

Public Veterinary Medicine: Public Health

Decision-based evaluation of recommendations for preexposure rabies vaccination

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Preexposure rabies vaccination is recommended for individuals who are more likely to be exposed to rabies virus than the general public.¹ This vaccination series consists of 3 doses of vaccine administered IM or intradermally (ID), which permits postexposure vaccination to consist of 3 doses of vaccine rather than 5 and eliminates the need for postexposure administration of human rabies immune globulin. Preexposure vaccination may provide protection for persons with unrecognized exposures and those encountering a delay in receiving postexposure vaccination.¹

Presently, 3 vaccines are approved for use in the United States; only the **human diploid cell vaccine (HDCV)** is prepackaged and approved for IM and ID use.^{2,3} The **rabies vaccine, adsorbed (RVA)** was approved by the FDA in 1988, and the **rabies vaccine, purified chicken embryo cell (PCEC)** was approved by the FDA in 1997; both are approved for IM use only.^{4,5} Vaccination by the ID and IM routes induces seroconversion in nearly 100% of healthy individuals.⁶ Successful seroconversion is defined by the Centers for Disease Control and Prevention (CDC) as **virus neutralizing antibody (VNA) \geq 1:5 serum dilution** as determined by the **rapid fluorescent focus inhibition test (RFFIT)**.¹

Differences between the ID and IM routes of administration include cost and longevity of the measurable immune response. Intradermally administered vaccines are approximately half the cost of IM administered vaccines but can have a shorter duration of measurable immune response, necessitating more frequent booster doses.⁷ Adverse reactions to vaccination range from mild local reactions such as pain at the injection site to more severe systemic type-III hypersensitivity (immune complex mediated) reactions such as serum sickness.⁸⁻¹⁰ There have also been infrequent reports of a neurologic syndrome (Guillain-Barre) associated with booster doses of rabies vaccine.¹¹

Recommendations set forth by the **Advisory Committee on Immunization Practices (ACIP)** for preexposure prophylaxis and maintenance of a detectable antibody titer differ depending on the estimated degree of risk of exposure to the rabies virus.¹ Four risk categories (continuous, frequent, infrequent, and rare) have been established, and classification depends on factors such as the occupation of the individual and geography (**Appendix**).¹ To maintain measurable immunity in individuals in the frequent risk group, the 1991 ACIP guidelines recommended that they receive a booster dose every 2 years or have serologic testing performed, with booster doses to be administered only when antibody concentrations were below an acceptable value. Because frequent booster doses of rabies vaccine have been associated with adverse reactions, we chose to examine costs associated with vaccination booster schedules and serologic testing strategies.⁸

Data Collection

Durations of measurable antibody responses and frequencies of adverse reactions to booster doses of vaccines were collected from the scientific literature. Of the adverse reactions, we chose to focus on type-III hypersensitivity reactions because these reactions are more clinically important than minor local reactions and develop more commonly than the rare neurologic reactions.

The cost of adverse reactions was calculated from the duration of clinical signs, costs of physician visits, hospital stays, treatments, and days missed from work. To calculate mean cost to a patient with an adverse reaction, information was extrapolated from a proprietary database that contains nationwide health insurance claims data.^a Direct medical costs were obtained from the database by use of an international disease code for serum sickness (code 999.5).¹³

Costs of preexposure vaccination series and boosters were calculated from the manufacturers' price for vaccines (via telephone interviews, as of July 1998), rounded to the nearest dollar, plus mean cost of an office visit to a physician and the cost of vaccine administration.^a Manufacturers' listed prices for HDCV, RVA, and PCEC vaccines for IM administration were

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all within \$10 of each other, so these vaccines were grouped together and cost was determined by calculation of mean cost of the 3 vaccines.

Probability of needing a booster was extrapolated from data obtained from published results comparing longevity of titer induced by vaccination by ID and IM routes.⁷ This data was extrapolated over 30 years by exponential curve estimation, using statistical software.^a Cost of serologic testing was based on mean prices quoted by 2 laboratories that perform RFFIT, and included prices for phlebotomy and shipping of serum.

Decision trees were constructed for all possible outcomes, and expenditures were calculated over a projected 30-year career for persons in the 3 risk categories. Probability of each outcome was used to determine estimated cost of expenditure for the different possible decisions, then was calculated for a 30-year period. To adjust for any discrepancy between present dollar value and future dollar value, projected costs were discounted to 1998 dollars by use of standard discounting techniques.¹³ Discount rate was set at 3%.

