International Journal of Research in Pharmacy and Biosciences
Volume 5, Issue 6, 2018, PP 1-12
ISSN 2394-5885 (Print) & ISSN 2394-5893 (Online)

Understanding the Infectious Bronchitis Virus Immunity and Evolution

M.M. Amer[1], A. M. Ghetas[2], M.A. Kutkat[2], M.H.H. Awaad[1]

[1]Department of Poultry Diseases, Cairo University, Egypt
[2]Department of Poultry Diseases, National Research Centre, Egypt

***Corresponding Author:** M.M. Amer, Department of Poultry Diseases, Cairo University, Egypt.*

ABSTRACT

Avian infectious bronchitis (IB) is an acute and highly contagious respiratory and urogenital disease of chickens. It causes a high economic losses to the poultry industry worldwide.Infectious bronchitis virus (IBV) strains have been classified into protectotypes, antigenic types (serotypes and epitope-types), or genotypes depending on biological or viral gene sequences. Different IBV serotypes and genotypes have been detected worldwide and new variants are still emergingdespite extensive vaccination against IB.Further understanding of the immune responses against IBV infection and the virus evolution mechanism can help to develop an effective IBV vaccines and improve the commercially available IBV live attenuated vaccines.

VIRUS CLASSIFICATION

Corona viruses were usually classified into three groups based on genetic makeup and antigenicity (Brian and Baric, 2005; Lai and Cavanagh, 1997; Masters, 2006; Ziebuhr, 2004). However, the Coronavirus Study Group of the International Committee for Taxonomy of Viruses recently classified coronaviruses into 4 genera: *Alphacoronavirus, Betacoronavirus, Gammacoronavirus,* and *Deltacoronavirus* (Wang et al., 2014; Woo et al., 2010). IBV is a member of the genus *Gammacoronavirus*, subfamily *Coronavirinae*, family *Coronaviridae*, in the order *Nidovirales* (World Organisation for Animal Health, 2013). The virus is a single stranded RNA virus, round to pleomorphic in shape, and possesses an envelope of about 120 nm in diameter with club shaped surface projections or spikes of about 20 nm in length (Cavanagh and Gelb, 2008).

IBV strains have been classified into protectotypes, antigenic types (serotypes and epitope-types), or genotypes depending on biological or viral gene sequences. Immunotypes or protectotypes provide practical information about the efficacy of a vaccine. IBV strains protecting against each other belong to the same protectotype (de Wit, 2000). Furthermore, different serotypes and genotypes can share common epitopes which provide cross-protection (Cavanagh et al., 1997).

IBV strains have been classified into serotypes based on features of the S1 protein which contains virus neutralizing and serotype specific epitopes. Serotyping is performed by virus neutralization (VN) or hemagglutination inhibition (HI) tests. The VN test is based on the reaction between an IBV strain and serotype specific antibodies produced in chickens. Two strains should be in the same serotype when two way heterologous neutralization titers differ less than 20-fold from the homologous titers in both directions (Hesselink, 1991). The VN test has been performed in various systems like chicken embryos (Cowen and Hitchner, 1975; Cunningham, 1973; Dawson and Gough, 1971), cell culture (Cowen and Hitchner, 1975; Csermelyi et al., 1988; Hopkins, 1974; Wadey and Faragher, 1981), or chicken tracheal organ culture (Cook, 1984; Darbyshire et al., 1979; Johnson and Marquardt, 1975). The HI test was initially suggested for IB by Bingham *et al.(Bingham et al., 1975)* and developed by Alexander *et al.*(Alexander et al., 1976) and Alexander and Chettle (1977). Several authors used HI tests for IBV serotyping (Brown and Bracewell, 1985; Cook et al., 1987; Lashgari and Newman, 1984).

IBV strains are also classified into genotypes based on genetic characterizations of a fragment of the viral genome. Different methods are used for IBV genotyping such as RT-PCR amplification of genotype-specific genes,

sequencing (Binns et al., 1985; Binns et al., 1986; Cavanagh and Davis, 1992; Cavanagh et al., 1986), or enzyme cleavage sites detection by restriction fragments length polymorphism (RFLP) (Song et al., 1998a). While a high correlation between the genotype and serotype of IBV strains has been detected (Keeler et al., 1998; Kwon et al., 1993; Lin et al., 1991), several authors have reported conflicting results (Clewley et al., 1981; Hein et al., 1998; Kusters et al., 1987). Therefore, serotyping and *in vivo* studies should be used with genotyping in order to have accurate results about antigenic nature of IBV isolates (Hein et al., 1998; Jia et al., 1995; Keeler et al., 1998).

VIRUS PROTEINS

The IBV genome of 27.6 kb encodes non-structural proteins (NSP) and structural proteins. The 5' two-thirds of the virus genome (the replicase genes) encode 15 non-structural proteins (NSP) including the RNA-dependent RNA polymerase. The remaining third of the genome encodes four structural proteins, interspersed with small nonstructural proteins, including the spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins (Cavanagh, 2003; Enjuanes et al., 2000a; Enjuanes et al., 2000b).

The replicase genes, which comprise two large overlapping open reading frames (ORF1a and ORF1b), is translated by frameshift a mechanism into two polyproteins 1a and 1ab.These polyproteins are subsequently cleaved into 15 nonstructural proteins (nsps), nsps 2 through 16 by a papain-like protease (PLP) and the 3C-like protease (van Hemert et al., 2008). The PLP domain within nsp 3 is divided into PL1 and PL2 proteases. In IBV, only PL2is active, and called PL^{pro} which cleaves nsps 2, 3, and 4 (Ziebuhr et al., 2001). The 3C-like protease within nsp 5 cleaves nsps 5 through 16.

The function of several coronavirus' NSPs in replication and transcription of the viral genome have been identified including for example RNA-dependent RNA polymerase (RdRp) activity in nsp12, helicase activity in nsp13, exonuclease activity in nsp14, endoribonuclease activity in nsp15, and methyltransferase activity in nsp16 (Bhardwaj et al., 2004; Cheng et al., 2005; Decroly et al., 2008; Ivanov et al., 2004a; Ivanov et al., 2004b; Ivanov and Ziebuhr, 2004; Ricagno et al., 2006; Ziebuhr, 2005).The interferon antagonist of papain-like protease domain 2 encoded in the NSP3 of coronaviruses was previously reported (Wang et al., 2011.; Zheng et al., 2008). The replicase proteins are also involved in IBV pathogenicity (Ammayappan et al., 2009; Armesto et al., 2009; Cavanagh, 2007).

The IBV structural proteins, S, E, M and N proteins are translated from subgenomic messenger RNAs 2, 3, 4 and 6, respectively (Lai and Holmes, 2001). The viral S protein,a club-shaped surface projection, is a dimer or trimer on the envelope surface.The S protein is glycosylated with N glycans into the rough endoplasmic reticulum (Lai and Holmes, 2001). The precursor S protein is cleaved into amino-terminal S1 subunit (520 amino acids) and carboxy-terminal S2 subunit (600 amino acids) with approximately 1160 amino acids (Cavanagh, 1995).The S1 portion has little or no contact with the membrane forming the major part of the bulbous end of the S protein and is attached to the membrane by the S2 portion (Cavanagh, 1983). There are weak intra-peptide and not inter-peptide disulfide bonds between S1 and S2 glycoproteins (Cavanagh, 1983).

