

THE LANCET

Infectious Diseases

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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Table S1: List of full literature search terms by database.

Database	Strategy	Run Date	Records
Medline (OVID) 1946-	(Rabies ADJ5 vaccin*) OR (Rabies AND (Immunoglobulin* OR immuno-globulin* OR immune globulin* OR IG OR RIG OR ERIG OR HRIG OR passive immun* OR passive vaccin* OR passive antibod* OR fragment* OR Fab OR (F AND (ab*))) OR hyperRab OR Imogam OR Kedrab OR antirabies virus globulin* OR bayrab OR verirab OR berirab OR favirab OR antiserum* OR anti-serum* OR immune serum* OR rabigam OR rauman berna)).ti,ab. AND Post-exposure OR postexposure OR PEP OR (possible ADJ5 expos*) OR (potential* ADJ5 expos*) OR (suspect* ADJ5 expos*) OR (expos* ADJ5 infected) OR (expos* ADJ5 rabi*) OR fail OR failure* OR failed OR "Bites and Stings"/co,th NOT (Exp animals/ NOT exp humans/)	12/13/2018	1418
		7/8/2020	141
		7/11/2022	140
Embase (OVID) 1947-	(Rabies ADJ5 vaccin*) OR (Rabies AND (Immunoglobulin* OR immuno-globulin* OR immune globulin* OR IG OR RIG OR ERIG OR HRIG OR passive immun* OR passive vaccin* OR passive antibod* OR fragment* OR Fab OR (F AND (ab*))) OR hyperRab OR Imogam OR Kedrab OR antirabies virus globulin* OR bayrab OR verirab OR berirab OR favirab OR antiserum* OR anti-serum* OR immune serum* OR rabigam OR rauman berna)).ti,ab. AND Post-exposure OR postexposure OR PEP OR (possible ADJ5 expos*) OR (potential* ADJ5 expos*) OR (suspect* ADJ5 expos*) OR (expos* ADJ5 infected) OR (expos* ADJ5 rabi*) OR fail OR failure* OR failed OR "Bites and Stings"/co,dt NOT (Exp animal/ NOT exp human/)	12/13/2018	1645 -1027 duplicates =618 unique items
		7/8/2020	194 -107 duplicates =87 unique items
		7/11/2022	188 -84 duplicates =104 unique items
Global Health (OVID) 1973-	(Rabies ADJ5 vaccin*) OR (Rabies AND (Immunoglobulin* OR immuno-globulin* OR immune globulin* OR IG OR RIG OR ERIG OR HRIG OR passive immun* OR passive vaccin* OR passive antibod* OR fragment* OR Fab OR (F AND (ab*))) OR hyperRab OR Imogam OR Kedrab OR antirabies virus globulin* OR bayrab OR verirab OR berirab OR favirab OR antiserum* OR anti-serum* OR immune serum* OR rabigam OR rauman berna)).ti,ab. AND Post-exposure OR postexposure OR PEP OR (possible ADJ5 expos*) OR (potential* ADJ5 expos*) OR (suspect* ADJ5 expos*) OR (expos* ADJ5 infected) OR (expos* ADJ5 rabi*) OR fail OR failure* OR failed	12/13/2018	1335 -619 duplicates = 716 unique items
		7/8/2020	117 -48 duplicates =69 unique items
		7/11/2022	129 -80 duplicates

			=49 unique items
CINAHL (Ebsco)	(Rabies N5 vaccin*) OR (TI (Rabies AND (Immunoglobulin* OR immuno-globulin* OR "immune globulin*" OR IG OR RIG OR ERIG OR HRIG OR "passive immun*" OR "passive vaccin*" OR "passive antibod*" OR fragment* OR Fab OR (F AND (ab*)) OR hyperRab OR Imogam OR Kedrab OR "antirabies virus globulin*" OR bayrab OR verirab OR berirab OR favirab OR antiserum* OR anti-serum* OR "immune serum*" OR rabigam OR "rauman berna"))) OR (AB (Rabies AND (Immunoglobulin* OR immuno-globulin* OR "immune globulin*" OR IG OR RIG OR ERIG OR HRIG OR "passive immun*" OR "passive vaccin*" OR "passive antibod*" OR fragment* OR Fab OR (F AND (ab*)) OR hyperRab OR Imogam OR Kedrab OR "antirabies virus globulin*" OR bayrab OR verirab OR berirab OR favirab OR antiserum* OR anti-serum* OR "immune serum*" OR rabigam OR "rauman berna"))) AND Post-exposure OR postexposure OR PEP OR (possible N5 expos*) OR (potential* N5 expos*) OR (suspect* N5 expos*) OR (expos* N5 infected) OR (expos* N5 rabi*) OR fail OR failure* OR failed Limiters Human ; exclude Medline journals	12/13/2018	14 -9 duplicates =5 unique items
		7/8/2020	7 -6 duplicates =1 unique items
		7/11/2022	9 -7 duplicates =2 unique items
Cochrane Library	((Rabies NEAR/5 vaccin*) OR (Rabies AND (Immunoglobulin* OR immuno-globulin* OR "immune globulin*" OR IG OR RIG OR ERIG OR HRIG OR "passive immun*" OR "passive vaccin*" OR "passive antibod*" OR fragment* OR Fab OR (F AND (ab*)) OR hyperRab OR Imogam OR Kedrab OR "antirabies virus globulin*" OR bayrab OR verirab OR berirab OR favirab OR antiserum* OR anti-serum* OR "immune serum*" OR rabigam OR "rauman berna"))):ti,ab AND (Post-exposure OR postexposure OR PEP OR (possible NEAR/5 expos*) OR (potential* NEAR/5 expos*) OR (suspect* NEAR/5 expos*) OR (expos* NEAR/5 infected) OR (expos* NEAR/5 rabi*) OR fail OR failure* OR failed):ti,ab	12/13/2018	116 -101 duplicates =15 unique items
		7/8/2020	34 -9 duplicates =25 unique items
		7/11/2022	18 -10 duplicates =8 unique items

Scopus	(TITLE-ABS-KEY(Rabies W/5 vaccin*) OR (TITLE-ABS-KEY(Rabies) AND TITLE-ABS-KEY(Immunoglobulin* OR immuno-globulin* OR "immune globulin*" OR IG OR RIG OR ERIG OR HRIG OR "passive immun*" OR "passive vaccin*" OR "passive antibod*" OR fragment* OR Fab OR (F AND (ab*)) OR hyperRab OR Imogam OR Kedrab OR "antirabies virus globulin*" OR bayrab OR verirab OR berirab OR favirab OR antiserum* OR anti-serum* OR "immune serum*" OR rabigam OR "rauman berna"))) AND (TITLE-ABS-KEY(Post-exposure OR postexposure OR PEP OR (possible W/5 expos*) OR (potential* W/5 expos*) OR (suspect* W/5 expos*) OR (expos* W/5 infected) OR (expos* W/5 rabi*) fail OR failure* OR failed)) AND NOT INDEX(medline) AND NOT INDEX(embase)	12/13/2018	8 -5 duplicates =3 unique items
		7/08/2020	0
		7/11/2022	1 -0 duplicates =1 unique items
Note: Duplicates were identified using the Endnote automated "find duplicates" function with preference set to match on title, author and year, and removed from the Endnote library. Additional duplicates were identified using Covidence (Cochrane, Melbourne VIC, Australia).			

Table S2. WHO-approved regimens for rabies post-exposure prophylaxis.

WHO-approved regimens	Route of administration	Number of doses per day*	Days
ESSEN 6-dose (pre-2004) ¹	IM	1-1-1-1-1-1	0, 3, 7, 14, 28, 90
ESSEN 5-dose (2004 to 2018) ^{1,2}	IM	1-1-1-1-1	0, 3, 7, 14, 28
ESSEN 4-dose (2018 to present) ³	IM	1-1-1-1-0	0, 3, 7, 14–28
Thai Red Cross (pre-2004) ¹	ID	2-2-2-0-1-1	0, 3, 7, 28, 90
Updated Thai Red Cross (2004 to 2018) ^{1,2}	ID	2-2-2-0-2	0, 3, 7, 28
Updated Thai Red Cross (2018 to present) ³	ID	2-2-2-0-0	0, 3, 7
Zagreb (2004 to present) ²	IM	2-0-1-0-1	0, 7, 21
Eight-site intradermal regimen (2004 to 2013) ²	ID	8-0-4-0-1-1	0, 7, 28, 90
Alternative four-site intradermal regimen (2018 to present) ³	ID	4-4-4-0-0	0, 3, 7

*Each number represents how many doses are given on a particular day; 0 means that no doses are given that day. Day 0 starts the date of vaccine initiation and the spacing of doses are day 0, 3, 7, 14, 21 or 28, and 90.
 WHO: World Health Organization; IM: Intramuscular; ID: Intradermal.

Table S3. Selected variables for breakthrough infections with no known deviations in core practices (N=54).

