Rabies is a deadly disease, and current preexposure vaccination schedules are lengthy and expensive. We identified nine studies investigating abbreviated schedules. Although initial responses were lower, accelerated adequate immune responses were elicited after booster vaccinations. Lower-dose (and therefore cheaper) vaccination schedules may constitute a valid alternative to current vaccination schedules.

**Keywords.** rabies; vaccination; intradermal; booster; preexposure prophylaxis.

Rabies is a viral zoonosis transmitted through mammalian bites, with lethal outcomes if left untreated. Rabies is endemic worldwide; the highest death rates occur in Asian and African countries [1, 2].

Postexposure prophylaxis (PEP) comprises rabies vaccination and passive immunization with human rabies immunoglobulin (HRIG). However, HRIG is expensive and not available in many Asian and African countries [3]. Preexposure vaccination (PreP) renders HRIG unnecessary in PEP situations. All current World Health Organization (WHO)–recognized schedules have been proven safe and effective. However, PreP schedules are expensive and time-consuming. To increase vaccination uptake in endemic countries and by travelers [4], simplified, cost-effective PreP schedules should be strived for, implying fewer clinical visits. In poor countries, these visits may involve great costs and hardship. Moreover, if efficient PreP schedules elicit effective immunity after postexposure boosters, HRIG is unnecessary.

Intradermal (ID) PreP schedules and intramuscular (IM) schedules are equally effective [5–7]. WHO approved the ID PreP scheme consisting of 0.1 mL on days 0, 7, and 28 or 21 [2]. Effective booster responses following this scheme have been described [8, 9]. However, routine implementation of ID vaccination has been stifled by pharmaceutical regulations [10].

Current consensus is that 3 PreP doses are necessary for 100% seroconversion [11], and shortened schedules induce antibodies that decline more rapidly over time. To date, no advantages of long-term antibody presence have been described. Most important, antibody is needed as soon as possible after exposure. We review here whether simplified ID schedules induce immunologic memory and elicit effective booster responses.

**METHODS**

We searched PubMed, Embase, and the Cochrane database on 16 May 2012 for the terms rabies, rabies vaccination, postexposure prophylaxis, intradermal injection, and intramuscular vaccination (Supplementary Appendix).

Abstracts received from the above databases (1.042, see Supplementary Appendix) were screened by authors T.L. and R.W.W. We selected human studies considering shortened or ID PreP schedules, including measurements of rabies virus–neutralizing antibodies (RVNAs) following boosters. Studies only concerning 0, 7, 28 (or 21) ID schedules were not included, as WHO guidelines already recommend this schedule [2].

**RESULTS**

Nine articles fulfilled the selection criteria. All studies used different timing, dosing, and routes of administration, rendering direct comparisons of various study arms impossible (Table 1). Therefore, we describe separately the effects of ID vs IM PreP schedules, various shortened or low-dose PreP schedules, and various timing and administrative routes of boosters.

**ID or IM PreP Schedules**

Turner and colleagues [12] vaccinated volunteers with human diploid cell vaccine (HDCV), either 0.1 mL ID or 1.0 mL IM (Table 1), and concluded that administrative routes did not influence booster responses. Both Khawplod et al [13] and

