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Abstract

Background: Many travellers sustain an animal-associated injury (AAI) that may lead to rabies. To avert infection the WHO recommends starting post-exposure prophylaxis (PEP) within 24 hours of the AAI. Many travellers experience PEP delay (60%). The reason for this is unclear, but delay leads to unnecessary health risks, anxiety, and potentially death. Therefore, this study aims to analyse which factors contribute to PEP delay while abroad.

Methods: A quantitative observational study was conducted among Dutch travellers between 2019 and 2024 using case records from the Eurocross Assistance database. The records consisted of information provided by the traveller during the trip. A multivariable logistic regression analysis with backward selection was performed to identify the factors contributing to PEP delay.

Results: Of the 1410 AAI notifications, 838 travellers required PEP of whom 59.4% experienced PEP delay. The analysis showed higher odds of delay for travellers requiring rabies immunoglobulins (RIG) (OR:6.46; 95%-CI:4.26–9.79), and those travelling to South America (OR:22.39; 95%-CI:9.78–51.21), Central America (OR:11.54; 95%-CI:4.57–29.16), North America (OR:5.53; 95%-CI:2.04–14.96), Europe (OR:4.08; 95%-CI:2.17–7.67), Africa (OR:3.34; 95%-CI:1.59–7.02), Eastern Mediterranean (OR:2.54; 95%-CI:1.38–4.67), and the Western Pacific (OR:2.37; 95%-CI:1.36–4.12) compared to Southeast Asia. PEP delay was mainly due to conflicting medical advice and unavailability of treatment. Absence of RIG led to repatriation of 65 (7.8%) travellers to the Netherlands. The median delay for RIG was 2 days (range: 0–10), and 0 days for rabies vaccinations (range: 0–15). The highest median delay for RIG was observed in Central and South America (4.5 days; range: 1–10 and 1–7, respectively), while no delay was observed in Southeast Asia.

Conclusions: Travellers to Central- and South America are at particularly high risk of PEP delay, primarily due to conflicting medical advice and unavailability of RIG. Our findings suggest that destination-specific pre-exposure prophylaxis advice may reduce preventable delays and improve rabies prevention outcomes.

Key words Rabies vaccines, rabies immunoglobulin, PrEP, PEP, treatment delay, annimal associated injury (AAI), travel destination

Introduction

Rabies is a zoonotic infectious disease caused by the rabies virus.[1–3] Despite the fact that rabies is a vaccine-preventable disease, it is estimated that 59.000 people worldwide, possibly more,[1,3,4] still die of rabies each year.[3,5]

The prevalence of rabies in high-income countries is low, and rabies is mostly an imported disease by travellers. Only 18 travel-related cases were reported between 2006 and 2019 in the European Union (EU) and European Economic Area.[6] Figures for an animal associated injury (AAI) are much higher: an estimated 0.4% of travellers are at risk of encountering an AAI.[7] Furthermore, since COVID-19 more AAIs have been recorded, and an increase in aggressive and rabies-infected dogs has been observed,[8,9] likely due to the fact that stray dogs were not being fed anymore, making them more aggressive and stray dog vaccination programs were not being carried out due to COVID-19 restrictions and shifted financial priorities in canine rabies-endemic countries.[8–10]

In the event of an animal-associated injury in a rabies-endemic area, the World Health Organization (WHO) recommends starting post-exposure prophylaxis (PEP) as soon as possible, preferably within 24 hours to prevent infection. PEP consists of washing the wound thoroughly with soap and water for 15 minutes immediately after the AAI, a series of rabies vaccinations (RV), and in some cases an injection of rabies immunoglobulin (RIG) (Supplementary Table 1). In healthy individuals who have received pre-exposure prophylaxis (PrEP), RIG is not indicated. PrEP currently consists of two pretravel vaccinations[3] and provides life-long immunological memory.[11] It is recommended for people travelling to endemic areas where PEP is not readily available or where the person is at high risk of contact with wild animals.[3,12] Despite these recommendations, only 22% of German travellers[13] and 13% of Dutch travellers to rabies-endemic areas, received PrEP.[14]

In the absence of PrEP, individuals are likely to need a more extensive PEP regimen, where RIG is indicated in the case of transdermal AAIs.[3,11,12] However, PEP is not widely available.[5,15,16] Particularly RIG is not only expensive but often scarce and difficult to obtain, especially in low- and middle-income countries.[3,17] Gautret *et al*.[18] stated that almost 65% of the travellers who needed RIG did not receive it, and only 24.7% of the travellers who did receive RIG received it in the country of exposure.

