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ROAD TO RABIES VACCINE: PASTEUR TO PRESENT

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Abstract

Rabies is one of the oldest known viral zoonotic diseases and remains a serious public health hazard, especially in the developing countries. It is the major viral disease in humans living in the tropics, but it is enzootic worldwide. Though its hundred percent preventable, it is estimated to cause 60,000 deaths annually. Rabies poses a threat to more than 3.3 billion people worldwide and is estimated to cause about 60,000 deaths a year. However, according to the WHO, it is still one of the most neglected diseases in developing countries. It is present in all continents except Antarctica, Australia, and mostly endemic in Asian and African countries. In countries like India and China, dogs are one of the major reservoir hosts for the transmission of this disease. This disease is unpreventable with the lack of awareness and proper prevention and treatment measures not being followed up with people who reside particularly in rural areas. It is because most Post Exposure Prophylaxis needs are borne by patients who can least afford to yield. Rabies vaccines have come a long way following the development of a vaccine by Louis Pasteur in 1885 which is still being used to control rabies in animals as well as humans. This review provides brief knowledge on rabies, its epidemiology, researches on rabies vaccines and its availability.

Introduction

Rabies is a rapidly progressive and uniformly fatal viral meningoencephalitis in humans caused by the rabies or related group of *Rhabdoviridae*, in the genus *Lyssavirus*, with a rich history of vaccine development (Christopher *et al.,* 1972). It is an acute viral infection caused by the highly neurotropic rabies virus, which is most often transmitted by the bite of a rabid animal. Once a person or animal begins to record symptoms, almost every case is fatal (Fitzpatrick *et al.,* 2012; Gsell *et al.,* 2012). This makes rabies a dreadful disease to humans. Human rabies is a major public health concern and is seen as a neglected disease worldwide by the World Health Organization (WHO, 2013a; Vigilato *et al.,* 2013).

The worldwide distribution of rabies has changed since 2010, and most of the rabies deaths occur in Africa, South-East Asia and Western Pacific regions (WHO, 2013a). Rabies has terrified man since olden times. The fear is by no means fallacious since the disease is inevitably lethal and perhaps the most atrocious and appalling of all communicable diseases in which the sick individual suffers at the same time with thirst and hydrophobia. The development of rabies can be prevented to a great extent if animal bites are managed appropriately on time.

Epidemiology of Rabies

Rabies is present in 150 countries and all continents except Antarctica and Australia. Stray dogs are a principal source of infections in humans in many parts of Asia and Africa (ECDC, 2016). Most of the cases of human rabies occur in poor regions of Africa and Asia; canine rabies is endemic and appropriate facilities are often not available for intensive medical care (Jackson, 2013). Rural areas of countries

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Vol-10 Issue-6 No. 13 June 2020

including Australia, Canada, Japan, United States, Western European countries and Island nations do not have rabies among dogs (CDC, 2014). As per CDC reports, some countries like Australia, New Zealand, the United Kingdom, Japan, Singapore, Papua New Guinea and the Pacific islands are free of dog rabies (CDC, 2017) though circulating viruses are prevalent, these countries are listed as rabies-free when importation of dogs to the USA is considered. A geographical map representing rabies affected areas worldwide is shown in Figure 1.

About 563 million United States dollars are spent in the world annually on measures to prevent rabies (Knobel DL *et al.,* 2005) yet in countries of south-eastern Asia the disease is still an important public health problem. An estimated 45% of all deaths from rabies occur in these parts of the world (Gongal G *et al.,* 2011). The situation is especially evident in India, which reports about 36% of the world's deaths from the disease (Dutta JK. *et al.,* 1995). Rabies incidence in India has been constant for a decade, without any declining trend, and in India rabies is still not a notifiable disease (Sudarshan MK, *et al.,* 2007)**.** This situation is fixed in a general lack of awareness of preventive measures, which translates into insufficient dog vaccination, an uncontrolled canine population, poor knowledge of proper post-exposure prophylaxis on the part of many medical professionals, and an irregular supply of anti-rabies vaccine and immunoglobulin, particularly in primary-health-care facilities.

