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Rabies post-exposure vaccination in 2 visits within a week: A 4-site intradermal regimen

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ABSTRACT

Rabies is fatal in all unvaccinated patients bitten by dogs, and so post-exposure vaccine regimens must be robust enough to ensure their survival under all conditions. Treatment tends to be excessive for most people, but there is justified anxiety about reducing vaccine dosage and shortening regimens. Recently, World Health Organisation (WHO) recommended one week primary post-exposure intradermal regimens requiring 3 clinic visits, but these are unlikely to prove economical where rabies vaccination is most needed, in deprived rural areas of Africa and Asia.

A highly immunogenic regimen involving two doses of intradermal vaccine given one week apart has advantages over other regimens. Anyone exposed to a possibly rabid animal would be given intradermal (ID) injections at 4 sites using a whole vial of vaccine. Those who had not been previously vaccinated would be given 2-site ID injections using half a vial one week later. Those who might be immunosuppressed could be given an optional single ID dose on day 28. The rationale for this regimen is discussed in the context of the recently revised WHO recommendations for rabies prophylaxis.

1. Introduction

Rabies is eminently vaccine preventable, but thousands of people die from this agonising infection each year because they have no access to treatment after rabid dog bites. Few countries provide expensive rabies vaccine free of charge and they are not widely distributed. Rabies immune globulin is unavailable in rural areas of Africa and Asia where up to 90% of rabies deaths occur [1]. Patients may have long journeys to reach the nearest clinic or they cannot afford the high cost of vaccine. If there is no treatment available, patients bitten by dogs do not go to health centres and so the scale of the problem is unknown.

International funding of rabies vaccine might become possible through Gavi, the Vaccine Alliance. The most immunogenic, economical and acceptable method of vaccination should be adopted to achieve the greatest benefit for communities in dog rabies endemic countries.

Following a scientific review by a SAGE (Strategic Advisory Group of Experts) working group [2], the WHO has recently revised their recommendations for rabies prophylaxis [3]. The 6 primary and 3 booster PEP vaccine regimens are explained to guide physicians in deciding which schedules best suit their practice. The relative immunogenicity and practicability of the proposed regimens are discussed in comparison with a new highly immunogenic vaccine regimen requiring only 2 clinic visits and 1½ vials of vaccine.

2. Post-Exposure prophylaxis

Where dog rabies is endemic, rabies vaccine is used almost entirely for Post-Exposure Prophylaxis (PEP), whereas pre-exposure immunisation predominates in Western countries for occupational and travel prophylaxis. Rabies infection is transmitted by virus in the saliva of a rabid mammal when inoculated under the skin or onto mucous membranes, usually of the eyes or mouth. Scratches or superficial bat bites can also be infectious. If exposure is suspected or proven, wound cleaning, rabies vaccination and possibly rabies immunoglobulin (RIG) treatment are urgently required. The aim is to neutralise or kill virus in the wound before it gains access to neurones. Effective PEP depends on a rapid induction of neutralising antibody effected by a powerful antigenic stimulus and so more vaccine is needed than for pre-exposure use.

There are three WHO prequalified vaccines: Human Diploid Cell Vaccine (HDCV) 1 ml/vial (Imovax® Sanofi); Purified Chick Embryo Cell Vaccine (PCECV) 1 ml/vial (Rabipur/RabAvert®,GSK) and Purified Vero Cell Vaccine (PVRV) 0·5 ml/vial (Verorab®, Sanofi). Several other Chinese and Indian vaccines of uncertain quality are also widely exported.

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The prohibitive cost of these rabies vaccines leaves many patients untreated especially in Asia and Africa, but they can be used more economically by injecting small amounts in multiple sites intradermally (ID). The antibody levels induced correlate not only with the amount of antigen injected ID [4,5] but also the design of the regimen. Since the early presence of this antibody is most important for protection against infection and inevitable death, the duration of post-exposure tissue culture vaccine regimens has decreased progressively from 3 months to less than one month. Now one week regimens are deemed to be safe.

