Pertinent fundamentals of rabies immunology

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Evolution of Human rabies vaccines

First human rabies vaccines – Produced from rabies infected brain tissue. Administered by injecting multiple doses into the abdomen region.

1960s – Duck embryo vaccine PEP required 14 doses; produced low titers

Photos from National Museum of American History Smithsonian Institute

Evolution of IM/ID administration of CCVs

1976 – First severe clinical field trial for Human Diploid Cell rabies Vaccine (HDCV); 45 patients severely bitten by wolves in Iran; 6 Subcutaneous doses. 44 patients also received antirabies serum.

THIS WAS PROOF OF EFFICACY

1980 – WHO endorsed Essen 6 dose IM PEP regimen; 3 dose PreP regimen; WHO urged investigation into alternate routes (including ID) of HDCV to reduce cost of vaccine as a replacement for NTVs

HDCV licensed in US for PreP & PEP

1980-90s – Several clinical trials conducted confirming that ID route is as immunogenic & efficacious as IM administration for PEP, PreP

1982 – HDCV packaged in 0.1 mL syringe for PreP in US – cost 75% of IM vial

1989 – 2010s – Clinical data confirming CCVs that meet WHO Prequalification standards are equivalent in immunogenicity and efficacy (HDCV; PCECV; PVRV) when administered IM or ID for PreP and PEP

1997 – PCECV licensed in US for PEP & PreP

2001 – ID PreP pre-packaged vaccine taken off of the market in the US – cost of packaging

Purpose

- Show how intradermal (ID) schedules compare to intramuscular (IM) schedules
  - Much of the published literature is about ID data
  - Will inform whether ID data can be used to inform recommendations for IM ACIP schedules

- Show the efficacy of rabies cell culture vaccines

Verifying Equivalence of IM and ID Route

1. Efficacy
2. Primary Immunogenicity
3. Long-term immunogenicity (i.e., Anamnestic Response)

1. Efficacy – PEP ID

- 58 patients with minor risk to rabies exposure
- CCV – Purified Vero Cell Rabies Vaccine (PVRV)

Four regimens – different volumes & routes:

- Full IM vial (day 0,3,7,14,28)
- 4-site ID (0.1 mL per site) (day 0,3,7)
- 2-site ID (0.1 mL per site) (day 0,3,7)
- 1-site ID (0.1 mL per site) (day 0,3,7)
- All ID patients received 1 0.1 mL dose on day 28

