VACCINEINSIGHTS

REVIEW

Veterinary coronavirus vaccines: successes, challenges & lessons learned for SARS-CoV-2 control

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Members of the *Coronaviridae* family infect a large number of animal species, including humans. Coronaviruses of clinical significance in veterinary species include severe and fatal vasculitis in cats caused by feline infectious peritonitis virus (FIPV), and highly contagious and economically devastating diseases in livestock, including porcine epidemic diarrhea virus (PEDV), transmissible gastroenteritis virus (TGEV) in pigs, bovine coronavirus (BCoV) in dairy and beef cattle, and avian infectious bronchitis virus (IBV) in chickens. Knowledge of the viral replication, pathogenesis, protective immunity, and genomic mutations and evolution has led to the development of a variety of licensed vaccines against these veterinary coronaviruses. Some of the licensed animal coronavirus vaccines have been in commercial use for decades and have demonstrated many of the same challenges in veterinary species that are being faced today with the relatively new SARS-CoV-2 vaccines. Here we review the coronaviruses of high clinical impact in veterinary species, identify common themes regarding the challenges and successes of animal coronavirus vaccines that have been in commercial use for decades, and offer potential insights and lessons learned for SARS-CoV-2 vaccine and vaccination programs.

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Since 2002 three novel coronaviruses, Severe Acute respiratory syndrome-associated coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), and most recently, SARS-CoV-2, have caused deadly diseases in humans with immense social, economic and health impacts worldwide [1,2]. The SARS-CoV-2 pandemic introduced key concepts of virology into the consciousness of the world's populace, providing lessons on the importance of coronavirus vaccine development, 'herd health', and biosecurity measures as a means of disease control. In veterinary medicine, these concepts have been put to use for decades in many veterinary species to prevent and control deadly animal coronaviruses that have been the cause of clinically significant disease, increased treatment costs

in companion animals and livestock, and led to economic losses across several livestock and poultry industries worldwide.

The *Coronaviridae* family are enveloped, positive-sense, single-strand RNA viruses which are divided into four distinct genera that infect avian and mammalian species [1,3], including *Alpha-*, *Beta-*, *Gamma-*, and *Delta*-coronaviruses [4]. The *Alphacoronavirus* genus includes viruses that generally cause gastrointestinal disease in porcine, feline and canine hosts; the *Betacoronavirus* genus includes several viruses that cause respiratory diseases in humans, including SARS-CoV-1, MERS-CoV, and SARS-CoV-2, as well as the bovine coronavirus, which causes both enteric and respiratory disease [1,4]. The *Gammacoronavirus* genus includes an important virus in avian species, and the genus *Deltacoronavirus* infects mammalian and avian hosts [4].

Veterinarians and producers have been using licensed commercial vaccines for decades to prevent and control coronavirus infection in various animal populations (Table 1). A review of these veterinary coronavirus vaccines demonstrates the importance of understanding the pathogenesis of the virus, elucidates many important aspects of mucosal immunity, and illustrates the challenges faced specific to development of effective coronavirus vaccines. While there are many coronaviruses that infect a wide range of veterinary species, this review focuses only on a few selected animal coronaviruses with significant clinical and/or economic impact, and the efficacy of vaccines in controlling infection caused by these viruses. We hope that the knowledge gained during decades of use of these animal coronavirus vaccines will offer potential insight to the field of SARS-CoV-2 vaccine and vaccination programs.

ALPHACORONAVIRUSES

Members in the genus *alphacoronavirus* cause animal diseases of great economic importance, including porcine epidemic diarrhea virus (PEDV) and transmissible gastroenteritis virus of swine (TGEV). The highly contagious but relatively clinically quiet, feline enteric coronavirus (FeCV) and canine coronavirus (CCoV) also belong to this genus. Feline infectious peritonitis virus (FIPV) is a, unique, randomly mutated FeCV with severe and fatal clinical consequences in cats [4]. The economic impact of PEDV, TGEV, and the fatal consequences of FIPV, have led to considerable interest in developing vaccines against these animal alphacoronaviruses.

