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## **Use of a Reduced (4-Dose) Vaccine Schedule for Postexposure Prophylaxis to Prevent Human Rabies**

**Recommendations of the Advisory Committee  
on Immunization Practices**

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**CONTENTS**

Introduction ..... 1  
 Methods ..... 2  
 Rationale for Reduced Doses of Human Rabies Vaccine ..... 2  
 Revised Rabies Postexposure Prophylaxis Recommendations ..... 5  
 Vaccination and Serologic Testing ..... 7  
 Management of Adverse Reactions, Precautions,  
 and Contraindications ..... 7  
 Variation from Human Rabies Vaccine Package Inserts ..... 7  
 References ..... 8

# Use of a Reduced (4-Dose) Vaccine Schedule for Postexposure Prophylaxis to Prevent Human Rabies

## Recommendations of the Advisory Committee on Immunization Practices

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### Summary

*This report summarizes new recommendation and updates previous recommendations of the Advisory Committee on Immunization Practices (ACIP) for postexposure prophylaxis (PEP) to prevent human rabies (CDC. Human rabies prevention—United States, 2008: recommendations of the Advisory Committee on Immunization Practices. MMWR 2008;57[No. RR-3]). Previously, ACIP recommended a 5-dose rabies vaccination regimen with human diploid cell vaccine (HDCV) or purified chick embryo cell vaccine (PCECV). These new recommendations reduce the number of vaccine doses to four. The reduction in doses recommended for PEP was based in part on evidence from rabies virus pathogenesis data, experimental animal work, clinical studies, and epidemiologic surveillance. These studies indicated that 4 vaccine doses in combination with rabies immune globulin (RIG) elicited adequate immune responses and that a fifth dose of vaccine did not contribute to more favorable outcomes. For persons previously unvaccinated with rabies vaccine, the reduced regimen of 4 1-mL doses of HDCV or PCECV should be administered intramuscularly. The first dose of the 4-dose course should be administered as soon as possible after exposure (day 0). Additional doses then should be administered on days 3, 7, and 14 after the first vaccination. ACIP recommendations for the use of RIG remain unchanged. For persons who previously received a complete vaccination series (pre- or postexposure prophylaxis) with a cell-culture vaccine or who previously had a documented adequate rabies virus-neutralizing antibody titer following vaccination with noncell-culture vaccine, the recommendation for a 2-dose PEP vaccination series has not changed. Similarly, the number of doses recommended for persons with altered immunocompetence has not changed; for such persons, PEP should continue to comprise a 5-dose vaccination regimen with 1 dose of RIG. Recommendations for pre-exposure prophylaxis also remain unchanged, with 3 doses of vaccine administered on days 0, 7, and 21 or 28. Prompt rabies PEP combining wound care, infiltration of RIG into and around the wound, and multiple doses of rabies cell-culture vaccine continue to be highly effective in preventing human rabies.*

### Introduction

Rabies is a zoonotic disease caused by RNA viruses in the family *Rhabdoviridae*, genus *Lyssavirus* (1). Virus is transmitted in the saliva of rabid mammals via a bite. After entry to the central nervous system, these viruses cause an acute, progressive encephalomyelitis. The incubation period usually ranges from 1 to 3 months after exposure, but can range from days to

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years. Rabies can be prevented by avoidance of viral exposure and initiation of prompt medical intervention when exposure does occur. In the United States, animal rabies is common. In a recent study, approximately 23,000 persons per year were estimated to have been exposed to potentially rabid animals and received rabies postexposure prophylaxis (PEP) (2). With the elimination of canine rabies virus variants and enzootic transmission among dogs, human rabies is now rare in the United States, with an average of one or two cases occurring annually since 1960 (3).

Prompt wound care and the administration of rabies immune globulin (RIG) and vaccine are highly effective in preventing human rabies following exposure. A variety of empirical schedules and vaccine doses have been recommended over time, based in part on immunogenicity and clinical experience in areas of the world with enzootic canine or wildlife rabies (4). As more potent vaccines were developed, the number of vaccine doses recommended for PEP has decreased, and studies aimed at further revision and reduction of PEP schedules and doses in humans have been encouraged. By the latter half of the 20th century, a 4- to 6-dose, intramuscular regimen using human diploid cell vaccine (HDCV) or purified chick embryo cell vaccine (PCECV) was being recommended (5–8). In the United States, a 5-dose PEP vaccine regimen was adopted during the 1980s (9–12). In 2007, when human rabies vaccine was in limited supply, an ad hoc National Rabies Working Group was formed to reassess the recommendations for rabies prevention and control in humans and other animals. In 2008, a smaller Advisory Committee on Immunization Practices (ACIP) Rabies Workgroup was formed to review rabies vaccine regimen options. This report provides updated ACIP recommendations regarding the use of a 4-dose vaccination regimen, replacing the previously recommended 5-dose regimen, for rabies PEP in previously unvaccinated persons.

