Handbook of Egg Science and Technology

Eggs are one of the most popular foods worldwide due to their great taste and versatility, economical value and high nutritional content. The egg plays an important role in the human diet, both for the nutritional value of its many components (e.g., proteins, vitamins, minerals, choline and specific long chain fatty acids) and its wide range of functional characteristics, including foaming, gelling and emulsifying properties. The egg sector is a vibrant field with many new developments in terms of production, processing and commercialization as well as research. Since the beginning of the 21st century, the global production of eggs has grown by 69.5%, farm production systems have evolved to improve the welfare of laying hens, many shell eggs and egg products have been developed to address the changing demands of consumers and our knowledge of the composition of the egg has been boosted by the latest gene-based technologies. Information on the science and technology of egg and egg processing is essential to governments, academia and industry.

The *Handbook of Egg Science and Technology* aims to be the first book providing a complete source of information about egg science and technology, covering topics such as world egg production, marketing of eggs, chemistry of egg components, functional properties of egg components, egg processing, egg product development, eggshell quality, grading, egg microbiology, egg pasteurization, egg nutrition and bioactive components, egg biotechnology and sustainability of egg production.

Key Features

- This book includes the most current and comprehensive scientific and technical information about egg science and technology
- This book presents an ideal guide for professionals in related food industries, egg business consultants, regulatory agencies and research groups
- This book answers the need for a comprehensive textbook for upper-level undergraduate and graduate courses in food science, animal science and poultry departments

A global panel of experts in the field of egg science was gathered with the aim of providing the most updated information and development on many topics likely to interest readers, ranging from academia and food science students to managers working in the food production and egg processing sectors. This handbook is an excellent resource for the food and poultry industry, R&D sectors, as well as for experts in the field of food and nutrition.

Handbook of Egg Science and Technology

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Egg Yolk Antibody-IgY

Shofiqur Rahman

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27.1 Introduction

27.1.1 History of Immunoglobulins in Yolk (IgY)

In 1969, G.A. Leslie and L.W. Clem suggested the name Immunoglobulin Y. Other synonymous names are Chicken IgG, Egg Yolk IgG, and 7S-IgG. In 1893, the first scientific report of IgY was published by Felix Klemperer. In 1959, Russell and Burch proliferated animal welfare research extensively. Since the 1980s, IgY has been frequently studied due to the revolution of overall technology. In the 1990s, the term "IgY technology" was introduced to describe a procedure to produce polyclonal antibodies of the Y class (IgYs).

In 1995 Warr et al., reported that the IgY is a key isotype in antibody evolution. IgY is thought to have diverged from an ancestral IgM, and it is a widely held belief that an IgM gene duplication event led to the formation of IgY (Warr et al., 1995). IgY is also thought to be the precursor of IgG and IgE.

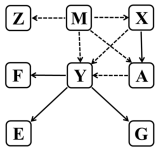

FIGURE 27.1 The central position of IgY in immunoglobulin evolution. Solid arrows indicate an orthologous relationship between isotypes. Broken arrows connect isotypes that have a putative orthologous relationship, not yet verified. The broken arrow that relates IgA to IgY refers to an ancestral form of IgA. (Adapted from Zhang et al., 2017.)

At some point during the evolution of the mammalian lineage, IgY underwent a gene duplication event and diversified into IgE and IgG. Thus, the proposal that IgM gave rise to the mucosal antibody IgX and then to IgA, which gave rise to IgY and the serum antibodies IgG and IgE. These relationships are depicted in Figure 27.1, which highlights the central role of IgY.

Physicochemical and antigenic evidence obtained during the past three decades has indicated that IgY occurs throughout the vertebrate classes Amphibia, Reptilia, and Aves. It is clear from the diverse capabilities of IgY in so many species that molecular genetic studies of this molecule will broadly contribute to our understanding of Ig evolution. Perhaps looking backward in evolution will take us forwards in our knowledge of mammalian antibody function.

In 1996, the European Centre for the Validation of Alternative Methods to animal testing (ECVAM) strongly recommended avian antibodies as alternatives to mammalian ones (Schade et al., 1996). In parallel, in 1999, the IgY technology was approved as an alternative method for supporting animal welfare by the Veterinary Office of the Swiss Government. The field is more than 120 years old. However, in the last decades, major advances in research and development areas such as Genetics, Biochemistry, Bioengineering, and Bioprocessing, have prompted new approaches to this old technology.

In 2001, the world's first standardized laboratory practice of IgY technology, known as the "IgY laboratory manual" was reported (Schade et al., 2001). In 2002–2006, the project *Multidisciplinary Hen Egg Research* was started through a Cooperative Organization Science and Technology action (COST 923) in the European Union framework for the versatile utilization of eggs. In 2007, Huopalahti et al. summarized one project where the biomedical use of IgY became the focus of the action plan. In 2011, a Chinese version of IgY monograph was published. NCBI database with different search terms, namely "IgY Technology", "IgY Antibodies" and "IgY" surveyed for timeline 1893–2022. NCBI database surveys for the three time periods, (e.g., 1893~1955, 1956~1987, 1988~2022) of avian IgY publications, show a progressive increase in the number of published works since the 1988s (Figure 27.2).