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DOI: 10.1093/cid/cis853
Table 1. Vaccination Schedules and Booster Details as Described in 9 Studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Subjects</th>
<th>No.</th>
<th>ROA</th>
<th>Vaccine</th>
<th>Vaccine Brand</th>
<th>Vaccine Potency</th>
<th>Dose</th>
<th>Days</th>
<th>Injections</th>
<th>RVNA Test</th>
<th>Booster</th>
<th>GMT [range], Prebooster % ≥0.5 UI/mL</th>
<th>GMT [range], Postbooster % ≥0.5 UI/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turner et al (1982) [12]</td>
<td>Healthy, 14–68 y</td>
<td>33</td>
<td>ID</td>
<td>HDCV</td>
<td>Merieux</td>
<td>1.1–5.9 antigenic value</td>
<td>0.1 mL</td>
<td>0</td>
<td>1</td>
<td>ELISA</td>
<td>Random</td>
<td>0.4 [2.4–389]</td>
<td>44.5 [0.7–954]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>33</td>
<td>ID</td>
<td></td>
<td></td>
<td></td>
<td>0.1 mL</td>
<td>0</td>
<td>1</td>
<td>ID/1.0 mL SC, random at 6/12/24 mo</td>
<td></td>
<td>1.4</td>
<td>23.8 [0.7–316]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>39</td>
<td>ID</td>
<td></td>
<td></td>
<td></td>
<td>0.1 mL</td>
<td>0</td>
<td>1</td>
<td></td>
<td>1.1, 11</td>
<td>73%</td>
<td>49.7 [2.4–389]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25</td>
<td>IM</td>
<td></td>
<td></td>
<td></td>
<td>1 mL</td>
<td>0</td>
<td>1</td>
<td></td>
<td>1, 1</td>
<td>4.4</td>
<td>44.5 [0.7–954]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>24</td>
<td>IM</td>
<td></td>
<td></td>
<td></td>
<td>1 mL</td>
<td>0</td>
<td>1</td>
<td></td>
<td>1, 1</td>
<td>49.7 [2.4–389]</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40</td>
<td>IM</td>
<td></td>
<td></td>
<td></td>
<td>1 mL</td>
<td>0</td>
<td>1</td>
<td></td>
<td>1, 1</td>
<td>2.7</td>
<td>23.8 [0.7–316]</td>
</tr>
<tr>
<td>Arai et al (1991) [15]</td>
<td>Males, 23–57 y</td>
<td>30</td>
<td>SC</td>
<td>PCECV</td>
<td>NR</td>
<td>0.8–13 antigenic value</td>
<td>1 mL</td>
<td>0</td>
<td>1</td>
<td>RFFIT</td>
<td>PCECV 1.0 mL SC, 8–14 mo</td>
<td>73%</td>
<td>90%, d 365</td>
</tr>
<tr>
<td>Yang and Zhang (1999) [20]</td>
<td>Healthy, 11–15 y</td>
<td>30</td>
<td>ID</td>
<td>PHKCV</td>
<td>NR</td>
<td>&lt;2.5 IU dose</td>
<td>0.1 mL</td>
<td>0</td>
<td>1</td>
<td>ELISA</td>
<td>2 mL IM d 366</td>
<td>0.96, 81.3%</td>
<td>29.1, 100% d 7, 49.4, 100% d 14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>31</td>
<td>ID</td>
<td>NR</td>
<td></td>
<td></td>
<td>0.1 mL</td>
<td>0</td>
<td>1</td>
<td>RFFIT</td>
<td>2 mL IM d 366</td>
<td>1.12, 93.8%</td>
<td>22.9, 100% d 7, 105.1, 100% d 14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30</td>
<td>ID</td>
<td>NR</td>
<td></td>
<td></td>
<td>0.1 mL</td>
<td>0</td>
<td>1</td>
<td>RFFIT</td>
<td>2 mL IM d 366</td>
<td>0.97, 80.0%</td>
<td>35.2, 100% d 7, 125.0, 100% d 14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>27</td>
<td>ID</td>
<td>NR</td>
<td></td>
<td></td>
<td>0.1 mL</td>
<td>0</td>
<td>1</td>
<td>RFFIT</td>
<td>2 mL IM d 366</td>
<td>0.41, 38.5%</td>
<td>9.1, 100% d 7, 52.0, 100% d 14</td>
</tr>
<tr>
<td>Khawplod et al (2007) [13]</td>
<td>NR</td>
<td>16</td>
<td>ID</td>
<td>PVRV</td>
<td>Aventis-Pasteur</td>
<td>NR</td>
<td>0.1 mL</td>
<td>0, 7</td>
<td>28</td>
<td>RFFIT</td>
<td>0.1 mL ID d 360, 363</td>
<td>0.61, 81.3%</td>
<td>22.9, 100% d 7, 105.1, 100% d 14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>16</td>
<td>ID</td>
<td>NR</td>
<td></td>
<td></td>
<td>0.1 mL</td>
<td>0, 3</td>
<td>7</td>
<td>RFFIT</td>
<td>0.1 mL ID d 360, 363</td>
<td>1.12, 93.8%</td>
<td>22.9, 100% d 7, 105.1, 100% d 14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20</td>
<td>IM</td>
<td>NR</td>
<td></td>
<td></td>
<td>1 mL</td>
<td>0, 3</td>
<td>7</td>
<td>RFFIT</td>
<td>0.1 mL ID d 360, 363</td>
<td>0.97, 80.0%</td>
<td>35.2, 100% d 7, 125.0, 100% d 14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14</td>
<td>ID</td>
<td>NR</td>
<td></td>
<td></td>
<td>0.1 mL</td>
<td>0</td>
<td>2</td>
<td>RFFIT</td>
<td>0.1 mL ID d 0, 3, 1 y</td>
<td>0.41, 38.5%</td>
<td>9.1, 100% d 7, 52.0, 100% d 14</td>
</tr>
<tr>
<td>Kamoltham et al (2007; 2011) [16, 17]</td>
<td>Healthy, 4–8 y</td>
<td>NR</td>
<td>ID</td>
<td>PCECV</td>
<td>Rabipur-Novartis</td>
<td>NR</td>
<td>0.1 mL</td>
<td>0, 28</td>
<td>1, 1</td>
<td>RFFIT</td>
<td>0.1 mL ID d 0, 3, 1 y</td>
<td>0.11, 7%</td>
<td>4.7, 96% d 7, 10.8, 100% d 14</td>
</tr>
</tbody>
</table>

