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### Summary

### Zusammenfassung



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## Vaccines against Coronaviruses of Veterinary Importance

### *Impfstoffe gegen veterinärmedizinisch relevante Coronaviren*

Emmelie Eckhardt, Max Bastian

The COVID-19-pandemic has unprecedentedly spurred vaccine development against SARS-CoV-2. Around 170 vaccine projects are listed by WHO and 29 have already entered clinical phase trials. But as scientist all over the world are striving to develop an efficacious vaccine it may be helpful to risk a glance into the backyard of coronavirus research. In veterinary medicine there is a long record of vaccine development against coronaviruses. This review focuses on vaccination approaches against coronaviruses in chicken, pigs and cats. Strain variation, induction of effective, mucosal immunity and avoidance of immunopathology are just a few of the manifold challenges to be faced on the way to the efficacious coronavirus vaccine. Although it proved hard to achieve sterile immunity, in veterinary medicine live-attenuated vaccines helped to reduce clinical symptoms and minimize economic losses. In the case of SARS-CoV-2 innovative reverse vaccinology may be the conduit to surpass all obstacles and rapidly provide an efficacious vaccine against the pandemic virus.

**Keywords:** Feline Infectious Peritonitis, Infectious Bronchitis, Porcine Endemic Diarrhea, Transmissible Porcine Gastroenteritis, Veterinary Vaccines

Die COVID-19-Pandemie hat die Entwicklung von Impfstoffen gegen SARS-CoV-2 in beispielloser Weise vorangetrieben. Rund 170 Impfstoffprojekte sind von der WHO gelistet und bei 29 dieser Projekte wurde bereits mit klinischen Studien begonnen. Während Wissenschaftler auf der ganzen Welt bestrebt sind, einen wirksamen Impfstoff zu entwickeln, kann es hilfreich sein, einen Blick in den Hinterhof der Coronavirus-Forschung zu riskieren. In der Veterinärmedizin gibt es eine lange Geschichte der Impfstoffentwicklung gegen Coronaviren. Der vorliegende Übersichtsartikel will Impfansätze gegen Coronaviren bei Hühnern, Schweinen, Rindern und Katzen vorstellen. Stammvariationen der Viren, die Induktion einer wirksamen Schleimhautimmunität und die Vermeidung von Immunopathologie sind nur einige der vielfältigen Herausforderungen, denen man sich auf dem Weg zum wirksamen Coronavirus-Impfstoff stellen muss. Obwohl es sich immer wieder als schwierig erwiesen hat, eine sterile Immunität zu erreichen, haben sich in der Veterinärmedizin abgeschwächte Lebendimpfstoffe bewährt. Sie tragen dazu bei, die klinischen Symptome zu verringern und wirtschaftliche Verluste zu minimieren. Für SARS-CoV-2 werden möglicherweise Ansätze der reversen Vakzinologie die vielfältigen Herausforderungen überwinden und zu einer schnellen Entwicklung eines wirksamen Impfstoffes gegen das Pandemievirus führen.

**Schlüsselwörter:** Feline Infektiöse Peritonitis, Infektiöse Bronchitis der Hühner-vögel, Epidemische Virusdiarrhö der Schweine, Übertragbare Gastroenteritis der Schweine, Veterinärimpfstoffe

