

Ethical Considerations in Rabies mAb Development

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Rabies Prevention/Treatment

- Mass dog vaccination
- Mass human vaccination
- **Post exposure prophylaxis (PEP)**
- Public education
- Provider education
- Bite treatment centers

Sources: Dimaano, Scholand, Alera et al 2011; Shankaraiah, Gangaboraiah, Narayana et al 2012; Wilde, Lumlertdacha, Meslin et al 2015; Wilde, Hemachudha, Wacharapluesadee et al 2015; Wilde, Ghai and Hemachudha 2016

Challenges

- Human Rabies immune globulin (RIG)
 - Product
 - “Inconsistency between batches,
 - Potential contamination with blood borne diseases, and
 - ...severe allergic reactions (with equine RIG)
 - Expense
 - Supply in low resource settings where incidence highest and rising

Source: Tsekoa, Lotter-Stark, Buthelezi, et al 2016

Goal

- “Safer, efficacious, and potentially more economical alternative biologic.”
 - Rabies monoclonal antibody (RmAb) cocktail

Source: Tsekoa, Lotter-Stark, Buthelezi, et al 2016

Considerations

- Beneficence/Study Design
 - conducting PEP trials of RmAb as an alternative to available RIG
- Respect/Vulnerable Populations
 - conducting PEP trials in children
- Justice/Exploitation
 - conducting PEP trials in rural/developing areas

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Study Design

- What is the standard of care?
 - Prompt wound care followed by:
 - 1 dose RIG into and around wound as well as intramuscularly
 - 4 doses of vaccine

Source: MMWR 2010

Study Design

- Randomized controlled trial
 - Placebo trial
 - Wound cleaning and vaccine v. wound cleaning, mAb and vaccine
 - Superiority trial
 - Wound cleaning, vaccine w/mAb \geq wound cleaning, vaccine w/RIG (standard)
 - Equivalency trial
 - Wound cleaning, vaccine w/mAb = wound cleaning, vaccine w/RIG (standard)

Source: MMWR 2010

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Vulnerable Population

- Rabies disproportionately effects children in countries where it is endemic
- 40% of those bitten by rabid dogs are children under 15

Source: WHO 2013; WHO 2017

Vulnerable Population

- Research with children allowed when
 - No more than minimal risk, or
 - More than minimal risk with potential for **direct benefit**, or
 - **No more than minimal risk** with potential for benefit to children with disease/condition
- *otherwise not approval, referred to expert panel

Source: WHO 2013

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Exploitation

- Exploitation
 - **A** exploits **B** when **A** receives an unfair level of benefits and/or **B** receives unfair burden of risks as a result of interacting with **A**
- Non-exploitation
 - Only those likely to benefit from results ought to be exposed to risk and burden of research enrollment

Source: Emanuel et al (2004)

Exploitation

- What increases likelihood of exploitation?
 - Less experience with scientific research
 - Less local infrastructure for health care and treatment
 - Less ability to give voluntary informed consent, due to social, gender, class inequities
 - Less experience or capacity with scientific and/or ethical review
 - Less infrastructure to conduct own research

Source: UNAIDS(2007)

Exploitation

- How do we minimize risk of exploitation?
 - Where is the study being conducted?
 - In what types of capacity building ought investigators invest?
 - Who will have access to the intervention if research is a success?
 - Who is responsible for assuring access?

Exploitation

- Why is research proposed in the low resource setting?
 - Greater prevalence
 - Question/intervention more relevant there
 - Convenience/familiarity: preexisting relationship
 - Cost/expediency: relevant but not decisive

Source: Kass (2013)

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