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Research Article

# The Status of Rabies Post Exposure Prophylaxis Using Nerve Tissue Anti-Rabies Vaccine in Ethiopia

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## ABSTRACT

The use of anti-rabies vaccine as post-exposure prophylaxis started during the year 1885 and play significant role in preventing rabies cases in humans. Since then, anti-rabies vaccines have undergone several developments in terms of safety and efficacy. Ethiopia has been producing nerve tissue anti-rabies vaccine since 1960s for post exposure prophylaxis. Such type of vaccine was discouraged by WHO due to its low immunogenicity and sever nerve complication. During the last years, anti-rabies vaccine needs increasing from time to time due to the lack of effective rabies prevention and control measures. Although nerve tissue vaccine production capacity increased significantly, still demand has not met. According to WHO report, from 0.14 to 7 out of 1000 people received this nerve tissue vaccine has the probability to develop vaccine associated complications. This study reveals that during the last seven years of NTV production and distribution (213,856 doses), few vaccines associated complications reported to EPHI or recorded at health facilities with only minor local reaction (8.72%). In other cases, health professionals informally report severe nerve complications in some patients following vaccination. This indicates documentation problem at health facilities during full course of vaccination, making difficult to show exact vaccine related complication. The other problems identified during supportive supervision were vaccine shortage, health professionals' knowledge gap in rabies case screening, vaccination dose/site of inoculation and inappropriate vaccine handling and transportation. To overcome such problems, it is recommended to give emphasis to current vaccine production technology transfer and avail cell culture anti-rabies vaccine for accessible, safe and effective post exposure prophylaxis. In addition, comprehensive training should be provided for health professionals in the area of vaccine handling and storage, rabies case screening and vaccination.

**Keywords:** Health facilities; Nerve tissue vaccine; Rabies; Vaccine distribution; Vaccine associated complications

## INTRODUCTION

Rabies is a viral disease that can affect humans and other mammalians. The disease causes inflammation of the brain by retrograde movement from the site of infection through nerve ending to the central nervous system [1]. The virus is classified under Lyssavirus, family Rahabdoviridae. Rabies disease causes invariable fatality once sign and symptom appear, but 100% preventable using modern vaccine. Regardless of available effective vaccine, more than 59,000 peoples die of rabies every year worldwide. Majority of deaths (more than 95%) occurs in Africa and Asia mostly in rural population setting [2].

From global estimated human rabies death every year, 21,000 cases were occurring in Africa. According to CDC report, annual rabies human death in Ethiopia estimated to be 2,700 with the highest rabies death in the world and the number of cases still under reported due to poor surveillance system and lack of effective diagnostic laboratories at national and regional level [3].

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As the majority of the cases are due to dog bite, global control and elimination of rabies consider mass vaccination of the dog population with high-quality modern anti-rabies vaccine. Thus, the effort in developed countries like America and Europe showed possibilities to eliminate the disease with mass vaccination of 70% dog population. Based on the existing developed countries experience, World Health Organization (WHO), World Organization for Animal Health (OIE), Food and Agricultural Organization (FAO) and Global Alliance for Rabies Control (GARC) have committed to eliminating rabies death in human by 2030 [4]. The main challenge for rabies control and elimination in developing countries is the lack of quality and accessible modern ant-rabies vaccine. To overcome such difficulties, WHO planning to create a human anti-rabies vaccine bank similar to dog rabies vaccine bank established by OIE.

