Using a modified rabies immunoglobulin protocol in a crisis of unavailability: Ethical and practical challenges with Commentary by Dr. Yogesh and Dr.Richard

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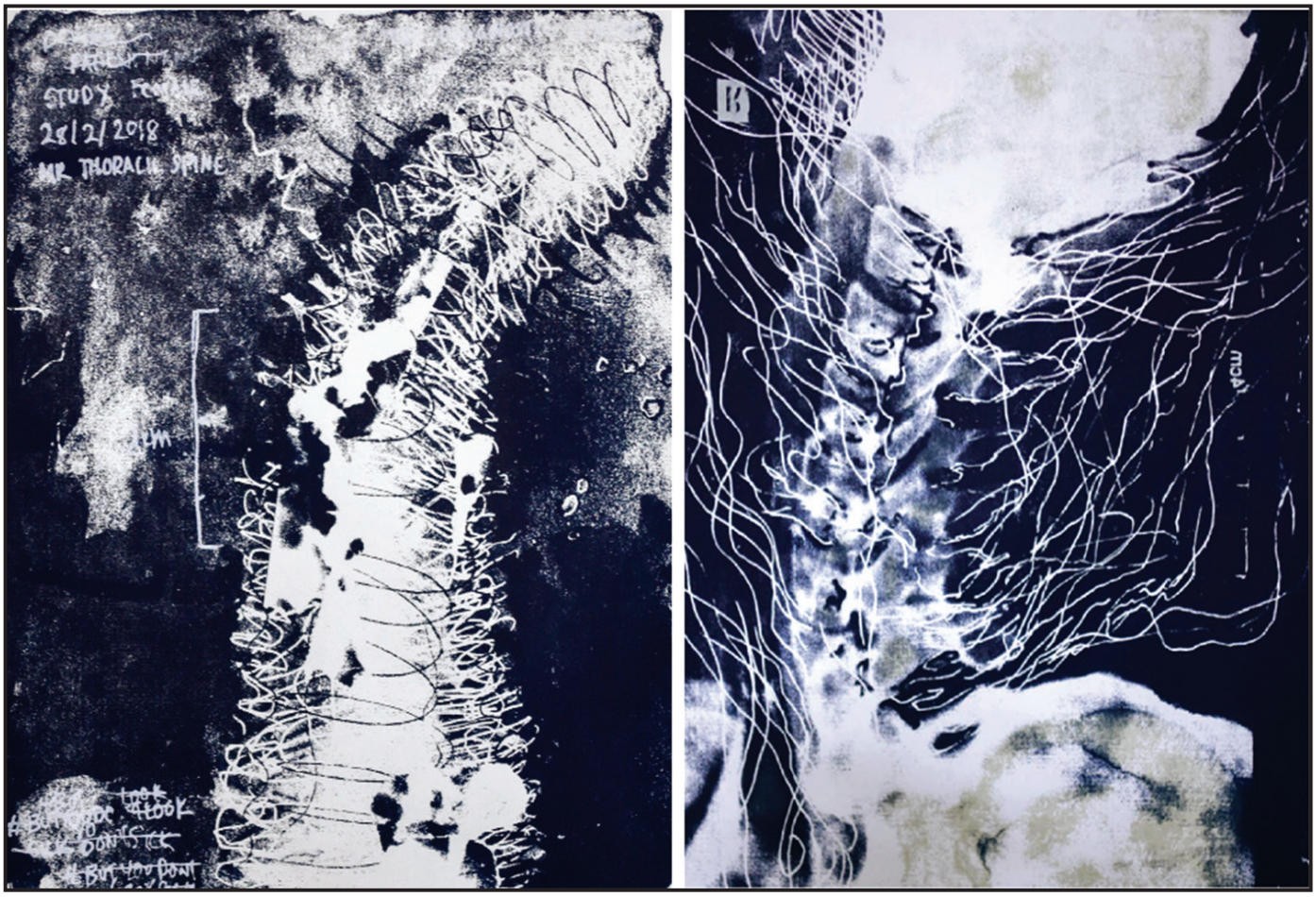

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Using a modified rabies immunoglobulin protocol in a crisis of unavailability: Ethical and practical challenges

OMESH KUMAR BHARTI

Abstract

Rabies is a dreaded disease of zoonotic origin, responsible for an estimated 55,000 deaths annually, of which 20,000 deaths are in India. Some animal bite patients need rabies immunoglobulin (RIG) for post exposure prophylaxis, in addition to the vaccine against rabies. The major reason for the high death rate in India is the high cost of RIG. Until 2017, the WHO-recommended protocol required a large amount of RIG. I describe how a cost-saving protocol for RIG was implemented in Himachal Pradesh. The published results contributed to the modification of the WHO's global recommendations on RIG use.