ALL PATIENTS SURVIVED

ALL PATIENTS DEVELOPED NEUTRALIZING ANTIBODIES ABOVE 0.5 IU/mL BY DAY 14

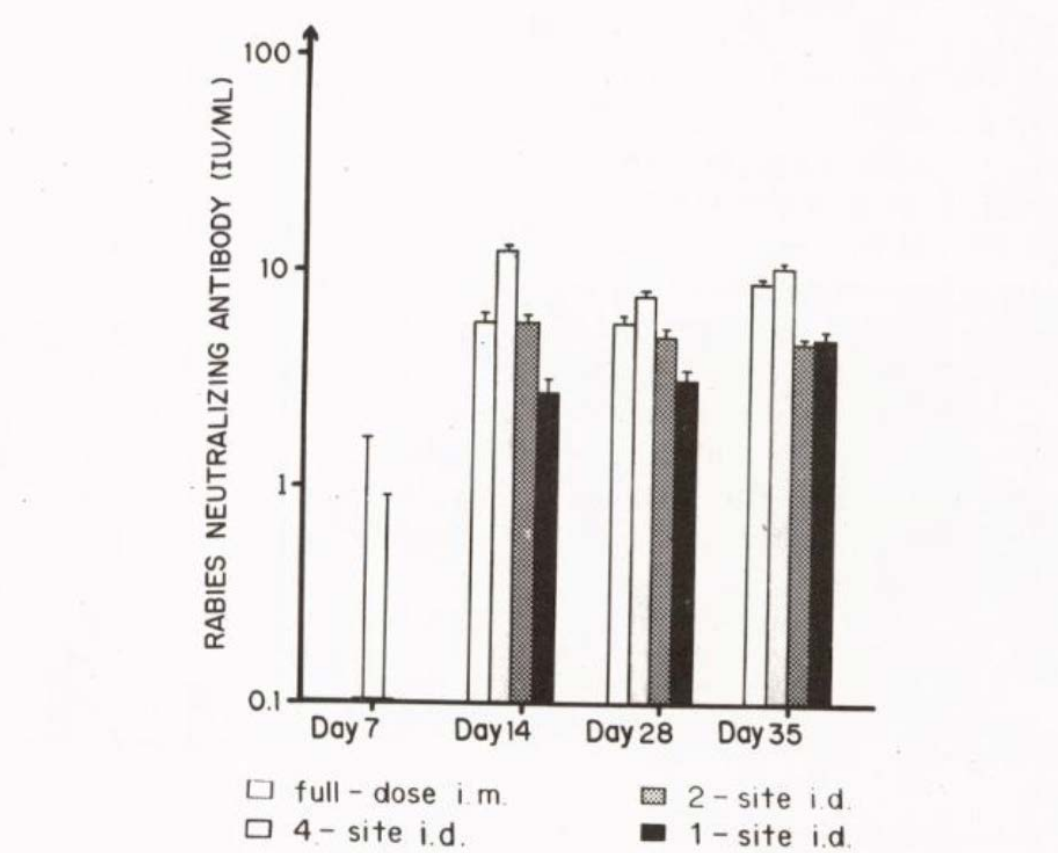


Fig. 1 Neutralizing antibody responses in different regimens of post-exposure purified Vero cell rabies vaccine immunization. Each column respresents the geometric mean titre with bar as SEM.

Phanuphak et al. 1987. Asian Pacific J Allergy & Immunol. 5:33-37.

1. Efficacy ID PEP

"Thai Red Cross Regimen"
Two (0.1 mL) ID doses day 0,3,7 and one (0.1 mL) ID dose day 30 & 90

100 patients severely bitten by confirmed rabid dogs
Follow up: One Year; ALL SURVIVED

TABLE I—LOCATION OF ANIMAL BITES AND EXPECTED NUMBER OF DEATHS BASED ON HISTORICAL STUDIES*

No of patients	Location of bite	Expected mortality rate (%)
2	Face	45
2	Head	45
1	Neck	40
6	Trunk	3
6	Arms	3
18	Hands	15
29	Fingers	15
18	Multiple	15
20	Legs	3
16	Feet	3

*Ref 11

TABLE II—ANTIBODY TITRES IN SEVERELY EXPOSED THAI PATIENTS TREATED WITH THAI RED CROSS INTRADERMAL POSTEXPOSURE RABIES VACCINE*

Patient	Days after first dose of vaccine		
	14	90	360
1	4·33	2·22	0·62
2	6·94	2·22	0·83
3	2·77	0·62	0·62
4	1·38	0·62	0·62
5	2·55	0·77	0·55
6	6·94	0·55	0·62
7	1·05	0·55	0·62
8	6·94	0·62	0·62
9	6·94	3·11	3·00
10	2·55	0·62	0·62
No with titre	10/10	10/10	10/10

*Purified Vero cell rabies vaccine.

Chutivongse S, Wilde H, Supich C, Baer G, Fishbein D. 1990. Lancet 335:896-8.