**TABLE 1:** *Coronavirus-vaccines for veterinary use; authorized for the German market (VETIDATA-Database 2020)*

Species	Vaccine Name (Manufacturer)	Antigens
<b>1. Feline Coronavirus (Alphacoronavirus)</b>	Primucell FIP (Zoetis)	Feline Coronavirus (live-attenuated)
<b>2. Bovine Coronavirus (Betacoronavirus)</b>	Bovigen Scour (Virbac)	Bovine Rotavirus (inactivated) Bovine Coronavirus (inactivated) <i>Escherichia (E.) coli</i> (inactivated)
	Lactovac (Zoetis)	Bovine Rotavirus, strain 1005/78 (inactivated) Bovine Rotavirus, strain Holland (inactivated) Bovine Coronavirus (inactivated) <i>E. coli</i> (inactivated)
	Scourgard 3 (Zoetis)	Bovine Rotavirus (Live-attenuated) Bovine Coronavirus (Live-attenuated) <i>E. coli</i> (inactivated)
	Trivacton (Merial)	<i>E. coli</i> , Stamm O:101 / F5 (K99)-Antigen (inactivated) <i>E. coli</i> , Stamm O:117 / Y-Antigen (inactivated) <i>E. coli</i> , Stamm O:78 / 31A-Antigen (inactivated) <i>E. coli</i> , Stamm O:101 / F41-Antigen (inactivated) Rotavirus, Strain Rol (inactivated) Coronavirus, Strain CR1 (inactivated)
	Rotavec Corona (Intervet)	<i>E. coli</i> , Fimbrien-Adhesin F5 <i>E. coli</i> , capsular antigen 99 (K99) Bovine Coronavirus, strain Mebus (inactivated) Bovine Rotavirus, strain G6P5 (inactivated)
	Aniserin orinject (aniMedica)	Colostrale Gammaglobulin against: (I) <i>E. coli</i> 78:80 B > 1:160 (LA) (II) <i>E. coli</i> K 99 + > 1:1600 (ELISA) (III) Rotavirus > 1:3200 (ELISA) (IV) Coronavirus > 1:1600 (ELISA)
	Biofakt Albrecht (Albrecht)	Colostrale Gammaglobulin against: (I) <i>E. coli</i> 078:80 B > 1:160 (LA) (II) <i>E. coli</i> K 99 + > 1:1600 (ELISA) (III) Rotavirus > 1:3200 (ELISA) (IV) Coronavirus > 1:1600 (ELISA)
<b>3. Aviary Coronavirus (Gammacoronavirus)</b>	Avishield IB H120 (Dechra Veterinary Products)	Infectious Bronchitis Virus, Strain Massachusetts (Live-attenuated)
	Cevac IBird (CEVA Tiergesundheits)	Infectious Bronchitis Virus, Strain 1/96 (Live-attenuated)
	Cevac Mass L (CEVA Tiergesundheits)	Infectious Bronchitis Virus, Strain Massachusetts B-48 (Live-attenuated)
	Gallimune – line (Boehringer Ingelheim)	Products of this line contain: – Infectious Bronchitis Virus, Strain Mass41 (inactivated) The product line comprises: – Gallimune 302 ND + IB + EDS – Gallimune 303 ND + IB + ART – Gallimune 407 ND + IB + EDS + ART
	Gallivac IB88 (Merial)	Infectious Bronchitis Virus, Strain CR88121 (live-attenuated)
	Nobilis IB Ma5 (Intervet)	Infectious Bronchitis Virus, Strain Ma5 (live-attenuated)
	Nobilis IB 4-91 (Intervet)	Infectious Bronchitis Virus, Strain 4-91 (live-attenuated)
	Nobilis IB Primo QX (Intervet)	Infectious Bronchitis Virus, Strain D388 (live-attenuated)
	Nobilis Ma5 + Clone 30 (Intervet)	Infectious Bronchitis Virus, Strain Ma5 (live-attenuated) Newcastle Disease Virus, Strain Clone 30 (live-attenuated)
	Nobilis IB + ND – line (Intervet)	This product line contains: – Infectious Bronchitis Virus, Strain M41 (inactivated) – Newcastle-Disease-Virus, Strain Clone 30 (inactivated) The product line comprises: – Nobilis IB + ND – Nobilis IB + G + ND – Nobilis IB + ND + EDS – Nobilis Reo + IB + G + ND
	Nobilis IBmulti + ND – line (Intervet)	This product line contains: – Infectious Bronchitis Virus, Strain D274 (inactivated) – Infectious Bronchitis Virus, Strain M41 (inactivated) – Newcastle-Disease-Virus, Strain Clone 30 (inactivated) The product line comprises: – Nobilis IBmulti + ND – Nobilis IBmulti + ND + EDS – Nobilis RT + IBmulti + G + ND – Nobilis RT + IBmulti + ND + EDS
	Poulvac IB Primer (Zoetis)	Infectious Bronchitis Virus, Strain D274 (live-attenuated) Infectious Bronchitis Virus, Strain H120 (live-attenuated)
	Poulvac IB QX (Zoetis)	Infectious Bronchitis Virus, Strain L1148 (live-attenuated)

## **Introduction**

As the SARS-CoV-2 pandemic is overrunning countries and health systems, scientists all over the world strive to develop an efficacious vaccine against the virus that will allow us returning to normality. However, experiences that were made with coronaviruses in the field of veterinary medicine may tell us that this task is easier commenced than accomplished. Coronaviruses infecting livestock and pet animals are very common. Depending on virus characteristics and animal husbandry conditions, the symptoms range from mild disease - making the development or the application of vaccines unnecessary - to severe illness that may result in severe epidemics with great economic impact. As a consequence, there is a long history of vaccine development against veterinary coronaviruses, which resulted in several commercially available products. On the European and in particular on the German market vaccines are currently authorized against avian Infectious Bronchitis (IB), bovine neonatal diarrhea and Feline Infectious Peritonitis (FIP) (VETIDATA-Database 2020; Table 1). Globally, there is also great interest in porcine coronavirus vaccines. Very recently, Ian Tizard has published a detailed overview on veterinary coronavirus vaccines (Tizard 2020). In this manuscript, we will focus on vaccination approaches in the field of veterinary medicine that may help scientist to identify risks and opportunities in the development of SARS-CoV-2 vaccines.