27.2 Chicken: Natural Source of IgY

27.2.1 Chicken Immunity and Immune System

The avian immune system is the system of biological structures and cellular processes that protects *birds* from disease. Like other avian immune systems, the immune system of chickens is made up of two types of mechanisms—nonspecific and specific. Nonspecific immune mechanisms include the inherent ways (e.g., genetic factors, body temperature, anatomic features, normal microflora, respiratory tract-cilia) in which a chicken resists disease. Specific immune mechanisms, which make up the acquired immune system, comprise noncellular (humoral) and cellular components.

The noncellular component includes immunoglobulins (or antibodies) and the cells that produce them. The cellular component of the specific immune mechanisms includes all the cells that react with specificity to antigens except those associated with antibody production. The cells associated with this

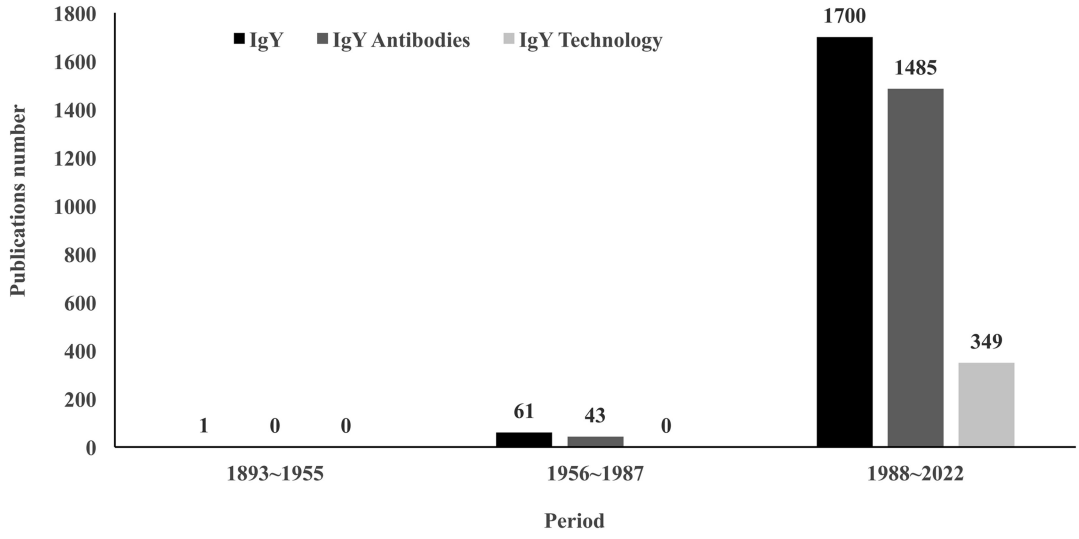

FIGURE 27.2 Evolution of publications on avian IgY antibodies. A search of publications on avian IgY antibodies and IgY Technology was performed on the NCBI database with different search terms over a time window from 1893 to 2022. The search terms were "IgY Technology", "IgY Antibodies" and "IgY" and the total number of publications for each term were 301, 1368, and 1583, respectively (June 4, 2022).

TABLE 27.1

The Avian Immune System

Organs/Tissues	Cellular Elements	Humoral Elements
Primary Lymphoid Organs: Bursa of fabricius and thymus Secondary Lymphoid Organs: Spleen, bone marrow, Harderian gland, pineal gland, mucosa-associated lymphoid tissue (MALT), and lymphoid nodules	Lymphocytes, T-cells, B-cells, and macrophages	Immunoglobulins (IgY, IgA, IgM), complement, and cytokines

system, T-lymphocytes (T-cells), begin as the same stem cells as B-lymphocytes (B-cells). Birds are the first vertebrates in which a clear dichotomy of the lymphoid system has been established: (1) Thymus-derived (T) lymphocytes, the effector cells in cell-mediated immunity, and (2) Bursa-derived (B) lymphocytes are the precursor cells of the antibody-synthesizing plasma cell. Table 27.1 summarizes the chicken immune system.

27.2.2 Immunoglobulin Classes in Chickens

Avians and mammals' specific or adaptive immune system is based on immunoglobulins. Birds produce three types of immunoglobulins (IgM, IgY, and IgA), and mammals five (IgM, IgD, IgG, IgE, and IgA) (Benedict et al., 1963; Leslie & Chem, 1969). A basic comparison of the Immunoglobulin classes or isotypes between avian and mammals is shown in Table 27.2. Immunoglobulin classes in other avian species (Ostrich, Quail, Turkey, Duck, and Goose) are also the same (Härtle et al., 2014) like chicken, e.g., IgM, IgA, and IgY.

