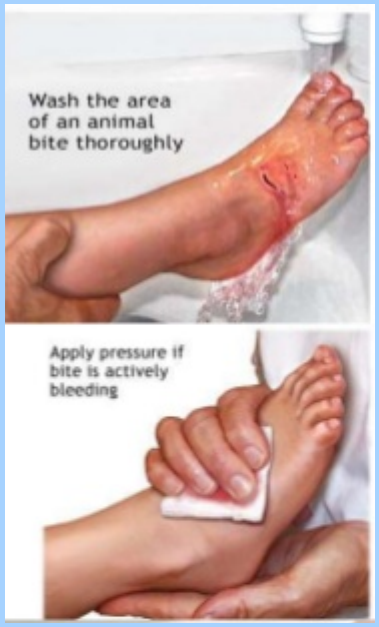
Post-Exposure Prophylaxis (PEP)

Questions 5, 6, 7, 8, 9



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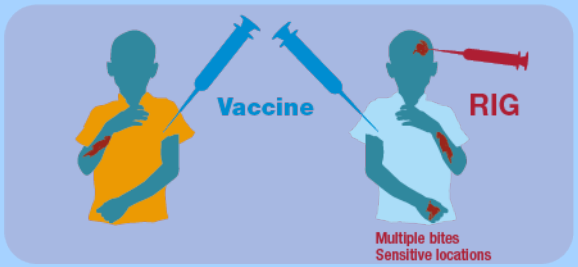


PEP depends on the type of contact with rabid animal:

Category I: touching or feeding animals, licks on intact skin);

Category II: nibbling of uncovered skin, minor scratches or abrasions **without bleeding**;

Category III: single or **multiple transdermal bites** or **scratches**, contamination of mucous membrane with saliva from licks, licks on broken skin, direct contact with bats.

Key issues:

1. Current PEP regimens require require ~1 month to complete
2. Many patients do not complete the full course of vaccination remaining insufficiently protected and susceptible to rabies
3. High cost of rabies vaccine reduces use and access
4. RVs are highly immunogenic and efficacious, but programmatic delivery to rabies-exposed communities ↓↓
5. Countries face difficulties forecasting rabies vaccine needs
6. No preservatives in rabies vaccines

Question 5: Which (operational) parameters affect cost-effectiveness of intradermal (ID) compared to intramuscular (IM) administration route of PEP? a. in urban settings; b. in rural settings.

Question 6: Can the **duration** of the entire course of current PEP regimens be reduced while maintaining immunogenicity and clinical protection?

Question 7: Can the **number of doses** administered in current PEP regimens be reduced while maintaining immunogenicity and clinical protection?

Summary current recommendations

- There is no medical contraindication for life-saving PEP
- PEP consists of
  - thorough wound washing
  - series rabies vaccine (RV) injections and
  - rabies immunoglobulin, if indicated (see RIG)
- Cost-saving ID administration of RV has been promoted since 1992
- IM, not ID, regimes are recommended for immunocompromised patients

2010 WHO recommended PEP regimens:

Regimen	Route	Doses/Day 0,3,7,14,21-28	Days	Clinic Visits	Duration (days)
5-dose Essen	IM	(1-1-1-1-1)	0, 3, 7, 14, 28	5	28
Zagreb	IM	(2-0-1-0-1)	0, 7, 21	3	21
4-dose Essen	IM	(1-1-1-1-0)	0, 3, 7, 14	4	14
Updated TRC	ID	(2-2-2-0-2)	0, 3, 7, 28	4	28

Question 5, 6 & 7: Review of new evidence

Review of 5 RCT, 2 observational studies, 1 unpublished RCT & cost-effectiveness modelling

- Criteria for evaluation of non-inferiority (see Table 5 p 44):
  1. *Immunogenicity data*
  2. *Data on clinical outcomes*
  3. *Improved feasibility*

     OR
  4. *Cost and supply improved with equal effectiveness*
- Main findings:
  - Evidence supports PEP regimens of reduced duration and/or number of doses, many RCTs only in individuals without proven rabies exposures
  - Inference from ID to IM regimens (or vice versa) could not be fully established
  - Modelling:
    - **ID is more cost-effective than IM**, even in small clinics
    - Proposed PEP regimens were all more cost-effective than the current IM or ID PEP regimens