Feline infectious peritonitis virus (FIPV)

Feline coronaviruses (FCoV) consist of two serotypes: type I FCoV and type II FCoV [5]. Either of these types can take one of two different pathotypes, remaining an enteric coronaviruses (FeCV) or mutating into the highly pathogenic and fatal FIPV [5]. The majority of circulating FeCV are type I, which are ubiquitous within feline populations, especially in group-housed settings such as catteries or shelters, and tend to be asymptomatic or cause mild enteric disease [6]. FeCV initially infects enterocytes and can lead to viremia by infecting monocytes [7]. A small percentage (5–20%) of FeCV mutate to FIPV by gaining the ability to replicate rapidly within monocytes and macrophages [7–9]. The mechanism for this adaptation is not well understood, but mutations in the Spike protein are thought to play at least a partial role in altering cell tropism [10,11]. FIPV causes phlebitis, peritonitis, and serositis, as well as granulomatous inflammation in almost any organ system; it can present with ('wet', 'effusive' form) or without ('dry', 'non-effusive' form) body effusions, and is almost always fatal [12,13].

Vaccine development against FIPV has been ongoing since the 1980s and has involved a myriad of vaccine platforms and approaches, with early studies focusing mainly on live-attenuated FIPV [6,14–17] and heterologous live vaccines (canine coronavirus, transmissible gastroenteritis of swine,

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TABLE 1

Examples of licensed commercial vaccines in the United States against selected economically important animal coronaviruses in various veterinary species.

Animal coronavirus	Genus	Clinical diseases	Licensed vaccine (United States)	Vaccine type	Recommended vaccination route
Feline infectious peritonitis (FIPV)	*Alphacoronavirus*	Phlebitis Peritonitis +/ – effusion Serositis High mortality	Vanguard® FIP/ Felocell® FIP (Zoetis)	Modified-live	Intranasal
Transmissible gastroenteritis virus of swine (TGEV)	*Alphacoronavirus*	Diarrhea Vomiting Severe disease in neonatal piglets High neonatal mortality	USDA licensed	Modified-live	
Porcine epidemic diarrhea virus (PEDV)	*Alphacoronavirus*	Diarrhea Vomiting Anorexia Severe dehydration Severe disease and high mortality in neonatal piglets	PED vaccine (Zoetis) SEQUIVITY (personalized vaccine, Merck)	Killed vaccine RNA particle vaccine	• IM • Administer 2 doses to pregnant sow/ gilt prior to farrowing
Bovine coronavirus (BCoV)	*Betacoronavirus*	Calf diarrhea Winter dysentery (adults) Respiratory disease Generally mild disease unless there are comorbidities	Bovilis (Merck) Bovilis Guardian (Merck) Scourguard 4KC (Zoetis)	Modified live Killed virus vaccine	• Intranasal • Administer to neonatal calves • IM or SQ in pregnant cattle • Administer 2 doses prior to calving
Infectious bronchitis virus (IBV)	*Gammacoronavirus*	Primarily mild upper respiratory disease, complications with co-infections Pneumonia & airsacculitis Nephritis Decreased egg production and quality Stunted growth	**Merck** Massachusetts serotype **Zoetis** Massachusetts serotype Vaccines targeting one or more of the following IBV serotypes: **Merck** • Massachusetts • Connecticut • Arkansas • GA-08 • Mildvac-MA5™ • Mildvac™ Mass+Conn • NEWHATCH-C2-M® • NEWHATCH-C2-MC® **Zoetis** • Massachusetts • Connecticut • GA08 • GA98 • Arkansas **Elanco** • Arkansas • Massachusetts • Connecticut **Boehringer Ingelheim** • Arkansas • Connecticut • Massachusetts	Inactivated virus vaccine Live virus vaccine	• IM or SQ vaccination • Best used to booster chickens previously immunized with live vaccine of the same strain (Merck) • Administered in drinking water or as coarse spray • Periodic re-vaccinations may be needed

IBV: Infectious bronchitis virus ; IM: Intramuscular ; SQ: Subcutaneous.

and human coronavirus 229E) [18–20]. A licensed, modified-live, intranasal FIPV vaccine is available in the United States (Vanguard® FIP, formerly: Felocell® FIP; Zoetis). However, vaccination against FIPV proved challenging from the onset, with vaccines unable to protect against disease, and frequent reports of vaccinated cats appearing to develop FIPV infection earlier compared to controls when challenged [6,19,21,22]. These results were caused by antibody-dependent enhancement (ADE) following vaccination, and were mediated by an imbalance between humoral and cell-mediated immune (CMI) responses [22–24] and by antibodies directed against specific regions within the FIPV S protein [24,25]. Subsequent studies developed vaccines that meant to stimulate CMI but not humoral immunity, using recombinant vaccines containing one or both of the FIPV nucleocapsid (N) or membrane (M) proteins [26,27]. While these vaccines avoided FIPV S protein-associated ADE, they had varying results in protecting against disease [26,27].

