Abstract. A 2-visit multiple-site intradermal (ID) vaccine protocol would be the most economical, immunogenic, and practicable regimen for postexposure rabies prophylaxis (PEP) in clinics seeing few patients a month. This regimen with an additional day 28 dose is now recommended by the WHO. The difficulties surrounding ID rabies vaccination have hindered progress in provision of prophylaxis, especially in rural Asia and Africa. Although the latest WHO recommendations include 1-week ID postexposure vaccine regimens, these are unlikely to prove economical where rabies vaccination is presently unavailable. The new protocol uses a whole vial of vaccine divided between 4-sites ID on the first day and half a vial at 2-sites ID on day 7. Gavi has recently approved support for rabies PEP. This 2-visit 4-site ID regimen, with or without a day 28 dose, should be considered for implementation in this remarkable new initiative.

TWO VISIT ID 4 SITE POSTEXPOSURE VACCINE REGIMEN

Another regimen, the 2-visit ID 4-site, was not considered by the Strategic Advisory Group of Experts on Immunization or WHO, although the same regimen with an additional 3rd dose on day 28 has been recommended by the WHO as an option for PEP (see Table 1). It is derived from the original 8-site ID regimen, which was recommended by the WHO for several years, using 1 mL/vial vaccines. The 8-site regimen was compared with the 2-site ID TRC regimen using the same amount of vaccine antigen. The neutralizing antibody response induced by the 8-site was significantly higher from day 7 up to a year later. Dividing the large ID dose on day 0 between days 0 and 3, as in the 2-site TRC regimen, was shown to be less immunogenic. Furthermore, in 200 Indian patients given a whole vial of vaccine at eight ID sites on 1 day, there was universal seroconversion by day 14. The superior immunogenicity of the 8-site regimen was acknowledged by the WHO.

The protocol of the 8-site ID regimen using 1 mL/vial vaccine was changed when rabies vaccines were produced with 0.5 mL/vial. The number of ID sites was halved and the dose per site doubled. This became the 4-site ID 1-month regimen which is now recommended by the WHO. A whole vial is divided between 4-sites ID on day 0, half a vial between 2-sites ID on day 7, and at one site on day 28 (Table 1). The ID dose for this regimen is 0.1 mL/site for 0.5 mL/vial vaccines and 0.2 mL/site for 1 mL/vial. If injecting 0.2 mL ID is difficult, the needle can be withdrawn and the remaining dose is given at an adjacent site. In this regimen, the amount of vaccine antigen remains constant, unlike in the 2-site regimens, which use an ID dose of 0.1 mL with any vaccine, thereby halving the dose with 1 mL/vial vaccines. Because the dosage and timing of these 8-site and 4-site ID methods are identical, the proven efficacy of the 8-site regimen in postexposure trials and in the field over many years also applies to the 4-site version.

It is well established that the protective effect of PEP is due to the induction of neutralizing antibody within the first few days. Early immunogenicity following rabies vaccination is related to the initial amount of antigen injected.
**Simplified Scheme for 4-Site ID Postexposure Vaccination**

A simple plan is proposed for all PEP using the same first dose (Table 2). For previously vaccinated patients, the WHO has long recommended a 4-site ID single-day postexposure booster regimen. Therefore, a 4-site ID dose on day 0 could be given to all patients exposed to a possibly rabid mammal. If they have never had vaccine before, a second 2-site ID dose is given on day 7. Immunosuppressed patients would be given an additional single-site ID dose on or around day 28.2

CONCLUSION

The choice of postexposure regimen will influence whether widespread donation of expensive vaccines by Gavi is economically viable and can save thousands of lives.

Table 1: Selected WHO recommended postexposure rabies vaccine regimens

| WHO principle ID recommendation | Day 0 | Day 3 | Day 7 | Day 28 | Visits |
|-------------------------------|-------|-------|-------|--------|--------|
| ID 2-site 1-week “IPC”‡       | 2     | 2     | 2     | –      | 3      |
| ID alternative regimen        |       |       |       |        |        |
| ID 2-site Thai Red Cross      | 2     | 2     | 2     | 2      | 4      |
| ID 4-site 1 month             | 4     | 2     | –     | 1      | 3      |

Depends on vial size: 1–2 vials, 3 vials if no sharing

1 vial, 2 vials, 4 vials if no sharing

< 2 vials, same for all vaccines, 3 vials if no sharing

| ID = intradermal; IPC = Institut Pasteur du Cambodge. |
| * Six regimens were recommended: two intramuscular and four ID. |

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### Table 2: Simplified scheme for economical 4-site ID rabies postexposure vaccination

| Primary Postexposure Regimens | Day 0 | Day 3 | Day 7 | Day 28 | Visits |
|-------------------------------|-------|-------|-------|--------|--------|
| 2-visit 4-site PEP*           | 4†    | –     | 2     | –      | 2      |
| 2-visit 4-site PEP with 3rd dose for immunosuppressed patients, optional if healthy* | 4† | – | 2 | 1 | 3 |
| Postexposure booster regimen for those previously immunized | | | | |
| Single day, 4-site         | 4‡    | –     | –     | –      | 1      |

1 vial, 1.5 vials, same for all vaccines, 2 vials if no sharing

< 2 vials, same for all vaccines, 3 vials if no sharing

0.5–1 vial

ID = intradermal; PEP = postexposure rabies prophylaxis.

* ID doses are 0.1 mL/site for 0.5 mL/vial vaccine (Purified Vero cell Rabies Vaccine, Verorab; Sanofi, Lyon, France) or 0.2 mL/site for 1.0 mL/vial vaccine (Purified Chick Embryo Cell Vaccine, Rabipur/RabAvert; GSK, Marburg, Germany).

† Use whole vial.

‡ Preferably using a whole vial especially if previously vaccinated several years before, but half vial can be used with 1-mL vaccines.
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