Since the first discovery of anti-rabies vaccine by Luis Pasteur during the year 1885, several anti-rabies vaccines were developed to protect humans and animals from rabies. Such discoveries contribute to dramatic reduction of rabies cases both in humans and animals with estimated 40% case reduction. Anti-rabies vaccines can be divided into two types according to production processes as neural and non-neural [5]. Neural type of anti-rabies vaccine is the type of vaccine produced by propagating the virus on suckling mice (Fuenzalida) or sheep brain (Semple type). This type of vaccine known by its poor immunogenicity, patient discomfort due to high since the first discovery of anti-rabies vaccine by Luis Pasteur during the year 1885, several anti-rabies vaccines were developed to protect humans and animals from rabies. Such discoveries contribute to dramatic reduction of rabies cases both in humans and animals with estimated 40% case reduction [6]. Anti-rabies vaccines can be divided into two types according to production processes as neural and non-neural. Neural type of anti-rabies vaccine is the type of vaccine produced by propagating the virus on suckling mice (Fuenzalida) or sheep brain (Semple type). This type of vaccine known by its poor immunogenicity, patient discomfort due to high dosage and contain a reacting agent (myelin) which is responsible for neuroparalytic side effect. The incidence of neural complication for vaccine prepared by using adult animal for virus propagation is estimated to be 0.14-7 in 1,000 vaccinated populations. This condition may result in serious nerve paralysis or even cause death [7]. Due to the stated unwanted reactions and related conditions, WHO discouraged the use of nerve tissue anti-rabies vaccine during 2005. To replace neural vaccine, a non-neural (duck embryo and cell culture) vaccine was developed which can overcome the problem associated with nerve tissue vaccine. Thus, embryonated egg and cell culture based rabies vaccine have proven safety and efficacy in preventing rabies both in humans and animals. Even though there is advancement in vaccine development and available effective vaccine; due to its high cost and lack of production technology, some countries in Asia and Africa still use this outdated nerve tissue derived anti-rabies vaccine for post-exposure prophylaxis.

Since 1960's, Ethiopia Public Health Institute (EPHI) producing and distributing nerve tissue based (Semple type) anti-rabies vaccine for post exposure prophylaxis. This vaccine prepared from 5% aqueous suspension of sheep brain inoculated with Pasteur virus (PV-12) fixed rabies virus strain, live attenuated with phenol. Following administration of the Semple vaccine, the incidence of neurological complication cases reported in different literatures varies greatly. According to data published during 2010, anti-rabies vaccine produced and distributed by EPHI for post exposure prophylaxis was 21,832 every year [8]. Data shows that, more than thousand doses increase in vaccine production and distribution every year and still below demands due to old production technology. Ethiopia is currently working to produce safe and efficacious cell culture anti-rabies vaccine which can replace the old production method and overcome the problem of vaccine shortage. The purpose of this study was to identify vaccine associated complications, indicate gaps in vaccine demand and supply and to identify professional skill gaps in case screening and vaccine delivery for decision making.

# MATERIALS AND METHODS

## Study design

This study is a type of retrospective data collection and review recording to gather data related to fermi type anti-rabies vaccine production and distribution, vaccine associated complications, gaps at health facilities in rabies case management and vaccine delivery. Amount of nerve tissue vaccine produced and distributed by EPHI were reviewed and vaccine related complication reported following post-exposure prophylaxis were assessed [9].

## Study area

Recorded data from health facilities actively receiving Nerve Tissue Vaccine (NTV) were included. Those health facilities receiving modern cell culture vaccine from Pharmaceutical Fund Supply Agency (PFSA) were also included to identify the problem associated with change in vaccine type and route/dose of vaccine administration. Neurologists at Black Lion and Saint Paul's Millennium medical college hospitals were interviewed for vaccine associated complication [10].

## Methodology

Health facility visit and vaccination feedback reports were used to assess the safety status of nerve tissue vaccine currently produced and distributed by EPHI. All data's were collected during supportive supervision and feedback control data from health facilities receiving nerve tissue anti-rabies vaccine were included. To evaluate increasing health facilities vaccine demand, new health facility receiving vaccine, and regional health bureaus readiness to distribute the vaccine was considered. Doses of vaccine distributed from EPHI within seven years were assessed and compared from year to year to see the status demand and supply. Modern cell culture vaccines imported from other country were also included to consider demand in addition to the vaccine produced and distributed from EPHI. Data related to vaccine associated complications reported at specialized hospitals were included to identify the level of vaccine associated complications. Health professionals at each health facility were interviewed to identify undocumented

case history related to vaccine associated complications. From all health facilities receiving vaccine, those selected for supportive supervision were based on frequency they receive vaccine and up on formal inquiry for support in an emergency case. When asked by health facilities for support in an emergency case, a group of professionals is sent to identify the problem and give appropriate professional response for immediate control of the disease [11].