Many authors reported the importance of S glycoprotein to determine the species and tissue-cell tropism of many coronaviruses including IBV (Ballesteros et al., 1997; Baric et al., 1997; Casais et al., 2003; Fang et al., 2005; Fazakerley et al., 1992; Hingley et al., 1994; Leparc-Goffart et al., 1998; Li et al., 2005; Ontiveros et al., 2003; Phillips et al., 2002; Wesley et al., 1991). IBV reverse-genetic system has been used to replace only the ectodomain of the Beaudette S glycoprotein with the M41-CK analogue. The recombinant IBV had the same *in vitro* growth characteristics of the M41-CK, demonstrating that the IBV S protein is a determinant of cell tropism (Casais et al., 2003). The majority of mutations in the IBV genome during adaptation to primate cells were also detected in the S gene; 26 out of 49 amino acid substitutions were identified after adaptation of the IBV Beaudette strain from chicken embryo to Vero cells (Fang et al., 2005). Selection of embryo adapted IBV vaccine virus S1 gene subpopulations in vaccinated chickens has also been reported (McKinley et al., 2008; van Santen and Toro, 2008). Moreover, the S1 phenotypic differences were detected between IBV vaccine viral subpopulations in various chicken tissues, confirming the role of S1 in cell tropism (Gallardo et al., 2010).

The highly variable S1 domain differs from 20% to up to 50% in amino acid sequence among

IBV serotypes (Gelb et al., 1997). A few mutations in the virus neutralizing antibody inducing S1 subunit can result in changes of the serotype and reduction in cross protection (Cavanagh et al., 1992a; Kant et al., 1992). Several reports have also suggested that while the differences between S1 sequences of IBV's strains increase, the degree of cross protection between these strains decreases (Cavanagh et al., 1997; Gelb et al., 1997; Ladman et al., 2006).

The S1 subunit is a major determinant of host protective immune response by inducing virus neutralization (VN) and hemagglutination inhibition (HI) antibodies (Koch et al., 1990; Mockett et al., 1984). IBV from which the S1 had been removed by urea, failed to induce protection, VN, or HI antibodies in vaccinated chickens (Cavanagh and Davis, 1986). Thus, the S1 glycoprotein expressed by a recombinant vectors protects chickens against challenge with virulent IBV (Johnson et al., 2003; Song et al., 1998b; Toro et al., 2014). While IBV S1 portion is variable, the S2 portion is conserved among different IBV strains (Kusters et al., 1989a). During the analysis of the antigenic structure of the IBV peplomer protein, eight epitope clusters were defined (S-A to S-H) by using monoclonal antibodies (MAbs) directed against IBV structural proteins. Consequently, six clusters (A to F) on S1 subunit and two (G and H) on the S2 subunit have been identified.Furthermore, IBV has been neutralized at titers higher than 2 $\log_{10}$ by monoclonal antibodies directed against epitope clusters A to E and one MAb directed against cluster G (Koch et al., 1990). Since the epitope cluster G on S2 induced moderately to strongly neutralizing antibodies (Koch et al., 1990) and the S2 portion is conserved among different IBV strains (Kusters et al., 1989a), The S2 domain was suggested to be suitable for IBV vaccine development (Lenstra et al., 1989). The S protein is relevant during the first step in virus infection by binding the virus to cell surface receptors, the virulent M41 spike ectodomain was not sufficient to restore the pathogenicity on a recombinant Beaudette virus *in vivo*(Hodgson et al., 2004). It has been indicated that replicase proteins are important determinant of the IBV pathogenicity (Armesto et al., 2009).

The phosphorylated N protein is highly conserved between IBV strains, especially the region between amino acid residues 238 and 293 (Williams et al., 1992). The N protein which has 409 amino acid residues, binds to RNA genome to form the viral ribonucleoprotein complex (Davies et al., 1981). Furthermore, stimulation of the cytotoxic T lymphocytes and protection of the chickens from acute infection by the carboxyl-terminal 120-residue polypeptide of the IBV nucleocapsid has been reported (Seo et al., 1997).

VIRUS IMMUNITY

Both humoral and cell mediated immune responses are important in protection against IBV infection. Chickens recovered from IB are protected against reinfection with the same viral strain, but they may not be protected against challenge with heterologous strains (Cavanagh and Gelb, 2008).The humoral immune response has been evaluated by measuring IBV specific immunoglobulins in serum, lachrymal fluid, and tracheal washes (Cook et al., 1992; Ganapathy et al., 2005; Gelb et al., 1998; Toro et al., 1994).Many serological tests are used to detect IBV antibodies such as ELISA, AGPT,VN, and HI test; and the factors influencing the successful IBV antibody detection has been reviewed (de Wit, 2000).

After IBV inoculation, the immunoglobulin M (IgM) reaches the peak 8 days and then its level declines. IgM antibody was detected as early as 3 days post IBV-M41 inoculation (Mockett and Cook, 1986). Thus, the detection of IBV specific in serum is important to identify recent infections (Da Silva Martins et al., 1991; Mockett and Cook, 1986). The major circulating antibody is immunoglobulin G (IgG), which can be detected in serum as early as 4 days post IBV inoculation, then peaks at 21 day and maintains high serum titers for a long time (Mockett and Darbyshire, 1981). However, serum antibody levels do not always correlate with protection against IBV infection (Raggi and Lee, 1965). Thus, the experimental evaluation of protection against virulent IBV is performed by viral isolation from chickens after challenge, analysis of clinical signs, and histological evaluation of tracheal lesions (Cavanagh and Gelb, 2008). The correlation between high IBV specific antibodies in serum and absence of virus isolation from kidneys and oviduct (Yachida et al., 1985) and protection of egg production (Box et al., 1988) has also been reported.

The importance of local immunity in protection of the upper respiratory tract against IBV infection has been demonstrated (Gillette, 1981; Gomez and Raggi, 1974). Local antibodies against IBV (IgA and IgG) have been detected

in lachrymal fluid (Davelaar et al., 1982; Toro et al., 1994), tracheal washes (Hawkes et al., 1983), and oviduct washes, duodenal and cecal contents (Raj and Jones, 1996). The levels of IBV-specific IgA in tears were higher than IgG levels after primary ocular vaccination with live attenuated IBV Ark DPI vaccine. However, the IgG levels in both tears and plasma were higher than the IgA during the secondary immune response (Orr-Burks et al., 2014).Additionally, it has been demonstrated that the levels of lachrymal IgA are correlated with resistance against IBV reinfection (Toro and Fernandez, 1994). Secretory IgA protects mucosal surfaces against viral infections by neutralizing the viruses and blocking their attachment to receptors on target cells (Sharma, 2008).

Harderian gland is the main source for lacrimal IgA which is playing a prominent role in mucosal humoral immunity (Davelaar and Kouwenhoven, 1980; Davelaar et al., 1982). Therefore, the protection against IBV challenge 3 weeks after vaccination was decreased in chicks where Harderian glands were removed (Davelaar and Kouwenhoven, 1980). An early and higher IBV-specific IgA-producing B cells were also detected in Harderian glands of IBV-infected chickens as compared with the response seen in the cecal tonsils by using enzyme-linked immuno-spot forming assays (van Ginkel et al., 2008) .

