Pre-exposure rabies prophylaxis: a systematic review

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Objective To review the safety and immunogenicity of pre-exposure rabies prophylaxis (including accelerated schedules, co-administration with other vaccines and booster doses), its cost–effectiveness and recommendations for use, particularly in high-risk settings.

Methods We searched the PubMed, Centre for Agriculture and Biosciences International, Cochrane Library and Web of Science databases for papers on pre-exposure rabies prophylaxis published between 2007 and 29 January 2016. We reviewed field data from pre-exposure prophylaxis campaigns in Peru and the Philippines.

Findings Pre-exposure rabies prophylaxis was safe and immunogenic in children and adults, also when co-administered with routine childhood vaccinations and the Japanese encephalitis vaccine. The evidence available indicates that shorter regimens and regimens involving fewer doses are safe and immunogenic and that booster intervals could be extended up to 10 years. The few studies on cost suggest that, at current vaccine and delivery costs, pre-exposure prophylaxis campaigns would not be cost-effective in most situations. Although pre-exposure prophylaxis has been advocated for high-risk populations, only Peru and the Philippines have implemented appropriate national programmes. In the future, accelerated regimens and novel vaccines could simplify delivery and increase affordability.

Conclusion Pre-exposure rabies prophylaxis is safe and immunogenic and should be considered: (i) where access to postexposure prophylaxis is limited or delayed; (ii) where the risk of exposure is high and may go unrecognized; and (iii) where controlling rabies in the animal reservoir is difficult. Pre-exposure prophylaxis should not distract from canine vaccination efforts, provision of postexposure prophylaxis or education to increase rabies awareness in local communities.

Introduction

Rabies is a preventable yet fatal disease that is responsible for approximately 59 000 deaths each year.1 However, widespread underreporting of rabies cases means that the actual number of deaths is likely to be higher. Poor and rural populations are disproportionately affected, with the majority of deaths occurring in children younger than 15 years in Asia and Africa.2 Ninety-nine per cent of human rabies cases result from dog bites and, once symptoms begin, the disease is almost invariably fatal.3 Human rabies is preventable through canine vaccination to eliminate rabies at its source or by administering rabies vaccines and immunoglobulin following bites, scratches or saliva exposure from suspected rabid mammals (i.e. postexposure prophylaxis).4

Another preventive strategy is pre-exposure prophylaxis, which involves giving a series of intramuscular or intradermal injections of rabies vaccine to prime the immune system. This enables fast recall of memory immune responses once a person is re-exposed to the virus.4 Moreover, people who have received pre-exposure prophylaxis require fewer doses of postexposure rabies vaccine and can be treated without rabies immunoglobulin, which is costly and difficult to procure.4 Although preventing rabies in dogs is the most cost-effective way of preventing human rabies deaths, pre-exposure prophylaxis is valuable for people at a high disease risk,5 particularly in areas where controlling disease in the animal reservoir is difficult or has not been implemented and in areas where access to postexposure prophylaxis and rabies immunoglobulin is unreliable or nonexistent. National pre-exposure prophylaxis programmes for high-risk populations have been implemented in Peru and the Philippines.6,7

In 2010, a World Health Organization (WHO) position paper on rabies vaccines called for studies on the feasibility, cost–effectiveness and long-term impact of incorporating vaccines derived from cell culture or embryonated eggs into immunization programmes for children where canine rabies is a public health problem.8 The paper also made recommendations on pre-exposure prophylaxis regimens and on the frequency of booster vaccinations and serological surveillance for at-risk individuals, such as veterinarians. The aim of this study was to review the scientific literature published between 2007 and 2016, as well as field data, to assess the current use and cost–effectiveness of pre-exposure rabies prophylaxis (excluding travel vaccines), particularly in children and in high-risk settings, in the context of recommendations made in the 2010 WHO rabies vaccine position paper on pre-exposure prophylaxis and booster vaccine administration.

Abstracts in العربية, 中文, Français, Русский and Español at the end of each article.

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Methods

Literature search

Our literature review was intended as an update of the review of the evidence on pre-exposure prophylaxis carried out for the 2010 WHO rabies vaccine position paper. Our search was conducted according to preferred reporting items for systematic reviews and meta-analyses guidelines. We searched the PubMed, Centre for Agriculture and Biosciences International, Cochrane Library and Web of Science databases for papers on pre-exposure rabies prophylaxis published between 2007 and 29 January 2016 (Fig. 1) using the search string: “rabies” AND “pre-exposure” AND (“prophylaxis” OR “vaccin*”). We started at 2007 to include studies published after completion of the review for the WHO position paper. Additional references were obtained from citations in relevant publications. We excluded studies that assessed: (i) postexposure prophylaxis; (ii) pre-exposure prophylaxis in children; (iii) the cost-effectiveness of pre-exposure prophylaxis; (iv) accelerated or revised pre-exposure prophylaxis regimens; or (v) booster vaccination recommendations. Studies that assessed the cost of pre-exposure prophylaxis and its use in children were included regardless of publication date.

