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Review

Evaluating new rabies post-exposure prophylaxis (PEP) regimens or vaccines

Arnaud Tarantola [a], Mathurin Cyrille Tejiokem [b], Deborah J. Briggs [c,*]

[a] Unité d'Epidémiologie, Institut Pasteur de Nouvelle-Calédonie, Nouméa, New Caledonia
[b] Service d'Epidémiologie et de Santé Publique, Centre Pasteur du Cameroun, Yaoundé, Cameroon
[c] Department of Diagnostic Medicine/Pathobiology, College of Veterinary Medicine, Kansas State University, Manhattan, KS, United States

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ABSTRACT

The development of human rabies vaccines has evolved dramatically from the first crude nerve tissue vaccine produced then administered in the presence of Louis Pasteur in 1885. New cell culture technology has enabled highly potent and well-tolerated rabies vaccines to be produced that have reduced the volume and number of doses required to save human lives after exposure. However, these highly potent vaccines are still unaffordable to many patients living at risk of exposure on a daily basis. The cost of post-exposure prophylaxis (PEP) is not only related to the direct cost of rabies biologicals and equipment but is also associated with indirect costs that patients incur as a result of travel, loss of work time (income loss), and accommodation over the period of time that a PEP regimen requires to be completed. This paper summarizes the particular criteria that the SAGE Working Group and WHO personnel reviewed as part of the evaluation process for recommending the new one-week intradermal vaccination regimen (2-2-2-0-0) for rabies post-exposure prophylaxis. These criteria included: Cost-effectiveness; evaluation of number of doses; seroconversion after vaccination; efficacy; safety; and patient follow-up.

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* Corresponding author.
E-mail addresses: atarantola@pasteur.nc (A. Tarantola), tejiokem@pasteur-yaounde.org (M.C. Tejiokem), briggs@vet.ksu.edu (D.J. Briggs).

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1. Introduction

Rabies is an acute encephalitis caused by infection with a virus from the genus *lyssavirus*, family *Rhabdoviridae.* Over 99% of all global human rabies deaths occur in Asia and Africa as a result of a bite from an infected dog [1–3]. Rabies has the highest case fatality rate of all known infectious diseases and once clinical signs are present, death is almost always inevitable [3]. In humans, the incubation period from infection to clinical disease averages between 15 and 90 days. Thus, it is possible to prevent clinical rabies in humans, even after exposure occurs, through prompt and effective post-exposure prophylaxis (PEP) including: Effective washing of all wounds that occurred during exposure; administration of rabies immunoglobulin (RIG) if indicated; and the administration of an effective rabies vaccine according to country guidelines and WHO recommendations [4].

The WHO has specific guidelines on the protocol for the clinical evaluation of vaccines based on an evidence-based approach [5]. For several decades, the World Health Organization (WHO) has reviewed, updated, and recommended vaccination regimens for both pre-exposure vaccination (PreP) and post-exposure prophylaxis (PEP) to prevent rabies in humans [4,6–9]. Revisions and updates to these WHO recommendations are based on clinical data that have been reviewed and critically analyzed by a group of experts in the field of rabies. New and/or updated WHO recommendations are published, accessible online and the further adoption of all new updates and/or changes at a national level are the responsibility of the governing bodies in each country in charge of vaccination protocols.

