Coronaviridae: Infectious Bronchitis Virus

5

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5.1 History

Infectious bronchitis was first reported in 1931 who had observed the disease in North Dakota in the spring of 1930 (Schalk and Hawn 1931), and in 1936, the virus etiology was established (Beach and Schalm 1936). Initially, IBV was recognized as primarily a disease of young chickens; however it was later recorded to be common in semi-mature and laying flocks. Other manifestations of IBV include decline in egg production in laying flocks noted following the typical respiratory disease in the 1940s, kidney lesions observed in the 1960s (Cavanagh and Gelb 2008), enteric lesions observed in 1985, and more recently proventriculus affection in 1998.

5.2 Classification

IBV is a large, enveloped, positive-stranded RNA gammacoronavirus that is related to the family *Coronaviridae*, subfamily *Coronavirinae*, and within the order *Nidovirales* (Table 5.1). The coronaviruses possess the largest RNA genome of all RNA viruses and replicate by a unique mechanism associated with a multiple subgenomic nested set of mRNAs and high frequency of recombination. The subfamily *Coronavirinae* contains four distinct genera: *Alphacoronavirus*, *Betacoronavirus*, *Deltacoronavirus*, and *Gammacoronavirus*. To date, viruses of *Alphacoronavirus* and *Betacoronavirus* have been isolated from mammals, while deltacoronaviruses have been isolated from birds and pigs (Table 5.1) (Woo et al. 2012). Meanwhile, gammacoronaviruses are

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Table 5.1 Taxonomy of coronaviruses

Order: *Nidovirales* Family: *Coronaviridae* Subfamily: *Coronavirinae*	
Genus: *Alphacoronavirus*	*Alphacoronavirus* 1a Canine coronavirus (CCoV) Feline coronavirus (FCoV)
	Alphacoronavirus 1b Human coronavirus 229E (HCoV-229E) Human coronavirus NL63 (HCoV-NL63)
Genus: *Betacoronavirus*	*Betacoronavirus* A Human coronavirus OC43 (HCoV-OC43) Human coronavirus HKU1 (HCoV-HKU1) Bovine coronavirus (BCoV) Murine hepatitis coronavirus (MHV) Canine respiratory coronavirus Dromedary camel coronavirus HKU23 Equine coronavirus Porcine hemagglutinating encephalomyelitis virus
	Betacoronavirus B Severe acute respiratory syndrome (SARS)-related coronavirus
	Betacoronavirus C Pipistrellus bat coronavirus HKU5 Tylonycteris bat coronavirus HKU4 Middle East Respiratory Syndrome (MERS-CoV) *Betacoronavirus* D Rousettus bat coronavirus HKU9 (BtCoV-HKU9)
Genus: *Deltacoronavirus*	Munia coronavirus HKU13 Porcine coronavirus HKU15 Sparrow coronavirus HKU17
Genus: *Gammacoronavirus*	Infectious bronchitis virus (IBV) Turkey coronavirus (TCoV) Duck coronavirus Goose coronavirus Pigeon coronavirus Pheasant coronavirus Beluga whale coronavirus SW1

found in birds, except for the coronaviruses detected in beluga whale and bottlenose dolphin (Mihindukulasuriya et al. 2008; Woo et al. 2010).

5.3 Morphology and Structure

The virus possesses a round structure that is often 100 to 160 nm in diameter and with long, petal-shaped spikes on the virus surface (Gonzalez et al. 2003). Inside the virion is a single-stranded, positive-sense linear RNA genome. The helical nucleocapsid, unusual for positive-stranded RNA animal viruses, is enclosed by a lipoprotein envelope that contains long petal-shaped spike glycoprotein (S); an integral membrane glycoprotein (M) which spans the lipid bilayer three times; and an

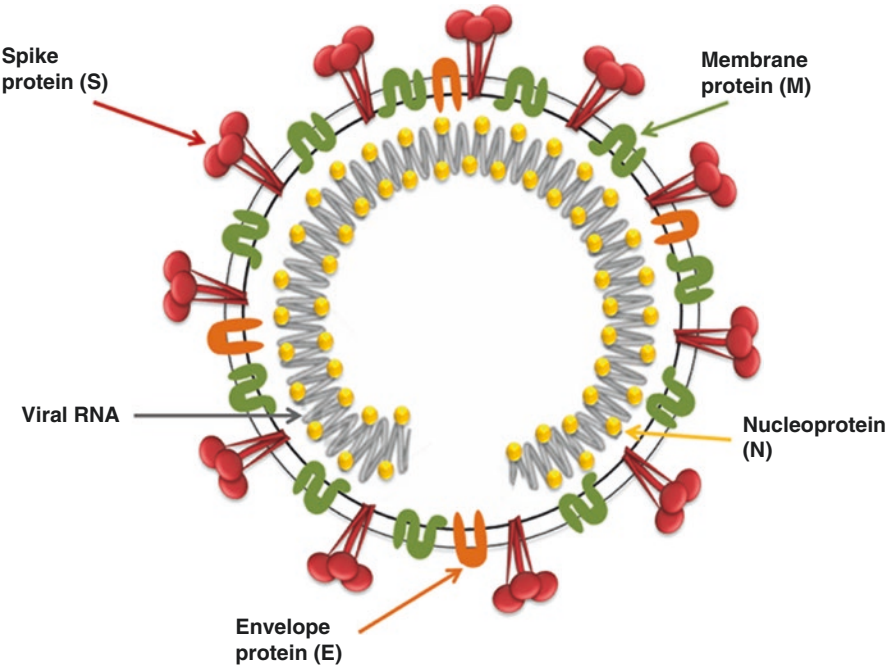

Fig. 5.1 Schematic diagram of the infectious bronchitis virus

envelope or small membrane (E) protein which is present in much smaller amounts than the other viral envelope proteins (Fig. 5.1).

5.4 Genome

IBV genome is a single-stranded, positive-sense linear genome with a cap at the 5′ end and poly(A) tail at the 3′ end (Boursnell et al. 1987). The viral genome is 27,620–27,661 nucleotides (nts) in length excluding the polyadenylated tail. At the 5′ end of the genome, there is a leader sequence (64 nt), which is followed by 5′ untranslated region (5′-UTR) of 528 nts (Ammayappan et al. 2008; Zhang et al. 2010; Abro et al. 2012). At the 3′ end of the RNA genome, there is 507–528 nts UTR, followed by a poly(A) sequence of variable length. At least ten open reading frames (ORFs) were detected (Zhang et al. 2010; Ammayappan et al. 2008): ORF1ab nonstructural protein (nsp) (529–20,360), ORF2 spike S glycoprotein (20,311–23,820, 3489 nts and 1162 amino acids [aa]), ORF3abc [3a, (23,820–23,993, 174 nts, 57 aa), 3b (23,993–24,187, 195 nts, 64aa), 3c small envelope protein (E) (24,168–24,491, 330 nts, 109 aa), ORF4, membrane glycoprotein (M) (24,469–25,140, 678 nts; 225 aa), ORF5ab [5a 198 nts (25,500–25,697), 5b 294 nts (25,694–25,942)], and ORF6 nucleoprotein N (25,885–27,114, 1230 nt, 409 aa). The genome organization of classical IBV is 5'UTR-ORF1a-ORF1b-S-3a-3b-E-M-5a-5b-N- UTR 3′ (Fig. 5.2); however, different genetic organizations were recorded 5′ UTR-Pol-S-X1-E-M-N-UTR-3′ or 5′ UTR -Pol-S-X1-E-M-5b-N-UTR3′ (Mardani et al. 2008).

