National Center for Emerging and Zoonotic Infectious Diseases



Systematic Review: Rabies Pre-exposure Prophylaxis immunogenicity

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CDC Rabies PreEP Systematic Review and Meta-Analysis

- Review of immunologic response to rabies PreEP
 - Primary Response, duration of immunity, and booster response
- Started 2017, Updated through 2019
- Review Question
 - Population: Persons at risk of rabies exposure
 - Interventions: 1) Persons receiving alternate rabies vaccination schedules using modern cell culture vaccines; 2) Persons receiving rabies vaccination by alternate routes using modern cell culture vaccines (i.e. ID)
 - Comparison: Persons receiving ACIP recommended rabies preexposure prophylaxis regimen by the IM route using modern cell culture vaccines
 - Outcomes: Rabies neutralizing antibodies reported as IU/mL 1-3 weeks after primary vaccination, 1 year post vaccination, and after booster

Literature Search

- Databases: MEDLINE, Embase, Cochrane Library, WHO Index Medicus, citation sampling
- Jan 1965 Dec 2019
- Search Term:

(rabies OR rabies vaccine) AND (antibodies) AND (human) AND (preexposure OR pre-exposure)

Results: 258 Unique papers

Selection Criteria

- Exclusion Criteria
 - Use of nervous tissue or experimental vaccines*
 - Immunocompromised populations
- Inclusion Criteria
 - Subjects received PrEP (schedule of 1-3 doses)
 - Immune response to vaccination measured by RFFIT
 - Findings reported as GMT (IU/mL) or as a seroconversion rate to a stated cut-off (e.g. 0.5 IU/mL)

*not a licensed vaccine or ever evaluated by WHO; RFFIT: Rapid Fluorescent Focus Inhibition Test; GMT: geometric mean titer

Study Selection



Study Characteristics

- Study Types
 - Randomized clinical trial (59%)
 - Controlled clinical trial (16%)
 - Cohort study (13%)
 - Case/Time series (12%)
- Study Locations
 - Asia (41%)
 - North America (29%)
 - Europe (25%)
 - South America (3%)
 - Africa (2%)

Primary Response – Cohort Characteristics

- Schedules (cohorts)
 - Single dose
 - 2-dose: day 0,28; day 0,60; day 0,7
 - 3-dose: day 0,3,7; day 0,7,14; day 0,7,21/28
- Vaccines (cohort)
 - PVRV, PCEC, HDCV, and Others
- Route (cohorts)
 - IM, ID, SC

Primary Seroconversion of ACIP recommended schedule

- Day 0,7,21/28 schedule well established with broad evidence base
 - Recommended schedule for >40 years
 - High (>97%) seroconversion regardless of vaccine or administration route

Primary titer response of ACIP recommended schedule

- Heterogeneity between studies higher for GMT
- IM produces significantly higher GMT
 - Not clinically significant
- **Primary IM GMT** >13.99 IU/mL (lowest 95% CI)
- Primary ID GMT >4.50 IU/mL (lowest 95% CI)

