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Commentary

Avoiding preventable deaths: The scourge of counterfeit rabies vaccines

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1. Introduction

Rabies is a feared global disease, largely due to the extreme case-fatality rate, which approaches 100% once a patient becomes ill [4]. The true burden of disease remains undefined, but rabies causes tens of thousands of human deaths annually and is responsible for major economic losses, including dog vaccination costs in excess of US$130 million, and US$512 million in livestock deaths in rabies-endemic countries. After exposure, rabies virus causes an acute, progressive fatal encephalitis, which is prevented with timely post-exposure prophylaxis (PEP). Pre-immunisation in populations at risk, using modern, safe and efficacious cell culture vaccines, also prevents rabies. Where the disease burden is greatest, vaccines are not always readily available, and they can be prohibitively expensive.

Rabies cases in vaccinated individuals are becoming increasingly recognised [6]. The challenge of ineffective vaccines is complex and multifactorial but could be part of an apparent growing global trend for counterfeit vaccines [2]. The World Health Organization (WHO) defines counterfeit medicines, including vaccines, as products containing either incorrect, little or no active ingredient, which are marketed and sold as authentic medicines. Such products are illegal if the contents have been altered deliberately and the authorisation forged. The increasing availability and administration of counterfeit rabies vaccines, especially for PEP, may result in otherwise preventable deaths.

In 2015, the WHO, the World Organisation for Animal Health, and the Food and Agriculture Organization of the United Nations, in partnership with the Global Alliance for Rabies Control, proposed the global goal of zero human deaths as a result of dog-mediated rabies, by 2030. This goal is supported by a strategic plan, aiming to save lives, reduce costs, and enable clear communications on the validation of canine rabies elimination in endemic countries.

2. Global counterfeit vaccination activity

The sale of human counterfeit medicines is of worldwide concern. During 2015, the International Criminal Police Organisation completed a widespread seizure of counterfeit medicines worth US$79 million, with 115 countries participating. The international media allege instances where counterfeit vaccines are sold often at a more affordable price than genuine products [3].

Administration of ineffective vaccines results in children and adults unknowingly living without protection from preventable diseases such as hepatitis B, polio and rabies. Approximately 10% of global human medicines could be counterfeit, with 35% originating from the Indian sub-continent. In China, the media report incidents involving potentially fatal counterfeit human vaccines, including rabies, polio and mumps vaccines, distributed across two thirds of the country [9,7,10]. In 2010, counterfeit human rabies vaccines were allegedly administered to more than 1600 people, including hundreds of children, in Guangxi province. A child

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died of respiratory failure after receiving the first PEP dose of rabies vaccine. An investigation concluded that the vaccine used was out-of-date and revealed a sophisticated supply chain via a network of sellers. However, the report failed to conclude whether there was a direct link between the counterfeit vaccine and the child's death. The problem persists, as reported by the China Food and Drug Administration, who announced approximately 113,000 human rabies vaccine doses were forged in 2018 [5]. Although these are large numbers, they must be considered in the context of the 12–15 million genuine human rabies vaccine doses per annum delivered by China's health authorities, making China the world's largest administrator of rabies vaccine [8]. In the Philippines, a human rabies vaccine is reportedly in circulation that mimics the Indian-produced Rabipur vaccine, despite not having authorisation. The national authorities in China, Thailand and the Philippines, should be commended in proactively reporting investigations into vaccine misuse or counterfeit vaccines, and suggest the development of a centralised database of such investigations for both animal and human vaccines. The examples above illustrate the risks of counterfeit human rabies vaccines. The strategic plan to eliminate dog-mediated human rabies by 2030 depends on successfully controlling canine-mediated rabies via dog vaccination campaigns. Studies have also confirmed the risk of counterfeit animal vaccines associated with vaccine potency and storage. In China, inferior rabies vaccines used to vaccinate dogs were linked to an increased number of human fatalities [6]. In 2016, Thailand's Livestock Development Department and Food and Drug Administration reported on the discovery of three batches of substandard rabies vaccine for animal use, which had been imported from Spain.