Coronaviruses are enveloped viruses with a fringe of club-shaped projections resembling a solar corona, hence the name. They harbor a single-stranded, positive-sense RNA genome. Two thirds of the genome at the 5'-end encode for the replicase complex, the remaining 3'-part for the essential structure proteins and in dependence of the genus for a varying number of accessory proteins (Vlasova et al. 2020). The trimerizing spike proteins (S) form the coronar fringe. They contain two domains, the first (S1) is responsible for receptor binding, the second domain (S2) mediates membrane fusion. As a consequence, the spike protein is the main target for neutralizing antibodies (Chang et al. 2002, Reguera et al. 2012). The two membrane proteins (M and E) are essential for virion assembly, they also contain B cell epitopes (Zhang et al. 2012). The nucleoprotein (N) packages the RNA genome into the helical nucleocapsid. While the overall structure and genome organization is similar for the different coronaviruses, the different genera show some variability in the number and distribution of open reading frames. In particular, the variable, minor and non-essential accessory genes seem to be relevant for virus survival in the infected host (Cruz et al. 2011). In Table 2 the veterinary relevant coronaviruses are listed.

## **Concepts of immune protection against Coronaviruses**

The knowledge about immune responses against veterinary coronaviruses is by far not as detailed as the information that was gathered on human SARS-coronavirus immunity. In this paragraph we will therefore amalgamate a general concept of anti-coronavirus immune mechanisms from publications on SARS-coronaviruses and discuss specific aspects for the respec-

tive veterinary coronaviruses in the corresponding chapters. Epithelia of the respiratory and the digestive tract together with the various layers of innate defense mechanisms are the first barrier against invading pathogens. In particular in response to viruses, the type-1 interferon-system has a pivotal role in rapidly shutting down metabolic pathways that are utilized by viruses and ramping up intracellular defense mechanisms [this has excellently been reviewed elsewhere (Ivashkiv and Donlin 2014)]. Because it is so important, coronaviruses have developed a number of mechanisms that lead to inhibition of the type-1 interferon system (Park and Iwasaki 2020). This has been directly demonstrated for SARS-CoV-2 (Blanco-Melo et al. 2020), but seems to be a general feature of coronaviruses (Sa Ribero et al. 2020). In elder people the type-1 interferon-system is less effective than in young adults or children. This phenomenon is part of a process that is called immune senescence and is probably the reason why elder people are much more susceptible to Covid-19 (Sa Ribero et al. 2020). In the absence of an effective type-1 interferon-response the immune system fails to control early virus replication. This can lead to a compensatory overshooting secretion of proinflammatory mediators like Interleukin-6, Interleukin-8 and eotaxins through infected monocytes or macrophages (Merad and Martin 2020), which results in immunopathology characterized by leukocyte and eosinophilic infiltrates and severe illness (Hadjadj et al. 2020, Hotez et al. 2020). But even if the innate immune system is able to check uncontrolled early virus replication, additional mechanisms are required to clear the infection. One to two weeks after infection the adaptive immune system begins to take over control. For SARS-CoV-2 it has been shown that convalescent patients develop antibody and T cell responses (Ni et al. 2020). It could be demonstrated that a primary exposure induces protective, adaptive immune responses in SARS-CoV-2 exposed macaques rendering them refractory to a second infection (Deng et al. 2020). The relevance of the different branches of the adaptive immune system is not entirely understood. It is clear that neutralizing antibodies that target the receptor binding domain of the Spike-protein have the ability to prevent virus entry into the host cell (Reguera et al. 2012). However, it seems that the titer and the fine specificity of neutralizing antibodies is critical. Low titers of neutralizing antibodies or antibodies that target non-blocking epitopes can lead to Antibody-Dependent-Enhancement (ADE), a phenomenon that is characterized by enhanced virus replication due to misdirected cell entry into monocytes via Fc-gamma receptor II (Bournazos et al. 2020, Fierz and Walz 2020). Along that line, Chinese colleagues reported early this year that high titres of SARS-CoV-2 specific IgG antibodies correlate with disease severity (Tan et al. 2020). So, it seems that antibodies contribute to virus control, but they have to target the right epitope in the right confirmation and they need to prevail in the right location, as an early report indicates that mucosal IgA but not systemic IgG are associated with protection from respiratory coronaviruses (Callow 1985). Cellular immunity represents the second branch of the adaptive immune system, and it is believed that virus-specific T cells are as important as neutralizing antibodies for antiviral protection (Ni et al. 2020). Numerous epitopes recognized by CD4-

**TABLE 2:** *Veterinary Coronaviruses (adapted from König and Thiel 2015)*

Genus	Species	Disease
Alphacoronavirus	Canine Coronavirus (CCoV)	Gastroenteritis
	Feline Coronavirus (FCoV)	FIP, Enteritis
	Transmissible Gastroenteritis Virus (TGEV)	Gastroenteritis
	Porcine Respiratory Coronavirus (PRCoV)	Respiratory Symptoms
	Porcine Endemic Diarrhea Virus (PEDV)	Diarrhea
	Human Coronavirus 229E (HCoV 229E)	Respiratory Symptoms
	Ferret Coronavirus (FECoV)	Enteritis
Betacoronavirus	Bovine Coronavirus (BCoV)	Respiratory Symptoms, Enteritis
	Porcine Haemagglutinating Encephalomyelitis Virus (PHEV)	Vomiting and Wasting Disease
	Canine Respiratory Coronavirus (CrCoV)	Respiratory Symptoms
	Equine Coronavirus (ECoV)	Enteritis
	Human Coronavirus OC (HCoV-OC)	Respiratory Symptoms
	Human Enteric Coronavirus (HECoV)	Enteritis
	Murine Hepatitis Virus (MHV)	Hepatitis, Encephalitis, Enteritis
	Severe-Acute-Respiratory-Syndrome-Coronavirus (SARS-CoV)	Respiratory Symptoms (Humans)
	Middle-East-Respiratory-Syndrome-Coronavirus (MERS-CoV)	Respiratory Symptoms (Humans, Camelids)
	Severe-Acute-Respiratory-Syndrome-Coronavirus-2 (SARS-CoV-2)	Respiratory Symptoms (Humans)
Gammacoronavirus	Infectious Bronchitis Virus (IBV)	Respiratory Symptoms, Enteritis
	Pheasant Coronavirus (PhCoV)	Respiratory Symptoms, Enteritis
	Turkey Coronavirus (TCoV)	Respiratory Symptoms, Enteritis
Deltacoronavirus	Bulbul Coronavirus (HKU11)	several bird species affected