Publication*	Age (years)	Sex	Date of exposure	Country of exposure	RIG given	Immunocompromised as reported by the authors	WHO case classification†	Vaccine regimen (number and spacing of doses, administration route, reported deviations, name of regimen)	Reasons for breakthrough infection according to author	Other relevant data
Amin, M et al. ⁴	50	M	Unknown	Bangladesh	No	Not stated	Probable	PVRV IM days 0, 3, 7, 14. ESSEN 5-dose. No schedule deviations reported. Developed symptoms the day he received his fourth dose (day 14).	RIG not administered.	
Bharti, OK et al. ⁵	8	F	2019	India	Yes	Not stated	Confirmed	PCEV ID days 0, 3, 7 (3 doses/day). This was reported as the "latest 2018 WHO regimen" although updated Thai Red Cross regimens recommend 2 dose/day and an alternative ID regimen is 4 doses/day, so we were unable to identify this regimen. Completed series with no schedule deviations reported.	Direct inoculation into facial nerve; head/neck wound; delay of 1 day for wound washing (not immediately done by family) and PEP; wound cleansed but not flushed per WHO recommendations.	
Chaitra, KM et al. ⁶	4.5	M	Unknown	India	Yes	Not stated	Confirmed	PVRV days 0, 3, 7, 14, 28. Patient received IM doses day 0, 14, and ID days 3 and 7. ESSEN 5-dose. No deviations reported. Developed symptoms 11 days after 4th dose and was given 5th dose on day 28 while symptomatic.	May have missed infiltrating wounds with RIG given large wound area; suturing of the wound; direct nerve inoculation of rabies virus.	
Deshmukh, RA & Yemul, V L ⁷	64	F	Unknown	India	No	Yes: uncontrolled diabetes, diabetic neuropathy, and endocarditis	Confirmed	PVRV IM days 0, 3, 7, 14, 30. Specific regimen not stated. Completed series with no schedule deviations noted. Developed symptoms on day 23 prior to completion of series.	RIG not administered at time of exposure; patient immunocompromised (uncontrolled diabetes, diabetic neuropathy, and endarteritis); possible minor antigenic differences in infecting strain and vaccinating strain causing variable degree of protection.	Patient received RIG but was given after patient developed symptoms, one day prior to her death.
Dutta, JK ⁸	12	M	Unknown	India	No	Not stated	Probable	PCEC received 4 doses. Administration route (IM/ID), vaccine spacing, and specific regimen not stated. No reported schedule deviations. Developed symptoms 10 days after 4th dose.	5-day delay in administration of vaccine; RIG not administered; financial constraints contributed to delay in purchasing vaccine.	

Publication*	Age (years)	Sex	Date of exposure	Country of exposure	RIG given	Immunocompromised as reported by the authors	WHO case classification†	Vaccine regimen (number and spacing of doses, administration route, reported deviations, name of regimen)	Reasons for breakthrough infection according to author	Other relevant data
Farahatj, F et al. ⁹	0.92	M	2008	Iran	No	Not stated	Confirmed	Author confirmed either PCEC or PVRV vaccine days 0, 3, 7, 14. Vaccine type, administration site, and specific regimen not specified. Completed series with no reported deviations.	RIG not administered.	
Farahatj, F et al. ⁹	4	M	2003	Iran	Yes	Not stated	Probable	Author confirmed either PCEC or PVRV vaccine days 0, 3, 7. Vaccine type, administration site, and specific regimen not specified. No reported deviations. Developed symptoms 1 day after 1st dose.	40-day delay in vaccine and RIG administration; did not receive enough vaccine doses.	
Farahatj, F et al. ⁹	6	F	2002	Iran	Yes	Not stated	Confirmed	Author confirmed either PCEC or PVRV vaccine days 0, 3, 7, 14. Vaccine type, administration site, and specific regimen not specified. Completed series with no reported deviations.	Enhanced viral spread (maybe due to suturing) which facilitated entry into peripheral nerves.	Wounds were sutured.
Farahatj, F et al. ⁹	8	M	2005	Iran	Yes	Not stated	Confirmed	Author confirmed either PCEC or PVRV vaccine days 0, 3, 7, 14. Vaccine type, administration site, and specific regimen not specified. Completed series with no reported deviations.	No specific reason given.	
Farahatj, F et al. ⁹	9	M	2006	Iran	Yes	Not stated	Probable	Author confirmed either PCEC or PVRV vaccine days 0, 3, 7, 14. Vaccine type, administration site, and specific regimen not specified. Completed series with no reported deviations.	No specific reason given.	
Farahatj, F et al. ⁹	10	F	2009	Iran	No	Not stated	Confirmed	Author confirmed either PCEC or PVRV vaccine days 0, 3, 7, 14. Vaccine type, administration site, and specific regimen not specified. Completed series with no reported deviations.	RIG not administered.	
Farahatj, F et al. ⁹	13	M	2007	Iran	Yes	Not stated	Confirmed	Author confirmed either PCEC or PVRV vaccine days 0, 3, 7, 14. Vaccine type, administration site, and specific regimen not specified. Completed series with no reported deviations.	No specific reason given.	

Publication*	Age (years)	Sex	Date of exposure	Country of exposure	RIG given	Immunocompromised as reported by the authors	WHO case classification†	Vaccine regimen (number and spacing of doses, administration route, reported deviations, name of regimen)	Reasons for breakthrough infection according to author	Other relevant data
Farahataj, F et al. ⁹	23	F	2003	Iran	Yes	Not stated	Probable	Author confirmed either PCEC or PVRV vaccine days 0, 3, 7, 14. Vaccine type, administration site, and specific regimen not specified. Completed series with no reported deviations.	No specific reason given.	
Farahataj, F et al. ⁹	26	M	2003	Iran	Yes	Not stated	Probable	Author confirmed either PCEC or PVRV vaccine days 0, 3, 7, 14. Vaccine type, administration site, and specific regimen not specified. Completed series with no reported deviations.	No specific reason given.	
Farahataj, F et al. ⁹	39	M	2006	Iran	Yes	Not stated	Confirmed	Author confirmed either PCEC or PVRV vaccine days 0, 3, 7, 14. Vaccine type, administration site, and specific regimen not specified. Completed series with no reported deviations.	No specific reason given.	
Farahataj, F et al. ⁹	50	M	2005	Iran	Yes	Not stated	Confirmed	Author confirmed either PCEC or PVRV vaccine days 0, 3, 7, 14. Vaccine type, administration site, and specific regimen not specified. Completed series with no reported deviations.	3-day delay of vaccine and RIG administration.	
Farahataj, F et al. ⁹	50	M	2006	Iran	Yes	Not stated	Confirmed	Author confirmed either PCEC or PVRV vaccine. Vaccine type, administration site, and specific regimen not specified. Received one dose and developed symptoms the following day.	22-day delay of vaccine and RIG administration.	
Farahataj, F et al. ⁹	58	M	2010	Iran	No	Not stated	Confirmed	Author confirmed either PCEC or PVRV vaccine days 0,3,7,14. Vaccine type, administration site, and specific regimen not specified. Completed series with no reported deviations.	RIG not administered.	
Farahataj, F et al. ⁹	67	F	2011	Iran	Yes	Not stated	Confirmed	Author confirmed either PCEC or PVRV vaccine days 0,3,7,14. Vaccine type, administration site, and specific regimen not specified. Completed series with no reported deviations.	No specific reason given.	

Publication*	Age (years)	Sex	Date of exposure	Country of exposure	RIG given	Immunocompromised as reported by the authors	WHO case classification†	Vaccine regimen (number and spacing of doses, administration route, reported deviations, name of regimen)	Reasons for breakthrough infection according to author	Other relevant data
Farahatj, F et al. ⁹	80	M	2006	Iran	Yes	Not stated	Probable	Author confirmed either PCEC or PVRV vaccine days 0,3,7,14. Vaccine type, administration site, and specific regimen not specified. Completed series with no reported deviations.	No specific reason given.	
Fescharek, R et al. ¹⁰ and Wilde, H et al. ¹¹	6	M	1991	India	Yes	Not stated	Probable	PCEC IM days 0, 3, 7, 14. Regimen not specified. No deviations reported. Developed symptoms 2 days after the 4th injection.	Injuries on head/face; short incubation period could be caused by wound location or very virulent street virus; 1-day delay of RIG administration; ketamine administration as anesthesia and surgical stress could interfere with sufficient immune response.	No suturing was done, but patient had surgery on face with ketamine given as anesthesia. Had 8-year-old brother bitten by the same dog who received PEP and survived.
Fescharek, R et al. ¹²	3	M	1990	India	No	Not stated	Probable	PCEC 4 doses. Administration site, vaccine spacing, and regimen not specified. No deviations reported. Developed symptoms 5 days after the 4th dose.	Delay of more than 24 hours in giving PEP; RIG not administered; multiple wounds especially in high-risk areas like head, neck, arm, or fingers.	
Fescharek, R et al. ¹²	4	M	1990	India	Yes	Not stated	Probable	PCEC IM 4 doses. Vaccine spacing and regimen not specified. No deviations reported. Developed symptoms 3 days after the 4th dose.	Delay of more than 24 hours in giving PEP; multiple wounds.	Wound was sutured.
Fescharek, R et al. ¹²	41	F	1990	India	No	Not stated	Probable	PCEC IM 4 doses. Vaccine spacing and regimen not specified. No deviations reported. Developed symptoms 2 days after the 4th dose.	No RIG administered.	
Gacouin, A et al. ¹³	50	F	1996	India	No	No	Confirmed	PCEC IM days 0, 2 in India then PVRV IM days 6, 16, 29 in France. Regimen not specified. Developed symptoms 5 days after 3rd dose. Deviations of 1-3 days noted in presumed ESSEN regimen.	Suturing wound closed; RIG not administered; could not verify conservation of vaccine at 4 degrees C; co-administration of chloroquine and proguanil antimalarial could delay antibody response; short incubation period; severity of bite; particular strain of virus.	Patient tested negative for HIV.