Study	DeltaVax	n	Mean		MLN	95%-CI	(fixed)	(random
	Studi	es	: .					
Tantawichien-2014(A)	14	32	+		5.02	[4 25: 5 93]	0.0%	3.69
Recuenco-2017(1)	14	30	+		4 27	[3.38: 5.39]	0.0%	3.59
Dreesen-1984(A)	21	40	+		8.90	[6.99:11.34]	0.0%	3.59
Dreesen-1982(3)	21	86	+		8.22	[7.79:8.67]	0.4%	3.79
Fixed effect model			6		7 69	[7.32:8.07]	0.5%	
Random effects model			\diamond		6.32	[4.50: 8.87]		14.3%
Heterogeneity: $I^2 = 95\%$, τ^2	= 0.1112, p < 0	0.01				L,		
RouteLabel = 1	Studi	es						
Sampath-2010(1A)	7	174	E		18.80	[18.53; 19.08]	5.8%	3.79
Sampath-2010(1B)	7	56			18.50	[18.11; 18.89]	2.8%	3.79
Naravana-2014(1)	7	34	+		7.50	[7.04; 7.99]	0.3%	3.79
Ajjan-1989(2)	14	69			30.00	[29.44; 30.57]	3.5%	3.79
Strady-1998(B2)	14	67			27.40	[26.89; 27.92]	3.5%	3.79
Ajjan-1989(1)	14	69			23.00	[22.49; 23.52]	2.5%	3.79
Strady-1998(A2)	14	32	1	+	33.60	[32.90; 34.32]	2.8%	3.79
Tantawichien-2014(B)	14	31	+		14.23	[13.36; 15.16]	0.3%	3.79
Lang-1998(1)	14	159			23.00	[22.70; 23.31]	7.1%	3.79
Sabchareon-1999(1)	14	195		•	32.90	[32.61; 33.19]	16.6%	3.79
Lang-1998(2)	14	162	1		29.60	[29.34; 29.87]	15.7%	3.79
Tantawichien-2014(C)	14	31	+		11.49	[10.74; 12.29]	0.3%	3.79
Pichon-2013(A)	14	251			13.50	[13.19; 13.82]	2.3%	3.79
Pichon-2013(B)	14	127	0		14.80	[14.41; 15.20]	1.8%	3.79
Favi-2004(1)	14	30	+		8.50	[7.90; 9.14]	0.2%	3.79
Sabchareon-1999(2)	14	190			47.60	[47.27; 47.93]	26.1%	3.79
Recuenco-2017(2)	14	29	+		9.05	[8.18; 10.01]	0.1%	3.79
Lalosevic-2008(1)	16	118	+		6.86	[6.25; 7.53]	0.1%	3.79
Dreesen-1984(B)	21	20			13.80	[11.72; 16.25]	0.0%	3.69
Shanbag-2008(A)	21	58			13.80	[13.49; 14.12]	2.4%	3.79
Shanbag-2008(C)	21	55			12.90	[12.58; 13.23]	2.0%	3.79
Shanbag-2008(B)	21	57	0		12.80	[12.50; 13.11]	2.2%	3.79
Fixed effect model					28.99	[28.89; 29.10]	98.6%	-
Random effects model			\diamond		16.87	[13.99; 20.35]		81.9%
Heterogeneity: $I^2 = 100\%$, τ^2	² = 0.2006, <i>p</i> =	0						

Weight

Weight

GMT: Geometric Mean Titer, IM: intramuscular, ID: intradermal

Rabies Pre-exposure Prophylaxis 2-dose, 1 week Schedule (day 0 and 7)

Primary Response

Study Characteristics – primary immunogenicity

	Original Study				Study Subjects (in
Study	Type(1)	Population	Intervention(1,2)	Comparison(1,2)	analysis)
Ajjan , 1989	ССТ	Europe, veterinary students	PVRV-IM [0,7,21/28]	HDCV-IM [0,7,21/28]	144 (72)
Jaijaroensup , 1999	RCT	Asia, veterinary students	PCEGID [0,7,21/28] PCEG2xID [0,7,21/28]	PCEGIM [0,7,21/28]	138 (84)
Arora, 2004	RCT	North America, veterinary students	PVRVIM [0,7,21/28]	HDCV-IM [0,7,21/28]	135 (44)
Sabchareon, 1999	RCT	Asia, children	PVRVIM [0,7,21/28]	HDCV-IM [0,7,21/28]	400 (190)
Briggs, 1996	Case Series	North America, veterinary students	HDCV-IM [0,7,21/28]	n/a	157
Hacibektasoglu, 1992	RCT	Europe, at risk population	PVRV-IM [0,7,21/28]	HDCV-IM [0,7,21/28]	60 (30)
Kitala, 1990	ССТ	Africa, veterinary students	PVRV-IM [0,7,21/28]	HDCV-IM [0,7,21/28]	80 (37)
Vodopija, 1986	RCT	Europe, general population	PCEGIM [0,7,21/28] PVRV-IM [0,7,21/28] FBKGIM [0,7,21/28]	HDCV-IM [0,7,21/28]	92 (46)
Cramer, 2016	RCT	Europe, general population	PCEGIM [0,3,7]	PCEGIM [0,7,21/28]	605 (371)
Recuenco, 2017	ССТ	North America, at risk population	PCEGID [0,7,21/28]	PCEGIM [0,7,21/28]	66 (30)
Soentjens, 2019	RCT	Europe, military	HDCV-2xID [0,7]	HDCV-ID [0,7,21/28]	500 (242)
Endy, 2019	RCT	North America, general population	PCEGID [0,7,21/28] PCEGID [0,7] PCEGIM [0,7]	PCEGIM [0,7,21/28]	60 (35)

1: Individual study arms were treated as observational cohorts for pooled analysis. 2: Serology data taken between day 14-28 (before 3rd dose administered in [0,7,21/28] cohorts) used as proxy of [0,7] schedule

