Review

Morbillivirus vaccines: Recent successes and future hopes

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A B S T R A C T

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 being 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.

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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
Although 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 (CEF), 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
long-lasting controversy despite the fact that subsequent reports extensively discredited the initial data [27,28]. Although the Wakefield publication has been fully retracted on both ethical and methodological grounds [29], the article and the public concern caused by the accompanying press coverage had a profound effect on the uptake of MMR vaccine [30]. A study on vaccine uptake in UK revealed that a conscious parental choice was a reason for 75% parents refusing to vaccinate their children with MMR, with the safety concerns being in part the legacy of the original publication [31,32]. A significant impact of this has been the re-emergence of measles virus in populations across Europe where it was previously absent, following a drop in immunity afforded where vaccination coverage drops below a level required to prevent virus spread within a community [33] (Fig. 1). In the UK, where the MMR controversy originally started, the measles vaccination coverage has also dropped and consequently a significant increase in the disease cases has been observed [30]. Between April and June 1995, 92.5% of children received their first dose of MMR before 2 years of age, compared to only 78.9% in the same period in 2003 [34,35]. The importance of vaccination was shown by a study summarising measles incidents in five European countries in which the majority of cases were unvaccinated or incompletely vaccinated children [36].

Despite the public concerns, MMR is regarded in the scientific community as one of the safest vaccines available. Moreover, measles virus possesses several features which make it an ideal candidate for recombinant vaccine development. The development of reverse genetics techniques has made manipulation and subsequent generation of recombinant live viruses possible and these tools have been extensively utilised for the morbillivirus. Contrary to what might have been expected of an RNA virus, MeV recombinants are genetically stable and have been shown to not revert back to the virulent phenotypes. The risk of accumulation of mutations in neutralising epitopes in order to escape the protective immune responses conferred by vaccine strain could be theoretically expected, but despite high degree of mutations in RNA viruses, no such event has ever been observed not only in measles [37], but also in other morbilliviruses, such as RPV and PPRV. These assets along with the capability to accept up to 6 kb of foreign sequences, induction of both humoral and cellular immune responses, and the good safety record of vaccine strains and their low production costs have made MeV a vector of choice for the development of vaccines against numerous foreign pathogens and recombinant oncolytic viruses [38]. To date, surface proteins of several heterologous viruses have been expressed in MeV backbone and the immunogenicity of the foreign proteins examined in susceptible hosts (Table 1 and references therein).

The successful global elimination of rinderpest virus has highlighted the feasibility of measles eradication. Several factors related to the biology of the virus and the characteristics of the current vaccine favour the eradication idea. The measles virus, like all other morbilliviruses, is antigenically monotypic, which means that seroconversion after recovery from the disease or successful vaccination protects from all strains of the virus. There are no known animal reservoirs of the virus and where infected, susceptible non-human primates are considered “dead end” hosts due to insufficient population size [49]. Therefore the risk of “spill over” events is unlikely to hamper control efforts. For MeV, licensed vaccines are safe and can be administered to immunocompromised individuals safely with the two doses of vaccine, administered around 9–15 months and then 4–5 years of age, being able to induce protection for at least several decades if not for a life time [50]. The existing diagnostic assays are of great utility although point-of-care tests would improve diagnostic potential, similar to those being developed for ruminant morbilliviruses [51]. Limitations to MeV vaccines do, however, exist including the potential for interference from maternal antibodies in young children preventing a strong protective response [49]. This factor has led to the re-emergence of MeV in highly vaccinated populations [52]. Efforts to overcome the poor paediatric vaccine efficacy by using high titre vaccine were attempted but were stopped when mortalities were reported [53]. DNA vaccines have been proposed as an alternative vaccination
strategy for infants and in vivo studies have demonstrated their potential utility [54–56]. Alternative viral vectors for delivery of MeV glycoproteins are also being assessed [57,58].

4. Canine distemper virus

A disease with clinical manifestations matching those of canine distemper has been reported for centuries plaguing animals across the globe [59]. Canine distemper virus (CDV), was initially thought to being restricted to infection of members of the Canidae, although in the last 20 years it has caused outbreaks in a wide variety of hosts including members of Felidae, Hyaenidae, Mustelidae, Procyonidae, Ursidae, Viveridae, Aluridae and Mephitidae [60,61]. Alongside this CDV has been implicated as the cause of extensive distemper outbreaks in seal populations [60,62].