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Background

Rabies is a disease caused by the bite of a rabid animal. An estimated 55,000 people die a painful death due to rabies every year, out of which 20,000 deaths are reported from India alone (1). The annual cost of medicines for animal bite treatment in India was estimated in 2003 at Rs 2 billion (2).

According to the World Health Organisation's classification of animal bite wounds, intact skin if licked by rabid animals is called a Type-I bite and does not pose any threat of rabies, and requires only washing with soap and water. Bites that breach the skin surface but do not bleed are known as Type-II wounds and require only vaccination for protection after thorough wound wash with soap and water and application of antiseptic. Wounds that bleed are known as Type-III bites. In the case of Type III wounds, WHO advocates administration of the rabies vaccine along with additional injection of rabies immunoglobulin (RIG) into the wound/s to neutralise any virus present in the surface of the wound.

Until recently, WHO recommendations required injection of a certain quantity of RIG, according to the patient's weight (3). In this report, I describe how a modified protocol was

implemented in Himachal Pradesh, that contributed to modification of the WHO's global recommendations on RIG use.

The main reason for the high rabies death rate in India has been the high cost of the rabies vaccine and RIG. Over seventy percent of patients in the state of Himachal Pradesh, where I work, use government health services. However, for a long time, the rabies vaccine was not available free to everyone in government hospitals, due to its high cost. Patients were forced to purchase it from private chemist shops. Only very poor patients were given the vaccine free.

The rabies vaccine can be given by either the intra-dermal (ID) or intramuscular (IM) route. ID administration needs one-fifth of the vaccine volume compared to when given IM, and has the same or superior efficacy. Though the WHO has, since 1992, endorsed ID administration (4**),** the Government of India, until 2006, continued with IM administration (5), requiring a larger quantity of the vaccine, and this led to frequent stockouts of the vaccine.

I joined the Himachal Pradesh government health services in 1993.In 2000, I joined the state government-run Deen Dayal Upadhyaya (DDU) Hospital in the state capital of Shimla. I am a member of the Jan Swasthya Abhiyan, a network of health advocacy groups campaigning for the right to healthcare for poor patients. Our efforts contributed to the state government's switch to ID administration of the vaccine, making it affordable (6). It is now given free by the Himachal Government, thereby saving many lives.

However, deaths due to rabies were still being reported. The high cost of RIG, which is required for Type III bites, made it unaffordable for patients, and it was not routinely stocked in all government services.

While the dose of the rabies vaccine is fixed, the dose of RIG is calculated based on the patient's body weight. The WHO's 2010 position paper on rabies vaccines (1) prescribed that all the RIG as calculated by body weight formula (40 IU/kg for eRIG), or as much as anatomically possible (to avoid compartment syndrome ie excess dose injection causing pressure on the arteries, blocking them and causing necrosis of the organ), should be administered into or around the wound site/s; the remaining RIG, if any, should be injected IM at a site distant from the site of vaccine administration. The estimated cost of treatment for a patient weighing 60 kg was Rs 1,200 with equine RIG and Rs 30,000 with human RIG (7).

In 2009, a 38-year-old woman died of rabies due to a dog bite in Theog block of Shimla district. As a medical professional with a knowledge of rabies epidemiology, I was asked by the government to enquire into the matter. I learnt that the victim was well-off and could have afforded the cost of treatment. She had taken the full course of vaccination, but RIG was not administered as it was not available in the Civil Hospital at Theog or in private chemist shops there. Though RIG is on the essential drugs list, because of its high cost it was stocked only in district hospitals and medical colleges. Fear of anaphylactic reaction with cheaper equine RIG further discouraged its stocking at lower level health facilities. And private chemists did not stock RIG because few patients could afford to buy it, and chemists lost money when stocks remained unsold past the expiry date. If a medicine is not widely used, chemists tend not to stock it and it becomes unavailable for even those who can afford it.

