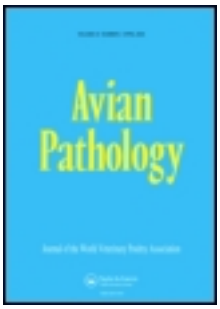

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Turkey coronavirus is more closely related to avian infectious bronchitis virus than to mammalian coronaviruses: A review

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GUEST EDITORIAL

Turkey coronavirus is more closely related to avian infectious bronchitis virus than to mammalian coronaviruses: a review

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Turkey coronavirus (TCoV) is the cause of an acute highly contagious enteric disease of turkeys. In recent years, TCoV has been increasingly recognized in North America as an important pathogen of young turkeys, resulting in economic loss due to impaired growth and poor feed conversion. While the epidemiology and pathogenesis of TCoV have been extensively studied, TCoV remains one of the least characterized of the known coronaviruses.

Avian and mammalian coronaviruses have been subdivided into distinct antigenic/genotypic groups; however, classification of TCoV has been controversial. Previous studies indicated that TCoV was closely related to bovine coronavirus and other group 2 mammalian coronaviruses, but more recent antigenic and genome sequence analyses contradict these findings and, instead, provide evidence that TCoV is closely related to avian infectious bronchitis virus (IBV). Additionally, experimental studies have indicated that the host range of TCoV, once thought to be restricted to turkeys, includes chickens. These studies have raised additional questions regarding the classification of TCoV; particularly, whether IBV and TCoV are taxonomically distinct viruses, or whether TCoV is merely a variant of IBV.

Sequence analyses of TCoV have given credence to the idea that TCoV is a variant of IBV, as these studies have shown that TCoV and IBV are very closely related. However, these studies have been limited to only three TCoV strains and relatively small portions of the TCoV genome. TCoV is readily distinguished from IBV based on antigenic and biological differences, and these differences suggest that TCoV should be considered a distinct virus species.

Additional studies will be needed to better define the relationship between TCoV and IBV, and to resolve this taxonomic question. Based on our current understanding, it seems prudent to consider TCoV and IBV as distinct virus species that share a close phylogenetic relationship and together comprise group 3 of the coronavirus major antigenic groups.

Turkey Coronavirus

Turkey coronavirus (TCoV) is the cause of an acute highly contagious enteric disease of turkeys that initially was referred to as bluecomb disease (Nagaraja & Pomeroy, 1997). Bluecomb disease was first identified in turkeys in 1951 and a coronavirus was identified as the cause of the disease in 1973 (Panigrahy *et al*., 1973; Ritchie *et al*., 1973). In recent years, TCoV has been increasingly recognized in North America as an important cause of enteric disease in turkeys, resulting in economic loss due to impaired growth and poor feed conversion. The virus also has been associated as a cause of poult enteritis and mortality syndrome, a disease of unknown etiology characterized by high mortality, severe growth depression and immune dysfunction (Barnes & Guy, 1997).

Antigenic and molecular characterization of TCoV has lagged behind most other known coro-

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naviruses due to difficulties associated with *in vitro* cultivation of the virus. TCoV strains have been successfully propagated in embryonated chicken and turkey eggs by inoculation of the amniotic cavity (Nagaraja & Pomeroy, 1997). In inoculated embryos, virus replication occurs exclusively in intestinal epithelial cells and epithelium of the bursa of Fabricius (Pomeroy *et al*., 1978); virus replication has not been detected in allantoic, yolk or amniotic membranes.

Attempts to propagate TCoV in a variety of avian and mammalian cell cultures generally have been unsuccessful (Nagaraja & Pomeroy, 1997). Dea *et al*. (1989) reported the cell culture adaptation and serial propagation of TCoV using a human rectal adenocarcinoma (HRT) cell line. However, this finding has not been corroborated by other investigators (Guy *et al*., 1997). HRT cells previously have been shown to support the propagation of several different coronaviruses, including bovine coronavirus (Laporte *et al*., 1980) and human coronavirus (OC43) (Mounir & Talbot, 1992).