## Methods

The ACIP Rabies Workgroup\* was formed in October 2008 to review 1) previous recommendations; 2) published and unpublished data from both national and global sources regarding rabies PEP; and 3) the immunogenicity, effectiveness, and safety of a 4-dose PEP rabies vaccination regimen. The ACIP Rabies Workgroup used an evidence-based process for consideration of a reduced vaccination regimen in human rabies PEP. This approach consisted of a review of information available from basic and applied studies of rabies prevention. Because rabies is almost always fatal among immunologically naïve

persons once clinical symptoms of rabies occur, randomized, placebo-controlled efficacy studies of vaccine in humans cannot be conducted. The ACIP Rabies Workgroup reviewed six areas: 1) rabies virus pathogenesis, 2) experimental animal models, 3) human immunogenicity studies, 4) prophylaxis effectiveness in humans, 5) documented failures of prophylaxis in humans, and 6) vaccine safety. Studies for review were identified by searching the PubMed database and other relevant references and by consulting subject-matter experts. When definitive research evidence was lacking, the recommendations incorporated the expert opinion of the ACIP Rabies Workgroup members. The ACIP Rabies Workgroup also sought advice and comment from representatives of the vaccine industry, the National Association of State Public Health Veterinarians, the Council of State and Territorial Epidemiologists, state and local public health officials, additional national stakeholder groups, and other national and international experts. The proposed revised recommendations and a draft statement from the ACIP Rabies Workgroup were presented to the full ACIP during February 2009. After review and comment by ACIP, a revised draft, recommending a reduced regimen of 4 1-mL doses of rabies vaccine for PEP in previously unvaccinated persons, was prepared for consideration. These recommendations were discussed and accepted by ACIP at the June 2009 meeting (13).

## Rationale for Reduced Doses of Human Rabies Vaccine

A detailed review of the evidence in support of a reduced, 4-dose schedule for human PEP has been published (14). The totality of the evidence, obtained from the available peer-reviewed literature, unpublished data sources, epidemiologic reviews, and expert opinion strongly supports a reduced vaccination schedule (Table 1). Since the 19th century, prophylactic interventions against rabies have recognized the highly neurotropic characteristics of lyssaviruses and have aimed at neutralizing the virus at the site of infection before it can enter the human central nervous system (Figure 1) (4,15,16). To accomplish this, immunologic interventions must be prompt and must be directed toward local virus neutralization, such as local infiltration with RIG and vaccination. Modern recommended rabies PEP regimens emphasize early wound care and passive immunization (i.e., infiltration of RIG in and around the wound) combined with active immunization (i.e., serial doses of rabies vaccine). Accumulated scientific evidence indicates that, following rabies virus exposure, successful neutralization and clearance of rabies virus mediated via appropriate PEP generally ensures patient survival (8).

\*A list of the membership appears on page 9 of this report.

**TABLE 1. Summary of evidence in support of a 4-dose postexposure prophylaxis regimen — United States, 2010**

| Evidence                   | Conclusion  | Sources   |
|----------------------------|---|---|
| Rabies virus pathogenesis  | High neurotropism of rabies virus requires immediate immunization (local infiltration with human rabies immune globulin [HRIG] and vaccination) to neutralize virus at the site of infection and prevent viral entry into the central nervous system. | Published literature,* expert national and international opinion, and historic observations |
| Experimental animal models | Protection in animal models was elicited without regard to the absolute number of vaccine doses used.   | Published literature,† expert national and international opinion, and unpublished data      |
| Human clinical studies     | All patients develop adequate levels of virus-neutralizing antibodies by day 14, without any additive value of a 5th dose of vaccine administered at day 28 (in regards to any substantive increase in measured virus-neutralizing antibody levels).  | Published literature,§ expert national and international opinion, and unpublished data      |
| Epidemiologic surveillance | No human rabies cases were identified in patients who received appropriate wound care, HRIG, and 4 doses of vaccine.  | Published literature,¶ expert national and international opinion, and unpublished data      |
| Health economics           | Expected positive national benefits are related to omission of a 5th dose (e.g., minimized travel expenses, reduced time out of work, health-care workers have more time for other patients, and fewer adverse reactions).                            | Published literature** and expert national opinion  |

