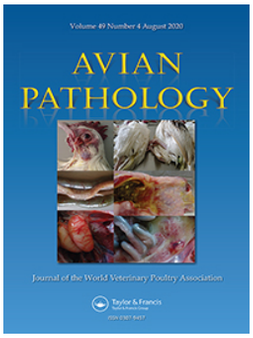

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GUEST EDITORIAL

Spotlight on avian coronaviruses

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ABSTRACT
Coronaviruses (CoVs) mainly cause enteric and/or respiratory signs. Mammalian CoVs including COVID-19 (now officially named SARS-CoV-2) belong to either the Alphacoronavirus or Betacoronavirus genera. In birds, the majority of the known CoVs belong to the Gammacoronavirus genus, whilst a small number are classified as Deltacoronaviruses. Gammacoronaviruses continue to be reported in an increasing number of avian species, generally by detection of viral RNA. Apart from infectious bronchitis virus in chickens, the only avian species in which CoV has been definitively associated with disease are the turkey, pheasant and guinea fowl. Whilst there is strong evidence for recombination between gammacoronaviruses of different avian species, and between betacoronaviruses in different mammals, evidence of recombination between coronaviruses of different genera is lacking. Furthermore, the recombination of an alpha or betacoronavirus with a gammacoronavirus is extremely unlikely. For recombination to happen, the two viruses would need to be present in the same cell of the same animal at the same time, a highly unlikely scenario as they cannot replicate in the same host!

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Introduction

The current pandemic in humans, caused by a coronavirus (CoV), commonly referred to as COVID-19, but now officially named SARS-CoV-2 has resulted in a high level of interest in CoVs generally, including those found in birds. The importance of the CoV, infectious bronchitis virus (IBV) as a major pathogen in chickens of all ages and types is well known, but less is known about CoVs found in other avian species and how they might relate to CoVs in mammals. We will address these and other issues in this Editorial.

Coronaviruses

Coronaviruses (CoVs) are enveloped, nonsegmented positive-sense RNA viruses that form the largest group of viruses belonging to the *Nidovirales* order. The *Coronavirinae* comprise one of two subfamilies in the *Coronaviridae* family; the other being the *Torovirinae*. The *Orthocoronavirinae* subfamily is divided into four genera based on genetic differences and serological cross-reactivity: Alphacoronavirus, Betacoronavirus, Gammacoronavirus and Deltacoronavirus. The viruses were initially sorted into these genera based on serology, but are now divided by phylogenetic clustering (Fehr & Perlman, 2015). With a few exceptions, alpha and beta CoVs infect mammals, while gamma and delta CoVs are found in birds. One possible exception to this is the report by Ismail *et al.* (2001) who demonstrated enteritis and reduced weight gain in turkey poults experimentally infected with the DB2 strain of bovine coronavirus, a betacoronavirus. A second exception is the reported isolation by Nuttall and Harrap in 1982 (reviewed by Cavanagh, 2005) of a betacoronavirus from a Manx shearwater. This finding does not appear to have been followed up and, as the isolation was made by passage in mouse brains, it must remain possible that the virus isolated was actually of murine origin.

CoVs mainly cause enteric and/or respiratory signs. The S (spike) protein is the main surface protein and is responsible for the name of these viruses (the spikes give these viruses a crown-like appearance in electron microscopic images). The S protein mediates host cell attachment, virus and cell membrane fusion, and entry into the host cell (Jackwood & de Wit, 2020). It consists of two subdomains, S1 and S2, where S1 is required for attachment to the receptor and S2 for fusion of virus and cell membranes. The S1 protein contains multiple immunodominant epitopes/domains and is the most variable protein of the four structural proteins (spike, matrix, envelope and nucleoprotein). Serotype neutralizing antibodies are induced by S1. Changes in the genetic material may result from mutations and recombinations, which are relatively frequent in CoVs and are important strategies for their survival. These changes can lead to changes in tissue and host tropism or in the ability of the virus to transmit to, or infect, different species.