Fig. 5.2 Schematic diagram of IBV genome organization

5.5 Structural Proteins

5.5.1 Spike Protein

The spike protein is petal-shaped protrusions of about 20 nm in length that emerge from the virion envelope. A cleaved N-terminal signal peptide (Binns et al. 1985) directs the S protein toward the endoplasmic reticulum (ER) where it undergoes terminal N-linked glycosylation (Cavanagh 1983a, b). After glycosylation, the monomers oligomerize to form dimers or trimers (Cavanagh 1983a, b; Delmas and Laude 1990; Lewicki and Gallagher 2002). The S protein of IBV is cleaved by a furin-like host cell protease at the highly basic motif RRFRR generating S1 (90 kDa) and S2 (84 kDa) subunits of about 500 and 600 amino acids in size, respectively (Cavanagh 1983a, b). The N-terminal part of S1 forms an ectodomain, while the C-terminal S2 subunit comprises a narrow stalk ectodomain, short transmembrane, and endodomain. All the receptor-binding domains (RBD) of IBV are located in S1 domain (Masters and Perlman 2013; Promkuntod et al. 2014). After endocytosis, conformational changes in the S protein are triggered by exposure to acidic pH in endosomes (Chu et al. 2006), resulting in fusion of the viral envelope with the cellular membrane. The nucleotide sequence of the S1 subunit is used for genotyping IBV isolates (OIE 2013). S protein contains epitopes for neutralization (Cavanagh 1983a, b; Kant et al. 1992; Koch et al. 1990; Mockett et al. 1984; Niesters et al. 1987b). In the S1 subunit, three hypervariable regions (HVRs) are located within amino acids 38–67, 91–141, and 274–387 (Kant et al. 1992; Koch et al. 1991). Neutralizing-serotype-specific epitopes are associated within the defined serotypes (Cavanagh et al. 1988; Niesters et al. 1987a; Jia et al. 1996). N38S, H43Q, P63S, and T69I amino acid substitutions lead to loss of the ability of M41 strain to bind to the trachea (Promkuntod et al. 2014).

5.5.2 Matrix Protein

Small domain of the M glycoprotein (25–33 kDa) is exposed to the exterior of the viral envelope. There is a triple membrane and a large carboxyl-terminal domain inside the viral envelope (Lai and Cavanagh 1997). M protein is glycosylated by N linkage (Lai and Cavanagh 1997). The M proteins are targeted to the pre-Golgi region. The M protein plays a key role in virus assembly and interacts with both N and S proteins (Kuo and Masters 2002; de Haan et al. 2002). The M protein may also be critical for packaging viral RNA into nucleocapsids, by specifically interacting with the viral RNA packaging signal (Narayanan et al. 2003).

5.5.3 Nucleocapsid Protein

The N protein is a phosphoprotein of 50 to 60 kDa that binds to the genomic RNA to form a helical ribonucleoprotein complex (Jayaram et al. 2005). The N protein interacts with M, leading to the incorporation of nucleocapsid into virus particles (Kuo and Masters 2002). It plays a role in the induction of cytotoxic T lymphocytes (Seo et al. 1997; Collisson et al. 2000). In addition, novel linear B-cell epitope peptides were found in N-terminal domain of N protein (Yu et al. 2010).

5.5.4 Envelope Protein

It is 9 to 12 kDa protein associated with the viral envelope (Godet et al. 1992). The E protein transverses the lipid bilayer twice, with both termini of the protein present in the virus lumen (Maeda et al. 2001). Both the M and E proteins are required for budding from infected cells (Vennema et al. 1996). The expression of E alone is sufficient for vesicle release from transfected cells (Maeda et al. 1999). This protein is associated with viral envelope formation, assembly, budding, ion channel activity, and apoptosis (Corse and Machamer 2003; Wilson et al. 2006).

5.6 IBV Genotypes

It is suggested that the emergence of IBV appears to be a regular influx, and up to date, more than 65 different types do exist worldwide (Table 5.2). Different serotypes generally have large differences (20–50 %) in the deduced amino acid sequences of the S1 subunit (Kusters et al. 1989). IBV serotypes that share more than 95 % amino acid identity in S1 should have cross protection, whereas IBV strains of other serotypes share less than 85 % amino acid identity did not cross protect each other (Cavanagh and Gelb 2008). Poor cross protection was found in viruses that are clearly distinguishable in only 2–3% differences in amino acid sequences (Cavanagh 1991; Abdel-Moneim et al. 2006). This diversity in S1 probably results from mutation, recombination, and strong positive selection in vivo (Cavanagh et al. 1988, 1990). The widespread use of live attenuated vaccine strains and the subsequent selective pressure induced by neutralizing antibodies against the spike may force the adaptation of the virus to escape immunity and hence result in faster evolutionary rates (Jackwood 2012). Error prone during replication is not expected to constitute a major role in the evolution of IBV, since RdRp possesses exoribonuclease (ExoN) activity that provides some proofreading errors during coronavirus replication (Minskaia et al. 2006). During the replication of the IBV, both full genomic minus-strand template and the subgenomic minus-strand templates are generated by continuous and discontinuous unique mechanisms, respectively; the latter allows recombination between RNA viruses (Sawicki and Sawicki 1995). Although recombination was found throughout the whole IBV genome, hot spots of recombination have been found in the upstream of S glycoprotein gene in

