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Ending Rabies as an Epidemiologic and Global Public Health Problem

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ABSTRACT

Rabies remains a public health problem since ancient times and kills at least 59,000 annually, almost all transmitted via dog bites. It creates considerable economic impacts on developing countries, primarily in Africa and Asia. The World Health Organization has launched the elimination of rabies, as a global goal in the reduction of human rabies prevalence to zero cases by the end of 2030. Several countries, in Western Europe and North America, have adopted an elimination strategy for controlling rabies and have achieved elimination in the domestic dog population. The goal of elimination of rabies is achievable and would require substantial resources addressing this global health problem on individuals and health authorities, following WHO guidelines on the mass vaccination of dogs as well as increasing public awareness about rabies and its epidemiology.

Keywords: Rabies, Humans, Dogs, Animals, Prevalence, World Health Organization, and Mass vaccination.

INTRODUCTION:

Rabies is one of the most terrible zoonotic diseases known to humans (Alan C. Jackson, 2016). Although the disease can be prevented by vaccination, it kills about 59,000 people each year, mainly in low to middle-income countries (Singh *et al.*, 2017). The domestic dog is responsible for 99% of human death worldwide and, approximately 40% of the victims are children under the age of 15 (K. Hampson *et al.*, 2015; Liu & Cahill, 2020). The fatality rate is nearly 100%, once the clinical signs begin to develop in the infected host. Virus main transmission is via animal bites, but transmission through close contact with broken skin, a mucous membrane with the saliva of rabid animals, and organ transplantation is also reported (Lu *et al.*, 2018; C. E. Rupprecht *et al.*, 2002; Harun *et al.*, 2022). The etiological agent belongs to the genus Lyssavirus, family Rhabdoviridae and order Mononegavirals (C. Rupprecht *et al.*, 2017). The genus comprises a growing number of viral genotypes and so far, 17 officially classified genotypes have been characterized. The Rabies virus is the prototype of lyssavirus (Calvelage *et al.*, 2021). All lyssaviruses are capable of causing lethal encephalitis in susceptible animals. Iran is an ancient country located in the Middle East, a region between Asia, Europe, and Africa (Mehrdad). All neighboring counties suffer from rabies health problems in **Fig. 1** (Ahmad *et al.*, 2021; Atıcı & Oğuzoğlu, 2022; Hasanov *et al.*, 2017). Rabies is a significant health problem in Iran and the disease is reported in all 31 provinces of the country (Simani *et al.*, 2004). Due to high habitat diversity in Iran (Farashi & Shariati,

2017), a wide range of wildlife animals are found in the country, and the rabies virus is isolated from wolfs, jackals, foxes, and other wild animals (Bannazadeh Baghi *et al.*, 2018). Epidemiological studies show that domestic dog is responsible for most of the animal bites in Iran and is considered the main reservoir of the virus (Gholami *et al.*, 2017; Rahpeyma *et al.*, 2015). In Iran, animal bite statistics have increased over the past three decades, from 35 cases per 100,000 populations in 1987 to 177 cases per 100,000 in 2016 (Bay *et al.*, 2021). Therefore, the rabies elimination campaign is considered a complex task (Miao *et al.*, 2021) and requires strict intersectoral collaboration between human and veterinary authorities and policymakers.

Dogs play as the main vectors of human rabies (Bourhy *et al.*, 2010) and are responsible for more than 99% of human cases, Therefore, controlling rabies in dog population through mass vaccination campaigns, particularly in stray dogs, are the priority for human rabies prevention (Ceballos *et al.*, 2014; Denduangboripant *et al.*, 2005; Pastoret *et al.*, 2014). In this regard, zero by 2030 was launched in 2015 by the World Health Organization (WHO), the United Nations Food & Agriculture Organization (FAO), the World Organization for Animal Health (OIE), and the Global Alliance for Rabies Control (GARC) to help countries speed up their efforts to end human rabies by 2030 (Organization, 2018b). The main objective of this study was a systemic review of information and existing platforms towards this WHO mission.

World Epidemiology

While rabies is prevalent all around the world, except Antarctica (Malerczyk *et al.*, 2010), approximately 95% of human death is reported in Asia and Africa (Katie Hampson *et al.*, 2015). Around 15 million human exposures to rabies are estimated, which causes a significant economic loss of 8.6 billion US dollars (USD) annually and it is associated with a loss of 3.7 million disease-associated life years (DALY) (Beyene *et al.*, 2018).

On the other hand, rabies is considered one of the neglected tropical diseases, and it is assumed that rabies is underreported and the estimated burden is higher than of registered numbers in endemic regions (Taylor *et al.*, 2017).

