A PRIMER OF NEW ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES GUIDELINES ON HUMAN RABIES PROPHYLAXIS

Clinician Outreach and Communication Activity (COCA) Conference Call

April **6, 2010**

TODAY'S PRESENTER

Charles E. Rupprecht, VMD, MS, PhD

Chief, Rabies Program

Centers for Disease Control and Prevention

Objectives

At the conclusion of this hour, each participant should be able to:

1. Discuss the Advisory Committee on Immunization Practices recent vaccination changes for post-exposure to prevent human rabies vaccine
2. Explain the rational for reduced doses in human rabies
3. Identify exceptions to the recommended human rabies vaccine protocol

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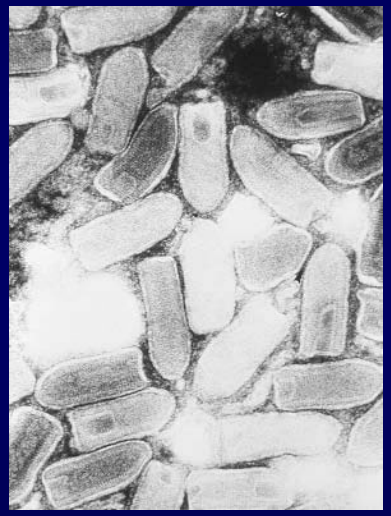
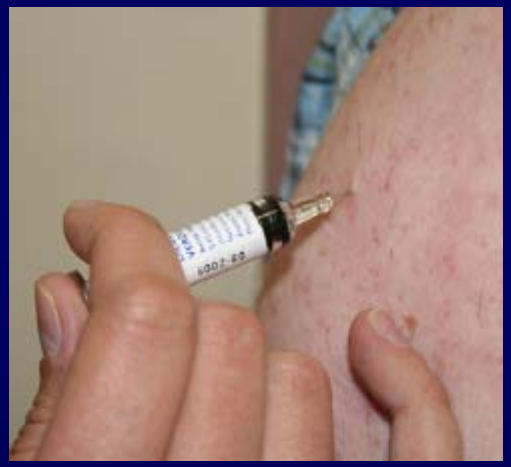
HUMAN RABIES BIOLOGICS:
ACIP RECOMMENDATIONS FOR A REDUCED VACCINE SCHEDULE IN POSTEXPOSURE PROPHYLAXIS





C.E. Rupprecht & the ACIP RABIES WORK GROUP

The views expressed in this presentation are those of the author and not necessarily the institution.

Background

- Human rabies vaccine supply became tenuous during 2007-09.
- Draft interim recommendations in the event of a shortage of rabies biologics were developed and distributed to ACIP.
  - Alternative schedules were proposed initially by the work group for use during vaccine shortages.
  - Work group was asked to evaluate alternative schedules for routine use regardless of supply.

ACIP Rabies Work Group Members

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HHS Work Group Members, 2009

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ACIP Rabies Work Group
Terms of Reference

- Review the evidence for a reduced schedule of human rabies postexposure prophylaxis.
- Provide the available data to ACIP for discussion of dropping the 5th and last rabies vaccine dose on day 28.
- Revise the previous 2008 ACIP statement.

Sources of Evidence

- Studies of rabies virus pathogenesis
- Immunization principles and kinetics
- Human clinical trials of rabies biologics
- Epidemiologic surveillance data
- Consultation with industrial/international SMEs

Rationale

- Recommendations before the onset of any shortage.
- Minimization of adverse biomedical events.
- Limitation of additional health expenditures.
- Rational legacy for development of future biologics.
- Application of comparative health effectiveness and a modern evidence-based approach to vaccinology.