3. Two primary intramuscular (IM) Post-Exposure vaccine regimens recommended by WHO 2018 (Table 1)

The two IM regimens listed are a **4 dose 'Essen'**, which is a combination of the two previous IM regimens, the 5 dose Essen (days 0,3,7,14 and 28) and the CDC 4 dose version (days 0, 3, 7 and 14) [6]. The result is an IM dose on days 0, 3, 7 and between days 14 and 28. The antibody level maybe enhanced by delaying the final dose until day 28 [7].

The second recommendation, the **Zagreb '2-1-1'** regimen has been unchanged for more than 25 years: 2 IM doses on day 0 followed by single injections on days 7 and 21. This has the advantage of only 3 visits.

4. Four primary ID Post-Exposure regimens recommended by WHO 2018 [3] (Table 1)

4.1. Three regimens based on the 2-site ID Thai Red Cross (TRC)

The **2-site ID 1 week 'IPC'** (Institut Pasteur Cambodge) regimen, 0·1 ml ID at 2 ID sites on days 0, 3 and 7, is the principle recommendation. This is the 2-site ID 1 month, or TRC regimen missing the final day 28 dose. The alternative recommendations include the **TRC** and a **4-site ID 1 week regimen** which is double the dose of the 2-site principle recommendation: 0·1 ml ID injections at 4 sites on days 0, 3 and 7 [8,9]. These 3 regimens are essentially the same up to a week, and one has a dose on day 28.

The **2-site ID TRC regimen** is the only primary ID PEP regimen recommended by WHO in recent years. (Table 1, Fig. 1). It consists of 2-site ID 0·1 ml injections in the deltoid areas on days 0, 3, 7 and 28. The dose finding study followed the timing of the IM regimen and varied the ID doses. It showed that 0·1 ml of PVRV injected at 2 ID sites (total dose ½ vial per visit), induced seroconversion, but also that doubling the ID dose to 4 sites gave a higher antibody response ($p < 0.0005$). Halving the dose to $^1/_5$ vial per visit gave lower levels and some people failed to seroconvert by day 14 [10]. The 2-site regimen is known as the 'Updated TRC regimen' since the 3 month dose was deleted, as in the case of all the PEP regimens.

The amount of vaccine antigen varies depending on the vaccine used. For PCECV and HDCV (1 ml/vial) the equivalent dose is 0·2 ml/ ID site, which the WHO recommended in 1997 [11]. However, several years later the WHO stipulated a 0·1 ml ID dose for all rabies vaccine, which halved the ID dose when 1 ml/vial vaccines were used.(Fig. 1) As a result higher potency vaccines are now demanded for ID use in Thailand, the Philippines and Sri Lanka [12]. Vaccine wastage has been estimated at 25% [13]. The 2-site TRC regimen has been the only ID regimen in use, in Asian and a very few African urban hospitals. It was intended that it's use should be restricted to the WHO prequalified vaccines [14], but it is also used with Indian and Chinese vaccines.

The evidence supporting the **2-site ID 1 week 'IPC'** (Fig. 1) recommendation rests on a study in Cambodia. Only preliminary

Table 1
Rabies post-exposure vaccine regimens.

PRIMARY PEP REGIMENS	NUMBER OF SITES INJECTED						VISITS	TOTAL VACCINE
Days of vaccination	0	3	7	14	21	28		
WHO recommended								
IM 4 dose adapted Essen	1	1	1	←	1	→	4	4 vials
IM '2-1-1' Zagreb	2		1		1		3	4 vials
WHO primary recommendation								Depends on vial size
ID 2-site 1 week 'IPC'	2	2	2				3	1 – 3 vials
WHO Alternative ID regimens								
ID 2-site Thai Red Cross	2	2	2			2	4	< 2 – 4 vials
ID 4-site 1 week	4	4	4				3	1·5 – 3 vials
4-site one month	4		2			1	3	< 2 vials, same for all vaccines
2 visit ID 4-site one week (optional day 28)	4		2			(1)	2	1·5 vials all vaccines
PEP BOOSTER REGIMENS for previously immunised								
WHO recommended								
IM 2 visit	1	1					2	2 vials
ID 2 visit 0.1 ml	1	1					2	< 1 vial
4-site ID single day regimen	4						1	½ – 1