2. Immune response in IM and ID PrEP

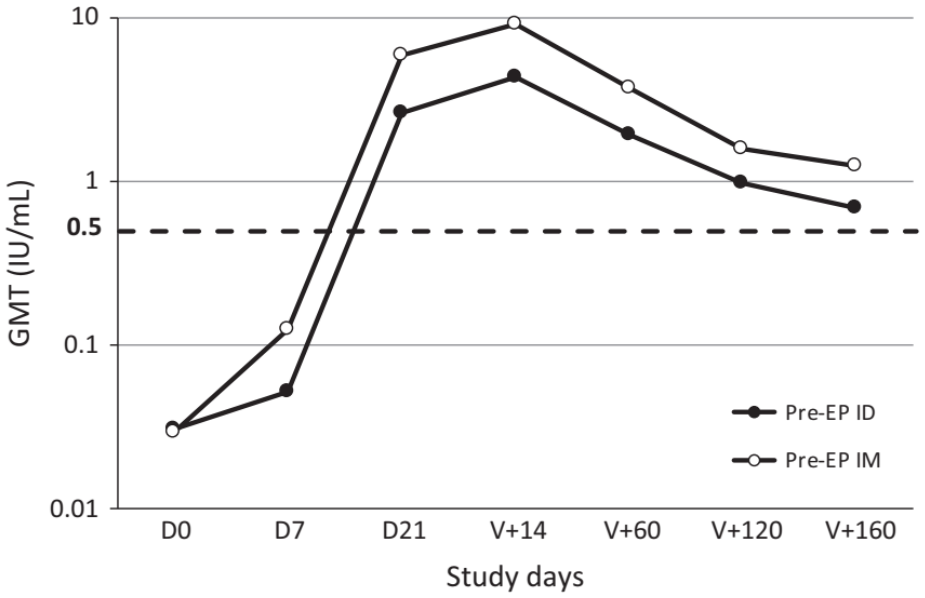


Fig. 1. Distribution of GMT values of rabies virus neutralizing antibodies obtained via the RFFIT, for Pre-exposure (Pre-EP) groups by time. Dashed line equal to and arbitrary defined value of the adequate immune response expected.

128 subjects in 4 arms of the study

Group 1: Naïve subjects received 3 ID PreP doses days 0,7,21

Group 2: Naïve subjects received 3 IM PreP doses days 0,7,21

Blood samples taken prior to vaccination and then on days 7, 21, and 14 days after series finished (V+14), as well as 60, 120 and 160 days after the series finished.

Recuenco, S. et al. 2017. Vaccine 35:4315-20

2. Immune response in IM and ID PrEP

Table 2
Proportion of participants with levels of adequate virus neutralizing antibodies (VNA)[b] by vaccination day and follow-up visits post vaccination.

	D0	D7	D21	V+14	V+60	V+120	V+160
Pre-EP[a] ID							
% VNA	0	26.66	100	100	100	100	100
n/tested	0/30	8/30	30/30	30/30	28/28	28/28	26/26
Pre-EP IM							
% VNA	0	60	100	100	100	100	100
n/tested	0/30	18/30	30/30	29/29	28/28	28/28	28/28
Booster ID							
% VNA	100	–	–	100	100	100	100
n/tested	30/30	–	–	30/30	28/28	27/27	27/27
Booster IM							
% VNA	100	–	–	100	100	100	100
n/tested	33/33	–	–	32/32	31/31	31/31	30/30

[a] Pre-EP: Pre-exposure prophylaxis; ID: intradermal; IM: intramuscular; VNA: virus neutralizing antibodies.
[b] VNA considered adequate when titers were at least 1:5 (~0.1 IU/ml) by RFFIT.

3 dose PreP regimen administered for ID and IM on day 0, 3, 21
V+14 : 14 days after last dose of vaccine administered on day 21

Recuenco, S. et al. 2017. Vaccine 35:4315-20

3. Anamnestic Response

Group A – ID PreP – Day 0, 21
Group B – IM PreP – Day 0, 21

Day 365 – Booster series: 1 dose ID on day 0, 3

Table 1
Rabies neutralizing antibody titers in patients who received pre-exposure vaccination either intradermal (group A) or intramuscular vaccination (group B) and received simulate post-exposure booster vaccination one year after pre-exposure vaccination.

Pre-exposure regimen	Day after pre-exposure vaccination					
	Day 35		Day 365		Day 379 (14 days after booster)	
	Rabies Nab titers (IU/ml)					
	GMT	Range	GMT	Range	GMT	Range
ID Group A ($n=39$)	4.51	1.69–13.0				
IM Group B ($n=16$)	6.74	2.20–14.23				
2-dose ID Group A ($n=36$)			0.35	0.11–1.76	14.38	2.99–308.44
2-dose ID Group B ($n=15$)			0.76	0.18–2.83	14.06	3.12–62.09

NOTE: NO significant difference between the GMT on day 379 in the IM and ID Group (after receiving 2-dose 0.1 mL ID booster series) on day 0, 3

Wongsaroj P et al. 2013. Rabies neutralizing antibody after 2 intradermal doses on days 0 and 21 for pre-exposure prophylaxis. Vaccine. 31:1748-51.