The route of transmission for FeCV is fecal-oral and as such, induction of mucosal immunity is an important vaccination strategy to prevent FIPV infection. Several studies utilize either an intranasal or oral route of immunization in attempts to induce a mucosal immune response [14,17,19,21]. Two of these studies reported protection against challenge with homologous FIPV and no ADE [14,17]. One study documented neutralizing mucosal IgA responses and a CMI response in addition to protection [14]. This live-attenuated vaccine consisted of a temperature-sensitive FIPV DF2 (type II FIPV) and was successfully licensed for commercial use (Vanguard® FIP, formerly: Felocell® FIP; Zoetis) [14,28]. Several large post-marketing follow-up studies of this commercial vaccine concluded that the vaccine was safe, with no evidence of ADE under field conditions [15], and can protect cats that have no or low serum FCoV antibodies at the time of first vaccination [16]. However, in cats that had previous exposure or current infection at the time of vaccination, the vaccine showed no protection against disease [16]. The absence of ADE following vaccination may be attributed to the low infectious dose in a natural setting compared to high doses of virus during experimental challenge [16,29].

As of 2020, the feline vaccination guidelines from the American Animal Hospital Association (AAHA)/American Association of Feline Practitioners (AAFP) do not recommend vaccination for FIPV. The vaccines currently available are labeled for administration at 16 weeks of age, however, it is assumed that most cats have already been exposed and/or infected by the virus before this age [16,30].

The potential for ADE following natural infection or vaccination with SARS-CoV-2 has also been reported [31–35], however, currently this does not seem to be clinically problematic. Certainly, this will need to be monitored for future variants of concern. Regardless, the importance of CMI in the control of viral infection is well-known and is illustrated in the case of FIPV. Strategies targeting non-surface viral proteins for FIPV vaccine development can help guide future coronavirus vaccine designs to augment humoral immune responses and produce a more well-rounded and robust T cell response.

Transmissible gastroenteritis virus of swine (TGEV)

TGEV causes gastrointestinal disease in pigs worldwide [36] and disease epidemiology depends on the herd's immune status. In naïve herds, older pigs exhibit inappetence, mild diarrhea and vomiting, and have a low mortality rate [37]. In contrast, neonatal piglets less than 2 weeks of age experience severe disease, including diarrhea, vomiting and dehydration, and mortality rates can be as high as 100% [38–40]. In herds that are persistently infected with TGEV, disease and the highest mortality occurs in piglets of newly introduced, naive animals, and to a lesser extent, in 2–3-week-old piglets as

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protection from maternal antibodies wanes [37,40].

TGEV infects enterocytes that line the surface of the small intestinal villi; infection is initiated by binding between the TGEV spike protein and host cell Aminopeptidase N receptors [41,42]. A decrease in severity of TGEV-associated disease and mortality is seen in neonatal suckling piglets due to lactogenic immunity from sow to piglet in either colostrum or milk [38,43]. Effectiveness of passive immunity requires that piglets regularly receive and maintain adequate levels of neutralizing IgA within the small intestine [38,43,44]. These neutralizing antibodies target the antigenically and immunogenically important spike protein of TGEV [45,46]. Therefore, the goal of developing an effective TGEV vaccine is to elicit the production of mucosal, anti-spike IgA antibodies in the small intestine of neonatal pigs. Modified-live TGEV vaccines in combination with other enteric pathogens (rotavirus, *Clostridium perfringens* Type C, *E. coli* bacterin-toxoid) are currently licensed in the United States (United States Department of Agriculture (USDA), Current Veterinary Biologics Product Catalog, Feb 2, 2023).

The two most used vaccine platforms for TGEV are live-attenuated and inactivated vaccines, which are administered to pregnant sows by various routes. Whereas natural TGEV infection induces protective IgA antibodies in colostrum and milk, the majority of orally-administered, live-attenuated TGEV vaccine studies report IgG antibody secretion in milk [47]. Although not as protective as natural infection, these studies do report less severe disease and lower mortality rates in neonatal pigs born to vaccinated sows when challenged with TGEV, compared to unvaccinated controls [47,48]. Interestingly, these vaccines do not seem to produce protective immunity in vaccinated sows, as some developed clinical signs and began secreting IgA in milk when their nursing piglets were experimentally challenged [47]. The ineffectiveness of oral administration of a live-attenuated TGEV vaccine may be due to several factors, including degradation and loss of replicative ability as the vaccine moves through the stomach [43]. Other routes of inoculation of live-attenuated TGEV vaccines also report IgG antibodies in milk, decreased severity of disease, and variable levels of protection upon challenge, with a moderate level of protection against mortality by intramammary routes [38,49], and varying levels of protection by intramuscular (IM) or IM+oral administration [38,48,49]. The most promising finding of the IM vaccines reported high levels of protection comparable to the then-available vaccine [50]. Inactivated TGEV vaccines have also struggled to replicate the effective lactogenic immunity noted in natural TGEV infection, reporting varying degrees of protection against challenge regardless of administration route, as well as stimulation of IgG (but not IgA) antibodies in colostrum and milk [41,51,52].