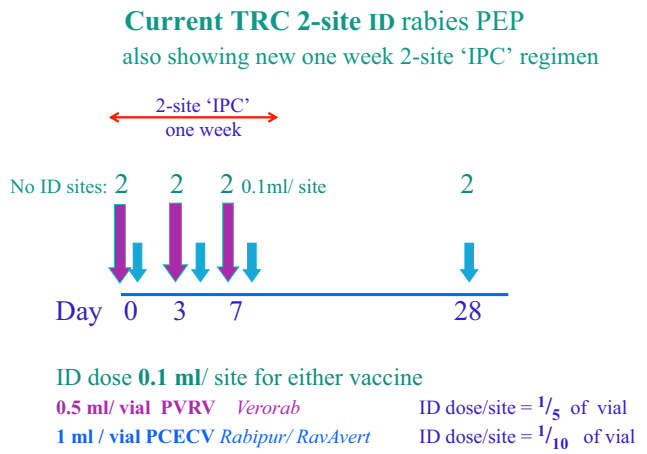

Fig. 1. Current TRC 2-site ID regimens. 1 ml/vial vaccines use half the amount of vaccine of the original regimen. The new 'IPC' 2-site ID one week regimen is the same but the day 28 dose is removed. The size of the arrows is proportional to the amount of vaccine given.

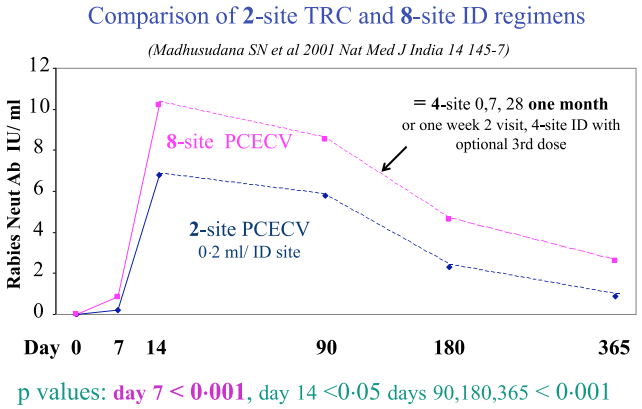

Fig. 2. Comparison of TRC 2-site ID (0·2 ml/ site) and 8-site (0·1 ml/site) PEP regimens. PCECV vaccine 1 ml/vial. Total amount of vaccine used is the same for both regimens. The difference between them is the 8-site has a whole vial on day 0, whereas in the 2-site regimen a vial is divided ID between day 0 and day 3. The whole dose on day 0 must account for the higher antibody response of the 8-site.

serological results were available to the WHO committee [3] (see Appendix below). Using PCECV, the ID dose is half as much but the equivalent antibody response has not been evaluated with this lower dose. These 2-site ID regimens would be economical in a clinic seeing several patients a day, but not in small hospitals, clinics and health centres where few patients present in a week. Vaccine vials must be shared at each visit and opened vials must be discarded after 8 h.

The **4-site ID one week** regimen [8–10] with PCECV is identical to the 2-site using PVRV, ½ a vial per visit. However, PVRV uses a whole vial at each visit which is expensive and a waste of vaccine.

4.2. Regimen based on the original 8-site ID

4-site ID one month regimen (Table 1) is a modification of the **8-site ID regimen**.

