Rationale for the widespread adoption of multi-site intradermal rabies vaccination

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I have no conflicts of interest
Rabies prophylaxis is unsatisfactory everywhere

- Rabies vaccine costs:
  - Per vial: USA $200, UK $53–63, DR Congo $60, S Africa $15–27, Thailand $8–10, India $5

- Vaccine shortages, not stocked in rural tropics

- Inconvenient, confusing schedules
  - WHO recommends 9 different regimens

- Some vaccines not recognised by WHO used ID for PEP

- RIG rarely available in Govt. Clinics in Africa
  - Painful – so some Drs in India refuse to give RIG

- Pre-exposure vaccination is neglected
The result is that:

- Thousands still die of rabies
- It’s fatal in unvaccinated patients with one exception: an infection due to American bat rabies virus
- BUT no deaths recorded if pre-exposure immunisation is followed by post-exposure booster vaccination, 100% effective
- So all rabies deaths due to lack of adequate prophylaxis

How can the method of prophylaxis be changed to deliver effective anti-rabies treatment worldwide?
IM rabies primary post-exposure vaccine regimen - Essen

1 vial x 5 doses

Day 0 3 7 14 28

Rabies Immunoglobulin

Vaccine course:
USA $1,200
Africa $75
Asia $45
India $25
Primary Post-Exposure Vaccine Regimens currently approved in some countries

1. **Standard IM 5 dose** (Essen): [5 visits, one month]
2. **IM 4 dose** Omitting the last dose: days 0, 3, 7 & 14 [4 visits, 2 weeks]
3. **IM 4 dose** (Zagreb, 2-1-1) regimen: days 0, 7 & 21 [3 visits, 3 weeks]
   IM regimens expensive, waste of vaccine

4. **Intradermal 2-site regimen:** days 0, 3, 7 & 28 [4 visits, one month]
   1. 1997 *(WHO)* ID dose per site = one fifth of vial, 0.2ml or 0.1 ml
   2. 1 ml vial = PCECV Purified Chick Embryo Cell (Rabipur / RabAvert)
   3. 0.5 ml vial = PVRV Purified Vero cell Rabies Vaccine (Verorab)

2005 *(WHO)* changed ID Dose = 0.1 ml per site for all vaccines
2-site ID rabies PEP regimen

ID dose 0.1 ml/ site for either vaccine

0.5 ml PVRV  Verorab  ID dose/site = $\frac{1}{5}$ of vial
1 ml PCECV, HDCV Rabipur/ RavAvert  ID dose/site = $\frac{1}{10}$ of vial

Used mainly in urban areas in a few countries in Asia,

vaccine wastage = 25%  (Gongal G, Wright AE. Adv Prev Med 2011)
Pragmatic approach to resolve problems of rabies vaccination

Aim

To give the most immunogenic treatment, which is acceptable and can safely and easily be delivered when and where needed.
How to resolve problems of rabies prophylaxis:

Problems to overcome:

1. **Vaccine expensive**
   - Reduce total vaccine used - but maintain immunogenicity
   - Use small doses by ID route

2. **Poor compliance**
   - Fewer clinic visits - which is cheaper

3. **Errors in ID treatment**
   - Reduce mistakes in dosage & timing - Simplify regimens
   - ID injection technique errors - Use multiple site injections

4. **RIG is often not available**
5. **ID Regimens are used with untested vaccines Chinese / Indian**
6. **ID Regimens will be used in immunosuppressed patients**
   - Regimens must be highly immunogenic

7. **Risk averse society says ID injection is not safe or practicable**
3 types of rabies vaccine regimens needed:
Economical ID methods

1 **Pre-exposure ID regimen:** [3 visits]
   Days 0, 7 & 28  Dose = 0.1 ml any vaccine
   improvement possible?

2 **Post-exposure Booster ID:** [1 visit]
   Single day 4-site ID regimen, WHO recommended:
   Day 0  Dose = 0.1 ml/site x 4

3 **Primary ID post-exposure:** new regimen needed

Data show:-  most immunogenic regimens give
   a larger priming vaccine dose followed by smaller doses
CRITERIA FOR ACCEPTING A NEW REGIMEN

Immunogenic:
- Comparative trial with current recommended regimen
- > 0.5 IU/ml neutralising antibody in 100% people
  - Pre-exposure: at any time
  - Post-exposure fast < 14 days, not suppressed by RIG
  - Test in patients with Category III exposure to proven rabid animals

Duration of antibody:
- Pre-exposure: > 1 year, rapid booster response measure early ab
- Post-exposure not important for current event, but persistence advantageous in endemic areas

Advantage over current regimen

Zero risk approach to safety:
- Dose will be overkill for some but immunogenic for all
  - Not minimal immunogenic dose in healthy volunteers
INTRODUCING A NEW REGIMEN INTO A COUNTRY

“The requirement for local, in-country data and the reluctance to accept foreign data for the purposes of licensure in any particular country….”