27.3 Properties of IgY

27.3.1 Maternal Antibody (MA) Transfer from the Hen to the Progeny

Maternal Antibodies (MA), also known as passive immunity, are the natural transfer of immunoglobulins from one individual to another. Evidence for maternal IgY transfer from chicken to egg yolk for embryo protection was first reported more than 100 years ago (Klemperer, 1893). In birds, maternal antibodies are passed from hyper-immunized or naturally infected breeder hens to the progeny through the egg. This passive immunity has a relatively short duration, commonly 1–2 weeks and generally less than 4 weeks, and its function is to protect young chicks during a period (first few weeks) when their immune system is not fully developed to properly react to an early challenge. The chicken transfer MA to the egg by depositing the antibodies [IgY, IgA, and IgM)] in the egg yolk and albumin. Transport of IgY from maternal serum to the offspring (Ferreira Júnior et al., 2018) is unique process. This process comprises two steps. First step: MA Transfer from the Hen to the Egg; the first is the transfer from circulating maternal blood to the yolks of maturing oocytes in ovarian follicles, (which is in analogy to the cross placental transfer of antibodies in mammals). The passage of IgY into the ova is regulated by the follicular epithelium, which goes through morphologic changes as the ova grows. This epithelium becomes flatter and thinner in the larger ovum allowing the passage of a large amount of IgY. The transfer of IgY through the ovarian follicular epithelium reaches its maximum 3–4 days before ovulation. It starts to decrease due to the development of the vitelline membrane between the ovum and the follicular epithelium of the ovary in preparation for ovulation. Therefore, as a single hen has several ovas in different stages of development and the amount of IgY transferred to each one is not the same. The IgA and IgM are mainly found in the albumen (Rose et al., 1974) and they are transferred to the albumen due to mucosal secretion in the oviduct, specifically in the Magnum. Second step: MA Transfer from the Egg to Embryo. The second involves IgY transfer from the egg yolks to the embryonic circulation (to the developing embryo) through the yolk sac membrane (Linden & Roth, 1978; Tressler & Roth, 1987) (Figure 27.3). The second step of MA transfer relies on the IgY Fc receptor, FcRY (West et al., 2004); the relevant receptor involved in IgY transport is unknown. The IgY is transferred from the egg yolk to the offspring via embryonic circulation. The transfer starts from day 7 of embryonic development and reaches its maximum rate 3–4 days before hatch.

TABLE 27.2

Comparison of the Immunoglobulin Classes between Avian and Mammals

	Vertebrate Class	
Immunoglobulin	Avian	Mammals
Isotype	IgM (10%)	IgM (10%)
	Homologus proposed by Chen et al. (1982)	IgD (1%)
	IgY (75%)	IgG (70–75%)
	IgA (15%)	IgA (10–15%)
	Homologus proposed by Burns and Maxwell (1981)	IgE (0.001%)

27.4 Characteristics of IgY

27.4.1 Molecular Structural Characterization of IgY

Phylogenetic studies have shown that the IgY antibody, a homolog of mammalian IgG, has similarities with both mammalian IgG and IgE antibodies. Although chicken IgY is the functional equivalent of mammalian IgG, there are some profound differences in their molecular structure. The general structure of the IgY molecule is the same as the IgG molecule, with two heavy (H) chains and two light (L) chains, but IgY has a molecular mass of 180 kDa, which is larger than that of mammalian IgG (150 kDa) (Figure 27.4). The molecular mass (67–70 kDa) of the H chain in IgY is larger than the H chain in mammals (50 kDa). The greater molecular mass of IgY is due to an increased number of heavy-chain constant domains and carbohydrate chains (Warr et al., 1995). IgG has 3 C regions ($C_\gamma1$–$C_\gamma3$/CH1–CH3),

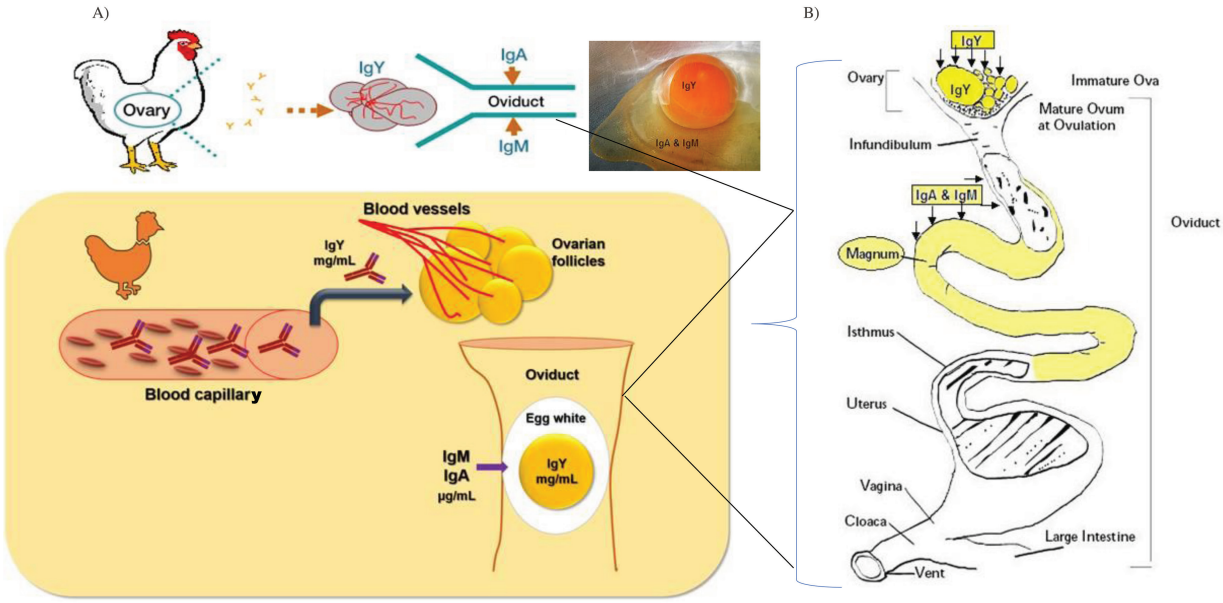

FIGURE 27.3 (A) Maternal antibody (MA) transfer from the hen to the egg. (B) Schematic representation of the IgY antibody translocation from the hens' blood to egg yolk in the ovarian follicle, and IgM and IgA deposition into egg whites through the oviduct epithelium. (Modified and adapted from Ferreira Júnior et al., 2018.)