HUMAN RABIES VACCINE HISTORY [1]

1889 Pasteur: rabbit spinal cord vaccine, ~13 doses

1910 Fermi/Semple: ~ 14-21 vaccine doses

1956 Fuenzalida/Palacios: mouse brain ~ 14-23 doses

1956 Duck Embryo Vaccine: ~ 14-23 doses

1973 HDCV: ~ 6 doses originally proposed (WHO)

1984 HDCV, PCEC, FBKC: ~ 4 doses: 2-1-1 schedule*

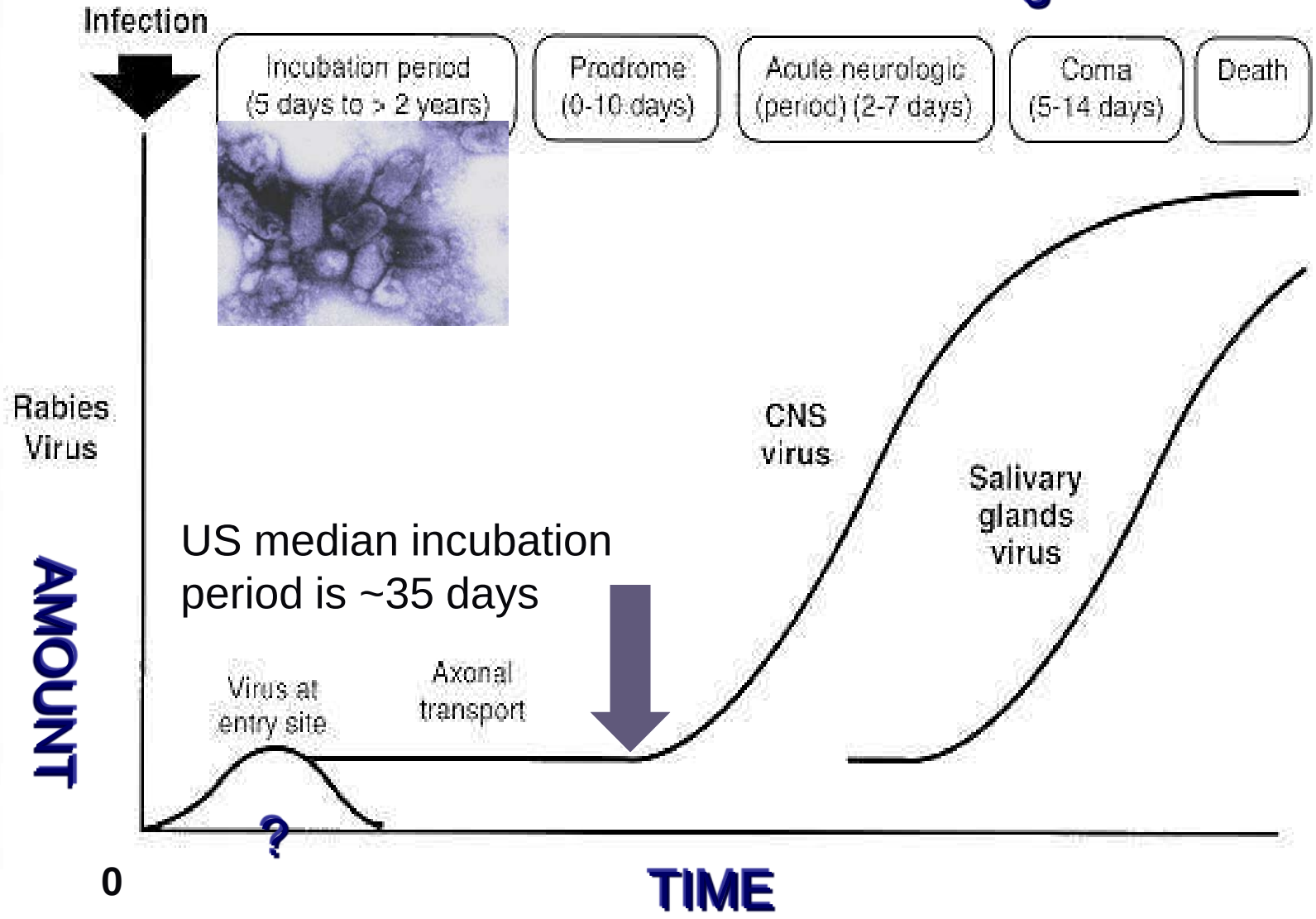
*Requires availability of both vaccine doses on day 0, limits IM sites for HRIG, etc.