TRC: Thai Red Cross PEP Regimen: 2 ID doses on days 0, 3, 7 and 1 ID dose on day 28 and 90

Equivalence of CCVs

Table 2 **Rabies virus neutralizing antibody titers (IU/mL) in subjects receiving ID 0.1 mL doses of PCECV and PVRV in the TRC (2-2-2-0-1-1) regimen**

		GMT (95% CI)* (IU/mL)*		
Day	**14**	**30**	**90**	**180**
PCECV (n = 55)	4.3 (4.1 - 4.6)	9.0 (8.4 - 9.6)	6.7 (6.4 - 6.9)	3.7 (3.4 - 4.0)
PVRV (n = 50)	4.6 (4.4 - 4.9)	8.7 (8.1 - 9.4)	6.8 (6.5 - 7.1)	3.6 (3.4 - 4.0)
		GMR (95% CI)**		
PCECV/PVRV (0.86-1.01)	0.93 (0.93-1.13)	1.03 (0.93-1.04)	0.98 (0.91-1.14)	1.02

*GMT (95% CI) = Geometric Mean Titer (95% Confidence Intervals). **GMR (95% CI) = Geometric Mean Ratio (95% Confidence Intervals). PCECV, Purified chick embryo cell vaccine. PVRV, Purified vero cell rabies vaccine.

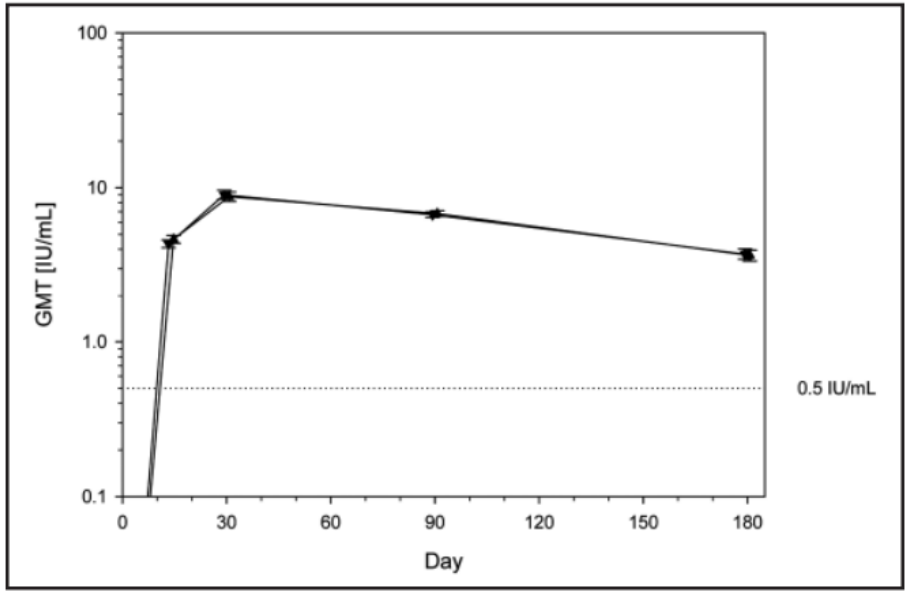


Figure 1. Rabies virus neutralizing antibody titers as determined by RFFIT (geometric mean titers ± 95% confidence intervals) following 0.1 mL of PCECV (▼) or PVRV (▲) per ID site in the Thai Red Cross post-exposure prophylaxis regimen are depicted over the time course throughout the study period.

Madhusudana et al. 2006. Human Vaccines. 2:200-04.

