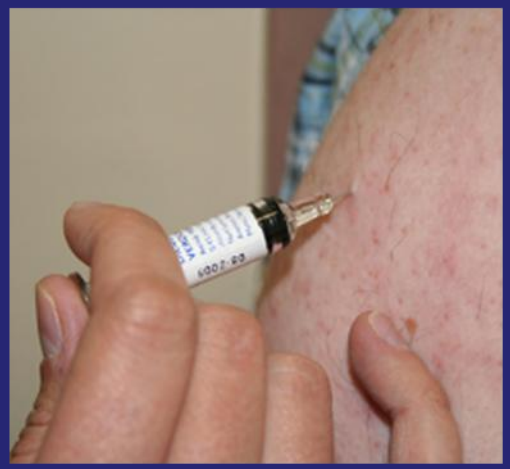
HUMAN RABIES BIOLOGICALS: UPDATE ON SUPPLY



Charles E. Rupprecht VMD, MS, PhD
Chief, Rabies Program
PRB/DVRD/NCZVED/CCID/CDC

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INTRODUCTION

- As a major zoonosis in the USA, rabies occurrence is difficult to predict with accuracy.
- While the disease is controlled in domestic animals, wildlife serve as enzootic reservoirs.
- National surveillance provides basic information on animal rabies trends, but human rabies exposures are not reportable.
- Concomitant with the above points, emerging production and regulatory issues, commercial market shifts, etc., complicate the ability to plan accurately for the supply of human rabies biologicals or to forecast shortage situations.

MAJOR EVENTS IN 2008

- 3/5: Formation of ad hoc rabies working group
- 4/24: Draft interim plans in event of shortage
- 5/7: 2008 ACIP rabies prevention document
- 5/19: Sanofi announcement on restrictions of vaccine for postexposure (PEP) use only
- 6/17: Further restrictions to Novartis supply
- 7/15 Sanofi halts distribution, as Novartis re-enters the market
- 8/29 Sanofi distributes cleared lots of vaccine
- 9/4 Novartis halts distribution

OBJECTIVE OF THE AD HOC WORKING GROUP

- To draft interim recommendations for human rabies prevention in the event of a forecast shortage of biologicals used in prophylaxis

TIPPING POINTS FOR USE OF INTERIM ACTIONS

- Based upon a combination of historical animal rabies surveillance data, prior mass human rabies exposure situations, and conventional aggregate commercial seasonal distributions of product over time, a national shortage in biologicals would be forecast when expected PEP needs are projected to out strip estimated rate of use of available supplies of human rabies vaccines or immune globulins.

FOCUS OF THE AD HOC WORKING GROUP

- Coordination and communications
- Diagnostic and animal control focus
- Risk assessments under various scenarios
- Alternative schedules and routes
- Travel medicine
- Economic implications
- Investigational products

AD HOC WORKING GROUP MEMBERS

D. Briggs, Kansas State University, *Alliance for Rabies Control*
B. Cherry, NY State Department of Health, *CDC Zoonoses Working Group Liaison*
R. Chipman, USDA/APHIS/WS, *Wildlife Society Infectious Diseases Work Group*
P. Cieslak, OR Public Health Division, *ACIP*
L. Conti, FL Department of Health, *Am. College of Veterinary Preventive Medicine*
V. Dato, PA Department of Health, *Am. Association of Public Health Physicians*
J. Duchin, Public Health, Seattle & King County, & University of Washington, *National Association of County and City Health Officials*
S. Fryhofer, Emory University School of Medicine, *American College of Physicians*
P. Garman, U.S. Army, *Department of Defense*
B. Grogg, OK International Travel Medicine Clinic, *International Society of Travel Medicine*
G. Hansen, KS Department of Health & Environment, *AVMA Congressional Fellow*
S. Jenkins, VA Department of Health, *American Veterinary Epidemiology Society*
S. Katz, Duke Children's Health Center, *Infectious Diseases Society of America*
J. Kazmierczak, WI Division of Public Health, *National Assoc. of State Public Health Veterinarians, Inc.*
D. Kerr, *American College of Emergency Physicians*
K. Nusbaum, Auburn University, *American Association of Veterinary Colleges*
R. Ratad, LA Department of Health, *Council of State & Territorial Epidemiologists*
L. Robinson, TX Department of State Health Services, *Binational Rabies Committee*
W. Schaffner, Vanderbilt University School of Medicine, *National Foundation for Infectious Diseases*
D. Shlim, Jackson Hole Wyoming Travel and Tropical Medicine Clinic, *International Society of Travel Medicine*
B. Sun, CA Department of Public Health, *Compendium of Animal Rabies Prevention & Control Committee*
C. Trimarchi, NY State Department of Health, *American Public Health Laboratory Association*
J. Turner, University of Virginia, *American College Health Association*

