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Review

Morbillivirus vaccines: Recent successes and future hopes

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ABSTRACT

The impact of morbilliviruses on both human and animal populations is well documented in the history of mankind. Indeed, prior to the development of vaccines for these diseases, morbilliviruses plagued both humans and their livestock that were heavily relied upon for food and motor power within communities. Measles virus (MeV) was responsible for the death of millions of people annually across the world and those fortunate enough to escape the disease often faced starvation where their livestock had died following infection with rinderpest virus (RPV) or peste des petits ruminants virus (PPRV). Canine distemper virus has affected dog populations for centuries and in the past few decades appears to have jumped species, now causing disease in a number of non-canid species, some of which are been pushed to the brink of extinction by the virus. During the age of vaccination, the introduction and successful application of vaccines against rinderpest and measles has led to the eradication of the former and the greater control of the latter. Vaccines against PPR and canine distemper have also been generated; however, the diseases still pose a threat to susceptible species. Here we review the currently available vaccines against these four morbilliviruses and discuss the prospects for the development of new generation vaccines.

1. Introduction

Morbilliviruses form a separate genus within the *Paramyxovirinae* sub-family of the *Paramyxoviridae* family, Order *Mononegavirales*. Currently there are six viruses classified within the morbillivirus genus: rinderpest virus (RPV), measles virus (MeV), canine distemper virus (CDV), peste des petits ruminants (PPRV), phocine distemper virus (PDV) and cetacean morbillivirus (CeMV). Until recently, rinderpest was considered the archetypal morbillivirus with a predicted existence of 9000 years [1]. In 2010, however, it was proposed that rinderpest and measles diverged from the same ancestral virus in more recent times during the 11th or 12th century [2]. MeV caused millions of human deaths annually before vaccines became available in the early 1960s. CDV, which affects many terrestrial and marine carnivores and PPRV which infects small ruminants and some large ruminants, can be as deadly to those they infect as rinderpest was to large bovids. Two other morbilliviruses, phocine distemper virus (PDV), affecting seals and other pinnipeds and cetacean morbillivirus (CeMV), threatening dolphins and porpoises, have also caused mass die-offs of these marine species.

All viruses within the Order *Mononegavirales* contain a negative-sense single-stranded RNA genome that consists of six open reading frames encoding six structural and two non-structural proteins. The nucleocapsid (N), phosphoprotein (P) and large polymerase protein (L), in tandem with the viral RNA, form the ribonucleoprotein complex (RNP). The matrix (M) protein forms a link between the RNP and the host cell derived plasma membrane, covered evenly with distinctive spikes of the viral glycoproteins, the haemagglutinin (H) and fusion proteins (F). The interaction between the H and F proteins governs the virus entry into a host cell. Here we review existing vaccines for morbilliviruses and discuss ideas for future vaccine development and potential eradication.

2. Rinderpest virus: the template for morbillivirus eradication

Early experiments with rinderpest virus (RPV) shifted a focus in animal disease management that altered the direction of veterinary science and had important ramifications for medical science. Indeed, repeated attempts to cure rinderpest virus led to the observation that serum obtained from recovered individuals was protective when administered to naïve animals that were subsequently exposed. This altered the scientific emphasis from treatment to prevention and heralded the new dawn of vaccinology. For RPV, early techniques aimed at preventing disease involved

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the inoculation of both virus and immune serum from convalescent animals and the preparation of hyperimmune serum in goats [3]. This was progressed with the application of immune serum, given either alone or in combination with infected blood where Robert Koch demonstrated that the combination of immune serum with virulent blood induced an active immunity. This approach was termed the "serum-virus simultaneous" method and was applied widely across Africa and India to protect livestock against rinderpest. Whilst highly effective the method suffered drawbacks including the induction of disease in both young and immunosuppressed animals (including pregnant animals), the infectious nature of vaccinees, instability of the preparations and the potential for transmission of piroplasms present within the inoculated preparation.

The next stage in vaccine generation against RPV involved the development of inactivated RPV vaccines. Early inactivated vaccine preparations were produced from infected bovine tissues that were chemically inactivated. Field application of inactivated RPV vaccines successfully cleared RPV from several countries including Iran, the Philippines, Sri Lanka, Thailand and Russia [4]. However, the immunity produced by these inactivated vaccines was short lived and as such, live attenuated vaccine strains were developed following multiple passage in different hosts. The first were produced in goats, and were cheap, efficacious, did not transmit piroplasms and one of them, the Kabete Attenuated Goat (KAG) vaccine was shown to induce a long lived neutralising antibody response to RPV [5,6]. A lapinized version of the RPV vaccine was developed in Korea and Japan, due to a shortage of goats, and was found to be better suited to Asiatic breeds of cattle [7]. Limitations in the number of doses produced in a single rabbit led to further passage in goats and then sheep, with the final product being used to eradicate RPV from China [4]. In Japan and Korea a vaccine was also generated *in ovo* to overcome adverse reactions seen with the lapinized vaccine in highly susceptible cattle. This development of attenuated vaccines in different host species reduced the labour required for mass production of vaccines but it was not until the development of tissue culture based vaccines that mass production at an economically viable cost could be achieved.