In naïve dogs, CDV is generally associated with a pessimistic prognosis but its dramatic impact on wildlife species has increased awareness of the disease. In 1992, outbreaks of CDV killed several tigers, lions and leopards kept in American zoos [63], an unexpected event since CDV was not previously thought to cause clinical disease in Felids. Two years later, in 1994, a large outbreak decimated a population of lions in Serengeti National Park in Tanzania, reducing their population by an estimated 30% [64]. During this outbreak several hyena cubs also fell victim to CDV [65]. In Tanzania, a recent outbreak among African wild dogs (Lycaon pictus) killed 49 out of 52 breeding animals in just 2 months [66]. In fact, distemper outbreaks in domesticated and wildlife species are regularly reported across the world [67–69]. Moreover, recently the virus has expanded its host range to non-human primates, namely rhesus monkeys (Macaca mulatta) in China and cynomolgus monkeys (Macaca fascicularis) in Japan [70–72]. These reports have highlighted the need for a CDV vaccine that can be used for the control of the disease in both domesticated and wild animals.

Until recently only modified live vaccines (MLV) against CDV, both introduced in early 1960s, were available. The first, the Onderstepoort vaccine, was developed from a natural isolate which was passaged in ferrets and then adapted to chicken embryos, later replaced with chicken cell culture [73]. The other was generated by adaptation of the Rockborn strain to canine kidney cell culture [74]. The canine adapted cell culture vaccine offers protection to almost 100% vaccinated dogs, but on rare occasions can cause post-vaccination encephalitis [75]. These two vaccines have significantly reduced CDV infection in domestic dog populations, although these vaccines have found to be insufficiently attenuated for use in wildlife species. For example, a CDV vaccine generated in canine cells causes disease in grey foxes (Urocyon cinereoargenteus) and ferrets (Mustela nigripes) [76,77], while an avian attenuated vaccine can be fatal for European mink (Mustela lutreola) and ferrets [77,78]. Generally, the avian cell adapted vaccine is considered safer for wildlife species, and is tolerated by both grey and red foxes (Vulpes vulpes), bush dogs (Speothos venaticus), maned wolves (Chrysocyon brachyurus) and fennec foxes (Vulpes zerda) [76,79–81]. In contrast, out of all of the above mentioned species, the canine cell adapted vaccine was found safe for red foxes only [76]. Problems associated with MLV vaccines, especially their unsuitability for many endangered species, are the incentive for development of recombinant vaccines, which could be safely used for all species. The recently generated recombinant CDV vaccine, incorporating the fusion (F) and haemagglutinin (H) proteins of CDV in a strain of canarypox virus was shown to be safe to all susceptible species tested to date, including dogs, European ferrets (Mustela putorius furo), giant pandas (Ailuropoda melanoleuca), fennec foxes, meerkats (Suricata suricatta) and Siberian polecats (Mustela eversmanni) [82–85]. Whilst the canarypox vectored vaccine is safe in numerous target species, it is replication incompetent and as such induces a milder immunological response than MLV vaccines [86]. However, this latter feature highlights its applicability for immunisation of young animals in the presence of maternal antibodies [87].

Other attempts have employed reverse genetics techniques for the study and development of novel vaccines. The concept of rational attenuation of the CDV by modifying the viral RNA polymerase (L protein) to express a reporter gene from within its open reading frame led to viral attenuation, as previously demonstrated for other morbilliviruses [88,89]. Similarly, depleting the CDV H protein of N-linked glycosylation sites has produced a virus with an attenuated phenotype, that was no longer able to cause disease in ferrets [90]. A further approach centred around generating a chimeric virus combining the replication complex of the MeV Moraten strain with the glycoproteins of wild-type CDV [46]. The resulting recombinant did not cause any clinical signs or immunosuppression in vaccinated animals and induced protective immunity from lethal challenge. DNA vaccines, formulated in a similar way to those described for MeV have also shown promise inducing a strong protective humoral and cell-mediated immune response [91,92]. Although effective and relatively inexpensive to produce, problems

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associated with vaccination regime and delivery routes must be resolved to make DNA vaccines an effective alternative to MLVs for wildlife populations. Finally, CDV has recently been used as a vector to express the rabies virus glycoprotein. The chimeric virus induced a strong rabies neutralising antibody response and protected mice from a lethal dose of rabies [93]. The virus was shown to be safe for both mice and dogs, and although no CDV challenge experiments were carried out, the vaccine resulted in production of long-lasting neutralising antibodies against both CDV and rabies and demonstrate the potential for multivalent morbillivirus vaccines.