Coronaviridae

The *Coronaviridae* comprises a large family of RNA-containing viruses that infect a wide variety of avian and mammalian species (Robb & Bond, 1979; Wege *et al*., 1982). The family *Coronaviridae* is in the order *Nidovirales*, an order composed of viruses having linear, nonsegmented, positive-sense, single-stranded RNA genomes with similar genomic organization and nested sets of subgenomic mRNAs (Cavanagh *et al*., 1997). The coronavirus genome consists of an RNA molecule that is 28 to 32 kilobases (kb) in size (Lai & Cavanagh, 1997). Virions are enveloped, pleomorphic, 80 to 220 nm in diameter, and have club-shaped surface projections approximately 20 nm in length. Four structural proteins are known: the surface (S) glycoprotein (90 to 180 kDa), an integral membrane (M) protein (20 to 35 kDa), a small envelope (E) protein (12.5 kDa) and a nucleocapsid (N) protein (50 to 60 kDa) (Siddell, 1995; Murphy, 1996; Lai & Cavanagh, 1997). In addition, some coronaviruses also contain a fifth structural protein, the haemagglutinin-esterase protein (120 to 140 kDa) (Siddell, 1995; Holmes & Lai, 1996).

Pedersen *et al*. (1978) identified differences among coronaviruses based on antigenic relatedness of the structural proteins. Using immunofluorescence procedures, the mammalian coronaviruses were subdivided into two antigenically distinct groups, with group 1 being composed of transmissible gastroenteritis virus (TGEV), feline infectious peritonitis virus (FIPV), canine coronavirus (CCV) and human coronavirus (HCV) 229E. Antigenic group 2 was shown to comprise bovine coronavirus (BCV), porcine haemagglutinating encephalomyelitis virus, mouse hepatitis virus and HCV OC43. The studies of Pedersen *et al*. did not include the avian coronaviruses, infectious bronchitis virus (IBV) and TCoV. However, other studies using immune electron microscopy, haemagglutination inhibition and virus-neutralization assays indicated that IBV and TCoV were antigenically distinct from each other and the mammalian coronaviruses (Dea *et al*., 1986; Ritchie *et al*., 1973). Thus, these early studies subdivided the coronaviruses into four antigenic groups, with the mammalian coronaviruses comprising groups 1 and 2, and the avian coronaviruses, IBV and TCoV, comprising groups 3 and 4, respectively (Wege *et al*., 1982; Sturman & Holmes, 1983; Holmes, 1990).

Antigenic/Genomic Characterization of TCoV

Additional antigenic and genomic analyses of TCoV were carried out by Dea *et al*. (1990) in the early 1990s, using HRT cell-adapted TCoV strains. Based on immunoblotting and immunoprecipitaton studies, Dea *et al*. (1990) provided evidence suggesting a close antigenic relationship between TCoV and BCV, a group 2 coronavirus. These findings subsequently were supported by serological studies (virus neutralization and haemagglutination inhibition), DNA hybridization studies and genome sequence analyses (Dea *et al*., 1990; Verbeek & Tijssen, 1991; Verbeek *et al*., 1991). BCV cDNA was shown to hybridize to TCoV RNA, and sequence analyses indicated a 99% identity between TCoV and BCV M and N protein amino-acid sequences. These findings led to reclassification of TCoV with recognition of three coronavirus antigenic groups: two groups composed primarily of mammalian coronaviruses, with TCoV included in group 2, and one avian group consisting of a single member, IBV (Siddell, 1995; Holmes & Lai, 1996).