Although IgA antibodies at the mucosal surface following natural infection elicit the best protective efficacy, high levels of IgG in colostrum and milk after vaccination with either live-attenuated or inactivated TGEV appear to be capable of lowering mortality and severity of disease [38]. Licensed live-attenuated TGEV vaccines have historically been available in the United States. However, when post-marketing evaluation was performed on two such vaccines, survival in piglets from sows that received the live-attenuated TGEV vaccine was no different from unvaccinated sows [53].

One development that may have led to natural immunologic protection against TGEV disease came not from TGEV vaccines, but from the emergence of another coronavirus, porcine respiratory coronavirus (PRCV). PRCV, a deletion mutant in the S gene of TGEV, is antigenically and genetically related to TGEV but has altered tropism, infecting tonsillar and respiratory epithelial cells rather than small intestinal enterocytes, and is generally asymptomatic in infected pigs [40,54]. Pigs exposed to PRCV antigen by natural and experimental infection, or immunization,

have been shown to shed infectious TGEV for shorter periods of time compared to PRCV seronegative pigs, and these exposures induce varying degrees of protection against challenge with TGEV [40,45,54–56]. The prevalence of TGEV has decreased since the emergence of PRCV and this may be due to partial protection from natural PRCV exposure, increased biosecurity measures, or both [36,45]. This decrease in TGEV prevalence has likewise decreased the demand for a vaccine, although live-attenuated and killed TGEV vaccines are currently licensed by the USDA.

Porcine epidemic diarrhea virus (PEDV)

PEDV is antigenically distinct from TGEV, however, the two cannot be differentiated based on clinical disease or histological lesions in affected pigs [57]. PEDV can infect as many as 50% of small intestinal enterocytes, leading to acute necrosis of infected cells and contributing to malabsorptive diarrhea, severe dehydration, electrolyte imbalances, and death [57]. Disease patterns during PEDV outbreaks also depend on the herd's immune status. In naïve herds, the clinical picture includes disease in pigs of all age groups, with more severe clinical signs in neonates, in which mortality can reach 95% [57]. Clinical disease on an affected farm experiencing an epidemic typically lasts up to 4 weeks as animals either succumb to disease or develop immunity [57]. In contrast, in facilities with endemic PEDV, diarrhea is more severe in newly introduced and naïve gilts or piglets, while clinical disease is mild to absent in nursing neonatal piglets [57]. Low morbidity and mortality in this latter group is attributed to passive transfer of lactogenic immunity from sows [57].

PEDV initially was identified in Europe in the 1970s and over the next two decades, spread to many Asian countries [58]. Despite vaccine and vaccination programs in these countries, PEDV epidemics continued to occur, and in 2013, PEDV suddenly emerged for the first time in the United States, where it caused immense economic losses to the swine industry [59]. Two conditionally licensed vaccines became available within a year of the initial outbreak in the United States [60] but epidemics continue to occur. As with other coronaviruses, the most important PEDV immunogenic antigen is the S protein, which binds to the host cell aminopeptidase N receptor on small intestinal enterocytes and induces neutralizing antibodies [57]. There are two genotypes of PEDV: genotype 1 (subtypes G1a and G1b) and genotype 2 (subtypes G2a, G2b, G2c) [61]; the circulating genotypes play a role in vaccine effectiveness and escape, with G2 strains contributing to epidemics [62].

Like TGEV, the ideal vaccine against PEDV would induce a mucosal immune response targeting the S protein. The majority of early PEDV vaccines in Asia were live-attenuated vaccines administered by various routes, including orally administered to neonatal piglets [63], and oral and/or IM administration to pregnant sows/gilts pre-farrow [62,64,65]. While none of these vaccine strategies were completely protective against PEDV infection, piglets born to, and nursing from vaccinated pregnant sows that received an oral vaccine reported the best outcomes, with decreased severity of disease and decreased mortality when challenged with homologous virus [64]. PEDV vaccines have been on the market in Asia for many decades, and yet epidemics continue to occur, largely due to recombination between variants and vaccine strains, emergence of mutations leading to vaccine escape, incomplete protection provided by vaccines, and potentially increased virulence in newly emerging variants [57,66–70]. Many of the earlier vaccines targeted G1 strains, which have only partial to no cross protection against G2 epidemic strains [67,71].