The importance of cell-mediated immune response in protection against IBV has been reported (Collisson et al., 2000; Pei et al., 2003; Seo and Collisson, 1997; Seo and Collisson, 1998; Seo et al., 2000; Seo et al., 1997). Major histocompatibility complex restricted $CD8^+$ $CD4^-$ T cellsduring IBV acute infection were shown to be associated with initial elimination of virus in both lungs and kidneys and recovery from clinical signs (Seo and Collisson, 1997). Additionally, transfer of IBV-primed αβ T lymphocytes bearing $CD8^+$ collected at 10 days post IBV infection to naïve chickens that were challenged the next day with a homologous IBV strain, protected chicks against clinical signs and viral replication in the lungs (Seo et al., 2000). Furthermore, chicks inoculated with IBV-specific $CD8^+$ memory T cells, generated at 3 to 6 weeks post infection, were protected against acute IBV infection (Pei et al., 2003). Inoculation of DNA plasmids expressing the carboxyl-terminal 120-residue polypeptide of viral nucleocapsid protein stimulated cytotoxic T lymphocytes and protected chicks from acute IBV infection (Seo et al., 1997). Additionally, IBV nucleoprotein-specific T cell response was detected more rapidly than specific serum IgG after primary vaccination with H52 vaccine (Liu et al., 2012).

The relevance of maternally-derived antibody (MDA) in protection against IBV infection has been reported extensively (Klieve and Cumming, 1988; Mockett et al., 1987; Mondal and Naqi, 2001; Yachida et al., 1981). Maternal IgG transferred from vaccinated hens to the progeny via the yolk and can be detected in serum and respiratory mucus of newly hatched chicks (Hawkes et al., 1983; Jungherr and Terrel, 1948). Based on evaluation of IBV shedding 4 days post challenge, newly hatched chicks with high levels of MDA in serum (5.2 $\log_{10}$) and in the respiratory tract (2.7 $\log_{10}$) provided excellent protection (95%) against challenge at one day of age but not at seven days (30%). While there is no significant change in serum antibody titer between days 1 and 7, the antibody levels in respiratory tract dropped by about 50%, indicating that local respiratory antibody and not serum antibody protected chicks against intraocular challenge (Mondal and Naqi, 2001).

VIRUS EVOLUTION

The first IBV antigenic variation was reported in 1956 in the USA; the Connecticut isolated from 1951 neither cross-neutralized nor cross-protected with the original Mass isolate in the early 1940s (Jungherr et al., 1956). Since the initial discovery by Jungherr *et al.*, several IBV serotypes, genotypes, and variants have been detected worldwide (de Wit et al., 2011; Jackwood, 2012).The emergence of variant viruses is a potential risk especially when variant viruses persist and cause widespread disease, as was observed with Georgia variant (GAV) and GA98 among 82 different variant viruses identified during 11 years period (Jackwood et al., 2005).

IBV evolves by natural selection, i.e. generation of genetic diversity by high mutation frequency and recombination events followed by selection acting on diverse phenotypes (Toro et al., 2012). The genetic diversity originates from both mutations (insertions, deletions, and point mutations resulting from lack of proof reading ability of the RdRp), and recombination events during IBV replication . Thus, different phenotypes have been detected within IBV isolates and vaccines (McKinley et al., 2008; Nix et al., 2000; van Santen and Toro, 2008).

All coronaviruses including IBV have an average synonymous mutation rate of approximately 1.2 X 10^{-3} substitutions/site/year (Hanada et al., 2004; Holmes, 2009). The RNA proofreading and repair functions of the exoribonuclease domain in nsp14 has been reported (Minskaia, 2006; Snijder et al., 2003). Therefore, the nsp14 exoribonuclease mutants had defective growth and high mutation rates comparing to wild type coronaviruses (Eckerle et al., 2010; Eckerle et al., 2007). Indeed, the exoribonuclease domain contributes to the fidelity of the viral RdRp and allows the virus to maintain its large genome size (Holmes, 2009). Mutations accumulating in IBV gene especially S gene have a major effect on the viral evolutionary fitness, leading to emerge of new stains and serotypes (Jackwood et al., 2012).

In addition to mutations, recombination has been detected among IBV strains (Cavanagh and Davis, 1988; Cavanagh et al., 1992b; Kusters et al., 1990; Kusters et al., 1989b). Recombination is most probably due to switching of RdRp from RNA template to a different one during concurrent infection of the same cell (Lai, 1992). The regions showing the highest incidences of recombination breakpoints have been detected in IBV genome which are located in nsp2, nsp3, nsp16, and directly upstream of the S gene (Lee et al., 2001; Lee and Jackwood, 2000). Recombination also plays a significant role in the evolutionary fitness leading to new genetic types and strains of the coronaviruses which transmit to different host, especially when the S gene was involved. Thus, the replacement of the S gene in IBV with sequence of unknown virus caused emergence of turkey coronavirus (Jackwood et al., 2010).

Selection of the most fit IBV subpopulations have been detected in chickens after IBV vaccination (Gallardo et al., 2010; McKinley et al., 2008; van Santen and Toro, 2008). The predominant IBV subpopulations re-isolated from vaccinated chickens 3 days post ocular vaccination were differed from the predominant subpopulation in Arkansas (Ark)-type vaccine prior to vaccination (McKinley et al., 2008; van Santen and Toro, 2008). Furthermore, the S1 gene of the selected IBV subpopulations in vaccinated chickens was similar to the virulent Ark-Delmarva Poultry Industry (DPI) parental strain than to the predominant population in vaccine (van Santen and Toro, 2008).

The virus behavior in the host is influenced by presence of high proportion of distinct selected IBV subpopulations which lead to higher viral load in tears, higher incidence of respiratory signs, more sever tracheal lesions, and higher antibody responses, comparing to Ark DPI-derived vaccine contains low proportion of IBV subpopulations later selected in chickens (Ndegwa et al., 2012). Significant differences in the incidence of the selected IBV subpopulations in different tissues and fluids of vaccinated chickens were also detected after inoculation of chickens with Ark-type commercial vaccine. For example, the selected IBV phenotype component 1 (C1) had a significant high incidence in reproductive tract comparing to its incidence in trachea (Gallardo et al., 2010).

The selection of the more fit IBV subpopulations in chickens may explain the persistence of Ark-type IBV vaccine viruses in commercial broilers. Indeed, persistence of IBV vaccine viruses can increase the virus opportunities for recombination and/or mutations which lead to the emergence of virulent viruses (Domingo et al., 1998; McKinley et al., 2008; van Santen and Toro, 2008). Therefore, variant Ark viruses have been detected in vaccinated chickens (Alvarado et al., 2006; Jackwood et al., 2005; Jackwood et al., 2009; Nix et al., 2000).

CONCLUSION

Despite extensive vaccination against IB, new variants continue to emerge and periodically cause IB outbreaks worldwide. IBV evolves by natural selection; generation of genetic diversity followed by selection acting on diverse phenotypes. Thus, improvement of commercially available vaccines and development ofstable vaccines which provide strong protection against IBV challenge and do not undergo selection in chickens after vaccination is requiredfor effective control of the disease.