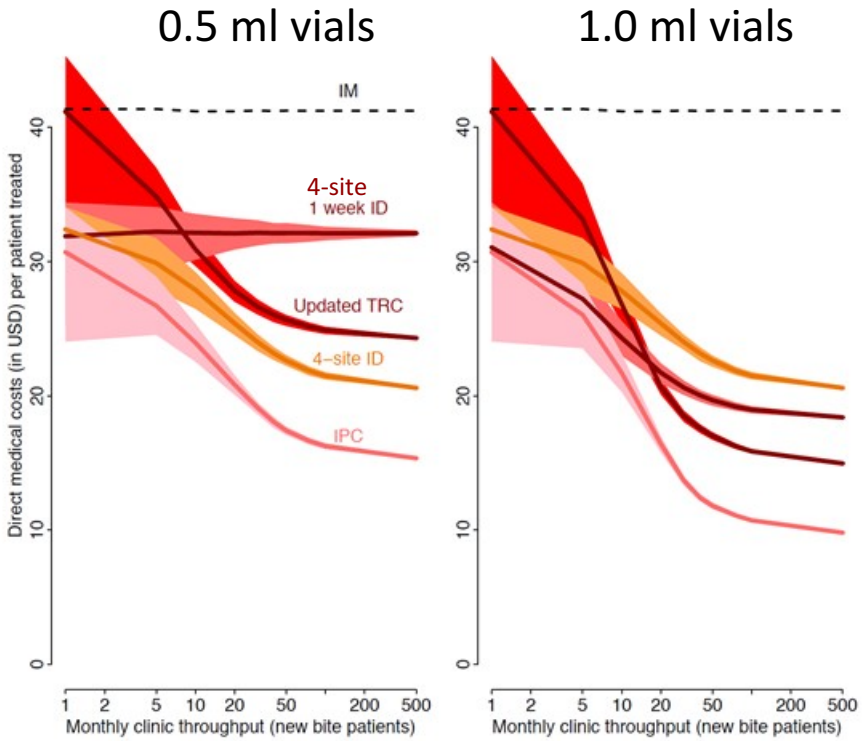
Question 6 & 7: Details of new evidence

Overview on established and investigational PEP regimens evaluated (see Table 5, p 44):

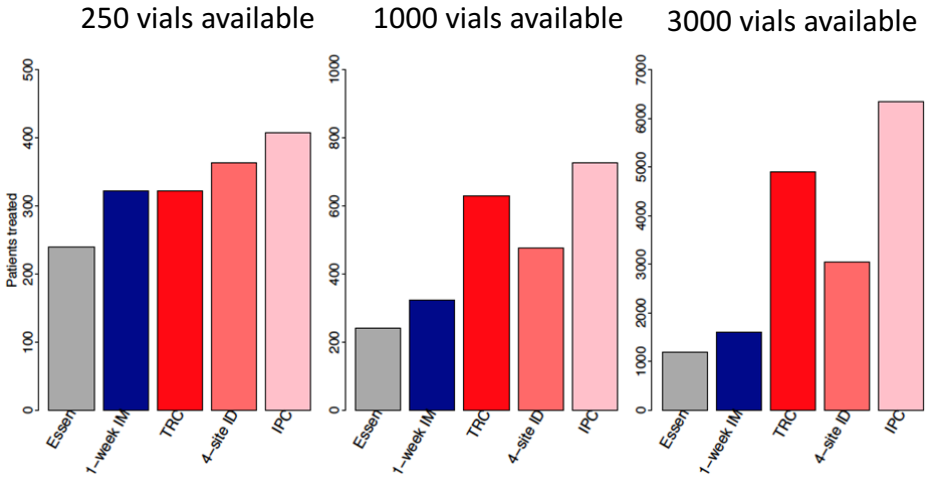
PEP regimens	Characteristics	Key evaluation criteria					
	Number of injection sites per visit on days 0, 3, 7, 14, 21 to 28	Immuno-genicity data	Clinical outcome data	Cost-effectiveness (Reference = TRC)		Feasibility	Acceptability
				small clinic	*large clinic*		
Proposed recommended intradermal regimen							
IPC regimen, 1 week	2-2-2-0-0	✓	✓	>	>	✓	✓
Proposed recommended intramuscular regimens							
Essen regimen, 14 to 28 days	1-1-1-1-0	✓	✓	≤	<	✓	✓
Zagreb regimen, 21 days	2-0-1-0-1	✓	✓	≤	<	✓	✓
Alternate immunogenic intradermal regimens							
Updated Thai Red Cross regimen, 1 month	2-2-2-0-2	✓	✓	REF	REF	✓	✓
Simplified 4-site regimen, 1 month	4-0-2-0-1	✓	○	>	>	○	✓
4-site regimen, 1-week	4-4-4-0-0	✓	○	=	<	○	○