In addition, a study conducted among Dutch travellers showed that PEP was delayed in up to 60% of cases, but the possible causes of this delay remained unknown.[19] Rabies PEP delay can result in anxiety and fear of affected individuals,[20] increased costs, such as repatriation or evacuation,[21] and most importantly unnecessary increased health risks, which could ultimately lead to death.[5]

Dutch travellers who have sustained an AAI can contact their medical assistance centre, which provides medical advice to travellers abroad, on behalf of the medical of travel insurance companies, such as Eurocross Assistance (ECA), which covers 30% of the Dutch market.[22]

Health insurance is mandatory in the Netherlands. This basic insurance covers all urgent care abroad at the Dutch market rate. Additional insurance (partly) covers care not included in the basic package, such as pre-travel vaccinations. Rabies PEP is considered urgent care, and all costs are therefore covered by the health insurance.[23]

In the summer of 2023, ECA reported 175 AAI notifications, an increase of 34% compared to the same period in 2022.[24] Additionally, a rise in PrEP uptake among travellers in recent years was noted.

Although the risk of rabies after an AAI is $< 0.001\%$,[4] once symptoms appear, it is lethal. This knowledge affects the psychological well-being of travellers after an AAI. This, combined with the increasing reported number of AAIs,[8,9,24] the vast lack of RIG,[18] and the frequent PEP delay,[19] requires examining factors leading to PEP delay and trends in PrEP uptake.

Methods

Study design and population

A quantitative retrospective observational study was conducted using case records from the ECA database. The study population consisted of insured Dutch travellers who actively contacted ECA after an AAI abroad, representing a specific subset of the Dutch travelling population. To provide good medical advice in line with WHO guidelines,[3] a standardized rabies questionnaire was sent by ECA consultants on the day of AAI notification to obtain detailed information on the characteristics and circumstances of the AAI. The National Institute for Public Health and the Environment was contacted when repatriation was required to provide the RIG or in cases of doubt.

Data collection

Between 1 October 2019, and 31 January 2024, 1410 AAI notifications were reported by Dutch travellers contacting ECA. Collected information provided by the client was anonymised. Upon return to the Netherlands, follow-up care was transferred from ECA to Dutch healthcare providers, such as the Municipal Public Health Services.

PEP administration was considered delayed if the traveller did not receive the first rabies vaccination (RV1) and/or RIG within 24 hours of the AAI.[3] Variables were included based on expert opinion and prior studies[9] and consisted of the traveller's gender, age, PrEP status, WHO region where the AAI was sustained, animal involved, RIG requirement, travel duration in days, WHO-category of injury, and location of body injury.

Multiple reasons were accounted for PEP delay, which were categorized into seven groups: 'Delayed traveller notification' (travellers notified AAI > 24 hours after exposure); 'Conflicting medical advice' (discrepancies between the recommendations given by local healthcare providers and WHO guidelines); 'Unavailability of treatment' (situations where RIG and/or RV were not available); 'Hospital-related logistical issues' (such as closed hospitals due to bank holidays or weekends, and a lack of medical staff); 'Traveller-related logistical issues' (delays caused by slow responses from the traveller or their remote location); 'Refusal of ECA advice' (travellers who declined repatriation to the Netherlands to receive appropriate treatment and instead followed local medical advice); and 'Other' (such as cases that were awaiting the possible animal vaccination certificate before seeking further treatment).

Statistical analyses

A descriptive analysis was performed to visualize the study population's characteristics and to provide an overview of the reasons for PEP delay. Means and standard deviations (SDs) were used for quantitative variables and percentages for categorical variables. Additionally, we made a stratification based on PrEP status. Subsequently, a chi-square test was used to analyse whether PrEP uptake had significantly increased between the period 2015–2019 and 2019–2024, using the data of a comparable study done by ECA.[19] This study consisted of 691 insured Dutch international travellers who actively contacted their medical assistance company because of an AAI.