Publication*	Age (years)	Sex	Date of exposure	Country of exposure	RIG given	Immunocompromised as reported by the authors	WHO case classification†	Vaccine regimen (number and spacing of doses, administration route, reported deviations, name of regimen)	Reasons for breakthrough infection according to author	Other relevant data
Hemachudha, T et al. ¹⁴ and Wilde, H ¹⁵	9	M	1997	Thailand	Yes	Not stated	Confirmed	PCEC IM days 0, 3, 7, 14. Regimen not specified. Completed series with no reported deviations.	Direct inoculation of nerve endings.	
Hemachudha, T et al. ¹⁴ and Wilde, H ¹⁵	72	F	1997	Thailand	Yes	Not stated	Confirmed	PVRV IM day 0 then PCEC IM days 3, 7, 14. Regimen not specified. Completed series with no reported deviations.	Direct inoculation of nerve endings.	
Jain, RS et al. ¹⁶	55	M	Unknown	India	Yes	Not stated	Probable	PCEC ID days 0, 3, 7, 28 (2 doses/day). Updated Thai Red Cross pre-2018. Completed series with no reported deviations.	Large injection of viral load given of multiple, large, and deep bite; unintentional missed infiltration of RIG into wounds by healthcare providers; unusual strain of rabies virus.	
John, BM et al. ¹⁷ and Wilde, H ¹⁵	5	F	Unknown	India	Yes	Not stated	Confirmed	PCEC IM days 0, ?, 7, 14. Regimen not specified and could not confirm day of 2nd dose. Developed symptoms 3 days after 4th dose.	Limited infiltration of RIG due to anatomic location of wound (near left eye); suturing of wound; short incubation period.	
Khalsi, F et al. ¹⁸	11	M	Unknown	Tunisia	Yes	Not stated	Confirmed	PCEC IM days 0, 3, 7, 14. ESSEN 4-dose. Completed series with no reported deviations.	High risk head/neck injury; wound was sutured prior to cleaning and RIG administration.	
Quiambao, BP et al. ¹⁹ and Wilde, H ¹⁵	6	M	2006	Philippines	Yes	Not stated	Confirmed	PVRV ID day 0 (2 doses/day) then PVRV IM day 3, 7. Unclear if regimen was Thai Red Cross or ESSEN or mix of both. Patient developed symptoms on day 22.	No disinfectant applied after washing wounds with soap and water; 2-day delay for vaccine and RIG administration; location of wound on lip made RIG infiltration challenging.	
Ren, J et al. ²⁰	5	M	Unknown	China	Yes	Not stated	Probable	Modern cell culture days 0 (2 doses), 7, 21. Zagreb. Vaccine type, administration site, schedule not stated. Completed series with no reported deviations.	No specific reason given.	Patient given ketamine. Wound sutured closed before RIG administration

Publication*	Age (years)	Sex	Date of exposure	Country of exposure	RIG given	Immunocompromised as reported by the authors	WHO case classification†	Vaccine regimen (number and spacing of doses, administration route, reported deviations, name of regimen)	Reasons for breakthrough infection according to author	Other relevant data
Scrimgeour, EM & Mehta, FR ²¹	17	F	1997	Oman	Yes	Not stated	Confirmed	HDCV IM day 0 (2 doses), 6. Zagreb. Received 3 doses with a one-day deviation of the 2nd session. Developed symptoms 7 days after 2nd visit.	48-hour delay in RIG administration; deep wound in upper lip.	RIG was given IM only with no wound infiltration.
Shantavasinkul, P et al. ²²	33	M	2009	Thailand	Yes	Not stated	Confirmed	PCEC ID days 0, 3, 7 (2 doses/day). Updated Thai Red Cross pre-2018. No reported deviations. Developed symptoms day 23 before completing series.	2nd dose of RIG given on day 4 which could have increased trauma to nerves at bite site; missing other wounds with RIG; 2nd RIG dose given on day 4; wound on nail bed challenging to infiltrate.	RIG potency confirmed.
Smith, MS & Janse van Rensburg, M N ²³	18	M	Unknown	South Africa	No	Not stated	Probable	HDCV SQ days 0, 3 and IM days 7, 14, 23. Regimen not stated. Completed series with deviation of 5th dose given 5 days early.	RIG not administered; 9-day delay in vaccine administration; administration of first two doses of vaccine subcutaneous.	
Sriaroon, C et al. ²⁴ and Wilde, H ¹⁵	7	F	2002	Thailand	No	Not stated	Probable	PCEC ID day 0 (8 doses), day 7 (4 doses). Eight-site intradermal regimen. No reported deviations. Developed symptoms 4 days after 2nd visit.	RIG not administered.	
Thongcharoen, P & Wasi, C ²⁵	65	M	1984	Thailand	Yes	Yes: alcoholic cirrhosis	Confirmed	Suckling mouse brain vaccine 5 doses daily. Administration route unknown. Day 7 post-exposure started HDCV days 0, 3, 7, 14. Administration route and regimen not stated. No reported deviations. Developed symptoms 8 days after 4th HDCV dose.	7-day delay in receiving cell culture vaccine (started on suckling mouse brain vaccine); liver impairment causing poor antibody response.	Patient had several reported co-morbidities: history of drug use, chronic hemorrhoids, alcoholic cirrhosis, asthma, and duodenal ulcer. Antibody response 12 days after 4th dose of HDCV was 1.87 IU/ml when expect it be ~10 IU/ml.
Tinsa, F et al. ²⁶	6	M	Unknown	Tunisia	Yes	Not stated	Confirmed	PCEC IM days 0, 3, 7, 14. ESSEN. Completed series with no reported deviations.	Wound sutured early on the same day as the bite (after RIG); Highly innervated wound in the head/neck; speculated on the possibility of wound management error or missing small wounds for infiltration with RIG.	

Publication*	Age (years)	Sex	Date of exposure	Country of exposure	RIG given	Immunocompromised as reported by the authors	WHO case classification†	Vaccine regimen (number and spacing of doses, administration route, reported deviations, name of regimen)	Reasons for breakthrough infection according to author	Other relevant data
Wattanasri, S et al. ²⁷ and Thongcharoen, P & Wasi, C ²⁵	35	F	1980	Thailand	No	Not stated	Probable	HDCV days 0, 2, 7, 13. Administration site and regimen not specified. Potential deviation with dose 2 of 1 day. Developed symptoms 6 days after 4th dose.	RIG not administered; 2-day delay in vaccine administration.	
Wilde, H et al. ¹¹	2.5	F	Unknown	Thailand	Yes	Not stated	Probable	PCEC ID days 0, 3, 7 (2 doses/day) Thai Red Cross. No reported deviations. Developed symptoms 3 days after 3rd visit.	Wound sutured closed before RIG was administered, which can enhance spread of viral and rapid viral entry into peripheral nerves; not all wounds were infiltrated with RIG.	
Wilde, H et al. ¹¹	4	M	1993	Sri Lanka	Yes	Not stated	Confirmed	PCEC IM days 0, 7, 21 (2 doses/day). Zagreb. Completed series with no schedule deviations reported.	Use of Zagreb regimen which was not recommended when RIG is given (category 3 wounds) because of reported antibody suppression with co-administration of regimen and RIG. Only half of the RIG was used in wounds so may not have had sufficient RIG to infiltrate all wounds.	Patient wounds were sutured with ketamine as anesthetic. At this time, guidelines did not recommend diluting RIG.
Wilde, H et al. ¹¹	6	M	1988	Thailand	Yes	Not stated	Probable	PVRV IM days 0,3,7. ESSEN. No reported deviations. Died 5 days after the 3rd dose.	No infiltration of RIG into wounds; high risk exposure because head/neck wounds.	
Wilde, H et al. ¹¹	9	M	1989	Thailand	Yes	Not stated	Confirmed	PVRV IM days 0, 3,7, 14. ESSEN. No deviations reported. Died 11 days after the 4th dose.	Undiluted RIG volume was inadequate to infiltrate 12 wounds on face, head, and arms.	Confirmed vaccine and RIG potency.
Wilde, H et al. ²⁸	11	M	1986	Thailand	Yes	No	Confirmed	PVRV IM days 0, 3,10, 13 IM. Essen (not clear if 5 or 6 dose). Deviation of 3 days (3rd dose) and 4 days (4th dose). Developed symptoms 1 day after 4th dose.	5-day delay in vaccine and RIG administration; wounds not infiltrated with RIG.	Provider recommended observing animal before starting PEP resulting in a 5-day delay. Patient reported as "healthy."
Wilde, H et al. ²⁸	53	M	1988	Thailand	Yes	Yes: Chronic alcoholism with advanced cirrhosis	Confirmed	PVRV ID days, 0, 3, 7 (2 doses/day) Thai Red Cross. No deviations reported. Developed symptoms 11 days after 3rd visit.	6-day delay in administration of vaccine and RIG. Alcoholism and cirrhosis contributed to poor immune response to vaccine.	