and CD8-positive T cells are known in the Spike and the Nucleocapsid-protein of SARS-coronaviruses (Grifoni et al. 2020, Janice Oh et al. 2012). It has been demonstrated that T cells from convalescent patients display a polyfunctional phenotype (Li et al. 2006), but interestingly Peng and colleagues observed that patients recovering from severe disease had higher and broader T cell responses compared to patients recovering from mild disease. This does not necessarily mean that T cells are not protective. It may rather indicate that in the absence of an early innate immune control, as discussed above, higher viral loads provoke more pronounced T cell responses. In addition, Peng et al. observed that the percentage of virus-specific CD8-T cells and the polyfunctionality of virus-specific T cells, i.e. the percentage of T cells producing two or three cytokines in parallel, was higher in patients with mild disease (Peng et al. 2020). This may indicate that cytolytic CD8 T cells are required to clear the virus after natural infection. In line with that notion, it is known from Non-Human-Primate models that a pre-existing T cell response protects from virulent coronavirus challenge (Deng et al. 2020, van Doremalen et al. 2020). All in all it becomes clear that an effective immune response to coronaviruses relies on the entire complexity of the immune system. An efficient anti-coronavirus vaccine has to address these different layers and induce both neutralizing antibodies that block the receptor binding domain of the spike protein in its prefusion state and polyfunctional CD4- and CD8-Tcells that secrete

the right amount of inflammatory cytokines, such as Interferon-gamma, Interleukin-2 and for example Tumor-Necrosis-Factor-alpha, and exert granulocyte-mediated cytolytic activity. In the following paragraphs we will describe some relevant veterinary coronaviruses and discuss the vaccination approaches that have been taken in veterinary medicine to protect from the corresponding diseases.

### **Vaccines against Infectious bronchitis virus (IBV)**

IBV is a chicken Gammacoronavirus and an important pathogen for the poultry industry. It mainly affects the upper respiratory tract of chicken but may cause systemic infections with the kidney and the reproductive tract as predilection sites (Jackwood and de Wit 2013). The disease is characterized by conjunctivitis, tracheitis and loss of ciliary activity in the upper respiratory tract. This predisposes the animals to secondary bacterial infections, which may cause severe economic losses due to reduced performance, increased mortality and condemned carcasses (Jordan 2017). Therefore, under industrial husbandry conditions vaccines against IBV are almost inevitably in use. Commercially available are whole virus vaccines that are often administered in prime-boost regimens, in which live-attenuated are followed by adjuvanted inactivated vaccines (Jordan 2017). The attenuation is classically achieved by

serial passaging of virulent wildtype strains in embryonated specific pathogen free (SPF) eggs (Bijlenga 1960). Live-attenuated vaccines are administered via drinking water, eye-drop or spray application (De Wit et al. 2010). Inactivated vaccines are produced by formaldehyde fixation of whole virus and are in general formulated with mineral oil. They have to be applied parenterally (Jordan 2017). As with other coronaviruses the S-protein is the most important target for neutralizing antibodies. Mucosal IgG and IgA antibodies contribute but are not the sole basis of protection (Gelb et al. 1998). CD8-positive T lymphocytes also seem to contribute to protection (Collisson et al. 2000, Seo et al. 2000), in particular if they are associated with upper respiratory tract mucosa (Okino et al. 2013). Clearly, live-attenuated virus strains that are administered via the natural route induce the most robust mucosal immune response. Here, the application technique is of importance, as it could be demonstrated that the individual eye-drop was 10.000 times more efficient compared to coarse spray or drinking water application (De Wit et al. 2010). However, it is not just a matter of antibody titer and strength of induced immune response that decide on success and failure. A major problem for immune-prophylaxis against IBV in the field is the high degree of genetic variability among IBV-strains (Sjaak de Wit et al. 2011), which is a result of spontaneous mutations due to the low fidelity of the viral RNA-dependent RNA polymerase (Hanada et al. 2004) and frequent recombination events between different virus strains (Kusters et al. 1990). The global diversity of IBV strains has profoundly been reviewed by de Wit and colleagues (Sjaak de Wit et al. 2011). Two complementary strategies have been taken to tackle the breadth of non-cross-reactive strains in the field: The rather straight-forward approach is to combine all relevant strains that prevail in a given region into one vaccine (Jackwood and de Wit 2013). For this “multi-monovalent” strategy to be successful it is important to know the strains and to have corresponding vaccine strains available. Sometimes this is not easy to achieve as new virus variants tend to particularly evolve under selective immune pressure and because the attenuation of a vaccine strain may take more than one year (Lee and Jackwood 2001). Alternatively, it has been shown that the sequential vaccination with two antigenically distinct vaccine strains can induce broad cross-protection (Cook et al. 1999, Terregino et al. 2008). This strategy is widely applied. However, it has to be empirically determined which combination works best for this so called “protectotypic” vaccination strategy. Furthermore, it is not guaranteed that a combination that works well for a selection of strains will also be protective against others (Ladman et al. 2002).