HHS WORKING GROUP MEMBERS

CDC

National Center for Immunization and Respiratory Diseases:

W. Atkinson, G. Wallace, J. Santoli

National Center for Preparedness, Detection and Control of Infectious Diseases:

N. Marano, M. Meltzer

National Center for Zoonotic, Vector-borne & Enteric Diseases:

P. Arguin, J. Blanton, K. Christian, R. Franka, H. Henderson, I. Kuzmin, S. Recuenco, K. Robertson, C. Rupprecht, A. Tumpey

FDA

Center for Biologics Evaluation & Research

R. Levis, D. Scott

CONTIGENCY PLANS DURING A SHORTAGE SITUATION

- Revised health communications/assessments.
- Renewed basic prevention and control activities.
- Alterations in rabies exposure criteria/triage.
- Pre-exposure vaccination changes.
- PEP management modifications.

ACTIONS IN A SHORTAGE FORECAST

- Centralized national-state health communications, to maximize use of supply.
- Mandatory consultations with knowledgeable public health officials, related to disease risk and need for PEP.
- Renewed education and outreach for key medical providers.

BASIC RABIES PREVENTION PRINCIPLES

- Postpone PEP administration until animal control can locate and capture any suspects.
- Forestall any PEP during observation period of domestic dogs, cats, and ferrets.
- Withhold PEP until timely diagnostic results are obtained for all rabies suspects.

REASSESSING EXPOSURES

- Interim guidelines would provide a new risk-stratified approach to human rabies PEP decisions.
- Such modifications conserve supplies by curtailing use in low risk situations, such as non-bite exposures.
- PEP may be withheld after bites from certain animals where adequate surveillance exists and documents no local terrestrial rabies reservoir.
- For bat scenarios, PEP should only be administered to individuals with a strong belief that they would not awaken from a bite, or be unable to report that actual physical contact occurred. Where available, all suspect bats should be captured, tested and PEP deferred until diagnostic confirmation.

RABIES VACCINATION OPTIONS

- Administer only 1 booster in prior vaccinates.
- Drop 5th (final dose) of vaccine in naïve patient.
- Use alternative schedules (e.g., 2-1-1).
- Utilize ID route for immunization.
- Consider other biologicals, based on INDs.

RELEVANT RABIES PRE-EXPOSURE VACCINE ISSUES

- Divert vaccine supplies to a primary PEP focus.
- Prioritize use towards true, ‘first responder’, highest groups at risk.
- Consider alternate routes for administration, such as intadermal use.

PRE-EXPOSURE NEEDS?

- Focused to ‘first responder’ subjects at risk, before occupational exposure to rabies.
- Subjects include animal control workers, diagnosticians, veterinary staff, etc.
- Staff activities directly determine potential PEP management of exposed patients.

TRAVEL MEDICINE ISSUES?

- In the event of a shortage, it would be prudent to de-prioritize vaccination for any international travel indications in favor of reserving supplies for use in PEP regimens.

- Greater primary education of travelers about rabies occurrence abroad and primary bite avoidance (e.g., not approaching mammals, and avoiding encountering them accidentally by being more aware of their presence) is critical.

- Currently, people who take up residence overseas, longer term travelers, and frequent at risk travelers may obtain vaccination abroad where safe injection practices are used with an approved cell culture vaccine.

ECONOMIC IMPLICATIONS?

- Dhankhar et al. cost effectiveness study (2008)
  - always cost effective to administer PEP if a patient is bitten by a laboratory diagnosed rabid animal or a major reservoir species.
  - for all other transmission risk situations, the net cost ranges from ~ $4million to $4 billion, per human life saved.

