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 pre-exposure 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

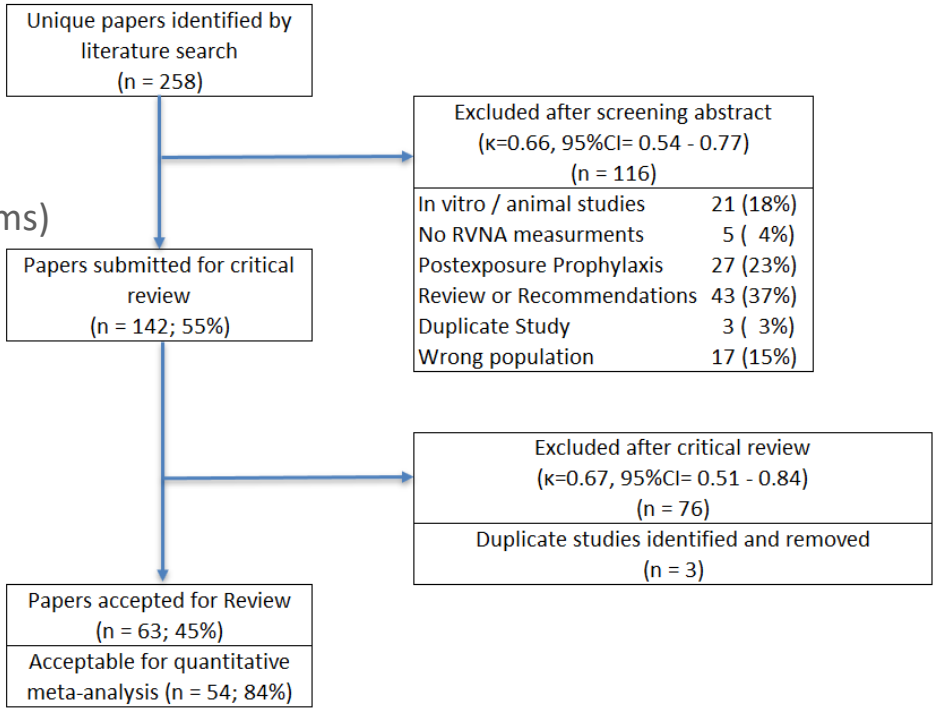
Selection Criteria

- 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

- Selected Studies
  - 1978 – 2019
  - 146 Cohorts (study arms)
  - 11,608 Subjects
    - Avg: 79.5 / cohort
    - Med: 32 / cohort



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

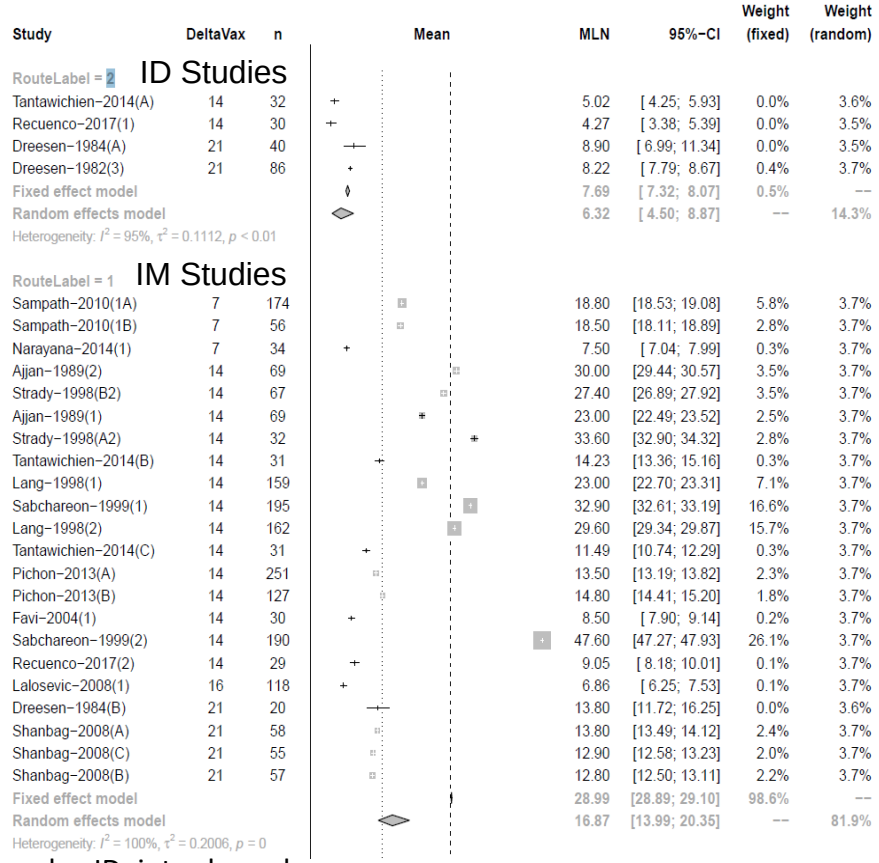
Purified Vero Rabies Vaccine (PVRV), Purified Chick Embryo Cell Vaccine (PCEC), Human Diploid Cell Vaccine (HDC