Legend : ✓ Criteria fulfilled ○ criteria partly fulfilled

Question 5: Details of new evidence



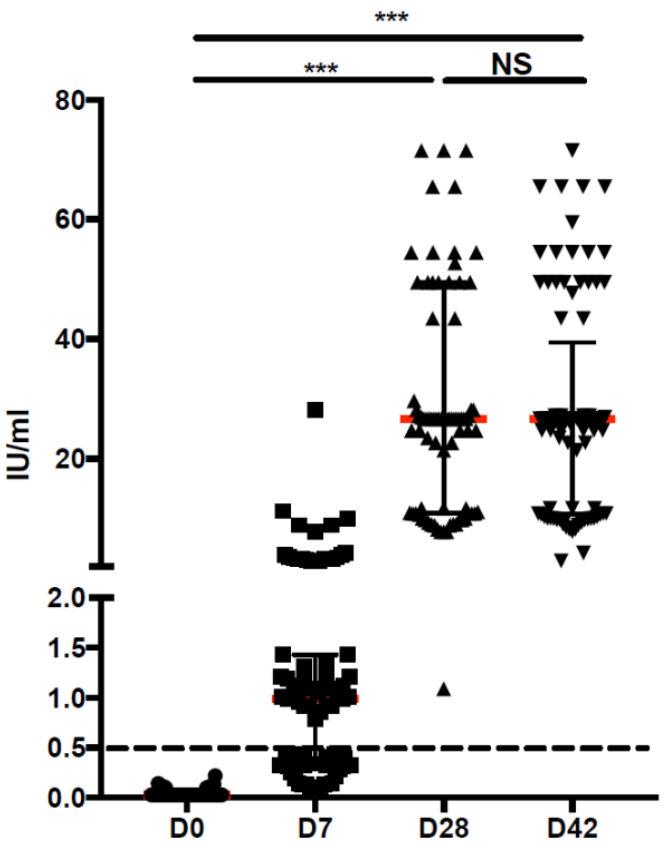
Direct medical costs per rabies death averted for selected ID regimens in relation to clinic monthly throughput (see p. 26)



Additional number of patients treated under different, selected regimens, given limited vaccine availability (see p. 26)

Detailed data IPC 1-week ID regimen (2-2-2-0-0)
(manuscript in preparation)

- 88 category III exposed patients (confirmed rabid dogs), Vaccine + RIG
- Tested titres after 3 clinic visits (7 days), compared to after 4 visits (28 days)
  - All protected by day 28
  - GMT day 28 higher than 42
  - Including underweight patients, all age groups
  - No rabies-related deaths reported ≥ 6 months



Dot plot of neutralizing antibody titres (n=88)

Question 6&7: Details new evidence

IM PEP regimens

- 3-visit **Zagreb IM regimen** (2-0-1-0-1) maintained
- 3-visit IM regimen(1-1-1-0-0): Supported by immunogenicity data, lack of clinical outcome data

  -> 4-dose Essen regimen
- No other investigational IM regimen met the non-inferiority criteria

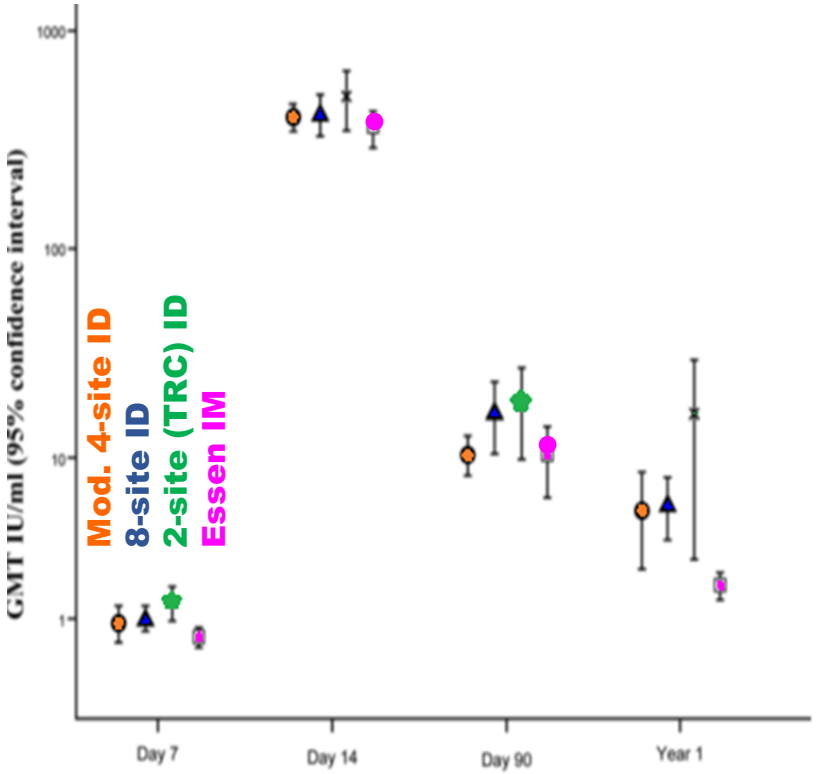


Figure extracted from Warrell et al 2008

Conclusion PEP questions

- Thorough wound washing plus timely administration of 1st dose of rabies vaccine are crucial
- Proposed PEP regimens
  - New 3-visit, 2-site ID regimen on days 0, 3, and 7 ('IPC regimen')
  - Maintain 4-dose Essen IM regimen and the Zagreb IM regimen
  - Adjusted PEP regimens for specific risk groups
- Alternate ID PEP regimens were evaluated and listed (see Table 5)
- Programmatic challenges call for:
  - Guidance on reporting and monitoring rabies PEP use and outcome;
  - Leveraging distribution systems for rabies vaccines and RIG;
  - Employing alternative delivery strategies
- Changes in the route of administration during a PEP course is acceptable & safe, if unavoidable