After the sudden emergence of PEDV in 2013 in the United States, two vaccines were quickly developed and both received conditional licenses from the USDA, including a killed-virus vaccine and an RNA particle

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vaccine [60]. The RNA particle vaccine was composed of the PEDV spike gene in a replication deficient Venezuelan equine encephalitis virus (VEEV) vector, and was tested on neonatal piglets as well as naïve and previously exposed pregnant sows pre-farrow, by both oral and IM administration [60]. Decreased disease severity and mortality but incomplete protection against infection were reported [60]. The killed vaccine consisted of an inactivated, whole-virus plus adjuvant, and was administered IM to sows pre-farrow and reported higher antibody titers in both the vaccinated sows and their piglets but no mortality data [60]. Field studies of each of these two conditionally-licensed vaccines yielded disappointing results, reporting increased IgG antibodies in the colostrum of vaccinated sows (RNA particle vaccine) but no protection against mortality between piglets born to sows vaccinated with either the RNA particle or inactivated vaccine [60].

One strategy for improving the immune response to the currently licensed vaccines is to utilize a prime-boost vaccination schedule. Several studies report increased IgA levels in milk, and colostrum, and protection against disease in piglets from sows that received a pre-farrow IM booster dose of killed PEDV vaccine following either natural infection or priming with an initial live-attenuated PED vaccine [72,73]. Due to the evolving mutations of PEDV, emerging PEDV variants are likely to continue to cause vaccine escape and outbreaks in regions where PEDV remains endemic, including in Asian countries and in the United States. Currently existing vaccines, such as the licensed killed vaccine (Zoetis, Inc.) in the United States, may need to be updated periodically in order to offer better protection against contemporary circulating strains.

BETACORONAVIRUS

Betacoronaviruses are known to cause deadly respiratory diseases in humans, including SARS-CoV-1, MERS-CoV, and SARS-CoV-2. One clinically and economically important betacoronavirus in veterinary species is the bovine coronavirus (BCoV), which causes both enteric and respiratory disease [1,4].

Bovine coronavirus (BCoV)

BCoV infects both the gastrointestinal and respiratory tracts and causes three distinct clinical syndromes: calf diarrhea, winter dysentery in adults, and respiratory disease at any age [74,75]. In calves, enteric BCoV infects the enterocytes throughout the small and large intestine, causing malabsorptive diarrhea [74,75]. Disease can be mild but co-infections with other pathogens such as rotavirus and enterotoxigenic *E. coli* can lead to severe dehydration and mortality [74,75]. In adults, enteric BCoV presents clinically as hemorrhagic diarrhea, with lesions mainly in the colon [74]. Mortality is low in adults but infection does cause economic loss in the form of a prolonged decrease in milk production [74]. Respiratory BCoV mainly infects the epithelium of the upper respiratory tract and can contribute to bovine respiratory disease complex (BRDC), which is a major cause of death and economic loss in feedlot cattle [75,76]. Importantly, no antigenic difference has been found between the BCoV causing these three syndromes; different serotypes of BCoV have good cross-protection and any serotype can cause either enteric or respiratory disease [74–78]. There are currently two licensed BCoV vaccines in the United States: a modified live vaccine and a killed vaccine (USDA, Current Veterinary Biologics Product Catalog, Feb 2, 2023).

BCoV is unique in that it has two structural proteins involved with attachment to the host cell: the prototypical spike (S) protein and the hemagglutinin-esterase (HE) protein [76,79]. The S protein is responsible for binding to sialic acid containing receptors on host cells and contains the main neutralizing epitopes, while the HE reverses hemagglutination [76]. Efficient binding to, and release from, host cells is thought to occur through

the right balance in the activities of these two proteins [80].

