

ethical framework that recognises that the intervention is not the standard.

Dr Bharti takes the position that this was not research but a clinical intervention and, therefore, research guidelines and ethical clearance had to prevail. Approval from his local IEC proved to be difficult because of prevailing opinions on the 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 cases of anaphylaxis among 150,000 patients who received eRIG at that institution (5). Finally, a champion, a recognised 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. All rabies deaths were investigated for whether the patient had received post-exposure prophylaxis. Human rabies has essentially a 100% mortality, so a comparative study randomly assigning patients to one of two treatments was unacceptable.

A major ethical dilemma would have occurred if the hospital had deliberately 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 potentially purchase eRIG in the market; and this was often not available or was 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 are the ethics of Himachal Pradesh or any state having a policy which requires a patient to purchase a life-saving drug from the market? Why wasn't eRIG available to all Indian citizens?

Low resource environments rightly challenge high cost preventions and interventions for diseases, especially for those common in their environments. There is a long history of the development of clinical interventions (eg, ORT to treat cholera and other diarrhoeas) as well as preventive efforts (eg, lower dose vaccines). What is important is that 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 defining the ethical issues. This has been well demonstrated in the recent Ebola outbreaks where ethical guidelines for the evaluations of new therapies and vaccines were developed taking the context and urgency of the issue into account (6, 7).

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Exemplary operational research on an important public health problem

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Abstract

Rabies is a fatal disease once contracted, and a serious public health problem. Immunisation was unaffordable and inaccessible

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for most affected people in India. Omesh Bharti's operational research allows us to reduce the unit dose needed for life saving rabies immunoglobulin (RIG) for class 3 rabid animal bites thereby raising hopes that access to this drug will improve. This study also suggests how public health research should question established guidelines that are rooted in impractical biomedicine without considering sociopolitical realities. The randomised controlled trial as a standard of research methodology is not only impractical but unnecessary. We discuss some of the challenges such as stockout of life saving medicines like RIG and suggest possible solutions. There is still a need to determine the correct RIG dose and the best technique for administering, storage and timing of this important drug.

The outcome of Omesh Bharti's work(1) is invaluable since estimates suggest that only about 2 percent of people requiring Rabies immunoglobulin (RIG) after a potentially rabid bite received appropriate post-exposure treatment in 2017 (2).

Class 3 bites by suspected rabid animals require not only thorough cleaning of the wound and anti-rabies vaccine, they also need ready antibodies for the rabies virus, in the form of rabies immunoglobulin (RIG), produced either in horses or in human volunteers, which has to be instilled locally to neutralise the virus that may have been deposited in the wound during the bite. This is essential since the body is able to produce antibodies on its own only after about 10 days. These immunoglobulin preparations are produced by a few companies and their production and supply have remained chronically inadequate. The World Health Organisation (WHO) had previously advised a fixed dose of 40 units per kilogram body weight of eRIG (equine RIG) or 20 units per kilogram body weight of hRIG (human RIG) to be instilled as much as possible locally into the depth of the wound, and the remaining quantity into the muscle, so that the rest may reach the wound through the blood stream (3).

Assuming that shortages occur due to the high cost of this preparation, Bharti wondered whether the intramuscular requirement of the RIG was of any use in preventing rabies. He therefore led an operational research study in the busy service set up of a government hospital in the capital city of Himachal Pradesh. He reviewed the literature and consulted experts regarding the basis of recommendations for RIG use, and saw enough unanswered questions to be able to plan this research, simultaneously ensuring that it was rooted in ethical principles. His two years of observational research using an appropriate design without any control group led him to infer that the intramuscular instilling of RIG was redundant. Further, through publication of his findings, he and his co-researchers could successfully press for WHO to rectify its global recommendations regarding the management of suspected rabid animal bites of class 3 severity. His intervention cuts costs dramatically by saving on the unit drug requirement, and may improve access for larger numbers of people with bites.

This research is exemplary in terms of problem analysis and constitutes a sterling example of how good public health research should question prevailing guidelines and have them modified depending upon the sociopolitical reality of the day. The technologists make guidelines based on purely biomedical principles and expect the social system to adjust to it. As a result, there are questions about how these interventions should be administered in different situations, for example: At what level of health facility should rabid animal bites be treated? Should insulin be dispensed from primary health centres (PHCs) or health subcentres where there are no refrigeration facilities? Should one administer streptokinase at a rural hospital where no CT scan is available to a patient with ischemic stroke who presents early within 2 hours?

This work also makes us realise that many of our established "standards" and doses of drugs are products without basis

in any systematic process to find the ideal; but it is difficult to question them. The classic gametocidal dose of primaquine in falciparum malaria was 45 mg for decades, and was reduced to 15 mg or 0.25 mg per kg body weight much later (4). Similarly, the dose of dexamethasone in laryngotracheobronchitis or severe childhood croup of 0.6mg/kg body weight (5) was recommended from one random use and was never systematically studied. This research also questions the obsession with the randomised controlled trial (RCT) as the standard of biomedical research methodology. Bharti's study shows that there was no need for controls, given the described feasibility. Public health is rife with such examples of other often richer research techniques available for observational study. Ring vaccination for smallpox was one of the successful methods of eradicating small pox and this also emerged from a shortage of the vaccine(6). The dosage and use of penicillin, DDT spraying and chloroquine for malaria were key public health initiatives that were not based on RCTs. Similarly, the role of clean water, clean air, housing, or sanitation in improving public health were not confirmed through any RCTs.