Costs of Vaccination and Serologic Testing

Cost for the primary immunization series that would be required for all 3 risk groups (continuous, frequent, and infrequent) was calculated for ID and IM routes of administration. Mean cost of the 3-dose ID series was \$288 (\$96/dose; range, \$60 to \$131/dose); mean cost of the 3-dose IM series was \$468 (\$156/dose; range, \$120 to \$191/dose). Mean cost of serologic testing was \$71 (range, \$56 to \$86).

Curve fitting regression analysis of published data on serologic titers after preexposure vaccination revealed a decrease in titer that most closely approximated an exponential decay (IM vaccination: $R^2 = 0.84$, $P = 0.03$; ID vaccination: $R^2 = 0.73$, $P = 0.06$). Based on these decay curves, the probability of requiring a booster dose after IM administration of rabies vaccine was $0.9981 - e^{(-0.012005)(\text{time}[y])}$, whereas the probability of requiring a booster dose after ID administration of rabies vaccine was $0.9415 - e^{(-0.012005)(\text{time}[y])}$. These probabilities were used in the decision tree for the continuous and frequent risk groups. Based on results of 3 studies, mean frequency of type-III reactions following booster doses, regardless of IM or ID route, was 7.5%.⁸⁻¹⁰

Mean cost of 11,000 payments made for outpatient visits for type-III hypersensitivity was \$45. It was assumed that each type-III hypersensitivity incident resulted in 3 outpatient visits, with each visit counting as a day missed from work; mean cost for each missed work day was estimated at \$100. Review of 17 records of payments for inpatient admissions for type III hypersensitivity revealed mean duration of hospitalization of 5 days and mean insurance payments of \$11,700. Accounting for the probability of hospitalization, mean weighted cost to the patient was \$490.

Decision trees allowed calculation of total approximate costs for each outcome in the continuous, frequent, and infrequent risk categories over a 30-year career. For the continuous risk group (Fig 1), costs for the 2 routes of inoculation were compared. Total cost

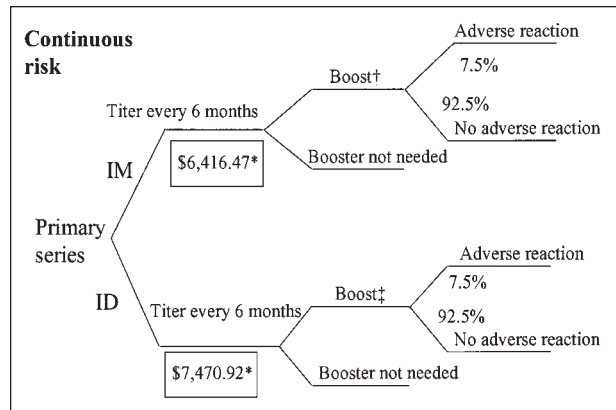


Figure 1—Decision tree for evaluation of preexposure rabies vaccination strategies for persons at continuous risk of exposure to rabies virus. Primary series = 3 doses of rabies vaccine. IM = intramuscular route of administration. ID = intradermal route of administration. *Total cost over a 30-year period. †Probability of requiring a booster dose for IM administration = $0.9981 - e^{(-0.012005)(\text{time}[y])}$. ‡Probability of requiring a booster dose for ID administration = $0.9415 - e^{(-0.012005)(\text{time}[y])}$. Notice the increased probability of requiring a booster dose, which increases probability of having an adverse reaction with the ID route of administration, compared with the IM route of administration.

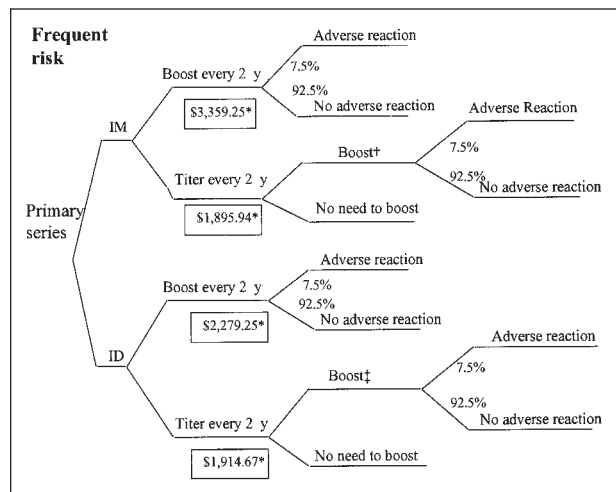


Figure 2—Decision tree for evaluation of preexposure rabies vaccination strategies for persons at frequent risk of exposure to rabies virus. Notice that the combination of IM administration of vaccine and determination of serologic titers every 2 years would result in lower cost and reduce the probability of adverse reactions, because of fewer booster doses needed over a 30-year period. See Figure 1 for key.