5. Peste des petits ruminants virus

Peste des petits ruminants (PPR) was first identified in 1942 as a disease of small ruminants distinct from RPV [94]. In 1979 it was classified as the fourth member of the morbillivirus genus alongside RPV, MeV and CDV [95]. PPR is endemic across large parts of Africa and Asia [96]. For many years the TCRV was used effectively to protect sheep and goats from PPRV with the cross-neutralising antibody response affording protection for at least 12 months [97]. However, the need to stop vaccinating animals with the TCRV during the rinderpest eradication meant that a homologous PPRV vaccine, Nigeria 75/1, was required. This vaccine was generated by serial passages of a virulent PPRV strain in cell culture [98] and was reported to be able to protect goats and sheep from challenge with wild-type PPRV isolates for at least 3 years post-vaccination. The existence of only one serotype of PPRV means that this vaccine protects against challenge with viruses from all four PPRV lineages. Currently, several PPRV vaccines are licensed alongside the Nigeria 75/1 vaccine, with live attenuated Sungri/96, Arasar/87 and Coimbatore/97 vaccines being used in India [99].

It is widely accepted that, as with the RPV eradication, a DIVA vaccine would be of great utility in combatting PPRV. However, development of such a vaccine was hampered through the lack of a reverse genetics system for PPRV. This hurdle has been overcome by Murali et al. and Hu et al. [100,101] who have reported the development of recombinant forms of PPRV. Alternatively, with RPV eradicated then TCRV based recombinants could be used for DIVA purposes, as developed by Das et al. who generated a chimeric RPV containing the glycoproteins of PPRV [102]. This recombinant vaccine protected animals from virulent challenge and fulfilled the DIVA principles [103] but a reluctance to utilise a vaccine virus based on RPV in the post-eradication era means that such DIVA tools are unlikely to be used.

Other research groups have proposed a different approach for designing DIVA vaccines by engineering capripox virus to express PPRV H protein. If used in the field, the serological profiles of animals vaccinated with this recombinant vaccine could be distinguished from those of naturally infected animals by the absence of antibodies directed against the viral proteins not included in vaccine formulation. Although initial trials showed that a capripox vaccine protected goats from challenge with a virulent strain of PPRV, no field studies have been carried out [104–106].

Given the similarities between RPV and PPRV, it is believed that any future plans for PPRV elimination will require the implementation of the same principles which led to rinderpest eradication. There are however some requirements, which will have to be met before any coordinated action against PPRV is initiated. Most importantly, our knowledge about the epidemiology of PPRV in wildlife has to be improved. While RPV was regularly reported in wildlife species [107], it was generally accepted that wildlife populations were the victims of virus circulating in domesticated cattle rather than the reservoirs of the infection. The role of wildlife in transmission of PPR remains to be elucidated although several species have been reported as susceptible [108–110]. In addition to gaps in our understanding of PPRV epidemiology, the financial costs of a possible eradication campaign are also unknown and may be difficult to estimate. The shorter life-span of small ruminants compared to cattle means that their turnover rate is higher. This in turn results in the need for more vaccine and trained veterinary services to carry out vaccine administration. All of these factors need addressing before formulating a viable eradication programme.

6. Conclusions

The successful elimination of RPV has highlighted the potential for eradication of other morbilliviruses and initiatives to eradicate MeV are underway coordinated by the WHO [31]. Despite this, MeV is still causing the death of thousands of children in Africa and, due to controversies associated with the MMR vaccine, even developed countries are experiencing extensive epidemics. While regular vaccinations helped to reduce CDV incidence in dogs, the same virus causes mass die-offs in wildlife species, some of them already on the verge of extinction. In addition, a new morbillivirus, named feline morbillivirus (FmoPV), was recently discovered in domestic cats (Felis catus) [111]. As the battle against morbilliviruses continues, further development of vaccines, in particular DIVA vaccines, will aid our ability to disrupt circulation of these viruses and potentially aid eradication of morbilliviruses in the wake of successful RPV eradication.

References


Virus in Rational Nature

Virol glutinin against Natural Pardo Carpenter Suricata. RNA-dependent DA.


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