[1]S. Plotkin et al. 2008. Vaccines 5th Ed, Saunders, Phila, PA, USA

Viral Pathogenesis

- Rabies is an acute, progressive encephalitis due to highly neurotropic RNA viruses (Genus *Lyssavirus*)
- Rationale for prophylaxis: prevent viral invasion of the central nervous system
- Rabies postexposure prophylaxis emphasizes early
  - wound care
  - passive immunity (i.e., infiltration of rabies immune globulin at the bite site)
  - rabies vaccine to stimulate the development of active immunity via a prime-boost strategy

General Scheme Of Rabies Virus Pathogenesis

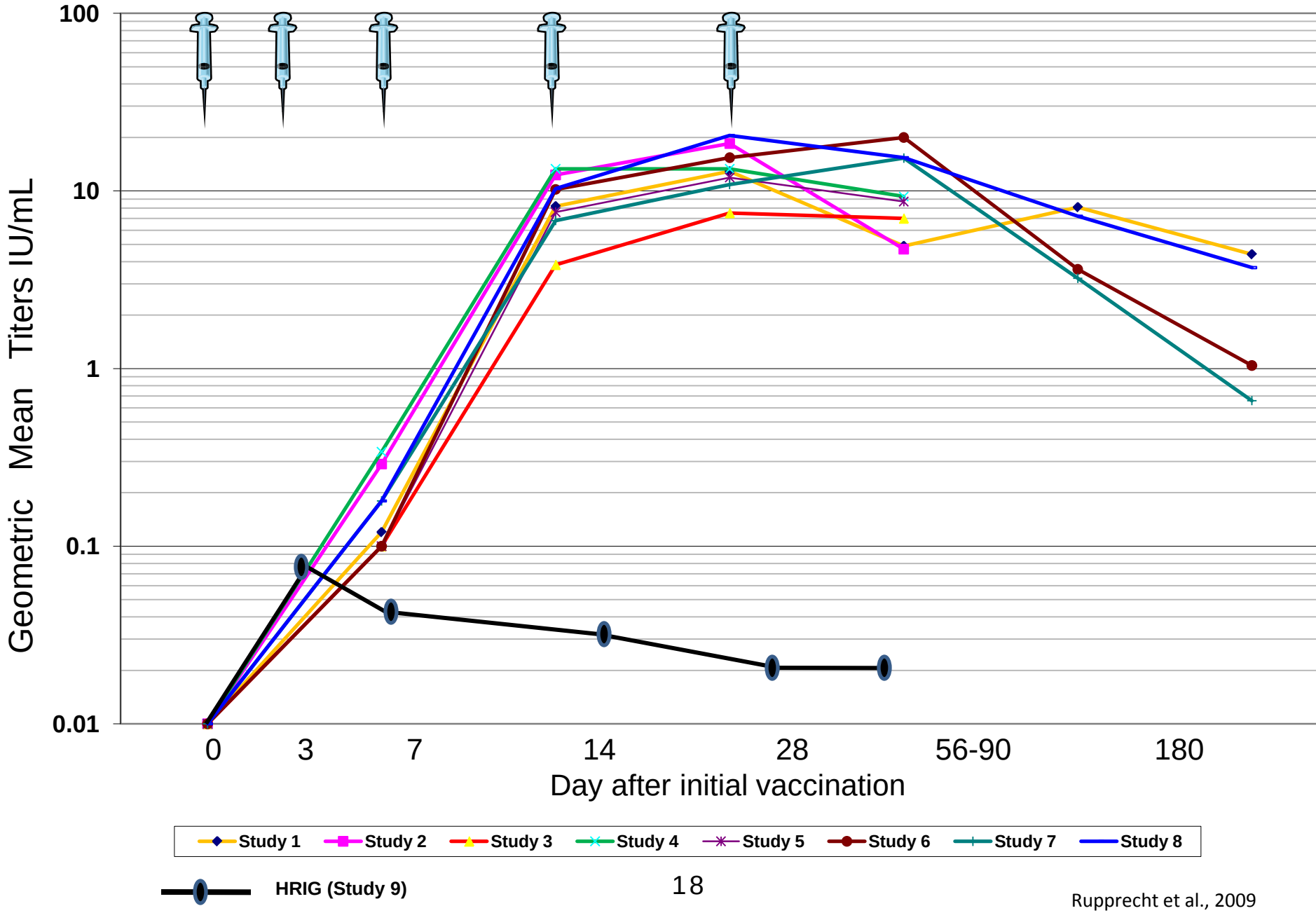


Neuronal retrograde viral transport is estimated at ~50 - 100 mm/day (Tsiang et al., 1991)