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)



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

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

Primary Response

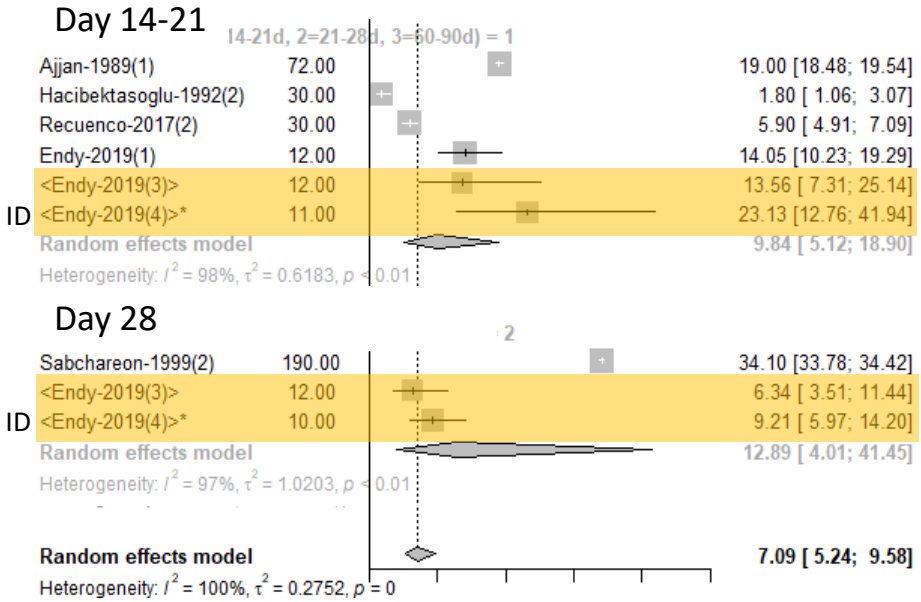
Study Characteristics – primary immunogenicity

Study	Original Study Type(1)	Population	Intervention(1,2)	Comparison(1,2)	Study Subjects (in analysis)
Ajjan , 1989	CCT	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	PVRV-IM [0,7,21/28]	HDCV-IM [0,7,21/28]	135 (44)
Sabchareon, 1999	RCT	Asia, children	PVRV-IM [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	CCT	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	CCT	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]

