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## Rabies - lessons from the Himachal Pradesh experience

*Omesh Kumar Bharti,*

Each year on September 28 we celebrate the World Rabies Day. The theme for 2016 is 'Educate. Vaccinate. Eliminate'. Rabies, the disease of the poor, remains a neglected area since centuries as there are no pressure groups in the field which can vie for attention to control rabies or to control the burgeoning population of stray dogs in the country. There have been incidents of foreign tourists bitten by stray dogs in different parts of the country, with few deaths also reported, which may affect tourism and brings a bad name to the country. Sanitation programmes (including appropriate management of food wastes), which are in vogue now, are also important for controlling rabies!

Rabies is a dreaded disease and an estimated 60,000 people die of rabies every year and out of that 31,000 deaths are reported from the Asian continent. About 20,000 deaths are reported from India, i.e. one death every half an hour<sup>1</sup>. The main reason for high death rate in India is high cost of treatment (vaccines and rabies immunoglobulins (RIG) in case of animal bites) and lack of awareness regarding first aid. While Himachal Government has taken a lead in lowering the cost of vaccination through introduction of only intra-dermal technique, the cost of RIG is still beyond the reach of common man.

Our state of Himachal Pradesh is in the North bordering China and is predominantly rural and hilly and villages are near forests where wild reservoirs of rabies exist. Since health facilities are not accessible easily, we were forced to innovate on existing schedules of rabies vaccination keeping in view the compliance of the patients and affordability to give them the best possible option of treatment. Nineteen rabies deaths had been registered from 2009- 2015 in IG Medical College, Shimla.

In the years 2006 and 2007, we at Deen Dyal Upadhyay Hospital, Shimla experienced a severe shortage of rabies vaccine and patients were running from pillar to post. During continued shortage of rabies vaccine in 2008, we contemplated to start an intra-dermal clinic to make vaccine affordable but there were four main hurdles: 1) Non-availability of the appropriate rabies vaccine vials ("For IM/ID use" or Intra-muscular/intra-dermal); 2) Low number of patients visiting the DDU Hospital (sometimes only two a day), which was insufficient to open a vaccine vial; 3) None of the vaccine producing companies were ready to supply cell culture "For IM/ID use" rabies vaccine vials for fear of losses due to more efficient usage; and 4) the reluctance of the hospital doctors to prescribe ID vaccine as this was not the practice at

higher teaching institutions including medical colleges.

We contacted a vaccine company in Mumbai (1200 km away from here), which agreed to supply us the appropriate vials. We requested the Chief Medical Officer, Shimla District to write a letter to all health facilities around DDU Hospital to give first aid to patients with animal bites and then refer them to DDU Hospital for vaccination. Now we were able to divide a single 1ml vaccine vial among four patients through pooling strategy<sup>2</sup>. We also consistently advocated that the ID use of rabies vaccine was approved by World Health Organization (WHO) with subsequent approval by the Government of India, which proved to be successful. We innovated a technique of extraction of last drop of vaccine from the vial to reduce wastage.

The first low cost anti-rabies clinic was started on August 2, 2008 after long advocacy with the authorities and doctors. This centre was formally launched as State Intra-dermal Anti-rabies Clinic and Research Centre (ARC&RC) by Mission Director National Rural Health Mission on September 28, 2012. Since then we have continued to innovate based on local requirements and patients' feedback and have given pre and post exposure prophylaxis to more than 15,000 animal bite victims over more than an eight-year period, saving lives as well as money of the poor patients and the government.

The shift from IM to ID made rabies vaccine accessible to all and since it was affordable to government, the vaccine was made free all over the state to every dog bite patient. However, some doctors continued practicing the costlier IM vaccine and the issue was taken to the high court by an NGO where government gave a commitment to use only ID vaccine in the state. After court orders, new clinics are being established upto PHC level for vaccine and anti-snake venom and upto CHC level for additional RIG application into the bite wounds.