It was this crisis that led me to discuss with my colleagues and rabies specialists in the country whether anything could be done to bring down the cost of RIG use, as had been done for the vaccine, so that it would reach the poor.

As I went through the literature for low-cost solutions to this problem, I found papers including animal studies, suggesting that injecting RIG into the wound would be sufficient to neutralise the virus, and there was no additional benefit in giving it IM; as well as papers reporting that RIG alone, when administered IM in the recommended dose, was almost undetectable in the blood (8-13). It was evident that giving the excess RIG in an IM injection was a waste of an expensive biological, and omitting it would reduce the dose, bringing costs per patient down and making the immunoglobulin available for more patients, as it is always in short supply in the market. I was particularly influenced by a commentary by David C Anderson (14) which argued against the WHO guidelines of the time.

However, conclusive evidence from human studies of the impact of local wound infiltration without additional IM was not available. No one was ready to use this protocol as it could have been construed as a violation of WHO guidelines. If a patient given RIG wound infiltration alone died of rabies, the doctor could be held liable in a court of law.

While reading these papers, we were faced with a new crisis. In 2014, there was a complete stockout of RIG in India. Panic grew over the deaths due to rabies, where the vaccine was given but RIG was not available. I discussed the matter with the then senior medical superintendent, in May 2014, Dr PL Gaunta. We held a consultation for DDU Hospital doctors, where the issue was deliberated upon. I presented what we knew from the literature on the use of local wound infiltration of RIG. The meeting ended with the decision to use wound infiltration alone in the crisis of non-availability, after completing the necessary formalities. We apprised the then Director, Health and Family Welfare, Dr DS Gurung, of the situation, and were told to consult experts before starting the intervention.

We asked the Central Research Institute (CRI) Kasauli to provide us with a few vials of equine RIG (eRIG) which they had stored for emergencies. CRI agreed to sell DDU Hospital 25 vials as a short-term measure since they too had limited stock. I drafted a protocol for a clinical intervention. We would give the vaccine intra-dermally as was being practised in the clinic. and eRIG – as much as was required would be injected into the wound to cover the surface and depth of the wound. Any amount remaining in the vial would be given to the next patient. eRIG would not be administered into the muscle.

How did we dare to use a protocol that went against WHO recommendations? Well, the alternative was to do nothing. Patients could not procure eRIG anywhere in North India, even if they could afford it. And we did not have enough eRIG to follow the WHO procedure (which used up to 10 ml of eRIG per patient – compared to what turned out to be an average of 1.26 ml with the new protocol). We felt that our intervention with this modified protocol would put patients at minimum risk and, in this situation, it was the only option to save lives.

This was not a study; it was a clinical intervention to save people's lives. But it generated evidence that had not been collected anywhere in the world and has contributed to saving the lives of many more people around the world.

Ethical and practical barriers

Before starting the intervention, as advised by our seniors, approval was sought from an institutional ethics committee (IEC). The state government's Department of Health and Family Welfare does not have an IEC, so research institutions in the area were approached. We found that IECs of medical colleges in Himachal do not review projects unless the principal investigator (PI) is from the college, and no one from any of these colleges was ready to be PI in this study. We were informed, verbally, that no one was ready to take up this protocol for fear of the legal consequences in case the protocol failed.