Treatment

Although rabies has been around for a long time (L. H. Nel, 2013), and considerable advances have been made in the scientific knowledge of the etiology and pathogenesis of the disease, the disease is considered non-curable when the clinical outcome appears (Dacheux *et al.*, 2011; Tarantola, 2017). In addition, the sporadic occurrence of human cases makes systematic clinical research therapies even more difficult. So far, only about 30 human cases have been well documented for survival that the majority of these survivors experienced severe neurological effects (de Souza & Madhusudana, 2014; Wilde & Hemachudha, 2015; Willoughby *et al.*, 2005). On the other hand, in rabies-endemic areas, patients' access to intensive critical care may be restricted, because of the cost and lack of clinical expertise (Baron *et al.*, 2022; Darryn L Knobel *et al.*, 2022). As the pathological processes of the rabies virus are complex and the outcome of infection is severe, a combination therapy approach is required for the successful treatment of rabies in the future (Banyard *et al.*, 2019; Alan C Jackson, 2005). This combination therapy briefly can be classified into four categories: 1- inhibition of viral propagation by using specific antiviral drugs or monoclonal antibodies. 2- Prevention of neuronal degeneration. 3- Modification of host inflammatory response in later stages of infection, as the studies show that host immune responses may be damaging in later stages of CNS infection. 4- Managing severe systemic compromise of patients in late-stage of disease. The treatment process for the four categories should be initiated as soon as possible and expected results will be improved in the early initiation of treatment (D. L. Knobel *et al.*, 2022).

Post- exposure prophylaxis (PEP)

WHO-recommended PEP for unvaccinated individuals exposed to rabid animals should be started with immediate washing or cleaning out the wound, administration of a rabies vaccine, and if Category III exposure is detected, an additional injection of rabies immunoglobulin (RIG) is required (World Health, 2018). Currently different PEP vaccination (with intramuscular or intradermal routes) is authorized for people who have not previously been vaccinated against rabies. Immunosuppressed persons should receive rabies PEP in a 5-dose vaccine regimen (i.e., 1 dose of vaccine on

days 0, 3, 7, 14, and 28) and it is recommended that rabies serum antibodies should be checked 1 to 2 weeks after the fifth dose of vaccine in this group (Gongal & Sampath, 2019; Kessels *et al.*, 2019; Liu & Cahill, 2020). Unfortunately, studies have shown that low education level and unawareness about timely PEP, and lack of RIG administration on the day (D0) were substantially associated with high risk of non-compliant PEP schedule and fatal outcomes in rabies endemic areas (Joseph *et al.*, 2013).

Vaccine

Vaccines against rabies virus are among the oldest antiviral interventions. The first vaccine against RABV was developed in 1885 by Louis Pasteur and was based on neuron-derived vaccines (Borutzki *et al.*, 2022; Dreesen, 1997). Despite having low immunegenicity and adverse side effects, neuron-derived RABV vaccines have been in widespread use for over a century but they have now been largely discontinued (Ertl, 2019; Wu *et al.*, 2011). Advances in cell culture technologies enabled the creation of rabies cell- culture -based vaccines. Currently licensed rabies vaccines in comparison with nerve-tissue-derived vaccines have many advantages. First, they are safe and have been administered to millions of people over the decades. Second, they are highly effective (high immunegenicity) when administered correctly. Third, the vaccines induce long-lasting immunity in recipients. The serum antibody titer of 0.5 IU/ml defined by the WHO is considered to measure adequate seroconversion after vaccination.

Fig. 1: Map of Iran showing the two highlighted provinces with high animal bites (Dehghani *et al.*, 2016). The icon ✦ indicates rabies prevalence in all 31 provinces of country. The ★ icon indicates rabies prevalence in neighbors' countries of Iran. Blank map from d-maps.com

Mass vaccination of dogs

Animal bites especially dogs, cause tens of millions of injuries each year and are a major public health problem for children and adults worldwide (Desai, 2020; Patel *et al.*, 2017). Dog bite death rates are higher in low- and middle-income countries because many of these countries have rabies problems and post-exposure treatment and adequate health care may be lacking (Duperrex *et al.*, 2009). It is estimated that 180000 animal bites are recorded each year in Iran (Sarbazi *et*

al., 2020). According to data published by the Center for Disease Control, Ardabil and Golestan provinces have the highest number of animal bites (450 in 100,000) in **Fig. 1**, followed by the Chaharmahal - Bakhtiari provinces (300- 450 in 100,000). The lowest rates are reported from Tehran (< 100 in 100,000) (Dehghani *et al.*, 2016). Dogs are responsible for most (99%) human cases of rabies, and controlling the disease in these animals is the priority for preventing human rabies (Bourhy *et al.*, 2010).

Most importantly Dog vaccination reduces necessity for PEP and the death from dog mediated rabies (Lechenne *et al.*, 2017). There are successful models of human rabies control through the mass vaccination of dogs in the world. For example, in Central and South America, strict dog population control measures and coordinated mass vaccinations have resulted in rabies control. In Japan, and many island nations or regions in Asia, rabies has been controlled or the eliminated for decades (Belotto *et al.*, 2005; Davlin & VonVille, 2012; Lembo *et al.*, 2011; Louis H. Nel *et al.*, 2017; Organization, 2018a).

CONCLUSION:

Rabies elimination needs a global response to rabies on a sustainable base. It requires close coordination and intersectoral collaborations between human and veterinary departments in all affected countries. In Iran, public health authorities identified rabies as a health problem during the early-mid 20th century, as the national center for reference on rabies was established at the Pasteur institute of Iran. However, the pathway to ending rabies requires aggressive implementation of WHO guidelines.

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CONFLICTS OF INTEREST:

We have no Conflicts of interest in this research.

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