\* **SOURCES:** Lyles DS, Rupprecht CE. *Rhabdoviridae*. In: Knipe D, Howley P, eds. *Fields virology*. 5th ed. Philadelphia, PA: Lippincott, Williams, & Wilkins; 2007:1363–408. Plotkin SA, Koprowski H, Rupprecht CE. Rabies vaccines. In: Plotkin SA, Orenstein WA, Offit PA, eds. *Vaccines*. 5th ed. Philadelphia, PA: Saunders; 2008:687–714. World Health Organization. WHO Expert Consultation on Rabies. 1st report. WHO Technical Report Series, No. 931. Geneva, Switzerland: World Health Organization; 2005. Rupprecht CE, Briggs D, Brown C, et al. Evidence for a 4-dose vaccine schedule for human rabies post-exposure prophylaxis in previously non-vaccinated individuals. *Vaccine* 2009;27:7141–8. Charlton KM, Nadin-Davis S, Casey GA, Wandeler AI. The long incubation period in rabies: delayed progression of infection in muscle at the site of exposure. *Acta Neuropathol* 1997;94:73–7. Dietzschold B, Schnell M, Koprowski H. Pathogenesis of rabies. *Curr Top Microbiol Immunol* 2005;292:45–56.

† **SOURCES:** Lyles DS, Rupprecht CE. *Rhabdoviridae*. In: Knipe D, Howley P, eds. *Fields Virology*. 5th Ed. Philadelphia, PA: Lippincott, Williams, & Wilkins; 2007:1363–408. World Health Organization. WHO Expert Consultation on Rabies. 1st Report. WHO Technical Report Series, No. 931. Geneva, Switzerland: World Health Organization; 2005. Rupprecht CE, Briggs D, Brown C, et al. Evidence for a 4-dose vaccine schedule for human rabies post-exposure prophylaxis in previously non-vaccinated individuals. *Vaccine* 2009;27:7141–8. Baer GM. Animal models in the pathogenesis and treatment of rabies. *Rev Infect Dis* 1988;10(Suppl 4):S739–50. Franka R, Wu X, Jackson RF, et al. Rabies virus pathogenesis in relationship to intervention with inactivated and attenuated rabies vaccines. *Vaccine* 2009;27:7149–55. Sikes RK, Cleary WF, Koprowski H, Wiktor TJ, Kaplan MM. Effective protection of monkeys against death from street virus by post-exposure administration of tissue-culture rabies vaccine. *Bull World Health Organ* 1971;45:1–11. Manickam R, Basheer MD, Jayakumar R. Post-exposure prophylaxis (PEP) of rabies-infected Indian street dogs. *Vaccine* 2008;26:6564–8.

§ **SOURCES:** Plotkin SA, Koprowski H, Rupprecht CE. Rabies vaccines. In: Plotkin SA, Orenstein WA, Offit PA, eds. *Vaccines*. 5th ed. Philadelphia, PA: Saunders; 2008:687–714. World Health Organization. WHO Expert Consultation on Rabies. 1st Report. WHO Technical Report Series, No. 931. Geneva, Switzerland: World Health Organization; 2005. Rupprecht CE, Briggs D, Brown C, et al. Evidence for a 4-dose vaccine schedule for human rabies post-exposure prophylaxis in previously non-vaccinated individuals. *Vaccine* 2009;27:7141–8.