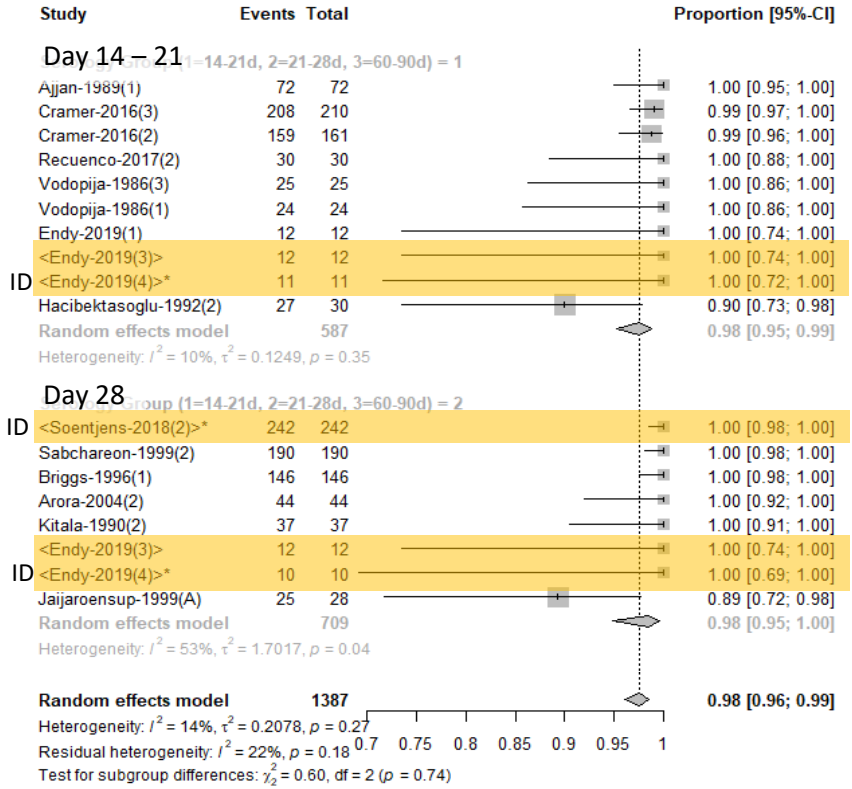
- 2 doses of vaccine days 0 and 7
- Comparable primary titer response to 3-dose schudule
- Limited number of studies, but similar heterogeneity as observed in 3-dose ACIP meta-analysis



GMT: Geometric Mean Titer

Primary Immunogenicity – SCR by serology day [2dose]

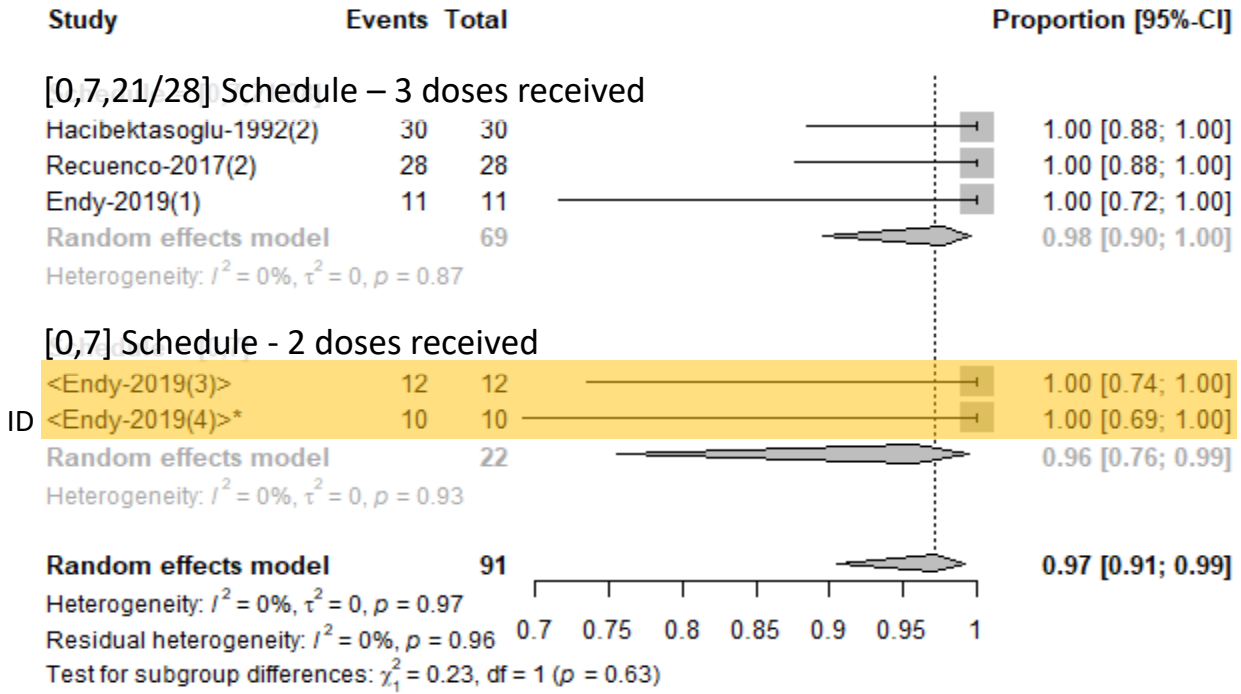
- High SCR (98%) achieved 7-14 days after second dose (day 7)
- No significant difference at between serology periods
- SCR consistent across studies (little heterogeneity)