In 2014 there was acute shortage of rabies immunoglobulins (RIG) in Himachal Pradesh and was not available in North India in general (due to limited production and also demand due to high cost). The reports of death due to rabies started pouring in from different states. In 2014, the death of a 32 year old man in Shimla District who was bitten on the lower lip by a stray dog and could not be treated with RIG became widely publicized in local media. Stocks were getting outdated and affordability was another issue. Demand for RIG started coming in from the public, and policy makers were getting worried. There were

patients who said they cannot afford to purchase RIG at all even if costs were lowered. Non-availability of RIGs in the market led us to innovate again for an affordable solution to save lives of the patients.

For post exposure prophylaxis, apart from thorough wound wash with soap and antiseptic and administration of intra-dermal vaccination we decided that the immunoglobulins would be injected into the depth and around margins of the wound/s to neutralize virus locally without giving the remaining RIG into muscles IM as prescribed by WHO. We decided to do a long term follow up of the patients bitten by lab confirmed rabid dogs to assess the clinical efficacy of this method of only local wound infiltration of RIG, based on the existing literature review<sup>3</sup>.

The recent WHO recommendation of giving as much of the RIG as possible around the wound site contradicts earlier recommendation of WHO to inject the rabies immunoglobulins into the muscle as per body weight. Cabasso et al had earlier concluded that 10 IU/kg RIG systemically is insufficient for early protection, that HRIGs at these doses interfered with active immunization, and that 20 IU/kg resulted in minimal interference. This dose was therefore selected for intramuscular inoculation at a site away from the site of vaccination. But if some serum has been injected locally, how logical would it be to give the remaining serum in the muscle? This dose would be less than that calculated for IM injection and may even interfere with active immunization as detailed above. The WHO recommendations are trapped in their own irrational history.

Over the course of the meeting in WHO/Bill & Melinda Gates Foundation Consultation in 2009, Dr David C. Anderson, proposed various amendments to the current WHO recommendations on the use of RIG ((WHO, 2005) sections A2 and A 3.2). His proposal can be summarized as follows: For passive immunization, the whole dose of RIG is given into the wound(s). The maximum total amount of RIG administered for all individuals, regardless of body weight, should be 1000 IU (normally a 5-ml vial). RIGs may be diluted up to a volume sufficient for the effective and safe infiltration of all wounds. It is not necessary or useful to inject any residual RIG into a distal site (i.e. IM); residual RIG may be used on another patient within 6 hours or otherwise discarded. In case, if it is difficult to administer RIG or the wound has completely healed, then this RIGs can be given as full calculated dose by intramuscular injection in the anterolateral thigh or at a site away from the site of vaccine administration<sup>3</sup>. Other studies have supported infiltration of RIG around injured site<sup>4</sup>.

Dr. Anderson also advocates that rabies endemic countries must take a much more active role in helping with production, standardization and distribution of RIGs. Recognizing that dog bites vary in number, size

and location, these recommendations allow RIG to be diluted in saline to ensure there is sufficient volume to inject into all wounds<sup>5</sup>. One 11 year-old boy died of rabies in 1987 when a single puncture wound of the finger was not infiltrated with RIGs, all of the 40-IU/kg dose had been given intramuscularly in the gluteal region<sup>6</sup>.

Therefore it is evident from the above literature review that there is no substitute to local infiltration of RIGs to neutralize virus at the wound site itself and maximize the chances of survival of the patient when RIGs are not affordable or are in scarcity.

Recent pilot study done at DDU Shimla has shown that the local infiltration of wound<sup>7</sup> is effective in saving rabid dog bite patients and this method of only local infiltration continues in DDU Hospital as RIG is still not available in the market and several patients are fine after a year of bite by rabid dogs. The model is also spreading to other district of the state including Indira Gandhi Medical College and appears to be successful as there are no reports of death. We have trained more than 15 batches of doctors and paramedics in the state on intradermal vaccination and local RIG infiltration since 2014.

Sometimes less can be more and we have proved it with intra-dermal rabies vaccination and only local wound infiltration of RIG. This has brought down the treatment cost from about Rs. 50,000 per case to about Rs. 400/- per case. Since this cost is easily affordable by the hospital administration, the Himachal Government has decided to give entire post exposure prophylaxis free to all animal bite victims in the state.

This model appears to be successful as patient having even a minor scratch now come to the hospital for post exposure prophylaxis this is free and we have not experienced any death due to rabies this year in 2016. We have replicated the model in Himachal, Let's replicate the model in other states and rein in this monster of rabies in India for ever.