More recent antigenic and genomic analyses of TCoV have questioned these taxonomic groupings, particularly the classification of TCoV (Guy *et al*., 1997; Breslin *et al*., 1999a,b; Stephensen *et al*., 1999). Antigenic analyses by Guy *et al*. (1997) demonstrated a close antigenic relationship between TCoV and IBV, and these studies failed to detect antigenic relatedness between TCoV and group 2 coronaviruses. Using immunofluorescence procedures, TCoV- and IBV-specific polyclonal antibodies did not recognize TGEV or BCV antigens, and *vice versa*. Polyclonal antibodies specific for IBV, and monoclonal antibodies specific for IBV M protein, reacted strongly against TCoV.

While antigenic similarities between TCoV and IBV were identified in the studies of Guy *et al*. (1997), antigenic differences were also apparent. Polyclonal antibodies specific for TCoV failed to recognize IBV, thus indicating a one-way antigenic relationship between these viruses. A similar one-way antigenic relationship between the mammalian coronaviruses, TGEV, FIPV and CCV was

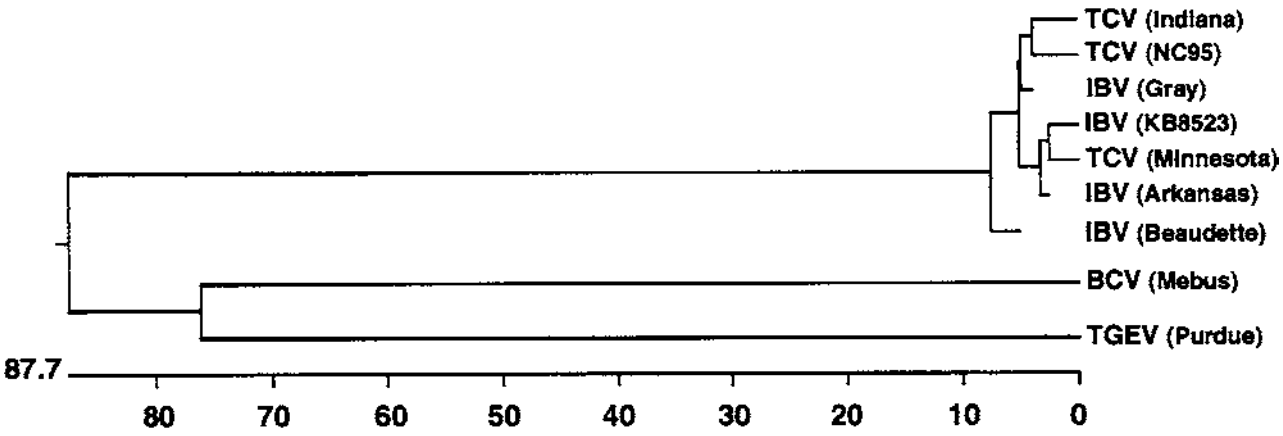

Figure 1. *Phylogenetic relationship of avian and mammalian coronaviruses. The complete nucleocapsid protein amino acid sequences of three TCoV stains (Breslin* et al.*, 1999b) are compared with published sequences of selected IBV strains and representative members of mammalian coronaviruses, group 1 (TGEV) and group 2 (BCV). Nucleotide sequences were aligned using the CLUSTAL method (Thompson* et al.*, 1997) and phylogenetic trees were constructed using the neighbor-joining method. Analyses were made using the MegAlign application of the Lasergene software package (DNASTAR). The scale beneath the tree measures the distance between sequences, with units indicating the number of substitution events.*

observed by Pedersen *et al.* (1978). TGEV- and FIPV-specific antibodies reacted strongly against CCV, but antibodies specific for CCV failed to recognize TGEV and FIPV antigens. Antigenic differences between TCoV and IBV were also demonstrated by the failure of an IBV group specific, S protein specific monoclonal antibody to recognize TCoV antigens (Karaca *et al.*, 1992).