After much searching, we found a friend, a member of the IEC of Jaypee University of Information Technology, who agreed to discuss the protocol in the IEC meeting. But the IEC asked for written technical clearance of the study's feasibility from a reputed institution or expert working on rabies. This put us in a quandary. We found that rabies experts were reluctant to go against the recommendations of the WHO. During a number of informal interactions, we asked these experts to carry out the study themselves since they had the necessary facilities, but found that they feared an adverse outcome. At the same time, they did not offer any solution to the problem of unavailability of RIG and consequent rabies deaths as observed in Himachal. After approaching many experts, I was eventually rewarded when I met Dr SN Madhusudana, an eminent neurovirologist and expert on rabies, from the National Institute of Mental Health and Neurosciences (NIMHANS), Bengaluru. NIMHANS is also a WHO Collaborating Centre for Reference and Research in Rabies. Dr Madhusudana, who was the main author of one of the papers on animal studies advocating this modified protocol (13), wrote me a letter testifying to the scientific rationale of our protocol: "This study will show us the way to manage the patients with severe dog bites but who cannot afford full course of expensive rabies immunoglobulins. Please go ahead with the study and you have my full support for laboratory investigations as and when required." (Madhusudana SN. Letter to author, dated May 13, 2014) Above all, he also offered to do free testing of human blood samples for antibody titres.

After I made a presentation and submitted the letter of technical clearance from NIMHANS, clearance was obtained from the IEC of Jaypee University in a meeting (IEC Project No 11-2014, approval dated May 23, 2014).

From June 2014, with the approval of the hospital's senior medical superintendent, we started implementing the new protocol for all patients attending our anti-rabies clinic in DDU Hospital, Shimla. We would take informed consent from the patient or, if the patient was a minor, from the guardian. The consent form to be signed by patients included the following statements:

> *As discussed with the treating physician, I cannot afford the full calculated dose of immunoglobulins. Since I am told that at least local infiltration of immunoglobulin can minimize* ***the risk of getting rabies****, [emphasis in original] I agree to purchase a minimum volume of RIG* ***required*** *for local wound treatment. I would keep a watch on the animal that had bitten me and in case of the death of the animal, I would immediately inform the hospital of the same as in such circumstances the hospital agrees to provide the booster dose of vaccine free of cost. If animal dies within 10 days of initiation of vaccination, and local infiltration of RIGs, I am fully responsible for the delay in seeking treatment. … I know that if I still do not want to get included in this low dose immunoglobulin methodology, I can still opt out.*

A lawyer, who had first gone to a private hospital for suspected rabid dog bite management where he could not get RIG and was referred to our clinic, refused to sign the consent form. He was told to procure RIG himself if he wished it to be administered as per WHO norms. When he found he could not obtain it anywhere in North India, he gave his consent, but unwillingly, threatening to sue us in case of any mishap. This incident brought home to us the risks we faced, but we decided to continue in the interest of saving patients' lives.

From May 2014 to May 2015, more than 2,000 bite patients were treated in our hospital using this protocol. Each patient's consent was taken along with his/her address and telephone number, and each was followed up regularly. If the biting animal was known, it too was followed up. However, many dogs could not be traced or tested for rabies. A subgroup of 26 of our patients who were bitten by lab-confirmed rabid dogs were followed for more than a year and all were found to be healthy.

In the meantime, we received the report of a man who had been badly bitten by a suspected rabid dog and was given all four doses of rabies vaccine (as recommended by WHO) but was not given eRIG, as it was not available in the market. We were informed that he had developed rabies and succumbed to it. In another case, a village woman and her daughter who were bitten by a suspected rabid dog were referred to our clinic. They were treated according to our protocol and survived. However, we were informed by the family that the woman's cow, which was bitten by the same dog, died of suspected rabies after two weeks.

Some of the patients bitten by suspected rabid dogs would come to our clinic terrified as the reports of deaths due to

unavailability of eRIG appeared in the media. I would assure them that we were giving them the correct treatment, and nothing would happen to them. But such cases would put my determination to the test in this crisis. While I had the moral support of seniors like Dr Madhusudana, Dr Henry Wilde, Dr MK Sudarshan, and Dr PL Gaunta, and the practical support of people like Sister Nirmal Gupta, staff nurse at the clinic, I felt that I alone would be held legally liable if something went wrong. I had to reassure myself that we were doing what was necessary in the interest of our patients.

We followed up patients referred to our clinic and administered our intervention. All these patients survived (15). Our clinic became one of the few centres in India offering post-exposure prophylaxis (PEP) at that time to all patients, using ID vaccine and only wound/s infiltration of eRIG. The total cost of ID vaccine along with local wound infiltration of eRIG was one fifth of the cost of just the vaccine that was being provided IM before 2008. The government is now in a position to offer complete PEP including vaccine and eRIG free to all patients in Himachal. This "Himachal Model" can help India and other countries overcome the burden of rabies in the years to come.

