SPECIAL ARTICLE

Rabies prophylaxis: What is new in WHO, 2018 recommendations & its implementation in India - A commentary[1]

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ABSTRACT

The World Health Organization following expert reviews and consultations recently in 2018 released two documents i. e. Technical Report Series on rabies, no. 1012 and Position Paper on rabies vaccines in weekly epidemiological record, no. 16. In India, the last national guidelines on rabies prophylaxis were provided in 2015. Hence, following the WHO, 2018 guidelines in January, 2019, a Government of India expert group on rabies met in New Delhi, reviewed the recent WHO guidelines for adaptation and issuing revised national guidelines. In this context, a critical appraisal of the rabies prophylaxis in the current situation is elaborated in this article for the information of both private medical practitioner and service provider in government institutions.

Key words: Rabies prophylaxis, rabies vaccine, rabies immunoglobulin, rabies monoclonal antibody.

The World Health Organization was established in 1948 as a specialized agency of the United Nations serving as the directing and coordination authority for international health matters and public health. One of WHO's constitutional functions is to provide objective and reliable information and advice in the field of human health, a responsibility that it fulfils in part through its extensive programme of publications. The latest updated information on rabies is available mainly from two WHO publications - 1. WHO Technical Report Series (TRS), 1012, WHO expert consultation on rabies, 2018 and 2. Weekly Epidemiological Record (WER), Rabies vaccines: WHO position paper (PP), 16,2018. The TRS makes available the finding of various international groups of experts that provide WHO with the latest scientific and technical advice on a broad range of medical and public health subjects. Members of such expert groups serve without remuneration in their personal capacities rather than as representatives of governments or other bodies; their views do not necessarily reflect the decisions or the stated policy of WHO[1]. The PP summarizes the essential.

It must be noted here that information provided by WHO through its publications are only recommendatory in nature and for consideration of the national governments, professionals and others and not binding on them. Hence, the national governments review these recommendations that are largely global in nature and mostly through expert consultation in the local context and then subsequently adapt and implement them.

In this context, on 8th January, 2019 a Government of India (GoI) expert group met at National Centre for Disease Control, Delhi, and reviewed the national guidelines on rabies prophylaxis[3]. This paper provides an expert review and crisp summary of these three reports.

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[1]A. L. Saha Memorial Oration Lecture, 64th Foundation day programme, 27th September, 2019, Indian Public Health Association, Kolkata

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Information on rabies and rabies vaccines and concludes with the current WHO position on the use of rabies vaccines worldwide. The PP is intended for use mainly by national public health officials[2].

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1. Rabies prophylaxis

1.1. Post – Exposure (PEP) Regimens

WHO recommendations list of preferred PEP regimens and alternatives, all of which have been assessed for immunogenicity, clinical outcome, feasibility and cost effectiveness is given below[1]:

Table – 1. WHO – recommended and alternative post-exposure prophylactic regimens

PEP Regimen	Duration of course	No. of injection sites per clinic visit (day 0,3,7,14,21-28)
WHO recommended intradermal regimen		
1 week, two sites	7 days	2-2-2-0-0
WHO recommended intramuscular regimens		
2 weeks	14-28 days	1-1-1-1-0
3 weeks	21 days	2-0-1-0-1
Alternative immunogenic intradermal regimens		
1 month, two sites	≤28 days	2-2-2-0-2
1 month, simplified four sites	≤28 days	4-0-2-0-1
1 week, four sites	7 days	4-4-4-0-0

However, from the above list, only the one month, two sites (2-2-2-0-2) ID regimen was approved by Government of India in 2006 and is in use in the country since then. All other above listed regimens are not approved by Government of India and also the product inserts/labels of the manufacturers that accompany rabies vaccines do not specify these other regimens. Consequently, it is advised not to use these other regimens and if used will amount to "off label" use.

In January, 2019, a Government of India expert group observed lack of evidence with respect to this WHO recommendation in Indian settings and recommended multi-centric studies to generate more evidence[3]. As a result, the Association for Prevention and Control of Rabies in India (APCRI) is planning to conduct an Indian multicentric randomized controlled trial (RCT) using indigenous rabies vaccines, equine rabies immunoglobulin (eRIG) and rabies monoclonal antibody (rmAb) to assess the immunogenicity and safety of new one week, Institute Pasteur, Cambodia, IPC- ID regimen (2-2-2-0-0) and only wound infiltration of eRIG and rmAb without systemic injection. [4]

1.2. Post-exposure prophylaxis (PEP) following re-exposure in previously vaccinated individuals

1.2.1. Re-exposure less than three months of previous full course PEP or PrEP (with documentary evidence)

Only wound management and no PEP immunization[1,2]

The GoI, 2019 expert group endorsed this line of management.