*Omesh Bharati is field epidemiologist cum state master trainer in intradermal rabies vaccination in HP, India.*

*Email: [bhartiomes@yaho.com](mailto:bhartiomes@yaho.com)*

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## HPV vaccination for the greater good – but is it?

*Sarojini N, Madhavi Y, Veena Johari*

Vaccines are given to healthy children as a public health measure to prevent diseases. It is essential that before introducing a vaccine, there should be evidence that it is safe, effective, and has minimal side effects. Moreover, it should also be cost-effective, affordable and feasible in the country as compared to other interventions, that may be equally effective in controlling or curbing the concerned disease.

Earlier this year, the Delhi government announced the introduction of the Human-Papilloma –Virus (HPV) vaccine in government schools.<sup>1</sup> The intention is to vaccinate girls in the age group of 9 to 13 years. The Delhi government also intends to introduce the vaccine in private schools through a public-private partnership along with Delhi State Cancer Institute and Global Alliance for Vaccines and Immunization (GAVI).<sup>2</sup> Punjab government is also considering introduction of HPV vaccine in the State. However, we see the absence of a caution that needs to be taken before introducing new vaccines in a health care system that is crippled in some areas and in many instances incapable of handling the adverse events that may occur in girls who are administered the HPV vaccine.

The question is whether it is necessary to vaccinate girls mandatorily for HPV or are there alternatives that could be as effective? Also, the question is that once the HPV vaccine is introduced in the Universal Immunization Programme (UIP), or under any State vaccination programme, who will be responsible for the ill-effects or adverse events that the girls may face, and what compensation will be paid to them, and by whom?

### **Necessity**

HPV vaccine is used as a public health measure due to its relation with cervical cancer and related diseases. Exposure to HPV can also be reduced by behavioural change, and therefore mandatory HPV vaccination is not justified in a similar vein as some other vaccines in the UIP.

Mandatory HPV vaccination is also not justified by necessity in the given context. The current HPV vaccine prevents infections from just two of the HPV types (16 and 18) that may cause cervical cancer and also HPV types 6 and 11 which can lead to genital warts. However, there are over 100 HPV types and a critical concern is that if the vaccine was to work and indeed 'block' types 16 and 18, other types might become more virulent, and contribute to the

carcinogenicity in the absence of these more carcinogenic subtypes.

There is a lack of reliable information regarding the period of immunological protection the vaccine confers against HPV types 16 and 18. Since the highest incidence of cervical cancer in India is in women above 35 years of age, it is not clear whether a 3-dose schedule will successfully provide lasting immunity or boosters will be required when they reach 50 years of age. If boosters are required say once every 3-5 years, the cost of vaccination per woman rises phenomenally.

HPV is a sexually transmitted infection (STI) with varied incidence and mortality rates in different communities of the world. For example, in Australia, a country with low incidence and mortality due to HPV, it is found 4 times higher in its indigenous Aboriginal communities.<sup>3</sup> Around 80% of the women globally are infected with HPV in their life time without any symptoms, without cancer or genital warts as the virus is expelled from the body on its own within 1 to 2 years. The lifetime risk of cervical cancer is 0.8 % before the age of 64 in a developed country and 1.5% in a developing country.<sup>4</sup> Time series data indicates that cervical cancer rates are declining and it is low in developed countries compared to developing countries [during 60's and 70's, the rates were similar]. Declining cervical cancer rates in the developed world is attributed to the improved living standards, greater access to screening programs and use of condoms since the 1960's.

In countries that conduct regular testing or screening for HPV, the incidence of HPV has reduced substantially, even without the introduction of the HPV vaccine under any mandatory program of the government.

### **Universal Immunization Program (UIP)**

It is important to carefully consider which vaccines should be added to the national immunization schedule, so that they are offered to all children in the country. Decision to introduce new vaccines should be based on evidence that a particular vaccine is not only effective but is also safe, is also cost effective and feasible to administer when compared to other interventions, and is affordable for the country. Further, the system that delivers this new vaccine should have the organizational capacity to deliver this additional vaccine without a negative impact on the coverage of the previously used vaccines, and it should