Table 5.2 IBV genotypes in different countries

Mass	Worldwide
IBV types distributed worldwide or in multiple countries	
793B(CR88/ 4-91vaccine) (Cavanagh et al. 2005)	UK (Gough et al. 1992)/Brazil (De Wit et al. 2015)/France (Cavanagh et al. 2005)/India (Sumi et al. 2012)/Egypt (Sultan et al. 2004)/Israel (Gelb Jr et al. 2005)/India (Elankumaran et al. 1999)/Spain (Worthington et al. 2008)/Ukrania (Ovchinnikova et al. 2011)/Nigeria (Ducatez et al. 2009)/ Mexico (Jackwood et al. 2005; Cook et al. 1996)/Thailand (Promkuntod et al. 2015)/China (Han et al. 2011)/Japan (Ariyoshi et al. 2010)/Thailand (Cook et al. 1996)/Canada (Martin et al. 2014)/Russia (Bochkov et al. 2006)/Morocco (Fellahi et al. 2015)
China-type I (LX4-type)/QX	China (Han et al. 2011)/Russia (Bochkov et al. 2006)/Europe (Worthington et al. 2008)/Korea(K-II) (Lim et al. 2012)/Japan (Ariyoshi et al. 2010)/South Africa (Sigrist et al. 2012) (Knoetze et al. 2014)/Thailand (Promkuntod et al. 2015)
China-type IV(LDL/Q1)	China (Han et al. 2011)/Taiwan (Chen et al. 2009)/Colombia (Jackwood 2012)/Chile (Jackwood 2012)/Italy (Toffan et al. 2013a)/Canada (Martin et al. 2014)/Saudi Arabia (Ababneh et al. 2012), Jordan (Ababneh et al. 2012), Iraq (Ababneh et al. 2012)
D207 (D274)	Europe (Davelaar et al. 1984; Worthington et al. 2008)/ Nigeria (Ducatez et al. 2009)/Egypt (Madbouly et al. 2002)/ Russia (Bochkov et al. 2006)
Arkansas [Gray/JMK]	Kazakhstan (Ovchinnikova et al. 2011)/Mexico (Quiroz et al. 1993)/Japan (Ariyoshi et al. 2010)/Brazil (De Wit et al. 2015)
USA/Connecticut	USA/Canada (Martin et al. 2014)/Mexico (Jackwood et al. 2005)/Argentina (Rimondi et al. 2009)/Colombia (Alvarado et al. 2005)
Italy-02	Europe (Jones et al. 2005)/Morocco (Fellahi et al. 2015)/ Ukraine148]/Slovania (Ovchinnikova et al. 2011) Russia (Bochkov et al. 2006)
Eg-Var-I/IS-Var II	Egypt (Abdel-Moneim et al. 2002;Abdel-Moneim et al. 2012)/Israel (Gelb Jr et al. 2005)/Turkey[HM802259.1]/Iraq (Mahmood et al. 2011)/Libya (Awad et al. 2014)/Oman (Al-Shekaili et al. 2015)
Eg-Var-II	Egypt (Abdel-Moneim et al. 2012)/Libya (Awad et al. 2014)/ Oman (Al-Shekaili et al. 2015)
B1648	Russia (Bochkov et al. 2006)/Belgium (Reddy et al. 2015)/ Nigeria (Ducatez et al. 2009)/Cuba (Acevedo et al. 2013)
Australia/Group I (Vic.S, N1/62, N3/62, N9/74)	Australia (Ignjatovic et al. 2006) New Zealand (McFarlane and Verma 2008)/China (Han et al. 2011;Jackwood 2012)
IBV types restricted to certain region or country	
USA/California/CA 99 USA (Mondal and Cardona 2007)/ Canada (Martin et al. 2014)	Netherlands/D3128(Davelaar et al. 1984) Egypt (El-Kady 1989)
USA/California / CA/557/03(Jackwood et al. 2007)	Italy/624/I (Capua et al. 1994)

Table 5.2 (continued)

Mass	Worldwide
USA/California CA/1737/04 USA (Jackwood et al. 2007)/ Canada (Martin et al. 2014)/ Cuba (Acevedo et al. 2013)	Turkey/IBV/Turkey/BB012/VIR9657/2012 [C404845]
USA/Delaware 072 USA (Gelb et al. 1997)/Canada (Martin et al. 2014)	Russia/RF1(Bochkov et al. 2006)
USA/Georgia/GA98 (Lee et al. 2001)	Russia/RF1(Bochkov et al. 2006)
USA/Georgia/GA11 (Jackwood 2012)	Russia/RF2 (Bochkov et al. 2006)
USA/Georgia/GA08 (Jackwood et al. 2010b)	Russia/RF3(Bochkov et al. 2006)
USA/Georgia/GA07 (Jackwood 2012)	Russia/RF4(Bochkov et al. 2006)
USA/PA/Wolgemuth/98 USA (Ziegler et al. 2002)/Canada (Martin et al. 2014)	Russia/RF5(Bochkov et al. 2006)
USA/PA/1220/98 USA (Ziegler et al. 2002)/Canada (Martin et al. 2014)	Russia/RF6(Bochkov et al. 2006)
Canada/Qu_mv (Martin et al. 2014)	China-type II (CK/CH/LSC/99I–type) (Han et al. 2011)
Mexico/47/UNAM/01 (Jackwood 2012)	China-type III (KM-91-like)(Korea/K-II) (Han et al. 2011) (Lim et al. 2012)
Mexico/7277/99 (Gelb et al. 2001)	China/BJ (Han et al. 2011)
Mexico/07,484/98 (Callison et al. 2001)	China/CK/CH/LHLJ/95I–type (Han et al. 2011)
Mexico/UNAM-97/97 (Escorcia et al. 2000)	Japan/JP-I (Ariyoshi et al. 2010)
Mexico/2001/47/UNAM [EU526405.1]	Japan/JP-II (Ariyoshi et al. 2010)
Argentina/Clus A (Rimondi et al. 2009)	Korea/K-I (Lim et al. 2012)
Argentina/Clus B (Rimondi et al. 2009)	Korea/New cluster 1 (Lim et al. 2012)
Argentina/Clus C (Rimondi et al. 2009)	Korea/New cluster 2 (Lim et al. 2012)
Brazil/01 (De Wit et al. 2015)	Taiwan/Group I (Ma et al. 2012)
Brazil/02(De Wit et al. 2015)	Taiwan /Group II (Taiwan/China)(Ma et al. 2012)
Brazil/03(De Wit et al. 2015)	Thailand/THA001(Promkuntod et al. 2015)
Brazil/04(De Wit et al. 2015)	Malaysia/MH5365/95 (Zulperi et al. 2009)

(continued)

Table 5.2 (continued)

Mass	Worldwide
Australia Group II (N1/88, Q3/88 / V18/91) (Ignjatovic et al. 2006)	India/PDRC/Pune/Ind/1/00 (Bayry et al. 2005)
Australia/subgroup 3/ (N1/03, N4/02, N5/03, N4/03) (Ignjatovic et al. 2006)	Tunisia/TN20/00 (Bourogaa et al. 2009)
Netherlands/D212 (D1466 vaccine) (Davelaar et al. 1984)	Morocco/Moroccan type (Fellahi et al. 2015)

the nonstructural proteins 2, 3, and 16, in the E and M genes as well as the area near the 3′ UTR (Thor et al. 2011). Recombination in different genes of IBV could affect the pathogenicity and virus virulence, but recombination of the S gene may result in the emergence of new strains, new serotypes, or even new viruses infecting other hosts (Jackwood et al. 2010a). Natural intergenic and intertypic recombination occurs naturally in an extensive manner (Cavanagh et al. 1992b; Wang et al. 1993; Jia et al. 1995; Lee and Jackwood 2000; Brooks et al. 2004; Bochkov et al. 2007; Ammayappan et al. 2008; Kuo et al. 2010; Mardani et al. 2010; Pohuang et al. 2011; Ovchinnikova et al. 2011; Thor et al. 2011; Liu et al. 2013; Song et al. 2013; Zhao et al. 2013; Hewson et al. 2014; Zhang et al. 2015). Interestingly, mosaic S1-containing recombinants from three different genotypes (H120, QX, D274) were reported in Russia (Ovchinnikova et al. 2011). In addition, recombination of distant unrecognized gammacoronavirus with a known IBV strain resulted in the evolution of gammacoronavirus able to infect turkeys (Jackwood et al. 2010a).