SCR: Seroconversion Rate (>0.5IU/mL)

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

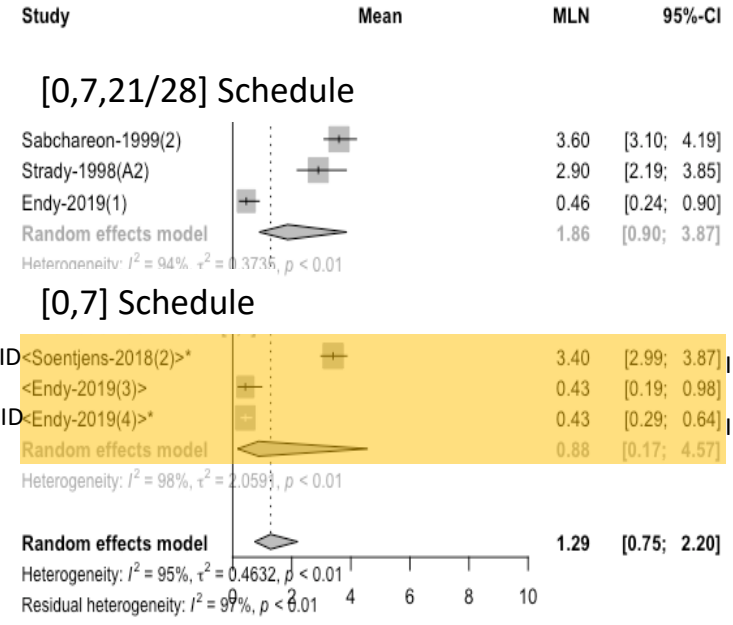
Study	Study Type(1)	Population	Intervention(1,2)	Comparison(1,2)	Time @ Booster (m)	Total follow -up (m)	N @ booster
Pengsa, 2009	RCT	Asia, Children	PCEGID [0,7,21/28]	PCEGIM [0,7,21/28]	12	36	176
Ajjan , 1989	CCT	Europe, veterinary students	PVRV-IM [0,7,21/28]	HDCV-IM [0,7,21/28]	n/a	21	98
Jaijaroensup , 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

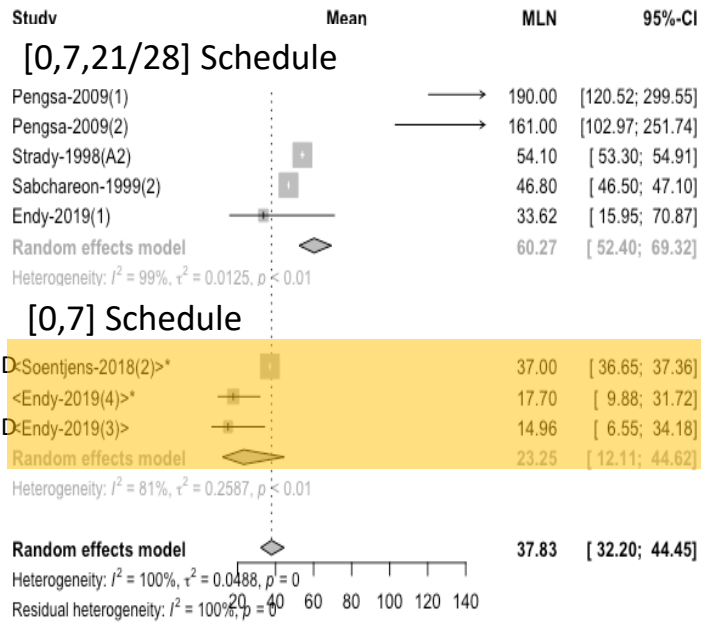
1 year immunogenicity and response to booster - GMT