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Table 1 continued.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Subjects</th>
<th>No.</th>
<th>ROA</th>
<th>Vaccine</th>
<th>Vaccine Brand</th>
<th>Vaccine Potency</th>
<th>Dose</th>
<th>Days</th>
<th>Injections</th>
<th>RVNA Test</th>
<th>Booster</th>
<th>GMT [range], Prebooster % ≥0.5 UI/mL</th>
<th>GMT [range], Postbooster % ≥0.5 UI/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pengsaa et al (2009) [14]</td>
<td>Healthy children</td>
<td>44</td>
<td>ID</td>
<td>PCECV</td>
<td>Rabipur-Novartis &gt;2.5 IU/mL</td>
<td>0.1 mL</td>
<td>0, 7, 28</td>
<td>1, 1, 1</td>
<td>RFFIT</td>
<td>0.1 mL ID 1 y</td>
<td>NR</td>
<td>0.33, 35%</td>
<td>11.0, 100% d 7, 22.1, 100% d 14</td>
</tr>
<tr>
<td></td>
<td>44</td>
<td>ID</td>
<td>0.1 mL</td>
<td>0, 7, 28</td>
<td>1, 1, 1</td>
<td>0.1 mL ID 1 y</td>
<td>NR</td>
<td>25, 100% d 7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>IM</td>
<td>1 mL</td>
<td>0, 7, 28</td>
<td>1, 1, 1</td>
<td>1 mL ID 1 y</td>
<td>NR</td>
<td>13, 100% d 7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>44</td>
<td>IM</td>
<td>0.5 mL</td>
<td>0, 7, 28</td>
<td>1, 1, 1</td>
<td>0.5 mL ID 1 y</td>
<td>NR</td>
<td>190, 100% d 7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>28</td>
<td>IM</td>
<td>1 mL</td>
<td>0, 28</td>
<td>1, 1</td>
<td>RFFIT</td>
<td>1.0 mL IM on d 0, 3, 1 y</td>
<td>0.25 [0.1–12]</td>
<td>31.3 [0.6–328]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strady et al (2009) [18]</td>
<td>Healthy, 12–79 y</td>
<td>96</td>
<td>IM</td>
<td>HDCV/ PVRV Pasteur Merieux 1.06–4.54 IU/dose</td>
<td>1 mL</td>
<td>0, 7, 28</td>
<td>1, 1, 1</td>
<td>RFFIT</td>
<td>1.0 mL IM on d 0, 3, 1 y</td>
<td>0.60 [0.1–48]</td>
<td>51.6 [1.4–1356]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Khawplod et al (2012) [19]</td>
<td>Healthy, 19–45 y</td>
<td>17</td>
<td>ID</td>
<td>PCECV</td>
<td>Rabipur-Chiron 9.48–10.23 IU/mL</td>
<td>0.1 mL</td>
<td>0, 7, 21</td>
<td>1, 1, 1</td>
<td>RFFIT</td>
<td>1.0 mL IM on d 0, 3, 1 y</td>
<td>0.49 [0.1–2.1]</td>
<td>11.3, 100% d 7, 54.5, 100% d 14</td>
<td></td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>ID</td>
<td>0.1 mL</td>
<td>0, 7, 21</td>
<td>1, 1, 1</td>
<td>0.1 mL ID 4 sites d 0, 1 y</td>
<td>0.30 [0.1–2.7]</td>
<td>42.5, 100% d 7, 114, 100% d 14</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>16</td>
<td>ID</td>
<td>0.1 mL</td>
<td>0</td>
<td>2</td>
<td>1.0 mL IM on d 0, 3, 1 yr</td>
<td>0.15 [0.03–0.9]</td>
<td>9.7, 100% d 7, 46.2, 100% d 14</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>ID</td>
<td>0.1 mL</td>
<td>0</td>
<td>2</td>
<td>0.1 mL ID 4 sites d 0, 1 y</td>
<td>0.10 [0.03–1.1]</td>
<td>12.0, 100% d 7, 54.3, 100% d 14</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>17</td>
<td>IM</td>
<td>1 mL</td>
<td>0</td>
<td>1</td>
<td>1.0 mL IM on d 0, 3, 1 y</td>
<td>0.08 [0.03–2.2]</td>
<td>10.1, 100% d 7, 19.0, 100% d 14</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>IM</td>
<td>1 mL</td>
<td>0</td>
<td>1</td>
<td>0.1 mL ID 4 sites d 0, 1 y</td>
<td>0.11 [0.03–1.7]</td>
<td>13.3, 100% d 7, 46.9, 100% d 14</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ELISA, enzyme-linked immunosorbent assay; GMT, geometric mean titer; HDCV, human diploid cell vaccine; ID, intradermal; IM, intramuscular; NR, not reported; PCECV, purified chick embryo cell vaccine; PHKCV, primary hamster kidney cell rabies vaccine; PVRV, purified vero rabies vaccine; RFFIT, rapid fluorescent focus inhibition test; ROA, route of administration; RVNA, rabies virus–neutralizing antibody; SC, subcutaneous.
Pengsaa and colleagues [14] compared booster responses 1 year after ID (0.1 mL) to IM (1.0 mL) schedules. In both studies, 7 days after boosters, RVNAs were above the WHO threshold of protection (≥0.5 IU/mL) in 100% of vaccinees, though slightly lower in the ID group.