for preexposure vaccination by the ID route, including the primary series, serologic testing every 6 months, and costs for administration of booster doses with their associated adverse reactions, was \$7,470.92. Total cost for the IM route of vaccination was \$6,416.47; the IM route of administration would cause fewer adverse reactions.

Calculations for the frequent risk category compared costs of IM and ID routes of administration and costs of the 2 methods of maintaining a measurable immune response (scheduled boosters vs serologic testing with boosters as needed). Costs ranged from \$1,895.94 to \$3,359.25 (Fig 2) for a 30-year period. The strategy using serologic testing was less expensive

Table 1—Comparison of present and future costs of various rabies preexposure vaccination and serologic testing regimens over a 30-year period for persons at frequent risk of exposure

Method	Cost present dollar value	Cost future dollar value
IM vaccination with serologic testing	\$1,895.94	\$1,321.44
IM vaccination with scheduled booster	\$3,359.25	\$2,307.63
ID vaccination with serologic testing	\$1,914.67	\$1,258.12
ID vaccination with scheduled booster	\$2,279.25	\$1,556.01

IM = Intramuscular. ID = Intradermal.

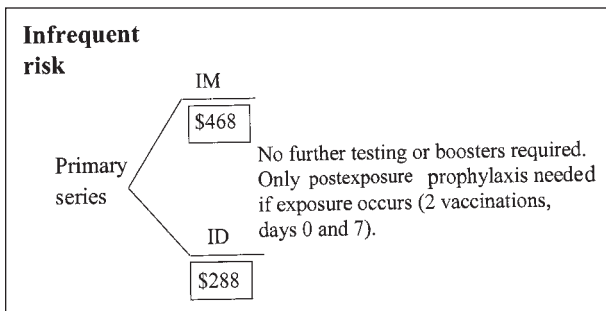


Figure 3—Decision tree for evaluation of preexposure rabies vaccination strategies for persons at infrequent risk of exposure to rabies virus. Notice that vaccination by the ID route of administration is less expensive than by the IM route of administration.

and resulted in 2 times fewer adverse reactions than the scheduled booster strategy. For the IM route of administration, serologic testing cost approximately \$1,463.31 less than did scheduled boosters. For the ID route of administration, serologic testing cost approximately \$364.58 less than did scheduled boosters. Although route of administration did not affect costs greatly (particularly within the serologic testing strategy), the IM route resulted in a lower likely number of adverse reactions over a projected 30-year career. When the calculated costs in the frequent risk category were discounted to adjust for differences between present and future dollar value (Table 1), serologic testing remained less expensive than the scheduled booster although the cost saving was less substantial. Also, at present dollar value, IM serologic testing was slightly less expensive (\$18.73) than ID serologic testing; however, after discounting, ID became less expensive (difference of \$63.32).

Persons in the infrequent risk category only require the primary vaccination series and are not required to maintain a measurable immune response (Fig 3). Therefore, the only factor evaluated was the difference in the up-front cost of ID and IM administered vaccinations; mean cost for the ID series was \$288, whereas mean cost for the IM series was \$468.

The 1999 ACIP Guidelines

This study was conducted prior to release of the 1999 ACIP guidelines for human rabies prevention.¹⁴ For persons in the frequent risk category, the new guidelines recommend only serologic testing every 2 years and administration of a booster vaccine if the

antibody titer is below that considered protective; maintenance of antibody concentration by administration of booster doses every 2 years, as suggested by the 1991 ACIP guidelines, is no longer recommended. In the past, routine booster doses were used by some institutions because of perceived benefits of protecting individuals from unpredictable decreases in antibody titer and simplifying the algorithm by eliminating the serologic testing step. However, in addition to causing more adverse reactions, boosters administered every 1 or 2 years will not induce sustained high titers.⁶ Instead, successive doses of antigen can result in antibody titers reaching a plateau somewhere beneath the ceiling of maximum response.⁶ This phenomenon has been documented for diphtheria toxoid and suggests that frequent administration of boosters might not be advantageous.¹⁵