Field data

We reviewed field data from completed and ongoing pre-exposure prophylaxis campaigns in Peru and the Philippines. In Peru, the campaigns targeted people living in remote areas who were at risk of contracting rabies from vampire bats, whereas in the Philippines they targeted children at risk of dog-transmitted rabies.

Peru

In Peru, vampire bats are a common source of rabies: the life-time risk of a bat bite in rural Amazon basin populations is reported to be 41 to 88%. In 2011, Peru began a mass pre-exposure prophylaxis vaccination campaign that targeted people in Condorcanqui and Bagua Provinces at a high risk of rabies from vampire bats. The risk was regarded as high in these provinces because: (i) bat bites were common; (ii) there was evidence of rabies in circulation; (iii) housing conditions increased vulnerability; (iv) protective measures among the population were lacking; (v) tools for vector control were lacking; and (vi) the remote location of villages delayed health service responses. The campaign involved administering three intramuscular doses of human diploid cell or purified Vero cell vaccine on days 0, 7 and 28. Villages were prioritized to receive the intervention by classifying their epidemiological risk using the following variables: (i) the endemicity of rabies; (ii) the number of human rabies cases within the previous 6 months; (iii) the number of livestock rabies cases within the previous 6 months; (iv) the frequency of vampire bat bites (where there was bite surveillance); (v) history of postexposure prophylaxis; and (vi) important, recent ecological changes, such as an increase in the population, a change in the feeding habits of vampire bats, illegal mining or deforestation. Among villages with a history of postexposure prophylaxis interventions, priority was given to those in which the intervention took place more than 1 year previously, those where a low percentage of the population had received postexposure prophylaxis and those close to the site of a recent outbreak or of documented circulation of the rabies virus.

Philippines

In the Philippines, pre-exposure rabies prophylaxis is recommended as an additional intervention for high-risk
individuals, such as children and people at occupational exposure. In 2007, the Philippine Government implemented a Department of Health recommendation that free routine pre-exposure prophylaxis should be provided for school children aged 5 to 14 years who are living in high-risk areas. To be included an area had to have: (i) an incidence of human and canine rabies above the national average; (ii) an incidence of animal bites above the national average; (iii) no or low canine vaccination coverage, which was defined as less than 30% coverage of the estimated dog population; and (iv) limited access to postexposure prophylaxis, for example, due to geographical isolation, inadequate treatment facilities or poverty. Schoolchildren were targeted because almost 50% of all rabies exposure in the Philippines occurs in children younger than 15 years. Child deaths due to rabies are associated with poverty and, where postexposure prophylaxis is available, with limited or delayed access to health services. The rationale for pre-exposure prophylaxis was that: (i) may protect children who do not receive postexposure prophylaxis, for example, after unremarked exposure (i.e. if their antibody titre at exposure is ≥ 0.5 IU/mL); (ii) may protect patients when postexposure prophylaxis is delayed; (iii) accelerates antibody responses to postexposure prophylaxis; and (iv) reduces the cost of postexposure prophylaxis by removing the need for rabies immunoglobulin and reducing the number of postexposure prophylaxis doses required from 8 to 2 (Table 1). The pre-exposure prophylaxis schedule consisted of administering three intradermal doses of purified Vero cell or chick embryo cell vaccine on days 0, 7 and 28.

Results
The systematic review of the literature identified 31 publications on pre-exposure rabies prophylaxis that met inclusion criteria (Table 2).

Safety and immunogenicity in children

Literature search
The search identified 11 studies on the safety and immunogenicity of pre-exposure prophylaxis in children aged 2 months to 15 years, including two published before 2007 (Table 3). All found it safe and immunogenic in both infants and children. Three found it safe and immunogenic for up to 5 years when given in combination with other childhood vaccines such as those against Japanese encephalitis, diphtheria, tetanus, pertussis and poliomyelitis (both oral and inactivated vaccines). Pre-exposure prophylaxis programmes

| Exposure category | Following pre-exposure rabies prophylaxis | Without pre-exposure rabies prophylaxis |
|-------------------|------------------------------------------|----------------------------------------|
| Category II       | Rabies vaccine 1 intradermal dose on days 0 and 3 (i.e. 2 doses) | Rabies vaccine 2 intradermal doses on days 0, 3, 7 and 28 (i.e. 8 doses) |
| Category III      | Rabies vaccine 1 intradermal dose on days 0 and 3 (i.e. 2 doses) | Rabies vaccine 2 intradermal doses on days 0, 3, 7 and 28 (i.e. 8 doses) |

* Category-II exposure is defined as nipping of uncovered skin, minor scratches or abrasions without bleeding and category-III exposure, as single or multiple transdermal bites or scratches, contamination of mucous membranes with saliva from licks, licks on broken skin, exposures to bats.