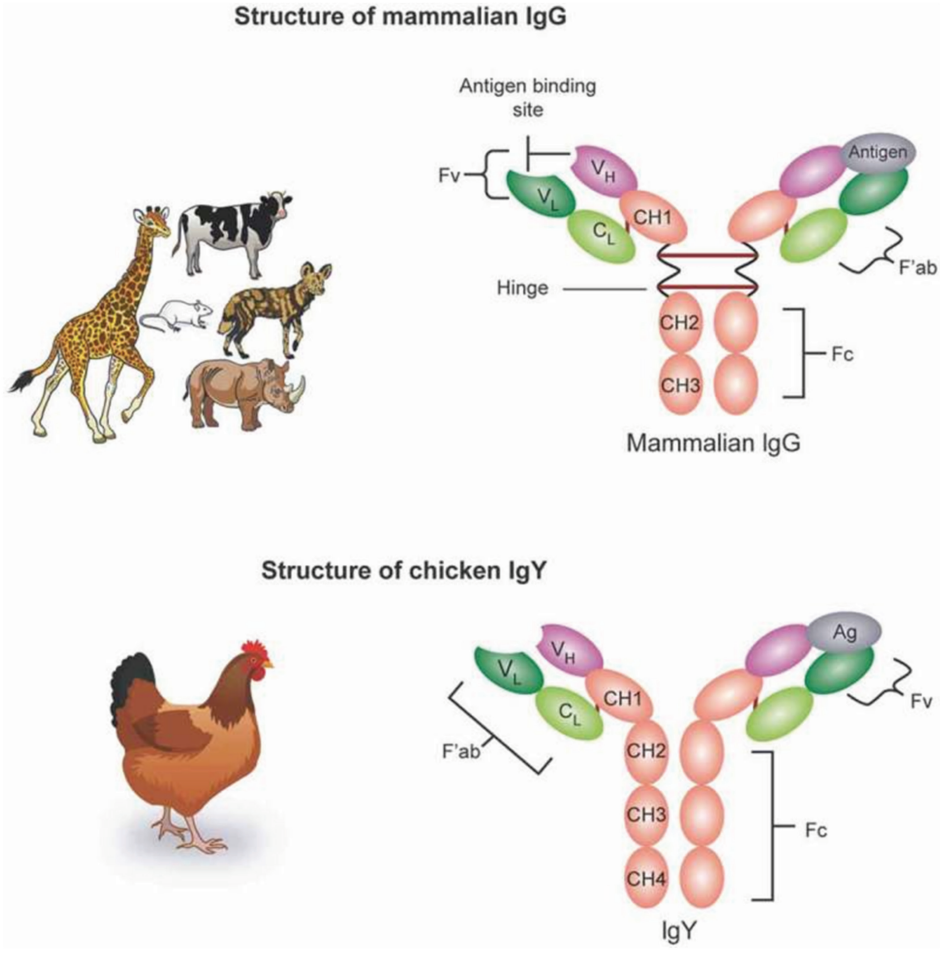

FIGURE 27.4 Structural comparison between mammalian IgG and avian IgY. (Adapted from Abbas et al., 2019.)

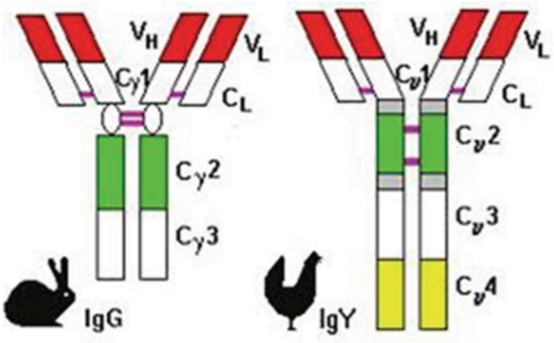

FIGURE 27.5 Comparison of the characteristics of mammalian IgG (rabbit) and chicken IgY. (Modified and adapted from Schade et al., 2005.)

while IgY has 4 C regions ($C_\upsilon1$–$C_\upsilon4$/CH1–CH4), and the presence of one additional C region with its two corresponding carbohydrate chains logically results in a greater molecular mass of IgY compared with IgG (Figure 27.5).

Other differences in the structure include the fact that the hinged region of IgY is much less flexible than mammalian IgG. It has also been suggested that IgY is a more hydrophobic molecule than IgG (Dávalos-Pantoja et al., 2000). Finally, IgY has an isoelectric point of pH 5.7–7.6, whereas IgG lies between 6.1 and 8.5 (Sun et al., 2001). Unlike mammalian IgG, IgY does not fix mammalian complement and does not interact with mammalian Fc and complement receptors (Carlander et al., 1999; Carlander et al., 2000). As well, IgY does not bind to protein A, protein G, or rheumatoid factor, so no false positives are obtained on immunoassay, which is a problem with IgG-based mammalian assays. These differences provide significant advantages to the application of IgY technology in many areas of research, such as diagnostics (Erhard et al., 2000), antibiotic-alternative therapy (Carlander et al., 2000), and xenotransplantation (Fryer et al., 1999). Figure 27.5 and Table 27.3 summarize the overall comparison of the characteristics of mammalian IgG and chicken IgY.