BCoV vaccine development has focused mainly on establishing protection against diarrhea in neonatal calves. 'Scours' in calves is often caused by mixed infections composed of not only BCoV, but other enteric pathogens as well such as rotavirus, enterotoxigenic *E. coli* (K99) and *C. perfringens* Types C and D [74], and as such, many of the historical and current BCoV vaccines are formulated together with immunogens from these other pathogens [81–83]. Experimental and field studies have reported increased antibody responses in serum, colostrum, and milk of cows and/or heifers that were vaccinated (IM or subcutaneous) with an inactivated vaccine plus adjuvant [84–86], and, in pregnant cows, a corresponding increase in antibody responses in their calves' serum [85]. Many studies on BCoV vaccination were performed in the field, and few studies report virus challenge results due to the difficulties in assessing clinical disease in the field and in the face of mixed infections. Initial field studies reported little to no protection following vaccination, however, more recent vaccination studies have shown some promise, with increased antibody responses in cows vaccinated with a single dose of inactivated (IM) vaccine prior to calving, and decreased diarrhea after challenge in their calves [87]. Calves have also been directly vaccinated with an orally administered, modified-live BCoV vaccine; after virus challenge, vaccinated calves remained clinically normal, had a faster rate of gain, and had no fecal viral shedding, compared to unvaccinated controls [88].

There is evidence that respiratory shedding of BCoV may be a source of continual exposure of a herd or to newly mingled animals on feedlots [74,89]. However, the current vaccines are directed against enteric disease and only a few studies have addressed efficacy in preventing respiratory disease. There is evidence that intranasal vaccination with a modified-live BCoV vaccine upon entry into a feedlot decreases the risk of being treated for respiratory disease [90]. Development of a live-attenuated BCoV vaccine targeting respiratory disease reported a high safety profile and high antibody titers but no virus challenge was performed [91]. Unfortunately, no experimental virus challenge studies on respiratory protection following vaccination have been reported, and to date there is no licensed vaccine targeting the respiratory disease associated with BCoV infection.

The relative paucity of research on BCoV vaccines is likely due to several challenges, including: (1) the virus has a wide range of cell tropism and establishing mucosal immunity in multiple sites is unlikely to be accomplished with a single vaccine; (2) the benefits of enteric mucosal immunity are well understood due to the extensive research in coronaviruses of pigs, however, passive, lactogenic immunity is more challenging to practically achieve in large beef herds and in dairy herds in general; and (3) both the enteric and respiratory syndromes experienced with BCoV infection are often seen in conjunction with co-infections with one or more other pathogens, further complicating experimental methods and assessment of outcomes associated with the protective efficacy of vaccines. Nonetheless, multiple modified live and killed virus vaccines are licensed and in use in the United States.

GAMMACORONAVIRUS

The gammacoronaviruses include an economically important veterinary virus infecting poultry, the infectious bronchitis virus (IBV), and many commercial vaccines have been licensed and are in use.

Avian infectious bronchitis virus (IBV)

IBV is primarily a disease of the upper respiratory tract and infects the ciliated and mucous-secreting epithelial cells, causing clinical signs such as gasping, snicking, sneezing, coughing, and nasal discharge in birds [92,93].

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IBV infection compromises mucociliary function, and predisposes animals to secondary infections that are often the actual cause of death [93,94]. While the upper respiratory tract is the primary site of virus infection, IBV is capable of infecting many other organ systems, including the lower respiratory tract, the gastrointestinal tract, kidneys, and reproductive tract [92]. As a result, IBV can be isolated from both respiratory secretions and feces, and disease can include pneumonia and airsacculitis, decreased egg production and decreased egg quality, including soft and deformed shells [92]. Nephropathogenic strains of IBV target renal tubular epithelial cells and cause severe, acute, necrotizing nephritis, renal failure, and increased mortality in birds [92,94]. When exposed at a young age, IBV can cause enteritis, stunted growth, and chronic cystic oviduct that prevents egg formation [94]. IBV is extremely contagious: morbidity in an affected flock is typically 100% and mortality is usually low, unless the IBV strain is nephropathogenic or there are coinfections with other pathogens [92,93].

The IBV S protein mediates host cell binding and is cleaved into the S1 and S2 subunits. S1 is responsible for cell tropism and binding to a sialic acid receptor on host cell membranes, as well as inducing virus neutralizing antibodies [95–97]. There are many different serotypes of IBV and neutralizing antibodies for each type have poor cross-protection for other serotypes [93]. As such, there are many different licensed IBV vaccines in the United States that are composed of a variety of serotypes, in live-attenuated virus, and killed vaccine platforms, and often in combination with other avian pathogens, including Newcastle disease virus and infectious bursal disease virus (USDA, Current Veterinary Biologics Product Catalog, Feb 2, 2023).