Antibodies and Immunity

For persons whose occupation places them in a high risk category, there is a need to ensure that immunity is maintained throughout their career. It is important to understand, however, that specific antibody titers do not reliably predict protective immunity. An anamnestic response to a vaccine is predictable after an individual has been immunologically sensitized by administration of any effective primary rabies vaccination series.⁶ The CDC has determined antibody titers that are considered adequate and are surrogate markers for continuing immunity. These titers provide proof that the immune system has processed and reacted to rabies antigen and is capable of producing rabies-specific antibodies. There is no evidence to suggest that a lower antibody titer indicates that an exposed individual would not be protected; however, persons who remain in high risk groups are faced with the need for periodic boosters.

Adverse Reactions

Adverse reactions associated with FDA-approved rabies vaccines available in the United States (HDCV, RVA, and PCEC), are not as serious or common as those associated with previously available rabies vaccines. Nevertheless, reactions can and do develop in persons receiving booster doses and may sensitize the individuals at risk in the event of a true rabies exposure.¹⁰

Results of studies indicate that 19 to 74% of those who receive HDCV complain of local reactions at the injection site that include pain, erythema, itching, and swelling.¹³ Approximately 5 to 40% complain of systemic reactions with symptoms including headache, dizziness, muscle aches, abdominal pain, and nausea. Three cases of a rare neurologic illness (Guillain-Barre syndrome) have been reported, all of which resolved within 12 weeks.^{11,16,17} Central and peripheral nervous system disorders that seem to be associated with the HDCV vaccine have been reported rarely.¹⁸ A factor that is implicated as a cause of type-III hypersensitivity to rabies vaccine is the production of IgE antibodies against beta-propiolactone-altered human serum albumin, an allergen in HDCV.^{8,19,20}

The HDCV, PCEC, and RVA are considered equal-

ly safe and efficacious.¹⁴ During the manufacturing process of PCEC, most of the human albumin implicated as an allergen in HDCV is removed. Human albumin is not a component of RVA, and type-III hypersensitivity reactions associated with its administration may be less common.^{4,5} Alternatively, results of a study that compared HDCV and PCEC among groups chosen for preexposure prophylaxis indicated that 15% of those administered PCEC by IM injection developed systemic reactions, whereas only 10% of other groups (PCEC administered ID, HDCV administered ID, and HDCV administered IM) developed reactions.⁵

*MarketScan, the MEDSTAT group, Ann Arbor, Mich.

^bSPSS, *SPSS/PC base manual*. Version 8.0. Chicago: SPSS Inc, 1998.

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Appendix

Recommendations for preexposure rabies vaccination and serologic testing for persons in various risk categories¹

Risk category	Nature of risk	Typical populations	Preexposure recommendation
Continuous	Virus present continuously, often in high concentrations. Aerosol, mucous membrane, bite, or nonbite exposure. Specific exposures may go unrecognized.	Rabies research laboratory workers; * rabies biologics production workers.	Primary series. Serologic testing every 6 months; booster vaccination when titer decreases below acceptable value.†
Frequent	Exposure usually episodic, with source recognized or unrecognized. Aerosol, mucous membrane, bite, or nonbite exposure.	Rabies diagnostic laboratory workers,* spelunkers, veterinarians and staff, and wildlife workers in areas enzootic for rabies. Travelers visiting (> 30 d) foreign areas enzootic for rabies.	Primary series. Serologic testing or booster vaccination every 2 years.†
Infrequent (greater than population at large)	Exposure usually episodic, with source recognized. Mucous membrane, bite, or nonbite exposure.	Veterinarians and animal control and wildlife workers in areas of low rabies enzooticity. Veterinary students.	Primary series; no serologic testing or booster vaccination.
Rare (population at large)	Exposure episodic. Mucous membrane, or bite with source recognized.	US population at large, including persons in areas epizootic for rabies.	No vaccination necessary.

*Judgment of relative risk and extra monitoring of serologic titers of laboratory workers is the responsibility of the laboratory supervisor. †Minimum acceptable antibody titer is complete virus neutralization at 1:5 serum dilution determined by use of the rapid fluorescent focus inhibition test.