Clinical Studies

- Rapid induction of rabies virus neutralizing antibodies is accepted as a critical surrogate of successful intervention, although no ‘protective’ level is defined.
- In clinical trials of rabies vaccination, all healthy individuals developed detectable rabies virus neutralizing antibodies by ~day 14.
- No significant differences were documented between a 4- vs. a 5-dose rabies vaccine schedule in the relative amount of neutralizing antibodies produced.
- In comparison of studies using 4 doses of vaccine, when given in a regimen that included rabies immune globulin, equivalent outcomes were observed.

Rabies virus neutralizing antibody response in humans after rabies vaccine and HRIG



Rupprecht et al., 2009

Epidemiologic Surveillance

- In the USA, no failure of human postexposure prophylaxis was identified during the past 30 years (since use of modern cell culture vaccines and RIG).
- Outside of the USA, rabies occurred in human patients who had:
  - no prophylaxis
  - substantial delays in initiation of prophylaxis
  - significant deviations from recommended prophylaxis
- We could find no failures attributable to an absence of the fifth and last rabies vaccine dose on day 28.

Public Compliance?

- Cross-sectional studies at the state or county level indicated that public adherence to the existing human PEP schedule is not 100%.
- One study of human PEP in NY (1998-2000) found that ~ 13% of persons did not complete the full schedule, and ~2% only completed 4 vaccine doses (2 of which involved documented exposures to laboratory confirmed rabid animals), without incident.
- Grossly extrapolated, ~1,000 persons likely receive <5 doses of vaccine in the USA each year, of which ~30-40 would involve exposures to rabid animals.

