Rabies pre-exposure prophylaxis schedules and serological monitoring of high-risk exposure populations

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Overview

- Question for consideration
- Historical perspective of Pre-exposure prophylaxis schedules
- Vaccine potency and immunogenicity
- Routes of administration
- Review of evaluated PrEP schedules
- Boosters and duration of immunogenicity
- Special Populations
For your consideration...

- **Status quo**
  - 3-dose, 3-4 week schedule [0,7, 21 or 28]
  - Serological monitoring and boosters based on risk category

- **Should a 2-dose, 1-week schedule [0,7] for rabies PrEP be recommended?**
  - Recommended routes of administration
  - Special populations
    - High risk categories: booster/serological monitoring?
    - Immunocompromised: alternate schedules/serological monitoring?
  - All rabies vaccines are FDA approved as 3-dose series for PrEP
Rabies PrEP Recommendations

- 1885: Pasteur develops rabies vaccine
- 1967: [0, 28] + [196] SQ or [0, 7, 14] + [98] SQ
- 1980: [0, 7, 21/28] IM
- 1984: [0, 7, 21/28] IM/ID
- 2008: [0, 7, 21/28] IM
- 2018: WHO [0, 7] IM/ID or [0] + [w/in 1 year]

*Timeline not to scale*
Vaccine Potency

- Modern rabies vaccine highly potent
- WHO and ACIP recommend ≥2.5 IU potency
- Potency and immune response correlated up to 2.5IU / IM dose
  - No significant association identified above 2.5IU (or 0.5IU / dose ID)

Sudarshan et al. (2005 and 2010). Hum Vaccin.
Kinetics of Rabies Vaccine Immune Response

- Limited Studies beyond neutralizing antibody response
Neutralizing Antibody as Surrogate of Protection

- 0.5 IU/mL rabies neutralizing antibodies (RFFIT)
  - Not a measure of protection
  - Measure of adequate response
  - Reliable detection limit
- Correlation between antibody titer and survival
- Variability between species
- Adequate antibody response after primary vaccination and anamnestic response to challenge best surrogates

Rabies Virus Antibodies from Oral Vaccination as Correlate of Protection against Lethal Infection in Wildlife

Vaccination Route

- ID globally recommended vaccination route since 1980s
  - ACIP recommendation 1984-2008
- ID found more cost effective in most settings and dose sparing in supply limited settings
- No licensed single use ID packaging or multi-draw vials for rabies vaccine
- Injection safety not well studied in setting of rabies ID administration
- Cost effectiveness (ID v IM) relational to PrEP or PEP patient volume

Pre-exposure Prophylaxis (PrEP) Schedules

- **3-dose**
  - 0, 7, 21/28*
  - 0, 3, 7
- **2-dose**
  - 0, 28
  - 0, 7**
- **1-dose**

- Childhood immunization schedules (typically 2-dose, 2-3 months apart)
- Most schedules evaluated by both IM and ID routes

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*Current ACIP recommended schedule
**Recently recommended WHO schedule
2-dose, 1-week Schedule

- 2018: Recommended WHO PrEP Schedule (IM or ID)
- 1 dose vaccine administered IM on days 0 and 7
- Primary response well documented
  - Infer from existing 3-dose schedule

Recuenco et al. (2017) Vaccine
Clinical Trials
- ID
- N=500
- 100% adequate response at day 35
- 2-dose group had significantly higher GMT at 1 year compared to 3-dose
- No difference in post-booster response at 1 year

Soentjens et al. (2018) CID.
Duration of Immunogenicity - Evidence

- **Follow-up typically less than 1 year**

- **Longer follow-up**
  - Mostly [0, 7, 21/28] schedules
  - Few [0, 28]

- **Primary response titer not effective at predicting duration of immunogenicity**
  - Titer at 1 year or post booster significantly associated with titer 2-7 years later
  - Titers >30 IU/mL post 1 year booster associated with adequate response 5-10 years later
Booster at 1 year associated with long term immunogenicity

Booster Response

- Anamnestic response nearly universal to vaccine booster
  - One non-responder reported in study (later diagnosed with B-cell Lymphoma)

- Survival following exposure w/o booster
  - 2010 Liver recipient from rabid donor in Germany
    - Vaccinated >20 years prior, anamnestic response documented
  - Reports of significant titer increases following bat bites among wildlife biologist
  - Reduction in rabies cases in Amazonia region of Peru after mass childhood immunization campaign

PrEP Failure

- **1 well documented PrEP failure reported**
  - 1982, Peace Corp Volunteer, Vaccinated ID with HDCV vaccine in Kenya
    - Bitten by dog ~6 months later
    - Died of rabies 3 months after bite
  - Classically attributed to co-administration of chloroquine during PrEP series
    - Study at time found other groups give ID HDCV abroad at time had lower or undetectable titers compared to those in the US
    - Likely multiple causes

- **Inadequate response to primary vaccination reported in immunocompromised persons**

Bernard et al. (1985) AJTMH
Special Populations – High Risk

- **High risk (Continuous and Frequent) categories**
  - High rate of exposure events, high risk of rabies from exposure
  - High titer (>0.5 IU/mL)
    - Unrecognized exposure or risk under underappreciated
    - Higher titer correlated with protection
  - Booster at 6-12 months after primary vaccination improve likelihood of maintaining adequate titer
    - Reduce frequency of serological monitoring
Special Populations – High Risk

- **Moderate risk (Infrequent) category**
  - High rate of exposure events, low risk of rabies from exposure
  - Increased risk sporadic and shortly after primary vaccination (e.g. travelers)
    - Often limited time to complete vaccination series
  - Routine booster at 6-12 months and routine serological monitoring not critical
  - Adequate anamnestic response expected regardless of titer
  - Serology or booster if risk status changes
Special Populations - Immunocompromised

- Data scarce for any schedule
- Risk reduction
  - Increased focus on exposure avoidance, appropriate PPE, and prompt health seeking behavior
- Serological confirmation of adequate immune response recommended
  - >0.5 IU/mL
Special Populations – Pregnant Women

- **No safety concerns reported**
  - Scarce data

- **Risk reduction**
  - Increased focus on exposure avoidance, appropriate PPE, and prompt health seeking behavior
  - May consider deferring where risk reduction possible and PEP readily available
Working Group Plans

- **February 2020 ACIP meeting**
  - Systematic review presentation
  - GRADE for 2-dose PrEP schedule

- **Future ACIP meetings**
  - Vote on PrEP schedule
  - Additional data for consideration of alternate PEP Schedule
Thank you!

For more information please contact Centers for Disease Control and Prevention

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