27.4.2 Immuno-Functional Characterization of IgY and Passive Immunity

Passive immunity is the transfer of active humoral immunity in the form of ready-made antibodies from one individual to another. Passive immunization was first introduced more than 100 years ago by Albert Calmette, and others (Calmette, 1896). As such, passive immunotherapy by antigen specific IgY acquires a special value as a tool for infection control and immunologic research with global commercial application as raw material for nutraceutical and pharmaceutical products and for applications in numerous medical and research fields since the 1980s. Specific IgY antibodies are obtained by immunizing the hen with the antigen of interest. The antibody fragment (Fab) domain containing a structure of the IgY with no hinge region, (Figure 27.4) gives IgY less flexibility to antigen binding with a broad array of antigenic epitopes (on, e.g., proteins, carbohydrates, and nucleic acids). A small amount of antigen in the milligram or microgram range usually elicits enough IgY response, and the antibody titers persist over several weeks to several months. It is reported that antigen-antibody interactions are characterized as noncovalent interactions (like the "lock and key" fit of enzyme-substrate). This interaction does not lead to irreversible alteration of antigen (Ag) or antibody (Ab) (Figure 27.6).

Compared to mammalian IgG, chicken IgY has 3–5 times more affinity and reacts more rapidly to the same antigens (Stuart et al., 1988; Ikemori et al., 1993; Lemamy et al., 1999) when tested in competition assays.

The advantages of using chicken IgY have been recognized by many authors (Schade et al., 2005). Since antibiotics are commonly used or misused for the treatment of gastrointestinal infections, the frequency of antibiotic-resistance organisms has been on the rise at an alarming rate against a backdrop of decreasing numbers of new antibiotics being developed and added to the market. We are therefore compelled to fall back to simple and yet effective natural remedies of which IgY comprises the most potent and easily generated substitute to antibiotics.

IgY can have different qualities because its production is "tailor-made", production conditions can be optimized to produce the standardized IgY antibody by producing a specific antibody, where the animals must be challenged with the respective specific antigen. With standardized antibody titers per batch, the product can deliver consistent results. IgY is more effective than IgG because (1) customized production: IgY is tailor-made and is specific against gut/infected area pathogens (compared to nonspecific IgG); (2) genetic selection theory: repeated hyperimmunization creates stronger antibody molecules; (3) molecular structure: IgY is much bigger than IgG; size is bigger; (4) protease resistance (against pancreatic enzymes: trypsin and chymotrypsin; sensitive to pepsin and papain; (5) maternal antibody transfer mechanism: God-gifted, genetically strong. Because milk-based IgG is provided daily baby till certain periods (few days to years). But Yolk-based IgY was provided only once to the chick before hatching; (6) repeated vaccination (hyperimmunization) with the same antigen creates stronger IgY (antibody) molecules as trained soldiers, protect the country from imminent enemies with well pre-prepared know-hows; and (7) IgY enhances colostrum IgG uptake. (Erhard et al., 1999; Quezada-Tristán et al., 2014). Moreover, IgG in colostrum (1) using bovine colostrum for swine or other animals will be less effective due to different pathogens; (2) high-quality colostrum is an excellent source of Ig, but the quality of colostrum is very variable.

IgY immunotherapy has several attractive features, including: (1) lack of reactivity with the human complement system and human Fc-receptors, thereby preventing nonspecific inflammation (Larsson et al., 1993); (2) excludes the use of toxic compounds or additives for their preparation from egg yolks; (3) egg cholesterols and triglycerides can be controlled to infinitesimally low levels (Nilsson et al., 2008); (4) IgY exerts beneficial antimicrobial and immuno-stimulatory effects in conjunction with other egg proteins (Kovacs-Nolan et al., 2005); and (5) high content of sialic acid (Gilgunn et al., 2016), which is reported to increase the half-life of the drug (Liu, 2015) compared with those with lower sialic acid content. It indicates that IgY-based therapy could have a longer circulating half-life, increasing its efficacy against infections. Egg allergies usually involve egg albumin components which