REFERENCES

[1] Alexander, D.J., Bracewell, C.D., Gough, R.E., 1976. Preliminary evaluation of the haemagglutination and haemagglutination inhibition tests for avian infectious bronchitis virus. A vian Pathology 5, 125-134.

[2] Alexander, D.J., Chettle, N.J., 1977. Procedures for the haemagglutination and the haemagglutination inhibition tests for avian infectious bronchitis virus. Avian Pathology 6, 9-17.

[3] Alvarado, I.R., Villegas, P., El-Attrache, J., Jackwood, M.W., 2006. Detection of

Massachusetts and Arkansas serotypes of infectious bronchitis virus in broilers. . Avian Diseases 50, 292-297.

[4] Ammayappan, A., Upadhyay, C., Gelb, J., Jr., Vakharia, V.N., 2009. Identification of sequence changes responsible for the attenuation of avian infectious bronchitis virus strain Arkansas DPI. Archives of Virology 154, 495-499.

[5] Armesto, M., Cavanagh, D., Britton, P., 2009. The replicase gene of avian coronavirus infectious bronchitis virus is a determinant of pathogenicity. PLoS one 4, e7384.

[6] Ballesteros, M.L., Sánchez, C.M., Enjuanes, L., 1997. Two amino acid changes at the N-terminus of transmissible gastroenteritis coronavirus spike protein result in the loss of enteric tropism. Virology 227, 378-388.

[7] Baric, R.S., Yount, B., Hensley, L., Peel, S.A., Chen, W., 1997. Episodic evolution mediates interspecies transfer of a murine coronavirus. Journal of virology 71, 1946-1955.

[8] Bhardwaj, K., Guarino, L., Kao, C.C., 2004. The severe acute respiratory syndrome coronavirus Nsp15 protein is an endoribonuclease that prefers manganese as a cofactor. . Journal of virology 78, 12218–12224.

[9] Bingham, R.W., Madge, M.H., Tyrrell, D.A.J., 1975. Haemagglutination by avian infectious bronchitis virus — a coronavirus. Journal of General Virology 28, 381-390.

[10] Binns, M.M., Boursnell, M.E.G., Cavanagh, D., Pappin, D.J.C., Brown, T.D.K., 1985. Cloning and sequencing of the gene encoding the spike protein of the coronavirus IBV. Journal of General Virology 66, 719-726.

[11] Binns, M.M., Boursnell, M.E.G., Tomley, F.M., Brown, T.D.K., 1986. Comparison of the spike precursor sequences of coronaviru s IBV strains M41 and 6/82 with that of IBV Beaudette. Journal of General Virology 67 2825-2831.

[12] Box, P.G., Holmes, H.C., Finney, P.M., Froymann, R., 1988. Infectious bronchitis in laying hens: the relationship between haemagglutination inhibition antibody levels and resistance to experimental challenge. Avian Pathology 17, 349-361.

[13] Brian, D.A., Baric, R.S., 2005. Coronavirus genome structure and replication. . Current Topics in Microbiology and Immunology 287, 1-30.

[14] Brown, A.J., Bracewell, C.D., 1985. Application of the haemagglutination inhibition test to typing of infectious bronchitis virus. . Veterinary Record 116, 47- 48.

[15] Casais, R., Dove, B., Cavanagh, D., Britton, P., 2003. Recombinant avian infectious bronchitis virus expressing a heterologous spike gene demonstrates that the spike protein is a determinant of cell tropism. Journal of virology 77, 9084-9089.

[16] Cavanagh, D., 1983. Coronavirus IBV: structural characterization of the spike protein. Journal of general virology 64, 2577-2583.

[17] Cavanagh, D., 1995. The coronavirus surface glycoprotein. In: The Coronaviridae. . 73-103. .

[18] Cavanagh, D., 2003. Severe acute respiratory syndrome vaccine development: experiences of vaccination against avian infectious bronchitis coronavirus. Avian Pathology 32, 567-582.

[19] Cavanagh, D., 2007. Coronavirus avian infectious bronchitis. Veterinary Research 38, 281–297.

[20] Cavanagh, D., Davis, P.J., 1986. Coronavirus IBV: removal of spike glycopolypeptide S1 by urea abolishes infectivity and haemagglutination but not attachment to cells. Journal of General Virology 67, 1443-1448.

[21] Cavanagh, D., Davis, P.J., 1988. Evolution of avian coronavirus IBV: sequence of the matrix glycoprotein gene and intergenic region of several serotypes. Journal of general virology 69, 621-629.

[22] Cavanagh, D., Davis, P.J., 1992. Sequence analyses of strains of avain infectious bronchitis coronavirus isolated during the 1960s in the U.K. . Archives of Virology 130, 471- 476.

[23] Cavanagh, D., Davis, P.J., Cook, J., Li, D., Kant, A., Koch, G., 1992a. Location of the amino acid differences in the S1 spike glycoprotein subunit of closely related serotypes of infectious bronchitis virus. Avian Pathology 21, 33-43.

[24] Cavanagh, D., Davis, P.J., Cook, J.K.A., 1992b. Infectious bronchitis virus: evidence for recombination within the Massachusetts serotype. Avian Pathology 21, 401– 408.

[25] Cavanagh, D., Davis, P.J., Pappin, D.J., Binns, M.M., Boursnell, M.E., Brown, T.D., 1986. Coronavirus IBV: partial amino terminal sequencing of spike polypeptide S2 identifies the sequence Arg-Arg-Phe-Arg-Arg at the cleavage site of the spike precursor propolypeptide of IBV strains Beaudette and M41. Virus research 4, 133-143.

[26] Cavanagh, D., Ellis, M.M., Cook, J.K.A., 1997. Relationship between variation in the S1 spike protein of infectious bronchitis virus and the extent of cross-protection. Avian Pathology 26, 63-74.

[27] Cavanagh, D., Gelb, J., 2008. Infectious bronchitis, in: Y. M. Saif, A. M. Fadly, J. R. Glisson, L. R. McDougald, L. K. Nolan, Swayne, D.E. (Eds.), Diseases of Poultry, 12th

ed. Blackwell Publishing, Ames, Iowa, pp. 117-135.

[28] Cheng, A., Zhang., W., Xie., Y., Jiang., W., Arnold., E., Sarafianos., S.G., Ding., J., 2005. Expression, purification, and characterization of SARS coronavirus RNA polymerase. . Virology 335, 165–176.

[29] Clewley, J.P., Morser, J., Avery, R.J., Lomniczi, B., 1981. Oligonucleotide fingerprinting of ribonucleic acids of infectious bronchitis virus strains Infection and Immunity 32, 1227-1233.

[30] Collisson, E.W., Pei, J., Dzielawa, J., Seo, S.H., 2000. Cytotoxic T lymphocytes are critical in the control of infectious bronchitis virus in poultry. Developmental & Comparative Immunology 24, 187-200.

[31] Cook, J.K.A., 1984. The classification of new serotypes of infectious bronchitis virus isolated from poultry flocks in Britain between 1981 and 1983 Avian Pathology 13 733-741.