- 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

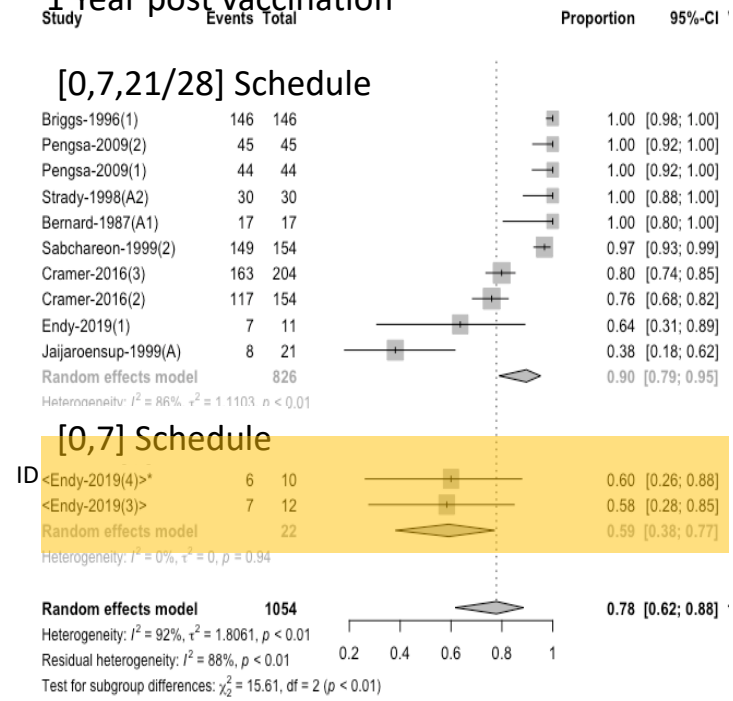


GMT: Geometric Mean Titer

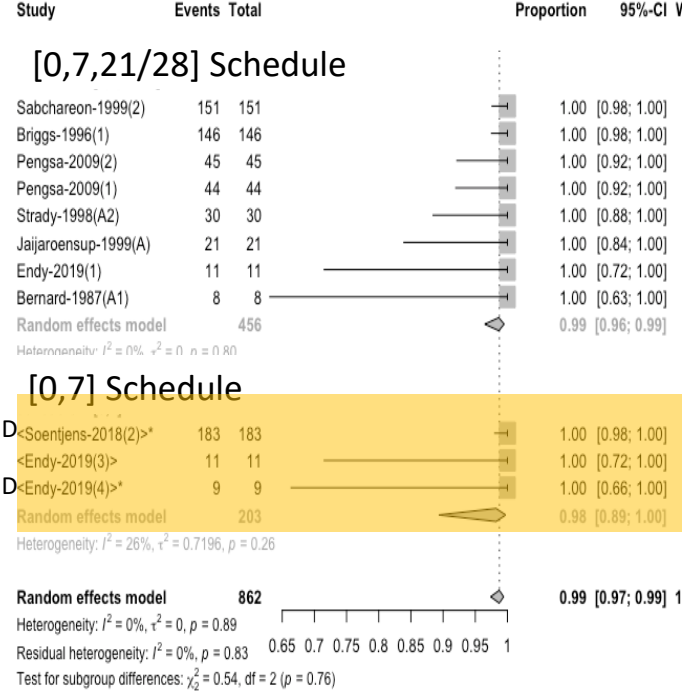
1 year immunogenicity and response to booster - SCR

- 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

1 Year post vaccination



7-14 days post booster (at 1 year)



SCR: Seroconversion Rate (>0.5IU/mL)

