Travel related diseases and optimizing preventive strategies

Wieten, R.W.

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Chapter 10

Rabies Vaccinations: Are Abbreviated Intradermal Schedules the Future?


Rosanne W. Wieten, Tjalling Leenstra, Pieter P.A.M. van Thiel, Michèle van Vugt, Cees Stijnis, Abraham Goorhuis, and Martin P. Grobusch
**ABSTRACT**

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.
BACKGROUND

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, post exposure prophylaxis, intradermal injection, and intramuscular vaccination (Supplemental File 1). Abstracts received from the above databases (1,042, see Supplemental File 1) 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 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 Schedule

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 schedules (Table 1), either 2 x ID (0.1 mL) or 1 x IM (1.0 mL) [19].
<table>
<thead>
<tr>
<th>Subjects</th>
<th>N</th>
<th>Roa</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] Pre-booster, % ≥ 0.5UI/mL</th>
<th>GMT [range] Post-booster, % ≥ 0.5UI/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.3; Turner, 1982 [12]</td>
<td>33</td>
<td>ID</td>
<td>HDCV Merieux</td>
<td>1.1-5.9 antigenic value</td>
<td>0.1 mL</td>
<td>0,28</td>
<td>1,1</td>
<td>ELISA</td>
<td>random 0.1 mL ID/1.0 mL SC, random at 6/12/24 m</td>
<td>44.5 [0.7-954]</td>
<td>1.4</td>
</tr>
<tr>
<td>Healthy, 14-68 years</td>
<td>39</td>
<td>ID</td>
<td>PHKCV NR</td>
<td>0.8-13 antigenic value</td>
<td>1 mL</td>
<td>0,28</td>
<td>1,1</td>
<td>RFFIT</td>
<td>PECV 1.0 mL SC, 8-14 m</td>
<td>73%</td>
<td>90 %, d365</td>
</tr>
<tr>
<td>Males, 23-57 yrs</td>
<td>30</td>
<td>SC</td>
<td>PECV NR</td>
<td>0.1 mL</td>
<td>0,7</td>
<td>1,1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.1 Yang, 1999 [20]</td>
<td>27</td>
<td>ID</td>
<td>PHKCV NR</td>
<td>&lt; 2.5 IU/dose</td>
<td>0.1 mL</td>
<td>0,28</td>
<td>1,1</td>
<td>ELISA</td>
<td>2 mL IM d180 + 0.3,7,14,30</td>
<td>NR</td>
<td>100 %, d14</td>
</tr>
<tr>
<td>Healthy, 11-15 years</td>
<td>30</td>
<td>ID</td>
<td>PHKCV NR</td>
<td>0.1 mL</td>
<td>0,28</td>
<td>1,1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>ID</td>
<td>NR</td>
<td>PHKCV NR</td>
<td>0.1 mL</td>
<td>0,28</td>
<td>1,1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Table 1. Vaccination Schedules and Booster Details as Described in 9 Studies (continued)