Timing of PreP Schedules

**Comparison of 1-Day (0), 2-Day (0, 28), or 3-Day (0, 28, 56) PreP Schedules**

Turner et al compared booster responses following either 1, 2, or 3 PreP vaccinations [12]. They concluded that a more elaborate PreP scheme initially increased antibodies but did not influence antibody quantities after booster vaccinations.

**Days 0, 7 PreP Scheme**

Arai et al vaccinated volunteers subcutaneously on days 0 and 7 [15]. After 8–14 months, a booster vaccination was administered. Ninety percent of participants still had detectable antibodies 12 months after the booster.

**Comparison of PreP Schedules: 3 Doses (Days 0, 7, 28) vs 2 Doses (Days 0, 28)**

Three studies compared 0, 7, 28 schedules to 0, 28 schedules. Kamoltham et al [16, 17] vaccinated ID with purified chick embryo cell vaccine (PCECV), Pengsaa et al [14] IM with PCECV, and Strady et al [18] IM with HDCV and purified vero rabies vaccine (PVRV). In all 3 studies, booster vaccinations were administered after 1 year. After 7–14 days, in 100% of vaccinees RVNAs exceeded the WHO threshold, although slightly lower in the groups with 2 vaccinations.

**Comparison of Various Shortened ID Schedules**

Khawplod et al conducted a second study with 6 groups of volunteers. All subjects received shortened PVRV schemes (Table 1), either 2 × ID (0.1 mL) or 1 × IM (1.0 mL) [19]. All groups, including 1 group with only 0.1 mL ID at 2 sites on one day, responded with adequate accelerated antibody responses when given booster injections after 1 year.

**Timing and Dosing of Booster Vaccinations**

Seven studies in this review describe booster vaccinations administered 1–1.5 years after the first PreP vaccination (Table 1).

