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# A single center, open label study of intradermal administration of an inactivated purified chick embryo cell culture rabies virus vaccine in adults

Sergio Recuenco *, Eli Warnock, Modupe O.V. Osinubi, Charles E. Rupprecht [1]

*Rabies Program, National Center for High-Consequence Pathogens and Pathology, Centers for Disease Control and Prevention, Atlanta, GA, USA*

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ABSTRACT

In the USA, rabies vaccines (RVs) are licensed for intramuscular (IM) use only, although RVs are licensed for use by the intradermal (ID) route in many other countries. Recent limitations in supplies of RV in the USA reopened discussions on the more efficient use of available biologics, including utilization of more stringent risk assessments, and potential ID RV administration. A clinical trial was designed to compare the immunogenic and adverse effects of a purified chicken embryo cell (PCEC) RV administered ID or IM. Enrollment was designed in four arms, ID Pre-Exposure Prophylaxis (Pre-EP), IM Pre-EP, ID Booster, and IM Booster vaccination. Enrollment included 130 adult volunteers. The arms with IM administration received vaccine according to the current ACIP recommendations: Pre-EP, three 1 mL (2.5 I.U.) RV doses, each on day 0, 7, and 21; or a routine Booster, one 1 ml dose. The ID groups received the same schedule, but doses administered were in a volume of 0.1 mL (0.25 I.U.). The rate of increase in rabies virus neutralizing antibody titers 14–21 days after vaccination were similar in the ID and correspondent IM groups. The GMT values for ID vaccination were slightly lower than those for IM vaccination, for both naïve and booster groups, and these differences were statistically significant by *t*-test. Fourteen days after completing vaccination, all individuals developed RV neutralizing antibody titers over the minimum arbitrary value obtained with the rapid fluorescent focus inhibition test (RFFIT). Antibodies were over the set threshold until the end of the trial, 160 days after completed vaccination. No serious adverse reactions were reported. Most frequent adverse reactions were erythema, induration and tenderness, localized at the site of injection. Multi use of 1 mL rabies vaccine vials for ID doses of 0.1 was demonstrated to be both safe and inmunogenic.



## 1. Introduction

Since 1885, rabies vaccines have successfully prevented humans deaths after exposure to rabies virus [1]. Rabies vaccine is a critical component of modern post-exposure prophylaxis (PEP), which includes wound care and the infiltration of rabies immunoglobulin (RIG). When PEP is timely and properly administered, expected survivorship approaches 100% [2]. Maintaining the availability of rabies vaccines is a high public health priority given the extreme case fatality rate and global distribution of disease.

Worldwide, approximately 60,000 people die from rabies every year. While most human cases occur in Asia and Africa, likely due to poor access to PEP, cases in other regions confirms the persisting global rabies risk due to exposures to rabid dogs or wildlife [3].

In the United States, exposures to animal reservoirs such as raccoons, skunks, foxes, bats, and other suspect animals, including spillover to domestic animals, are common occurrences [4]. Human exposures to suspect rabid animals accounts for a high demand for vaccine. Human rabies vaccine supply is heavily dependent upon production. The vaccine industry monitors vaccine demand to maintain and project production of an adequate supply to satisfy market demands. Events such as upgrading production plants, product recalls, may affect industry flexibility to respond to sudden changes in demand. For example, from 2007 to 2009, such events led to a situation of limited supply of rabies vaccine in the United States, forcing the health care system to plan accordingly for a more efficient use of existing vaccine stocks, with focal risk assessment to guarantee that no exposed person would be left without critical vaccine, and reducing potential unnecessary

* Corresponding author at: Department of Preventive Medicine and Public Health, Facultad de Medicina "San Fernando", Universidad Nacional Mayor de San Marcos, Av. Grau 755, Lima, Peru.
*E-mail address:* sergio.recuenco@gmail.com (S. Recuenco).
[1] Current address: LYSSA LLC, Atlanta, GA, USA.

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use of existing supply [5]. The use of rabies vaccine was prioritized. Pre-exposure vaccination (Pre-EP) was restricted to first responders, such as those capturing suspect animals or personnel working in diagnostic laboratories. Other common uses of Pre-EP, such as vaccination of travelers, or of veterinary students, were temporally suspended. Moreover, PEP was provided only after risk assessment approval by state and local health departments. Vaccine requests orders from hospitals and other vaccine providers underwent approval by state health departments and CDC. Such restrictions were in place until June 2009, when vaccine supply was again restored.

Given the verge of a potential vaccine shortage, which was prevented successfully, alternatives were explored to increase efficiency of national rabies vaccine use. One proposed alternative considered the use of rabies vaccine administered intradermally. PEP regimens recommended by World Health Organization (WHO) include schedules for both intramuscular (IM), and intradermal (ID) administration of the rabies vaccine [6,7]. In the United States, there are two types of rabies vaccines licensed and available for use: purified chicken embryo cell vaccine (PCECV) and human diploid cell vaccine (HDCV). Both are licensed only for IM use. Under current ACIP recommendations, PEP includes human rabies immunoglobulin (HRIG) (20 IU per kilogram of body weight) and 1 ml of RV IM in the first visit and 3 more RV IM doses for days 3, 7 and 14 [2,8]. Intradermal RV administration was briefly licensed in the US from 1982, only for HDCV, and exclusively for Pre-EP, with three 0.1 ml vaccine doses [9]. The references to that use were removed from the ACIP recommendations by 2008, because intradermal presentation of HDCV was not longer available in the USA [2]. Additional schedules for administration recommended by WHO includes multisite RV ID doses [7]. Previous clinical trials on RV ID use in several countries focused mostly on PEP use. Demonstrated safety and immunogenicity were reported for both PEP and Pre-EP using standard a variety of investigational vaccination schedules [10–25]. Current WHO recommendation for ID Pre-EP includes a total of three 0.1 ml doses of RV given at days 0, 7 and 21 or 28 [7].