TABLE 27.3

Comparison of the Characteristics of IgG and IgY

Characteristics	IgG	IgY
Species	Mammals	Birds, reptiles, amphibians and lungfish
Sites of generation	Lymph nodes, spleen and bone marrow	Bursa of fabricius, spleen, and bone marrow
Antibody subclasses	IgG_1, IgG_2, IgG_3 and IgG_4	Not for chicken
Source of antibodies	Serum	Serum and Egg
Antibody collection	Invasive, painful	Meets 3R principle of animal welfare
Average antibody levels per animal	5 mg/mL of blood, blood collection up to 40 mL/month	50–100 mg/egg yolk
Monthly antibody yield per animal	200 mg/rabbit/month	1,000–2,800 mg/chicken/ month
Concentration (mg/mL)	10–15 (Serum)	8–10[a] (Serum), 10–20[b] (egg yolk)
Amount of antigen-specific antibodies	50–200 μg/mL serum	0.5% –10% total IgY
Phylogenetic distance to mammals	Near	310 Mya
Immune response to mammalian conserved antigens	Weak	Strong
Affinity	$1 \times 10^{-8} – 1 \times 10^{-10}$ mol/L	Comparable to rabbit IgG
Antibody avidity	High	3–4 times higher in compare to IgG
Molecular weight (kDa)	150	180
Isoelectric point (pI)	6.4–9.0[c]	5.7–7.6[d]
pH stability	2.0–11.0	3.5–11.0
Extinction coefficient (mL mg^1 cm^1 at 280 nm)	1.4	1.094, 1.33, 1.35
Trypsin stability	Weaker than IgY	Generally stable
Heat stability	Generally higher than IgY, Up to 75°C–80°C	Generally Up to 70 °C, specifically at 65°C > 2 months; 100°C > 6 min; 4°C > 6 months,
Proteolytic degradation	Pepsin, papain, trypsin and chymotrypsin	Pepsin and papain
Pepsin stability	Higher than IgY,	91% IgY activity at pH 4 for 1 hour, 63% after 10 hour
Fc chain (type of chain/number of domains/hinge region between Fab and Fc chains)	γ chain/2 constant domains/yes	υ chain/3 constant domains/ no
Hinge region	Yes	No
Number of constant domains	4 (3H and 1L)	5 (4H and 1L)
Fab chain (type of chain/number of domains)	κ or λ chains/1 variable domain and 1 constant domain	λ chain/1 variable domain and 1 constant domain
Mammalian complement binding	Yes	No
Rheumatoid factor binding	Yes	No
Fc receptor binding	Yes	No
Mediates anaphylaxis	No	Yes
Binding to protein A and G	Yes	No
Cross-reactivity with rheumatoid factor	Yes	No
Cross-reactivity with human anti- mouse antibody (HAMA)	Yes	No
Reaction to hetero-agglutinins(Coombs, blood group classification)	Yes	No
Non-affinity separation	Remove plasma mixture from blood	Remove lipid mixture from egg yolk
Purification by salting-out	Yes	Yes
Purification by affinity columns	Yes (protein A and G)	Protein M[e]
Conjugation with enzymes, fluorophores and colloidal gold	Yes	Yes
Immunoprecipitation	Good	Relatively inefficient
Immunosuppression applications	Several products are under development	Can be used for xenotransplantation
Diagnostic applications	Widely used, especially monoclonal antibodies	Studied and applied for detection/ diagnosis
Therapeutic applications	Well developed	Under development
Generation of full-length monoclonal antibody by hybridoma technology	Routinely and commercially applied	Difficult, and lower yield of monoclonal IgY obtained
Generation of scFv antibody fragment by phage display	Easily produced	Easily produced

Source: Adapted and Modified from Ferreira Júnior et al. (2021).

[a] Wang et al., 2000
[b] Carlander, D., 2002
[c] Li et al., 2002
[d] Dávalos-Pantoja et al., 2000

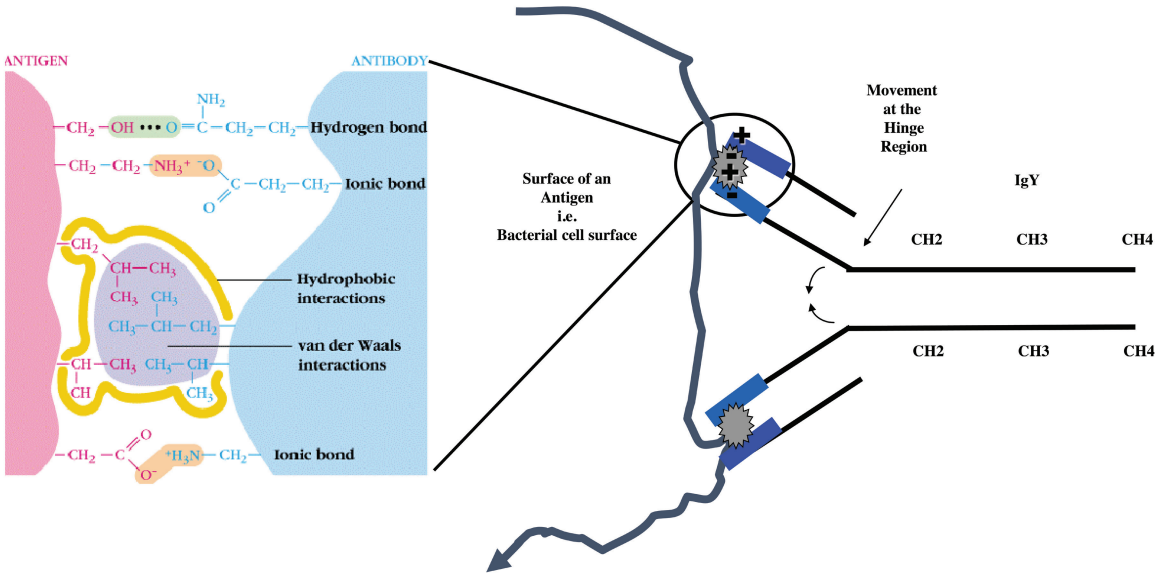

FIGURE 27.6 The noncovalent interactions that form the basis of antigen-antibody (Ag-Ab) binding. (Adapted from Goldsby et al., 2000.)

may explain why no reactivity issues have been encountered in consumer use of several products now in the market containing purified IgY.

Compared to vaccination, passive immunotherapy using IgY has distinct advantages such as (1) rapid and local onset of action, (2) highly specific activity, and (3) applicability to a broader age range of patients from infants to adults, including immunodeficient patients, and (4) it is nontoxic being a normal part of the human diet. While immunity derived from passive immunization lasts for only a short period coterminous with antibodies in the recipient, it nonetheless provides immediate and efficient host protection when properly concentrated onto the target organ.