Summary

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

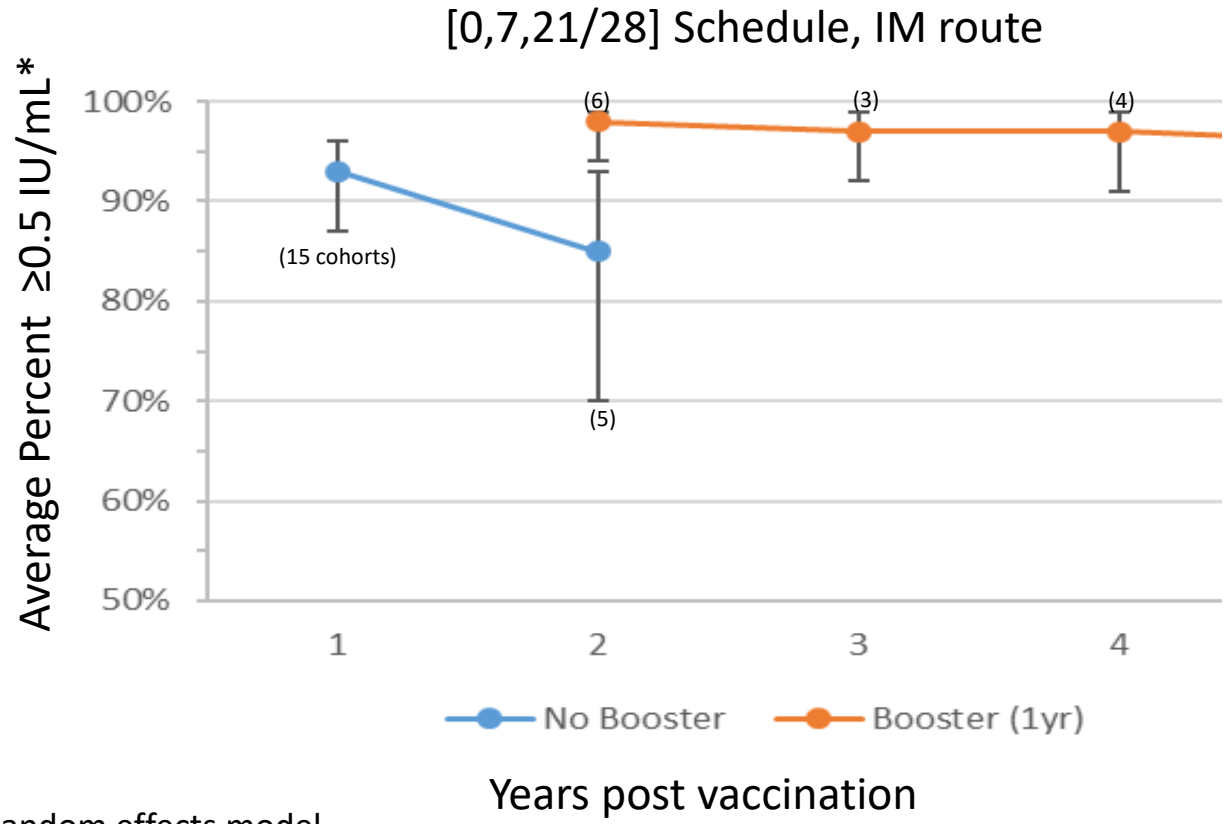
- Soentjens et al. (n=183) ID
  - Pre-booster (1-3 years post vaccination): 2-dose ID GMT (3.4 IU/mL) was significantly higher compared to 3-dose ID (2.0 IU/mL)
  - 100% of both groups had an adequate titer (>0.5 IU/mL) after booster
- Endy et al. (n=22) IM/ID
  - Compared to 3-dose IM series, no significant 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



*Random effects model

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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