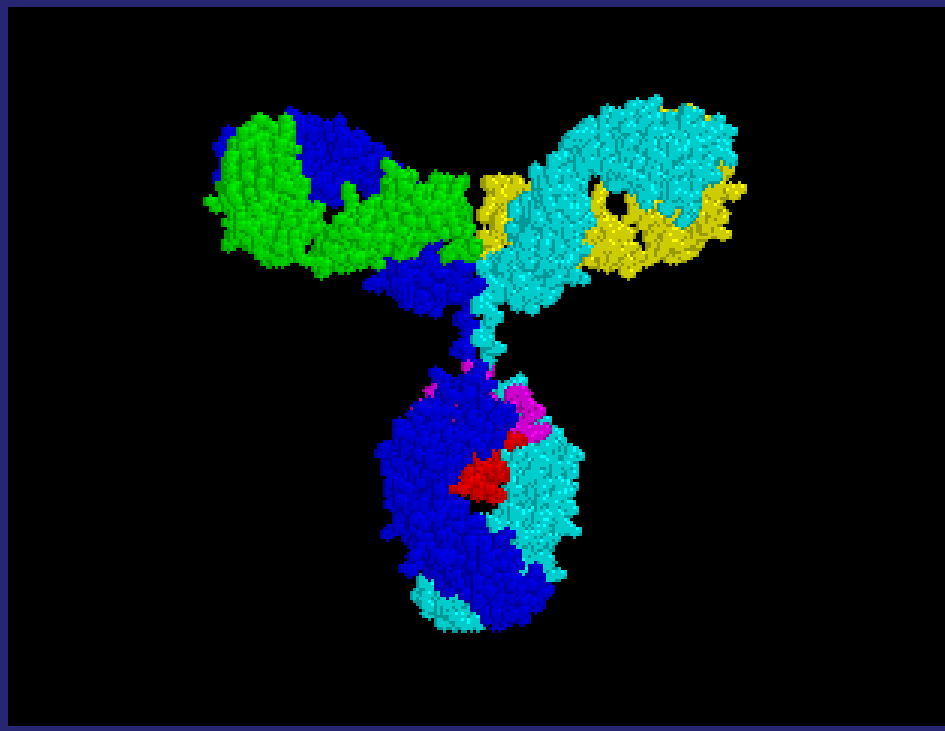
- One strategy to conserve vaccine supply is by administering PEP up to a maximum defined risk of rabies virus transmission.

- Precise risk estimates of rabies virus transmission do not exist.

- Until more precise estimates for transmission are obtained, it is not possible to examine definitively the economics of alternative strategies attempting to limit the use of biologicals by use of pre-set thresholds of risk alone.

RABIES IMMUNE GLOBULINS?

- No immediate supply limitations forecast at this time.
- Vaccine supply may impact future campaigns in volunteers.
- Market changes in plasma collection could create impacts beyond 2009.



STOCKPILE CREATION?

- Approximately 100,000 doses of vaccine would provide buffer in a shortage.
- Used only for PEP.
- Inventory managed by producers ad hoc.
- Generation of at least a 3 month supply would allow flexibility with other management options.

SUMMARY

- Supplies of biologicals used in human rabies prophylaxis are expected to remain less than ideal over the next several year.
- CDC, FDA, HHS, industry, state health departments, and other national stake holders continue to work together towards productive solutions to mitigate current human rabies vaccine supply issues.
- Deliberations of an ad hoc national rabies working group has resulted in the development of draft interim recommendations related to contingency actions that would be utilized in the event of any forecast actual shortages in the future.
- Development of a stockpile is one potential long term solution to minimize the effect of a vaccine shortage.

REFERENCES

- Advisory Committee on Immunization Practices, Human Rabies Prevention, 2008, MMWR 57: RR-3.

- NASPHV, Compendium of Animal Rabies Prevention & Control, 2008, MMWR 57:RR-2.

- World Health Organization, Expert Consultation on Rabies, Geneva, Switzerland, 2005, Tech Rep Ser 931:1-88.