[32] Cook, J.K.A., Brown, A.J., Bracewell, C.D., 1987. Comparison of the haemagglutination inhibition test and the serum neutralisation test in tracheal organ cultures for typing infectious bronchitis virus strains. Avian Pathology 16, 505- 511.

[33] Cook, K.A., Otsuki, K., Martins, N.R., Ellis, M.M., Huggins, M.B., 1992. The secretory antibody response of inbred lines of chicken to avian infectious bronchitis virus infection. Avian Pathology 21, 681-692.

[34] Cowen, B.S., Hitchner, S.B., 1975. Serotyping of avian infectious bronchitis viruses by the virus-neutralization test. Avian Diseases 19, 583- 595.

[35] Csermelyi, M., Thijssen, R., Orthel, F., Burger, A.G., Kouwenhoven, B., Lutticken, D., 1988. Serological classification of recent infectious bronchitis virus isolates by the neutralisation of immunofluorescent foci. . Avian Pathology 17, 139-148.

[36] Cunningham, C.H., 1973. Immunologic methods in avian research: neutralization test. Avian Diseases 17, 227- 235.

[37] Da Silva Martins, N.R., Mockett, A.P.A., Barrett, A.D.T., Cook, J.K.A., 1991. IgM responses in chicken serum to live and inactivated infectious bronchitis virus vaccines. . Avian Diseases 35, 470-475.

[38] Darbyshire, J.H., Rowell, J.G., Cook, J.K.A., Peters, R.W., 1979. Taxonomic studies on strains of avian infectious bronchitis virus using neutralization tests in tracheal organ cultures. Archives of Virology 61, 227- 238.

[39] Davelaar, F.G., Kouwenhoven, B., 1980. Effect of the removal of the Harderian gland in 1-day-old chicks on immunity following IB vaccination. Avian Pathology 9, 489-497.

[40] Davelaar, F.G., Noordizij, A., van der Donk, J.A., 1982. A study on the synthesis and secretion of immunoglobulins by the Harderian gland of the fowl after eyedrop vaccination against infectious bronchitis at 1-day-old. Avian Pathology 11, 63-79.

[41] Davies, H.A., Dourmashkin, R.R., Macnaughton, M.R., 1981. Ribonucleoprotein of avian infectious bronchitis virus. Journal of General Virology 53, 67-74.

[42] Dawson, P.S., Gough, R.E., 1971. Antigenic variation in strains of avian infectious bronchitis virus. Archiv f¨ur gesamte Virusforschung 34, 32-39.

[43] de Wit, J.J., 2000. Detection of infectious bronchitis virus. Avian Pathology 29, 71-93.

[44] de Wit, J.J., Cook, J.K.A., van der Heijden, H.M.J.F., 2011. Infectious bronchitis virus variants: a review of the history, current situation and control measures. Avian Pathology 40, 223-235.

[45] Decroly, E., Imbert, I., Coutard, B., Bouvet, M., Selisko, B., Alvarez, K., Gorbalenya, A.E., Snijder, E.J., Canard, B., 2008. Coronavirus nonstructural protein 16 is a Cap-0 binding enzyme possessing (nucleoside-2O)-methyltransferase activity. . Journal of virology 82, 8071–8084.

[46] Domingo, E., Baranowski, E., Ruiz-Jarabo, C.M., Martin-Hernandez, A.M., Saiz, J.C., Escarmis, C., 1998. Quasispecies structure and persistence of RNA viruses. Emerging infectious diseases 4, 521-527.

[47] Eckerle, L.D., Becker, M.M., Halpin, R.A., Li, K., Venter, E., Lu, X., Scherbakova, S., Graham, R.L., Baric, R.S., Stockwell, T.B., Spiro, D.J., Denison, M.R., 2010. Infidelity of SARS-CoV Nsp14-exonuclease mutant virus replication is revealed by complete genome sequencing. PLoS Pathogens 6, e1000896.

[48] Eckerle, L.D., Lu, X., Sperry, S.M., Choi, L., Denison, M.R., 2007. High fidelity of murine hepatitis virus replication is decreased in nsp14 exoribonuclease mutants. . Journal of virology 81, 12135-12144.

[49] Enjuanes, L., Brian, D., Cavanagh, D., Holmes, K., Lai, M.M.C., Laude, H., Masters, P., Rottier, P., Siddell, S.G., Spaan, W.J.M., Taguchi, F., Talbot, P., 2000a. Coronaviridae, in: van Regenmortel, M.H.V., Fauquet, C.M., Bishop, D.H.L., Carstens, E.B., Estes, M.K., Lemon, S., Maniloff, J., Mayo, M., McGeoch, D.J., Pringle, C.R., Wickner, R.B. (Eds.), Virus taxonomy. Classification and nomenclature of viruses. Academic Press, New York, N.Y., pp. 835-849.

[50] Enjuanes, L., Spaan, W.J., Snijder, E.J., Cavanagh, D., 2000b. Nidovirales, in: Regenmortel, M.H.V.v., Fauquet, C.M., Bishop, D.H.L., Carsten, E.B., Estes, M.K.,

Lemon, S.M., McGeoch, D.J., Maniloff, J., Mayo, M.A., Pringle, C.R., Wickner, R.B. (Eds.), Virus taxonomy. Classification and nomenclature of viruses Academic Press, New York, N.Y., pp. 827–834.

[51] Fang, S.G., Shen, S., Tay, F.P., Liu, D.X., 2005. Selection of and recombination between minor variants lead to the adaptation of an avian coronavirus to primate cells. Biochemical and Biophysical Research Communications 336, 417-423.

[52] Fazakerley, J.K., Parker, S.E., Bloom, F., Buchmeier, M.J., 1992. The V5A13.1 envelope glycoprotein deletion mutant of mouse hepatitis virus type-4 is neuroattenuated by its reduced rate of spread in the central nervous system. Virology 187, 178-188.

[53] Gallardo, R.A., van Santen, V.L., Toro, H., 2010. Host intraspatial selection of infectious bronchitis virus populations. Avian Diseases 54, 807-813.

[54] Ganapathy, K., Cargill, P.W., Jones, R.C., 2005. A comparison of methods of inducing lachrymation and tear collection in chickens for detection of virus specific immunoglobulins after infection with infectious bronchitis virus. Avian Pathology 34, 248-251.

[55] Gelb, J., Jr., Keeler, C.L., Jr., Nix, W.A., Rosenberger, J.K., Cloud, S.S., 1997. Antigenic and S-1 genomic characterization of the Delaware variant serotype of infectious bronchitis virus. Avian Diseases 41, 661-669.

[56] Gelb, J., Jr., Nix, W.A., Gellman, S.D., 1998. Infectious bronchitis virus antibodies in tears and their relationship to immunity. Avian Diseases 42, 364-374.

[57] Gillette, K.G., 1981. Local antibody responses to avian infectious bronchitis: virus neutralising antibody in tracheobronchial secretions. Avian Diseases 25, 431-443.

[58] Gomez, L., Raggi, L., 1974. Local immunity to avian infectious bronchitis in tracheal organ culture. . Avian Diseases, 346-368.