Philippines
By April 2010, the routine pre-exposure prophylaxis immunization programme had achieved an average coverage of 47.25% in the target population: 21,637 high-risk children in 31 schools in seven regions were immunized (unpublished data, 2010). In the town of Cabusao, 188 schoolchildren received at least one vaccine dose (i.e. 86% of those eligible) and 90% of the 188 completed the pre-exposure prophylaxis regimen. Subsequently, 3.5% received postexposure prophylaxis within 3 years following suspected exposure. The programme was stopped in 2011 because a large increase in rabies exposure led to a vaccine shortage and priority was given to the immunization of people involved in canine vaccination campaigns. Pre-exposure prophylaxis of schoolchildren was planned to restart in 2016.

Cost-effectiveness

Literature search
Few recent studies have assessed the cost-effectiveness of pre-exposure rabies prophylaxis. One study estimated...
the annual global direct cost of administering postexposure rabies prophylaxis at 1.7 billion United States dollars (US$), plus an additional US$ 1.3 billion in lost income. In a cost assessment of pre-exposure prophylaxis, researchers showed that it would be cost-neutral if 1% of children were exposed to rabies each year and if the price of the vaccine did not exceed US$ 1.32 per dose, once the cost of postexposure prophylaxis boosters required after exposure was taken into account. The acceptable vaccine cost increased in proportion to the incidence of rabies. In a Thai study, the estimated cost of pre-exposure prophylaxis for children ranged from US$ 2.00 to 7.25 per child depending on the schedule and vaccine used: there was an additional cost of US$ 18.00 to 23.50 per child if postexposure prophylaxis was required later. Pre-exposure prophylaxis became cost-comparable to the least expensive postexposure schedule (i.e. intradermal immunization without rabies immunoglobulin) when the annual risk of a dog bite was approximately 23%. If equine or human rabies immunoglobulin was used with postexposure vaccines, pre-exposure prophylaxis was cost-comparable when the annual risk of a dog bite was 7% or 3%, respectively. As over 30% of Thai children had been bitten by a dog by the age of 15 years, it was estimated that the actual incidence of dog bites in the population of central
Table 3. Pre-exposure rabies prophylaxis in children, systematic review of the literature, 1989–2016

| Reference          | Age group (years) | Vaccine | Vaccination route | Regimen | Antibody titre (IU/mL)* | Comments                                                                 |
|--------------------|-------------------|---------|-------------------|---------|------------------------|-------------------------------------------------------------------------|
| Lang et al.⁴²       | < 1               | PVRV    | Intramuscular     | 2 doses at 2 and 4 months of age | 20.1 | > 1 (assessed after 5 years) | Combined with vaccination against diphtheria, tetanus, pertussis and polio (inactivated vaccine)²³⁴⁵ |
| Vien et al.³⁶ and   | 1–1.5             | PCECV   | Intramuscular or  | 1 dose on days 0, 7 and 28; or 1 dose on days 0 and 28 | 15–41 (intramuscular); 4.1–8.5 (intradermal) | Combination with vaccination against Japanese encephalitis; antibody titres were higher following intramuscular than intradermal administration |
| Lang et al.²⁶       | 2–15              | PCECV   | Intramuscular or  | 1 dose on days 0, 7 and 28 | 4.7–47 | ND | Antibody titres were higher following intramuscular than intradermal administration |
| Lumbiganon et al.¹²| 2–15              | PCECV   | Intramuscular or  | 1 dose on days 0, 7 and 28; or 1 dose on days 0 and 28 | > 2 | 8.9–27.3 (assessed after ≥ 1 year) | All children had an antibody titre > 0.5 IU/mL within 14 days of the booster dose, regardless of the time interval and the number of doses initially received |
| Kamoltham et al.¹¹ | 5–8               | PCECV   | Intradermal       | 1 dose on days 0, 7 and 28; or 1 dose on days 0 and 28 | ND | ND | None |
| Kamoltham et al.²²  | 5–10              | PCECV   | Intradermal       | 1 dose on days 0, 7 and 21 | ND | ND | None |
| Ravish et al.³⁵     | 6–13              | PVRV or | Intramuscular     | 1 dose on days 0, 7 and 28 | 12.2–14.5 | ND | None |
| Pengsaa et al.³⁶    | 12–79             | HDCV or | Intramuscular     | 1 dose on days 0, 7 and 28; or 1 dose on days 0 and 28 | 0.1–48 (assessed after 1 year) | 51 (3 doses); 13 (2 doses) – both assessed after 1 year | This review of > 1200 children treated over > 25 years concluded that the vaccine was safe and immunogenic, whether given intramuscularly or intradermally |
| Malerczyk et al.¹²  | < 15              | PCECV   | N/A               | N/A                 | N/A | N/A | None |