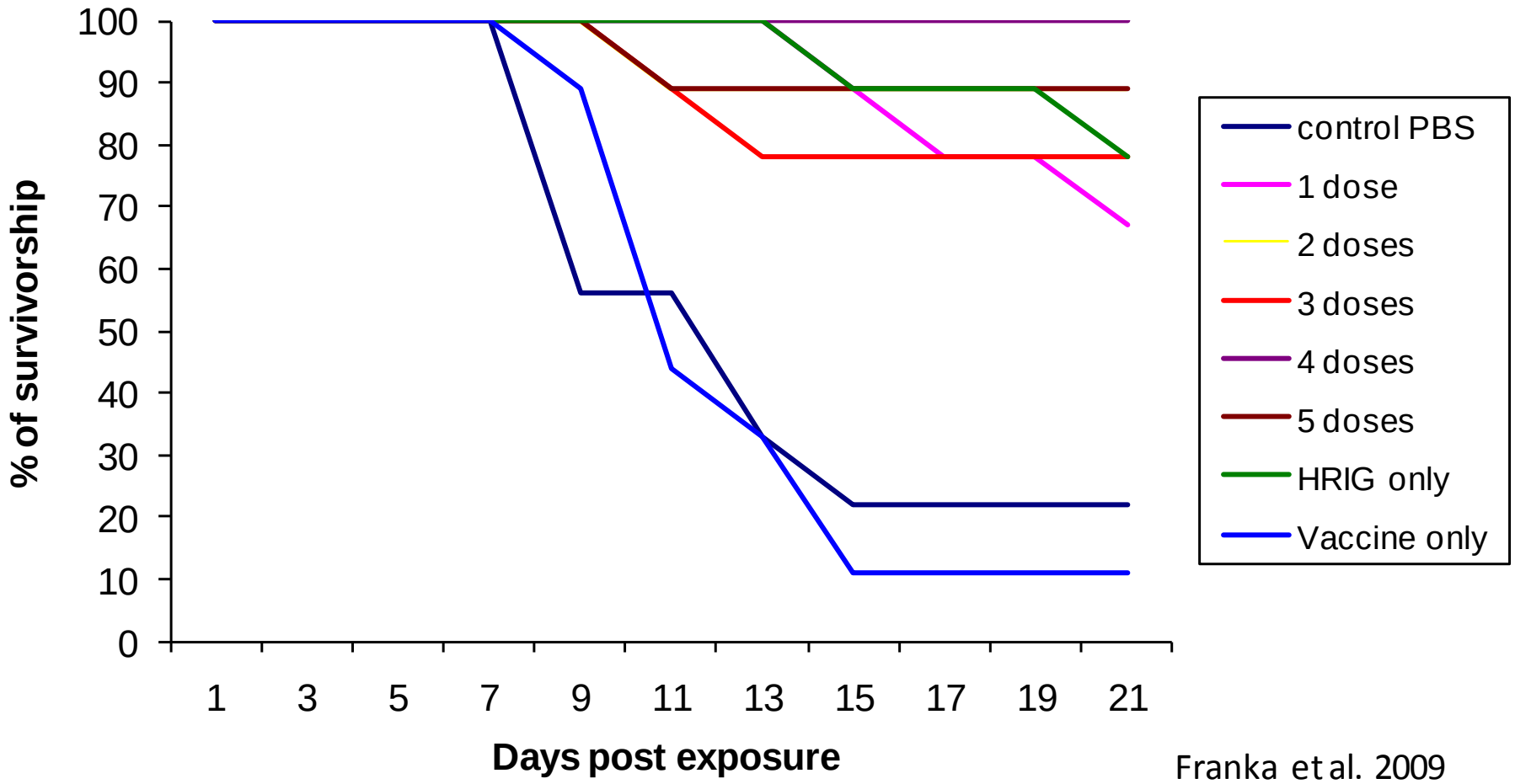
Animal Models

- From the time of Pasteur, animals have been used as important surrogates in preclinical testing of rabies vaccines intended for humans.

- Such research on basic immune response and efficacy outcomes with a variety of species have provided significant inferences to human clinical trials.

- Examples from laboratory rodents to nonhuman primates demonstrate that the absolute number of doses of a potent rabies vaccine is not critical if timely intervention occurs after experimental infection, including the combined use of immune globulins.

Survivorship of Syrian hamsters after exposure to rabies virus, and prophylaxis 24 hr later, with varying doses of commercial rabies vaccine and/or human rabies immune globulin (HRIG)



Franka et al. 2009

Health Economics

- Perspectives on anticipated impacts:
  - Health care payers and health care system
    - Cost per dose could increase?
    - Number of visits/ patient would decrease
    - Number of patients may increase?
  - Consumers
    - Insured – unlikely to “see” increased costs
    - Uninsured – indigent care/ local state health costs - payers of last resort?