This uses the same dose of antigen with all vaccines. On the first day a whole vial of vaccine is divided between four ID sites. On day 7, 2 ID injections are given, a total of ½ vial, with a single ID injection on day 28. This is now recommended by the WHO [3].

The dose per ID site depends on the volume per vial: for PVRV (0·5 ml/vial) the ID dose is 0·1 ml/site. PCECV and HDCV (1 ml/vial) the equivalent ID dose is 0·2 ml/ site. The sites of injection, the deltoids and either the thighs or suprascapular areas, were chosen with the aim of recruiting several groups of lymph nodes to produce antibody. If injecting 0·2 ml ID proves difficult, the needle is withdrawn and the remainder injected into an adjacent area. Alternatively, give two ID injections ≈ 0·1 ml side by side in each site.

The first ID PEP regimen was the 8-site ID, devised when HDCV was the only tissue culture vaccine available. The dosage and timing were decided following dose finding immunogenicity studies [15,16] and a randomised controlled trial in patients bitten by proven rabid animals confirmed an early antibody response [17]. A whole vial is divided between 8 ID sites 0·1 ml/site on day 0, half a vial at 4-sites on day 7 and a single ID injection on day 28. This 8-site regimen was recommended by WHO in 1997 [11].

A comparison of the TRC and 8-site regimens using the same total amount of the same vaccine showed significantly higher antibody levels from day 7 ($p < 0.001$) to 1 year with the 8-site [18]. (Fig. 2). The only difference between them is that the large dose on day 0 is divided between days 0 and 3 with the 2-site schedule, which must account for the higher antibody. Showing that the design of the regimen influences the immune response. The immunogenicity of the 8-site regimen was commended by the WHO [14], but it was not suitable for use with PVRV as the ID dose would be 0·05, which was not practicable. The regimen was therefore changed to half the number of ID sites and double the dose per site. This is the 4-site ID one month regimen [19].

The dose and timing of visits in the 4-site one month regimen is identical to that of the 8-site method. The immunogenicity is unaffected by changing the number of ID sites from 8 to 4 [19]. The clinical effectiveness of the 8-site during years in routine use can be assumed for this 4-site regimen. No vaccine is wasted on the first day. If few patients present each month, they can be asked to bring relatives to the appointment on day 7. Any left-over vaccine can be given as pre-exposure prophylaxis, 0·1 ml ID. The exact timing of the final day 28 dose is not important, so patients could be seen on just one or two days a week to share a vial and prevent wastage.

This 4-site ID regimen would be the most immunogenic in patients who default after the first visit (Fig. 2). Accidental subcutaneous injection should not greatly impair the immunogenicity because half the dose proved immunogenic in young healthy volunteers [20]. Experience of giving ID injections is less important as a whole vial of vaccine is used, which enhances the safety of the regimen. This could be highly cost-effective for the health provider and the patient in comparison with other ID regimens [21].

The WHO did not recommend the 4-site ID one month regimen in 2010 because a 0·2 ml ID dose does not comply with their stipulation for a universal ID dose of 0·1 ml [22]. This ignores the fact that a 0·2 ml dose was originally recommended for the 2-site ID TRC regimen [11], and was in use for 8 years without criticism.

5. New 2 visit one week 4-site ID PEP regimen

Rabies is prevented post-exposure by early induction of neutralising antibody. A vaccine regimen can be shortened as long as rapid seroconversion is guaranteed in all recipients. This is the case for the 4-site one month regimen by day 14. A study in Bangalore showed that a single 8-site ID dose of HDCV resulted in seroconversion on day 14 in all 200 patients, 40 of whom also had RIG, which tends to lower the titres [23]. Hence, if patients default after the first visit, they are still likely to seroconvert.

The 4-site one month is at least as immunogenic as the TRC regimen (Fig. 2) and so the day 28 dose can be omitted as has been done with the 2-site ID one week, IPC regimen.