HDCV: human diploid cell vaccine; N/A: not applicable; ND: not determined; PCECV: purified chick embryo cell vaccine; PVRV: purified Vero cell rabies vaccine.

* The values are either geometric means or ranges, as appropriate.

Although this study was published before 2007, it has been included because the results are still relevant.

Thailand was only 2.3% per year. Consequently, pre-exposure prophylaxis with currently licensed vaccines would not be cost-effective in this setting.

**Peru**

The cost of the mass pre-exposure prophylaxis campaign was estimated to be US$ 4 111 000, of which US$ 3 560 000 was the cost of the vaccine. The average cost per immunized person was US$ 69. By assuming that the risk of rabies was constant (i.e. the rabies virus remained in circulation and the risk of a bat bite was unchanged) and that, each year, rabies caused 20 deaths per 50 000 people in Condorcanqui Province without pre-exposure prophylaxis, we estimated the cost of pre-exposure prophylaxis to be US$ 205 000 per life saved after the first year.⁶ After 5 years, the cost decreased to US$ 41 000 per life saved. This amount is comparable to the cost of treating one rabies-infected individual, including the cost of transport, laboratory diagnosis and hospitalization. The use of intradermal vaccinations would reduce the vaccination cost by 80%. However, intramuscular vaccination continues to be used in Peru because: (i) there is no shortage of rabies vaccine in the country; (ii) staff have not been trained in the multiple uses of rabies vaccine vials for intradermal administration; and (iii) the national authorities elected to use the intramuscular route to minimize the risk of errors in vaccine administration.

**Philippines**

Pre-exposure prophylaxis with three doses of purified Vero cell or chick embryo cell vaccine was estimated to cost US$ 4.77 per patient (unpublished data, 2015; Table 5). For a patient weighing between 26 and 50 kg, pre-exposure prophylaxis reduced the cost of post-exposure prophylaxis by up to 38% following category-II exposure (i.e. “nibbling of uncovered skin, minor scratches or abrasions without bleeding”)⁷ and by up to 85% following category-III exposure (i.e. “single or multiple transdermal bites or scratches, contamination of mucous membranes with saliva from licks, licks on broken skin, exposures to bats”), after the cost of pre-exposure prophylaxis was taken into account.

**Accelerated or revised regimens**

Nine studies investigated the safety and immunogenicity of an accelerated or revised pre-exposure prophylaxis regimen (Table 6; available at http://www.who.org.)
Booster vaccinations

Four studies investigated recommendations on booster vaccines (Table 7; available at http://www.who.int/bulletin/volume/95/03-16-173039). They concluded that: (i) the interval between booster vaccinations could be extended by up to 10 years;16 (ii) serological surveillance or booster vaccination after 1 year is advisable for people in high-risk occupations;29 (iii) serological testing after the third intramuscular or intradermal pre-exposure prophylaxis dose is unnecessary;16 and (iv) healthy subjects may not require postexposure prophylaxis boosters on re-exposure to rabies for up to 3 months after pre-exposure or previous postexposure prophylaxis.30

Discussion

Several studies demonstrated that pre-exposure rabies prophylaxis was safe and immunogenic in children and could be co-administered with other childhood vaccines.31,32,27,28,34,37,40 In addition, it could be given with the Japanese encephalitis vaccine in both adults and children. In most African countries pre-exposure rabies prophylaxis is unlikely to be included in the expanded programme on immunization because of competing priorities and because postexposure prophylaxis would still be required following suspected contact. Nevertheless, expert consultations advocate vaccination for people in remote, high-risk areas,6,19,36 and national pre-exposure prophylaxis programmes have been implemented in Peru and the Philippines.57 In Peru, the programme was successful in preventing child deaths due to bat rabies in high-risk areas, which demonstrates the value of targeted pre-exposure prophylaxis in places where controlling disease in the animal reservoir is challenging.11 Although it can be difficult for individuals to recall the date of pre-exposure prophylaxis, this does not undermine its usefulness for saving human lives in situations where exposure is uncertain or there is limited access to biologicals. Vaccination certificates are often treasured and kept safe and, in Peru, the identification and recording of vaccinated individuals has improved nationally.