[59] Hanada, K., Suzuki, Y., Gojobori, T., 2004. A large variation in the rates of synonymous substitution for RNA viruses and its relationship to a diversity of viral infection and transmission modes. Molecular Biology and Evolution 21, 1074-1080.

[60] Hawkes, R.A., Darbyshire, J.H., Peters, R.W., Mockett, A.P.A., Cavanagh, D., 1983. Presence of viral antigens and antibody in the trachea of chickens infected with avian infectious bronchitis virus. Avian Pathology 12 331-340.

[61] Hein, R.G., Slacum, G., Lynch, P., 1998. In-vivo characterization of recent infectious bronchitis virus (IBV) variants isolated from broilers in the USA., in: Kaleta, E.F., Heffels-Redmann, U. (Eds.), International Symposium on Infectious Bronchitis and Pneumovirus infections in Poultry., Rauischholzhausen, Germany., pp. 220-225.

[62] Hesselink, W.G., 1991. Serotyping avian infectious bronchitis virus: selection of a unified method. , in: Kaleta, E.F., Heffels-Redmann, U. (Eds.), Proceedings of the II International Symposium on Infectious Bronchitis Rauischholzhausen, Germany., pp. 87-97.

[63] Hingley, S.T., Gombold, J.L., Lavi, E., Weiss, S.R., 1994. MHV-A59 fusion mutants are attenuated and display altered hepatotropism. Virology 200, 1-10.

[64] Hodgson, T., Casais, R., Dove, B., Britton, P., Cavanagh, D., 2004. Recombinant infectious bronchitis coronavirus Beaudette with the spike protein gene of the pathogenic M41 strain remains attenuated but induces protective immunity. Journal of virology 78, 13804 - 13811.

[65] Holmes, E.C., 2009. The Evolution and Emergence of RNA Viruses. , first ed. ed. Oxford University Press Inc., New York.

[66] Hopkins, S.R., 1974. Serological comparisons of strains of infectious bronchitis virus using plaque-purified isolants. Avian Diseases 18, 231-239.

[67] Ivanov, K.A., Hertzig., T., Rozanov., M., Bayer., S., Thiel., V., Gorbalenya., A.E., Ziebuhr., J., 2004a. Major genetic marker of nidoviruses encodes a replicative endoribonuclease. Proc. . PNAS of U.S.A. 101, 12694–12699.

[68] Ivanov, K.A., Thiel, V., Dobbe, J.C., van der Meer, Y., Snijder, E.J., Ziebuhr, V.J., 2004b. Multiple enzymatic activities associated with severe acute respiratory syndrome coronavirus helicase. . Journal of virology 78, 5619–5632.

[69] Ivanov, K.A., Ziebuhr, J., 2004. Human coronavirus 229E nonstructural protein 13: characterization of duplex-unwinding, nucleoside triphosphatase, and RNA 5-triphosphatase activities. . Journal of virology 78, 7833–7838.

[70] Jackwood, M., 2012. Review of Infectious bronchitis virus around the world. Avian Diseases 56, 634-641.

[71] Jackwood, M.W., Boynton, T.O., Hilt, D.A., McKinley, E.T., Kissinger, J.C., Paterson, A.H., Robertson, J., Lemke, C., McCall, A.W., Williams, S.M., Jackwood, J.W., Byrd, L.A., 2010. Emergence of a group 3 coronavirus through recombination. Virology 398, 98-108.

[72] Jackwood, M.W., Hall, D., Handel, A., 2012. Molecular evolution and emergence of avian gammacoronaviruses. Infection, Genetics and Evolution 12, 1305-1311.

[73] Jackwood, M.W., Hilt, D.A., Lee, C.W., Kwon, H.M., Callison, S.A., Moore, K.M., Moscoso, H., Sellers, H., Thayer, S., 2005. Data from 11 years of molecular typing infectious bronchitis virus field isolates. Avian Diseases 49, 614-618.

[74] Jackwood, M.W., Hilt, D.A., McCall, A.W., Polizzi, C.N., McKinley, E.T., Williams, S.M., 2009. Infectious bronchitis virus field vaccination coverage and persistence of Arkansas-type viruses in commercial broilers. Avian Diseases 53, 175-183.

[75] Jia, W., Karaca, K., Parrish, C.R., Naqi, S.A., 1995. A novel variant of avian infectious bronchitis virus resulting from recombination among three different strains. Archives of Virology 140, 259-271.

[76] Johnson, M.A., Pooley, C., Ignjatovic, J., Tyack, S.G., 2003. A recombinant fowl adenovirus expressing the S1 gene of infectious bronchitis virus protects against challenge with infectious bronchitis virus. Vaccine 21, 2730-2736.

[77] Johnson, R.B., Marquardt, W.W., 1975. The neutralizing characteristics of strains of infectious bronchitis virus as measured by constant virus variable serum method in chicken tracheal cultures. Avian Diseases 19, 82-90.

[78] Jungherr, E.I., Chomiak, T.W., Luginbuhl, R.E., 1956. Immunologic differences in strains of infectious bronchitis virus. In: Proceedings 60th Annual Meeting U.S. Livestock Sanitary Association, 203-209.

[79] Jungherr, E.L., Terrel, N.L., 1948. Naturally acquired passive immunity to infectious bronchitis in chicks. . American Journal of Veterinary Research 9, 201-205.

[80] Kant, A., Koch, G., van Roozelaar, D.J., Kusters, J.G., Poelwijk, F.A., van der Zeijst, B.A., 1992. Location of antigenic sites defined by neutralizing monoclonal antibodies on the S1 avian infectious bronchitis virus glycopolypeptide. Journal of General Virology 73, 591-596.

[81] Keeler, C.L., Jr., Reed, K.L., Nix, W.A., Gelb, J., Jr., 1998. Serotype identification of avian infectious bronchitis virus by RT-PCR of the peplomer (S-1) gene. Avian Diseases 42, 275-284.

[82] Klieve, A.V., Cumming, R.B., 1988. Infectious bronchitis: Safety and protection in chickens with maternal antibody. Australian Veterinary Journal 65, 396-397.

[83] Koch, G., Hartog, L., Kant, A., van Roozelaar, D.J., 1990. Antigenic domains on the peplomer protein of avian infectious bronchitis virus: Correlation with biological functions. Journal of General Virology 71, 1929-1935.

[84] Kusters, J.G., Jager, E.J., Lenstra, J.A., Koch, G., Posthumus, W.P., Meloen, R.H., van der Zeijst, B.A., 1989a. Analysis of an immunodominant region of infectious bronchitis virus. Journal of Immunology 143, 2692-2698.

[85] Kusters, J.G., Jager, E.J., Niesters, H.G., van der Zeijst, B.A., 1990. Sequence evidence for RNA recombination in field isolates of avian coronavirus infectious bronchitis virus. Vaccine 8, 605-608.

[86] Kusters, J.G., Niesters, H.G., Bleumink-Pluym, N.M., Davelaar, F.G., Horzinek, M.C., van der Zeijst, B.A., 1987. Molecular epidemiology of infectious bronchitis virus in The Netherlands. Journal of General Virology 68, 343-352.

[87] Kusters, J.G., Niesters, H.G.M., Lenstra, J.A., Horzinek, M.C., van der Zeijst, B.A.M., 1989b. Phylogeny of antigenic variants of avian coronavirus IBV. Virology 169, 217-221.