The resulting regimen is the first 2 doses of the 4-site one month regimen: on day 0 give 4-site ID injections using a whole vial and on day 7, 2 ID injections, a total of ½ vial (Fig. 3).

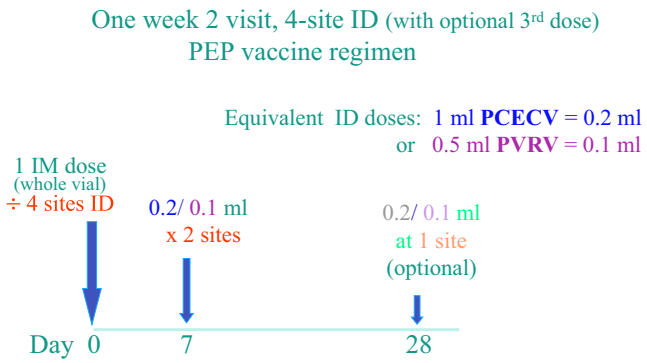

Fig. 3. 2 visit 4-site ID one week regimen with an optional day 28 dose for immunosuppressed or vulnerable. This 2 visit one week regimen would be the most economical method of all. The injection sites are over the deltoids and thighs or suprascapular. The size of the arrows is proportional to the amount of vaccine given.

5.1. Optional day 28 ID dose

Two doses are sufficiently immunogenic for the general population, but any one week regimen should also cater for immunosuppressed vaccinees including HIV infected patients. An optional day 28 dose is then desirable with all one week regimens, especially if RIG has also been given. The later dose will prolong and enhance the antibody response.

The 2 visit regimen has all the advantages of the 4-site one month scheme described above. In addition, having the fewest visits means it is the most economical with least vaccine wastage in small clinics, saving syringes and clinic time, also travel costs and time off work for patients.. If vial sharing is not possible or not permitted, only 2 vials are used.

Rabies is fatal and greatly feared by people bitten by possibly rabid dogs. Problems using multiple site injections have not been reported with the other 4-site ID regimens [9,10,24]. The procedure of multiple site vaccine administration may be more easily accepted by, for example shielding a child's view of the needle and site while injecting. If a 1 ml/ vial vaccine is used with the regimen, the ID dose is 0.2 ml/site. This dose was recommended by WHO for the original TRC regimen in 1997 [11] and used in Asia for several years without any report of difficulties with injection.

6. Choosing an ID PEP regimen

The most important feature of PEP is high immunogenicity. It should also be economical; involve a minimum number of clinic visits; be least likely to waste vaccine; be easy to understand and administer and have a wide margin of safety. The ID regimens can be used globally with the approval of government authorities.

7. Passive immunisation with RIG

It is recommended that RIG is injected into the wound as soon as possible after major (category III) exposure to a rabid animal if the patient has not been previously vaccinated. It is most important after severe exposure with bites on the head, neck, hands or multiple bites. RIG is expensive, scarce and unavailable in some African countries. Having wounds injected is painful and so some doctors will only give the dose IM which is less effective. Local analgesia by injection or aerosol is advisable before RIG injection. This is occasionally practiced by compassionate doctors but no instructions exist. A study of possible methods is urgent.

If supplies are restricted, WHO now recommends that RIG can be reserved for patients at the highest risk, with severe exposure [3]. The global need for RIG would be reduced if pre-exposure immunisation was encouraged for everyone living in dog rabies endemic areas who can afford it, especially children.

8. Rabies vaccination in immunosuppressed patients

Whether immunosuppression is due to old age, drugs or a chronic disease most commonly HIV infection, reduction in antibody response to vaccine is expected. Low-responders and immunosuppressed patients may not be recognised in a clinic.

The effect of HIV infection on the immunogenicity of IM [25,26] and ID [27,28] rabies vaccine is related to the severity of immunodeficiency reflected by the patient's CD4+ cell count. Continuous antiretroviral treatment should enhance the antibody response [29]. ID vaccination is not contraindicated and may even be advantageous [30,31].