5.7 Replication

5.7.1 Attachment

The first step in the viral replication cycle is the binding of virions to the plasma membranes of the target cells. The cell receptor for IBV has yet to be elucidated. Only α-2, 3-linked sialic acid has shown to be essential for spike attachment (Wickramasinghe et al. 2011; Winter et al. 2008; Abd El Rahman et al. 2009; Promkuntod et al. 2014). After the virus binds to a specific receptor, it enters the cell, a step that involves fusion of the viral envelope with plasma membrane.

5.7.2 Penetration and Uncoating

The binding of virus with the receptor induces a conformational change of the S protein that activates the membrane fusion activity. After virus-membrane fusion, the viral nucleocapsid is released into the cytoplasm, and the RNA is uncoated to become available for translation and transcription.

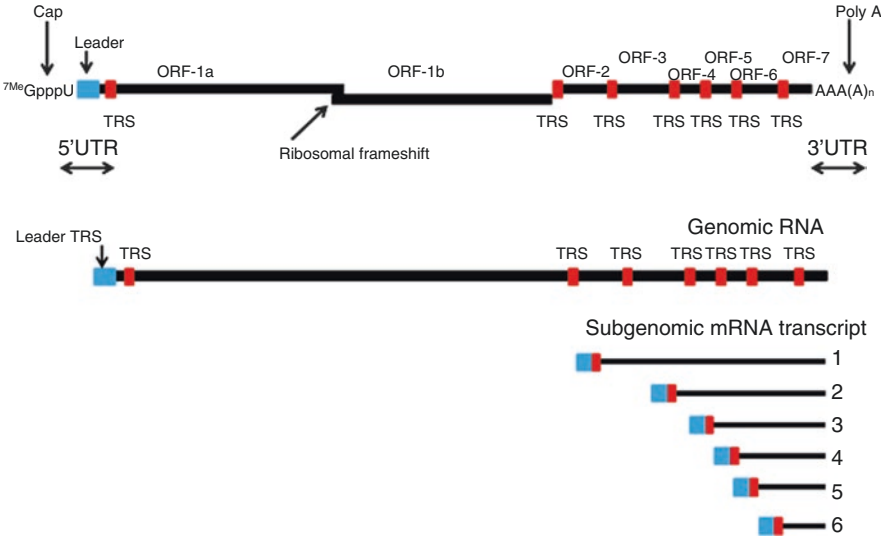

Fig. 5.3 Schematic diagram of the IBV genomic RNA and subgenomic mRNA transcripts. The nested set of seven IBV mRNAs (genome and sg mRNAs 2–6) is depicted below. The *blue box* is leader TRS, while *red boxes* indicate the position of the body TRSs

5.7.3 Transcription and Translation of Viral RNA

After the release of the viral RNA into the cytoplasm, the ORFs 1a and 1b are translated into functional nonstructural proteins, which comprise the RNA replicase-transcriptase complex. This replicase-transcriptase complex synthesizes a full-length negative-sense RNA copy, which is used as a template for the transcription of full-length and six subgenomic mRNAs that possess identical 3′ ends but different lengths (Fig. 5.3) (Sawicki and Sawicki 1990; Sethna et al. 1989). The initiation point of each mRNA corresponds to a stretch of consensus sequences, called intergenic sequences or transcription-regulatory sequences (TRSs, 5′ CT(T/G) AACAA(A/T)3′) that are found at the 3′ end of the leader sequence and at different positions upstream of genes in the genomic 3′-proximal domain of IBV. The 5′ two-thirds of the genome, 1a and 1b, encoding polyprotein precursor that is translated into a large polyprotein, 1ab, through a ribosomal frameshift mechanism (Brierley et al. 1989) and processed into 15 nonstructural proteins (nsp2–16) involved in virus replication. Papain-like proteinase (PL^{pro}), main protease (M^{pro}) or $3CL^{pro}$ (because it has some similarities to the 3C proteases of picornaviruses), adenosine diphosphate-ribose 1-phosphatase (nsp3), RNA-dependent RNA polymerase (nsp12, RdRp), and RNA helicase (nsp13), exonuclease (nsp14), endoribonuclease (nsp15), and 2-O-methyltransferase (nsp16) (Snijder et al. 2003; Fang et al. 2010) are among the important replication enzymes encoded by the replicase gene. Exonuclease and endoribonuclease are involved in processing RNA (Ivanov et al. 2004; Fang et al. 2010). The remaining 3′ third of the genome encoding the

structural genes in addition to accessory genes interspersed within the structural gene region. Each viral subgenomic mRNA is used for translation of a single viral protein. The four structural proteins, spike (S), nucleocapsid (N), membrane (M), and envelope (E) proteins, are translated from separate mRNA. The accessory genes encode gene products although not essential for virus replication, but their deletion often causes viral attenuation (de Haan et al. 2002).

5.7.4 Replication of Viral Genomic RNA

IBV genome replication occurs through continuous transcription, while the subgenomic RNA synthesis occurs through discontinuous transcription (Fig. 5.3) (Masters 2006; Pasternak et al. 2006; Sawicki and Sawicki 2005; Tan et al. 2012). In addition to the replicase gene, the 5′ and 3′ end UTR sequences, with some specific secondary structures, are required for genomic RNA replication. The nucleocapsid (N) is also required for efficient viral RNA synthesis (Verheije et al. 2010; Zuniga et al. 2010). The genome-size transcripts are packaged into progeny virions.

5.7.5 Assembly and Release

IBV assembles and buds intracellularly into the lumen of a smooth-walled, tubulovesicular compartment located intermediately between the rough endoplasmic reticulum and Golgi (Klumperman et al. 1994). After budding, virus particles are transported through a functional Golgi stack and are released out of the host cells by the exocytic pathway. A strong interaction between IBV E and M occurs where E protein provides a temporary anchor to relocate M in the pre-Golgi compartments, as it "prepares" the membranes for budding (Raamsman et al. 2000). The spike (S) protein contains a canonical dilysine endoplasmic reticulum retrieval signal (–KKXX-COOH) in its cytoplasmic tail that plays an important role in protein accumulation near the budding sites (Ujike and Taguchi 2015). The virus nucleocapsid is enclosed by a lipoprotein envelope during virus budding from intracellular membranes. The envelope contains S, M, and E proteins.

5.8 Epizootiology

5.8.1 Hosts

All ages of chicken are susceptible to infection with IBV. The virus induces more severe disease in baby chicks, and the severity decreases as the age increases. IBV infection was also recorded in peafowl and also in non-galliform birds, e.g., the teal (Liu et al. 2005).