Rabies virus and its structure

Rabies virus belongs to the order *Mononegavirales* i.e. viruses with non-segmented and negative-stranded RNA genomes. They belong to the genus - *Lyssa virus* in the *Rhabdoviridae* family that targets the central nervous system. They are bullet shaped and measures about approximately 180 nm long and 75 nm wide. The genome encodes five proteins classified as Nucleoprotein (N), Phosphoprotein (P), Matrix protein (M), Glycoprotein (G) and Large protein (L). The ordination and placement of these proteins encoding genes in the genome influence the structure of the virus. The RNA genome is enwrapped by N protein (also called the nucleocapsid). Phosphoprotein binds the Large protein to the Nucleoprotein–RNA template through an interaction of Nucleoprotein–Phosphoprotein complex that involves two adjacent Nucleoproteins in the nucleocapsid during RNA synthesis. Large protein–Phosphoprotein binding to the Nucleoprotein–RNA complex triggers conformational changes which allow the access of polymers to the RNA. Ribonucleoprotein (RNP), the component active in transcription and replication is formed by the RNA, Nucleoprotein, Phosphoprotein, and Large protein complex. The matrix protein M (202 aa) and glycoprotein G (505 aa) are membrane-associated proteins where the later is an integral transmembrane protein involved in viral entry. (Albertini *et al.,* 2011)

Prospects of vaccine development

Louis Pasteur**,** a French scientist acquired a vaccine in 1885 which predated the age of virology. In the year 1887, rabies vaccine developed by Pasteur was recognized by the Medical Community for therapeutic purpose. The rabies vaccine produced during Pasteur's period was applied worldwide for more than 10 years until 1895. Later on, carbolic acid-inactivated nervous tissue derived vaccines were introduced which were followed by phenol inactivated nervous tissue derived vaccines in the year 1915 (McGettigan, 2010). Pasteur's method was used before significant modifications were introduced in rabies vaccine. There are three primary types of rabies viral vaccines – nervous tissue vaccines, cell

ISSN: 2278-4632
Vol-10 Issue-6 No. 13 June 2020

culture based vaccines, and Embryonated egg vaccines. The presently available vaccines are discussed below:

Neural tissue vaccine

Neural vaccines are produced by introducing the virus in the spinal cord of rabbit and then inactivating by beta-propiolactone (BPL). Nerve tissue vaccines are less immunogenic and may cause serious adverse reactions, which also includes a possible risk of rabies from incomplete virus inactivation (Plotkin, 2008). They are however used in many developing countries (WHO, 2012). Adverse reactions are caused due to hypersensitivity reaction to the myelin thus it has been replaced by a human diploid cell culture-derived vaccine (also inactivated) which is safe and easily tolerated (Briggs *et al.,* 2000; Ajjan *et al.,* 1989). Neural tissue vaccines have been superseded by cell culture vaccines and Embryonated egg vaccines in industrialized nations.

Semple rabies vaccine

It was prepared by rabies virus infected goat or sheep brain tissue. The Semple Anti Rabies vaccine was produced by David Semple in India in 1911. Semple prepared this vaccine by using carbolized dead virus. It needs administration around the stomach over a period of 7 -14 days, which is a course that many not finish and so WHO abandoned its use in 1993 (Chakrabarti, 2010).

Embryonated egg based vaccines

Purified duck embryo vaccine (PDEV)

PDEV is a type of non neural vaccine that is prepared from duck embryo cells. It contains thiomersal (WHO, 2012). This was the first vaccine produced for human use and was produced in 1957 as a β-propiolactone inactivated vaccine purified by ultracentrifugation. It is given as an intradermal injection for several days.

First generation vaccine/cell culture based vaccines

Human Diploid Cell Vaccine (HDCV)

HDCV is also non neural vaccine which was introduced in 1978 as a first generation vaccine with strains like *Flury* or *Pitman-Moore L503* of rabies virus. It is a β-propiolactone inactivated intramuscular vaccine for use in human (Wiktor *et al.,* 1980; Keller *et al.,* 1984).

Second generation vaccine

Purified Chick Embryo Cell Vaccine (PCECV)

PCECV is produced in primary cultures of chick fibroblasts by growing *Flury LEP-25* strain (Gluck *et al.,* 1984). Virus is inactivated by β-propiolactone, purified and concentrated by zonal centrifugation (CDC, 1998; Dreesen, 1997). This vaccine was first marketed in 1984 and is now available in more than 70 countries. It is formulated as a vial of single dose containing lyophilized vaccine (Shayam, 2006).

Purified Vero Cell Rabies Vaccine (PVRV)

PVRV comprises of lyophilized *Wistar* strain of rabies virus grown in vero cell cultures and produced in fermentor for mass cultivation followed by inactivation by β-propiolactone and purification by ultracentrifugation (Jaiiaroensup *et al.,* 1998).

Primary Hamster Kidney Cell vaccine (PHKCV)

PHKCV is a formalin-inactivated vaccine which contains *Beijing* strain, propagated in primary kidney cell line of Syrian hamster and is adsorbed to aluminum hydroxide. It contains human albumin and thiomersal (Dutta, 1994; WHO, 2010a). It is used in China and Russia locally.

