**SLUG: COMMENTARY**

**TITLE:** **Exemplary operational research on an important public health problem**

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The outcomes of Omesh Bharti’s work make fascinating reading and his fleshing out of the research question, putting it into action, taking a stand and then ensuring that the fruits of this research get translated into public health policy at a global level is admirable. The work is invaluable since estimates suggest that only about 2 percent of people requiring RIG after a potentially rabid bite received appropriate post-exposure treatment in 2017(1).

Class 3 bites by suspected rabid animals deserve not only thorough cleaning of the wound and anti-rabies vaccine, they also need ready antibodies to the rabies virus, as rabies immunoglobulin (RIG) produced either in horses, or in human volunteers 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 few companies and their production and supply have been inadequate chronically. The WHO had been previously advising a fixed dose of 40 units per kilogram body weight of ERIG or 20 Units per kilogram body weight of HRIG to be instilled as much as possible locally into the depth of the wound, and the remaining in the muscle so that the rest may reach the wound by the blood stream(2).

Assuming that the shortage occurs due to the high cost of this preparation, and also wondering whether the intramuscular part of the RIG being of any use in preventing rabies illness, Bharti could lead an operational research study being carried out in the busy service set up of a municipal hospital of the capital city of Himachal Pradesh. He reviewed the literature and consulted experts for the basis of recommendations for RIG use, and saw enough unanswered questions to be able to plan this research, which was clearly rooted in ethical principles. His 2 years of observational research using an appropriate design of not using any controls led him to infer the uselessness of any other instillation of RIG except in the local wound. Further, through publication of his findings, he could successfully advocate WHO to rectify their global recommendations regarding managing suspected rabid animal bites of class 3 severity. His intervention not only cuts down costs but also saves on the unit drug requirement leading to access to larger numbers of people with bites.

This research is exemplary in terms of problem analysis and brings forth a sterling example of how good public health research should be done and its results advocated for. How should guidelines be questioned and 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. For example, at what level of health facility should rabid animal bites be treated? Should insulin be dispensed from PHC or health subcenters where there are no refrigeration facilities? Should one administer streptokinase at a rural hospital where CT scan is not available to a patient with ischemic stroke who presents early within 2 hours.

This work makes us realize that many of our established "standards" and doses of drugs are products of initial habit rather than any systematic process to find the ideal and how difficult it is to question them. The classic gametocidal dose of primaquine in falciparum malaria was 45mg for decades, which got reduced to 15 mg or 0.25 mg per kg body weight much later(3).Similarly, the dose of dexamethasone in laryngotracheobronchitis or severe childhood croup of 0.6mg/kg body weight was recommended from one random use and was never studied systematically.

It also questions the obsession with the randomized controlled trials (RCTs) 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 with other often richer forms exist for observational research. Ring vaccination for smallpox was one of the successful methods of eradicating small pox and this also arose emerged from a shortage of the vaccine(4). The dose and use of 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 this work, one also needs to be aware and dive deeper in this issue of public health importance. We discuss some of the issues with possible solutions for stockout, RIG dose, technique of administration, storage and timing.

Rabies is a neglected disease defined by WHO, who has ambitiously proposed its elimination by 2030(5).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(6). People continue to die of rabies because animal bites are neglected and awareness regarding early washing of wound, basic medical care, such as PEP, following an exposure is yet to reach in remote and poor areas. These factors coupled with uncontrolled rabies in dogs and other animals demand major push in our efforts in dog vaccination as well as in improving awareness of the disease. Ensuring RIG alone will not eliminate rabies related deaths completely.

Bharti’s quest begins with attributing stockout of RIG to its relatively high cost. . RIG is short in supply all over the world owing to its cost and difficult to scale production mechanisms in living equine or human body. Manufacturers are not willing to produce RIG due to less attractive market and price capping by Drug Price Control Order. Monoclonal antibody (mAbs) cocktail trials has shown similar efficacy as RIG for prevention of rabies and WHO has recommended use of mAb cocktails as an alternative to RIG in cases of stockout. While mAbs cocktails can be produced more generously in laboratories, cost will continue to limit their availability for masses. We think ERIG at a retail price of INR 600 for 1000 units, (meaning INR 1200 for a 50 kilogram adult), is not too expensive for a one time 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, cost varies from INR 600 to 6000 depending on brands but the prices of RIG for a health system would be as low as INR 400 for an adult(7).Cost does not seem to be a good enough reason for RIG stockout and health systems should negotiate with manufacturers for pricing and availability. We also think if stocks can be maintained at district hospitals with transport of drug within hours to respective PHC/CHCs in case of demand can help resolve problem of unutilized stock leading to wastage.

In future, to avoid the problem of stockout of this essential drug either due to cost or reduced production some action is warranted. In India, at least 5 companies make equine rabies immunoglobulin and a similar number make human rabies immunoglobulin. Lately, Serum India company is also making a monoclonal antibody preparation and is already marketing it. If still the production does not match the demand, the Drugs controller general of India should issue compulsory licensing and if necessary can use 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 for price lowering competition to allow cheaper and more stocks of essential drugs(8). Stock outs as happened nationally in 2016 should be 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(9) emphasizes this further. After this order, these lifesaving drugs are available in Chhattisgarh in public health facilities. WHO in its elimination strategy also propose making biological banks and stockpiles of RIG to support member countries. We in India can also use these provisions per our need.

Another point worth noticing is RIG doses. There does seem to be a larger problem with the dose. For example, it is clear that the antisera were meant to neutralize the virus, as it is for the anti-snake venom (ASV) against the snake venom or for the anti-scorpion antivenom against the scorpion venom. Dose of these antisera logically depends solely on the expected virus volume or the venom that may have been injected rather than the size of the person receiving it. It is now clear that RIG's role is to neutralize virus at wound site till body evokes antibody response and yet we do not have minimum recommended dose. The dose of 20 IU/Kg and 40 IU/Kg for Human and Equine RIG is maximum recommended dose and was decided based on serum antibody levels rather than neutralization of virus(10). Animal studies have shown protection from rabies with lower doses. We think dosing requires further experimentation for minimum recommended dose.

For using saved RIG from the opened vial in the next patient, appropriate storage is essential especially in a health facility like a CHC or PHC where the rabid bite events may not be daily. WHO recommends the remainder of the calculated dose to be fractionated in smaller, individual syringes to be used for other patients and advises aseptic retention should be done(11). Perhaps we need smaller volume vials and ampoules as well as addition of preservatives in the antisera to cut down costs and wastage.

This note 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 distant functional facility or other 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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