Primary Immunogenicity –GMT by serology day [2dose]

- 2 doses of vaccine days 0 and 7
- Comparable primary titer response to 3dose schudule
- Limited number of studies, but similar heterogeneity as observed in 3-dose ACIP meta-analysis



Primary Immunogenicity – SCR by serology day [2dose]

- High SCR (98%) achieved 7-14 days after second dose (day 7)
- No significant difference at between serology periods
- SCR consistent across studies (little heterogeneity)

	Study	Events	Total	Proportion [95%-CI]
	Day 14 - 21 - 14	21d, 2=2	1-28d, 3	=60-90d) = 1
	Ajjan-1989(1)	72	72	1.00 [0.95; 1.00]
	Cramer-2016(3)	208	210	0.99 [0.97; 1.00]
	Cramer-2016(2)	159	161	0.99 [0.96; 1.00]
	Recuenco-2017(2)	30	30	1.00 [0.88; 1.00]
	Vodopija-1986(3)	25	25	1.00 [0.86; 1.00]
	Vodopija-1986(1)	24	24	1.00 [0.86; 1.00]
	Endy-2019(1)	12	12	1.00 [0.74; 1.00]
	<endy-2019(3)></endy-2019(3)>	12	12	1.00 [0.74; 1.00]
ID	<endy-2019(4)>*</endy-2019(4)>	11	11	1.00 [0.72; 1.00]
	Hacibektasoglu-1992(2)	27	30	• 0.90 [0.73; 0.98]
	Random effects model		587	• 0.98 [0.95; 0.99]
	Heterogeneity: $I^2 = 10\%$, τ^2	= 0.1249	, p = 0.3	5
	Day 28 roup (1=14-2	21d, 2=2	1-28d, 3	=60-90d) = 2
ID	<soentjens-2018(2)>*</soentjens-2018(2)>	242	242	- 1.00 [0.98; 1.00]
	Sabchareon-1999(2)	190	190	1.00 [0.98; 1.00]
	Briggs-1996(1)	146	146	1.00 [0.98; 1.00]
	Arora-2004(2)	44	44	1.00 [0.92; 1.00]
	Kitala-1990(2)	37	37	1.00 [0.91; 1.00]
	<endy-2019(3)></endy-2019(3)>	12	12	1.00 [0.74; 1.00]
ID	<endy-2019(4)>*</endy-2019(4)>	10	10 -	1.00 [0.69; 1.00]
	Jaijaroensup-1999(A)	25	28	0.89 [0.72; 0.98]
	Random effects model		709	0.98 [0.95; 1.00]
	Heterogeneity: $I^2 = 53\%$, τ^2	= 1.7017	, p = 0.04	4
	Random effects model		1387	O.98 [0.96; 0.99] O.98 O.98
	Heterogeneity: $I^2 = 14\%$, τ^2	= 0.2078	, p = 0.2	
	Residual heterogeneity: / ²	= 22%, p	= 0.18 0	.7 0.75 0.8 0.85 0.9 0.95 1
	Test for subgroup difference	$\cos (\chi_2^2 = 0)$.60, df =	2 (p = 0.74)

Primary Immunogenicity – SCR 3-dose vs 2-dose

- 30-60 days post vaccination
 - No significant difference in SCR between 3-dose and 2-dose schedules
 - Limited number of 2-dose studies with small cohort sizes



SCR: Seroconversion Rate (>0.5IU/mL)

