidence to avoid vaccine interference but is not informed by evidence on the mechanism of efficacy of RIG which is instead predicated on sufficiency of volume of RIG used for infiltration.[30] Recently, new guidelines issued in several European countries have integrated volume-based and wound-based dosing minimums with weight-based maximums, thus approaching a comprehensive evidence-based guideline to ensure both efficacy and safety.[31]

Limitations

IDV data are not generalisable to the entire nation. Rather, they are only applicable to the population studied and included in the data set: adults and children who presented with suspected rabies and received rabies prophylaxis treatment. Selection bias may be present in this study as only those injuries that are deemed to be severe enough for presentation to a centre captured by the data are represented here. It may be possible that many cases that presented to centres not captured by the data set may have a different profile. Nevertheless, frequency of reporting in adult and paediatric populations is not expected to differ in a biased manner.

Anatomical locations of wound repair codes in the CPT codebook are categorised by groups of anatomical regions. Thus, based on the present data set, we were not able to further precisely discern the relationship between the severity of wounds and their specific anatomical location, and some effects may be driven by increased prevalence in wounds in one particular location rather than all locations in a group.

RIG is not always administered on the day of presentation, such as in instances when the exposing animal is captured and available for testing to confirm rabies infection status prior to initiation of PEP. In some instances, procedures associated with an animal exposure may have been performed prior to or after administration of RIG outside of the studied time window, and thus not included in codes retrieved in the current data set. Furthermore, retrieved procedures are temporally associated on the index date with RIG claims, but a definitive causative link cannot be confirmed due to the nature of claims data; thus, it is possible that some wounds are sustained independently of the qualifying suspected rabies exposure.

CONCLUSION

Paediatric patients represent a significant proportion of the patient population receiving RIG, and associate with higher prevalence of CPT codes reporting repair of larger, more complex wounds in highly innervated anatomical regions.

Contributors RVB interpreted the data, drafted the initial manuscript and critically reviewed and revised the manuscript. PR, MS and WW analysed the data and critically reviewed and revised the manuscript. NA conceptualised and designed the study and critically reviewed the manuscript for important intellectual content. H-BN conceptualised and designed the study, critically reviewed the manuscript for important intellectual content and oversaw the entire study effort. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. H-BN acts as gaurantor of the study.

Funding Research funding was provided by Kedrion Biopharma.

Competing interests RVB, WW: consultants for Kedrion Biopharma. PR, MS: employees of Eversana Life Science Services, analytics providers for Kedrion Biopharma. NA, H-BN: employees of Kedrion Biopharma.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval This study involves human participants but an ethics committee or institutional review board exempted this study. WCG IRB reviewed and approved this study (confirmation number: 44790287).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. Study data were queried from the Symphony Integrated Dataverse (IDV), an integrated healthcare database that includes claims (medical, hospital and prescription), point-of-sale prescription, non-retail invoice and

demographic data, encompassing data on nearly 250 million patient lives in the USA. Contact: parusso@eversana.com.

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