While strongly appreciating Bharti's work, we feel this issue of public health importance calls for deeper study. We discuss some of the challenges with possible solutions for stockout, determining the correct RIG dose and the best technique for administering, storage and timing of RIG.

Rabies is a neglected disease as defined by WHO, which has drawn up an ambitious proposal for its elimination by 2030 (7). WHO claims that approximately 80% of human rabies cases occur in rural areas, and over 40% of rabies deaths occur in children aged under 15 years, among the world's poorest and most disadvantaged communities (8). People continue to die of rabies because animal bites are neglected and awareness regarding early washing of wounds, basic medical care, and post exposure prophylaxis (PEP) is yet to reach remote and resource-poor areas. These factors coupled with uncontrolled rabies in dogs and other animals demand a major push in our efforts at dog vaccination, as well as in improving awareness of the disease. Ensuring RIG supply alone will not eliminate rabies-related deaths.

Bharti's quest began with attributing stockout of RIG to its relatively high cost. RIG is in short supply all over the world owing to its cost and difficulty in scaling production mechanisms in the living equine or human body. Manufacturers are not willing to produce RIG due to a limited market and price capping by the Drug Price Control Order. Monoclonal antibody (mAb) cocktail trials have shown similar efficacy to RIG for prevention of rabies and WHO has recommended use of mAb cocktails as an alternative to RIG in cases of stockout (8). While mAb cocktails can be produced more abundantly in laboratories, the cost will continue to limit their availability for the masses. We think eRIG at a retail price of INR 600 for 1000 units (or INR 1200 for a 50-kg adult) is not too expensive for a single-use drug to prevent an almost fatal disease. In comparison, anti-snake venom for an envenomation would cost INR 5000 for 10 vials, which is the

prescribed minimum dose. If a person has to buy it from the market, the cost varies from INR 600 to 6000 depending on the brand, but the price of RIG for a health system would be as low as INR 400 for an adult (9). Cost does not seem to be a good enough reason for RIG stockout, and health systems should negotiate with manufacturers over pricing and availability. We also think that if stocks can be maintained at district hospitals, with transport of the drug within hours to the respective PHC/CHCs in case of demand, this can help resolve the problem of unutilised stock leading to wastage.

To avoid the problem of stockout of this essential drug either due to its high cost or reduced production, some concrete action is warranted. In India, at least five companies make equine rabies immunoglobulin and a similar number make human rabies immunoglobulin. Currently, Serum Institute of India is also making a monoclonal antibody preparation and is already marketing it. If production still does not match the demand, the Drugs Controller General of India should decree compulsory licensing and if necessary can use the Doha Declaration on the TRIPS Agreement and Public Health and the United Nations High-Level Panel on Access to Medicines (UNHLP) international trade rules for its production by multiple companies to allow for cheaper and larger stocks of essential drugs (10). Stockouts, such as occurred nationally in 2016, are unacceptable. The High Court of Chhattisgarh's instruction to the public health system in 2017 to ensure the supply of RIG and rabies vaccine at PHC, CHC and district hospitals at all times (11) emphasises this. After this order, these lifesaving drugs have been available in Chhattisgarh in public health facilities. WHO, in its elimination strategy, also proposes to set up biological banks and stockpiles of RIG to support member countries. We in India can also use these provisions according to our need.

The antisera are meant to neutralise the virus, as it is for the anti-snake venom (ASV) against snake venom or for anti-scorpion antivenom against scorpion venom. The recommended dose of 20 IU/kg and 40 IU/kg for human and equine RIG was decided based on serum antibody levels rather than on neutralisation of virus (12). Animal studies have shown protection from rabies with lower doses. It is likely that we might be able to bring down even further the recommended doses for rabid animal bites.

For using saved RIG from an opened vial on the next patient, appropriate storage is essential especially in a health facility like a CHC or PHC where rabid bite events may not occur daily. WHO recommends that the remainder of the calculated dose should be fractionated in smaller, individual syringes to be used for other patients and advises that aseptic retention should be ensured (13) This would require vials and ampoules

of smaller volumes, as well as the addition of preservatives in the antisera to cut down costs and wastage.

Bharti's note (1) comments that RIG only works if it is administered within hours of the bite. Often people arrive at a health facility several days after they have been bitten by a potentially rabid animal due to distance, or for financial reasons. The RIG works best if it is given within hours of the bite, but even if someone presents up to 7 days later, they should be offered RIG for class 3 bites in addition to the anti-rabies vaccine.

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