3. What can be done to counteract illegal activity?

For over 50 years, WHO Collaborating Centres and Expert Committees on Biological Standardization have been working with WHO member states to standardize vaccines by implementing international guidelines and recommendations. These include production and control protocols to ensure quality, safety and efficacy of biological medicines globally, and preparation guidance on standardizing purity and potency of vaccinations. To complement technical standardisation efforts, there is a further need to coordinate international legislation and sanctions. The European Directorate for the Quality of Medicines and Healthcare (EDQM) has been actively involved on the subject of counterfeit vaccinations since 2011, implementing the Medicrime Convention, a binding international criminal law instrument used to criminalise manufacturing, supplying, and falsification of counterfeit medicinal products.

The WHO currently publishes a list of approved human rabies vaccines. To combat substandard vaccines, a One Health approach, with the introduction of a similar list of approved veterinary vaccines, appears logical. This inventory-style, industry-led, global repository of vaccines should provide details of those products that have been administered, where, at what prices, by whom (e.g. national programmes), and in what quantity. Importantly, accounting should detail any records of adverse effects. The Official Control Authority Batch Release has been implemented by the EDQM and allows for the request of samples from both human biological medicinal products and immunological veterinary medicinal products, to be submitted for competency testing prior to being placed on the market. This batch control-based system forbids human and veterinary vaccines, which are no longer pre-qualified to be sold on the world market. Governments in countries that import human and animal vaccines, which are not pre-qualified should implement a system to check vaccine potency on arrival and before use. In addition, vaccine manufacturers should be compelled to provide data on the potency of each exported vaccine batch.

Furthermore, the OIE's World Fund has experience in the management of canine rabies vaccine banks. These vaccine banks ensure the procurement of high-quality vaccines manufactured in line with OIE intergovernmental standards and therefore limit the use of counterfeit rabies vaccines.

Introduction of blockchain technology could replace the current system, which does not always allow for visibility and control within the supply chain and cannot prevent counterfeit vaccine entry [5]. Blockchain technology is a service platform, which supports and enables management of the supply chain, eliminating illegal activity and is being considered within human healthcare industries to create transparent data transactions, preventing counterfeit vaccines entering the supply chain. Whilst implementation of blockchain into human healthcare is still prototypic, there is now a strong potential for this technology to be applied successfully to the veterinary health industry [1].

Illegal activity in producing and selling counterfeit vaccines is most commonly reported from countries where community-based interventions are implemented. These interventions enable activities in a community to be coordinated and vaccination rates increased within a targeted human population. Yet, these countries often lack any effective healthcare systems to coordinate the manufacture, supply and distribution of efficacious vaccines. A gap in the vaccine market will often be seized upon by criminal organisations and the niche will often be filled with sub-standard and low potency vaccines. An investigation addressing differences in global wage versus cost of vaccine payment would be useful in documenting current health care inequalities and will help identify the most vulnerable populations at greater risk of being marketed cheaper counterfeit human vaccines.

4. Further challenges: public perceptions of vaccine hesitancy

During the 1990 s, the measles, mumps and rubella (MMR) human vaccine was falsely linked to autism. A significant decrease in parents choosing to vaccinate their children followed. This damaging assertion contributed to a dangerously reduced herd immunity, the effects of which continue to produce severe outbreaks of measles and mumps today with increasing numbers of human cases.

This anti-vaccination mind-set is also prevalent amongst pet owners worldwide. Owners choose not to vaccinate for many different reasons, including poor understanding of the risks and benefits. Therefore, ineffective and counterfeit human and animal vaccines have the potential to further fuel public resistance and hesitancy to vaccination, complicating the challenges of preventing and controlling infectious diseases. National governments should ensure that not only are counterfeit vaccines withdrawn immediately once recognised but guarantee that these vaccines do not ever enter the marketplace. Blockchain technology will support the vaccine supply chain, by ensuring that imported vaccines meet international standards of potency, preventing inferior low potency vaccines and unregulated products entering the supply chain. Consequently, to meet the vision of zero human deaths by 2030, all human and animal rabies vaccines should only be used if they meet international standards of quality and potency.

Conflicts of interest

H.B. is an inventor on several patent applications and provisional patent applications related to rabies virus vaccines.

R.S.M provides laboratory support for a rabies vaccine clinical trial, CPL Biologicals Pvt Ltd, Gujarat, India.

C.E.R. is an inventor on several patents related to rabies virus biologics.

M.J.S. is an inventor on several patent applications and provisional patent applications related to rabies virus vaccines and rabies virus-based vectors as vaccines.

A.R.F. is an Associate Editor for the journal, *Vaccine*. He declares no patents or patent applications related to rabies virus.

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