“The perceived need to require local data should not deter the introduction of efficacious vaccines for populations of greatest need at the earliest appropriate moment and where possible, to avoid conduct of small studies with no valid scientific purpose.”

Knezevic et al. WHO consultation on clinical evaluation of vaccines. 2015 Vaccine 33; 1999
Recently suggested new regimens

• For **Pre-exposure**
  
  ID 2-site various studies (1 or 2 visits, which vaccine/ dose?)
  
  IM 3 visits in 8 days

• For **Primary post-exposure** :
  
  – 4-site ID **one week** days: 0, 3, 7 [3 visits]
  
  – 4-site ID **one month** days: 0, 7, 28 [3 visits]
Proposed **4-site ID one week rabies PEP regimen**

4 ID injections 0.1 ml/site of **PVRV** or **PCECV**

Day 0 3 7

Either a **whole** or **half** vial divided between 4 ID sites x 3
0.5 ml vaccine **PVRV** Total dose = **3 vials** expensive
1.0 ml vaccine **PCECV** Total dose = **1.5 vials**

sharing vials on each occasion

*(Sudarshan et al. Hum Vaccin Immunother. 2012)*
Proposed 4-site ID one month rabies PEP regimen

- **Whole vial**: 4 sites
- **Half vial**: 2 sites* 
- **20% vial**: 0.1 / 0.2 ml 1 site

<table>
<thead>
<tr>
<th>Day</th>
<th>0</th>
<th>7</th>
<th>28</th>
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</table>

* Dose PCECV, HDCV = 0.2 ml/ ID site
Dose equivalent antigen PVRV = 0.1 ml/ ID site
Total dose = 1.5 vials

Injection Sites: Deltoids & Thighs or Suprascapular
### 8-site ID rabies post-exposure vaccine regimen HDCV


<table>
<thead>
<tr>
<th>Day</th>
<th>0</th>
<th>7</th>
<th>28</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0 ml whole vial</td>
<td>0.4 ml half vial</td>
<td>0.2 ml</td>
<td></td>
</tr>
<tr>
<td>$\div$ 8 sites</td>
<td>$\div$ 4 sites</td>
<td>$\div$ 2 sites</td>
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</table>

### 4-site ID one month rabies vaccine regimen

(Warrell et al, PlosNTD 2008)

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<th>Day</th>
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<tr>
<td>whole vial</td>
<td>half vial</td>
<td>Equivalent doses:</td>
<td></td>
</tr>
<tr>
<td>$\div$ 4 sites</td>
<td>0.2/0.4 ml</td>
<td>$0.5 \text{ ml PVRV} = 0.1 \text{ ml/site}$</td>
<td></td>
</tr>
<tr>
<td>$\div$ 2 sites</td>
<td>0.1/0.2 ml</td>
<td>$1 \text{ ml PCECV} = 0.2 \text{ ml/site}$</td>
<td></td>
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</tbody>
</table>
Clinical trial comparison of ID regimens *(Warrell et al, PlosNTD 2008)*

Neut Ab GMT IU/ml (95% confidence interval)

Time after first dose of vaccine
Comparison of 2-site and 8-site ID regimens

(Madhusudana SN et al 2001 Nat Med J India 14 145-7)

p values: day 7 < 0.001, day 14 <0.05 days 90,180,365 < 0.001
Comparison of 2-site and 8-site ID regimens

(Madhusudana SN et al 2001 Nat Med J India 14 145-7)

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Neutralising Ab IU/ml

Days

2-site PCECV = 4-site 0,7,28 one month

8-site PCECV = 4-site 0,7,28 one month

2-site PCECV 0.2 ml/ID site = 4-site 0,3,7 one week

\begin{align*}
\text{p values: day } 7 & < 0.001, \text{ day } 14 & <0.05 \text{ days } 90,180,365 & < 0.001
\end{align*}
Advantages of the 4-site ID one month regimen

- As immunogenic as the ‘gold standard’ 5 dose IM Essen regimen
- No vaccine wastage on first day – whole vial given
  - Use in small clinics
- Wide margin of safety: Accidental subcutaneous injection should not impair immunogenicity
  - Half the dose is immunogenic in trial conditions

(Ambrozaitis et al 2006 Vaccine 24: 4116)
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  – is best treatment if patients default

• Wide margin of safety: Accidental subcutaneous injection should not impair immunogenicity
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• Only 3 visits = pre-exposure course (0, 7 & 28)