<table>
<thead>
<tr>
<th>Subjects</th>
<th>N</th>
<th>Roa</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] Pre-booster, % ≥ 0.5UI/mL</th>
<th>GMT [range] Post-booster, % ≥ 0.5UI/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>NR</td>
<td>16</td>
<td>ID</td>
<td>NR</td>
<td>NR</td>
<td>0.1 mL</td>
<td>0,7,28</td>
<td>2,2,2</td>
<td>RFFIT</td>
<td>0.1 mL ID d 360, 363</td>
<td>0.96, 81.3 %</td>
<td>29.1, 100 % d7, 49.4, 100 % d14</td>
</tr>
<tr>
<td>4.1; Khawplod, 2007 [13]</td>
<td>NR</td>
<td>ID</td>
<td>Aventis-Pasteur</td>
<td>NR</td>
<td>0.1 mL</td>
<td>0,3,7</td>
<td>2,2,2</td>
<td>RFFIT</td>
<td>0.1 mL ID d 360, 363</td>
<td>1.12, 93.8 %</td>
<td>22.9, 100 % d7, 105.1, 100 % d14</td>
</tr>
<tr>
<td>NR</td>
<td>20</td>
<td>IM</td>
<td>NR</td>
<td>NR</td>
<td>1 mL</td>
<td>0,3,7</td>
<td>1,1,1</td>
<td>RFFIT</td>
<td>0.1 mL ID d 360, 363</td>
<td>0.97, 80.0 %</td>
<td>35.2, 100 % d7, 125.0, 100 % d14</td>
</tr>
<tr>
<td>NR</td>
<td>14</td>
<td>ID</td>
<td>NR</td>
<td>NR</td>
<td>0.1 mL</td>
<td>0</td>
<td>2</td>
<td>RFFIT</td>
<td>0.1 mL ID d 360, 363</td>
<td>0.41, 38.5 %</td>
<td>9.1, 100 % d7, 52.0, 100 % d14</td>
</tr>
<tr>
<td>5.1, 6.1; Kamoltham, 07, 11 [16, 17]</td>
<td>NR</td>
<td>ID</td>
<td>PCECV 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</td>
<td>0.11, 7 %</td>
<td>4.7, 96 % d7, 10.8, 100 % d14</td>
</tr>
<tr>
<td>Healthy, 4-8 years</td>
<td>NR</td>
<td>ID</td>
<td>PCECV Rabipur-Novartis</td>
<td>NR</td>
<td>0.1 mL</td>
<td>0,7,28</td>
<td>1,1,1</td>
<td>RFFIT</td>
<td>0.1 mL</td>
<td>0.33, 35 %</td>
<td>11.0, 100 % d7, 22.1, 100 % d14</td>
</tr>
<tr>
<td>7.1; Pengsaa, 2009 [14]</td>
<td>44</td>
<td>ID</td>
<td>PCECV 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</td>
<td>25, 100 % d7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy children, 12-18 months</td>
<td>44</td>
<td>ID</td>
<td>PCECV 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</td>
<td>13, 100 % d7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>45</td>
<td>IM</td>
<td>1 mL</td>
<td>0.7,28</td>
<td>1,1,1</td>
<td>RFFIT</td>
<td>0.1 mL</td>
<td>0.5 mL</td>
<td>0.7,28</td>
<td>190, 100 % d7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>44</td>
<td>IM</td>
<td>0.5 mL</td>
<td>0.7,28</td>
<td>1,1,1</td>
<td>RFFIT</td>
<td>0.1 mL</td>
<td>0.5 mL</td>
<td>0.7,28</td>
<td>161, 100 % d7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects</td>
<td>N</td>
<td>Roa</td>
<td>Vaccine brand</td>
<td>Vaccine potency</td>
<td>Dose</td>
<td>Days</td>
<td>Injections</td>
<td>RVNA test</td>
<td>Booster</td>
<td>GMT [range] Pre-booster, % ≥ 0.5UI/mL</td>
<td>GMT [range] Post-booster, % ≥ 0.5UI/mL</td>
</tr>
<tr>
<td>----------</td>
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<td>-----------------------------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>8.1 Strady, Healthy, 12-79 years</td>
<td>28</td>
<td>IM</td>
<td>HDCV/PVRV Pasteur Merieux</td>
<td>1.06-4.54 IU/dose</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 yr</td>
<td>0.25 [0.1-12]</td>
<td>31.3 [0.6-328]</td>
</tr>
<tr>
<td>96</td>
<td>IM</td>
<td></td>
<td></td>
<td></td>
<td>1 mL</td>
<td>0.7,28</td>
<td>1,1,1</td>
<td></td>
<td>0.1 mL IM on d 0, 3 1 yr</td>
<td>0.60 [0.1-48]</td>
<td>51.6 [1.4-1356]</td>
</tr>
<tr>
<td>17; Khawplod, Healthy, 19-45 years</td>
<td>17</td>
<td>ID</td>
<td>PCECV Rabipur-Chiron</td>
<td>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 yr</td>
<td>0.49 [0.1-2.1]</td>
<td>11.3 100 % d7, 54.5 100 % d14</td>
</tr>
<tr>
<td>19</td>
<td>ID</td>
<td></td>
<td></td>
<td></td>
<td>0.1 mL</td>
<td>0,7,21</td>
<td>1,1,1</td>
<td></td>
<td>0.1 mL ID 4 sites d 0 1 yr</td>
<td>0.30 [0.1-2.7]</td>
<td>42.5 100 % d7, 114 100 % d14</td>
</tr>
<tr>
<td>16</td>
<td>ID</td>
<td></td>
<td></td>
<td></td>
<td>0.1 mL</td>
<td>0</td>
<td>2</td>
<td>RFFIT</td>
<td>1.0 mL IM on d 0, 3 1 yr</td>
<td>0.15 [&lt;0.03-0.9]</td>
<td>9.7 100 % d7, 46.2 100 % d14</td>
</tr>
<tr>
<td>24</td>
<td>ID</td>
<td></td>
<td></td>
<td></td>
<td>0.1 mL</td>
<td>0</td>
<td>2</td>
<td></td>
<td>0.1 mL ID 4 sites d 0 1 yr</td>
<td>0.10 [&lt;0.03-1.1]</td>
<td>12.0 100 % d7, 54.3 100 % d14</td>
</tr>
<tr>
<td>17</td>
<td>IM</td>
<td></td>
<td></td>
<td></td>
<td>1 mL</td>
<td>0</td>
<td>1</td>
<td></td>
<td>1.0 mL IM on d 0, 3 1 yr</td>
<td>0.08 [&lt;0.03-2.2]</td>
<td>10.1 100 % d7, 19.0 100 % d14</td>
</tr>
<tr>
<td>16</td>
<td>IM</td>
<td></td>
<td></td>
<td></td>
<td>1 mL</td>
<td>0</td>
<td>1</td>
<td></td>
<td>0.1 mL ID 4 sites d 0 1 yr</td>
<td>0.11 [0.03-1.7]</td>
<td>13.3 100 % d7, 46.9 100 % d14</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.
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 x 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 of protection [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 x 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 x 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 x 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 x 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 x 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.
ACKNOWLEDGMENTS