5.8.2 Transmission

IBV is a highly contagious airborne infection (Cumming 1970; OIE 2013) that can be easily transmitted directly by chicken to chicken through aerosols and indirectly contact via contamination of personnel or equipment, egg packing materials, litter, and farm visits (OIE 2013; Cavanagh and Gelb 2008). IBV can establish persistent infections when it affects the genital system of birds during early days of life; virus shedding is detected approximately when the egg production started. Reports of extended and intermittent shedding through nasal and fecal discharge are evident and could constitute a potential risk of flock-to-flock transmission (Jones and Ambali 1987; Adzhar et al. 1996; Alexander and Gough 1978; Cook 1968; Alexander and Gough 1977).

5.8.3 Incubation Period

The incubation period of IBV is very short 18–36 h and it depends on the infecting dose of the virus, and the clinical signs appear within 24–48 h of virus exposure (Hofstad and Yoder 1966).

5.8.4 Clinical Signs

The clinical picture includes decreased in the general bird vitality, huddling under a heat source, and decrease in both food and water consumption. The respiratory clinical form of IBV infection in chicks includes: nasal discharge, sneezing, coughing, and gasping. Some chicks may develop wet eyes and swollen sinuses. In chickens more than 6 weeks of age and older, the signs are similar to those in chicks, and the respiratory clinical form occurs but in a milder form (Cavanagh and Gelb 2008). Nephropathogenic viruses induce respiratory distress in addition to signs of ruffled feathers, wet droppings, increased water intake, and mortality (Winterfield and Hitchner 1962). In laying flocks, declines in egg production and quality are seen in addition to respiratory signs. About 6 to 8 weeks may elapse before production returns to the pre-infection level, but in some cases, this is never attained. The severity of the production declines may vary with the period of lay (van Eck 1983). In addition to production declines, the number of eggs unacceptable for setting is increased, hatchability is reduced, and soft-shelled, misshapen, and rough-shelled eggs are produced (Crinion 1972). The albumen may be thin and watery without definite demarcation between the thick and thin albumen of the normal fresh egg. Infectious bronchitis virus infection of 1-day-old chicks can produce permanent damage to oviducts leading to reduced egg production and inferior quality eggs when the chickens come into lay. The severity of oviduct lesions is likely to be less in infections of older chickens, and some serotypes may fail to produce any pathologic change even in infections of 1-day-old chicks. The presence of specific

maternal antibody was also shown to protect the oviduct from damage due to IBV infection in early life (Chew et al. 1997).

5.8.5 Gross Lesions

Infected chicken showed petechial lesions in the larynx and tracheal exudate, which can be serous or caseous. Cloudy air sacs may be noticed in some birds. Caseous plug in the tracheal bifurcation could also be seen in some birds. Small areas of pneumonia may be observed in the lungs (Cavanagh and Gelb 2008). In nephropathogenic strains, the kidneys are swollen and the ureters are distended with urates (Ziegler et al. 2002; Abdel-Moneim et al. 2005). Some IBV strains are associated with thickening of the proventricular wall with congestion at the point of emergence of the glandular ducts (Toffan et al. 2013b). Cystic oviducts were observed in layer birds infected very early during the first days of life. Birds infected at the time of lay have reduced size and weight of the oviduct and regression of the ovaries. The fluid yok material may be observed in the abdominal cavity.

5.8.6 Histopathology

Loss of cilia of the tracheal mucosa and minor infiltration of heterophils and lymphocytes are detected 18–24 h after infection. Hyperplasia is followed by massive lymphocytic infiltration of the lamina propria may be present after 7 days. In nephrogenic strains, interstitial nephritis, infiltration of heterophils in the interstitium, and (Cavanagh and Gelb 2008; Abdel-Moneim et al. 2006) sometime renal hemorrhages are observed (Abdel-Moneim et al. 2005; Abdel-Moneim et al. 2006) (Fig. 5.4). The oviduct of mature hens showed decreased height and loss of cilia, infiltration by lymphocytes, and edema as well as fibroplasia of the mucosa of all regions of the oviduct (Sevoian and Levine 1957). Multifocal erosion and necrosis of the tunica mucosa and glandular epithelium of the proventriculus are associated with lymphocytic infiltration and fibroplasia in the lamina propria (Toffan et al. 2013b).

5.9 Pathogenicity

IBV initially infects ciliated and mucus-secreting cells of the upper respiratory tract (Raj and Jones 1997). Maximum virus shedding occurs 3–5 days after infection in the nose and trachea (Cavanagh 2003; Hofstad and Yoder 1966; Ambali and Jones 1990). High virus titers occur also in the lungs and air sacs (Raj and Jones 1997).