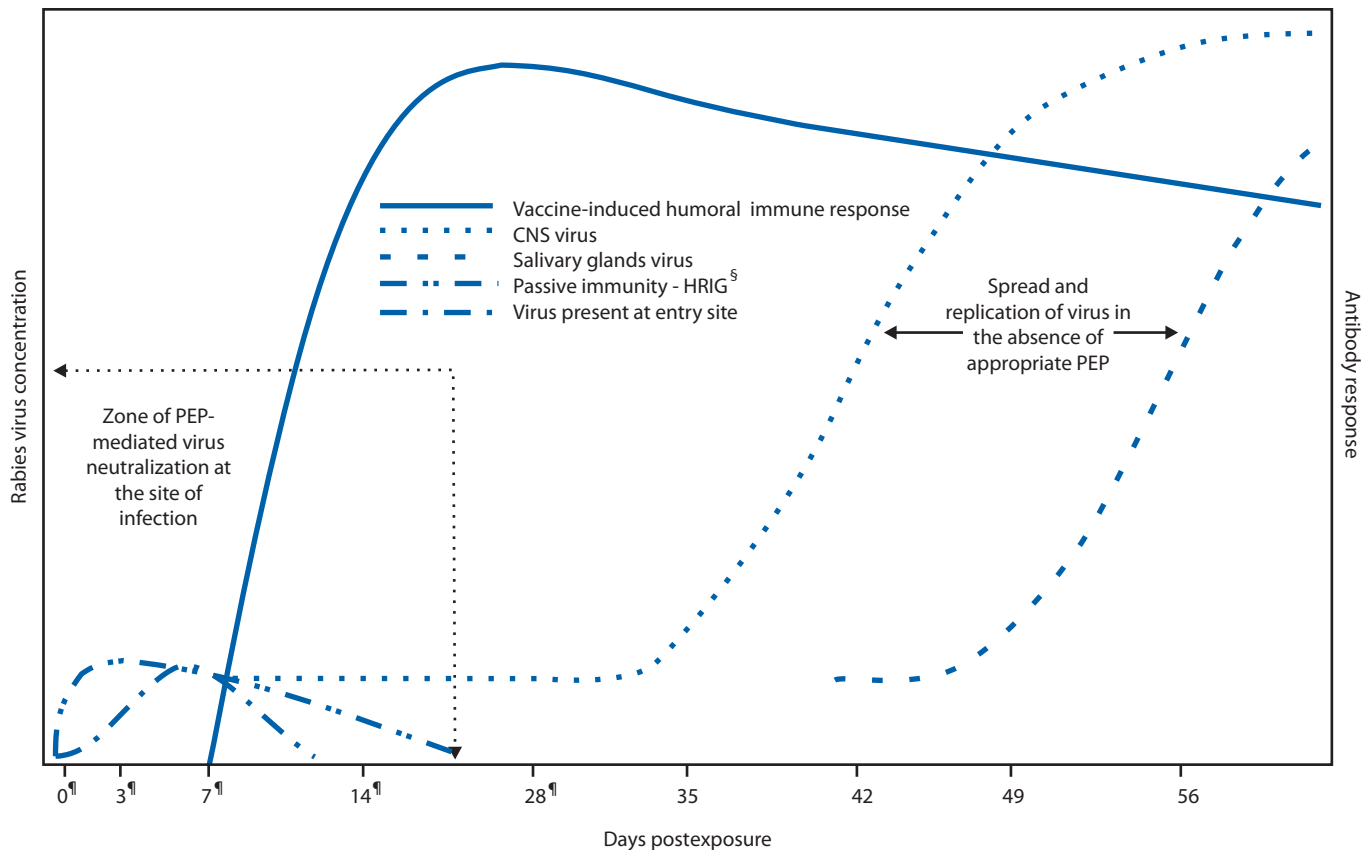
¶ **SOURCES:** Plotkin SA, Koprowski H, Rupprecht CE. Rabies vaccines. In: Plotkin SA, Orenstein WA, Offit PA, eds. *Vaccines*. 5th ed. Philadelphia, PA: Saunders; 2008:687–714. Rupprecht CE, Briggs D, Brown C, et al. Evidence for a 4-dose vaccine schedule for human rabies post-exposure prophylaxis in previously non-vaccinated individuals. *Vaccine* 2009; 27:7141–8. Wilde H. Failures of post-exposure rabies prophylaxis. *Vaccine* 2007;25:7605–9.

\*\* **SOURCES:** Meltzer MI, Rupprecht CE. A review of the economics of the prevention and control of rabies: I: global impact and rabies in humans. *Pharmacoeconomics* 1998;14:365–83. Dhankhar P, Vaidya SA, Fishbien DB, Meltzer MI. Cost effectiveness of rabies post exposure prophylaxis in the United States. *Vaccine* 2008;26:4251–5.