[88] Kwon, H.M., Jackwood, M.W., Gelb, J., Jr., 1993. Differentiation of infectious bronchitis virus serotypes using polymerase chain reaction and restriction fragment length polymorphism analysis. Avian Diseases 37, 194-202.

[89] Ladman, B.S., Loupos, A.B., Gelb, J.J., 2006. Infectious bronchitis virus S1 gene sequence comparison is a better predictor of challenge of immunity in chickens than serotyping by virus neutralization. . Avian Pathology 35, 127-133.

[90] Lai, M.M.C., 1992. RNA Recombination in Animal and Plant Viruses. Microbiological Reviews 56, 61-79.

[91] Lai, M.M.C., Cavanagh, D., 1997. The molecular biology of coronaviruses. Advances in Virus Research 48, 1-100.

[92] Lai, M.M.C., Holmes, K.V., 2001. Coronaviridae: The viruses and their replication, in: Knipe, D.M., Howley, P.M. (Eds.), Fundamental Virology, 4th ed. Lippincott Williams & Wilkins, Philadelphia, pp. 641-663.

[93] Lashgari, M.S., Newman, J.A., 1984. Serological comparison and antigenetic relationships of seven serotypes of infectious bronchitis virus using the haemagglutination-inhibition test

[94] Avian Diseases 28 435- 443.

[95] Lee, C.W., Hilt, D.A., Jackwood, M.W., 2001. Identification and analysis of the Georgia 98 serotype, a new serotype of infectious bronchitis virus. Avian Diseases 45, 164-172.

[96] Lee, C.W., Jackwood, M.W., 2000. Evidence of genetic diversity generated by recombination among avian coronavirus IBV. Archives of virology. 145, 2135-2148.

[97] Lenstra, J.A., Kusters, J.G., Koch, G., van der Zeijst, B.A., 1989. Antigenicity of the peplomer

protein of infectious bronchitis virus. Molecular Immunology 26, 7-16.

[98] Leparc-Goffart, I., Hingley, S.T., Chua, M.M., Phillips, J., Lavi, E., Weiss, S.R., 1998. Targeted recombination within the spike gene of murine coronavirus mouse hepatitis virus-A59: Q159 is a determinant of hepatotropism. Journal of virology 72, 9628-9636.

[99] Li, W., Zhang, C., Sui, J., Kuhn, J.H., Moore, M.J., Luo, S., Wong, S.K., Huang, I.C., Xu, K., Vasilieva, N., Murakami, A., He, Y., Marasco, W.A., Guan, Y., Choe, H., Farzan, M., 2005. Receptor and viral determinants of SARS-coronavirus adaptation to human ACE2. EMBO 24, 1634-1643.

[100] Lin, Z., Kato, A., Kudou, Y., Ueda, S., 1991. A new typing method for the avian infectious bronchitis virus using polymerase chain reaction and restriction enzyme fragment length polymorphism. Archives of Virology 116 19-31.

[101] Liu, G., Wang, Q., Liu, N., Xiao, Y., Tong, T., Liu, S., Wu, D., 2012. Infectious bronchitis virus nucleoprotein specific CTL response is generated prior to serum IgG. Veterinary Immunology and Immunopathology 148, 353-358.

[102] Masters, P.S., 2006. The molecular biology of coronaviruses. Advances in Virus Research 66, 193-292.

[103] McKinley, E.T., Hilt, D.A., Jackwood, M.W., 2008. Avian coronavirus infectious bronchitis attenuated live vaccines undergo selection of subpopulations and mutations following vaccination. Vaccine 26, 1274-1284.

[104] Minskaia, E., 2006. Discovery of an RNA virus 3'->5' exoribonuclease that is critically involved in coronavirus RNA synthesis. Proceedings of the National Academy of Sciences 103, 5108-5113.

[105] Mockett, A., Cook, J., Huggins, M.B., 1987. Maternally-derived antibody to infectious bronchitis virus: Its detection in chicken trachea and serum and its role in protection. Avian Pathology 16, 407-416.

[106] Mockett, A.P., Cavanagh, D., Brown, T.D., 1984. Monoclonal antibodies to the S1 spike and membrane proteins of avian infectious bronchitis coronavirus strain Massachusetts M41. Journal of General Virology 65, 2281-2286.

[107] Mockett, A.P., Darbyshire, J.H., 1981. Comparative studies with an enzyme-linked immunosorbent assay (ELISA) for antibodies to avian infectious bronchitis virus. Avian Pathology 10, 1-10.

[108] Mockett, A.P.A., Cook, J.K.A., 1986. The detection of specific IgM to infectious bronchitis virus in chicken serum using an ELISA. Avian Pathology 15, 437-446.

[109] Mondal, S.P., Naqi, S.A., 2001. Maternal antibody to infectious bronchitis virus: Its role in protection against infection and development of active immunity to vaccine. Veterinary Immunology and Immunopathology 79, 31-40.

[110] Ndegwa, E.N., Joiner, K.S., Toro, H., van Ginkel, F.W., van Santen, V.L., 2012. The proportion of specific viral subpopulations in attenuated ArkDPI infectious bronchitis vaccines influences vaccination outcome. Avian Diseases 56, 642-653.

[111] Nix, W.A., Troeber, D.S., Kingham, B.F., Keeler, C.L., Jr., Gelb, J., Jr., 2000. Emergence of subtype strains of the Arkansas serotype of infectious bronchitis virus in Delmarva broiler chickens. Avian Diseases 44, 568-581.

[112] Ontiveros, E., Kim, T.S., Gallagher, T.M., Perlman, S., 2003. Enhanced virulence mediated by the murine coronavirus, mouse hepatitis virus strain JHM, is associated with a glycine at residue 310 of the spike glycoprotein. Journal of virology 77, 10260-10269.

[113] Orr-Burks, N., Gulley, S.L., Toro, H., van Ginkel, F.W., 2014. Immunoglobulin A as an Early Humoral Responder After Mucosal Avian Coronavirus Vaccination. Avian Diseases 58, 279-286.

[114] Pei, J., Briles, W.E., Collisson, E.W., 2003. Memory T cells protect chicks from acute infectious bronchitis virus infection. Virology 306, 376-384.

[115] Phillips, J.J., Chua, M.M., Rall, G.F., Weiss, S.R., 2002. Murine coronavirus spike glycoprotein mediates degree of viral spread, inflammation, and virus-induced immunopathology in the central nervous system. Virology 301, 109-120.

[116] Raggi, L., Lee, G., 1965. Lack of correlation between infectivity, serologic response and challenge results in immunization with an avian infectious bronchitis vaccine. Journal of Immunology 94, 538-543.

[117] Raj, G.D., Jones, R., 1996. Local antibody production in the oviduct and gut of hens infected with a variant strain of infectious bronchitis virus. . Veterinary Immunology and Immunopathology 53, 147-161.

[118] Ricagno, S., Egloff, M.P., Ulferts, R., Coutard, B., Nurizzo, D., Campanacci, V., Cambillau, C., Ziebuhr, J., Canard, B., 2006. Crystal structure and mechanistic determinants of SARS coronavirus nonstructural protein 15 define an endoribonuclease family. Proc. . PNAS U.S.A. 103, 11892–11897.