• Use left-over vaccine on days 7 & 28 as pre-exposure ID eg. for relatives

• If no vials are shared uses 3 vials, cheaper than any IM regimen

• Cheapest regimen for health provider and for all patients’ costs

  (Hampson K et al. PLoS Negl Trop Dis 2011;5:e982 Comment)
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- Cheapest regimen for health provider and for all patients’ costs
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BUT

- 0.2 ml ID dose does not comply with the WHO ‘rule’ for a standard ID 0.1 ml dose so not WHO recommended
Criticisms of 4-site one month ID:

1. Need more Immunogenicity studies including with RIG

2. Adaptation of the 8-site ID regimen, keeping same timing and dose of rabies vaccine

3. Changing 8 injection sites to 4 has no effect on immunogenicity
   \((Warrell \text{ et al, } \textit{PlosNTD} \text{ 2008})\)

4. 8-site validated: Randomised controlled trial, category III exposure to proven rabid animals, not all received RIG. No immunosuppressive effect of RIG shown
   \((Warrell \text{ et al, } \textit{Lancet} \text{ 1985})\)

5. Half dose, 0.1 ml ID x 4 PCECV day 0 tested with HRIG / ERIG small study - immunogenicity at least as good as IM
   \((Suntharasamai \text{ et al 1987 Epidemiol Infect 99:755})\)

5. WHO 2005: “This (8-site) regimen. . .generally produces a higher antibody response than the other recommended schedules by day 14”
Criticisms of 4-site one month ID:

2 Short vaccine course is best - patients default

**Default after 2 visits:** days 0, 7  (omit day 28)
- Antibody reached 0.5 IU/ml by day 14
- Day 28 dose may not be vital, but it should increase antibody duration and increases safety
  - Advantageous if **re-exposure** occurs with delay in booster PEP
    - if exposure is not **recognised**

**Default after one visit, day 0**  (omit days 7 and 28)
- Maximum available ID treatment given, IM vial, no waste
If patient defaults after 2 doses, **days 0 and 7** all have rabies neutralising antibody by day 14

*Could this be a new 2 dose PEP ID regimen of the future?*
Criticisms of 4-site one month ID:

3  WHO rule: standard ID dose is 0.1 ml

- **Human Rabies vaccine potency > 2.5 IU / vial**
  
  Amount of antigen $\propto$ the immunity induced
  
  The vaccine dose is critical in designing a regimen

  “the antigen…content per ID dose varies according to the vaccine used”

  “rabies vaccine the **only pharmaceutical product not defined by the quantity of active component** applied”  
  
  (Dodet B. Biologicals 2011; 39(6):444-5)

- **Pre-exposure** dose evaluated with HDCV 0.1 ml, 30+ years ago
  
  PVRV invented later - 0.1 ml is larger antigen dose

- **Post-exposure** 2-site regimen ID dose for HDCV = 0.2 ml/site for 7 years then changed to 0.1 ml/site as immunogenic in controlled trials

  *Narrow safety margins (HIV+, ID inj)*

  **Comply with the 0.1 ml/site dictum** for 4-site ID regimen using 1 ml vial:
  
  Inject 0.1 ml at 2 adjacent sites

  If problem injecting 0.2 ml ID, withdraw needle and inject remainder nearby
Criticisms of this 4-site ID one month regimen?

1. Need more immunogenicity studies including with RIG

2. A short vaccine course is best because patients default: ‘Patients don’t come back on day 28’

3. Does not comply with WHO rule of 0.1 ml / ID dose

4. **Some vaccines are not recognised by WHO**
   If potency is uncertain, use regimens with wide safety margins

5. **Vaccines not licensed for ID use**
   Not in the interest of manufacturers
Economical practical regimens:

Pre-exposure ID regimen:
In use:
  Days 0, 7 & 28  Dose = 0.1 ml any vaccine  [3 visits]

Rapid schedule:
  Day 0, 4-site ID and 1 or 2 smaller doses?
  Recommended in UK for 22yrs
HDCV: Rapid Prophylactic Immunisation of Volunteers with Small Doses


ALL INTRADERMAL

Antibody titres following three different rapid immunisation schedules (based on 10 subjects in each group).
Pre-exposure rabies prophylaxis

↓ = 1 dose 0.1 ID any vaccine

Day 0  7  21  28

KEEP RECORD OF IMMUNISATION
Pre-exposure rabies prophylaxis

= 1 dose **0.1 ID any vaccine**

<table>
<thead>
<tr>
<th>Day</th>
<th>0</th>
<th>7</th>
<th>21</th>
<th>28</th>
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</thead>
</table>

RAPID

4-site ID

| Day | 0 | 7 | 28 | ? |
Economical practical regimens for rabies prophylaxis:

1. **Pre-exposure ID regimen:**
   In use:
   Days 0, 7 & 28  Dose = 0.1 ml any vaccine  [3 visits]
   Rapid schedule: (previously recommended)
   Day 0 4-site, any vaccine