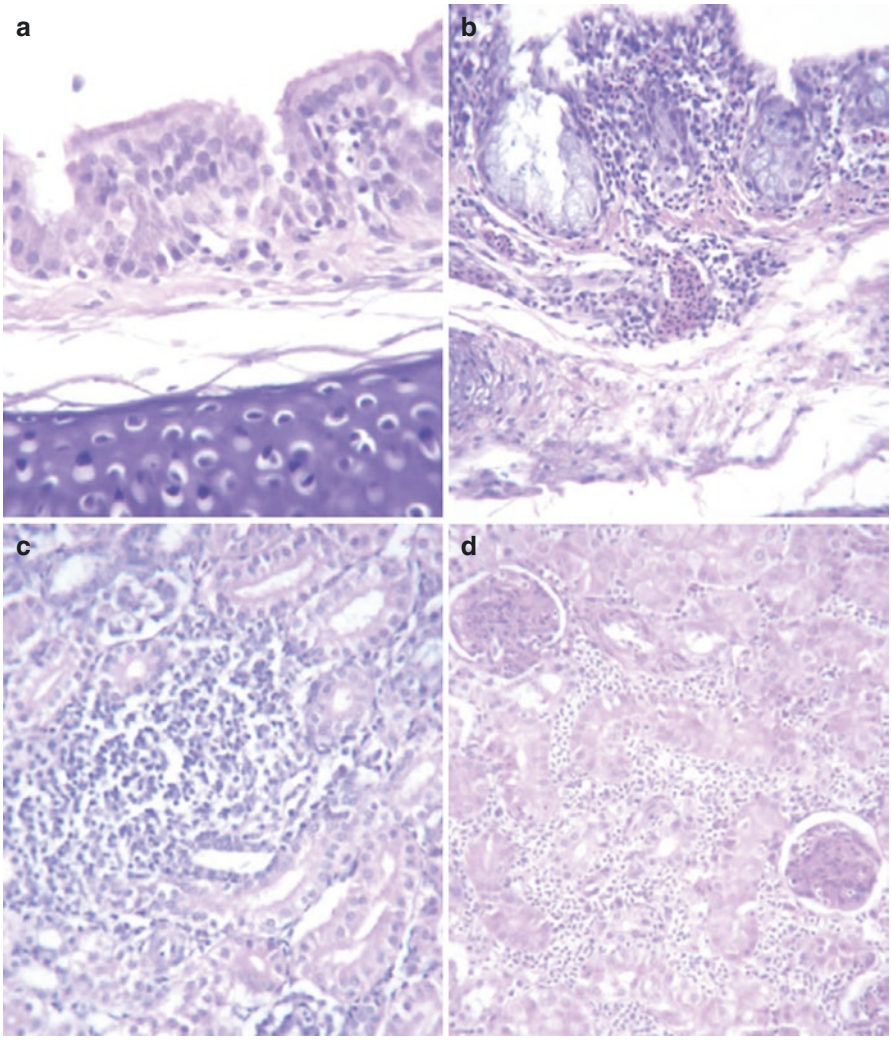

Fig. 5.4 Trachea and kidney histopathology following experimental infection of 1-day-old chicken with Egypt/F/03 (Abdel-Moneim et al. 2006). Trachea and kidney stained with H&E. **(a)** Trachea of chickens 5 days postinfection with Egypt/F/03 showing hyperplasia, lymphocytic infiltration, and edema (40 ×). (**b**) Trachea of chickens 7 days postinfection with Egypt/F/03 showing diffuse lymphocytic aggregation, degeneration of the epithelium mucus, and hemorrhages (20 ×). (**c**) Kidney of chickens 5 days postinfection with Egypt/F/03 showing focal lymphocytic aggregation in the interstitium and glomeruli, as well as degenerative changes in tubular epithelium (40 ×). (**d**) Kidney of chickens 7 days postinfection with Egypt/F/03 showing massive renal hemorrhages and degeneration of renal tubular epithelium (20 ×)

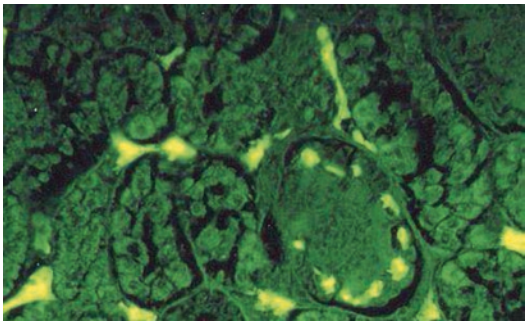

Fig. 5.5 Immunofluorescent staining of kidney paraffin section of kidney 5 days postinfection with Egypt/Beni-Suef/01 (Abdel-Moneim et al. 2005). Intracytoplasmic fluorescence in glomerular tuft and endothelial lining of renal blood vessels in the intertubular areas (40 ×)

IBV grows also in the epithelial lining of the kidney, oviduct, testes, esophagus, proventriculus, duodenum, jejunum, spleen, bursa of Fabricius, cecal tonsils, Harderian gland, rectum, and cloaca (Cavanagh 2003; Raj and Jones 1997; Abdel-Moneim et al. 2005; Ambali and Jones 1990; Seo et al. 1997) with minimal pathological effect. The virus commonly persists in the alimentary tract in young chickens (Ambali and Jones 1990; Alvarado et al. 2006) and in layers in the absence of clinical disease (Jones and Ambali 1987). Proventricular-type IBV (QX) reported in 1996 in China induces hemorrhagic ulceration of proventriculi and diarrhea followed by obvious signs of respiratory disease and high mortality (Zhou et al. 1998; GenCheng et al. 1998). Nephropathogenic strains result in considerable mortalities in meat-type birds (Cook et al. 2001; Lambrechts et al. 1993; Li and Yang 2001; Pensaert and Lambrechts 1994). The virus replicates in renal tubules and ducts, distal convoluted tubules, and Henle's loops (Chen and Itakura 1996) but may also replicate in the renal glomeruli (Fig. 5.5) (Abdel-Moneim et al. 2005). Modest to high titers of IBV in the kidney do not necessarily correlate with overt kidney disease, and there may be no gross kidney lesion (Ambali and Jones 1990). IBV infection of the chicken reproductive system leads to decreased egg production and quality due to the infection of the oviduct. In roosters, the virus results in epididymal stones, decreases sperm production, and decreases serum testosterone concentrations (Boltz et al. 2004). Infection is commonly followed by secondary bacterial infections, which may increase the mortality and complicate the clinical situation (Vandekerchove et al. 2004). Infection of enteric tissues usually does not manifest itself clinically.

5.10 Immunity

5.10.1 Innate Immunity

Hyperplasia of the goblet cells and alveolar mucous glands with subsequent increase in seromucous nasal discharge and catarrhal exudates in the trachea

are the first response of the innate immunity against IBV infection (Nakamura et al. 1991). Toll-like receptor (TLR) 21 is stimulated by the presence of deoxyoligonucleotides containing CpG motifs, and it induces NF-κB production, leading to enhanced transcription of a number of cytokines (Brownlie et al. 2009). A rapid influx of macrophages to the infected tissue, detected within hours postinfection, plays an important role in limiting the replication of IBV within respiratory tissues. Heterophils are responsible for the destruction of IBV-infected cells during initial infection by phagocytosis and oxidative lysosomal enzyme release (Fulton et al. 1997). However, at the tracheal epithelium, heterophils do not reduce virus replication but worsen the severity of lesions (Raj et al. 1997). Interferon production in the plasma and all over body tissues (Otsuki et al. 1987), with simultaneous upregulation of mRNA levels of pro-inflammatory cytokines (IL-6 and IL-1β) and lipopolysaccharide-induced tumor necrosis factor (TNF)-α factor, is produced during IBV infection. This coincides with the highest viral loads and microscopic lesions, indicating a potential role of these cytokines with high virus loads and the development of tracheal and kidney lesions (Okino et al. 2014; Jang et al. 2013; Chhabra et al. 2015). In contrast, *il6* gene expression and upregulation of IFN-γ, IL-8 (CXCLi2), and MIP-1β genes together with mannose-binding lectin (MBL), which activates complement, inhibit the propagation of the virus (Juul-Madsen et al. 2007). Apoptosis is another nonspecific defense mechanism against IBV infection by premature lysis of infected cells, thereby aborting viral multiplication (Cong et al. 2013).

5.10.2 Role of Antibodies in Protection

Circulating antibody titers do not highly correlate with protection from IBV infection (Raggi and Lee 1965; Gough and Alexander 1979). In contrast, it has also been reported that high titers of humoral antibodies correlate well with the absence of virus re-isolation from the kidneys and genital tract (Gough et al. 1977; Macdonald et al. 1981; Yachida et al. 1985) and protection against a drop in egg production (Box et al. 1988). IBV-specific antibodies were suggested to be involved in limiting IBV spread by viremia from the trachea to other susceptible organs, including the kidneys and oviduct (Raj and Jones 1997). In general, serum antibody levels do not closely correlate with tissue protection, but local antibodies may contribute to the protection of the respiratory tract (Ignjatovic and McWaters 1991; Raggi and Lee 1965). Furthermore, IBV-specific IgA antibodies were first detected in tears and later in serum, which suggests that IgA is important in neutralizing IBV at mucosal surfaces and is thought to play a role in the control of IBV locally (Davelaar et al. 1982; Gelb et al. 1998). However, IgA might not be important in protection against IBV infection of the upper respiratory tract, whereas locally produced IgY, after a secondary immunization, provided effective protection against IBV by neutralizing this virus (Guo et al. 2008; Orr-Burks et al. 2014).