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Naming of avian coronaviruses

In 2018, the International Committee on Taxonomy of Viruses (ICTV) decided to withdraw all previously recognized different avian gammacoronaviruses and recognize only 'avian coronavirus' as the official species name within the genus Gammacoronavirus https://talk.ictvonline.org//taxonomy/p/taxonomy-history?taxnode_id=201851880. This means that, under the present rules, all Gammacoronaviruses from any bird species are considered to be the same species of virus despite their different hosts and tropism, different antigenicity, lack of cross-protection and significant differences in the genomes. Out of respect for these relevant differences between the viruses and clarity for the reader, we will use here the well-known species names from before 2018 that respect the biological aspects of the virus and its host.

CoVs in the chicken

The only CoV reported in chickens is IBV. IBV is by far the best-studied Gammacoronavirus and the only one which causes disease of major economic and welfare concern. Vaccination is widely used to control IBV infections. Live vaccines are needed to protect broilers and for priming of layers and breeders. Inactivated oil-emulsion vaccines are administered to layers and breeders before the onset of egg production to boost the level of antibodies against IBV. In layers and breeders, a higher level of serotype-specific antibodies against the challenge strain is correlated with higher protection against a drop in egg production. In young birds, local immunity is most important for protection. A general overview of the different aspects of IBV is described by Jackwood and de Wit (2020).

CoVs in avian species other than the chicken

The majority of the known CoVs of birds belong to the Gammacoronavirus genus, although a small number are classified as Deltacoronaviruses (see below).

Avian gammacoronaviruses

Apart from IBV in chickens, the only avian species in which CoV has been definitively associated with disease are the turkey, pheasant and guinea fowl.

CoV of turkeys

Turkey coronavirus (TCoV) is the best characterized, and economically most important, avian CoV after IBV. Known since the 1940s as a cause of enteric disease in turkeys in the USA, it is now reported as a problem in most turkey-producing areas of the world. TCoV affects turkeys of all ages and causes high mortality in young poults. Clinical signs include decreased feed and water intake, wet droppings, diarrhoea and loss of bodyweight. TCoV is also believed to cause poult enteritis and mortality syndrome (PEMS), a condition associated with high mortality, growth retardation and immune dysfunction. In breeding turkeys, aberrant egg-laying performance is associated with TCoV infection, similar to that seen following IBV infections in chickens. However, unlike IBV, TCoV replication is mainly in the intestinal tract and bursa of Fabricius, and transmission is generally by the faecal oral route. As with IBV, infection together with other pathogens may increase the severity of the disease.

Cross neutralization tests suggest that there are antigenic differences between TCoV strains, but variants do not appear to exist in the numbers seen with IBV. The relationship between IBV and TCoV has been a cause of much debate, and the fact that IBV vaccines have occasionally been isolated from turkeys adds to the confusion. Whilst TCoV has been shown to replicate in the chicken, there is no evidence to suggest it causes disease. The two viruses are clearly closely related and Cavanagh (2005) reported similarities of over 80% in some genes of the two viruses, but only approximately 34% similarity in the important spike proteins. Molecular studies of the TCoV and IBV genomes suggest that the two viruses are distinct virus species, but probably have a common origin. For more information on TCoVs see Jindal *et al.* (2014); Guy (2020).

CoVs of pheasants (PhCoV)

CoV infections are increasingly reported in pheasants associated with both respiratory and renal problems. PhCoV has been identified as the causal agent and appears to be closely related to IBV and TCoV. PhCoV can replicate in the chicken, but evidence that it also causes disease in that species is lacking.

CoVs of guinea fowl (GfCoV)

GfCoV has been associated with fulminating disease in guinea fowl (Liais *et al.*, 2014), an acute enteritis with a very high death rate and possibly pancreatic degeneration. Genetically, the virus shows similarity to both IBV and TCoV, differences being greatest in the spike gene, and a common ancestor has been proposed for the three viruses.

Gammacoronaviruses in other gallinaceous birds

In addition to TCoV, PhCoV and GfCoV, where an association between the virus and disease has been established, Gammacoronaviruses have been detected in other gallinaceous species including quail, peafowl and partridge. In some cases, these are believed to be isolation of IBV vaccine. Whether or not IBV can cause disease in these species, or whether CoVs specific to these species exist, remains to be clarified.