[119] Seo, H.S., Collisson, E.W., 1997. Specific cytotoxic T lymphocytes are involved in in vivo

clearance of infectious bronchitis virus. Journal of virology 71, 5173-5177.

[120]Seo, S.H., Collisson, E.W., 1998. Cytotoxic T lymphocyte response to infectious bronchitis virus infection. . Advances in Experimental Medicine and Biology 440, 455-460.

[121]Seo, S.H., Pei, J., Briles, W.E., Dzielawa, J., Collisson, E.W., 2000. Adoptive transfer of infectious bronchitis virus primed alphabeta T cells bearing CD8 antigen protects chicks from acute infection. Virology 269, 183-189.

[122]Seo, S.H., Wang, L., Smith, R., Collisson, E.W., 1997. The carboxyl-terminal 120-residue polypeptide of infectious bronchitis virus nucleocapsid induces cytotoxic T lymphocytes and protects chickens from acute infection. Journal of virology 71, 7889-7894.

[123]Sharma, J.M., 2008. Host Factors for Disease Resistance., in: Y. M. Saif, A. M. Fadly, J. R. Glisson, L. R. McDougald, L. K. Nolan, D.E. Swayne, J.R.G., M.W. Jackwood, J.E. Pearson, W.M. Reed (Eds.), Diseases of Poultry, 12th ed. Blackwell Publishing, Ames, Iowa, pp. 47-72.

[124]Snijder, E.J., Bredenbeek, P.J., Dobbe, J.C., Thiel, V., Ziebuhr, J., Poon, L.L., Guan, Y., Rozanov, M., Spaan, W.J., Gorbalenya, A.E., 2003. Unique and conserved features of genome and proteome of SARS-coronavirus, an early split-off from the coronavirus group 2 lineage. . Journal of Molecular Biology 331, 991-1004.

[125]Song, C.-S., Lee, Y.-J., Kim, J.-H., Sung, H.-W., Lee, C.W., Izumiya, Y., Miyazawa, T., Jang, H.-K., Mikami, T., 1998a. Epidemiological classification of infectious bronchitis virus isolated in Korea between 1986 and 1997. Avian Pathology 27, 409- 416.

[126]Song, C.S., Lee, Y.J., Lee, C.W., Sung, H.W., Kim, J.H., Mo, I.P., Izumiya, Y., Jang, H.K., Mikami, T., 1998b. Induction of protective immunity in chickens vaccinated with infectious bronchitis virus S1 glycoprotein expressed by a recombinant baculovirus. . Journal of General Virology 79, 719-723.

[127]Toro, H., Fernandez, I., 1994. Avian infectious bronchitis: specific lachrymal IgA level and resistance against challenge. Journal of veterinary medicine. Series B. 41, 467-472.

[128]Toro, H., Hidalgo, H., Collingwood-Selby, A.N., 1994. Lachrymal antibody response of specific pathogen free chickens and chickens with maternal immunity after infectious bronchitis virus vaccination. Preventive Veterinary Medicine 18, 267-274.

[129]Toro, H., Jackwood, J.W., van Santen, V.L., 2012. Genetic diversity and selection regulates evolution of infectious bronchitis virus Avian Diseases 56, 449-455.

[130]Toro, H., Zhang, J.F., Gallardo, R.A., van Santen, V.L., van Ginkel, F.W., Joiner, K.S., Breedlove, C., 2014. S1 of Distinct IBV Population Expressed from Recombinant Adenovirus Confers Protection Against Challenge. Avian Diseases 58, 211-215.

[131]van Ginkel, F.W., van Santen, V.L., Gulley, S.L., Toro, H., 2008. Infectious bronchitis virus in the chicken Harderian gland and lachrymal fluid: viral load, infectivity, immune cell responses, and effects of viral immunodeficiency. Avian Diseases 52, 608-617.

[132]van Hemert, M.J., van den Worm, S.H., Knoops, K., Mommaas, A.M., Gorbalenya, A.E., Snijder, E.J., 2008. SARS-Coronavirus Replication/Transcription Complexes Are Membrane-Protected and Need a Host Factor for Activity In Vitro. . PLoS Pathogens 4(5) e1000054.

[133]van Santen, V.L., Toro, H., 2008. Rapid selection in chickens of subpopulations within ArkDPI-derived infectious bronchitis virus vaccines. Avian Pathology 37, 293-306.

[134]Wadey, C.N., Faragher, J.T., 1981. Australian infectious bronchitis viruses: identification of nine subtypes by a neutralisation test. Research in Veterinary Science 30, 70-74.

[135]Wang, G., Chen, G., Zheng, D., Cheng, G., Tang, H., 2011. PLP2 of mouse hepatitis virus A59 (MHV-A59) targets TBK1 to negatively regulate cellular type I interferon signaling pathway. . PloS one 6(2), e17192.

[136]Wang, L., Byrum, B., Zhang, Y., 2014. Detection and genetic characterization of deltacoronavirus in pigs, Ohio, USA, 2014. Emerging infectious diseases 20, 1227-1230.

[137]Wesley, R.D., Woods, R.D., Cheung, A.K., 1991. Genetic analysis of porcine respiratory coronavirus, an attenuated variant of transmissible gastroenteritis virus. Journal of virology 65, 3369-3373.

[138]Williams, A.K., Wang, L., Sneed, L.W., Collisson, E.W., 1992. Comparative analyses of the nucleocapsid genes of several strains of infectious bronchitis virus and other coronaviruses. Virus research 25, 213-222.

[139]Woo, P.C., Huang, Y., Lau, S.K., Yuen, K.Y., 2010. Coronavirus genomics and bioinformatics analysis. Viruses 2, 1804-1820.

[140]World Organisation for Animal Health, 2013. OIE Terrestrial Manual 2013, 7th ed.

[141]Yachida, S., Aoyama, S., Sawaguchi, K., Takahashi, N., Iritani, Y., Hayashi, Y., 1985. Relationship between several criteria of challenge-immunity and humoral immunity in chickens vaccinated with avian infectious bronchitis vaccines. Avian Pathology 14, 199-211.

[142] Yachida, S., Sugimori, G., Aoyama, S., Takahashi, N., Iritani, Y., Katagiri, K., 1981. Effectiveness of maternal antibody against challenge with infectious bronchitis viruses. Avian Diseases 25, 736-741.

[143] Zheng, D., Chen, G., Guo, B., Cheng, G., Tang, H., 2008. PLP2, a potent deubiquitinase from murine hepatitis virus, strongly inhibits cellular type I interferon production. . Cell Research 18, 1105-1113.

[144] Ziebuhr, J., 2005. The coronavirus replicase. . Current Topics in Microbiology and Immunology 287, 57–94.

[145] Ziebuhr, J., 2004. Molecular biology of severe acute respiratory syndrome coronavirus. Current Opinion in Microbiology 7, 412- 419.

[146] Ziebuhr, V.J., Thiel, A.E., Gorbalenya, J., 2001. The autocatalytic release of a putative RNA virus transcription factor from its polyprotein precursor involves two paralogous papain-like proteases that cleave the same peptide bond. . Biological Chemistry 276, 33220–33232.