To satisfy current regulatory requirements, an investigational new drug (IND) evaluation is necessary to support requests that currently available licensed vaccines manufactured for IM use could be used by the ID route with safety and efficient multiuse of the vaccine vial available (designed for IM use). This IND study was designed to evaluate the use of PCEC RV for Pre-EP indications in healthy adult volunteers.

The objective of this study was to determine the immunogenicity of PCEC RV to induce adequate levels of rabies virus neutralizing antibodies in subjects following receipt of three 0.1 mL (0.25 I.U.).) ID doses, as recommended by WHO, compared to three 1.0 mL (2.5 I.U. IM doses, or single booster doses, of the same vaccine. Moreover, we sought to compare the relative safety of PCEC RV administered via the ID route, in comparison with the IM route.

## 2. Methods

The study was designed as a single center, open-label comparison. Two occupational health clinics (OHC) at CDC in Atlanta, participated as enrollment Pre-EP administration, and follow-up patient visit sites: the Roybal Campus OHC, and the Chamblee campus OHC. Enrollment was open to all CDC staff, focusing upon at-risk laboratory workers and epidemiologists, as well as first responders. Although other adult volunteers outside of CDC were considered in case recruitment was incomplete during the targeted time, this was unnecessary. Activities of the study were performed according to CDC IRB protocol # 5506/IND # 13814.

An arbitrary sample size of 30 individuals was targeted for each arm of the study described below. A 10% additional was planned to recruit to compensate potential losses to follow-up. After recruitment, up to 130 male and female subjects, aged 18 years and older, were enrolled in this non-randomized study, from June 2009 with participation completed by February 2010. Two individuals declined participation after recruiting; 128 participants were entered in the population for safety analysis; and 5 more individuals entered to wrong study arm due to incorrect vaccination history at entry were also excluded, resulting in 123 participants entering the population for the immunological portion of the analysis. Participants were divided into naïve to rabies vaccination [Pre-Exposure Prophylaxis (Pre-EP) group], or previously vaccinated (Booster group) subjects. The RV naïve subjects (Pre-EP group) received three single doses of either 0.1 mL of the rabies vaccine by the ID route, or 1.0 mL by the IM route, given on Days 0, 7 and 21. For persons who received rabies vaccination previously (Booster group), one dose of vaccine was administered either ID (0.1 mL) or IM (1.0 mL) on Day 0 only.

The IM route was used as a comparison control because this is the only current standard use of PCECV approved in the USA. Vital signs were assessed, and a blood sample was collected for immunogenicity evaluation prior to each vaccination, and with each targeted physical exam. Symptoms and signs of potential adverse reactions were assessed in the OHC for at least 15 min after vaccination. Subjects maintained a memory aid to record systemic and local adverse events (AEs) for 7 days after vaccination. At approximately 14 days after the third vaccination in the Pre-EP group (Day 35) and the single dose in the Booster Group (Day 14), subjects returned to the OHC for evaluation of vital signs, blood sample collection and safety follow-up. At approximately Day 81-PreEP/60-Booster (or about 60 days after the last vaccination), subjects returned to the clinic for the blood sample collection, the AE and concomitant medication assessment, and the targeted physical examination (if indicated). At approximately Day 141-Pre-EP/120-Booster (approximately 4 months after full vaccination schedule), a follow-visit was scheduled for blood sample collection, the AE and concomitant medication assessment, and a targeted physical examination (if indicated). At Day 180-Pre-EP/160-Booster, subjects returned to the OHC for a final blood sample collection and for follow-up (which included a targeted physical examination [if indicated], and assessment of concomitant medications). The duration of the study for each subject was approximately 6 months.

Participation in this study was entirely voluntary and free of any type of coercion or undue influence of supervisors, peers or any other group. Volunteers were asked to sign an informed consent form, after explaining that the participant could choose freely to enroll or not, and that their decision would not affect their work. In case an individual interested initially in participating in the study, but after being informed decided not to participate, RV was delivered as suggested by the ACIP recommendations for human rabies prevention. Personnel under the direct supervision of the study investigators were not eligible to enroll, to minimize opportunities for situations where the worker might feel pressure to participate.

Subjects had to meet all of the following inclusion criteria to participate in this study: being a CDC employee; a healthy adult; non-pregnant women; and located in the Atlanta metropolitan area, to be able to attend all follow-up visits. Exclusion criteria considered: having a known allergy to PCECV, eggs, or latex; pregnancy; immunosuppression as a result of an underlying illness or treatment; active neoplastic disease or a history of any hematologic malignancy; use of oral or parenteral steroids, high-dose inhaled steroids (>800 μg/day of beclomethasone dipropionate or equivalent) or other immunosuppressive or cytotoxic drugs;

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