Equivalence of CCVs

ID REGIMEN: “Thai Red Cross Regimen” : Two (0.1 mL) ID doses day 0,3,7 and one (0.1 mL) ID dose day 30 & 90
IM REGIMEN: “Essen Regimen” : One IM dose on day 0, 3, 7, 14 and 28

211 Patients with Cat II & III Wounds ALL PATIENTS SURVIVED

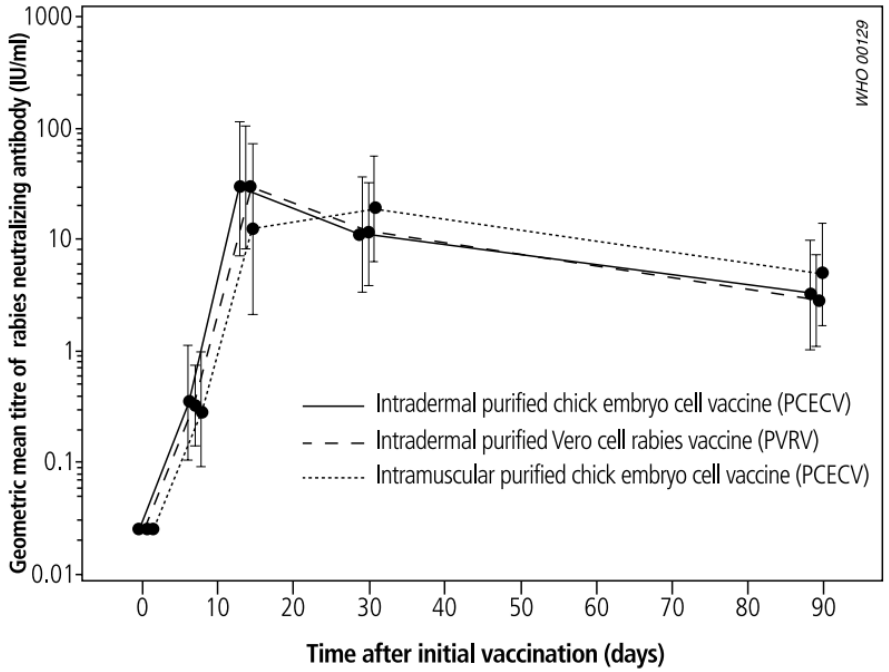
Table 2. **Rabies virus neutralization antibody titres for the per-protocol population**

Day	No. of patients/GMT	Intradermal PCECV	Intradermal PVRV	Intramuscular PCECV
7	*n*[a]	58	59	37
	GMT (IU/ml)[b]	0.34 (0.05–19.1)	0.32 (0.1–2.2)	0.29 (<0.05–19.1)
14	*n*	59	59	37
	GMT (IU/ml)	28.5 (1.1–1318.0)	28.9 (1.6–350.0)	12.3 (0.4–301.0)
30	*n*	55	57	36
	GMT (IU/ml)	10.9 (1.5–171.0)	10.9 (0.6–157.0)	18.5 (0.5–217.0)
90	*n*	53	58	36
	GMT (IU/ml)	3.0 (0.4–59.1)	2.7 (0.5–47.0)	4.7 (0.5–60.9)

[a] *n* = the number of patients per protocol.

[b] GMT = geometric mean titre of rabies virus neutralizing antibodies. Values in parentheses are the range.

Fig. 1. **Concentration of rabies neutralizing antibody (per protocol population)**



Briggs et al. 2000. Bull WHO. 78(5):693-98.

Conclusions

- **EFFICACY**:
  - ID and IM PEP are equally efficacious in patients exposed to confirmed rabid animals
- **PRIMARY IMMUNOGENICITY**:
  - ID and IM PreP are both highly immunogenic routes of vaccination, with IM producing slightly higher titers in most clinical trials.
    - There is no known clinical relevance attributed to the increased immunogenicity reported with the IM route
  - CCVs that meet WHO Pre-qualification standards will produce equitable immunogenicity responses in both PreP and PEP regimens & when administered IM and ID
- **LONG-TERM IMMUNOGENICITY, I.E., ANAMNESTIC RESPONSE:**
  - Patients/subjects that receive PreP administered IM or ID will both have robust anamnestic response to booster vaccination when administered either by the IM or ID route
- **INTERPRETATION**:
  - When using high-quality cell-culture vaccines, ID and IM routes of administration are equivalent among three clinically relevant immunologic factors: efficacy, immunogenicity, and anamnestic response

Brief list of Clinical data on IM and ID administration of CCVs for PEP and PrEP

Efficacy data on the first use of CCV for PEP in patients exposed to rabies

Bahmanyar, M, Fayaz, A, Nour-Salehi, S, Mohammadi, M, Koprowski, H. 1976. Successful protection of humans exposed to rabies infection. Postexposure treatment with the new Human Diploid Cell Rabies Vaccine and anti-rabies serum. JAMA; 236:2751-54.