The induction of a rabies virus-specific antibody response is one important immunologic component of response to vaccination (4). Development of detectable rabies virus-specific neutralizing antibodies is a surrogate for an adequate immune response to vaccination. Clinical trials of human rabies vaccination indicate that all healthy persons develop detectable rabies virus-neutralizing antibody titer rapidly after initiation of PEP. For example, in a literature review conducted by the ACIP Rabies Workgroup of at least 12 published rabies vaccination studies during 1976–2008 representing approximately 1,000 human subjects, all subjects developed rabies virus-neutralizing antibodies by day 14 (14).

Observational studies indicate that PEP is universally effective in preventing human rabies when administered promptly and appropriately. Of the >55,000 persons who die annually of rabies worldwide, the majority either did not receive any PEP, received some form of PEP (usually without RIG) after substantial delays, or were administered PEP according to schedules that deviated substantially from current ACIP or World Health Organization recommendations (17). For example, a review of a series of 21 fatal human cases in which patients received some form of PEP indicated that 20 patients developed signs of illness, and most died before day 28 (Figure 2). In such cases, in which widespread infection of the central

**FIGURE 1. Schematic of dynamics of rabies virus pathogenesis\* in the presence and absence of postexposure prophylaxis (PEP)–mediated immune responses†**



\* Rabies can progress through five stages: incubation period (5 days to >2 years: U.S. median ~35 days), prodrome state (0–10 days), acute neurologic period (2–7 days), coma (5–14 days), and death.

† Once in tissues at the entry site, rabies virus can be neutralized by passively administered rabies immune globulin (RIG). Active immunization (vaccine) stimulates the host immune system, and, as a result, virus-neutralizing antibodies (VNA) are produced approximately 7–10 days after initiation of vaccination. By approximately day 14–28 (after administration of 4 vaccine doses), VNAs peak. In the absence of early and adequate PEP, virus enters host neurons, spreads to the central nervous system (CNS), and causes disease, with inevitably fatal consequence.

§ Human rabies immune globulin.

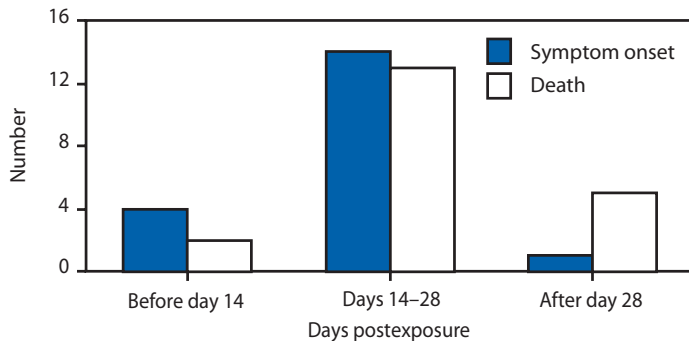
¶ Day vaccine administered.

nervous system occurs before the due date (i.e., day 28) of the fifth vaccine dose, the utility of that dose must be nil. In the United States, of the 27 human rabies cases reported during 2000–2008, none of the patients had a history of receiving any PEP before illness, and this is the most common situation for human rabies deaths in both developed and developing countries (3,8). In India, an analysis from two animal bite centers during 2001–2002 demonstrated that in 192 human rabies cases, all deaths could be attributed to failure to seek timely and appropriate PEP, and none of them could be attributed to a failure to receive the fifth (day 28) vaccine dose (18). Even when PEP is administered imperfectly or not according to established scheduled dose recommendations, it might be generally effective. Several studies have reported cases involving persons who were exposed to potentially rabid animals and who received less than 5, 4, or even 3 doses of rabies vaccine but

who nevertheless did not acquire rabies (Table 2). For example, in one series from New York, 147 (13%) of 1,132 patients had no report of receiving the complete 5-dose vaccine regimen. Of these patients, 26 (18%) received only 4 doses of vaccine, and two of these patients were exposed to animals with laboratory-confirmed rabies. However, no documented cases of human rabies occurred (CDC, unpublished data, 2003). The ACIP Rabies Working Group estimates that >1,000 persons in the United States receive rabies prophylaxis annually of only 3 or 4 doses, with no resulting documented cases of human rabies, even though >30% of these persons likely have exposure to confirmed rabid animals (14). In addition, no case of human rabies in the United States has been reported in which failure of PEP was attributable to receiving less than the 5-dose vaccine course. Worldwide, although human PEP failures have been reported very rarely, even in cases in which intervention



**FIGURE 2. Number of documented rabies postexposure prophylaxis (PEP) failures — Burma, India, the Philippines, South Africa, Sri Lanka, and Thailand, 1984–2007\***



**SOURCES:** Wilde H. Failures of post-exposure rabies prophylaxis. *Vaccine* 2007;25:7605–9; Wilde H, Sirikawin S, Sabcharoen A, et al. Failure of postexposure treatment of rabies in children. *Clin Infect Dis* 1996;22:228–32; Matha IS, Salunke SR. Immunogenicity of purified vero cell rabies vaccine used in the treatment of fox-bite victims in India. *Clin Infect Dis* 2005;40:611–3.