Additional evidence of a close relationship between TCoV and IBV has come from sequence analyses of TCoV structural protein genes and the polymerase gene. These studies have been conducted in two independent laboratories (Breslin *et al.*, 1999a,b; Stephensen *et al.*, 1999). Breslin *et al.* (1999a,b) sequenced the 3 end of the TCoV genome (approximately 2.6 kb) encompassing the entire N protein gene, 3 untranslated region (UTR), and a portion of the M protein gene. Three epidemiologically distinct TCoV strains were sequenced, and these sequences were compared with published sequences of other avian and mammalian coronaviruses. Based on these comparisons, a high degree of sequence identity (> 90%) was observed between the M and N protein sequences of TCoV strains and published sequences of IBV. M and N protein sequences of TCoV had only limited sequence identity (< 30%) with M and N protein sequences of mammalian coronaviruses. In addition, sequence identity between the 3 UTRs of TCoV and IBV was > 78%; < 30% sequence identity was observed between TCoV 3 UTRs and those of BCV and TGEV.

The findings of Breslin *et al.* (1999a,b) are supported by concurrent studies performed by Stephensen *et al.* (1999), who sequenced a highly conserved region of the polymerase gene (ORF 1b) of TCoV (922 bases) and compared this sequence with that of IBV and nine mammalian coronaviruses representing coronavirus antigenic groups 1 and 2. Based on polymerase gene sequence data, TCoV and IBV were very closely related, and only distantly related to mammalian coronaviruses.

Phylogenetic analyses performed by Breslin *et al.* (1999a) and Stephensen *et al.* (1999) provide additional evidence of a close genetic relationship between TCoV and IBV. In addition, these analyses demonstrate that the avian coronaviruses, TCoV and IBV, constitute a distinct genotype within the *Coronavirus* genus. A phylogenetic tree is shown in Figure 1 that compares the complete N protein amino acid sequences of three TCoV strains (Breslin *et al.*, 1999b) with published sequence data for selected IBV strains, and representative group 1 and group 2 mammalian coronaviruses, TGEV and BCV, respectively. This phylogenetic tree demonstrates that TCoV is very closely related to IBV, to such an extent that they cannot be distinguished based on this region of the genome.

Host Range and Tissue Tropisms

The turkey is believed to be the only natural host for TCoV. TCoV replication occurs exclusively in intestinal epithelium and epithelium of the bursa of Fabricius; virus replication has not been detected in other tissues (Naqi *et al.*, 1972; Patel *et al.*, 1975). Using immunohistochemistry, TCoV antigens are detected in infected turkeys in enterocytes lining the upper portion of intestinal villi, and in follicular and interfollicular epithelium of the bursa of Fabricius.

Early studies indicated that the host range of TCoV was restricted to turkeys. In these studies, chickens, pheasants, sea gulls and coturnix quail were shown to be refractory to infection (Nagaraja & Pomeroy, 1997). However, more recent studies indicate that chickens also are susceptible to TCoV infection (Guy *et al.*, 1999). In experimental

studies, 1-day-old specific pathogen free chickens were inoculated with embryo-propagated TCoV by combined oral and intratracheal routes. TCoV-inoculated chickens did not develop clinically apparent disease and they gained weight at a rate comparable with uninoculated controls. Despite the lack of clinical effects, TCoV infection was demonstrated in inoculated chickens by seroconversion, and detection of virus and viral antigens in intestinal tissues and bursa of Fabricius (days 2 to 8 post-exposure). TCoV was not detected in trachea, lung or kidney. These studies indicate that chickens are susceptible to TCoV, and the virus has a tropism in this species identical to that in turkeys.

IBV, like TCoV and other coronaviruses, has a limited host range. Chickens were believed to be the only natural host for IBV. However, pheasants also have been shown to be susceptible to IBV infection (Spackman & Cameron, 1983; Gough *et al*., 1996). Experimental attempts to infect a variety of other avian species, including turkeys, have been unsuccessful.