1.2.2. Re-exposure more than three months of previous full course PEP or PrEP

Wound management and PEP immunization[1,2]

The dosage is one vial by IM route or 0.1mL by ID route

Regimens

1-site ID on days 0 and 3 (1-1-0-0-0);

or at 4-sites ID on day 0(4-0-0-0-0);

or at 1-site IM on days 0 and 3 (1-1-0-0-0)

No RIG is needed, irrespective of category II or category III exposure.

However, the GoI 2019, expert group recommended continuation of the currently approved regimens of ID or IM vaccinations given on days 0 & 3.

2. Pre-exposure prophylaxis (PrEP) regimens

The following are the WHO-recommended PrEP regimens

Table -2. WHO-recommended PrEP regimens

PrEP Regimen	Duration of course	No. of injection sites per clinic visit (day 0,3,7,14,21-28)
WHO recommended intradermal regimen		
Two visits	7 days	2-0-2-0-0
WHO recommended intramuscular regimen		
Two visits	7 days	1-0-1-0-0
PrEP under specific circumstances		
Single visit, ID	1 day	2-0-0-0-0
Single visit, IM	1 day	1-0-0-0-0

In January, 2019, the GoI expert group however, recommended continuation of the currently approved three dose regimen (0.1mL ID at one site or 1 vial IM given on days 0,7 and 21 or 28).

3. Using rabies vaccines labelled for intramuscular (IM) use by intradermal (ID) route

Rabies vaccines labelled for intramuscular use can be used safely via the intradermal route, even if this constitutes "off –label" use[1].

The GoI expert group recommendation is awaited.

4. Evidence suggests that a change in the route of administration or in vaccine product during a PEP or PrEP course is safe and immunogenic[2].

However, the GoI, 2019 expert group approved the change in vaccine product and approval for change in route of administration is awaited.

5. Prioritizing rabies exposures when limited amount of RIG is available[1]

If a limited amount of RIG is available, it should be prioritized for exposed patients on the basis of the following criteria:

- Multiple bites
- Deep wounds
- Bites to highly innervated parts of the body, such as the head, neck and hands
- Severe immunodeficiency
- Bites from an animal with confirmed or probable rabies
- A bite, scratch or exposure to mucous membranes from a bat

Restricting RIG or vaccine to people with high-risk exposure to rabies may endanger those with lower – risk exposure and should be considered carefully before being implemented.

In January, 2019, the Government of India expert group did not accept this recommendation and recommended continuation of the current practice that in all patients with category III exposure RIG should be given[3].

6. Using RIG for only wound infiltration without systemic injection

WHO no longer recommends injecting the remainder of the calculated RIG dose –IM at a distance from the wound. Instead, the calculated RIG dose can be fractionated in smaller, individual syringes to be used for several patients. This requires handling and storage in aseptic conditions. Unused fractionated doses and open vials of RIG should be discarded by the end of the day[2].

However, in January, 2019 a Government of India expert group recommended continuation of the existing practice of injecting the remaining RIG volume intramuscularly, as close as possible to the presumed exposure site, to the

degree that is anatomically feasible[3].

7. For mucosal exposure with no wound, rinsing with (diluted[2]) RIG can be considered[1].

The GOI expert group recommendation is awaited.

8. Consumption of meat or milk from a rabid animal is strongly discouraged and should be avoided but if it occurs, PEP is not indicated[2]. Milk that has been pasteurized presents no risk for rabies virus (RABV) transmission[1].

The GoI, 2019 expert group endorsed this recommendation[3] (for milk only and about meat it is silent)

9. If any doses are delayed, vaccination should be resumed and not restarted[2].

The GoI, 2019 expert group has endorsed this recommendation[3]

10. People who have received at least two doses (intradermal or intramuscular) of a cell culture vaccine on an appropriate schedule before discontinuation should be considered as having received PrEP[2].

The GOI expert group recommendation is awaited.

11. If available, the use of mAb products instead of RIG is encouraged[2].

In October, 2017, Serum Institute of India Pvt. Ltd. Pune launched the world's first rabies monoclonal antibody (RMAb) and is now available in the market.

The GoI expert group recommended that rmAb needs to be studied for its effectiveness, safety in multi-centric Indian settings[3].

12. What is "off label "use?

All medicines, including rabies vaccines and immunoglobulins/ rabies monoclonal antibody are accompanied by product inserts (or also known as labels or enclosures, etc.) that provide guidance for their use in the patients. These labels or product inserts are approved by the Drug Controller General of India (DCGI). Any usage that involves deviation from the guidelines provided in these product inserts/labels is considered as "off label "use. The private medical practitioners in particular must avoid "off label "use as in the event of any mishap, as they are liable to be sued under consumer protection act.

In conclusion, in government institutions and in private practice the recommendations of Government of India and the guidelines given in the product (rabies vaccines, RIG & RMAb) insert shall be followed. Any use of WHO recommendation that is not endorsed by GoI or in the product insert may be made only in exceptional circumstances and solely with the intention of saving the life of the patient and it shall be defendable in a court of law, if the need arises. Lastly, the GoI national guidelines on rabies prophylaxis are expected to be issued soon this year.

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