2. History of changing rabies vaccine protocols

Historically, rabies vaccine was the third vaccine to be developed, and has a special place in vaccine development due to the spectacular news that was circulated around the world after Louis Pasteur and his colleagues successfully inoculated the first two at-risk patients Joseph Meister and later Jean-Baptiste Jupille with their newly developed live attenuated rabies vaccine in 1885 [10,11]. Pasteur and his colleagues thus initiated the first PEP for prevention of rabies in humans. These early PEP protocols consisted of up to 40 injections over 12 or more days [11]. The use of multiple injections for rabies PEP has continued through each stage in the development of new and improved human rabies vaccines and vaccine protocols until today. An excellent review of the development of human rabies vaccines has been published by Wu et al. [12]. Very briefly, the Pasteur vaccine developed and first utilized in 1885 was improved by Fermi, Semple and others by using phenol to partially or completely inactivate live virus produced in nerve tissue and avoid iatrogenic infection [13]. However, both vaccines were required to be injected daily over at least a 14-day period. Cases of paralysis, due to the myelin protein or iatrogenic rabies due to live rabies virus remaining in the vaccine have been reported [14]. Sheep brain vaccine is still produced and used to vaccinate patients in one country [15]. Fuenzalida and his colleagues developed an improved nerve tissue rabies vaccine in neonatal mice, still requiring multiple injections over an extended period of time. Although the incidence of adverse reactions was lower in Fuenzalida's vaccine, they were generally more severe when they did occur [14,16]. In the 1930s virologists shifted from producing rabies vaccines in animal brain tissue to production in embryonated eggs. The first duck embryo vaccines (DEV) are no longer in use today due to problems with low antigenicity. Advanced technologies improved the purity, potency and uniformity of rabies vaccines produced in embryonated eggs and several highly potent and highly purified rabies vaccines have been produced using this technology [17,18]. The production process for modern avian-based vaccines enables manufacturers to remove virtually all egg proteins and myelin, thus providing a highly purified product. Modern, highly purified human rabies vaccines are produced in a variety of highly purified cell culture systems and have been used for over three decades with well-documented safety and effectiveness [17,19–21]. These highly purified egg-based and cell culture human rabies vaccines (CCEVs) are equivalent in clinical effectiveness and therefore are administered using the same PEP regimens as recommended by WHO [4]. CCEVs were initially administered by deep intramuscular injection in the deltoid muscle, or thigh in small children, in a series of 6 injections over a period of 90 days. However, as new clinical evidence emerged, the 6th dose was eliminated and a five-dose (Essen) regimen was recommended wherein one vial of vaccine is administered on each of days 0, 3, 7, 14 and 28. New IM PEP regimens were further reduced to 4 doses over a period of 14–21 days [22–24]. The first four-dose PEP regimen (Zagreb) was given as 2 doses on day 0, and one dose on each of days 7 and 21 [22]. The second four-dose PEP regimen simply dropped the dose on day 28 of the Essen regimen [24]. Shortages of CCEVs and the high cost of vaccines led to clinical trials using intradermal injections (ID) for PEP [25–27]. The first ID PEP regimens were administered over a period of 90 days but, again, as clinical evidence accumulated, the ID regimens were gradually reduced to a series of injections administered over a 28–30 day period, with two ID injections of 0.1 mL being administered in the deltoid regions of each arm [28]. Several ID PEP regimens have been developed over time and have proven to be highly effective [4,25,28–30].

Much of the economic burden of PEP is related to indirect costs associated with procurement of medical treatment including: travel to anti-rabies clinics multiple times to receive treatment; loss of wages or income due to the need to travel; food and lodging associated with travel to anti-rabies clinics [31,32]. Thus, the expense of acquiring PEP, in addition to the scarcity of available vaccines in remote areas, is a serious concern in the continued attempt to reduce the global human burden of rabies. In order to determine if PEP regimens could be safely reduced with no increase in risk to exposed patients, SAGE established a working group of rabies and vaccine experts (SAGE-WG) in 2016 to review available clinical and economic data. The following review briefly summarizes the criteria that were evaluated by SAGE-WG and WHO personnel and consequently approved by SAGE to update the PEP regimens currently recommended in the 2018 WHO Rabies Position Paper [4].

3. Evaluation of criteria

The WHO and the European Medicines Agency have provided guidelines for the clinical evaluation of vaccines [33,34]. Many of these criteria were considered in the SAGE-WG assessment of new PEP regimens including: Evaluation of number of visits and doses required; seroconversion after vaccination; effectiveness of vaccine regimen after proven exposure; safety of the vaccine regimen; patient follow-up after PEP; a wide range of patient types; and cost-effectiveness compared to other PEP regimens.

A variety of vaccination schedules have been recommended and altered over time, based in part on improved vaccine immunogenicity and clinical experience. As more potent vaccines were developed, it was possible to reduce the number of doses recommended for PEP [21,35–37]. It has been proven that ID PEP is capable of achieving comparable immune responses to IM PEP while using less vaccine and thus reducing the cost of PEP [38]. Reducing the duration and the number of doses required for PEP, without increasing risk of disease, will not only lower the direct costs (less

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vaccine and fewer consumables used), it will also reduce the number of vaccination sessions required, thus lowering indirect costs (repeated travel, accommodations, and loss of income) [31,39].

Real-time rabies research in exposed patients is like no other. Although rabies virus (RABV) transmission after a bite from a rabid animal is inconstant, once clinical signs are evident death is almost certain. Therefore, WHO recommends that every patient exposed to a suspect rabid animal should seek treatment [40]. The risks associated with rabies transmission proscribe controlled clinical trials for new vaccines or regimens compared to established ones, considering imperfect cleansing and antisepsis or rabies immunoglobulin (RIG) infiltration of wounds, as is often the case in developing countries, especially rural areas [31,39].