In the past two decades much research effort has been spent to develop new IBV vaccines with the aim to broaden cross-reactivity or to improve the efficacy and applicability. Experimental vaccines based on modern technologies, such as DNA or adjuvanted subunit peptides, have been tested and showed some efficacy in homologous challenge experiments (Guo et al. 2010, Yang et al. 2009). Also, recombinant vaccines theoretically allowing for mass application have been tested. Constructs were for example based on attenuated herpesvirus of turkeys (HVT) or Newcastle disease Virus (NDV) expressing parts of the IBV spike

protein. They provided some protection in homologous challenge experiments (Johnson et al. 2003, Toro et al. 2014), but performed not significantly better than conventional live-attenuated vaccine strains. Therefore, none of the experimental candidates has so far reached a commercial stage (Bande et al. 2015).

## **Vaccines against bovine coronaviruses**

The bovine coronaviruses belong to the genus Betacoronavirus and are thus relatively closely related to the human SARS-coronaviruses. They can cause enteric and respiratory symptoms and have been associated with pneumonia and a syndrome called winter dysentery in adult cattle (Boileau and Kapil 2010). Well known is their role in the disease complex of *Bovine Neonatal Diarrhea* (Clark 1993). For Australian dairy farms coronaviruses contributed with up to eight percent to this disease complex (Abuelo et al. 2019). The syndrome affects newborn calves. Passively acquired maternal immunity is the only way how neonates can be protected, because an active immunization takes three to four weeks to develop and would be too late. The concept of dam vaccination comprises booster immunizations during gestation in order to achieve a peripartur antibody maximum. Maternal immunity is then transferred to the calf through the uptake of colostrum (Crouch et al. 2000). While human fetuses are supplied with maternal antibodies during fetal development via the placenta, in livestock animals a different placentation prevents the intrauterine uptake. The antibodies are only acquired postnatally by colostrum. This fore milk is particularly rich in IgG, which is taken up orally and efficiently shoveled across the calf's gut-blood barrier by neonatal Fc receptor during the first 24 hours (Cervenak and Kacsokovics 2009). This mechanism is highly efficient. Within few hours the entire maternal antibody repertoire is installed. After 24 hours the neonatal Fc receptor is downregulated, antibodies that are present in the milk at later time points are no longer taken up systemically. But even in the digestive tract they can have a protective influence on enteric pathogens. Several multivalent dam vaccines are available that contain a bovine coronavirus component (Durel et al. 2017). The vaccines induce strong antibody titers in the dam and consecutively in the calf (Kohara et al. 1997). It is not easy to assess the contribution of the coronavirus component to the efficacy of the vaccines, because other infectious agents such as certain *E. coli* strains that are also covered by the multivalent vaccines are more frequent (Meganck et al. 2014). But regardless of the relevance of the coronavirus component, the vaccines are recommended and widely and successfully in use (StiKo Vet 2018).

## **Vaccines against porcine coronaviruses**

There are currently six porcine coronaviruses known. The *Transmissible Gastroenteritis Virus* (TGEV), the closely related *Porcine Respiratory Coronavirus* (PRCoV) and the *Porcine Epidemic Diarrhea Virus* (PEDV), as well as the *Swine Acute Diarrhea Syndrome-Coronavirus* (SADS-CoV) belong to the genus Alphacoronaviruses. The *Porcine Hemagglutinating Encephalomyelitis Virus* (PHEV) is a Beta-, the *Porcine Deltacoronavirus* (PDCoV) a Del-

tacoronavirus. The enteric viruses TGEV and PEDV are economically relevant.