Conclusions

Recent antigenic and genome sequence analyses indicate that the avian coronaviruses, IBV and TCoV, are very closely related (Guy *et al*., 1997; Breslin *et al*., 1999a,b; Stephensen *et al*., 1999). These studies refute previous investigations that failed to detect antigenic relatedness between TCoV and IBV (Ritchie *et al*., 1973; Dea *et al*., 1986), and those studies that indicated a close relationship between TCoV and group 2 coronaviruses (Dea *et al*., 1990; Verbeek & Tijssen, 1991).

The failure of previous investigators to recognize antigenic similarity between TCoV and IBV is readily explained by the types of antigenic analyses employed by these investigators. Procedures such as immune electron microscopy, haemagglutination inhibition and virus neutralization detect antigenic similarities among viruses only in those virus proteins at the virion surface, whereas immunofluorescence procedures potentially allow detection of antigenic similarities among all virus proteins.

The discrepancies between recent studies and the studies of Dea *et al*. (1990) and Verbeek & Tijssen (1991) that indicated a close relationship between TCoV and group 2 coronaviruses are much more difficult to explain. The studies of Dea *et al*. (1990) and Verbeek & Tijssen (1991) were based on HRT cell-propagated TCoV strains. Perhaps a laboratory error resulted in contamination of cell culture media or HRT cells with a group 2 coronavirus, contemporaneously with attempts to propagate TCoV. The use of such media or cell cultures would have led, unknowingly, to the erroneous supposition that cytopathic effects and haemagglutinating activity produced by the contaminant virus were due to TCoV replication.

Antigenic and genomic similarities between TCoV and IBV, and the determination that the host range of TCoV includes chickens, have led to the suggestion that TCoV may not be a unique coronavirus species, but rather a variant of IBV. This notion is supported by sequence analyses. Based on sequence analyses, the extent of genetic difference between sequenced TCoV strains and IBV strains is similar to the extent of difference between IBV strains. The M and N protein sequences of TCoV and IBV were shown to have > 90% identity (Breslin *et al*., 1999a,b). Similarly, N proteins of 27 different IBV strains isolated in the US, the UK, Holland, Saudi Arabia, and Japan were shown to have > 94% identity (Williams *et al*., 1992; Zwaagstra *et al*., 1992). Genetic similarity between TCoV and IBV also is evident in phylogenetic analyses; phylogenetic analysis using N protein amino acid sequences (Figure 1) shows that TCoV strains cannot be distinguished from IBV strains in this part of the genome. However, sequence studies have been limited to only three TCoV strains and they have been restricted to relatively small portions of the TCoV genome. Additionally, these sequence studies have focused on relatively conserved regions of the coronavirus genome, a conserved region of the polymerase gene and the 3 end, including the M and N genes. Additional sequence studies involving other TCoV strains and other regions of the genome, particularly the S gene, are needed to further assess differences between TCoV and IBV.

While limited sequence data might suggest otherwise, antigenic and biologic differences between TCoV and IBV suggest that these viruses are indeed distinct virus species. TCoV and IBV may be distinguished based on a one-way antigenic relationship between these viruses (Guy *et al*., 1997). In cross-immunofluorescence studies, polyclonal antibodies specific for IBV reacted strongly against TCoV antigens, but antibodies specific for TCoV did not recognize IBV antigens. Additionally, an IBV-specific monoclonal antibody with broad specificity for IBV strains (IBV group specific, S protein specific) did not recognize TCoV antigens.

The strict tropism of TCoV for intestinal epithelium and epithelium of the bursa of Fabricius is an important biological difference between TCoV and IBV. Several enterotropic IBV strains have been identified. However, all of these strains replicate *in vivo* in both respiratory and intestinal epithelium (Ambali & Jones, 1990; Cavanagh & Naqi, 1997). TCoV and IBV also differ in their *in vitro* growth characteristics. IBV strains are readily propagated in allantoic sac/membranes of embryonated chicken eggs and they are readily adapted to growth in chicken cell cultures; TCoV does not share these growth characteristics.