Duration of Immunogenicity and response to booster

Study Characteristics – Duration of immunogenicity

	Study			Comparison(Time @ Booster	Total follow - <u>up</u>	N @
Study	Type(1)	Population	Intervention(1,2)	1,2)	(m)	(m)	booster
Pengsa, 2009	RCT	Asia, Children	PCEGID [0,7,21/28]	PCEGIM [0,7,21/28]	12	36	176
Ajjan , 1989	ССТ	Europe, veterinary students	PVRV-IM [0,7,21/28]	HDCV-IM [0,7,21/28]	n/a	21	98
Jaijaroensup , 1999	RCT	Asia, veterinary students	PCEGID [0,7,21/28] PCEG2xID [0,7,21/28]	PCEGIM [0,7,21/28]	12	12+(14d)	110
Kamoltham , 2007	RCT	Asia, Children	PCEG2xID [0,28]	PCEGID [0,7,21/28]	12	24	147
Sabchareon, 1999	RCT	Asia, children	PVRV-IM [0,7,21/28]	HDCV-IM [0,7,21/28]	12	12+(14d)	310
Strady, 1998	RCT	Europe, at risk population	HDCV-IM [0,28] PVRV-IM [0,7,21/28] PVRV-IM [0,28]	HDCV-IM [0,7,21/28]	12 120	120+(14d)	286
Briggs, 1996	Case Series	North America, veterinary students	HDCV-IM [0,7,21/28]	n/a	12	12+(14d)	146
Dreesen, 1989	RCT	North America, general population	HDCV-ID [0,7,21/28] PCEGIM [0,7,21/28] PCEGID [0,7,21/28]	HDCV-IM [0,7,21/28]	24	24+(7d)	69
Bernard, 1987	RCT	North America, veterinary students	HDCV-ID [0,7,21/28] HDCV-SC [0,7,21/28]	HDCV-IM [0,7,21/28]	12 24	24+(21d)	48
Cramer, 2016	RCT	Europe, general population	PCEGIM [0,3,7]	PCEGIM [0,7,21/28]	n/a	12	584
Chatchen, 2017	RCT	Asia, Children	PCEG0.5IM [0,7,21/28] PCEGID [0,7,21/28]	PCEGIM [0,7,21/28]	12	96	68
Endy, 2019	RCT	North America, general population	PCEGID [0,7,21/28] PCEGID [0,7] PCEGIM [0,7]	PCEGIM [0,7,21/28]	12	12+(7d)	42
Soentjens, 2019	RCT	Europe, military	HDCV-2xID [0,7]	HDCV-ID [0,7,21/28]	~18	~18+(7d)	411

1: Individual study arms were treated as observational cohorts for pooled analysis. 2: Serology data taken between day 14-28 (before 3rd dose administered in [0,7,21/28] cohorts) used as proxy of [0,7] schedule

1 year immunogenicity and response to booster - GMT

- Lower GMT in 2 dose (day 0,7) recipients
 - not significantly different from 3 dose recipients
- Anamnestic response observed post booster in both 2 and 3 dose cohorts
- GMT in 3 dose recipients significantly higher
 1 Year post vaccination
 7-14 days post booster



GMT: Geometric Mean Titer

1 year immunogenicity and response to booster - SCR

- Lower proportion of 2 dose (day 0,7) recipients w/ adequate titer at 1 year: 59%
- Anamnestic response post booster
 - All recipients achieve adequate antibody level, no significant difference between groups
 7-14 days post booster (at 1 year)

1 Year post vaccination Study Events Total Proportion 95%-CI \ Proportion 95%-CI [0,7,21/28] Schedule [0,7,21/28] Schedule Sabchareon-1999(2) 1.00 [0.98; 1.00] 151 151 Briggs-1996(1) 146 146 -1 1.00 [0.98; 1.00] Briggs-1996(1) 146 146 1.00 [0.98; 1.00] 45 1.00 [0.92; 1.00] Penasa-2009(2) 45 Pengsa-2009(2) 45 45 1.00 [0.92; 1.00] Pengsa-2009(1) 1.00 [0.92; 1.00] 44 44 Pengsa-2009(1) 44 1.00 [0.92; 1.00] 44 1.00 [0.88; 1.00] Strady-1998(A2) 30 30 Strady-1998(A2) 30 30 1.00 [0.88; 1.00] Bernard-1987(A1) 17 17 1.00 [0.80; 1.00] Jaijaroensup-1999(A) 1.00 [0.84; 1.00] Sabchareon-1999(2) 149 154 0.97 [0.93; 0.99] 21 21 0.80 [0.74; 0.85] Endy-2019(1) 1.00 [0.72; 1.00] Cramer-2016(3) 163 204 11 11 Cramer-2016(2) 117 154 0.76 [0.68; 0.82] Bernard-1987(A1) 8 1.00 [0.63; 1.00] Endy-2019(1) 0.64 [0.31; 0.89] Random effects model 0.99 [0.96: 0.99] 7 11 21 0.38 [0.18; 0.62] Heterogeneity: $I^2 = 0\% \tau^2 = 0$, n = 0.80Jaijaroensup-1999(A) 8 Random effects model 826 0.90 [0.79: 0.95] [0,7] Schedule Heterogeneity: $l^2 = 86\%$, $\tau^2 = 1.1103$, p < 0.01ID<Soentiens-2018(2)>* [0,7] Schedule 183 183 1.00 [0.98; 1.00] <Endy-2019(3)> 11 1.00 [0.72; 1.00] ID <Endy-2019(4)>* 0.60 [0.26; 0.88] D<Endy-2019(4)>* 1.00 [0.66; 1.00] <Endy-2019(3)> 12 0.58 [0.28; 0.85] Heterogeneity: $I^2 = 26\%$, $\tau^2 = 0.7196$, p = 0.26Random effects model 862 0.99 [0.97; 0.99] 1 Random effects model 1054 0.78 [0.62; 0.88] Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p = 0.89Heterogeneity: $I^2 = 92\%$, $\tau^2 = 1.8061$, p < 0.010.65 0.7 0.75 0.8 0.85 0.9 0.95 1 Residual heterogeneity: I2 = 0%, p = 0.83 0.2 0.4 0.6 0.8 Residual heterogeneity: $I^2 = 88\%$, p < 0.01Test for subgroup differences: $\chi^2_2 = 0.54$, df = 2 (p = 0.76) Test for subgroup differences: $\chi^2_2 = 15.61$, df = 2 (p < 0.01) SCR: Seroconversion Rate (>0.5IU/mL)