A multivariable logistic regression analysis with manual backward selection, using the log-likelihood ratio, was performed to identify the variables contributing to PEP delay. The log-likelihood ratio required a P-value of < 0.05 with appropriate

degrees of freedom to develop the statistical model. The analysis was repeated until the most parsimonious model was selected. To reduce bias from missing data, a sensitivity analysis using imputation of missing data was performed if < 10% of the data was unavailable. The receiver operating characteristic (ROC) curve measured the quality of the model by calculating the area under the curve (AUC). The Nagelkerke R-square was used to test the model's goodness of fit.

As other studies showed that RIG requirement and WHO regions were strongly related to PEP delay,[9] additional analyses were performed to examine the reasons and the median delay of RV and RIG across the different WHO regions.

All statistical analyses were performed using IBM SPSS Statistics 29.

Results

General characteristics

Between October 2019 and January 2024, 1410 travellers reported an AAI, of which 13 did not complete the questionnaire (Table 1).

Within our sample 838 travellers required PEP. Geographically, most AAIs occurred in Southeast Asia (39.7%), followed by South America (14.4%) and Europe (11.3%). The AAIs were mainly caused by dogs and often occurred within the first 2 weeks of travel. Most injuries concerned a type III (69.1%), and in 38.8% local medical advice differed from the WHO guidelines.

Almost 60% of the travellers experienced PEP delay, which occurred mainly in Southeast Asia (24.9%) and South America (21.5%) compared to the whole sample. Within the group of PEP delay, 65.9% were not PrEP-ed, in 48.8% RIG was indicated, and 52.4% notified ECA late. Five travellers were immunocompromised, none of whom received PEP within 24 hours.

Results of the stratification based on PrEP are shown in Supplementary Table 2.

A total of 288 travellers required both RIG and RV (Table 2). Of this group, only 14.9% was not delayed. Among the delayed group, 14.9% received RIG and RV on the same delayed day and 31.6% of the travellers received RV on time, but RIG administration was delayed. In one case RIG was given on time, but the traveller received RV delayed.

Of the 107 travellers who received RIG in the Netherlands, 65 (60.7%) were repatriated due to the regional unavailability of RIG and therefore to ensure timely RIG administration. This group of 65 travellers represent 7.8% of the 838 travellers who required PEP. The remaining 42 travellers received RIG in the Netherlands after returning home, as the return date matched the date of PEP administration.

Travellers gave multiple reasons for delayed PEP administration (Figure 1). Unavailability of treatment and conflicting medical advice were most common in the group requiring RIG (resp. RIG: 27.7% vs RV: 15.3% and RIG: 33.9% vs RV: 13.4%), while a delayed traveller notification was more common in the group not requiring RIG (RV: 38.2% vs RIG: 19.9%). Among those who required rabies vaccinations and made a delayed notification, 81 (41.3%) had received PrEP before travel. Some clients refused ECAs advice (RV: 6 (1.2%) and RIG: 17 (4.6%)), 13 of those travellers saw no point in flying back to the Netherlands to receive the necessary treatment and chose to follow local advice.

PrEP incidence rate

To test whether the PrEP intake had increased between the period December 2015–February 2019[19] and October 2019–January 2024, the Chi-Square test of independence was analysed. In the period 2015–2019, 28.9% of the clients who reported an AAI to ECA had received PrEP, compared to 39.9% in the period 2019–2024, $X^2 = 23.83$ ($P < 0.001$).

Risk factors associated with PEP delay

A multivariable logistic regression analysis with backward selection was performed (Table 3). Based on the log-likelihood ratio the variables gender, age, and location of body injury were removed. In addition, the variables PrEP status, travel duration in days, involved animal and type of injurywere removed as they were highly insignificant. The −2 log-likelihood slightly increased and the Nagelkerke R^2 decreased, indicating only a minimal reduction in model fit.

The variable travel duration had 123 (14.7%) missing values. However, these missing data were evenly distributed across the outcome PEP delay, and were caused by travellers who had not booked their return ticket yet. A sensitivity analysis using imputation of missing data was conducted to assess whether these missing values would influence the results. The analysis showed little difference in outcome, supporting the decision to include the variable 'travel duration in days' in the primary analysis.

Clients who required RIG had higher odds of delay compared to those who did not require RIG. Travellers who sustained an AAI outside Southeast Asia were all more likely to experience PEP delay (Table 3).