Publication*	Age (years)	Sex	Date of exposure	Country of exposure	RIG given	Immunocompromised as reported by the authors	WHO case classification†	Vaccine regimen (number and spacing of doses, administration route, reported deviations, name of regimen)	Reasons for breakthrough infection according to author	Other relevant data
Wilde, H ¹⁵	2	F	1994	Thailand	Yes	Not stated	Probable	PCEC ID days 0, 3, 7 (2 doses/day). Thailand Red Cross. No reported deviations. Developed symptoms 3 days after the 3rd visit.	RIG was not diluted so possible not all wounds were infiltrated with RIG; wounds were sutured potentially before RIG administration.	Wounds were sutured under ketamine anesthesia.
Wilde, H ¹⁵	4	F	2004	Philippines	Yes	Not stated	Confirmed	PCEC ID days 0, 3, 7 (2 doses/day). Thailand Red Cross. No reported deviations. Developed symptoms 12 days after the 3rd visit.	Reported as probable true PEP failure.	
Wilde, H ¹⁵	4	M	2006	South Africa	Yes	Not stated	Confirmed	HDCV IM days 0, 3, 7, 14 IM. Regimen not specified, likely ESSEN five-dose. Developed symptoms 4 days after 4th dose.	Reported as probable true PEP failure.	
Wilde, H ¹⁵	7	M	2001	Thailand	Yes	Not stated	Probable	PVRV IM day 0 then PVRV ID days 3, 7 (2 doses/day). Started IM and then Thai Red Cross ID. No reported deviations. Developed symptoms 13 days after 3rd visit.	Reported as probable true PEP failure.	
Wilde, H ¹⁵	9	M	1987	Thailand	Yes	Not stated	Confirmed	PVRV IM days 0, 3, 7, 14. Regimen not specified, likely ESSEN 5-dose. No reported deviations. Developed symptoms 7 days after 4th dose.	Undiluted RIG was inadequate volume so cover all wounds.	
Wilde, H ¹⁵	41	M	1985	Thailand	Yes	Not stated	Probable	HDCV IM days 0, 2, 5. Regimen not stated. Schedule deviation 1 day early (dose 2) and 4 days early (dose 3). Developed symptoms 7 days after 3rd dose.	RIG not infiltrated in wounds.	Patient received HDCV 8 sites ID on the day that he started with symptoms of rabies.
Wilde, H ¹⁵	44	F	2005	Burma	Yes	Not stated	Probable	PCEC IM days 0, 3, 7. Regimen not stated, likely ESSEN. No deviations but given that patient developed symptoms within 1 day of administration of 4th dose, she was counted as a case that developed symptoms instead of incomplete	Wound was sutured prior to RIG administration.	Potency of RIG and vaccine confirmed.

Publication*	Age (years)	Sex	Date of exposure	Country of exposure	RIG given	Immunocompromised as reported by the authors	WHO case classification†	Vaccine regimen (number and spacing of doses, administration route, reported deviations, name of regimen)	Reasons for breakthrough infection according to author	Other relevant data
								vaccination. Developed symptoms 8 days after 3rd dose.		
Wilde, H ¹⁵	53	M	1987	Thailand	Yes	Not stated	Confirmed	PVRV ID days 0, 3, 6 (2 doses/day). Thai Red Cross. Deviation of 1 day (3rd visit). Symptoms started 14 days after 3rd visit.	6-day delay in vaccine and RIG administration. RIG not administered in all wounds.	Vaccine and RIG administration was delayed while dog was observed, and rabies testing was completed.
Wilde, H ¹⁵	57	M	2004	South Africa	Yes	Not stated	Confirmed	HDCV or PCEC IM days 0, 3, 7, 14. Regimen not stated, likely ESSEN 5-dose. No reported deviations. Developed symptoms the day of 4th dose.	Reported as probable true PEP failure.	Mongoose had to be manually removed from patient.
<p>* If a manuscript has two publications listed, the first one was the primary source.</p> <p>† Characterized as suspected, probable, or confirmed rabies cases based on standard definitions developed by WHO, which classifies cases based on clinical symptoms, history of contact with a rabid animal, and laboratory testing.³</p> <p>WHO: World Health Organization; M: Male; F:Female; PVRV: Purified Vero cell rabies vaccine; PCEC: Purified chick embryo cell rabies vaccine; HDCV: Human diploid cell vaccine; IM: Intramuscular; ID: Intradermal; SQ: Subcutaneous</p>										

Table S4. Selected variables for breakthrough infections with potential or known deviations in core practices (N=68).

Publication*	Age (yrs)	Sex	Date of exp	Country of exposure	RIG given	Core practice: Wound care done	Core practice: Vaccine given in the gluteal muscle	Core practice: Vaccine completed	Reason for vaccine non-completion	Immuno-compromised as reported by the authors	WHO case classification†	Vaccine regimen (number and spacing of doses, administration route, reported deviations, name of regimen)	Reasons for breakthrough infection according to author	Other relevant data
Bennasrallah, C et al. ²⁹	12	M	2015	Tunisia	Unk	Unk	Unk	Yes		Not stated	Probable	Authors confirmed modern cell culture vaccine and reported as ESSEN 5-dose. Administration site, vaccine spacing not specified. No reported deviations. Reported to have completed vaccine series.	Poor wound management; wound suturing.	
Bennasrallah, C et al. ²⁹	33	Unk	2017	Tunisia	Unk	Unk	Unk	No	Did not return for additional doses	Not stated	Probable	Authors confirmed modern cell culture vaccine and reported as ESSEN 5-dose. Administration site, vaccine spacing not specified. No reported deviations. Reported as incomplete PEP because the patient did not return for care.	Did not receive enough vaccine doses.	
Bharti, OK & Sharma, V ³⁰	48	M	2017	India	No	Yes	Yes	Developed symptoms		Not stated	Probable	Modern cell culture vaccine IM x 4 doses. Vaccine spacing and regimen not stated, reported as 5-dose regimen. No reported deviations. Patient developed symptoms after 4th dose.	Administration of vaccine in the gluteal muscle.	
Changalucha, J et al. ³¹	3	F	Unk	Tanzania	No	Unk	Unk	Yes		Not stated	Probable	Author confirmed modern cell culture vaccine IM x 4 doses. Vaccine spacing and regimen not specified. No reported deviations.	4-day delay in vaccine administration.	
Changalucha, J et al. ³¹	3	M	Unk	Tanzania	No	Unk	Unk	Yes		Not stated	Probable	Author confirmed modern cell culture vaccine IM x 3 doses. Vaccine spacing and	1-day delay in vaccine administration.	

Publication*	Age (yrs)	Sex	Date of exp	Country of exposure	RIG given	Core practice: Wound care done	Core practice: Vaccine given in the gluteal muscle	Core practice: Vaccine completed	Reason for vaccine non-completion	Immuno-compromised as reported by the authors	WHO case classification†	Vaccine regimen (number and spacing of doses, administration route, reported deviations, name of regimen)	Reasons for breakthrough infection according to author	Other relevant data
												regimen not specified. No reported deviations.		
Changalucha, J et al. ³¹	5	M	Unk	Tanzania	No	Unk	Unk	No	Unk	Not stated	Probable	Author confirmed modern cell culture vaccine IM day 0. Regimen not specified. No reported deviations.	3-day delay in vaccine administration; did not receive enough vaccine doses.	
Changalucha, J et al. ³¹	6	F	Unk	Tanzania	No	Unk	Unk	No	Unk	Not stated	Probable	Author confirmed modern cell culture vaccine IM x 2 doses. Vaccine spacing and regimen not specified. No reported deviations.	10-day delay in vaccine administration; did not receive enough vaccine doses.	
Changalucha, J et al. ³¹	7	M	Unk	Tanzania	No	Unk	Unk	No	Unk	Not stated	Probable	Author confirmed modern cell culture vaccine IM x 2 doses. Vaccine spacing and regimen not specified. No reported deviations.	1-day delay in vaccine administration; did not receive enough vaccine doses.	
Changalucha, J et al. ³¹	8	F	Unk	Tanzania	No	Unk	Unk	No	Unk	Not stated	Probable	Author confirmed modern cell culture vaccine IM x 2 doses. Vaccine spacing and regimen not specified. No reported deviations.	1-day delay in vaccine administration; did not receive enough vaccine doses.	
Changalucha, J et al. ³¹	8	M	Unk	Tanzania	No	Unk	No	No	Unk	Not stated	Probable	Author confirmed modern cell culture vaccine ID day 0. Regimen not specified. No reported deviations.	Did not receive enough vaccine doses.	
Changalucha, J et al. ³¹	9	M	Unk	Tanzania	No	Unk	No	No	Unk	Not stated	Probable	Author confirmed modern cell culture vaccine ID day 0. Regimen not specified. No reported deviations.	Did not receive enough vaccine doses.	
Changalucha, J et al. ³¹	11	M	Unk	Tanzania	No	Unk	No	No	Unk	Not stated	Probable	Author confirmed modern cell culture vaccine ID x2 doses. Vaccine spacing and	Did not receive enough vaccine doses.	