Pre-exposure rabies prophylaxis is also associated with cost savings because fewer postexposure vaccinations and no rabies immunoglobulin are required following suspected exposure. However, the few studies that assessed costs suggest that community vaccination at current vaccine and delivery costs would not be cost-effective in most situations.1,17,30,43 Preliminary studies on accelerated or revised regimens indicate that 1-week or even single-day regimens may be as effective as the recommended 3- to 4-week regimen: shorter treatment and fewer doses would make treatment simpler and less expensive.

The development of a more immunogenic rabies vaccine that provides life-long immunological memory with a single dose and that can be preserved at ambient temperatures, thereby eliminating the need for a cold chain, would make pre-exposure prophylaxis simpler and more cost-effective. The ideal vaccine would induce an antibody titre that remained above 0.5 IU/mL for decades and would protect people who fail to receive prompt booster immunization following exposure. In animal studies, attempts have been made to increase the current vaccine’s immunogenicity using adjuvants,44,46 genetic manipula-

Table 4. Bat bites by region, Peru, 2009–2013

| Region   | No. of bat bites reported | % of all reported bat bites |
|----------|---------------------------|----------------------------|
|          | 2009 | 2010 | 2011 | 2012 | 2013 | Total |                   |
| Amazonas | 1 576 | 5 714 | 2 145 | 1 733 | 833 | 12 001 | 59.2               |
| Cusco    | 50   | 169  | 36   | 441  | 20  | 716   | 3.5                |
| Loreto   | 1 122 | 856  | 1 458 | 1 380 | 590 | 5 406  | 26.7               |
| Junin    | 119  | 415  | 179  | 142  | 29  | 884   | 4.4                |
| Others   | 465  | 224  | 295  | 229  | 41  | 1 254  | 6.2                |
| All      | 3 332 | 7 378 | 4 113 | 3 925 | 1 513 | 20 261 | 100.0              |
tion,46,47 adenovirus vectors derived from chimpanzee viruses47 and attenuated measles viruses,48,49 which would enable it could be beneficial in: (i) remote vaccination areas; or (iii) places where controlling rabies in the animal reservoir is difficult and the risk of human exposure is high, such as in the Amazon basin where bat rabies is endemic. It is important that staff involved in canine rabies control

Table 5. Cost of postexposure rabies prophylaxis, the Philippines, 2007

| Exposure category | Cost in US$ per patient (treatment specifics) | Savings per patient (weight range: 26–50 kg) who had pre-exposure prophylaxis | US$ | (%) |
|-------------------|---------------------------------------------|-------------------------------------------------------------------------------------------------|-----|-----|
| Patients who had pre-exposure prophylaxis | 12.76 (8 intradermal doses of PCECV or PVRV at US$ 1.59 per dose; no RIG) | 4.80 | 38 |
| Category II patients (weight range: 26–50 kg) who did not have pre-exposure prophylaxis | 51.76 (8 intradermal doses of PCECV or PVRV at US$ 1.59 per dose; 2 vials of ERG at US$ 19.52 per vial) | 43.80 | 85 |
| Category III | | |

ERG: equine rabies immunoglobulin; PCECV: purified chick embryo cell vaccine; PVRV: purified Vero cell rabies vaccine; RIG: rabies immunoglobulin; US$: United States dollar.

Notes: The percentage saving is the cost saving divided by the cost of postexposure prophylaxis in a patient who did not have pre-exposure prophylaxis × 100. Prices were converted at a rate of US$ 1 per 47.65 Philippine pesos. The cost of postexposure rabies prophylaxis was the cost at bite centres taking part in a national pre-exposure rabies prophylaxis programme for high-risk populations, which was lower than in hospitals and private bite centres. The cost of pre-exposure prophylaxis was US$ 4.77 per patient (US$ 1.59 per intradermal dose × 3). In calculating savings, the cost of pre-exposure prophylaxis was taken into account.