27.4.3 Physicochemical Stability of IgY

Effects of heat, atmospheric pressure, pH, pepsin, and gut passage on IgY stability were studied extensively. IgY is the predominant immunoglobulin isotype in chicken eggs and acts as a major immunoglobulin fraction that confers passive gut immunity. IgY is proteinaceous and is therefore sensitive to heat, pH, and pepsin, properties that pose real challenges to its oral application for various digestive disorders. Within the past decade, several studies have been conducted to overcome these problems with various degrees of success. Shin et al. evaluated the heat, pH, and pepsin stabilities of anti-*Helicobacter pylori* IgY (IgY-Hp) (Figure 27.7) (Shin et al., 2002).

The binding activity of IgY with antigen decreased with increasing temperature and heating time. IgY is stable at temperatures ranging between 30°C and 70°C. The activity of IgY decreased by heating for 15 min at 70°C or higher, and IgY was denatured significantly when treated at temperatures higher than 75°C. IgY is relatively stable to pressure up to 4,000 kg per cm^2. The addition of high levels of sucrose, maltose, glycerol, or glycine conferred additional protection against pressure and thermal denaturation of IgY.

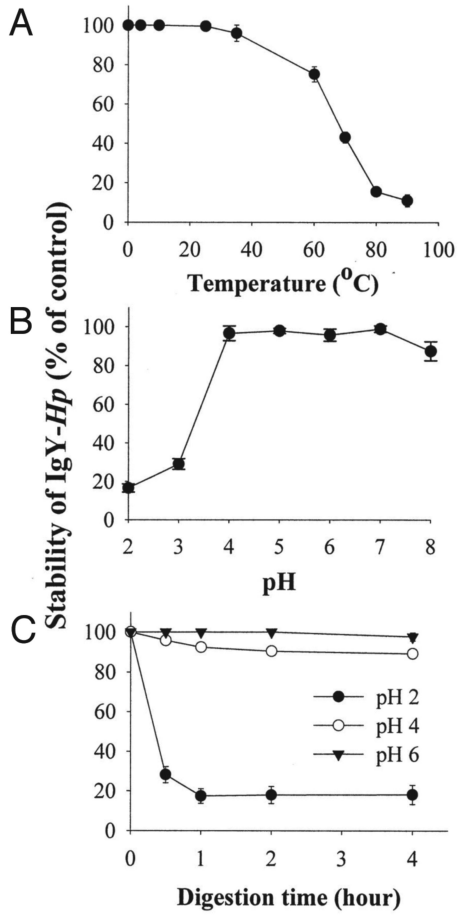

FIGURE 27.7 Effect of heat, pH, and pepsin on IgY-Hp. IgY-Hp was treated at various temperatures for 10 min (A), at various pHs for 4 hour (B), and with pepsin (15 mg/mL) (C) at pH 2, 4, and 6 for 0.5, 1, 2, and 4 hours. Remaining activities after the treatments were measured using ELISA and are expressed as a percentage of the initial activity. (Adapted with permission from Shin et al., 2002.)

The isoelectric point (pI) of IgY is in the range of 5.7–7.6, whereas that of IgG lies between 6.1 and 8.5 (Dávalos-Pantoja et al., 2000; Sun et al., 2001). The most hydrophobic moiety of the Ab molecule is the Fc fragment. Since the Fc fragment of the IgY is bigger than the IgG's, the IgY molecule is more hydrophobic than IgG. It has been demonstrated that this property might be useful for achieving stable adsorption of IgY onto latex particles (Dávalos-Pantoja et al., 2000). It could be demonstrated that preferentially at pH 8, the Fc part of IgY is firmly bound to the latex particles (Dávalos-Pantoja et al., 2001), hence IgY coated to latex microspheres retains its specific binding activity. The stability of IgY to acid and alkali has been studied under various conditions. It was found that the activity range of IgY for pH was pH 3.5~11. The stability of IgY at pH 3 was increased in the presence of sorbitol. IgY is quite resistant to trypsin and chymotrypsin inactivation but is degraded by pepsin (Hatta et al., 1993). The stability of IgY against pepsin appears to be highly dependent on pH and the enzyme/substrate ratio. At pH 5 or higher, IgY was fairly resistant to pepsin and retained its antigen-binding and cell-agglutinating activities. However, at pH 4.5 or below, both activities were lost. IgY digested with pepsin at pH 4 retained 91% and 63% of its activity after 1 hour and 4 hour incubation, respectively.

Several strategies to protect IgY from hydrolysis by gastric enzymes and acidic conditions have been investigated like dissolving in sodium carbonate buffer, encapsulation with liposomes, egg lecithin/cholesterol liposomes, and chitosan-alginate. Encapsulated IgY was released smoothly in in-vitro studies and was found to cure enteric colibacillosis in pigs more rapidly than non-coated IgY (Li et al., 2009). Encapsulated IgY was more resistant to pepsin and gastric conditions (Shimizu et al., 1993), but the uncoated IgY showed a better effect than the commonly used antibiotic. Another report showed that IgY and freeze-dried IgY coated with gum arabic were protected against hydrolysis by trypsin, chymotrypsin, and pepsin (Chang et al., 1999).