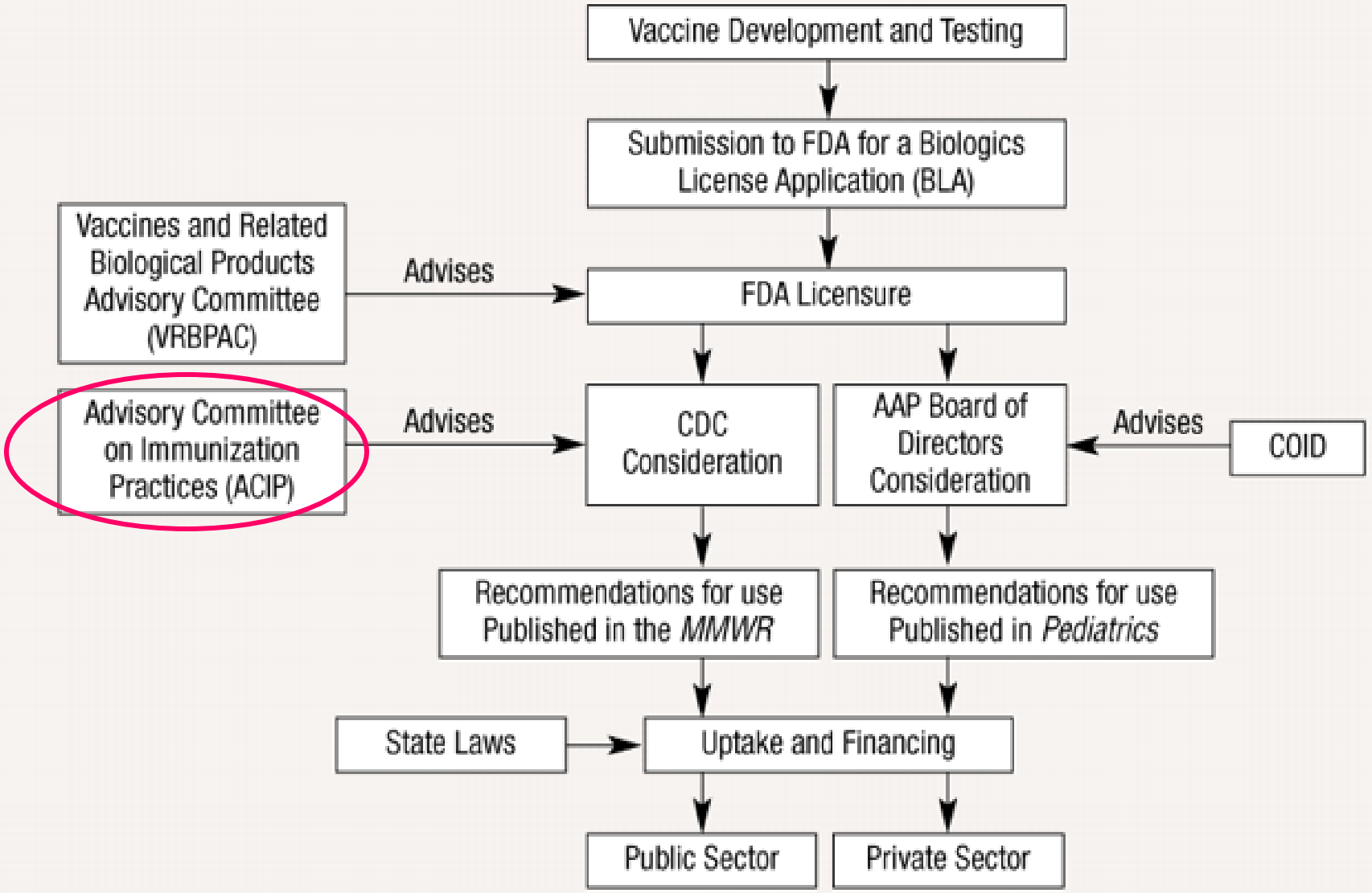
Health Economics (continued)

- Preliminary assessments supported the positive national health benefits associated with a reduced schedule of rabies vaccination.
- Overall, there was no anticipation that changing the current recommended schedule of five vaccine doses to four vaccine doses during rabies postexposure prophylaxis would substantially alter the health economics of human rabies prophylaxis in the USA.

Summary

- No direct post-exposure efficacy trials have compared 5 doses to 4, and no new label claims were expected.
- ACIP work Group review included various published and unpublished basic and applied studies of:
  - fundamental rabies virus pathogenesis
  - experimental animal studies
  - human clinical trials
  - epidemiologic surveillance data
- Conclusion: taken *in toto*, evidence suggests that no rabies case would result from reducing the post-exposure vaccination schedule from 5 doses to 4.
- Based upon the data presented, the ACIP voted to accept the recommendations at the 6/2009 meeting, with exceptions for the immune compromised patient.

Development of pediatric vaccine recommendations and policies



Modified from Pickering LK, Orenstein WA. Development of pediatric vaccine recommendation and polices. *Semin Pediatr Infect Dis.* 2002;13:148-154. Reprinted with permission.

Example Question 1

- A traveler has contact abroad with a suspect animal and begins prophylaxis before returning to the USA – how should this situation be managed in light of the new ACIP recommendations?

Example Question 2

- An 87 year-old, HIV-positive woman is bitten by a rabid bat in her apartment – should she receive the reduced rabies vaccine schedule?