The authors thank Marianne Kranenborg and Heleen Dyserinck for assisting with the literature searches.
REFERENCES


SUPPLEMENTAL MATERIAL

Appendix: Literature search

No limits were applied regarding publication language. Because new publications are not yet indexed in PubMed, ‘Mesh terms’ were only applied to search terms with subheadings. A subheading is allocated to a publication after indexation. Subheadings are recognizable in the given searches by the punctuation mark ‘slash’ between two search terms. Searches with OR are separated by a semicolon. Other search terms were searched through ‘all fields’.

Limits
Humans, Clinical Trial, Randomized Controlled Trial, Clinical Trial, Phase I, Clinical Trial, Phase II, Clinical Trial, Phase III, Clinical Trial, Phase IV, Controlled Clinic Trial

Search 1
Rabies ; Rabies/drug therapy ; Rabies/immunology ; Rabies/prevention and control ; Rabies/statistics and numerical data ; Rabies/therapy
AND
rabies vaccines ; Vaccination ; Rabies Vaccines/administration and dosage ; Rabies Vaccines/adverse effect ; Rabies Vaccines/therapeutic use ; Vaccination/administration and dosage ; Vaccination/adverse effects ; Vaccination/statistics and numerical data ; Vaccination/therapeutic use ; Vaccination/trends ; Vaccination/utilization
AND
pre-exposure vaccination

Search 2
Rabies ; Rabies/drug therapy ; Rabies/immunology ; Rabies/prevention and control ; Rabies/statistics and numerical data ; Rabies/therapy
AND
rabies vaccines ; Vaccination ; Rabies Vaccines/administration and dosage ; Rabies Vaccines/adverse effect ; Rabies Vaccines/therapeutic use ; Vaccination/administration and dosage ; Vaccination/adverse effects ; Vaccination/statistics and numerical data ; Vaccination/therapeutic use ; Vaccination/trends ; Vaccination/utilization
AND
post-exposure prevention ; post-exposure prophylaxis ; Post-Exposure Prophylaxis/methods ; Post-Exposure Prophylaxis/standards ; Post-Exposure Prophylaxis/statistics and numerical data ; Post-Exposure Prophylaxis/utilization ; secondary immunization ; Immunization, Secondary/adverse effects ; Immunization, Secondary/methods ; Im-
munization, Secondary/statistics and numerical data; Immunization, Secondary/trends; Immunization, Secondary/utilization

**Search 3**
Rabies; Rabies/drug therapy; Rabies/immunology; Rabies/prevention and control; Rabies/statistics and numerical data; Rabies/therapy
AND
rabies vaccines; Vaccination; Rabies Vaccines/administration and dosage; Rabies Vaccines/adverse effect; Rabies Vaccines/therapeutic use; Vaccination/administration and dosage; Vaccination/adverse effects; Vaccination/statistics and numerical data; Vaccination/therapeutic use; Vaccination/trends; Vaccination/utilization
AND
intradermal injections; Injections, Intradermal/adverse effects; Injections, Intradermal/therapeutic use; Injections, Intradermal/trends; Injections, Intradermal/utilization
AND
Intramuscular injections; Injections, Intramuscular/administration and dosage; Injections, Intramuscular/adverse effects; Injections, Intramuscular/methods; Injections, Intramuscular/statistics and numerical data; Injections, Intramuscular/trends; Injections, Intramuscular/utilization

**Search 4**
(search 2 AND Immunologic Memory/drug effects; Immunologic Memory/genetics; Immunologic Memory/immunology; Immunologic Memory/physiology; Immunologic Memory/radiation effects; immunologic memory) (search 2 AND immunization schedule; Immunization Schedule/standards; Immunization Schedule/veterinary)

**Search 5 = endresult**
searches (1 ; 2 ; 3 ; 4) AND Booster