TGEV infects enterocytes and causes vomiting and enteritis in pigs. In immunologically naïve herds morbidity reaches 100%. Mortality is particularly high in piglets during the first weeks of life. TGEV has first been described in 1947 in the United States (Doyle and Hutchings 1946), but is now globally prevalent (Gerdtts and Zakhartchouk 2017). For decades the virus has caused severe losses in pig production. In 1984 a respiratory variant of TGEV was first described in Belgium (Pensaert et al. 1986). The variant, PRCoV, has a deletion in the spike protein, which abolishes the binding to sialic acid. This changes its cell tropism, therefore PRCoV productively replicates in respiratory epithelial cells but not in enterocytes (Cox et al. 1990). The infection is generally benign and causes no significant morbidity or mortality. Since its first description in Belgium, PRCoV, has reached a wide distribution in Europe (Have 1990) and is also present in other parts of the world (Wesley et al. 1997). With the rise in PRCoV prevalence the severity of TGEV outbreaks declined. Due to the naturally acquired cross-immunity TGE is no longer an urging problem and only few vaccines are still commercially available (Gerdtts and Zakhartchouk 2017). Only sporadic outbreaks have recently been reported in Europe, North America and China (Vlasova et al. 2020).

In 1978, PEDV was identified as a genetically and antigenically distinct porcine coronavirus. Infections with PEDV are clinically almost indistinguishable from TGE (Vlasova et al. 2020): The virus also causes vomiting and watery diarrhea. The mortality is highest in young piglets during the first two weeks of live and can reach up to 100% in animals without maternal immunity (Jung and Saif 2015). Unlike TGEV, PEDV can also affect older pigs after weaning. Although the animals tend to recover, the reduced performance during the fattening period can cause severe financial losses (Gerdtts and Zakhartchouk 2017). Although PEDV was first identified in the UK, it only caused sporadic episodes in Europe. In Asia and North America however devastating epidemics occurred, prompting a great interest in vaccines. Immune protection of neonates against enteric coronavirus infections seems mainly to dependent on maternal antibodies: Although colostral IgG also seems to play a role, high levels of mucosal IgA are pivotal to maternally derived immunity. Saif et colleagues have proposed the concept that in immune sows IgA producing B cells migrate from the gut to the mammary gland. Whereas, the colostrum is particularly rich in serum IgG, IgG content continuously declines during the first weeks of lactation resulting in a shift in the prevailing isotype from IgG to IgA (Saif and Sestak 2006). Hence, for any vaccination concept against enteric coronaviruses, the challenge is to provoke mucosal IgA secretion and furthermore to initiate immunocyte migration from the gut to the mammary gland. In 1995 the first inactivated whole virus vaccine against PEDV was launched in China. No information about its efficacy is available (Gerdtts and Zakhartchouk 2017). Few years later live-attenuated vaccines were licensed in Japan, China and South-Korea (Vlasova et al. 2020). The attenuation of the Japanese vaccine strain was classically achieved by serial passaging on Vero-cells (Sato et al. 2011). Experimentally, it was shown that the oral vaccination of 11-day-old pigs with such an inactivated whole virus vaccine gave protection from homologous

challenge three weeks later (de Arriba et al. 2002). In a comprehensive comparison of several internationally available vaccines the South-Korean Animal and Plant Quarantine Agency could demonstrate that the vaccination of pregnant sows according to manufacturers' instructions reduced piglet mortality from over 80% to under 20%. However, there was no significant reduction in clinical symptoms nor in virus shedding [mentioned by (Lee 2015)]. The effect of these vaccines in the field is a matter of debate, but it is accepted that the vaccination programs helped to control the economic impact of PEDV on the pig industry. However, in 2010 new virus variants caused devastating outbreaks again in Asia (Li et al. 2012) and since 2013 in North America (Stevenson et al. 2013). The new variants belong to a new genotype, G2, and share distinct insertions and deletions in the genomic sequence of the spike protein when compared to the classical PEDV strains (Lee 2015). Due to the altered sequence and structure of the S-protein classical vaccines do not confer protection to the new variants. This spurred vaccine development both in America and in Asia: In 2013, an innovative vaccine based on a replication deficient Venezuelan Equine Encephalitis Virus derived RNA construct encoding a truncated version of the PEDV spike protein was licensed in the United States. This vaccine seems to protect weaned pigs from homologous challenge (Mogler et al. 2014). However, there is only a moderate protective effect on young piglets when naïve sows are vaccinated before farrowing (Crawford et al. 2014, Greiner et al. 2015, Mogler et al. 2015). In 2014 an inactivated adjuvanted whole virus vaccine that was made commercially available by Zoetis proved to be safe and immunogenic (Frederickson et al. 2014). The vaccine was tested in a young pig model using weaned pigs 8 and 20 weeks of age. Vaccinated pigs showed the highest neutralizing antibody titres 12 weeks after challenge, but this did not significantly alter the onset and severity of clinical symptoms (Crawford et al. 2016). In a field trial with 120 placebo controls and 120 vaccinated sows that was conducted by Zoetis in a pig producing facility, which had experienced a PEDV outbreak, pre-weaning mortality was reduced from 6.3 to 0.6% (Rapp-Gabrielson et al. 2014). The same vaccine was tested in PEDV-pre-exposed and naïve sows: It could be shown that it induced significant levels of IgG in vaccinated animals but barely any IgA in naïve sows. Upon challenge piglets from naïve-vaccinated dams invariably succumbed to the disease, while piglets from previously exposed sows -whether vaccinated or not- showed clearly reduced mortality (Schwartz et al. 2015). In 2015 Gerdtts and Zakhartchouk described another inactivated whole virus vaccine that reduced mortality from 50% among piglets from unvaccinated to 5% in piglets from vaccinated sows (Berube et al. 2015). Despite these promising results, it is unclear whether the development of this vaccine candidate was continued. Also in Asia researchers tested inactivated whole virus vaccines based on new emergent virus strains: In South-Korea sows were vaccinated with an inactivated G2-b PEDV strain six and three weeks prior to farrowing. Piglets born to vaccinated sows showed reduced morbidity and mortality when challenged 6 days after birth (Baek et al. 2016). Alternative techniques with plant or bacteria expressed virus proteins are under development, but still have to be evaluated in the field (Bae et al. 2003, Liu et al. 2012, Makadiya et al. 2016).