WHO Activities. 1980. Bull WHO 58:869-872.

Efficacy data on the use of ID PEP in patients exposed to rabies

Briggs, D, Banzhoff, A, Nicolay, U, Sirikwin, S, Dumavibhat, B, Tongswas, S, Wasi, C. 2000. Antibody response of patients after postexposure rabies vaccination with small intradermal doses of purified chick embryo cell vaccine or purified Vero cell rabies vaccine. Bull WHO. 78:693-8.

Chutivongse, S, Wilde, H, Supich C, Baer, G, Fishbein, D. 1990. Postexposure prophylaxis for rabies with antiserum and intradermal vaccination. Lancet. 335: 896-8.

Phanuphak, P, Khawplod P, Sirivichayakul, S, Siriprasomsub, W, Ubol, S, Thaweepathomwat, M. 1987. Humoral and cell-mediated immune responses to various economical regimens of Purified Vero Cell Rabies Vaccine. Asian Pacific J of Allergy & Immunology 5:33-37.

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Salahuddin, N, Gohar, M, Baig-Ansari, N. 2016. Reducing cost of rabies Post Exposure Prophylaxis: Experience of a teriary care hospital in Pakistan. PLoS NTD. 10(2):e0004448. Doi:10.1371/journal.pntd.0004448

Comparative data on PreP administered IM & ID

Dreesen DW, Fishbein DB, Kemp DT, Brown J. 1989. Two-year comparative trial on the immunogenicity and adverse effects of purified chick embryo cell rabies vaccine for pre-exposure immunization. Vaccine. Oct;7(5):397-400. doi: 10.1016/0264-410x(89)90152-7. PMID: 2815976.

Jaiiaroensup W, Lang, J, Thipkong, P, Wimalaratne, O, Samranwataya, P, et al. 1998. Safety and efficacy of purified vero cell rabies vaccine given intramuscularly and intradermally. (Results of a prospective randomized trial) Vaccine 16:1559-62.

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Endy, T, Keiser, P, Wang, D, Jarman, R, Cibula, D, Fang, H, Ware, L, Abbott, M, Thaomas, S, Polhemus, M. 2020. Serological response of 2 versus 3 doses of intradermal vs intramuscular administration of a licensed rabies vaccine for preexposure prophylaxis. J Inf Dis. 221:1494-98.

Clinical evidence of anamnestic response in subjects vaccinated via ID and subsequently boosted

Dreesen DW, Fishbein DB, Kemp DT, Brown J. 1989. Two-year comparative trial on the immunogenicity and adverse effects of purified chick embryo cell rabies vaccine for pre-exposure immunization. Vaccine. Oct;7(5):397-400. doi: 10.1016/0264-410x(89)90152-7. PMID: 2815976.

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Soentjens P, Andries P, Aerssens A, Tsoumanis A, Ravinetto R, Heuninckx W, van Loen H, Brochier B, Van Gucht S, Van Damme P, Van Herrewege Y, Bottieau E. Preexposure Intradermal Rabies Vaccination: A Noninferiority Trial in Healthy Adults on Shortening the Vaccination Schedule From 28 to 7 Days. 2019. Clin Infect Dis. 68:607-614. doi: 10.1093/cid/ciy513. PMID: 29939243.

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Immunogenicity data on the equivalent immunogenicity of CCVs that are manufactured according to the WHO Prequalification recommendations

Briggs, D, Banzhoff, A, Nicolay, U, Sirikwin, S, Dumavibhat, B, Tongswas, S, Wasi, C. 2000. Antibody response of patients after postexposure rabies vaccination with small intradermal doses of purified chick embryo cell vaccine or purified Vero cell rabies vaccine. Bull WHO. 78:693-8.

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Kamoltham, T, Singhsa, J, Promsaranee U, Sonthon, P, Mathean, P, Thinyounyong W. 2003. Elimination of human rabies in a canine endemic province in Thailand: five-year programme. Bull WHO 81:375-81.