Below, we examine methodological alternatives and points to consider for evaluation of a new vaccine or regimen. It is important to remember that only CCEVs with a potency of ≥2.5 International Units (IU) per IM dose are considered in this paper [40]. It is understood that clinical studies should be conducted only after Phase I studies have ascertained safety in healthy volunteers [41].

4. Serological studies

Serological studies can be conducted using recommended protocols and at little or no risk to human volunteers (efficacy studies) or patients bitten by a suspect or proven rabid animal (effectiveness studies). Seroconversion after vaccination is regarded as evidence that a patient will produce neutralizing antibody to rabies virus. Neutralizing antibody is recognized as being a key factor in protecting an exposed patient from developing rabies [42]. A serological titer of ≥0.5 IU by day 14 post-vaccination is considered evidence that a patient has responded immunologically after rabies vaccination. In order to prove that the antibody being analyzed is "neutralizing" rather than simply "binding", a neutralizing assay is used to assess the presence of antibody after vaccination. The two neutralizing assays that are routinely used and recommended by WHO are the Rapid Fluorescent Focus Inhibition Test (RFFIT) and the Fluorescent Antibody Virus Neutralization Test (FAVN). The height of the peak in antibodies is not an established proxy for the duration of response and may be clinically irrelevant. Several clinical studies have reported a rapid anamnestic response post-booster many years to decades after PreP or PEP was initially administered indicating that memory cells after primary vaccination (PreP or PEP) are very long lasting [43–47]. In addition, the primary objective in administering PEP to an exposed patient is to protect against disease as soon as is physiologically possible and not to maintain a measurable antibody titer for decades in the event that another exposure occurs.

Serological studies are only one part of the overall requirements for adopting a new vaccine or regimen. In moving from the Thai Red Cross (TRC) ID PEP regimen (2-2-2-0-2) to the Institute Pasteur of Cambodia (IPC) ID PEP regimen (2-2-2), more clinical data were evaluated [4,48].

5. Clinical proof of effectiveness

5.1. Randomized clinical trials

Randomized clinical trials (RCTs) in patients with potential or confirmed exposure to RABV are generally considered to bring the strongest proof of clinical effectiveness [49]. It is critical that all clinical trials undertaken adhere to good clinical practice (GCP) including ethical approval and informed consent and never against placebo in rabies PEP trials [50]. RCTs randomly allocate patients to the established or new intervention group, optimally blinding patients and clinicians to treatment assignment. From a methodological standpoint, patients and clinicians can be blinded to the vaccine being used but not blinded to the regimen used if the number of doses or volume is different. More importantly, RCTs may not be the best solution to provide first proof of noninferiority of new rabies vaccines or regimens, for ethical reasons, if an approved regimen is already effective against such a lethal disease [51,52]. The proposed new regimen must have an established comparator vaccine and regimen. Whether any new regimen evaluation should include RIG for all patients or RIG only as available in the country remains a hotly debated question [53,54]. All clinical trials should be registered at the website https://clinicaltrials.gov/.

5.2. Case-control studies

Case-control studies offer powerful and cost effective study designs [49]. They would however, require the comparison between cases and one or several controls, examining the association of rabies deaths with one or the other vaccine regimens. Unless conducted by multicenter collaborative studies in noncompleters, this may mean that the new vaccine or proposed regimen needs to be adopted upstream of the study. A case-control study therefore cannot serve to justify initial implementation, although it may be useful as part of downstream confirmation studies.

5.3. Observational patient cohorts

At present, observational data may be the most convincing and ethical method by which to undertake the evaluation of rabies vaccines or changes in PEP regimens, before an RCT can be conducted. With some methodological precautions, cohort studies can bring a level of confidence in the result that can match many RCTs [49]. Some studies may be conducted on existing data and records, i.e. "natural experiment" studies among noncompleters which are a very important source of data, especially in patients who did not complete PEP protocols for personal reasons or due to financial or geographical constraints [48]. It is therefore highly recommended to establish an electronic database to document consecutive patients seeking care, recording wound, biting animal status and patient contacts. An RCT can be performed *a posteriori*, after the adoption of a new regimen to verify efficacy and safety. Such studies would require significant *ad hoc* funding to be conducted on these routinely collected data, and more so in the case of a randomized controlled trial.