IBV was first described in the 1930's; the first vaccine became available in the 1950's, and vaccination has been practiced worldwide ever since [93]. As with other animal coronaviruses, mucosal and local immunity is important for anti-IBV immunity [98–105]. Many commercial IBV vaccines are administered either in drinking water or in coarse spray, both methods of delivery are efficient for producers and target local mucosal immune responses. Many of the first vaccines used were live-attenuated virus vaccines administered within a few weeks of hatch. Several studies reported protection against homologous challenge, with less severe clinical disease, maintained ciliary activity in the trachea, and decreased viral shedding [106,107]. Protection afforded by live-attenuated IBV vaccines was short-lived and declined about 9 weeks post-vaccination but could be prolonged with a booster dose [108,109]. The live-attenuated IBV vaccines have been shown to be capable of infecting susceptible contact chickens, undergoing recombination with circulating virulent strains, and/or mutating into virulent strains themselves [110,111]. While inactivated IBV vaccines have had mixed results on their own, they can be used in combination to extend immune protection. When administered as multiple doses by aerosol or subcutaneous routes, or as an aerosol-subcutaneous prime-boost schedule, inactivated vaccines could produce a virus neutralizing antibody response and decrease virus isolation from the trachea [112,113].

The main obstacle for successful IBV control is that vaccines offer limited to no protection against challenge with heterologous serotypes. IBV has a high mutation rate and only a few point mutations in the spike protein are thought to be necessary before commercial vaccines lose their protective efficacy [92]. For this reason, IBV continues to have a huge economic impact on poultry industries worldwide as newly emerging IBV strains are not protected by commercially available vaccines. Efforts at addressing waning protective efficacy and increasing cross-protection have focused on utilizing prime-boost vaccine strategies utilizing different IBV strains in combination to broaden protective coverage. When inactivated IBV vaccines were used as a booster following natural exposure or live-attenuated IBV vaccination, vaccinated

chicks experienced increased antibody titers in serum, protection against drop in egg production, and/or experienced a decrease in viral load in tissues (i.e., trachea, kidney) [101,114–117]. Currently many IBV vaccines are commercially available, the majority of which are live-attenuated virus vaccines, along with a few inactivated virus vaccines. Vaccine protocols for these IBV vaccines recommend booster doses after natural infection or primary vaccination.

TRANSLATION INSIGHTS

This concise review touches on a few of the important highlights of vaccine development for each of the selected clinically important veterinary coronaviruses, with a focus on licensed commercial animal vaccines. Individual and more detailed reviews could certainly be written on each of the selected viruses, as a variety of vaccine platforms, expression systems, administration routes, and many different adjuvants and co-stimulatory molecules, have been studied *in vitro* and in experimental models for each virus. Thus, the knowledge in searching for effective veterinary vaccines for these selected coronaviruses has the potential to inform future coronavirus vaccine development in any species, including humans. Across the animal coronaviruses discussed in this brief review, three common themes stand out: the battle to control disease in the face of constantly mutating coronaviruses, the importance of establishing mucosal immunity in mitigating the viral life cycle, and the challenge faced with the short-term and incomplete protection provided by these veterinary coronavirus vaccines.

Coronaviruses have one of the largest RNA genomes, thereby providing ample opportunity for mutations and recombination to occur [118], and enabling the emergence of new variants. This challenging scenario is illustrated in many of the animal coronaviruses discussed here, including IBV and PEDV. Despite decades of vaccination programs, disease associated with IBV infection is still a major concern for the global poultry industry due to newly emerging variants, often with poor or no cross-protection by existing licensed vaccines. Establishing the predominant circulating virus strains on a geographical basis is necessary for planning the vaccination program for a specific region and consideration must be given to 'regionalization' of available vaccine products based on these data. Surveillance and tracking of the emerging mutations across the globe may help identify areas of improvement for biosecurity measures or potential trends that contribute to important vaccine updates and modifications. Similarly, molecular epidemiologic methods have been widely used for SARS-CoV-2 surveillance, with many open access systems available to track number of cases, as well as genomic and phylogenetic trends of variants worldwide [119].

Emergence of variants also necessitates either periodic production of updated vaccines, as seen with development of the bivalent SARS-CoV-2 mRNA vaccines, or ideally, development of a broadly-protective or pan-coronavirus vaccines. The decrease noted in TGEV infection rates following emergence of PRCV provides some hope for pan-coronavirus vaccine development. Studies evaluating cross-protection between SARS-CoV-2 and other coronaviruses in either human (i.e., OC43, HUK1, NL63, 229E) or animal populations (i.e., bats) generally indicate that antibodies do not have significant cross-neutralizing effects and there is variable evidence for protection against severe disease [120]. However, there is evidence of pre-existing, cross-reactive CD4 and CD8 T cells to non-S1 structural and non-structural proteins [120–122]. Studies on cross-protection among coronaviruses have the potential to identify important humoral and cell-mediated immune mechanisms of protective immunity for developing broadly-protective vaccines in both veterinary and human medicine.