Early attempts to passage attenuate viruses in tissue culture were hampered by a lack of susceptible cell line for virus culture. Attempts using adapted strains of rinderpest in chicken embryo fibroblasts (CEFs), bovine kidney (BK) cells or bovine embryonic kidney cells were unsuccessful. Then, during the late 1950s [8,9], a virulent strain of RPV was successfully attenuated in primary calf kidney cultures. Initial passage resulted in an increased virulence but, following further passage, virulence was reduced until the virus was deemed to be completely attenuated and unable to cause disease even in the most susceptible breeds of cattle [10]. This vaccine, termed the tissue culture rinderpest vaccine (TCRV), was able to elicit a long term neutralising antibody response with protection from challenge several years post-vaccination without causing any adverse reactions.

The TCRV was used extensively across the developing World to vaccinate cattle against RPV and proved to be a highly effective tool in the eradication of rinderpest. There was, however, one drawback related to the TCRV: the serological signature of vaccinated animals was identical to that developed by animals infected naturally in the field that had survived infection. Since there was only one serotype of RPV, this meant that the OIE "gold standard" competitive ELISA based on an anti-H monoclonal antibody, was unable to fulfil 'DIVA' requirements – the ability to differentiate between the serological signature of naturally infected and vaccinated animals. Had the Global Rinderpest Eradication Programme not been successful then several candidate DIVA vaccines that had been developed may have found utility. Recombinant RPV vaccines that expressed foreign genes, such as GFP and HA, were developed although the serological response to the foreign genes was not sufficient [11]. A further development was a recombinant RPV that had the RPV N protein swapped with that from the closely related PPRV. Cattle vaccinated with this recombinant vaccine were protected from RPV challenge, and a companion ELISA test was developed to accompany the vaccine, enabling DIVA, although the successful eradication of RPV precluded its use [12]. A further alternative approach that showed promise for vaccine development for morbilliviruses in general was that of negative marking of vaccines by epitope deletion [13]. Such novel DIVA initiatives may find utility in the development of a DIVA vaccine for other morbilliviruses.

The successful global eradication of smallpox announced in 1980 was the incentive for OIE and FAO to examine the feasibility of setting the same goal for rinderpest by the year 2010 [14]. Several factors related to the virulence, pathology and epidemiology of rinderpest were recognised as favouring the Global Rinderpest Eradication Plan (GREP), including the limited geographical distribution of the disease, no latency or persistence of the virus in infected animals, the short infectious period and the requirement for direct or close indirect contact for transmission of the virus. The availability of the TCRV and highly sensitive and specific companion diagnostic tests was crucial for eradication campaign [14]. The economic significance of large ruminants across the developing world gave political and economic impetus to drive the eradication campaign to completion [3,15]. Finally in the year 2011, after a long campaign launched in 1994, the OIE announced RPV as only the second pathogen successfully eradicated from the world by human effort [16].

3. Measles virus

The development of vaccines against measles was facilitated by the isolation of the virus from human and monkey renal cells exposed to whole blood and throat washings obtained from patients infected with measles [17,18]. The cultivation of isolated viral material in chick embryo fibroblasts (CEFs) led to the generation of the first attenuated measles vaccine, the Edmonston-B strain [19], which was licensed for use in 1963. Although this vaccine was effective in preventing measles infection, it had to be administered with human gamma globulin as it commonly caused adverse reactions in vaccinees including fever and rash. In an attempt to ameliorate these side effects, studies were carried out on the development of an inactivated virus vaccine but the new formulation not only offered no protection against the disease, but also caused an atypical form of measles in those patients, who were exposed to wild-type virus post-vaccination [20,21]. In 1965, Maurice Hilleman propagated the Edmonston-B vaccine strain for a further forty passages in CEF cells to increase attenuation of the virus resulting in the generation of the Moraten strain (More Attenuated Enders) [22]. This new live attenuated version did not cause the side effects which accompanied the Enders vaccine, but was equally effective and as such it was licensed for human vaccination in 1968. In 1971 Stokes et al. published the results of studies on the trivalent vaccine against measles, mumps and rubella viruses [23]. The vaccine, known as the MMR, is a cocktail of three live attenuated viruses and has been shown to protect 96%, 95% and 94% of vaccinated individuals from measles, mumps and rubella, respectively. Since being licensed it has been used to vaccinate over 600 million people in over 60 countries across the world. It was originally administered as one-dose vaccine, but in 1989 a second dose was introduced to produce immunity high enough to disrupt measles transmission in a vaccinated population [24,25].

In 1998 a link between the MMR vaccine and the occurrence of autism and bowel disease was made by Wakefield et al. based on a study involving twelve children [26]. The publication sparked a