Additional sequence studies will be needed to fully address the taxonomic relationship between TCoV and IBV. However, based on our present

understanding of these viruses, it seems prudent to consider them as distinct virus species that share a close phylogenetic relationship and together comprise group 3 of the coronavirus major antigenic groups.

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RÉSUMÉ

Le coronavirus de la dinde est plus proche du virus de la bronchite infectieuse aviaire que des coronavirus des mammifères

Le coronavirus de la dinde (TVoC) est l'agent très contagieux de l'entérite aiguë des dindes. Au cours des dernières années, le TCoV a

été observé de façon croissante en Amérique du Nord, et représente un agent pathogène important pour les jeunes dindes, entraînant des pertes économiques dues à une diminution de croissance et a une mauvaise conversion alimentaire. Bien que l'épidémiologie et la pathogénie du TCoV ont été largement étudiées, le TCoV reste un des coronavirus le moins bien caractérisé.

Les coronavirus des oiseaux et des mammifères ont été subdivisés en groupes antigénique/génotypique distincts. Cependant, la classification du TCoV est controversée. Des études antérieures ont indiqué que le TCoV était proche du coronavirus bovin et du groupe 2 des coronavirus des mammifères, mais des études antigéniques plus récentes et les analyses de la séquence du génome et ont contredit ces observations et mettent en évidence que ce TCoV est proche du virus de la bronchite infectieuse aviaire (IBV). De plus, des études expérimentales ont montré que les hôtes sensibles au TCoV ne concernaient pas uniquement les dindes mais comprenaient également les poulets. Ces études ont soulevé d'autres questions au regard de la classification du TCoV, en particulier, les IBV et TCoV sont-ils des virus taxonomiquement différents? ou le TCoV n'est-il pas simplement un variant de l'IBV ?

Les analyses des séquences du TCoV ont donné foi à l'hypothèse selon laquelle le TCoV est un variant de l'IBV, du fait que les études ont montré que le TCoV et l'IBV étaient très proches. Cependant, ces études ont été limitées à seulement, trois souches de TCoV et à de petites portions du génome. Le TCoV est bien différent de l'IBV sur la base des caractéristiques biologiques et antigéniques et ces différences suggèrent que le TCoV devrait être considéré comme une espèce de virus différente.

Des études complémentaires seraient nécessaires pour mieux définir les relations entre le TCoV et l'IBV et résoudre ce problème de taxonomie. En se basant sur ce que nous avons compris, il est prudent de considérer le TCoV et l'IBV comme des espèces virales distinctes qui présentent des relations phylogéniques proches et forment ensemble le groupe 3 des coronavirus qui est le groupe le plus important.

ZUSAMMENFASSUNG

Das Puten-Coronavirus ist mit dem aviären Bronchitisvirus enger verwandt als mit Säugetier-Coronaviren

Das Puten-Coronavirus (PCoV) ist die Ursache einer akuten hochkontagiösen Darmerkrankung der Puten. In den letzten Jahren wurde PCoV in Nordamerika zunehmend als bedeutender Krankheitserreger junger Puten anerkannt, der zu wirtschaftlichen Einbußen durch vermindertes Wachstum und schlechter Futterverwertung führt. Während die Epidemiologie und Pathogenese von PCoV umfassend untersucht worden ist, bleibt PCoV eines der am wenigsten charakterisierten der bekannten Coronaviren.

Vogel- und Säugetier-Coronaviren werden in verschiedene Antigen-/Genotyp-Gruppen unterteilt; die Klassifizierung von PCoV ist jedoch umstritten. Frühere Untersuchungen deuteten darauf hin, dass PCoV mit Rinder-Coronavirus und anderen Säuger-Coronaviren der Gruppe 2 nahe verwandt war, aber neuere Antigen- und Genomsequenz-Analysen stehen in Widerspruch zu diesen Befunden und liefern stattdessen Anhaltspunkte dafür, dass PCoV mit dem aviären Bronchitisvirus (IBV) nahe verwandt ist. Außerdem haben experimentelle Untersuchungen gezeigt, dass das Wirtsspektrum von PCoV, von dem einst angenommen wurde, dass es auf Puten beschränkt sei, auch die Hühner einschließt. Diese Untersuchungen haben weitere Fragen im Hinblick auf die Klassifizierung von PCoV aufgeworfen, insbesondere ob IBV und PCoV taxonomisch unterschiedliche Viren sind, oder ob PCoV bloß eine Variante von IBV ist.