Publication*	Age (yrs)	Sex	Date of exp	Country of exposure	RIG given	Core practice: Wound care done	Core practice: Vaccine given in the gluteal muscle	Core practice: Vaccine completed	Reason for vaccine non-completion	Immuno-compromised as reported by the authors	WHO case classification†	Vaccine regimen (number and spacing of doses, administration route, reported deviations, name of regimen)	Reasons for breakthrough infection according to author	Other relevant data
												regimen not specified. No reported deviations.		
Changalucha, J et al. ³¹	14	M	Unk	Tanzania	No	Unk	Unk	Yes		Not stated	Probable	Author confirmed modern cell culture vaccine IM x 4 doses. Vaccine spacing and regimen not specified. No reported deviations.	5-day delay in vaccine administration.	
Changalucha, J et al. ³¹	16	M	Unk	Tanzania	No	Unk	Unk	No	Unk	Not stated	Probable	Author confirmed modern cell culture vaccine IM x 2 doses. Vaccine spacing and regimen not specified. No reported deviations.	6-day delay in vaccine administration; did not receive enough vaccine doses.	
Changalucha, J et al. ³¹	21	M	Unk	Tanzania	No	Unk	Unk	No	Unk	Not stated	Probable	Author confirmed modern cell culture vaccine IM day 0. Regimen not specified. No reported deviations.	1-day delay in vaccine administration; did not receive enough vaccine doses.	
Changalucha, J et al. ³¹	70	F	Unk	Tanzania	No	Unk	No	No	Unk	Not stated	Probable	Author confirmed modern cell culture vaccine ID day 0. Regimen not specified. No reported deviations.	Did not receive enough vaccine doses.	
Changalucha, J et al. ³¹	85	M	Unk	Tanzania	No	Unk	No	No	Unk	Not stated	Probable	Author confirmed modern cell culture vaccine ID day 0. Regimen not specified. No reported deviations.	Did not receive enough vaccine doses.	
Deshmukh, DG et al. ³²	3	M	2009	India	No	No	Unk	Developed symptoms		Not stated	Confirmed	PCEC days 0, 5, 11, 14. ESSEN 5-dose. Administration route not stated. Deviations noted 2 days late (dose 2), 1 day late (dose 3), 4 days early (dose 4). Developed symptoms 4 days after 4th dose.	No wound care done; RIG not administered.	RIG was not administered because the hospital did not have it available, and the family could not afford to pay for it.

Publication*	Age (yrs)	Sex	Date of exp	Country of exposure	RIG given	Core practice: Wound care done	Core practice: Vaccine given in the gluteal muscle	Core practice: Vaccine completed	Reason for vaccine non-completion	Immuno-compromised as reported by the authors	WHO case classification†	Vaccine regimen (number and spacing of doses, administration route, reported deviations, name of regimen)	Reasons for breakthrough infection according to author	Other relevant data
Devriendt, J et al. ³³	29	F	1981	Rwanda	No	Unk	Unk	Developed symptoms		Not stated	Confirmed	HDCV days 0, 3, 7, 14, ESSEN 6-dose. Administration route not specified. No reported deviations. Developed symptoms 6 days after 4th dose.	RIG not administered.	Vaccine potency confirmed. Patient received RIG after developed symptoms.
Farahtaj, F et al. ⁹	20	M	2003	Iran	Yes	Yes	Unk	No	Unk	Not stated	Probable	Author confirmed either PCEC or PVRV vaccine days 0, 3, 7. Vaccine type, administration site, and specific regimen not specified. No reported deviations.	1- day delay in vaccine and RIG administration; did not receive enough vaccine doses.	
Fescharek, R & Franke, V ³⁴ and Fescharek, R et al. ¹²	15	M	1989	Not stated	No	Yes	Yes	Developed symptoms		Not stated	Probable	PCEC IM days 0, 3, 7, 14. Regimen not stated. Received dose 1-2 in gluteal muscle & 3-4 in arm. No reported deviations. Developed symptoms 13 days after 4th dose.	RIG not administered; after symptoms developed, patient was diagnosed with post-vaccine Guillain-Barré syndrome and given high dose steroids vaccination before rabies diagnosis but after symptoms developed.	Patient diagnosed with typhoid fever 3 days after exposure and given antibiotics.
Fescharek, R. et al. ¹²	7	M	1989	India	No	No	No	Developed symptoms		Not stated	Probable	PCEC days 0, X, X, 16. Vaccine schedule, administration route, and regimen not stated. No deviations reported. Developed symptoms 8 days after 4th dose.	>24-hour delay in vaccine administration; RIG not administered; multiple wounds especially in high-risk areas like head, neck, arm, or fingers.	
Fescharek, R. et al. ¹²	11	F	1987	India	No	Unk	Unk	Unk		Not stated	Probable	PCEC days 0, X, 12. Vaccine schedule, administration route, and regimen not stated. Unable to evaluate if there were deviations but no WHO regimen has dose 3 on day 12.	>24-hour delay in vaccine administration; multiple wounds especially in high-risk areas like head, neck, arm, or fingers.	HRIG was given 3 days after patient started with symptoms of rabies as a treatment not as PEP.

Publication*	Age (yrs)	Sex	Date of exp	Country of exposure	RIG given	Core practice: Wound care done	Core practice: Vaccine given in the gluteal muscle	Core practice: Vaccine completed	Reason for vaccine non-completion	Immuno-compromised as reported by the authors	WHO case classification†	Vaccine regimen (number and spacing of doses, administration route, reported deviations, name of regimen)	Reasons for breakthrough infection according to author	Other relevant data
												Developed symptoms 10 days after 3rd dose.		
Fescharek, R. et al. ¹²	11	M	1990	India	No	Yes	Unk	Unk		Not stated	Confirmed	PCEC days 0, X, X, 14. Vaccine schedule, administration route, and regimen not stated. No deviations reported. According to vaccine card only one dose was given.	RIG not administered.	
Fescharek, R. et al. ¹²	12	M	1990	India	Unk	Unk	Unk	Developed symptoms		Not stated	Probable	PCEC days 0, X, 7. Vaccine schedule, administration route, and regimen not stated. No deviations reported. Developed symptoms 2 days after 3rd dose.	RIG not administered; multiple wounds especially in high-risk areas like head, neck, arm, or fingers.	
Fescharek, R. et al. ¹²	12	M	1989	India	No	Unk	Yes	Developed symptoms		Not stated	Probable	PCEC days 0, X, X, 14. Vaccine schedule, administration route, and regimen not stated. No deviations reported. Developed symptoms 2 days after 4th dose.	>24-hour delay in vaccine administration; RIG not administered; multiple wounds especially in high-risk areas like head, neck, arm, or fingers.	
Fescharek, R. et al. ¹²	26	F	1986	Thailand	Yes	Unk	Yes	Developed symptoms		Not stated	Probable	PCEC days 0, X, X, 21. Vaccine schedule, administration route, and regimen not stated. Unable to evaluate if there were deviations but no WHO regimen has dose 4 on day 21. Developed symptoms 2 days after 4th dose.	>24-hour delay in vaccine administration; wounds not infiltrated with RIG; multiple wounds especially in high-risk areas like head, neck, arm, or fingers.	

Publication*	Age (yrs)	Sex	Date of exp	Country of exposure	RIG given	Core practice: Wound care done	Core practice: Vaccine given in the gluteal muscle	Core practice: Vaccine completed	Reason for vaccine non-completion	Immuno-compromised as reported by the authors	WHO case classification†	Vaccine regimen (number and spacing of doses, administration route, reported deviations, name of regimen)	Reasons for breakthrough infection according to author	Other relevant data
Fescharek, R. et al. ¹²	65	M	1989	India	No	Unk	Unk	Developed symptoms		Not stated	Probable	PCEC days 0, X, 7. Vaccine schedule, administration route, and regimen not stated. No reported deviations. Developed symptoms 7 days after 3rd dose.	>24-hour delay in vaccine administration; RIG not administered.	
Fescharek, R. et al. ¹²	79	M	1987	India	No	Unk	No	No	Unk	Not stated	Probable	PCEC day 0. Administration route and regimen not stated.	>24-hour delay in vaccine administration; RIG not administered.	
Fescharek, R. et al. ¹² and Bock, HL et al. ³⁵	65	M	1986	Thailand	No	Yes	Ukn: Reported as upper arm by Fescharek et al. Bock et al. reports as possible gluteal muscle administration.	No	Unk	Yes: Alcoholism with liver cirrhosis	Probable	PCEC IM days 0, 2, 8. Regimen not stated and conflicting reports on route of administration (arm vs gluteal). Deviation noted 1-day early for dose 2 & 3. Developed symptoms 12 days after 3rd dose.	>24-hour delay in vaccine administration; RIG not administered; multiple wounds especially in high-risk areas like head, neck, arm, or fingers; suturing the wound; immunocompromised due to alcoholism; administration in gluteal muscle (Bock et al. only).	
Gadekar, RD et al. ³⁶	30	M	2010	India	No	No	Unk	Developed symptoms		Not stated	Probable	Modern cell culture vaccine IM days 0, 3, 7, 14. ESSEN 5-dose. Vaccine type not stated. No deviations. Developed symptoms after 4th dose.	Wound care not done; RIG not administered; bite on highly innervated, higher risk site (finger).	3-year-old also bitten by same animal. He received wound care, RIG and vaccine, and survived.
Gajurel, BP ³⁷	17	M	Unk	Nepal	Unk	Unk	Unk	Unk		Not stated	Probable	PCEC 4 doses. Administration site, vaccine spacing, and regimen not specified. No reported deviations. Developed symptoms 5 days after the 4th dose.	Multiple bites leading to shorter incubation period; Unk if RIG was administered.	