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Résumé
Prophylaxie pré-exposition à la rage: un examen systématique
Objectif Analyser l’innocuité et l’immunogénicité de la prophylaxie pré-exposition à la rage (notamment le schéma de vaccination accéléré, la co-administration d’autres vaccins et les injections de rappel), son rapport coût-efficacité ainsi que les recommandations d’utilisation, en particulier dans les zones à haut risque.
Méthodes Nous avons recherché, dans les bases de données de PubMed, du Centre for Agriculture and Biosciences International, de la Cochrane Library et de Web of Science, des articles sur la prophylaxie pré-exposition à la rage publiés entre 2007 et le 29 janvier 2016. Nous avons aussi analysé des données de terrain provenant de campagnes pour la prophylaxie pré-exposition menées au Pérou et aux Philippines.
Résultats La prophylaxie pré-exposition à la rage était sûre et immunogène pour les enfants et les adultes, même co-administrée avec les vaccins systématiques des enfants et le vaccin contre l’encéphalite japonaise. Les éléments disponibles indiquent que les programmes de vaccination plus courts ainsi que ceux comportant des doses plus faibles sont sûrs et immunogènes et que les intervalles de rappel pourraient aller jusqu’à 10 ans. Selon les rares études sur les coûts, en tenant compte du coût actuel des vaccins et de leur administration, dans la plupart des cas, les campagnes pour la prophylaxie pré-exposition ne seraient pas rentables. Même s’il a été recommandé d’appliquer une prophylaxie pré-exposition dans les populations à haut risque, seuls le Pérou et les Philippines ont mis en œuvre des programmes nationaux à cet égard. Dans l’avenir, des schémas de vaccination accélérés et de nouveaux vaccins pourraient en simplifier l’administration, à des prix plus abordables.
Conclusion La prophylaxie pré-exposition à la rage est sûre et immunogène et devrait être envisagée: (i) lorsque l’accès à la prophylaxie post-exposition est limité ou tardif; (ii) lorsque le risque d’exposition est élevé et pourrait passer inaperçu, et (iii) lorsqu’il est difficile de lutter contre la rage dans le réservoir animal. La prophylaxie pré-exposition ne doit pas empêcher les efforts de vaccination des chiens, la prophylaxie post-exposition ou la sensibilisation à la prévention de la rage dans les communautés locales.
количество доз безопасны, вызывают иммунный ответ и интервалы ревакцинации могут быть увеличены до 10 лет. Судя по результатам немногочисленных анализов расходов, при текущих затратах на вакцинацию применение имеющейся в настоящее время вакцины в кампаниях по доконтактной профилактике не было бы экономически эффективно в большинстве случаев. Хотя доконтактная профилактика рекомендуется для групп населения, подвергающихся высокому риску, соответствующие национальные программы были внедрены только в Перу и на Филиппинах. В будущем ускоренные курсы лечения и новые вакцины, возможно, позволят упростить выполнение вакцинации и повысить ее ценовую доступность.

Вывод Доконтактная профилактика бешенства безопасна, способна вызвать иммунный ответ и должна быть рекомендована: 1) когда доступ к постконтактной профилактике ограничен или предоставляется несоизмеримо; 2) когда риск заражения велик или может быть не распознан; 3) когда борьба с бешенством у животных-носителей затруднительна. Доконтактная профилактика бешенства не должна быть поводом для отказа от мероприятий по вакцинации собак, проведения постконтактной профилактики или информационно-просветительской работы для привлечения внимания местного населения к проблеме бешенства.

Resumen

Profilaxis pre exposición a la rabia: una revisión sistemática

Objetivo Analizar la seguridad y la inmunogenicidad de la profilaxis pre exposición a la rabia (incluidos programas acelerados, administración conjunta con otras vacunas y dosis de refuerzo), su rentabilidad y las recomendaciones de uso, especialmente en entornos de alto riesgo.

Métodos Se realizaron búsquedas en PubMed, el Centro Internacional de Agricultura y Ciencias Biológicas, la Biblioteca Cochrane y la base de datos de la Web of Science en busca de documentos sobre la profilaxis pre exposición a la rabia publicados entre 2007 y el 29 de enero de 2016. Se analizaron datos archivados de campañas de profilaxis pre exposición en Filipinas y Perú.

Resultados La profilaxis pre exposición a la rabia era segura e inmunogénica en niños y adultos, también cuando se administraba en conjunto con vacunas infantiles rutinarias y la vacuna de la encefalitis japonesa. Las pruebas disponibles indican que los regímenes más cortos y los que implican un menor número de dosis son seguros e inmunogénicos, y que los intervalos de refuerzo podrían ampliarse hasta 10 años. Los pocos estudios sobre el coste sugieren que, con los costes actuales de vacunación y suministro, las campañas de profilaxis pre exposición no serían rentables en la mayoría de las situaciones. A pesar de que la profilaxis pre exposición está destinada para poblaciones de alto riesgo, únicamente Filipinas y Perú han implementado los programas nacionales adecuados. En el futuro, los regímenes acelerados y las nuevas vacunas podrían simplificar el suministro y aumentar la accesibilidad.