It is an important lesson that enteric porcine coronaviruses cause severe epizootic outbreaks after emergence of new antigenically divergent variants, which is usually followed by an enzootic stabilization. In addition, it became clear that the vaccination of pregnant sows can reduce neonate mortality, but so far, the vaccination approaches did not suffice to confer sterile immunity neither to piglets nor to post-weaning pigs. Therefore, vaccination programs were able to reduce economic losses and may have helped to establish enzootic stability, but were unable to curtail infection cycles and eliminate the virus.

## **Vaccination against *Feline Coronavirus (FCoV)***

*Feline Infectious Peritonitis (FIP)* is one of the most important fatal infectious diseases of cats. The disease is either characterized by a proliferative-granulomatous or an exudative peritonitis. The pathoetiology of the disease has recently been comprehensively reviewed by Kipar and Meli (2014). A pioneering study by Osterhaus and colleagues that was published in 1976 in this journal described the causative agent of FIP as a coronavirus (Osterhaus et al. 1976). The overall structure of FCoV is very similar to TGEV and PEDV as both belong to the genus Alphacoronaviruses. Two serotypes can be differentiated, FCoV I and II (Shiba et al. 2007). In a very recent Italian study, it was proposed that FCoV I emerged during the early 1940s somewhere in the United States and was brought to Europe during the early 1960s (Lauzi et al. 2020). This is in line with first clinical descriptions in the United States dating from the early 1950s (Holzworth 1963), but somewhat in contrast to reports of a similar condition in Italian cats from 1942 (Bonaduce 1942). Less controversial is the origin of Serotype II, which is a result of a double-recombination between FCoV I and the canine coronavirus (Herrewegh et al. 1998). Both serotypes occur worldwide, but serotype I is by far more prevalent (Hohdatsu et al. 2003, Kummrow et al. 2005). As with all RNA-viruses, the RNA replication machinery is error prone. Frequent mutations in the spike protein gene allow for the genetic tracking of individual virus isolates (Addie et al. 2003). The high mutation rate also seems to play an important role in the pathogenesis of FIP: There are two pathotypes of the virus. The *Feline Enteric Coronavirus (FECV)* replicates predominantly in feline enterocytes and only causes benign, transient enteric symptoms (Vogel et al. 2010). Isolates that cause peritonitis are serologically and morphologically indistinguishable from FECV (Pedersen 2009). The *Feline Infectious Peritonitis Viruses (FIPV)* are characterized by the ability to efficiently replicate in feline blood monocytes (Simons et al. 2005). Although the initial paradigm that non-pathogenic FECV strains are incapable to replicate in monocytes seems not to hold true for every instance (Can-Sahna et al. 2007), the effective replication in and the concomitant activation of feline macrophages seems to be a hallmark of FIP-pathogenesis. A number of endogenous mutations have been identified that may contribute to the pathotype-switch (Licitra et al. 2013), but most prominent are mutations in the accessory 3c ORF (Chang et al. 2010). Importantly, it seems that FIPV bearing mutations in the 3c ORF -in contrast to enteric FECV- are not efficiently

shed with the feces but are rather retained in infected tissues (Pedersen et al. 2009). It is therefore believed, that cats do not get infected with pathogenic FIPV but that onset of disease is rather a consequence of a spontaneous mutation of an infecting FECV strain, which then results in a pathotype switch. Although this notion is now widely accepted, there were early *in vitro* reports on *Antibody Dependent Enhancement (ADE)* playing a role in the infection of feline macrophages by FIPV (Corapi et al. 1992, Olsen and Scott 1993, Olsen et al. 1992, 1993). These were recently confirmed in *in vivo* experiments (Takano et al. 2008, 2019). ADE occurs when monocytes take up antibody opsonized virus via the activation of Fc-receptors. The mechanism is not entirely understood, but it seems that after phagocytosis virus can escape from the endosome and replicate within the monocyte (Corapi et al. 1992, Olsen et al. 1992). In parallel, recent studies with SARS-CoV show that activation via the Fc-receptor alters the phenotype of the macrophage rendering it more proinflammatory (Liu et al. 2019). Epidemiological evidence argues against a major role of ADE during natural FCoV infection (Kipar and Meli 2014), but it is beyond any doubt that certain situations may occur in which ADE has a detrimental effect. One such instance was an attempt to develop a vaccine against FIP using a vaccinia virus construct expressing the full-length spike protein of virulent FCoV II strain 79-1146 (Vennema et al. 1990b). The authors observed that kittens vaccinated with this construct developed low titres of neutralizing antibodies, but unexpectedly succumbed rapidly to FIP after homologous oral challenge (Vennema et al. 1990a). The authors concluded that the induction of spike protein specific antibodies induced ADE and led to aggravated immunopathology. Consequently, the development of a FIP vaccine based on vaccinia virus was abandoned. At that time a couple of different approaches had already been tested. This comprised the vaccination with avirulent FCoV strains (Pedersen and Black 1983) or with heterologous coronaviruses, such as TGEV, canine coronavirus or even human coronavirus (Barlough et al. 1985, Stoddart et al. 1988, Woods and Pedersen 1979). However, none of these approaches showed any evidence for protection. Instead, the vaccination with avirulent FCoV rather seemed to sensitize kitten to the subsequent challenge infection also (Pedersen and Black 1983).