\* Of 21 reported PEP failures described, 20 patients had symptoms and 15 died before day 28.

appeared both prompt and appropriate (8), no cases have been attributed to the lack of receipt of the fifth human rabies vaccine dose on day 28 (4,17).

In vivo laboratory animal studies using multiple animal models from rodents to nonhuman primates have underscored the importance of timely PEP using RIG and vaccine, regardless of the absolute number of vaccine doses used or the schedule (14,19). For example, in a study in which 1, 2, 3, 4, or 5 doses of rabies vaccine were used in a Syrian hamster model in combination with human rabies immune globulin (HRIG), no statistically significant differences in elicited protection and consequent survivorship were observed among groups receiving different doses (20). In the same study, using a murine model, no differences were detected in immunogenicity and efficacy of PEP with 2, 3, or 4 vaccine doses. In another study using a nonhuman primate model, 1 dose of cell-culture vaccine, in combination with RIG administered 6 hours postexposure, provided substantial protection (21). In another study, a 3-dose

regime was evaluated in a canine model and determined to be effective in preventing rabies (22).

Compared with older, nerve tissue-based products, adverse reactions associated with modern human rabies vaccination are uncommon (4). A review by the Workgroup of published and unpublished human rabies vaccine clinical trials and Vaccine Adverse Event Reporting System data identified no adverse events that were correlated to a failure to receive the fifth vaccine dose. As some adverse reactions might be independent clinical events with each vaccine administration, the omission of the vaccine dose on day 28 might have some positive health benefits. Otherwise, the overall safety of human rabies PEP is expected to be unchanged from the evidence provided in the 2008 ACIP report (12).

Preliminary economic assessments support the cost savings associated with a reduced schedule of vaccination (23,24). The ACIP Rabies Workgroup has estimated that, assuming 100% compliance with a recommended vaccine regimen, a change in recommendation from a 5-dose schedule to a 4-dose schedule would save approximately \$16.6 million in costs to the U.S. health-care system. Persons who receive rabies vaccination might see some savings related to deletion of the fifth recommended dose of vaccine, measured in both the cost of the vaccine and the costs associated with the additional medical visit.

## Revised Rabies Postexposure Prophylaxis Recommendations

This report presents revised recommendations for human rabies PEP (Table 3). Rabies PEP includes wound care and administration of both RIG and vaccine.

### Postexposure Prophylaxis for Unvaccinated Persons

For unvaccinated persons, the combination of RIG and vaccine is recommended for both bite and nonbite exposures, regardless of the time interval between exposure and initiation

**TABLE 2. Number and percentage of patients with suspected rabies exposures who received <5 doses of vaccine — India, 2003; New York, 1998–2000; and Puerto Rico, 2008\***

| Location (year)                   | No. of persons exposed | Persons who received <5 doses of vaccine |      | No. of documented rabies deaths |
|-----------------------------------|------------------------|--|------|---------------------------------|
|                                   |                        | No.                                      | (%)  |                                 |
| New York (1998–2000) <sup>†</sup> | 1,132                  | 147                                      | (13) | 0                               |
| India (2003) <sup>§</sup>         | 439                    | 261                                      | (59) | 0                               |
| Puerto Rico (2008) <sup>¶</sup>   | 191                    | 30                                       | (16) | 0                               |

\* No cases of human rabies were recorded that were attributable to receipt of only 4 doses of vaccine.

<sup>†</sup> SOURCE: CDC, unpublished data, 2003.

<sup>§</sup> SOURCE: Association for the Prevention and Control of Rabies (APCRI) in India. Assessing the burden of rabies in India: WHO sponsored national multi-center rabies survey 2003. Final report May 2004. Available at <http://rabies.org.in>. Accessed March 8, 2010. Sudarshan MK, Madhusudana SN, Mahendra BJ, et al. Assessing the burden of human rabies in India: results of a national multi-center epidemiological survey. *Intl J Infect Dis* 2007;11:29–35.