The best management of this group is to recommend pre-exposure immunisation and if bitten, thorough wound care and a 28 day course of a WHO pre-qualified vaccine.

9. Post-Exposure booster vaccination if previously vaccinated, 2018 WHO recommendations (Table 1)

Provided that a complete pre- or post- exposure course of rabies vaccine has been given previously, RIG treatment is not necessary but a booster vaccination is imperative. The three IM and ID regimens remain unchanged in the latest WHO report [3].

Two visit regimens, either IM or ID, are given on days 0 and 3.

The third regimen consists of **single day 4-site ID vaccination**. This is at least as immunogenic as the 2 visit IM regimen [32,33]. The 0·1 ml ID dose can be used for all vaccines because half a vial is sufficient to boost an antibody response. For PVRV, 0·5 ml, a whole vial is used, without wastage. Treating only one patient with HDCV or PCECV, the remaining 0·4 ml can be used as ID PrEP for relatives or others. It would be simpler and safer in inexperienced hands, to use a whole vial of any vaccine for each patient, especially if revaccinating after many years.

It is not clear why the 2 visit ID regimen is still recommended. It has no advantages over the single day 4-site ID regimen and is likely to be less immunogenic [32–35].

10. Suggested simplified scheme for economical rabies prophylaxis

A cheap, easy to operate vaccine scheme would rely on widespread provision of small stocks of vaccine in dog rabies endemic areas. It is expected that RIG would not be available, so it is crucial that the vaccine regimen is highly immunogenic. A suggested simplified economical scheme using the 4-site ID regimens for PEP has the same first dose (Table 2).

Any patient at risk of infection by a rabid animal would be given 4-site ID vaccination, using a whole vial. If they have never had previous vaccination, a week later they would be given 2-site ID injections using half a vial. If they were possibly immunosuppressed, a single ID dose could be given on day 28.

An emergency single visit pre-exposure 4-site ID dose for travellers about to depart or hospital staff caring for a patient with rabies encephalitis [36] was recommended in the UK for several years [37], and should be reintroduced.

These economical regimens have a wide margin of safety and would be suitable to use globally with government authorities' approval or if individual doctors decide to act on evidence of immunogenicity and economy and in the interest of their patients.

Table 2
Simplified scheme for economical 4-site INTRADERMAL rabies PEP.

Vaccine regimen Days of vaccination	Number of id sites injected 0	7	28	Visits	Total vials
PRIMARY POST-EXPOSURE					
2 visit 4-site PEP [a]	4 [b]	2		2	1·5 if no vial sharing 2 vials
2 visit 4-site PEP with optional 3rd dose [a] For immunosuppressed patients, optional if healthy	4 [b]	2	1	3	< 2 vials
POST-EXPOSURE BOOSTER (if previously vaccinated)					
Single visit (no RIG)	4[(c)]			1	0·5 –1 vial

[a] ID doses are 0.1 ml/site for 0·5 ml/vial vaccine (PVRV), or 0·2 ml/site for 1·0 ml/vial vaccine (PCECV).
[b] Use whole vial.
[c] Using whole or half a vial, see text.

11. How can the historical problems with rabies ID immunisation be resolved?

The two vial types with different volumes of diluent cause problems with ID regimens. Normal pharmaceutical practice would be to give an equivalent dose of viral antigen, irrespective of the vial size. There is also confusion and concern about the potency of rabies vaccines, which is > 2·5 IU/ml. Rather than requesting higher potency for ID use [12], regimens must be designed to be effective at the lowest potency level. In Sri Lanka, since the WHO universal 0·1 ml ID dose was introduced, they doubled the dose of the TRC ID PEP regimen [38].