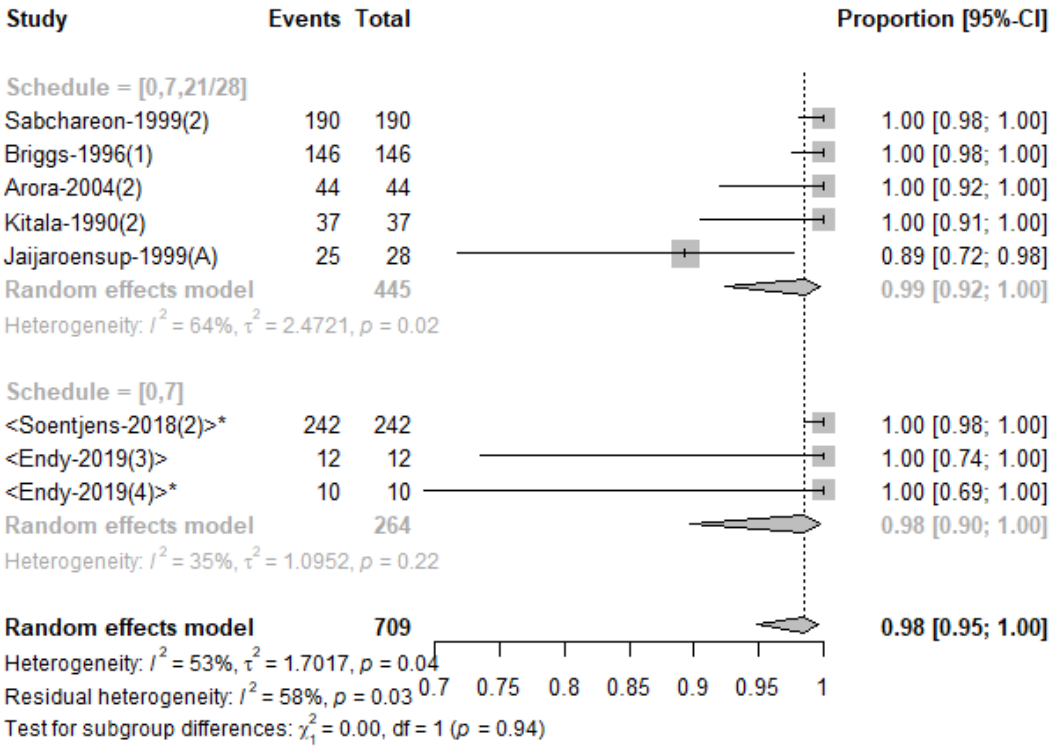
Meta-Analysis Summary

	IM – Route					ID – Route				
Schedule	**Cohorts (Subjects)**	**SCR†**	**95% CI**	**I2**	**p-value****	**Cohorts (Subjects)**	**SCR**	**95% CI**	**I2**	**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<0.01).
- ‡Significant difference between vaccination routes (p<0.01)

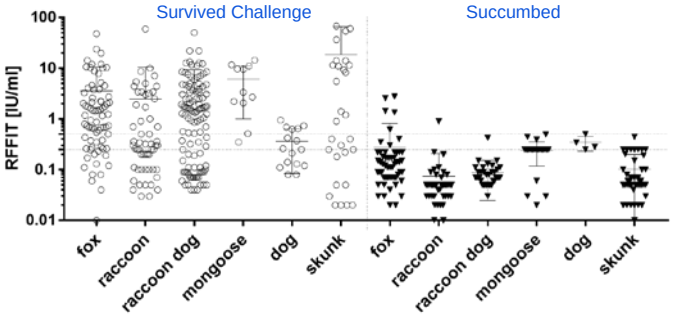
Primary Immunogenicity – Schedule Comparison

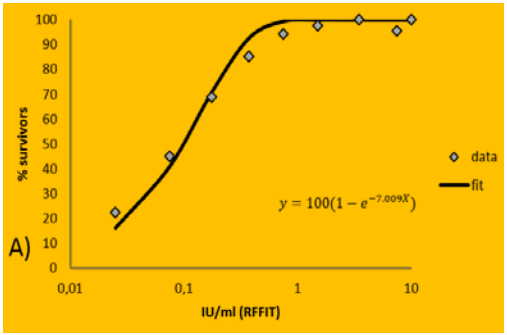
- 2 weeks post vaccination



Neutralizing Antibody as Surrogate of Protection

- 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.,