A ROC curve was used to calculate the AUC, which was 0.81 (95% CI: 0.78–0.84), indicating good discriminative ability and supporting the overall strength of the model. The Nagelkerke R^2 was 0.38, suggesting that ∼38% of the variance in the outcome could be explained by the model.

Delay factors by the travellers destination

Table 4 shows the reasons and the median delay of RV and RIG in the different WHO regions. Supplementary Table 3 shows an in-depth analysis of the top three countries per WHO region, where PEP-delay was experienced.

Conflicting medical advice (47.1%) was a common problem in Eastern Europe, and especially in Turkey, where local medical staff did not recommend RIG or thought rabies no longer existed in their country. Travellers to South America frequently cited conflicting medical advice, especially in Colombia, and unavailability of treatment, whereas travellers in Central America often made a delayed notification (37.0%). Travellers in Indonesia reported remote places as the main reason for delay, and clients in Mexico had to deal with closed hospitals due to festivities.

Table 1 General characteristics of Dutch travellers who actively contacted Eurocross Assistance after encountering an animal-associated injury and required post-exposure prophylaxis

	No PEP delay. n (%) N = 340 (40.6)	**PEP delay. n (%) N = 498 (59.4)**	**Total. n (%) N = 838 (100)**	***P*-value**
Age in years (mean ± SD ± range)	28.9 ± 12.0 ± 68	26.5 ± 11.7 ± 76	28.5 ± 11.8 ± 76	
Travel duration in days (median ± IQR ± range)	27.0 ± 37.0 ± 361	26.0 ± 52.0 ± 880	27.0 ± 45.0 ± 880	
Gender				0.272
Male	146 (42.9)	233 (46.8)	379 (45.2)	
Female	194 (57.1)	265 (53.2)	459 (54.8)	
WHO region				<0.001
Africa	16 (4.7)	26 (5.2)	42 (5.0)	
Southeast Asia	209 (61.5)	124 (24.9)	333 (39.7)	
Europe	21 (6.2)	74 (14.9)	95 (11.3)	
Eastern Mediterranean	25 (7.4)	51 (10.2)	76 (9.1)	
Western Pacific	42 (12.4)	45 (9.0)	87 (10.4)	
North America	7 (2.1)	25 (5.0)	32 (3.8)	
Central America	6 (1.8)	46 (9.2)	52 (6.2)	
South America	14 (4.1)	107 (21.5)	121 (14.4)	
Received PrEP				<0.001
Yes	195 (57.4)	169 (33.9)	364 (43.4)	
No	144 (42.4)	328 (65.9)	472 (56.3)	
Missing	1 (0.3)	1 (0.2)	2 (0.2)	
Wound classification				<0.001
Type I	9 (2.6)	6 (1.2)	15 (1.8)	
Type II	122 (35.9)	121 (24.3)	243 (29.0)	
Type III	208 (61.2)	371 (74.5)	579 (69.1)	
Missing	1 (0.3)	0 (0.0)	1 (0.1)	
Location of body injury				0.979
Head/neck area	20 (5.9)	31 (6.2)	51 (6.1)	
Other	318 (93.5)	464 (93.2)	782 (93.3)	
Missing	2 (0.5)	3 (0.6)	5 (0.6)	
Involved animal				<0.001
Cat	77 (22.6)	156 (31.3)	233 (27.8)	
Dog	172 (50.6)	276 (55.4)	448 (53.5)	
Monkey	82 (24.1)	52 (10.4)	134 (16.0)	
Bat	2 (0.6)	8 (1.6)	10 (1.2)	
Other	7 (2.2)	6 (1.2)	13 (1.6)	
Type AAI				0,865
Bite	174 (51.2)	253 (50.8)	427 (51.0)	
Scratch	132 (38.8)	199 (40.0)	331 (39.5)	
Lick on broken skin	24 (7.1)	37 (7.4)	61 (7.3)	
Lick	7 (2.1)	6 (1.2)	13 (1.6)	
Other	3 (0.9)	3 (0.6)	6 (0.7)	
Medical care needed: RIG				<0.001
Yes	45 (13.2)	243 (48.8)	288 (34.4)	
No	292 (86.5)	253 (50.8)	544 (64.2)	
Missing	1 (0.3)	2 (0.4)	3 (0.4)	
Immunocompromised				0.064
Yes	0 (0.0)	5 (1.0)	5 (0.6)	
No	340 (100.0)	493 (99.0)	833 (99.4)	
AAI after departure (median ± IQR ± Range)	13.0 ± 21.0 ± 375	14.0 ± 22.0 ± 841	13.0 ± 21.0 ± 841	0.971
Week 1	92 (27.1)	138 (27.7)	230 (27.4)	
Week 2	81 (23.8)	110 (22.1)	191 (22.8)	
Week 3	48 (14.1)	71 (14.3)	119 (14.2)	
Week 4	26 (7.6)	33 (6.6)	59 (7.0)	
More than 4 weeks	74 (21.8)	115 (23.1)	188 (22.6)	
Missing	19 (5.6)	31 (6.2)	50 (6.0)	
Time between AAI and notification				<0.001
Within 24 hours	288 (84.7)	232 (46.6)	520 (62.1)	
After 24 hours	51 (15.0)	261 (52.4)	312 (37.2)	
Missing	1 (0.3)	5 (1.0)	6 (0.7)	
Difference in advice				<0.001
Yes	106 (31.2)	219 (44.0)	325 (38.8)	
No	63 (18.6)	40 (8.0)	103 (12.3)	
Rectification of advice	1 (0.3)	2 (0.4)	3 (0.4)	
Missing	170 (50.0)	237 (47.6)	407 (48.6)	
Rabies advice				<0.001
Two vaccinations	186 (54.7)	161 (32.3)	347 (41.4)	
Four vaccinations	91 (26.8)	75 (15.1)	166 (19.8)	
Four vaccinations + RIG	45 (13.2)	242 (48.6)	287 (34.2)	
Other	18 (5.3)	20 (4.0)	38 (4.5)	