However, Turner et al administered booster vaccinations after 6, 12, or 24 months [12]. No differences were found between antibody titers at these various intervals. Yang and colleagues [20] found that a single 0.1 mL ID PreP dose, followed by a 5-shot booster series administered over 30 days nearly 2 years later (730 days), elicited protective responses in all volunteers by 14 days after the initial booster. Kamoltham and colleagues [16, 17] administered boosters 1, 3, and 5 years after PreP. The authors concluded that RVNA concentrations and the percentage of responders (100%) did not change over the years.

Khawplod et al [19] compared a 4 × ID (0.1 mL) booster on day 0 to an IM (1.0 mL) booster on days 0 and 3. No significant differences were found.

**DISCUSSION**

From the studies described, we learn that it is possible to induce an adequate response to booster vaccinations administered between 6 months to >1 year after PreP, both IM and ID, even after a single dose of ID 0.1 mL primary hamster kidney cell vaccine or ID 0.2 mL PVRV.

**Route of Administration of PreP**

ID schedules induce lower booster responses than IM schedules when a lower ID dose is used [12–14]. However, Warrell et al found higher RVNAs following ID boosters compared with equally dosed IM boosters [21].

**Dosing of PreP**

Although 2-dosed PreP schedules induce lower RVNAs compared with 3-dosed PreP schedules, all exceeded the WHO threshold [14, 17, 18]. No difference in speed of onset of booster responses was found.

**Route of Administration and Timing of Booster**

In the second Khawplod study [19], responses to the 4 × ID (0.1 mL) booster were not superior to those following the 0, 3 days IM (1.0 mL) booster. However, other studies compared these booster schedules and showed that the 4 × ID booster elicited higher antibody responses compared to the 0, 3 day IM boosters [22, 23].

In Turner et al’s study, no significant difference between various booster intervals was found [12]. However, the ratio of increase was significantly lower in subjects boosted at a short interval. Possibly, antibody presence negatively influenced booster responses. A sufficient timespan is therefore required before booster administration. Booster responses are elicited effectively up to at least 5 years after PreP series [18, 20].

**Possible PreP Schedules and Risks**

A future challenge is finding optimally reduced ID PreP schemes eliciting fast and robust booster responses. Potential schedules are double ID (2 × 0.1 mL) vaccinations on day 0 or a single ID (0.1 mL) vaccination on days 0 and 3, both followed by a series of 4 × ID (0.1 mL) boosters in case of exposure. This would reduce PreP and PEP costs by a factor of 15 and 10–20, respectively. Currently, shortened (1-week) IM PreP schedules are being investigated [24]. Risks of these schedules are more prevalent mild adverse events, reduced or absent responses, and inadequate ID administration. Although
local mild and transient adverse events have been described after ID vaccination, the lower costs likely outweigh this drawback [8, 16].

An estimated 3% of the healthy population produces low antibody levels to HDCV and PVRV after IM immunization [25, 26]. The studies described were conducted with limited subject numbers. Future studies including larger numbers should assess rates and prognostic factors of suboptimal immunologic response. In all studies, lower-dose schedules elicited reduced, though adequate, responses. It is likely that responses above the WHO threshold are sufficient and very high titers are not required for protection.

A final challenge concerning ID schedules is correct administration, as the Mantoux technique requires training. Recently, solutions applicable in low-resource countries have been developed, such as the PATH intradermal adapter [27].

CONCLUSIONS

Strong initial immune responses appear to induce strong booster responses, provided that sufficient time is taken between PreP and booster vaccinations. However, low initial responses also elicit booster responses above the WHO threshold. In addition, ID administration leads to higher booster responses than IM administration if equal doses are used. Booster responses following multiple dose ID PreP on 1 or 2 days are effective. Finally, boosters are more effective if 4 ID (0.1 mL) vaccinations are used compared with the routine (2 × 1.0 mL IM) schedule. Further studies investigating various schedules with larger numbers of vaccinees are required to verify these assumptions and assess predictive factors for low response or nonresponse. Hopefully, these schedules could be used in resource-poor countries and travelers to curb the number of rabies cases worldwide.

Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online (http://www.oxfordjournals.org/our_journals/cid/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyrighted. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References