In 1989 Christianson and colleagues described a temperature sensitive FIPV II strain that only replicates at 31°C and shows defective replication at higher temperatures (Christianson et al. 1989). Briefly thereafter it was demonstrated that the temperature sensitive strain conferred protection to the parenteral virulent DF2 strain. Of 10 vaccinated kitten 8 were protected while 4 of 5 non-vaccinated kitten developed FIP. Protection correlated with high titres of mucosal IgA (Gerber et al. 1990). The safety of the vaccine was confirmed in a large long-term study including 582 vaccinated cats. It could be shown that this vaccine did not sensitize cats for FIP (Reeves et al. 1992). In another large double-blinded study also no accelerated onset of disease was observed. The vaccine is therefore considered to be safe. However, over the entire study population there was no significant protective effect. In part, this may be due to the fact that the vaccine strain is derived from a serotype II isolate and does not confer sufficient cross-protection to the prevailing serotype I strains. However, the authors rather concluded

that the vaccine only protects cats without prior exposure to FCoV (Fehr et al. 1997), an explanation that was corroborated by another placebo-controlled trial showing that FCoV negative cats that were admitted to an infested cat shelter were protected from FIP (Postorino Reeves 1995). A similar observation was also made independently with recombinant attenuated FCoV strains. After vaccination with these constructs SPF-kittens were fully protected from homologous highly virulent challenge, whereas vaccinated non-SPF kittens showed accelerated onset of disease upon challenge (Balint et al. 2014a, b). If the protective mechanism depends on the prevention of virus entry through mucosal IgA secretion, it is well conceivable that the vaccination has no influence on the course of disease of an already established infection.

The temperature sensitive vaccine strain is so far the only licensed FIP vaccine. However, in view of the published studies, it is of limited use, because under field conditions it is almost impossible to identify FCoV-seronegative cats. International and national expert groups therefore refrain from recommending the vaccine for general use (Addie et al. 2009, StIKo Vet 2017).

## **Conclusion**

It is possible to develop vaccines against coronaviruses, which may help to reduce clinical burden and socio-economical losses. However, for veterinarians the road to efficacious coronavirus vaccines was bumpy. The best results were achieved with live-attenuated viruses, as the natural route particularly induces robust mucosal immune responses. Unfortunately, it takes time to establish safe attenuated virus strains. Modern techniques, such as recombinant viruses or nucleic acid- or peptide-based subunit vaccines allow for rational design, rapid development and fast track licensing. DNA- and peptide-vaccines have been tested for IBV and PEDV, but have not outcompeted classical vaccines. Recombinant viruses are a very interesting approach and hold great promise, but the choice of the right vector platform is critical. The experience with a vaccinia virus expressing full length spike protein of FCoV was discouraging (Vennema et al. 1990a). Along that line, there was a study last year reporting on reduced virus loads but aggravated lung pathology after challenge in macaques vaccinated with a vaccinia construct expressing the spike protein of SARS-CoV-1 (Liu et al. 2019). By contrast, a *Modified Vaccinia Virus Ankara* (MVA) construct expressing the MERS-CoV spike protein has recently been shown to reduce viral load in vaccinated camels without evidence for immunopathology (Haagmans et al. 2016).

These controversial findings illustrate that there are many open questions, but the dynamic in the field is tremendous. A recent WHO document lists 167 SARS-CoV-2 vaccine candidates. In only six months' time 29 candidates have already entered clinical trials (WHO 2020). This comprises new vector constructs, based for example on the chimpanzee adenovirus platform (van Doremalen et al. 2020) that is known to induce robust mucosal immune responses, or highly innovative RNA vaccines (Mulligan et al. 2020). Such a boost of innovation, rational design and rapid testing is unprecedented

in vaccinology. It is well conceivable that it will sweep away all obstacles and rapidly bring forth a vaccine that safely protects against SARS-CoV-2.

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## **Ethical approval**

The authors hereby declare that they have followed the universally accepted guidelines of good scientific practice while preparing the present paper.

## **Conflict of interest**

The authors hereby declare that they have no proprietary, professional or other personal interests in any product or company mentioned in this publication.

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