Publication*	Age (yrs)	Sex	Date of exp	Country of exposure	RIG given	Core practice: Wound care done	Core practice: Vaccine given in the gluteal muscle	Core practice: Vaccine completed	Reason for vaccine non-completion	Immuno-compromised as reported by the authors	WHO case classification†	Vaccine regimen (number and spacing of doses, administration route, reported deviations, name of regimen)	Reasons for breakthrough infection according to author	Other relevant data
Gerber, F et al. ³⁸	5	M	2017	Côte d'Ivoire	No	Unk	Unk		Developed symptoms	Not stated	Probable	PCEC day 0. Administration site and regimen not specified. No reported deviations. Patient died same day as receiving vaccine.	61-day delay in vaccine administration.	
Gerber, F et al. ³⁸	6	M	2017	Côte d'Ivoire	Yes	Unk	Unk	No	Unk	Not stated	Probable	PCEC 3 doses. Reported as Updated Thai Red Cross regimen (pre-2018). Administration site and vaccine spacing not specified. No reported deviations. Date of death unknown but within 6 weeks of exposure.	2-day delay in vaccine administration.	Patient noted to have been scratched and not bitten.
Gerber, F et al. ³⁸	10	F	2017	Côte d'Ivoire	No	Unk	Unk		Developed symptoms	Not stated	Probable	PCEC day 0. Reported as Updated Thai Red Cross regimen (pre-2018). Administration site not specified. No reported deviations. Patient died 2 days after receiving 1st dose.	55-day delay in vaccine administration.	
Gerber, F et al. ³⁸	13	F	2017	Côte d'Ivoire	No	Unk	Unk		Developed symptoms	Not stated	Probable	PCEC day 0. Administration site, vaccine spacing, number of doses, and regimen not specified. No reported deviations. Patient died one day after receiving 1st dose of vaccine.	65-day delay in vaccine administration.	
Gerber, F et al. ³⁸	25	M	2017	Côte d'Ivoire	Yes	Unk	Unk		Developed symptoms	Not stated	Probable	PCEC. Administration site, vaccine spacing, number of doses received, and regimen not specified. No reported deviations. Patient died before completing the series.	28-day delay in vaccine administration; "non-compliance to the active vaccination protocol."	

Publication*	Age (yrs)	Sex	Date of exp	Country of exposure	RIG given	Core practice: Wound care done	Core practice: Vaccine given in the gluteal muscle	Core practice: Vaccine completed	Reason for vaccine non-completion	Immuno-compromised as reported by the authors	WHO case classification†	Vaccine regimen (number and spacing of doses, administration route, reported deviations, name of regimen)	Reasons for breakthrough infection according to author	Other relevant data
Gerber, F et al. ³⁸	33	F	2017	Côte d'Ivoire	Yes	Unk	Unk	Developed symptoms		Not stated	Probable	PCEC. Reported as Updated Thai Red Cross regimen (pre-2018). Administration site and vaccine spacing not specified. No reported deviations. Patient died while receiving PEP regimen, specific date unknown.	3-day delay in vaccine administration.	
Ghosh, JB et al. ³⁹	6	F	Unk	Presumed India	No	Unk	No	Developed symptoms		Not stated	Confirmed	PCEC IM 0, 3, 7, 14. ESSEN 5-dose. No reported deviations. Developed symptoms after 4th dose.	RIG not administered.	
Ghosh, JB et al. ³⁹	10	M	Unk	Presumed India	No	Unk	No	Developed symptoms		Not stated	Probable	PCEC IM 0, 3, 7, 14. ESSEN 5-dose. No reported deviations. Developed symptoms 4 days after 4th dose.	RIG not administered.	
Gowda, VK et al. ⁴⁰	15	F	Unk	India	No	No	No	Yes		Not stated	Confirmed	Modern cell culture vaccine ID days 0, 3, 7, 14, 28 (2 doses/day). Updated Thai Red Cross (reported as 2-2-2-2-2). Vaccine type not stated. No deviations reported and completed schedule.	RIG not administered.	Reported as a category III cat scratch.
Kumar, SK et al. ^{41**}	29	M	2019	India	No	Unk	Unk	Yes		Not stated	Confirmed	PCEC days 0, 3, 7, 14, 21. Likely ESSEN 5-dose. Administration site and regimen not specified. No reported deviations.	RIG not administered or possibly true vaccine failures.	
Kumar, SK et al. ^{41**}	58	F	2019	India	No	Unk	Unk	Unk		Not stated	Confirmed	PCEC days 0, 3, 7. Administration site and regimen not specified. No reported deviations.	RIG not administered or possibly true vaccine failures.	Hospitalized for 16 days and then died one day after leaving against medical advice.

Publication*	Age (yrs)	Sex	Date of exp	Country of exposure	RIG given	Core practice: Wound care done	Core practice: Vaccine given in the gluteal muscle	Core practice: Vaccine completed	Reason for vaccine non-completion	Immuno-compromised as reported by the authors	WHO case classification†	Vaccine regimen (number and spacing of doses, administration route, reported deviations, name of regimen)	Reasons for breakthrough infection according to author	Other relevant data
Kuwert, E & Scheiermann, N ⁴²	60	F	1982	Iran	Yes	No	Unk	Developed symptoms		Yes: Age-related immunodeficiency could not be excluded	Confirmed	HDCV days 0, 3, 7, 14. Administration route and regimen not stated. No deviations reported. Developed symptoms day of 4th dose.	No wound care with disinfectants; wounds not infiltrated with RIG; severe lesions near central nervous system (i.e., face, eye, and possibly intra-eye); possible age-related immunodeficiency.	Viral strain was tested and did not show increased antigenicity compared with standard rabies virus. Authors noted RIG was dosed for a 40 kg person which could also indicate malnutrition and contributed to immunodeficiency.
Lumbiganon, P et al. ⁴³	10	M	1987	Thailand	Yes	Yes	Yes	Developed symptoms		Not stated	Confirmed	Suckling mouse rabies vaccine x1 dose. HDCV IM days 0, 2, 6, 13. Regimen not stated. Based on ESSEN spacing deviation of 1-day (dose 2), 3-days (dose 3). Developed symptoms 8 days after 4th dose.	Administration of vaccine in gluteal muscle; wound care did not include antiviral or anti-septic; severe wounds to the head with higher risk for rabies.	
Madhusudana, SN et al. ⁴⁴	12	M	Unk	India	Yes	No	Unk	Developed symptoms		Not stated	Confirmed	PCEC IM days 0, 3, 7. "WHO regimen," likely ESSEN. No reported deviations. Developed symptoms 8 days after 3rd dose.	No immediate wound cleaning with antiseptic; unpredictable incubation period of rabies (e.g., some <2 weeks) so insufficient time to developed antibodies.	
Mohindra, R et al. ⁴⁵	51	M	Unk	India	Yes	Unk	Unk	Yes		Yes: Chronic lymphoproliferative leukemia for which he completed six	Probable	Modern cell culture vaccine, days 0, 3, 7, 14, 28. Likely ESSEN 5-dose. Administration site, vaccine type, and regimen not specified. No	Failure to achieve adequate rabies antibody titers post-vaccination because of underlying immunocompromising	

Publication*	Age (yrs)	Sex	Date of exp	Country of exposure	RIG given	Core practice: Wound care done	Core practice: Vaccine given in the gluteal muscle	Core practice: Vaccine completed	Reason for vaccine non-completion	Immuno-compromised as reported by the authors	WHO case classification†	Vaccine regimen (number and spacing of doses, administration route, reported deviations, name of regimen)	Reasons for breakthrough infection according to author	Other relevant data
										cycles of bendamustine and rituximab 2-3 months before his exposure.		reported deviations. Patient died after completing vaccine series.	condition; hypothesized inappropriate storage of vaccine leading to reduced potency, faulty infection technique with the route or site of vaccine administration, or inadequate dose of RIG.	
Mohite, A et al. ⁴⁶	12	M	Unk	Presumed India	No	Unk	Unk	Either developed symptoms or completed the series.		Not stated	Confirmed	PCEC x 4 doses. Vaccine spacing, administration route, and regimen not stated. Developed symptoms after 4th dose. Either developed symptoms (if 5-dose regimen) or completed (if 4-dose regimen).	RIG not administered.	
Monson, MH ⁴⁷	16	M	1982	Liberia	Unk	Unk	Unk	No	Did not return for additional doses	Not stated	Probable	HDCV day 0. Administration route and regimen not specified.	Did not receive enough vaccine doses. RIG not administered;	
Nadeem, M & Panda, PK ⁴⁸	58	F	Unk	India	No	Unk	Unk	No	Incorrect dosing (3 doses at once)	Not stated	Confirmed	PCEC day 0 (3 doses in one day). Administration route and regimen not specified.	>6-hour delay in vaccine administration; wounds in highly innervated area (e.g., face); Incorrect administration of vaccine (3 doses x 1 day).	
Pannu, AK et al. ⁴⁹	50	M	Unk	India	No	No	Unk	Yes		Not stated	Confirmed	PVRV day 0, X, X, X. Vaccine spacing, administration route, and regimen not specified. Completed series with no deviations reported.	RIG not administered.	