5.4. Operational aspects

In theory, all mammals can transmit rabies but up to 99% of all human rabies cases occur as a result of exposure to infected dogs [4]. Therefore, it is logical that studies standardize exposure and the highest transmission risk by examining severe (Category III) dog bites alone. Exposure to rabies can be confirmed by virological testing in the biting dog after it has been humanely euthanized or died [55]. As part of a validation study, it is of great value to prove that the biting animal is confirmed to be rabid by a reliable laboratory.

Evaluations, whether clinical or serological, provide the most valuable information when conducted in real-life patients and not just in healthy young subjects. By selecting a real-life patient cohort that includes participants of different ages and sex it may be possible to determine if there is a variation in the immune response in patients with varying body-mass indexes [56,57]. Pregnant women and patients with co-morbidities or treatments should not be excluded [58–62]. Several simple tools must be routinely implemented for patient safety as well as research. An integrated vigilance system must be implemented for rabies, especially

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after the adoption of a new regimen or vaccine. Patients should be contacted six months or more after receiving PEP to assess vaccine effectiveness.

5.5. Sample size

The sample size and duration of the trial must be adequately justified according to the endpoints considered. The study power should be computed before the study, based on the number of patients with Category III exposure to confirmed rabies dogs and expected deaths. Patients exposed to suspect rabid dogs will help to evaluate real-life situations but it is important for validation studies to include sufficient patients that have been exposed to confirmed rabid dogs. In past evaluations of new vaccine regimens, 100 patients have been included. This number appears to be satisfactory but may fall short of the number of patients to be clinically evaluated if it is understood that the number of rabies deaths that will occur despite timely and adequate PEP may be in the order of 1 per 1000 [48]. Once the results are recorded, they should be submitted for publication in a refereed journal.

Studying the effectiveness of a newly proposed PEP regimen is a necessity in order to prove that patients exposed to proven rabid animals will be protected from clinical rabies. Clinical outcome should be survival at 6 months at minimum, by which time 68% of rabies deaths would have occurred without PEP intervention [A. Tarantola, personal data]. It is preferable that follow-up should extend to 12 months after PEP was initiated by which time 93% of all deaths will have occurred without PEP intervention. If any rabies-suspected death occurs, it should be thoroughly and rigorously investigated and include: vaccine lot quality; cold chain verification; type and anatomical site of wound; rabies confirmation or careful verbal autopsy. If referred patients have died, verbal autopsies have been reliably used to differentiate (especially furious) rabies from other deaths and can be readily undertaken in the community or in hospitals [63]. An independent panel should conduct any required investigation/assessment. Results should be expressed as a percentage of rabies deaths in each group.

Bayesian and modeling approaches may be useful to estimate vaccine effectiveness when the number of events (rabies deaths) are rare [64]. Associations can be measured between outcome and risk factors at the individual, collective and geographical level. A nonparametric unilateral statistical test can be used when evaluating an abridged regimen against an established one. Logistic regression is used to estimate the association between the new regimen and rabies deaths after adjustment for other variables in patients exposed to confirmed rabid dogs. In studies in patients bitten by rabies-suspected dogs, an unknown number of patients will be bitten by sick dogs but not truly exposed to rabies. In this case, a zero-inflated negative binomial regression may be used [65]. Analyses could further document vaccine effectiveness against expected deaths and historical data.

5.6. Study methods and goals

Fig. 1 summarizes a proposed strategy to guide the evaluation of new CCEVs or new regimens. There have been numerous reliable clinical data indicating that serological data are an excellent indicator of immunogenicity and production of memory cells [47,66–68]. In consideration of these data, testing a different CCEV in a regimen approved by WHO, can rely on serological studies alone. For example, the new IPC regimen was evaluated using Vero cell-based vaccine and if a different WHO-prequalified rabies vaccine is to be evaluated, serological studies would suffice. There would need to be more evidence than serological data, however, for rabies vaccines that are not based on cell culture technology or if a different route of administration were used. In this case, serological studies in healthy volunteers should precede a RCT, and be conducted according to guidelines outlined above. Strict integrated vigilance systems to periodically review and evaluate the accumulated study data for participant safety would enable early termination of the trial should an excess of number of deaths be detected.