Perhaps WHO intends the 2-site IPC to be used with PVRV and the 4-site day 0, 3 and 7, with 1 ml/vial vaccines, PCECV, HDCV. This would be a way of giving an equivalent amount of vaccine with one regimen, but might be confusing in the field and if vaccine sources changed.

Aseptic technique is essential when sharing vaccine vials. The vaccine is kept in a fridge and any opened vials must be discarded at the end of the day. Rabies vaccines do not contain preservative and so cannot be registered as multi-dose vials. Neither vaccine is licensed by the manufacturer for ID injection which is considered off-label use. This has inhibited ID use of rabies vaccine in Western countries, where staff are apparently not trusted to deliver ID injections and/or prevent contamination. Other vaccines are regularly used off-label [39] and the latest WHO guidelines suggest that this is acceptable for rabies [3].

The Criteria used by the WHO for accepting a new regimen are inconsistent. In 2012, two independent trials in peer reviewed journals were said to be needed before acceptance [40]. Now a new regimen has been recommended for which the full data from the one supporting study were not available to the committee and no paper had been published. This 2-site ID one week, IPC regimen has nevertheless become the WHO preferred PEP ID vaccine regimen.

The total number of approved vaccine regimens listed in the 2018 WHO Report has increased to 11, despite an intention to reduce and simplify them. These include pre-exposure and all PEP regimens. A review is published elsewhere [41]. The principle change is removal of the final doses of PEP and pre-exposure regimens. The 2-site ID TRC regimen has been recommended for 20 years but it has been taken up only in a few large clinics. Rural areas of Africa and many in Asia often do not stock rabies vaccine. Efforts to use the TRC regimen economically in rural areas have failed. The proposed 3 visit one week regimens (days 0, 3, 7) are not predicted to make a big difference, but a radical new approach can now be adopted. Since the 4-site ID one month regimen is recommended as a WHO alternative choice, the precedent of approving the 2-site ID 'IPC' one week regimen opens a clear path to using the 4-site ID regimen of 2 visits on days 0 and 7, especially as the immunogenicity of the first dose alone has been demonstrated [23].

12. Declarations of interest

none.

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Appendix

Extra data on 1 week 2-site ID regimen, 'IPC regimen'

[3 visits] (2-2-2-0-0) (table 1, figure 1) This one week regimen is the same as the current TRC schedule but omits the last dose. ID injections of 0 × 1 ml are given at 2-sites on days 0, 3 and 7. It is the principle new WHO recommendation for ID PEP, based on a study by Tarantola in Cambodia at the Institut Pasteur Cambodge (IPC). Rabies exposed patients received the full TRC regimen using PVRV ($^1/_2$vial per visit) and RIG. Preliminary serological results of 88 people after 3 doses were available at the time of the publication of the WHO report [3] and the full data are still unknown. The GMT did not rise between days 28 and 42, suggesting that the day 28 dose does not enhance the immunity. It is inferred that this final dose is not necessary [2].

On the basis of these scanty data the WHO has recommended this regimen not only for PVRV but also using PCECV, reducing the dose to $^1/_5$ vial per visit. This is even less economical where it is most needed, in small rural clinics. The lower dose should be tested before vaccines produced as 1 ml/ vial are used. The criteria for endorsement of PEP regimens have clearly changed [40].

In another study to determine the need for a dose on day 28, a large number of patients exposed to proven or suspect rabid animals were followed for mortality over 6 months. All received the TRC 2-site ID regimen with or without RIG (depending on the severity of exposure and supplies). Some failed to complete the vaccine course. 3 rabies deaths occurred, 2 after 19 days and one after 39 days. All 3 had had 3 vaccine doses, and one may have had all 4 [42]. Some patients were lost to follow-up and the efficacy of the one week schedule cannot be estimated, but the study confirms that no PEP method can prevent every death. Delayed presentation or inadequate treatment can and will occur in any setting. The consequence is failure to provide neutralising antibody soon after exposure. Therefore it is vital to use the most rapidly immunogenic vaccine regimen

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