<sup>¶</sup> SOURCE: CDC, unpublished data, 2008.

**TABLE 3. Rabies postexposure prophylaxis (PEP) schedule — United States, 2010**

| Vaccination status        | Intervention                        | Regimen*   |
|---------------------------|-------------------------------------|--|
| Not previously vaccinated | Wound cleansing                     | All PEP should begin with immediate thorough cleansing of all wounds with soap and water. If available, a virucidal agent (e.g., povidine-iodine solution) should be used to irrigate the wounds.  |
|                           | Human rabies immune globulin (HRIG) | Administer 20 IU/kg body weight. If anatomically feasible, the full dose should be infiltrated around and into the wound(s), and any remaining volume should be administered at an anatomical site (intramuscular [IM]) distant from vaccine administration. Also, HRIG should not be administered in the same syringe as vaccine. Because HRIG might partially suppress active production of rabies virus antibody, no more than the recommended dose should be administered. |
|                           | Vaccine                             | Human diploid cell vaccine (HDCV) or purified chick embryo cell vaccine (PCECV) 1.0 mL, IM (deltoid area <sup>†</sup> ), 1 each on days 0, <sup>§</sup> 3, 7 and 14. <sup>¶</sup>  |
| Previously vaccinated**   | Wound cleansing                     | All PEP should begin with immediate thorough cleansing of all wounds with soap and water. If available, a virucidal agent such as povidine-iodine solution should be used to irrigate the wounds.  |
|                           | HRIG                                | HRIG should not be administered.   |
|                           | Vaccine                             | HDCV or PCECV 1.0 mL, IM (deltoid area <sup>†</sup> ), 1 each on days 0 <sup>§</sup> and 3.  |

\* These regimens are applicable for persons in all age groups, including children.

<sup>†</sup> The deltoid area is the only acceptable site of vaccination for adults and older children. For younger children, the outer aspect of the thigh may be used. Vaccine should never be administered in the gluteal area.

<sup>§</sup> Day 0 is the day dose 1 of vaccine is administered.

<sup>¶</sup> For persons with immunosuppression, rabies PEP should be administered using all 5 doses of vaccine on days 0, 3, 7, 14, and 28.

\*\* Any person with a history of pre-exposure vaccination with HDCV, PCECV, or rabies vaccine adsorbed (RVA); prior PEP with HDCV, PCECV or RVA; or previous vaccination with any other type of rabies vaccine and a documented history of antibody response to the prior vaccination.

of PEP. If PEP has been initiated and appropriate laboratory diagnostic testing (i.e., the direct fluorescent antibody test) indicates that the animal that caused the exposure was not rabid, PEP may be discontinued.

### Vaccine Use

A regimen of 4 1-mL vaccine doses of HDCV or PCECV should be administered intramuscularly to previously unvaccinated persons (Table 3). The first dose of the 4-dose regimen should be administered as soon as possible after exposure. The date of the first dose is considered to be day 0 of the PEP series. Additional doses then should be administered on days 3, 7, and 14 after the first vaccination. Recommendations for the site of the intramuscular vaccination remain unchanged (e.g., for adults, the deltoid area; for children, the anterolateral aspect of the thigh also is acceptable). The gluteal area should not be used because administration of vaccine in this area might result in a diminished immunologic response. Children should receive the same vaccine dose (i.e., vaccine volume) as recommended for adults.

### HRIG Use

The recommendations for use of immune globulin in rabies prophylaxis remain unchanged by the revised recommendation of a reduced rabies vaccine schedule. HRIG is administered once to previously unvaccinated persons to provide rabies virus-neutralizing antibody coverage until the patient responds to

vaccination by actively producing virus-neutralizing antibodies. HRIG is administered once on day 0 at the time PEP is initiated, in conjunction with human rabies vaccines available for use in the United States. If HRIG was not administered when vaccination was begun on day 0, it can be administered up to and including day 7 of the PEP series (12,25). If anatomically feasible, the full dose of HRIG is infiltrated around and into any wounds. Any remaining volume is injected intramuscularly at a site distant from vaccine administration. HRIG is not administered in the same syringe or at the same anatomic site as the first vaccine dose. However, subsequent doses (i.e., on days 3, 7, and 14) of vaccine in the 4-dose vaccine series can be administered in the same anatomic location in which HRIG was administered.