Table 2 Detailed information about RIG and rabies vaccinations

	Total, n (%) n = 288 (100)
Difference in delay between RIG and the first rabies vaccination	
No delay	43 (14.9)
Delayed: received at the same day	43 (14.9)
Delayed: received at a different day (1 to 10 days)	57 (19.8)
RV on time, RIG delayed (0 to 10 days)	91 (31.6)
*Other**	33 (11,4)
Missing	21 (7.3)
Place of RIG receivement	
Netherlands	107 (37.2)
Country of exposure	122 (42.4)
Repatriation to country nearby	7 (2.4)
Missing	52 (18.1)

*Includes travellers who experienced a delay in receiving RV and/or did not receive RIG; travellers who received RV without delay but did not receive RIG; travellers who did not receive either RV or RIG; one traveller received RIG on time, but was delayed with RV.

Table 3 Multivariable logistic regression: predictors of PEP delay after an animal associated injury

Predictors		OR (95% CI)
Medical care needed: RIG	Yes	0.334 (0.231-0.482)
WHO Region	Southeast Asia	Reference*
	Africa	2.833 (1.395-5.755)
	Europe	2.976 (1.740-5.088)
	Eastern Mediteranean	2.617 (1.478-4.633)
	Western Pacific	2.124 (1.247-3.619)
	North America	3.846 (1.559-9.489)
	Central America	11.150 (4.494-27.666)
	South America	19.277 (8.901-41.747)

*South East Asia was used as reference category as this was the biggest group

The median delay for RIG was highest in Central and South America, whereas the median delay in Southeast Asia was 0 days. The median delay for rabies vaccinations overall was also 0 days (ranging from 0 to 15 days).

Discussion

This study aimed to objectify factors associated with rabies PEP delay and trends in PrEP uptake, among a group of 1410 Dutch travellers who actively contacted ECA after sustaining an AAI abroad. PEP delay occurred mainly among those travelling to Central- and South America and requiring RIG. Most travellers with a RIG indication were delayed due to its inaccessibility of treatment and conflicting medical advice. Travellers with a type II injury who had not received PrEP and therefore only required rabies vaccinations were mainly delayed due to a delayed traveller notification. Last, a significant increase in PrEP uptake was observed over time.