Publication*	Age (yrs)	Sex	Date of exp	Country of exposure	RIG given	Core practice: Wound care done	Core practice: Vaccine given in the gluteal muscle	Core practice: Vaccine completed	Reason for vaccine non-completion	Immuno-compromised as reported by the authors	WHO case classification†	Vaccine regimen (number and spacing of doses, administration route, reported deviations, name of regimen)	Reasons for breakthrough infection according to author	Other relevant data
Rasooli, A et al. ⁵⁰	10	M	2016	Iran	Yes	Yes: Reported as improper wound cleaning	Unk	Developed symptoms		Not stated	Confirmed	PVRV IM days 0, 3, 7. ESSEN 5-dose. No reported deviations. Developed symptoms 4 days after 3rd dose.	Improper wound cleaning; RIG not infiltrated in the wound, given IM only.	
Rasooli, A et al. ⁵⁰	32	M	2016	Iran	Yes	Unk	Unk	Yes		Not stated	Confirmed	PVRV IM days 0, 3, 7, 14, 28. ESSEN 5-dose. No reported deviations. Completed vaccine series.	RIG not infiltrated in the wound, given IM only.	
Rasooli, A et al. ⁵⁰	46	F	2017	Iran	Yes	Unk	Unk	Developed symptoms		Not stated	Confirmed	PVRV IM days 0, 3, 7, 14. ESSEN 5-dose. No reported deviations. Developed symptoms 8 days after 4th dose.	RIG not infiltrated in the wound, given IM only; suturing of the wound; direct inoculation of the virus into the nerve.	
Rasooli, A et al. ⁵⁰	50	M	2016	Iran	Yes	Yes: Reported as improper wound cleaning	Unk	Developed symptoms		Not stated	Confirmed	PVRV IM days 0, 3, 7, 14. ESSEN 5-dose. No reported deviations. Developed symptoms 4 days after 4th dose.	Improper wound cleaning; RIG not infiltrated in the wound, given IM only.	
Rasooli, A et al. ⁵⁰	55	M	2015	Iran	Yes	Unk	Unk	Yes		Not stated	Confirmed	PVRV IM days 0, 3, 7, 14, 28. ESSEN 5-dose. No reported deviations. Completed vaccine series	Reported as "delayed PEP" although states that first vaccine was given immediately after bite.	
Rasooli, A et al. ⁵⁰	58	M	2018	Iran	Yes	Unk	Unk	Developed symptoms	Yes: Reported as having an "advanced immunodeficiency" on long-term immunosuppressive medication.		Confirmed	PVRV IM days 0, 3, 7, 14. ESSEN 5-dose. No reported deviations. Developed symptoms 4 days after 4th dose.	Head wound very close to the brain; direct inoculation of the virus into the nerve; immunodeficiency leading to poor immune response to vaccination.	

Publication*	Age (yrs)	Sex	Date of exp	Country of exposure	RIG given	Core practice: Wound care done	Core practice: Vaccine given in the gluteal muscle	Core practice: Vaccine completed	Reason for vaccine non-completion	Immuno-compromised as reported by the authors	WHO case classification†	Vaccine regimen (number and spacing of doses, administration route, reported deviations, name of regimen)	Reasons for breakthrough infection according to author	Other relevant data
Rasooli, A et al. ⁵⁰	67	M	2018	Iran	Yes	Unk	Unk		Developed symptoms	Not stated	Confirmed	PVRV IM days 0, 3, 7, 14. ESSEN 5-dose. No reported deviations. Developed symptoms 11 days after 4th dose.	Injection of the vaccine and RIG into the same anatomical location.	
Sadeghi, M et al. ⁵¹	67	F	Unk	Iran	Yes	Unk	No		Developed symptoms	Not stated	Confirmed	HDCV IM days 0, 3, 7. ESSEN 5-dose. No deviations reported. Developed symptoms 2 days after 3rd dose.	No specific reason given.	
Shill, M et al. ⁵² and Wilde, H ¹⁵	19	M	1987	South Africa	Yes	Yes	Yes		Developed symptoms	No	Confirmed	HDCV IM days 0, 3, 7, 14. ESSEN 5-dose. No deviations reported. Developed symptoms 7 days after the 4th dose.	Administration of vaccine in the gluteal muscle.	Patient had low titers, but authors could not explain this finding; authors reported that patient was HIV negative with no history of substance abuse that could lead to immunosuppression. A 2nd patient was vaccinated with same lot had appropriate titers. Vaccine potency confirmed.
Tabbara, KF & Al-Omar, O ⁵³	7	F	Unk	Not stated (presumed Saudi Arabia)	Yes	Unk	Unk		Developed symptoms	Not stated	Probable	HDCV. ESSEN 5-dose. Administration route, vaccine schedule, and how many doses received not stated. No deviations reported. Developed symptoms 14 days after starting vaccine series.	>48-hour delay in vaccine administration; proximity of laceration to the cranial nerves; amount of rabies virus inoculated large.	Patient had sister who also was bitten in the face near eyelid by the same fox but received PEP and survived.

Publication*	Age (yrs)	Sex	Date of exp	Country of exposure	RIG given	Core practice: Wound care done	Core practice: Vaccine given in the gluteal muscle	Core practice: Vaccine completed	Reason for vaccine non-completion	Immuno-compromised as reported by the authors	WHO case classification†	Vaccine regimen (number and spacing of doses, administration route, reported deviations, name of regimen)	Reasons for breakthrough infection according to author	Other relevant data
Tarantola, A et al. ⁵⁴	5	M	2008	Cambodia	Yes	Unk	No	No	Unk	Not stated	Probable	PVRV ID days 0, 3, 7 (2 doses/day). Updated Thai Red Cross pre-2018. No deviations noted. Patient developed symptoms and died 39 days after 3rd session.	Several bites to highly innervated areas; suspected but could not confirm errors in PEP administration (e.g., failure to infiltrate all of the wounds with RIG) because two patients were seen at the clinic that day who later also developed rabies.	Patient treated the same day at the same clinic as another case (37-year-old M from Tarantola, A. et al. ⁵¹) who also developed rabies with a PEP failure. Authors reported either RIG/vaccine potency confirmed by manufacturer or because given to another patient with an exposure to a confirmed rabid animal who did not get rabies after PEP.
Tarantola, A et al. ⁵⁴	9	M	2011	Cambodia	Yes	Unk	No	Developed symptoms		Not stated	Probable	PVRV ID days 0, 3, 7 (2 doses/day). Updated Thai Red Cross pre-2018. No deviations noted. Developed symptoms and died 12 days after 3rd session.	Several bites to highly innervated areas (i.e., head); short incubation period associated with direct delivery of RABV into nervous ending.	Patient with extensive head wounds that were sutured before PEP. Authors reported either RIG/vaccine potency confirmed by manufacturer or because given to another patient with an exposure to a confirmed rabid animal who did not get rabies after PEP.

Publication*	Age (yrs)	Sex	Date of exp	Country of exposure	RIG given	Core practice: Wound care done	Core practice: Vaccine given in the gluteal muscle	Core practice: Vaccine completed	Reason for vaccine non-completion	Immuno-compromised as reported by the authors	WHO case classification†	Vaccine regimen (number and spacing of doses, administration route, reported deviations, name of regimen)	Reasons for breakthrough infection according to author	Other relevant data
Tarantola, A et al. ⁵⁴	37	M	2008	Cambodia	Yes	Unk	No	Developed symptoms		Not stated	Probable	PVRV ID days 0, 3, 7 (2 doses/day). Updated Thai Red Cros pre-2018. No deviations noted. Developed symptoms and died 12 days after 3rd session.	Several bites to highly innervated areas (i.e., finger); short incubation period associated with direct delivery of RABV into nervous ending; suspected but could not confirm errors in PEP administration (e.g., failure to infiltrated all of the wounds with RIG) because two patients were seen at the clinic that day who later also developed rabies.	Patient treated the same day at the same clinic as another case (5-year-old M from Tarantola, A. et al. ⁵¹) with a PEP failure. Authors reported either RIG/vaccine potency confirmed by manufacturer or because given to another patient with an exposure to a confirmed rabid animal who did not get rabies after PEP.
Thongcharoen, P & Wasi, C ²⁵	55	F	1983	Thailand	No	No	Unk	Developed symptoms	Yes: 7-year history of liver cirrhosis		Confirmed	HDCV day 0, 3, 7, 14. ESSEN 6-dose. Administration route not stated. No deviations reported. Patient developed symptoms 3 days after 4th dose.	Inadequate wound cleansing; RIG not administrated; cirrhosis of liver may have decreased immune response to HDCV vaccine; authors report that it is possible since patient was in malaria-endemic area that she could have been taking antimalarial medication that led to immunosuppression.	Vaccine lot given to another person who had adequate titers after PEP.
Tran, CH et al. ⁵⁵	6	M	2014	Vietnam	Yes	Unk	Unk	No	Unk	Not stated	Probable	Modern cell culture vaccine day 0. Either ESSEN 5-dose or Updated Thai Red Cross pre-2018. Administration	Did not follow PEP guidelines with sufficient vaccine.	