### Postexposure Prophylaxis for Previously Vaccinated Persons

Recommendations for PEP have not changed for persons who were vaccinated previously. Previously vaccinated persons are those who have received one of the ACIP-recommended pre- or postexposure prophylaxis regimens (with cell-culture vaccines) or those who received another vaccine regimen (or vaccines other than cell-culture vaccine) and had a documented adequate rabies virus-neutralizing antibody response. Previously vaccinated persons, as defined above, should receive 2 vaccine doses (1.0 mL each in the deltoid), the first dose



immediately and the second dose 3 days later. Administration of HRIG is unnecessary, and HRIG should not be administered to previously vaccinated persons to avoid possible inhibition of the relative strength or rapidity of an expected anamnestic response (26). Local wound care remains an important part of rabies PEP for any previously vaccinated persons.

## Vaccination and Serologic Testing

### Postvaccination Serologic Testing

All healthy persons tested in accordance with ACIP guidelines after completion of at least a 4-dose regimen of rabies PEP should demonstrate an adequate antibody response against rabies virus (14). Therefore, no routine testing of healthy patients completing PEP is necessary to document seroconversion (12). When titers are obtained, serum specimens collected 1–2 weeks after prophylaxis (after last dose of vaccine) should completely neutralize challenge virus at least at a 1:5 serum dilution by the rapid fluorescent focus inhibition test (RFFIT). The rabies virus-neutralizing antibody titers will decline gradually since the last vaccination. Minimal differences (i.e., within one dilution of sera) in the reported values of rabies virus-neutralizing antibody results might occur between laboratories that provide antibody determination using the recommended RFFIT. Commercial rabies virus antibody titer determination kits that are not approved by the Food and Drug Administration are not appropriate for use as a substitute for the RFFIT. Discrepant results might occur after the use of such tests, and actual virus-neutralizing activity in clinical specimens cannot be measured.

## Management of Adverse Reactions, Precautions, and Contraindications

### Management of Adverse Reactions

Recommendations for management and reporting of vaccine adverse events have not changed. These recommendations have been described in detail previously (12).

### Immunosuppression

Recommendations for rabies pre- and postexposure prophylaxis for persons with immunosuppression have not changed. General recommendations for active and passive immunization in persons with altered immunocompetence have been summarized previously (27,28). This updated report

discusses specific recommendations for patients with altered immunocompetence who require rabies pre- and postexposure prophylaxis. All rabies vaccines licensed in the United States are inactivated cell-culture vaccines that can be administered safely to persons with altered immunocompetence. Because corticosteroids, other immunosuppressive agents, antimalarials, and immunosuppressive illnesses might reduce immune responses to rabies vaccines substantially, for persons with immunosuppression, rabies PEP should be administered using a 5-dose vaccine regimen (i.e., 1 dose of vaccine on days 0, 3, 7, 14, and 28), with the understanding that the immune response still might be inadequate. Immunosuppressive agents should not be administered during rabies PEP unless essential for the treatment of other conditions. If possible, immunosuppressed patients should postpone rabies preexposure prophylaxis until the immunocompromising condition is resolved. When postponement is not possible, immunosuppressed persons who are at risk for rabies should have their virus-neutralizing antibody responses checked after completing the preexposure series. Postvaccination rabies virus-neutralizing antibody values might be less than adequate among immunosuppressed persons with HIV or other infections (29,30). When rabies pre- or postexposure prophylaxis is administered to an immunosuppressed person, one or more serum samples should be tested for rabies virus-neutralizing antibody by the RFFIT to ensure that an acceptable antibody response has developed after completing the series. If no acceptable antibody response is detected after the final dose in the pre- or postexposure prophylaxis series, the patient should be managed in consultation with their physician and appropriate public health officials.

## Variation from Human Rabies Vaccine Package Inserts

These new ACIP recommendations differ from current rabies vaccine label instructions, which still list the 5-dose series for PEP. Historically, ACIP review and subsequent public health recommendations for the use of various biologics has occurred after vaccine licensure and generally are in agreement with product labels. However, differences between ACIP recommendations and product labels are not unprecedented. For example, during the early 1980s, ACIP review and recommendations concerning the intradermal use of rabies vaccines occurred well in advance of actual label claims and licensing (9). On the basis of discussions with industry representatives, alterations of current product labels for HDCV and PCEC are not anticipated by the producers of human rabies vaccines licensed for use in the United States.

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