The unavailability of RIG was mainly responsible for PEP delay in travellers requiring both RIG and RV, as reported by other studies.[19,25,26] This also explains the high rate of delays in our study population, as almost half of the travellers required RIG. Furthermore, a considerable proportion of travellers required repatriation to the Netherlands due to the absence of RIG. This highlights the dependency on repatriation when RIG is unavailable abroad, which contributes substantially to treatment delays. Poverty and limited possibilities to preserve RIG in the countries of exposure are thought to be the most contributing factors.[27] Monkeypox presents a comparable challenge, as most outbreaks originate in remote areas with limited access to healthcare.[28] In addition, insufficient local knowledge about current rabies incidence and prevalence rates or not using the

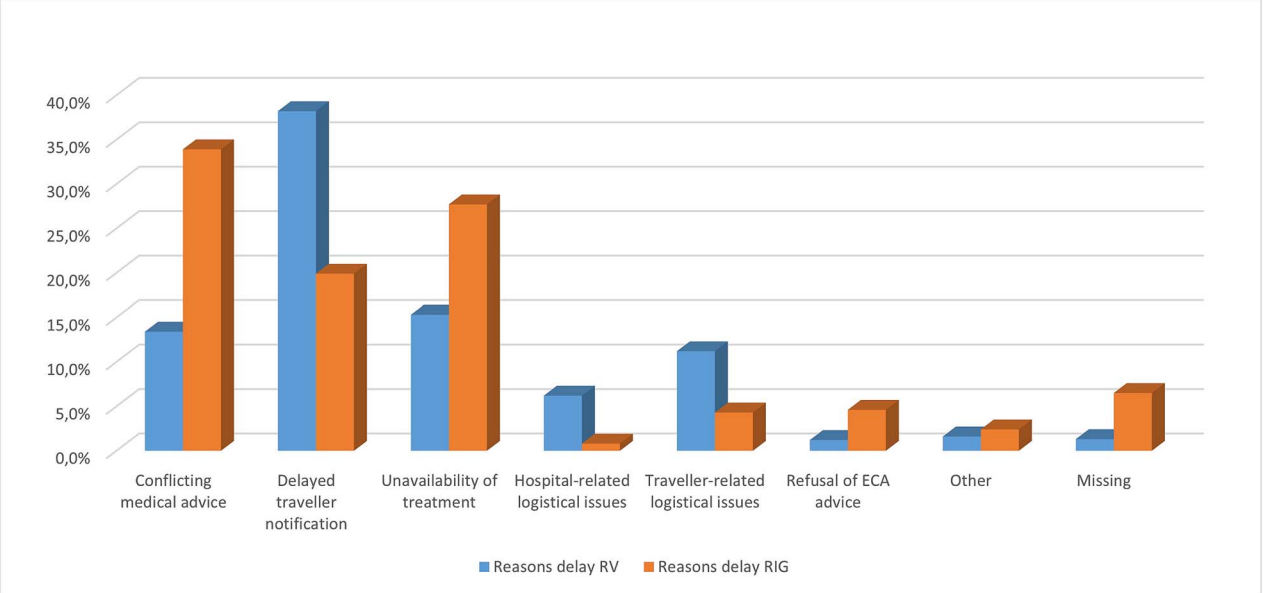

Figure 1 Reasons delayed RV and RIG. These reasons were given by clients during their contact with Eurocross Assistance. Abbreviations: RIG, Rabies Immunoglobulin; RV, rabies vaccinations; ECA, Eurocross Assistance