Conclusion La profilaxis pre exposición a la rabia es segura e inmunogénica y debe tenerse en cuenta: (i) cuando el acceso a la profilaxis post exposición sea limitada o se retrasa; (ii) cuando el riesgo de exposición sea alto y pueda pasar desapercibido; y (iii) cuando sea complicado controlar la rabia en un reservo animal. La profilaxis pre exposición no debe apartar la atención de las vacunas caninas, el suministro de profilaxis post exposición o la educación para aumentar la concienciación sobre la rabia en comunidades locales.

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| Reference | Study type | No. of study participants | Vaccine | Vaccination route | Regimen | Antibody titre (IU/mL) | Comments |
|-----------|------------|---------------------------|---------|-------------------|---------|------------------------|----------|
| Kamoltham et al. | Randomized, open-label phase-II clinical trial | 703 | PCECV | Intradermal | (i) 0.1 mL on days 0 and 28; and (ii) 0.1 mL on days 0, 7 and 28 | ND | (i) 10.76 (GMT; range: 1.87–37); and (ii) 22.12 (GMT; range: 2.13–199) – both measured 14 days after receiving 0.1 mL PCECV booster vaccination on days 365 and 368 |
| Khawplod et al. and Khawplod et al. | Randomized, prospective | 96 and 52 | PVRV and PCECV | Intradermal and intramuscular | (i) 0.1 mL PVRV intradermally at two sites on days 0, 7 and 28; (ii) 0.1 mL PVRV intradermally at two sites on days 0, 3 and 7; (iii) 1.0 mL PVRV intramuscularly at one site on days 0, 3 and 7; (iv) 0.1 mL PVRV intradermally at two sites on day 0; (v) 0.1 mL PVRV intradermally at two sites on days 0, 3 and 7 and at one site on days 28 and 90; and (vi) 0.1 mL PCECV intradermally at two sites on days 0, 3 and 7 and at one site on days 28 and 90 | (i) 0.96 (GMT) on day 360; (ii) 1.12 (GMT) on day 360; (iii) 0.97 (GMT) on day 360; (iv) 0.41 (GMT) on day 360; (v) 5.84 (GMT) on day 28; and (vi) 5.96 (GMT) on day 28 | Seroconversion a occurred after booster vaccination with all regimens; the two studies used the same regimens and reported the same data |
| Mills et al. | Case series | 420 | HDCV | Intradermal | 0.1 mL at two sites on days 0 and 7 | > 0.5 in 94.5% of vaccinees on day 28 | ND | Seroconversion a occurred within 14 days of booster vaccination in all vaccinees who received two or three doses of pre-exposure prophylaxis |

Seroconversion a occurred within 14 days of booster vaccination in all vaccinees who received two or three doses of pre-exposure prophylaxis.
| Reference        | Study type                      | No. of study participants | Vaccine          | Vaccination route          | Regimen                                                                                                                                  | Antibody titre (IU/mL)                                                                 | Comments                                                                 |
|------------------|--------------------------------|---------------------------|------------------|----------------------------|----------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------|-------------------------------------------------------------------------|
| Khawplod et al.  | Abbreviated, prospective        | 109                       | PCECV            | Intradermal and intramuscular | (i) 0.1 mL intradermally on days 0, 7 and 21, followed by a 1.0 mL intramuscular booster on days 360 and 363; (ii) 0.1 mL intradermally on days 0, 7 and 21, followed by a 0.1 mL intradermal booster at four sites on day 360; (iii) 0.1 mL intradermally at two sites on day 0, followed by a 1.0 mL intramuscular booster on days 360 and 363; (iv) 0.1 mL intradermally at two sites on day 0, followed by a 0.1 mL intradermal booster at four sites on day 360; (v) 1.0 mL intramuscularly on day 0, followed by a 1.0 mL intramuscular booster on days 360 and 363; and (vi) 1.0 mL intramuscularly on day 0, followed by a 0.1 mL intradermal booster at four sites on day 360; | (i) 0.49 (NAb); (ii) 0.30 (NAb); (iii) 0.15 (NAb); (iv) 0.10 (NAb); (v) 0.08 (NAb); and (vi) 0.11 (NAb) – all measured before booster vaccination on day 360 | (i) 11.27 (NAb); (ii) 42.49 (NAb); (iii) 9.71 (NAb); (iv) 11.96 (NAb); (v) 10.13 (NAb); and (vi) 13.33 (NAb) – all measured 7 days after booster vaccination |
| Lau & Hohl      | Case series                     | 54                        | PCECV            | Intradermal                 | 0.1 mL at two sites on days 0 and 7                                                                                                   | > 0.5 in 94.4% of vaccinees on day 28                                           | Serocorversion* occurred within 7 days of booster vaccination for all regimens assessed |
| Wongsaroj et al. | Randomized, prospective         | 55                        | PVRV             | Intradermal and intramuscular | (i) 0.1 mL intradermally at two sites on days 0 and 21; and (ii) 0.5 mL intramuscularly on days 0, 7 and 21                         | (i) 4.51 (NAb); and (ii) 6.74 (NAb) – both measured on day 35                   | Serocorversion* occurred within 14 days of booster vaccination with both regimens |
| Jelinek         | Randomized, observer-blinded, multicentre | 661                      | PCECV            | Intramuscular               | (i) 1.0 mL on days 0, 7 and 28, with standard Japanese encephalitis vaccine regimen; (ii) 1.0 mL on days 0, 3 and 7, with accelerated Japanese encephalitis vaccine regimen; and (iii) 1.0 mL PCECV alone on days 0, 7 and 28 | > 0.5 in 97–100% of vaccinees on day 57                                          | Serocorversion* occurred in 97–100% of vaccinees by day 57                  |
| Brown et al.    | Cohort study                    | 12                        | PVRV (booster dose) | Intradermal                 | People with an antibody titre < 0.5 IU/mL following initial pre-exposure prophylaxis received one booster dose after 2 years to give a total vaccine dose ≥ 2 IU                                      | 0.18 (mean) before booster 17.33 (mean) after booster                           | Serocorversion* occurred in all vaccinees who received ≥ 2 IU of vaccine     |