2. **Post-exposure Booster ID:**  [1 visit]
   Single day regimen, WHO recommended:
   Day 0  Dose 4-site
SINGLE DAY 4-site ID PEP for previously vaccinated WHO recommended (WHO 2010 Wkly Epidem Rec 85:309)

Day 0

0.1 ml all vaccines
4 sites ID

Total vaccine used:
1 vial (for 0.5 ml vaccines)
0.4 vial (for 1 ml vaccines)

Do not waste vaccine:
Use remainder as pre-exposure eg. for family

OR
Use whole vial of any vaccine
Booster post-exposure 4-site ID single day

PRACTICAL REGIMEN FOR USE IN SMALL CLINICS

If sharing ampoules is not possible use:

1 WHOLE VIAL 0.2 ml/site PCECV
or 0.1 ml/site PVRV

4 sites

1 IM dose

Day 0

Injection Sites: Deltoids & Thighs or Suprascapular
Economical practical regimens for rabies prophylaxis:

1  Pre-exposure ID regimen:
   In use:
      Days 0, 7 & 28  Dose = 0.1 ml any vaccine   [3 visits]
   Rapid schedule: (previously recommended)
      Day 0 4-site, any vaccine

2  Booster ID post-exposure:  [1 visit]
   Single day regimen, WHO recommended:
      Day 0  Dose 4-site

3  Primary ID post-exposure:
   Ready to go:
      4-site ID one month
      Day 0 4-site, day 7 2-site, day 28 1-site  [3 visits]
ID rabies vaccine regimens to **use now** globally

<table>
<thead>
<tr>
<th>INTRADERMAL VACCINE REGIMEN</th>
<th>NUMBER OF SITES INJECTED</th>
<th>DAY OF INJECTION</th>
<th>NUMBER OF VISITS</th>
<th>TOTAL VIALS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-exposure ID</td>
<td>1</td>
<td>0, 7, 28</td>
<td>3</td>
<td>0.3 ml</td>
</tr>
<tr>
<td>Booster Post-exposure</td>
<td>4</td>
<td></td>
<td>1</td>
<td>1 or 0.4</td>
</tr>
<tr>
<td>ID 4 –site</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary Post-exposure</td>
<td>4</td>
<td>1, 2, 28</td>
<td>3</td>
<td>&lt;2 (max 3)</td>
</tr>
<tr>
<td>ID 4 –site one month (+ RIG d 0)</td>
<td>1 vial, ½ vial</td>
<td>0.1/0.2 ml</td>
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## Pragmatic ID rabies vaccine regimens in future

<table>
<thead>
<tr>
<th>VACCINE REGIMEN</th>
<th>NUMBER OF SITES INJECTED</th>
<th>NUMBER of VISITS</th>
<th>TOTAL VIALS</th>
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<tbody>
<tr>
<td></td>
<td>Day of injection</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>7</td>
<td>28</td>
</tr>
<tr>
<td>Pre-exposure ID</td>
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<td></td>
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</tr>
<tr>
<td>Rapid regimen ID</td>
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<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>1or 2?</td>
<td>1?</td>
</tr>
<tr>
<td>Booster Post-exposure</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>ID 4 –site</td>
<td>4</td>
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<td>Primary Post-exposure (+ RIG d 0)</td>
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</tr>
<tr>
<td>ID 4 –site one month</td>
<td>4</td>
<td>2</td>
<td>28</td>
</tr>
<tr>
<td>ID 4 –site 2 visit</td>
<td>4</td>
<td>2</td>
<td>2</td>
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Conclusion:
ID rabies vaccine regimens are suitable for use in **developed** countries
Wide margin of safety: **even if lacking experience of ID injection technique**
<table>
<thead>
<tr>
<th>ID RABIES VACCINE REGIMEN</th>
<th>DAY OF INJECTION</th>
<th>TOTAL VIALS</th>
<th>VISITS</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>0</td>
<td>7</td>
<td>28</td>
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**Primary Post-exposure**

*4 site ID*

Volume per ID site:
- 0.2 ml for *RabAvert* (1.0/vial)
- 0.1 ml for *Verorab* (0.5ml/vial)

<table>
<thead>
<tr>
<th></th>
<th>WHOLE VIAL (÷4 sites)</th>
<th>HALF VIAL (÷2 sites)</th>
<th>0.1 / 0.2 ml (1 site)</th>
<th>&lt;2 (Max 3, if not shared)</th>
<th>3</th>
</tr>
</thead>
</table>

**Booster post-exposure**

if previously immunised

*4 site ID*

<table>
<thead>
<tr>
<th></th>
<th>4 Site</th>
<th>1</th>
<th>1</th>
</tr>
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