Table 4 Difference in delay by WHO region

	Southeast Asia, n (%) N = 69 (19.8)	Africa, n (%) N = 18 (5.2)	Europe, n (%) N = 87 (25.0)	Eastern Mediteranean, n (%) N = 43 (12.4)	Western Pacific, n (%) N = 27 (7.8)	North America, n (%) N = 11 (3.1)	Central America, n (%) N = 27 (7.8)	South America, n (%) N = 66 (18.9)	Total, n (%) N = 248 (100)
RV delay in days (median ± IQR ± ranges)	0.0 ± 1.0 ± 0 = 6	0.0 ± 1.0 ± 0–7	0.0 ± 1.0 ± 0–10	0.0 ± 1.0 ± 0–5	0.0 ± 1.0 ± 0–8	1.0 ± 2.0 ± 0–5	1.0 ± 1.0 ± 0–10	1.0 ± 1.0 ± 0–5	0.0 ± 1.0 ± 0–15
RIG delay in days (median ± IQR ± ranges)	0.0 ± 2.0 ± 0–7	3.0 ± 4.0 ± 2–7	2.0 ± 3.0 ± 0–8	3.0 ± 4.0 ± 0–9	2.0 ± 2.0 ± 0–6	1.0 ± 4.0 ± 0–7	4.5 ± 4.0 ± 1–10	4.5 ± 3.0 ± 1–7	2.0 ± 3.0 ± 0–10
Reasons of delay									
Conflicting medical advice	24 (34.8)	6 (33.3)	41 (47.1)	15 (34.9)	7 (25.9)	5 (45.5)	7 (25.9)	21 (31.8)	126 (36.2)
Delayed traveller notification	18 (26.1)	4 (22.4)	15 (7.2)	3 (7.0)	8 (29.6)	1 (9.1)	10 (37.0)	15 (22.7)	74 (21.3)
Unavailability of treatment	16 (23.2)	5 (27.8)	21 (24.1)	17 (39.5)	9 (33.3)	2 (18.2)	9 (33.3)	24 (36.4)	103 (29.6)
Hospital-related logistical issues	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	2 (18.2)	0 (0.0)	0 (0.0)	3 (0.9)
Client-related logistical issues	6 (8.7)	1 (6.3)	0 (0.0)	5 (11.6)	1 (3.7)	0 (0.0)	0 (0.0)	3 (4.5)	16 (4.6)
Refusal of ECA advice	1 (1.4)	2 (11.1)	8 (9.2)	3 (7.0)	1 (3.7)	1 (9.1)	0 (0.0)	1 (1.5)	17 (4.9)
Other	4 (5.8)	0 (0.0)	1 (1.1)	0 (0.0)	1 (3.7)	0 (0.0)	1 (3.7)	2 (2.3)	9 (2.6)

most up-to-date guidelines could be an important contributing factor.[29] This is further illustrated by the immunocompromised travellers, all of whom experienced delays in receiving PEP, primarily because local healthcare providers were unaware that this group always requires RIG. As travellers instinctively seek direct local medical care and want to trust it, once they contact a Dutch source of medical advice, like ECA, they need some time to overthink the situation. Especially if the advice is to interrupt the holiday to return to the Netherlands for PEP-treatment. From experience, convincing travellers to follow the Dutch medical advice can take some time, thus contributing to delayed PEP uptake.

Almost 20% of travellers requiring RIG were delayed due to a delayed notification by the traveller. This was especially the case in Indonesia, where travellers were too remote to visit a healthcare clinic on time, thus contributing to a delayed notification and PEP-treatment. Delayed travellers notification may also be caused by poor travel preparation: the client does not seek information or receives inadequate information from travel clinics. In an era of digital globalisation, it is also possible that travellers seek information and assistance only after sustaining an AAI.[30] This suggests that the client's pre-travel awareness is still insufficient. However, travellers who only required RV also reported delays. This might indicate that they have less fear of infection or no longer feel an urgent need for further prophylaxis, as some had already received PrEP, suggesting that their level of pre-travel preparation may be better than expected.

For PEP in general, barriers to access included a lack of supply and difficulties in the cold chain. Countries reported limited global availability and high costs as reasons for restricted access to RIG. Compared to the more common tetanus vaccination, the use of RIG is very limited and therefore low stocked and expensive.[27] Most Southeast Asian countries have a national rabies control program and provide PEP free of charge for their population, making it more affordable for healthcare providers to have enough stock. Access to PEP was more limited in Africa, where most delay was caused by RIG as African countries did not receive funds or did not have a control program.[19,27,31,32]

Most AAIs occurred in Southeast Asia, as it was the most popular destination among our travellers. Compared to the other regions, PEP delay in Southeast Asia was relatively uncommon. The longest median delays in PEP were reported in Central and South America, where travellers frequently cited the unavailability of treatment and conflicting medical advice. These findings align with those of Jentes et al.,[27] who reported limited access to rabies treatment—particularly RIG—in these regions. However, it is important to note that the overall risk of rabies in Central and South America is substantially lower than in Southeast Asia,[3] making a delay in PEP somewhat less critical in these regions. This is mainly because canine rabies has been better controlled in many Latin American countries through extensive dog vaccination programs, resulting in fewer human exposures.[33]

PrEP uptake has increased significantly over time, consistent with findings by Christiansen et al.,[34] who noted a parallel rise in international travel. This suggests that the increase in PrEP cannot be fully explained by heightened awareness of rabies risk. While increased vaccine hesitancy following the COVID-19 pandemic may have negatively influenced PrEP initiation,[35] this

effect appears to have been outweighed by other contributing factors. These include a rise in international travel, increased media attention to rabies in the Netherlands, and recent modifications to the PrEP regimen. The PrEP schedule has been reduced from three to two doses, and recent research indicates that even a single dose may confer sufficient protection.[36] These developments likely lowered logistical and financial barriers, contributing to the observed rise in PrEP uptake.