5.7. Cost-effectiveness

New vaccine regimens should add a benefit to established regimens. Clinical trials are expensive and time consuming and therefore a careful analysis of the benefits to be gained in evaluating a new regimen is of great importance. There is no point in investing

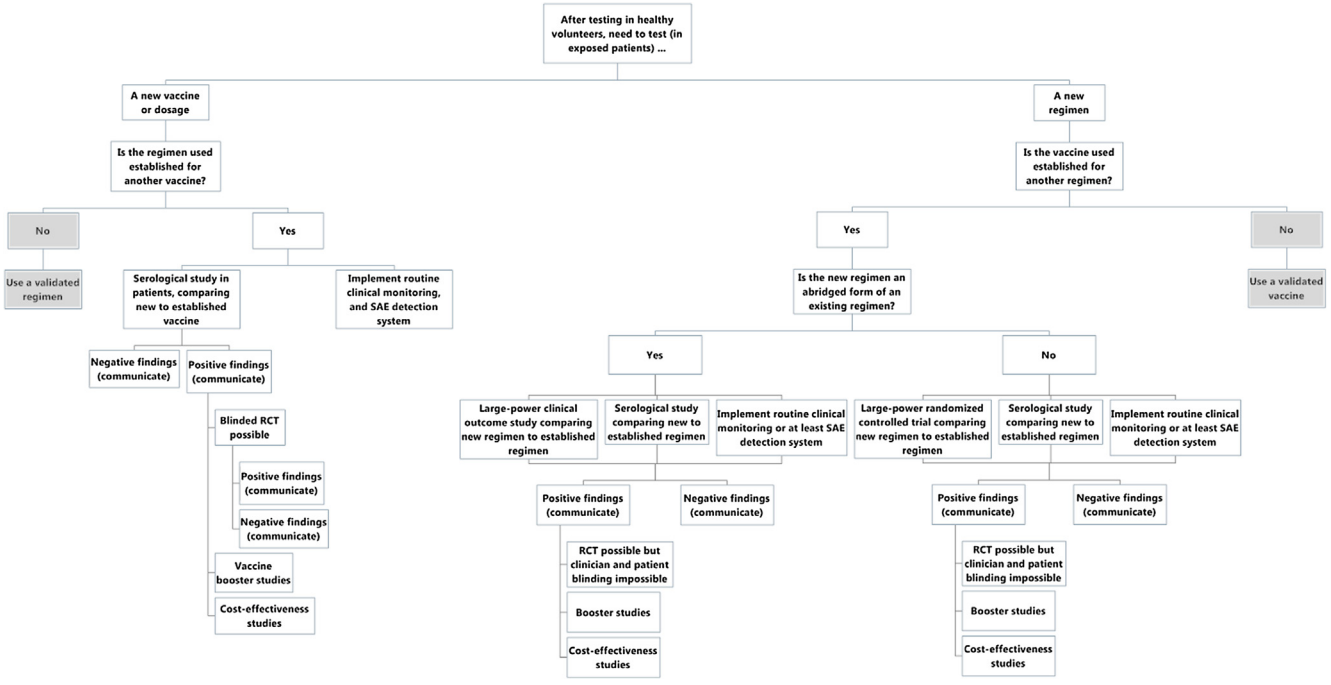


Fig. 1. Protocol for evaluation of a new vaccine or post-exposure prophylaxis regimen. RCT: Randomized Clinical Trial; SAE: Serious Adverse Event.

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time, energy and money in conducting clinical trials with no expected gain in protecting human health. Cost-effectiveness studies, including direct and indirect costs, prior to initiating a new study, will help determine if a clinical trial to test a new regimen is worthwhile.

6. Conclusions

Existing vaccine regimens for rabies PEP are close to 100% effective and WHO-prequalified vaccines are highly effective. The expected number of rabies deaths in patients receiving PEP after a confirmed rabies exposure is fortunately extremely low. As PEP regimens are reduced to one week and only a few ID doses, low-hanging fruit in terms of comparative effectiveness may have been picked. Unless new worldwide shortages lead to situations where no fatalities among vaccine noncompleters are documented, and unless revolutionary new techniques or biomarkers such as *in situ* rabies RNA replication can be assessed, the evaluation of further abridged regimens, future vaccines or new administration routes will likely require serological studies followed by clinical studies or trials in much larger numbers of exposed patients. An internationally-standardized PEP questionnaire with a minimal set of variables using common definitions would help aggregate data on a sufficient number of patients to conduct an observational or nested case-control study. This can only be achieved through international networking under the auspices of WHO with the help of international funders, using standardized tools and case definitions.

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Conflict of interest

All of the authors of this manuscript declare that they have NO Conflicts of interest to declare.

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