From total health facilities receiving anti-rabies vaccine during the last several years, 127 were selected for supportive supervision and retrospective data were collection. In addition to data from referral hospitals to identify the status of vaccine adverse reactions following vaccination, health professionals working on screening and vaccine delivery was interviewed to maintain data quality associated with poor documentation system observed at all health facilities. The result was compared with formal feedback report from all health facilities. Gaps in health professionals' knowledge on case management and screening, vaccine handling, storage and administration were also assessed.

## RESULTS AND DISCUSSION

From the total health facilities visited during the supportive supervision, the majority of them (99%) are receiving a nerve tissue vaccine from EPHI for the post exposure prophylaxis. Due to increase in public concern about the disease and dog related suspected rabies cases, vaccine demand is high in almost all health facilities visited. The major problem identified during supportive supervision was lack of effective screening, inappropriate vaccine handling, storage and delivery by health professionals and gaps in effective rabies case management. Vaccine production capacity is increasing from time to time to meet health facilities vaccine demand. The problem of effective case screening was identified as one of the gaps contributing to the vaccine shortage.

Demands of the vaccine increasing throughout the year with average 4.44% increase in vaccine production and distribution every year. Exceptional small amount of vaccine distributed was during the year 2018 (August 2017-September 2018) in which the number of doses distributed below 2017. This was identified as a result of vaccine production capacity limited at the time due to laboratory animal shortage and not associated with decrease in rabies case (Table 1).

**Table 1:** Yearly NTV production and distribution by region (in doses).

| Regions/City administration | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Year | Tigray | Amhara | Oromia | Somale | Binishangul Gumuz | SNNP | Gambela | A.A | D. Dewa | Total |
| 2014 | 2094 | 2129 | 14885 | 147 | 390 | 4936 | 61 | 1119 | 54 | 25815 |
| 2015 | 2447 | 3051 | 18085 | 155 | 550 | 4936 | 30 | 1235 | 59 | 30548 |
| 2016 | 1905 | 3105 | 18881 | 298 | 487 | 4936 | 29 | 1678 | 95 | 31414 |
| 2017 | 2359 | 3695 | 18877 | 145 | 520 | 4936 | 52 | 1260 | 103 | 31947 |
| 2018 | 2251 | 3095 | 18682 | 186 | 473 | 4936 | 43 | 1323 | 78 | 31067 |
| 2019 | 2279 | 3787 | 20397 | 206 | 524 | 4936 | 38 | 1452 | 105 | 30576 |
| 2020 | 2301 | 4045 | 21236 | 213 | 538 | 4936 | 37 | 1496 | 114 | 32489 |

During the last seven years, about 213,856 doses of NTV were produced and distributed throughout the country for post exposure prophylaxis; excluding the cell culture vaccine imported and distributed by Ethiopian Pharmaceutical Supply Agency (EPSA). Majority of the regions and city administrations are receiving the vaccine directly from EPHI except Afar and Harari. These two regions are known to cover their vaccine needs by referring suspected rabies cases to health facilities in border regions. Vaccine distribution increases throughout the year with exceptional change in demand associated with seasonal outbreaks of the disease. From the total doses of vaccine distributed within the specified year, yearly average production and distribution were around 29,610 doses. This data show increase in production by more than ten thousands of vaccine doses compared to data published during 2010, indicating that previous production capacity estimated at 21,832 doses per year. According to regional vaccine consumption data shown in Table 1, more than sixty percent of vaccines produced were distributed in Oromia region (60.40%) followed by South Nations Nationalities and People (SNNP) and Amhara regions, 14.82% and 10.18% respectively. This may reflect the burden of the disease and the need to set effective control measures by the regions by priority settings (Table 2).