DNA Based Vaccine/Sub-unit vaccines

It is the third generation of Rabies vaccine which are basically bacterial plasmids constructed to express and encode protein following in vivo administration and subsequent transfection of cells (M A liu., 2011). This type of vaccine is yet to witness significant commercial success.

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Vol-10 Issue-6 No. 13 June 2020

Challenges

The greatest challenge in the industry of anti-rabies vaccine production for humans as well as animals, especially in many developing countries, is non-availability of modern technologies in order to progress from production of nerve tissue vaccine to the tissue culture vaccines and Sub-unit vaccines which is necessary due to presence of high content of myelin in adult brain tissue in Semple vaccine which increases the chances of neuroparalysis after use of the NTV. (Ghosh TK *et al.,* 2005 ; Acha PN *et al.,*1981). NTV is not only paralyticogenic, it is less convenient, less immunogenic, more reactogenic, less tolerable and so less acceptable. In addition, more number of doses are needed and the administration is a painful procedure. Cell culture based vaccines are comparatively more antigenic, acceptable, well tolerated, and convenient with less reactogenicity (Ghosh TK *et al.,* 2005)).
Another important constraint of rabies vaccine production is high cost of reagents and other consumables. The cost of procurement and maintenance of equipment such as safety cabinets, dispensing machines, gene gun, freeze-drying machines, labeling machines, incubators and freezers, availability of SPF eggs and maintaince of cell lines etc can be alarming. The cost of production of tissue culture based vaccine is high and for subunit vaccines it can be outrageous. As in most developing countries, there are serious challenges with provision of constant electric power, which is an inevitable requirement in any facility where vaccines are produced, stored, handled and transported on industrial scale. This eventually translates to increase in cost of production and finally increase in the cost of the product. One other basic difficulty is that the economic demand for vaccines bears no relation to the social pay-off (Freeman P *et al., 1*991). From a commercial standpoint, the total vaccine market here, in India and abroad is small. People, who have greatest need for vaccines, cannot afford to purchase them at market prices.

Conclusion

Rabies is a global threat to public health. Unfortunately, it is also a neglected zoonotic disease. Limitations in supply of rabies biologicals occur not only in developing countries, but also in the developed countries. However, the modern world can no longer be viewed in terms of national boundaries, but as a single entity, the ‘global village’. Rabies, like many other infectious diseases, will not be confined solely to endemic regions but will spread to other regions, due to agricultural trade, animal farming, natural animal migrations and intentional translocations. Rabies virus infects a broad spectrum of mammalian hosts, including humans, and cannot be treated as a single isolated or regional phenomenon. Tremendous efforts are underway to eradicate Rabies and to prevent the majority of spillover infections in humans and animals still has a long way to go before ultimate success. Without fundamental alterations in vaccine production, transfer of existing modern technologies of vaccine development and awareness in people the current rabies situation may not change substantially.

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Vol-10 Issue-6 No. 13 June 2020

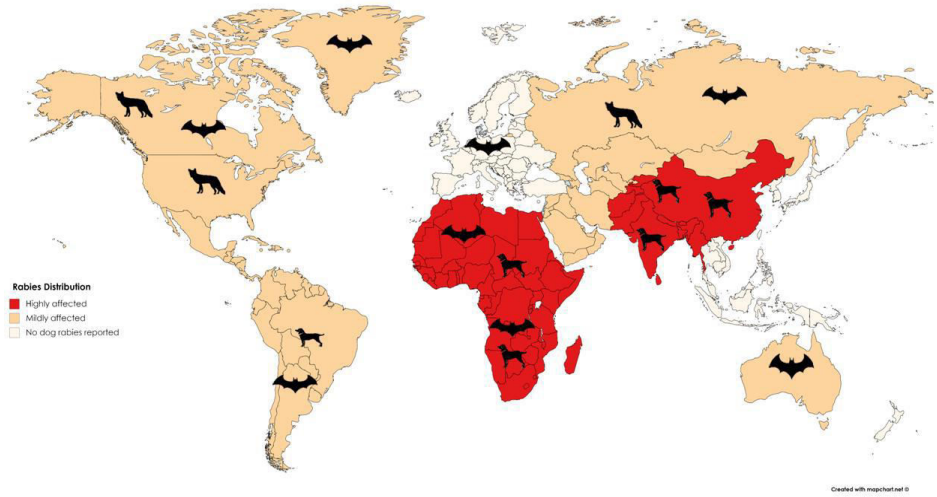

Fig.1 Representation of worldwide distribution of rabies virus affected area continent wise. Red indicates highly affected, pale yellow indicates mildly affected and white showing countries with rabies free of dogs.

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ISSN: 2278-4632
Vol-10 Issue-6 No. 13 June 2020

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