I have had many guides in this work. In addition to Dr SN Madhusudana, Dr Henry Wilde from Thailand directed me towards important papers on rabies PEP, helped me in drafting the protocol, and advised me on the need to obtain ethics clearance before implementing this protocol. He later kindly collaborated with me in one of the papers reporting on this intervention. Dr MK Sudarshan, former president of the Rabies in Asia Foundation and former member of the Global Alliance for Vaccines and Immunisation, also advised me, from time to time, on ethical and technical issues regarding this work.

Critical evidence towards WHO's updated global guidelines on RIG use, 2018

The state health department gave us verbal consent to use this modified protocol in June 2014, agreeing that there was no other option in this crisis of non-availability of RIG. We began implementing the new revised protocol after that from 2014. In two years, we trained more than 50 batches of doctors, nurses and pharmacists from all over the state in the new method of local eRIG infiltration of wounds. From June 2014 to July 2016 more than 4,500 patients were treated according to this protocol. We were able to follow up about 80% of all PEP patients on the phone and through house visits (all 26 patients bitten by lab-confirmed rabid animals were followed). We also got information from all the tertiary hospitals where rabid patients are referred. No rabies death was reported of any of the people who underwent PEP in our government hospitals. Earlier free treatment was restricted to the poorest of the poor, and eRIG was only available at district headquarters. Now rabies PEP is available upto the sub-divisional hospital level, and in some cases even at the primary health centre level. Himachal Pradesh reported four deaths due to rabies last year in 2017, but none of the four people had received PEP in government hospitals and one had been given vaccine but not RIG by a private hospital. Two deaths reported this year had not availed of any PEP.

Our initial findings, showing that this reduced quantity of locally infiltrated ERIG was sufficient for protection, were published and became part of the literature reviewed by WHO's Strategic Advisory Group of Experts (SAGE) (16) on immunisation. We were asked to provide a further analysis. Dr Madhusudana, my mentor, had passed away and my other advisor, Dr Henry Wilde was my co-researcher and author in this paper. We published a follow-up paper reporting that the 26 patients with lab-confirmed rabid bites were all healthy one year later (15). The evidence provided in both papers was reviewed by the SAGE and contributed to its updated recommendations on RIG use (2018) worldwide (17, 18).

> *Trials and programmatic experience indicate that infiltration of RIG in and around the wound neutralises rabies virus within hours, whereas RIG administered IM distant from the wound is of limited value. These procedures allow RIG dose-sparing by calculating the maximum dose based on body weight, and injecting only the volume needed to infiltrate the wound(s).*

Incidentally, the report of a 2009 WHO consultation (19) documented a heated debate on the subject of this very protocol. It noted:

> *Delegates … raised the need for further controlled prospective studies that would determine whether injecting the wounds alone is effective in preventing human rabies deaths. However, such studies are impossible to carry out ethically today. [emphasis added]*

While the experts could not agree on how to resolve this issue, the report highlighted the doctor's predicament when treating an animal bite victim with Type 3 bites:

> *The physician in an impoverished region must therefore make a decision whether to inject RIG into all wounds alone and then, either save the remnant of the calculated total dose for the next patient, or inject it intramuscularly at a site different from vaccine as is currently recommended by WHO… This clearly raises the probability that a physician, who does not use the total calculated RIG dose, may be held responsible if the patient dies of rabies. This threat further complicates decision making on how to solve the dilemma of avoiding waste of valuable excess RIG after wound injection.* (19)

Then came the most important suggestion:

> *Animal bite centers, which experience extreme shortages of RIG and have no choice but to inject wounds only, should collect prospective data.* ***This may allow making evidence-supported-changes in current RIG injection guidelines.*** [emphasis added]

In other words, as far back as 2009, experts were looking for evidence to modify the WHO rabies RIG protocol. But it was unethical to do a controlled study for this purpose. The only way to get this information was through the intervention that we were forced to implement in a situation of non-availability

of RIG, despite fearing the repercussions of violating the WHO protocol.