Publication*	Age (yrs)	Sex	Date of exp	Country of exposure	RIG given	Core practice: Wound care done	Core practice: Vaccine given in the gluteal muscle	Core practice: Vaccine completed	Reason for vaccine non-completion	Immuno-compromised as reported by the authors	WHO case classification†	Vaccine regimen (number and spacing of doses, administration route, reported deviations, name of regimen)	Reasons for breakthrough infection according to author	Other relevant data
												route not reported. Patient received only one dose of vaccine.		
Tran, CH et al. ⁵⁵	72	F	2014	Vietnam	Yes	Unk	Unk	No	Incorrect dosing (4 doses x 1 day)	Not stated	Probable	Modern cell culture vaccine day 0. Either ESSEN 5-dose IM or Updated Thai Red Cross pre-2018. Administration route not reported. Received all four doses of vaccine the day of her exposure.	Did not follow PEP guidelines with incorrect vaccine administration.	
Wilde, H. et al. ²⁸ and Fescharek, R et al. ¹²	20	M	1986	Thailand	Yes	Yes	Yes	Developed symptoms		No	Confirmed	PCEC IM days 0,3, 7, 14. Regimen not specified. No deviations reported. Developed symptoms 5 days after 4th dose.	2-day delay in administration of RIG; wounds not infiltrated with RIG; received at least one dose of vaccine in gluteal muscle.	Reported as "healthy."
<p>* If a manuscript has two publications listed, the first one was the primary source. † Characterized as suspected, probable, or confirmed rabies cases based on standard definitions developed by WHO, which classify cases based on clinical symptoms, history of contact with a rabid animal, and laboratory testing.³ ** 2 cases from Kumar SK et al. were not included because we could not confirm the patients received modern cell culture vaccine. Exp: Exposure; WHO: World Health Organization; Unk: Unknown; PVRV: Purified Vero cell rabies vaccine; PCEC: Purified chick embryo cell rabies vaccine; HDCV: Human diploid cell vaccine; IM: Intramuscular; ID: Intradermal; SQ: Subcutaneous</p>														

Table S5. Demographic and exposure characteristics of 56 breakthrough infections among confirmed human rabies cases with or without deviations from core practices.

	All cases (N=56)		Breakthrough infection with reported or possible deviations from core practices (N=24)*		Breakthrough infection without deviations from core practices (N=32)*	
	n	%	n	%	n	%
Age category (years)						
0-9	16	29%	2	8%	14	44%
10-19	12	21%	7	29%	5	16%
20-29	3	5%	3	13%	0	0%
30-39	3	5%	1	4%	2	6%
40-49	1	2%	1	4%	0	0%
50-59	14	25%	7	29%	7	22%
60-69	6	11%	3	13%	3	9%
70-79	1	2%	0	0%	1	3%
≥80	0	0%	0	0%	0	0%
Sex						
Female	19	34%	9	38%	10	31%
Male	37	66%	15	62%	22	69%
Exposure (N=49 with reported data)			(N=17)		(N=32)	
Dog	49	82%	14	82%	26	81%
Fox	3	6%	0	0%	3	9%
Wolf	2	4%	0	0%	2	6%
Mongoose	2	4%	1	6%	1	3%
Jackal	1	2%	1	6%	0	0%
Emin's pouched rat (<i>Cricetomys emini</i>)	0	0%	0	0%	0	0%
Feline	1	2%	1	6%	0	0%
Exposure type						
Bite	55	98%	23	96%	32	100%
Scratch	1	2%	1	4%	0	0%
Not specified	0	0%	0	0%	0	0%
Wound location (N=55 with reported data)			(N=23)		(N=32)	
Face/neck	31	56%	9	39%	22	69%
Arms/hands	26	47%	12	52%	14	44%
Trunk/back	5	9%	2	9%	3	9%
Legs/feet	9	16%	6	26%	3	9%
Number of anatomical wound locations (N=55 with reported data)			(N=23)		(N=32)	
1	39	71%	17	74%	22	69%
2	16	29%	6	26%	10	31%
3	0	0%	0	0%	0	0%
4	0	0%	0	0%	0	0%
* Breakthrough infections without deviations from core practices were defined as those for which the study reported wound cleaning (regardless of wound cleaning thoroughness), the study did not indicate a concern with the injection site of rabies vaccine(s) (i.e., about incorrect administration into the gluteal muscle); and the current authors could determine that vaccine doses had been given according to a validated vaccine schedule. Breakthrough infections with known or possible post-exposure prophylaxis deviations from core practices included those with deviations or possible deviations from at least one of the core practices.						

Table S6. Clinical characteristics of 56 breakthrough infections among confirmed human rabies cases with or without deviations from core practices.

Time between exposure and outcomes (days)	All cases (N=56)			Breakthrough infection with reported or possible deviations from core practices (N=24)*			Breakthrough infection without deviations from core practices (N=32)*		
	Total N with reported data	Median (IQR)	Range	Total N with reported data	Median (IQR)	Range	Total N with reported data	Median (IQR)	Range
Exposure and wound care	20	0 (0-0)	0-22	4	0 (0-0)	0-0	16	0 (0-0)	0-22
Exposure and RIG administration	39	0 (0-2)	0-31	13	0 (0-1)	0-26	26	0 (0-2)	0-31
Exposure and vaccine administration	54	0 (0-1)	0-22	22	0 (0-1)	0-2	32	0 (0-1·5)	0-22
Exposure and rabies symptom onset	51	20 (17-23)	9-60	20	20·5 (18-23·5)	9-60	31	20 (16-23)	11-39
Exposure to death	43	30 (22-37)	13-70	14	32·5 (22-37)	13-70	29	28 (25-37)	15-61
Rabies immunoglobulin administration		n	%		n	%		n	%
RIG given	56	40	71%	24	13	54%	32	27	84%
Type of RIG									
Human RIG	40	22	55%	13	10	77%	27	12	44%
Equine RIG	40	17	43%	13	2	15%	27	15	56%
Not Specified	40	1	2%	13	1	8%	27	0	0%

* Breakthrough infections without deviations from core practices were defined as those for which the study reported wound cleaning (regardless of wound cleaning thoroughness), the study did not indicate a concern with the injection site of rabies vaccine(s) (i.e., about incorrect administration into the gluteal muscle); and the current authors could determine that vaccine doses had been given according to a validated vaccine schedule. Breakthrough infections with known or possible post-exposure prophylaxis deviations from core practices included those with deviations or possible deviations from at least one of the core practices. RIG: rabies immunoglobulin.

Table S7. Potential causes of 56 breakthrough infections among confirmed human rabies cases with or without deviations from core practices.

	Breakthrough infection with reported or possible deviations from core practices (N=24)*			Breakthrough infection without deviations from core practices (N=32)*		
	Total N with complete data	n	%	Total N with complete data	n	%
Healthcare provider contributions						
<i>Wound care</i>						
No appropriate wound care	24	8	33%	32	0	0%
No information on wound care	24	12	50%	32	0	0%
<i>Vaccine administration</i>						
Vaccine administration in the gluteal muscle	24	3	13%	32	0	0%
Did not complete vaccine series (reason unknown)	24	0	0%	32	0	0%
Received incorrect vaccine regimen	24	1	4%	32	0	0%
Vaccine regimen and series completion unknown	24	3	13%	32	0	0%
Developed symptoms prior to completion of vaccine series	24	15	63%	32	30	94%
<i>RIG administration</i>						
No RIG administered	24	11	48%	32	5	16%
Of people who received RIG:						
RIG given IM only	13	8	62%	27	2	7%
Wound sutured before RIG	13	1	8%	27	1	4%
Not all wounds infiltrated with RIG	13	1	8%	27	2	7%
Patient behaviors	Total N with complete data	Median	IQR	Total N with complete data	Median	IQR
Time from exposure to wound care (days)	4	0	0-0	16	0	0-0
Time from exposure to vaccine administration (days)	22	0	0-1	32	0	0-1.5
Time from exposure to RIG administration (days)	13	0	0-1	26	0	0-2
	Total N with complete data	n	%	Total N with complete data	n	%
Did not return for additional doses of vaccine	24	0	0%	32	0	0%
Anatomic and health status attributes	Total N with complete data	n	%	Total N with complete data	n	%
Wounds to the head, neck, or face	23	9	39%	32	22	69%
Exposed at two or more anatomical locations	23	6	26%	32	10	31%
Immunosuppression	24	3‡	13%	32	3¶	9%
Integrity of PEP biologics						
RIG potency testing done**	24	0	0%	32	2	6%
Vaccine potency testing done**	24	2	8%	32	1	3%
<p>* Breakthrough infections without deviations from core practices were defined as those for which the study reported wound cleaning (regardless of wound cleaning thoroughness), the study did not indicate a concern with the injection site of rabies vaccine(s) (i.e., about incorrect administration into the gluteal muscle); and the current authors could determine that vaccine doses had been given according to a validated vaccine schedule. Breakthrough infections with known or possible post-exposure prophylaxis deviations from core practices included those with deviations or possible deviations from at least one of the core practices.</p> <p>‡ Immunosuppressing conditions specified as liver cirrhosis secondary to alcoholism (n=1), age-related immunosuppression (n=1), and unspecified “advanced immunodeficiency” (n=1).</p> <p>¶ Immunosuppressing conditions specified as uncontrolled diabetes (n=1) and liver cirrhosis secondary to alcoholism (n=2).</p> <p>** All RIG and vaccine tested were found potent.</p> <p>IQR: Interquartile range; RIG: Rabies immunoglobulin; PEP: Post-exposure prophylaxis.</p>						

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