HDCV: human diploid cell vaccine; GMT: geometric mean titre; NAb: neutralizing antibody; ND: not determined; PCECV: purified chick embryo cell vaccine; PVRV: purified Vero cell rabies vaccine.

*Seroconversion was defined as an antibody titre > 0.5 IU/mL.
### Table 7. Booster rabies vaccination recommendations, systematic review of the literature, 2007–2016

| Reference                  | Study type       | No. of participants | Vaccination regimen                                      | Antibody titre (IU/mL)                       | Conclusion                                                                 |
|----------------------------|------------------|---------------------|-----------------------------------------------------------|---------------------------------------------|---------------------------------------------------------------------------|
| Brown et al.16             | Retrospective    | 89                  | Intradermal pre-exposure prophylaxis                      | ≥0.5 after a mean of 5 years (range: 1–12)  | Intradermal pre-exposure prophylaxis with 0.6 mL of vaccine over three visits could extend the interval before booster vaccination to 10 years |
| Lim & Barkham,29 Cohort 1  | Retrospective    | 66                  | Three doses of PVRV pre-exposure prophylaxis              | >0.5 in 60.6% of vaccinees after 1 year     | Serological surveillance or a booster vaccination 1 year after primary pre-exposure prophylaxis is advised for people in high-risk occupations |
| Lim & Barkham,29 Cohort 2  | Retrospective    | 15                  | Four doses: three of pre-exposure prophylaxis and one booster dose given after a median of 10 years (range: 3–18) | >0.5 in 100% of vaccinees after a median of 10 years (range: 3–18) | Serological surveillance or a booster vaccination 1 year after primary pre-exposure prophylaxis is advised for people in high-risk occupations |
| Cunha et al.,18 Group 1    | Randomized       | 65                  | Intradermal pre-exposure prophylaxis                      | >0.5 in 97% of vaccinees after a mean of 10 days and >0.5 in 20–25% after a mean of 180 days | Serological testing after the third dose of pre-exposure prophylaxis is unnecessary* |
| Cunha et al.,18 Group 2    | Randomized       | 62                  | Intramuscular pre-exposure prophylaxis                    | >0.5 in 100% of vaccinees after a mean of 10 days and >0.5 in 63–65% after a mean of 180 days | Serological testing after the third dose of pre-exposure prophylaxis is unnecessary* |
| Sudarshan et al.,38 Group 1| Literature review| 577                 | Pre-exposure prophylaxis                                 | >0.5 in 100% after a mean of 3 months       | It may be safe not to administer postexposure prophylaxis in healthy individuals re-exposed to rabies within 3 months of pre-exposure or previous postexposure prophylaxis |
| Sudarshan et al.,38 Group 2| Literature review| 2795                | Postexposure prophylaxis                                 | >0.5 in 99.9% after a mean of 3 months     | It may be safe not to administer postexposure prophylaxis in healthy individuals re-exposed to rabies within 3 months of pre-exposure or previous postexposure prophylaxis |

PVRV: purified Vero cell rabies vaccine.

* This study did not follow up study participants 1 year after pre-exposure prophylaxis or simulate responses to postexposure prophylaxis.