The Dutch National Coordination Centre for Traveller Health Advice currently recommends rabies PrEP for individuals travelling abroad for <3 months, based on cumulative time spent in endemic areas.[12,37] However, our study and previous research indicate that most travellers sustained an AAI within the first few weeks of travel.[13,19,38] It should be noted, however, that this may not have been their first visit to a rabies-endemic area, meaning they had previously been exposed to this risk but were fortunate not to have sustained an AAI. Given these findings—along with the high PEP delays observed among travellers to Central and South America, particularly those requiring RIG—current PrEP guidelines may warrant reconsideration. Greater emphasis on destination-specific risk, rather than travel duration alone, may enhance preventive strategies. Furthermore, improving awareness among travellers and providing adequate training to healthcare providers (both national and international) remain essential to reduce the impact of rabies exposure during travel.

Providing PrEP to all travellers visiting rabies-endemic areas is more expensive than offering PEP to those who sustain an AAI.[21] However, the cost of PrEP is likely outweighed by the potential benefits in terms of quality of life and the ability to continue enjoying the trip without interruption.[20] Moreover, not receiving PrEP increases the risk of infection with all of its consequences. Therefore, it is important to raise rabies awareness and encourage travellers to take PrEP. This could be done by providing information about rabies through campaigns, (partial) reimbursement of vaccinations through health insurance, and making a single dose of PrEP the standard.[36] This will allow and encourage more travellers to receive the necessary vaccinations, thereby minimising the number of travellers who experience PEP delay.

Strengths and limitations

This study has several strengths. First, the study consisted of an adequate sample size, giving the results sufficient power to detect statistical differences. Second, the data were collected by trained ECA consultants using a standardised questionnaire, making the data used more detailed in terms of PEP delay. Last, all information was collected at the time the traveller consulted ECA whilst abroad, minimizing the risk of recall bias.

However, there are some limitations as well. Although we had an adequate sample size and comparable results with other Dutch medical assistance centres, some studies show that the proportion of people actively reporting their AAI is low, varying from 19% to 47%.[38,39] Therefore, it may be only the tip of the iceberg. In addition, we had a few missing data points about the travellers' return date, and our study population is limited to Dutch travellers who actively contacted ECA after an AAI, which introduces a risk of selection bias. Furthermore, the assistance provided by ECA ends when the traveller has returned to the Netherlands, resulting in some missing information. The final limitation was the lack of detailed information about the traveller, such as educational level, socio-economic status, religion, ethnicity and whether the traveller had received pre-travel advice. These factors may also play a part in PEP delay.[39–41]

Future research is needed to gain a fuller understanding of the risk factors for PEP delay. We recommend including personal information on the study population and collecting data at several different locations to identify additional risk factors for PEP delay.

Conclusion

Within our sample, almost 60% of Dutch international travellers who actively contacted ECA experienced PEP delay, which can lead to unnecessary health risks, stress and anxiety.[5,20] Especially travellers in Central and South America with, in particular, a RIG indication are at risk of PEP delay. In the majority of cases, this delay can be easily avoided by receiving PrEP. Increasing rabies awareness among travellers, making a single dose of PrEP the standard and vaccinating all travellers to rabies endemic areas might be an effective strategy to minimise PEP delay.

Supplementary data

Supplementary data are available at *JTM* online.

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Author contributions

L.G.V., J.A.V. and F.S.L. made the cooperation between the Leiden University Medical Centre and Eurocross Assistance possible. Together with M.F., they designed and put up the study. M.F. did the data collection, wrote the manuscript and performed all statistical analyses with the support of all co-authors, but especially with the support of F.S.L. All authors have approved the final manuscript.

Conflict of interest: The authors have declared no conflict of interest.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Ethical considerations

The study was performed in accordance with the standards of ethics outlined in the Declaration of Helsinki, and was ethically approved by the board of Eurocross Assistance. This study complies with the Code of Ethics of the Faculty of Science, Vrije Universiteit Amsterdam (Research Ethics Review Committee, reference number: 2014–016).

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