5.10.3 Cellular Immunity

IBV-specific cytotoxic T cell lymphocyte (CTL) activity is dependent on the S and N proteins of IBV (Collisson et al. 2000), while of $CD4^+$ T cells do not appear to be important in initially containing IBV infection in chickens (Seo et al. 2000); however, $CD4^+$ T cells and B cells could be more critical for long-term virus control (Chhabra et al. 2015). S1 and N but not the M protein proteins of IBV generated cytotoxic T cell responses. The whole N protein and its carboxy terminal region but not its amino terminal region were reported to induce a CTL response (Seo et al. 1997; Guo et al. 2010).

5.10.4 Maternally Derived Antibodies

Chicks hatched with high levels of maternally derived antibodies are protected against IBV challenge at 1 day of age but not at 7 days (>30 %) (Mondal and Naqi 2001). Protection is correlated with levels of local antibody but not humoral antibody (Mondal and Naqi 2001).

5.11 Diagnosis

5.11.1 Virus Isolation

5.11.1.1 Sampling

Samples should be obtained as soon as possible after the appearance of the clinical signs. Laryngotracheal swabs from live birds or tracheal and lung tissues from fresh carcasses can be used for laboratory diagnosis of IBV. Kidney, oviduct, or proventriculus samples are collected from birds with nephritis, egg production, or proventriculitis, respectively. All samples should be placed in virus transport medium containing penicillin (10,000 International Units [IU]/ml) and streptomycin (10 mg/ml) and kept in ice and then frozen (OIE 2013).

5.11.1.2 Virus Isolation in Embryonated Chicken Eggs

Specific pathogen-free embryonated chicken egg (SPF-ECE) is recommended for primary isolation of IBV. Processed samples (10–20 % w/v) in phosphate-buffered saline (PBS) are used for egg inoculation, after being clarified by low-speed centrifugation and filtration through bacteriological filters. 100–200 μl of the processed sample is inoculated into the allantoic cavity of 9–11-day-old embryos (Delaplane 1947). Embryo mortalities within the first 24 h is considered nonspecific death. The allantoic fluids of inoculated eggs (36–48h post-inoculation) are harvested and pooled (Cunningham 1973; Cunningham and El Dardiry 1948). Blind passage into another set of eggs for up to a total of three to four passages is conducted. The last passage is left for 7 days to screen the presence of pathognomonic embryonic changes: stunted and curled embryos (Fig. 5.6) with feather dystrophy and urate

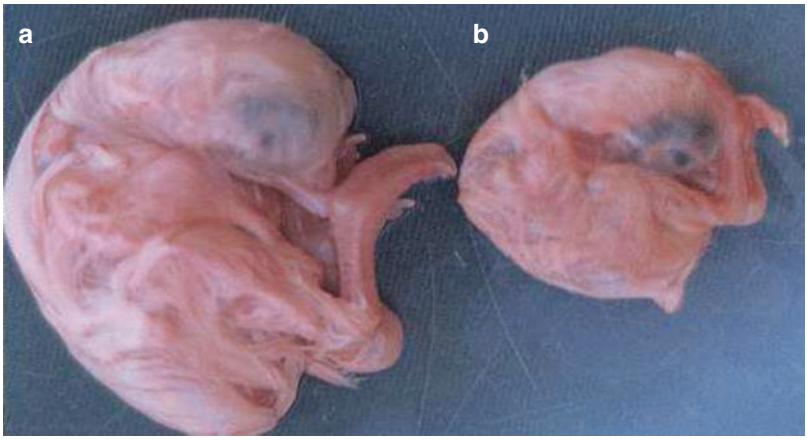

Fig. 5.6 Normal embryo (**a**) and stunted and dwarfed embryo following inoculation of specific pathogen-free embryonated chicken eggs with IBV (**b**)

deposits in the mesonephros. These lesions could also appear as early as the second passage (Delaplane 1947). The embryo-adapted strains induce more embryo mortalities. Isolation of IBV must be confirmed by serum neutralization or reverse transcription polymerase chain reaction (RT-PCR).

5.11.1.3 Tracheal Ring Culture

Tracheal ring culture (0.5–1.0 mm thick) from 19- to 20-day-old embryos can be used for primary isolation of IBV directly from field samples (Cook et al. 1976). The rings are maintained in Eagle's N-2-hydroxyethylpiperazine-N′-2- ethanesulfonic acid (HEPES) in roller drums (15 rev/hour) (OIE 2013). Ciliostasis within 24–48 h is an indication for virus multiplication; however, other viruses could produce similar lesions, so subsequent virus identification is needed.

5.11.2 Biological and Immunological Identification

IBV exerts hemagglutination (HA) activity only after phospholipase C treatment of concentrated virus infected allanto-aminiotic fluids (Bingham et al. 1975). A rapid plate HA test to detect neuraminidase-treated IBV in the allantoic fluid of ECE was introduced into the routine procedure of IBV identification and was found to correlate with the RT-PCR during the early stages of IBV detection and identification and isolation in ECE (Ruano et al. 2000). Such technique depends on the principle that IBV acquires its HA activity after removal of α 2, 3-linked N-acetyl neuraminic acid from the virion surface (Schultze et al. 1992). IBV can also be detected using immunofluorescence or immunoperoxidase on the tracheal or kidney section from the field isolates or on the chorioallantoic membrane or TOC from the inoculated embryos (Handberg et al. 1999; Abdel-Moneim et al. 2009; Bhattacharjee et al. 1994). However, nonspecific reactions or lower sensitivity especially in field

samples may occur (Braune and Gentry 1965; Yagyu and Ohta 1990; Benyeda et al. 2010). The specificity of IFA may possibly be improved by using monoclonal antibodies (MAbs) (Naqi 1990; Yagyu and Ohta 1990; De Wit et al. 1995). Agar gel precipitation can be used for IBV identification, however, it possesses lower sensitivity in comparison to other assays (De Wit et al. 1992). Enzyme immunoassays are quick, inexpensive, and sensitive assays, which are suitable for screening large number of samples, IBV diagnosis, and serotype identification as well (Naqi 1990; Ignjatovic and McWaters 1991; Cavanagh et al. 1992a; Karaca and Syed 1993).

5.11.3 Molecular Identification

In situ hybridization can be used to detect viral nucleic acid (Collisson et al. 1990). RT-PCR and restriction fragment length polymorphism (RFLP) are used to genetically identify IBV (Kwon et al. 1993).