Conclusion

We started our intervention in order to save patients in a crisis of RIG shortage. We had no idea of its potential global implications. Our initiative led to a major change in WHO guidelines on RIG use. It is evident that if creative minds are encouraged and supported by their superiors, they have the capacity to contribute to critical national and international policy decisions even while working in small institutions in resource-poor settings. It is also evident that when doctors are sensitive to the plight of poor patients and the circumstances that lead to such unnecessary deaths, they can be energised to challenge any protocol, to save lives not only in their own setting but even worldwide.

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DISCUSSION

Testing a low-cost approach to giving eRIG for rabies PEP: Ethical issues

RICHARD A CASH

Abstract

Ethical concerns in using a lower dose of equine rabies immune globulin (eRIG) to irrigate wounds from dog bites to prevent rabies are discussed. A lower dose of eRIG was used because of a general shortage of eRIG and the high market cost in the Himachal Pradesh state of India. The cost and availability of drugs in low- and middle-income countries (LMIC) often necessitates testing a lower dose of a vaccine or treatment than that recommended by international organizations (eg WHO). It raises the issue that recommendations may be designed for higher income countries without taking into consideration issues of supply and cost. Secondly a case-control design to compare dosages or delivery systems is usually not an option so investigators must often use historical data for comparison or other study designs. The ethical issues in the testing of drugs and vaccines in LMIC must be continuously reviewed by the international community

The author, Omesh Kumar Bharti, is to be congratulated on presenting a very clear narrative (1) on the rationale and development of the innovative preventive intervention that eventually led to changing the use of the World Health Organisation's Post Exposure Prophylaxis (PEP) for rabies. The principal ethical dilemma presented in this case occurred when researchers and clinicians attempted to evaluate the treatment or prevention of rabies, where standard recommendations were neither practical nor affordable. Low-resource settings are the primary venues where these situations play out as it happened in Himachal Pradesh.

The equine rabies immune globulin (eRIG) for Grade III exposure to a bite from an animal suspected of being infected with rabies is often unavailable and/or unaffordable to patients or institutions in the private market because of the large quantity of eRIG that is recommended by the World Health Organisation (WHO) prevention guidelines (2).

The first challenge to investigators is to define the "gold standard", in this case the recommendation by WHO (2). What is it? How was it arrived at? Is it 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? When Dr Bharti approached the Institutional Ethics Committee (IEC) with his proposed intervention of applying a reduced amount of eRIG at the site of the wound and eliminating the intra-muscular (IM) injection of the same drug, the IEC was initially reluctant to approve because of the WHO recommendations (1). But the WHO recommendations for the use of eRIG were based more on the opinion of WHO experts and less on solid research evidence. Control studies in humans could not be conducted and, therefore, did not inform the WHO recommendations. But opinions did. Dr Omesh Bharti, his colleagues, their patients, and the IECs were prisoners of opinions and not facts. The "gold standard" PEP guidelines may have reflected the concern of the "experts'" in insisting on the maximum intervention dose, given the high rabies mortality. But they did not take into consideration the difficulty in obtaining, or the cost of the PEP. Faith-based rather than evidence-based guidelines were given legitimacy by WHO. It is when shortages in the supply of PEP arose that the PEP standard was challenged.

A somewhat similar issue arose during an outbreak of yellow fever in the Democratic Republic of the Congo (DRC) in 2016 when there was a shortage of the vaccine (3). The government took a decision, with the support of WHO, to reduce the recommended dose of the vaccine to 1/5th of the standard so that larger numbers could be vaccinated to stem the epidemic. Though seroconversion rates had indicated that the lower dose of the vaccine could be effective, the actual efficacy could not be determined until the population immunised with the lower dose yellow fever vaccine was observed over a period of time to determine the incidence of the disease and the mortality in that population.

In Dr Bharti's view he did not conduct a study but rather a clinical intervention to save lives. It was, in fact, an innovative preventive intervention (4). 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 had been a research study? It could 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 (4). But it must be conducted within an

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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

YOGESH JAIN, GAJANAN PHUTKE

Abstract

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

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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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