Sequenzanalysen von PCoV haben die Vorstellung glaubwürdig gemacht, dass PCoV eine IBV-Variante ist, da diese Untersuchungen gezeigt haben, dass PCoV und IBV sehr eng verwandt sind. Diese Untersuchungen waren allerdings auf nur drei PCoV-Stämme und relativ kleine Anteile des PCoV-Genoms beschränkt. PCoV ist an Hand von von antigenen und biologischen Unterschieden leicht von IBV zu differenzieren, und diese Unterschiede weisen darauf hin, dass PCoV als eine eigene Virusspezies betrachtet werden sollte.

Weitere Untersuchungen werden nötig sein, um die Beziehung zwischen PCoV und IBV besser zu definieren und diese taxonomische Frage zu lösen. Auf der Basis unserer gegenwärtigen Kenntnisse erscheint es vernünftig, PCoV und IBV als verschiedene Virusspezies anzusehen, die eine enge phylogenetische Verwandtschaft teilen und zusammen die Gruppe 3 der Hauptantigengruppen des Coronavirus umfassen.

RESUMEN

El coronavirus del pavo esta mas estrechamente relacionado con el virus de la bronquitis aviar que con los coronavirus de mamiferos

El coronavirus del pavo (TCoV) da lugar a un proceso entérico agudo y altamente contagioso en pavos. En los últimos años, el TcoV se ha diagnosticado con mayor frecuencia en Norteamérica como un importante patógeno en pavos, dando lugar a pérdidas económicas debidas a una falta de crecimiento y a un bajo índice de conversión. Mientras que la epidemiología y la patogenia del TCoV han sido estudiadas intensamente, el TCoV propiamente dicho, es uno de los coronavirus conocidos menos caracterizado.

Los coronavirus aviares y de mamíferos han sido agrupados en dos grupos antigénicos/genotípicos diferentes; sin embargo la clasificación de TCoV es controvertida. Estudios previos indicaban que TCoV estaba estrechamente relacionado con el coronavirus bovino y otros coronavirus del grupo 2, aunque análisis antigénicos y de secuencia genómica más recientes contradicen estos estudios y presentan evidencias de que el TCoV está estrechamente relacionado con el virus de la bronquitis infecciosa aviar (IBV). Además estudios experimentales han demostrado que el espectro de especies sensibles al TCoV, inicialmente restringido a pavos, incluye a los pollos. Estos estudios plantean dudas adicionales relativas a la clasificación del TCoV, concretamente, si IBV y TCoV son dos virus taxonómicamente diferentes o si TCoV es una nueva variante de IBD.

Análisis de secuencia del TCoV han confirmado que el TCoV es una variante del IBD, dado que estos estudios han demostrado que el TCoV y el IBV están íntimamente relacionados. Sin embargo estos estudios se han limitado sólo a tres cepas de TCoV y a relativamente pequeñas porciones de su genoma. El TCoV se distingue claramente del IBV en función de sus diferencias antigénicas y propiedades biológicas, sugiriendo que deberían ser considerados diferentes especies víricas.

Se necesitarán estudios posteriores para definir con más precisión la relación entre TCoV e IBV y resolver este problema taxonómico. En nuestra opinión, parece prudente considerar el TCoV y el IBV dos especies víricas distintas que presentan una estrecha relación filogenética y juntos forman el grupo antigénico 3 de los coronavirus.