2-dose (day 0,7) schedule study summary

- Soentjens et al. (n=183) ID
 - Pre-booster (1-3 years post vaccination): 2-dose ID GMT (3.4 IU/mL) was significantly higher compared to 3-dose ID (2.0 IU/mL)
 - 100% of both groups had an adequate titer (>0.5 IU/mL) after booster
- Endy et al. (n=22) IM/ID
 - Compared to 3-dose IM series, no significant difference observed in the GMT at day 365 for 2-dose IM or 2-dose ID
 - 40-50% of 2-dose recipients had a titer of >0.5 IU/mL at day 365
 - 100% of recipients had an adequate titer after receiving booster at 1 year

Duration and kinetics of antibody response

- Most studies evaluated 3 dose (day 0,7,21/28) schedule (IM and ID)
- Rapid decay during first 6 months post vaccination
 - Slows to plateau between 6 months to 1 year
 - Decay more rapid when administered by ID route
 - ID >1.5 times more likely to not have an adequate titer at 1-2 years post vaccination
- Post booster response typically greater than primary response
 - Decay slower after booster

Banga et al. Vaccine. 2014; 32:979 Brown et al. Vaccine. 2008; 26:3909 Mansfield et al. Vaccine. 2016; 34:5959 Strady et al. JID. 1998; 177:1290

Booster effect on duration of immunogenicity





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Rabies Vaccine Work

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Thank you

Additional Slides

Titer cut-offs

- 0.5 IU/mL aligns with WHO.
 - Corresponds closer to assay threshold across laboratories

Meta-Analysis Summary

		M – Route	ID – Route							
Schedule	Cohorts (Subjects)	SCR†	95% CI	12	p- value**	Cohorts (Subjects)	SCR	95% CI	12	p- value* *
[0,7,21/28]	45 (2,899)	99%	(98% - 99%)	0%	1.0	21 (876)	98%	(97% - 99%)	0%	1.0
[0,3,7]	3 (209)	98%	(92% - 100%)	22%	0.29	-	-	-	-	-
[0,7]	25 (1,909)	98%	(97% - 99%)	41%	0.02	9 (653)	97%	(93% - 99%)	38%	0.12
[0,28]	3 (224)	99%	(94% - 100%)	20%	0.29	3 (126)	98%	(94% - 100%)	87%	<0.01
[0]	9 (574)	17%	(9% - 32%)	87%	<0.01	-	-	-	-	-

*Pooled SCR by random effects model.
**Cochran's Q Test.
* Significant difference between vaccines types (p-

+Significant difference between vaccination routes (p<0.01)



Primary Immunogenicity – Schedule Comparison

2 weeks post vaccination



Neutralizing Antibody as Surrogate of Protection

RFFIT [IU/m]]

- 0.5 IU/mL rabies neutralizing antibodies (RFFIT)
 - Not a measure of protection
 - Measure of adequate response
 - Reliable detection limit of assays
- Correlation between antibody titer and survival
- Variability between species
- Adequate antibody response after primary vaccination and anamnestic response post challenge is best surrogate of survival



Rabies Virus Antibodies from Oral Vaccination as Correlate of Protection against Lethal Infection in Wildlife Moore S, et al. (2017). Trop Med Infect Dis.,