**Table 2:** Number of health facilities visited.

| Year | HFs receiving vaccine | HFs visited | % covered |
|---|---|---|---|
| 2014 | 254 | 37 | 14.57 |
| 2015 | 269 | 44 | 16.36 |
| 2016 | 354 | 6 | 1.69 |
| 2017 | 297 | 20 | 6.73 |
| 2018 | 312 | 20 | 6.41 |
| 2019 | 349 | 22 | 6.3 |
| 2020 | 361 | 19 | 5.26 |

Health facilities were visited based on the status of their vaccine consumption and formal request following rabies related outbreaks and need for technical support calls. Regular supportive supervision was used to assess knowledge gaps in rabies case management, vaccine handling, storage and delivery and related problems observed in health professionals' service delivery. A total of 168 health facilities visited during the seven-year period with average 31 health facilities visited per year [12].

The number of health facilities visited during the year 2016 was the lowest of all time due to lack of commitment from the top management which was the reason for the increase of the cases during the following year. Due to several gaps identified at ground level to manage such cases at the time, several health facilities requests for the involvement of professionals from EPHI to control the emergency cases. This brings the need to re-initiate supportive supervision at the time and the management decides to continuous for the public health service.

To track vaccine associated complications, vaccination follow up format were developed and distributed to each health facilities receiving nerve tissue vaccine. During the course of vaccination, patient's full history were collected from all health facilities and compiled for further interpretation.

From systematic retrospective data review, vaccine associated complication following rabies post exposure prophylaxis were assessed. Previously collected feedback data from all health facilities show that there was no vaccine associated complication, even no minor complications like local reaction, swelling and edema, but during injection, most patients complain swelling of the injection site, edema and local reaction.

In addition, during health facilities supportive supervision and vaccine associated complication report assessment nearby hospitals, it was identified that even the serious nerve complication were reported in some patients (data not recorded). Specifically, neurologists at Black Lion and Saint Paul's Millennium Medical College hospitals indicate that at least five and two cases of nerve complication were observed respectively following NTV administration. Similar study indicate that administration of NTV anti-rabies vaccine shows nerve complication in patients after receiving 10 to 12 dose of the vaccine; four cases of nerve paralysis within six months. After developing vaccination follow up format for individual patient, the most reported NTV associated complication were pain, followed by swelling at the site of vaccination. During this retrospective data collection and patient based vaccination follow up, no severe complication was reported following the full course of vaccination.

## CONCLUSION

The risk of rabies is increasing from time to time due to lack of preventive measures and low public awareness towards currently available post exposure prophylaxis to prevent the disease. The major problem associated with rabies post exposure prophylaxis was identified as vaccine shortage due to old method of anti-rabies vaccine production technology, health professionals' knowledge gap about the disease and availability of affordable alternative effective vaccine on the market. During visit to health facilities, the main gaps identified were vaccine shortage, skill gap in case screening and inappropriate vaccine administration and wrong vaccine storage conditions.

Thus, intensive training and skill development are needed for health professionals working on case screening, vaccine handling and administration. As anti-rabies vaccine is currently produced and distributed by EPHI, health facilities face challenge to avail the vaccine at constant rate due to the long distance travel to get the vaccine. Although some regional states have vaccine handling centers, they have the problem of stock balance control and thus do not consider health facilities in remote areas in securing vaccine supply. Therefore, it is recommended that regional health bureaus and regional public health institutes have to consider vaccine needs at health facilities and establish vaccine centers to ensure availability at all times. Even though nerve tissue vaccine associated complication not documented, professionals at some referral hospitals indicate occurrence of nerve complications due to the vaccine. Thus, to avoid such unwanted reaction and guarantee full protection, it is needed to facilitate modern cell culture vaccine production technology transfer which can also overcome problem associated with supply shortage.

On the other hand, continuous training should be provided for health professionals working in the area of case screening, vaccine handling and storage and administration is recommended. Regardless of increasing vaccine production capacity and technology transfer to change existing technology, rabies prevention strategy should be considered by targeting dog mass vaccination and community sensitization for effective control of the disease.

In conclusion, although nerve tissue vaccine associated complications not reported due to inappropriate documentation, WHO already discouraged the use of nerve tissue anti-rabies vaccine and changing this production technology should be the first priority. Therefore, policy-makers and regulatory bodies should be aware and play their role in facilitating production and availing of cell culture vaccine locally which can replace existing nerve tissue vaccine.

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