**Ethical Issues in testing a low-cost approach to giving eRIG for rabies PEP**

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The author, Omesh Kumar Bharti, is to be congratulated on presenting a very clear narrative on the rationale and development of the innovative prevention that eventually led to changing WHO’s Post Exposure Prophylaxis (PEP) for rabies.(1) The principle ethical dilemma presented in this case occurred when researchers and clinicians attempt to evaluate treatment or prevention where standard recommendations were neither practical, or affordable. Low-resource settings are the primary venue where these situations play out as it was in Himachal Pradesh. WHO prevention guidelines for the use of equine rabies immune globulin (eRIG) for Grade III exposure of a bite from an animal suspected of rabies was often unavailable and/or unaffordable to patients or institutions in the private market because of the large quantity of eRIG that was recommended.

The first challenge to investigators is to define the ‘Gold Standard’, in this case the recommendation of WHO. What is it? How was it arrived at? It is the result of expert opinion only or is it based on solid scientific evidence? Did the standard take into consideration where the treatment/prevention would be implemented? Does the ‘Gold Standard’ only apply to wealthy countries where cost is not a factor and availability is assured? The Institutional Ethics Committees (IEC) initially consulted by Dr. Bharti did not want to approve of his proposed intervention which was a reduction in the amount of eRIG at the site of the wound and elimination of the IM injection of the same. They were reluctant to do so because of the WHO recommendations. But the recommendations for the use of eRIG were based on the opinion of WHO experts not on solid research evidence. Control studies in humans could not have been conducted and therefore did not inform the WHO recommendations. Opinions did. Dr. Omesh Bharti, his colleagues, their patients, and the IECs were prisoners of opinions and not fact. The ‘Gold Standard’ PEP guidelines may have reflected the concern of the ‘experts’ in not providing the maximum intervention given high rabies mortality. But they did not take into consideration the difficulty and cost of the PEP. Faith-based rather than evidence-based guidelines were given legitimacy by WHO. It is when shortages arose that the PEP standard was challenged.

A somewhat similar issue arose when there was a shortage of yellow fever vaccine developed during an outbreak in the Democratic Republic of the Congo (DRC) in 2016.(2) A decision was taken by the government, with the support of WHO, to reduce the recommended dose of vaccine to 1/5th of the standard so that larger numbers could be vaccinated to stem the epidemic. Though seroconversion rates indicated that the lower dose of vaccine could be effective the actual efficacy could not be determined until the population was followed to determine incidence and mortality from those immunized with the lower dose yellow fever vaccine.

In Dr. Bharti’s view he did not conduct a study but rather a clinical intervention to save lives. It was, in fact, a preventive intervention and innovation (3). There was no control group and one method was not compared prospectively with another. Does this mean that the intervention should be held to a different standard than if it was a research study? It might be thought of as the preventive side of innovative therapy which is defined as a newly introduced or modified therapy with unproven effect or side effect undertaken in the best interest of the patient. But it must be conducted within an ethical framework that recognizes that the intervention is not the standard.

The author took the position that this was not research, but was experimentation and therefore research guidelines and ethical clearance had to prevail. Approval from his local IEC proved to be difficult because of prevailing opinions on rabies PEP. Some IEC members were concerned that the use of cheaper eRIG would lead to anaphylactic reactions; however, data from Thailand recorded only 2 of 150,000 anaphylactic reactions in their use of eRIG. (4) Finally a champion, a recognized rabies expert, stepped forward to argue the case and convince the IEC of the validity of the study. Consent was taken, a protocol was developed and rigidly adhered to, and patients were followed for up to a year post-prophylaxis. The number of deaths were measured and compared to past cases that had received the WHO recommended eRIG dose. Human rabies has essentially a 100% mortality, so a comparative study was unacceptable

A major ethical dilemma would have occurred if the hospital had purposely withheld the eRIG recommended by WHO. But this is not what occurred. The hospital developed its policy based on the availability of eRIG in the market and at the hospital. Prior to this hospital policy, all patients in Himachal Pradesh, except for the very poor, had to purchase potentially eRIG in the market which was often not available or far too expensive for many. One of the cases presented in the article documents the death of a woman who could not find eRIG in her local hospitals or the market even though she could afford to purchase the drug. What is the ethics of this state or any state having such a policy? Why wasn’t eRIG available to all Indian citizens?

Low resource environments rightly challenge high cost preventions and interventions for diseases especially common in their environments. There is a long history of the development of clinical interventions (eg ORT to treat cholera and other diarrheas) as well as preventive efforts (eg lower dose vaccines). What is important is these innovations are conducted in an ethical framework that takes into consideration the quality of the information available and the context in which the intervention will be implemented. Context is critical in the defining the ethical issues. This has been well demonstrated in the recent Ebola outbreaks where ethical guidelines in the evaluations of new therapies and vaccines were developed taking context and urgency of the issue into account (5,6).

**References**

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