The potential impact and importance of a mucosal immune response for efficient

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protection is a strong and common theme throughout all of the animal coronaviruses discussed in this review. Many *in vitro*, *in vivo* experimental, and field studies consistently establish the beneficial effects that neutralizing mucosal IgA antibodies, as well as CMI responses, have on controlling coronavirus infection at the initial site of infection. Mucosal immunization routes across different animal species have a multitude of options, including vaccines administered via oral or intranasal routes, in eye drops or drinking water, or even applied as a coarse spray. In most instances, these routes of administration produce a better local mucosal immune response when compared to parenteral vaccines. TGEV and PEDV vaccines helped characterize the mucosal, lactogenic, passive immunity from dam to their neonates. Studies in livestock and poultry pushed the vaccine field to look at immunity in a new light, as serum antibodies, the outcome of focus for many coronavirus vaccines, were less predictive of protection against disease compared to IgA antibodies at mucosal sites and/or in mucosal secretions or fecal matter. The benefit of lactogenic immunity is driven home by the struggles with establishing protection against coronavirus in bovine species, where continuous exposure to milk containing adequate neutralizing antibodies is not practically possible. There have been many published reports across different veterinary coronaviruses on the inclusion of various mucosal adjuvants and co-stimulatory molecules to target mucosal cells and induce homing of immune cells to mucosal sites in order to induce or boost a mucosal immune response, and these strategies could be applied to future SARS-CoV-2 vaccine as well.

This review focuses mainly on experimental vaccines that were either integral to vaccine development in the respective species, and/or licensed and commercially available vaccines that have been used in a vaccination program. Many other vaccine platforms, from DNA to viral- or bacterial-vectored to virus-like-particles, have been studied for each of the veterinary coronavirus species reviewed here but are not detailed in this brief review. To date, the majority of vaccines on the market for veterinary species are modified-live or inactivated virus vaccines. With the honing of mRNA technology for successful vaccine development during the SARS-CoV-2 pandemic, it will be interesting to see how the field of veterinary vaccines evolves and whether this new mRNA platform can be applied cost-effectively to veterinary species to benefit patients of any species.

The potential benefits of vaccine-induced mucosal immunity in combating SARS-CoV-2 have been reviewed elegantly elsewhere [123–125]. As with other parenterally delivered vaccine platforms, the currently available mRNA vaccines induce strong protective neutralizing antibodies in serum but low levels of the same in respiratory mucosal secretions (nasal swab or bronchoalveolar lavage) [126,127]. Recent studies have begun to investigate the potential of mucosal vaccines for SARS-CoV-2 [127–129], and combined with the benefits consistently described in coronavirus vaccines for veterinary species, this approach provides hope for vaccine improvements in prevention of infection and further transmission in humans as well.

The final common theme from these animal coronavirus vaccines is that licensed vaccines for coronaviruses across veterinary species can decrease disease severity and lower mortality rates, but rarely confer complete protection. Observed benefits are usually short-lived, thereby requiring repeated booster immunizations. In most veterinary species, even natural infection induces only short-lived protective immunity. The closest mimic of this immune response is induced by live-attenuated coronavirus vaccines administered at the mucosal site where natural infection initially occurs. The same challenges are also known with SARS-CoV-2, as re-infection does occur following either natural infection or vaccination, further underscoring the importance of boosters and vaccine updates.

These decades of experience from animal coronavirus vaccines in veterinary species illustrate the shared challenges faced when developing long-lasting protective vaccines for coronaviruses in any species. One approach in animal coronavirus vaccination programs that seems to improve upon the incomplete protective efficacy, prolong duration of protection, improve mucosal immune responses, and provide better cross-protection, is the use of a prime-boost vaccination schedules. There is some evidence that this approach may also be beneficial in SARS-CoV-2 disease control. Neutralizing antibodies in the nasal mucosa have been isolated after natural breakthrough infection with SARS-CoV-2 in already vaccinated individuals [126]. This has been replicated experimentally, in which immunization of mice first with a SARS-CoV-2 IM mRNA vaccine followed by an IN vaccine induced strong neutralizing antibodies in the respiratory mucosa [127]. Collectively, the available data from veterinary coronavirus vaccines and available SARS-CoV-2 data support the recommendation for periodic SARS-CoV-2 vaccine update and booster doses, and for vaccination after recovery from SARS-CoV-2 infection.

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AUTHORSHIP & CONFLICT OF INTEREST

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