Gammacoronaviruses in nongallinaceous species

Gammacoronaviruses isolated from teal, housed near domestic chickens in China, and from racing pigeons in Australia may actually be isolations of IBV strains (Cavanagh, 2005). However, using RT-PCR Gammacoronaviruses have been detected in avian species including greylag geese, pigeons and mallard ducks, and all shown to be genetically different from IBV, TCoV, PhCoV and GfCoV (reviewed by Cavanagh, 2005). Using PCR, Hughes *et al.* (2009) detected CoVs in wildfowl and wading birds (ducks, whooper swans, red knots and oyster catchers) in England; all birds appeared healthy. Sequence analysis showed some, but not all, to be related to IBV.

Gammacoronaviruses continue to be reported in an increasing number of avian species, generally by detection of viral RNA. It remains to be determined whether or not any of them are capable of causing disease. An exception to the concept that Gammacoronaviruses are only found in avian species is the report by Mihindukulasuriya *et al.* (2008), reviewed by Milek and Blicharz-Domanska (2018), of the detection by molecular methods of a Gammacoronavirus in a white beluga whale, although no virus could be grown.

Deltacoronaviruses

In a large scale study in China, Woo *et al.* (2012) identified CoVs from a pig and from seven different avian species of the Passeriformes order, all of which showed a molecular structure distinct from that of all previously known CoVs and which form a fourth genus, Deltacoronavirus. Evidence that these avian CoVs may be causal agents of disease is lacking, but the authors suggest they may be a potential source of genes for other avian CoVs.

The number of avian species in which CoVs have been reported, usually by detection of viral RNA, continues to grow. These viruses have been associated with disease in only a few species, all galliform. However, IBV (either the virus itself or its genome) has been detected in a variety of wild bird species and this could be important in CoV epidemiology and transmission. Although not proven, wild birds may play a role in the spread of novel IBV variants, or even be the source of unusual variants, such as D1466, which emerge in commercial chicken flocks from time to time. An added concern must be the possibility of recombination between different avian CoVs replicating in wild bird species at the same time. For more details on avian CoVs of different avian species see reviews by Cavanagh (2005); Milek & Blicharz-Domanska (2018).

Cross-protection between CoVs of different genera

It is possible that viruses with common antigens that replicate and induce an immune response in the same bird might induce cross-protection against each other. Questions have been raised about whether avian CoVs, especially IBV or vaccines against it, might induce cross-protection against SARS-CoV-2 (COVID-19). This is very unlikely to be the case. IBV is not zoonotic; it does not replicate in mammals nor does it induce an immune response in them. Even if IBV could theoretically induce some protection in humans against IBV, it would not be useful against SARS-CoV-2. SARS-CoV-2 and IBV are members of different genera of the *Orthocoronavirinae* subfamily, therefore it is very unlikely that there will be any serological cross-reactions between them. Therefore, even if they were injected, IBV vaccines will not be able to induce any protection in humans against SARS-CoV-2. Another concern that has been raised is whether chickens need to be protected against SARS-CoV-2. This is not the case as this virus is not able to infect chickens (Shi *et al.*, 2020).

Can SARS-CoV-2 (COVID-19) recombine and adapt to poultry?

SARS-CoV-2 is a betacoronavirus, whereas IBV is a gammacoronavirus. Whilst there is strong evidence for recombination between gammacoronaviruses of different avian species, and between betacoronaviruses in different mammals, evidence of recombination between coronaviruses of different genera is lacking. Furthermore, the recombination of an alpha or betacoronavirus with a gammacoronavirus is extremely unlikely. For recombination to occur, the two viruses would need to be present in the same cell of the same bird at the same time, a highly unlikely scenario as they cannot replicate in the same host!

Conclusion

Despite avian and mammalian CoVs both belonging to the *Coronaviridae* family, they are very different from each other genetically and antigenically. They belong to different virus genera, replicate in different animal species, with no evidence of any ability to cross-rotect. For poultry, the main options for introduction and relevant spread of a new gammacoronavirus might be the result of interspecies transmission from wild birds and adaptation to the new host, or the result of a recombination of a poultry gammacoronavirus with another gammacoronavirus. Both options underline the importance of biosecurity.

Disclosure statement

No potential conflict of interest was reported by the authors.

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