5.11.4 Serotyping and Genotyping of IBV Strains

Serotyping of IBV isolates has been conducted using hemagglutination inhibition (HI) (Alexander et al. 1983; King and Hopkins 1984) and virus neutralization (VN) tests in chick embryos (Dawson and Gough 1971), TOCs (Darbyshire et al. 1979), and cell cultures (Hopkins 1974). Enzyme-linked immunosorbent assays (ELISA) using MAbs are successfully used in serotyping IBV strains (Ignjatovic and McWaters 1991). The limitations of MAb analysis for IBV serotype definition are the lack of availability of MAbs or hybridomas and the need to produce new MAbs with appropriate specificity to keep pace with the ever-growing number of emerging IBV-variant serotypes (Karaca et al. 1992). There is a good correlation between the S1 sequence results and the VN serotyping (OIE 2013). The emergence of vast majority of the strains circulated worldwide (Jackwood 2012) renders serotyping impossible in many cases, and hence genotyping methods replaced HI and VN typing of IBV strains. Restriction fragment length polymorphism (RFLP) analysis of the S1 gene following RT-PCR amplification has been used to identify IBV serotypes (Lin et al. 1991; Kwon et al. 1993). Identification of IBV serotype is also conducted using serotype-specific S1 gene primer. Despite the success of both RFLP and serotype-specific RT-PCR, RFLP-derived restriction patterns of some IBV serotypes may be difficult to distinguish from others. Furthermore, samples containing mixture of more than one serotype may be difficult to be differentiated (Keeler et al. 1998). On the other hand, a mutation at a specific primer site or at an endonuclease recognition site may result in false negative in both RT-PCR and RFLP techniques. Direct sequencing of the S1 gene provides the ability to rapidly identify field strains including unrecognized variant virus serotypes (Kingham et al. 2000; Kusters et al. 1989).

5.11.5 Determination of IBV Protectotypes

Antigenic and genetic variations among IBV alone are not adequate to define cross protection between strains (Cavanagh et al. 1997; Raggi and Lee 1965); hence, the term "protectotype" was suggested (Lohr 1988) to determine the cross protection afforded by the existing vaccines against the emerged serotypes/genotypes. Cross immunity tests (CIT) in experimental birds have been performed (Lambrechts et al. 1993; Darbyshire 1985, 1980); the use of tracheal organ cultures (TOCs) from IBV-immunized birds was also suggested (Darbyshire 1980) and used successfully (Hinze et al. 1991). Since IBV has a tropism for epithelial cells of the respiratory tract, kidney, oviduct, and gut of chickens, IBV vaccines are evaluated on the basis of protection afforded at the level of the trachea (McMartin 1993), the kidneys for nephropathogenic IBV (Lambrechts et al. 1993), and the oviduct level (Dhinakar Raj and Jones 1996).

5.11.6 Serodiagnosis

VN test may be performed in ECE, CKC, or tracheal organ culture (TOC). The test may be conducted using the constant serum-diluted virus or diluted virus content serum method (Gelb 1989). VN is highly specific and highly sensitive; it is rarely used because it is too expensive and time-consuming. HI test detects antibody earlier than NV and could be used for serology (Kaufhold et al. 1988; Gough and Alexander 1979, 1977). AGPT is proved to be specific but with poor sensitivity (De Wit et al. 1997). ELISA is used on a more frequent basis to measure IBV antibody (Garcia and Bankowski 1981; Marquardt et al. 1981; Soula and Moreau 1981; Snyder et al. 1985). Among the advantages of ELISA are the increased sensitivity and specificity (Garcia and Bankowski 1981; Marquardt et al. 1981; De Wit et al. 1997) and the automation of the ELISA steps and calculations (Snyder et al. 1983a, b).

5.12 Treatment and Vaccination

5.12.1 Treatment

No specific antiviral therapy is available to control IBV field infection. On the other hand, antimicrobial therapy may reduce the effect of the complicating bacterial infections. Increasing the ambient temperature may reduce mortalities in cold weather. Reduced mortalities in nephrogenic strains can be achieved by reducing the protein concentrations in ration, providing electrolytes in drinking water, and using diuretics.

5.12.2 Vaccination

5.12.2.1 Live Attenuated Vaccines

Live attenuated IB vaccines are used to control IBV infection. Live vaccines are frequently attenuated by serial passage in embryonated chicken eggs (Klieve and Cumming 1988); however, extensive passage should be avoided to prevent the reduction in immunogenicity. There is an evidence that some attenuated vaccines showed increased in virulence after back passage in chickens (Hopkins and Yoder 1986). Vaccination is conducted by drinking water or coarse spray at 1 day or within the first week of age. Live vaccination of 1-day-old chicks induced a rapid decline in maternally derived antibodies due to binding and partial neutralization of vaccine viruses (Mondal and Naqi 2001). Booster vaccination is carried out 2–3 weeks after the first vaccination (Cavanagh 2003). The vaccine is administered individually by eyedrop, intratracheal, or intranasal route. Mass application by coarse spray, aerosol, and drinking water is used. In case of drinking water, removal of sanitizers and the incorporation of 1:4000 skim milk help to stabilize the vaccine titer during vaccination (Gentry and Braune 1972). Live attenuated IBV with NDV is used frequently; however, if excess IBV component is present, IBV may interfere with the NDV response (Thornton and Muskett 1975). Most of the commercially available live attenuated vaccines are derived from Massachusetts-based M41 serotype and the Dutch H52 and H120 strains, although some strains with regional impact have been introduced in different parts of the world in addition to Mass serotype (Lee et al. 2010; Bande et al. 2015). In the USA, strains belong to Connecticut, and Arkansas serotypes are used, whereas other serotypes like DE072 are used regionally. In some parts of Europe, D274, D1466, 4/91, and QX are used. In Australia, strains B and C subtypes are used (Klieve and Cumming 1988). In Egypt, MASS + CONN and 4/91 live attenuated vaccines and D274/M41 inactivated are used (Abdel-Moneim et al. 2006). In China, LDT3-A and QX live vaccines are used (Feng et al. 2015). Limitations of live attenuated vaccines include reversion to virulence, tissue damage, and interference by MDA. H52 and H120 IBV vaccines have been found to induce considerable pathology in the trachea (Bijlenga et al. 2004; Zhang et al. 2010). Potential recombination between vaccine strains and virulent field strains may lead to the emergence of new IBV serotypes (Lee et al. 2010; McKinley et al. 2008).

5.12.2.2 Inactivated or Killed Vaccines

Inactivated IBV vaccines are administered by injection to layers and breeders at point of lay (13–18 weeks of age). The inactivated vaccine may contain two IBV types and in association with other virus vaccines including NDV, egg drop syndrome, and others. Of course, inactivated vaccines require priming with live attenuated vaccines. In addition, inactivated autogenous vaccines prepared from specific local isolates can be used to immunize commercial layers and breeder chickens.

5.12.2.3 Recombinant Vaccines

Recombinant IBV Beaudette with S proteins of virulent M41 (Hodgson et al. 2004; Hodgson et al., 2004) or 4/91 (S) (Armesto et al. 2011) or replacing the S1 ectodomain of the Beaudette with that of H120 (Wei et al. 2014) kept the viruses attenuated and provided homologous protection. Fowl pox virus vaccine expressing IBV-S1-gene and chicken interferon-γ gene [rFPV-IFNγS1] and fowl adenovirus vectors (Shi et al. 2011; Johnson et al. 2003) as well as BacMam (baculovirus with mammalian expression system) expressing S and N genes (Abdel-Moneim et al. 2014) or S1 gene(Zhang et al. 2014) could be good candidates for IBV vaccines, since vectors replicate well in the bird's respiratory tract (Cavanagh 2007).

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