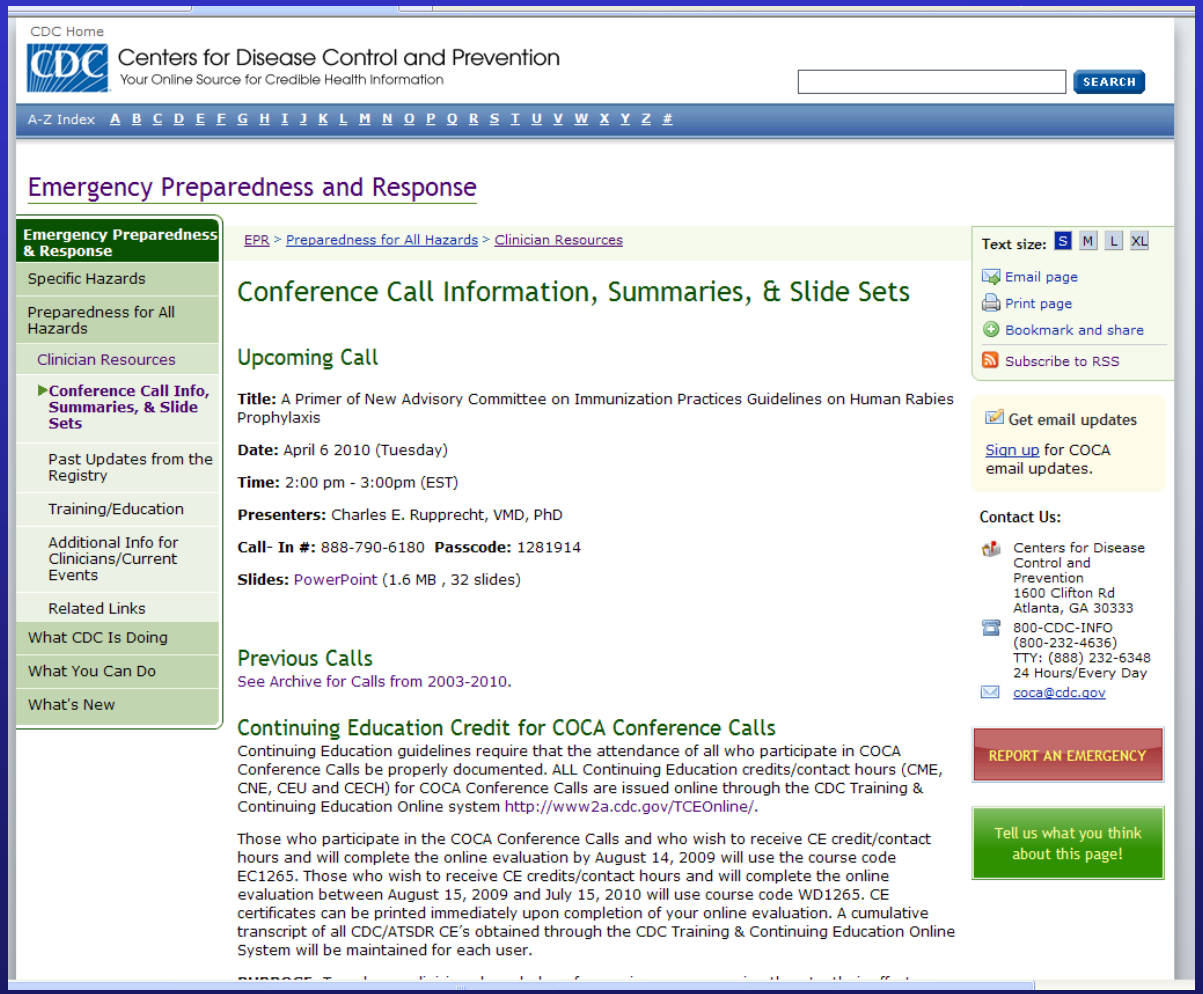
Example Question 3

- A previously vaccinated animal control officer is bitten in the finger while trying to capture a feral urban cat (which later escapes) – what type of prophylaxis should be administered under the new guidelines?

References

- CDC, Advisory Committee on Immunization Practices, Use of a reduced (4-dose) vaccine schedule for postexposure prophylaxis to prevent human rabies, 2010, MMWR 59: RR-2.
- World Health Organization, Expert Consultation on Rabies, Geneva, Switzerland, 2005, Tech Rep Ser 931:1-88.
- Vaccines (ed. S. Plotkin, W. Orenstein, P. Offit), 5th Edition, 2008, Saunders.

Thank You!



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Date: April 6 2010 (Tuesday)

Time: 2:00 pm - 3:00pm (EST)

Presenters: Charles E. Rupprecht, VMD, PhD

Call- In #: 888-790-6180 **Passcode:** 1281914

Slides: PowerPoint (1.6 MB , 32 slides)

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