Researchers have investigated the in vivo passage and the efficacy of IgY in the gastrointestinal tract of piglets (Yokoyama et al., 1993) and calves (Ikemori et al., 1996). Results indicated that IgY powder was transported as immunologically functional molecules from the stomach down to the small intestine of calves while retaining much of their original biological activity (Figure 27.8).

27.4.4 Storage Stability of IgY

IgY is naturally protected by the yolk granules. The stability of IgY during storage is reasonably good under specified conditions. Dried IgY preparations were stored for 5–10 years at 4°C without significant loss of antibody activity and the preparations also retained activity for 6 months at room temperature and for 1 month at 37°C (Larsson et al., 1993). While

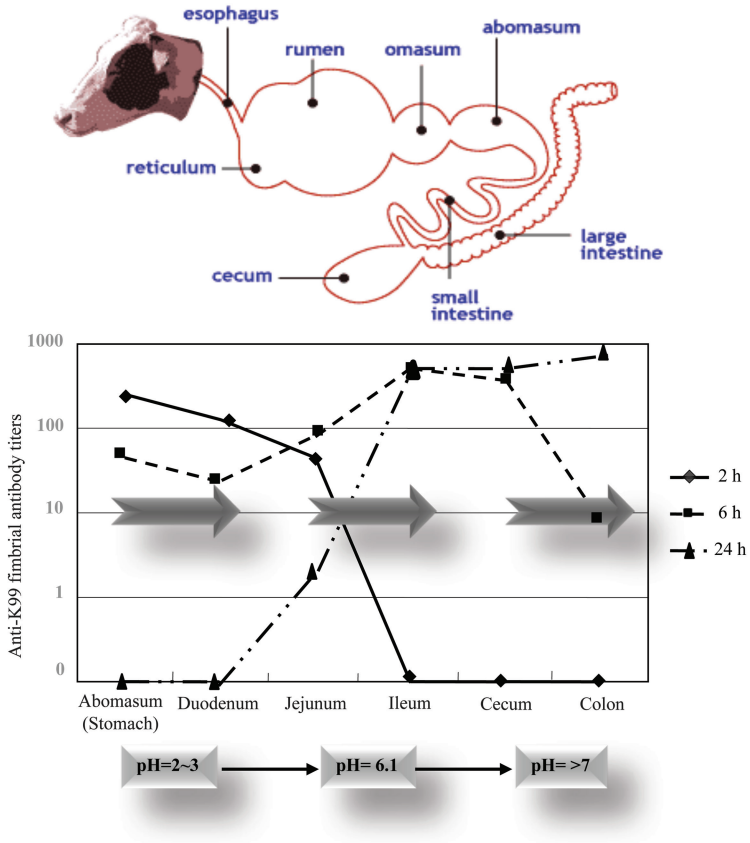

FIGURE 27.8 In vivo passage of IgY in the gastrointestinal tract of calves. Anti-K99 fimbriae antibody titers of IgY in the gastrointestinal tract of calves after 2, 6, and 24 hours post-administration. (Modified and adapted from Ikemori et al., 1996.)

lyophilization minimizes bacterial growth and maintains the better structural integrity of purified IgY, spray-drying is more economical (Yokoyama et al., 1992). The activity of IgY was well preserved after freeze-drying. Freezing at –70°C can cause the loss of up to 50% of IgY activity (Staak et al., 2000), so storage at –20°C is preferable. The addition of high levels of sucrose, maltose, glycerol or glycine displayed effective additional protection against thermal denaturation of IgY. If encapsulated, they are particularly resistant to pH and digestive enzymes. Encapsulation of IgY with egg lecithin/cholesterol liposomes reduced the activity loss of IgY under gastric conditions. IgY may be stable in 0.9% NaCl, 0.02% NaN_3 (sodium azide) at 4°C for periods ranging from months to a few years without any significant loss of antibody titer. Adding 0.03% w/v thimerosal or 50 µg/mL gentamicin in IgY solution helped to retard microbial growth (Schade et al., 2005). Two important points should be considered when storing IgY solutions with NaN_3 (sodium azide): (1) sodium azide can inhibit horseradish peroxidase (HRP) activity, especially when primary antibody is used in dilutions lower than 1:1,000; (2) IgY solutions stored with sodium azide should be dialyzed before the labeling of IgY antibodies with, for example, HRP. To avoid the effects of repetitive thawing/freezing of IgY, 10–50% (v/v) glycerol can be added. Collectively, these unique biological attributes make IgY an effective natural food antimicrobial system and immunotherapeutic agent.

27.4.5 Biological Safety of Oral IgY

Several properties make IgY attractive for oral immunotherapy (Schade et al., 2007). While the mouth is the portal of entry for many infectious agents, it is, therefore, logical to use this as the route for IgY to target specific infectious entities within the alimentary tract. IgY does not pass as intact molecules from the intestines to the blood circulation, thus precluding any systemic effect (Losonsky et al., 1985). IgY use is associated with much lower risk of inducing specific resistance among pathogenic microorganisms since it is directed to multiple antigenic targets that require multiple genes for their synthesis. IgY is superior to mammalian IgG in terms of safety issue. IgYs are safer than IgGs because they do not bind to human Fc receptors or fix mammalian complement components, hence they do not trigger potentially dangerous immune responses (Carlander et al., 1999). Kubickova et al exposed immortalized human lung epithelial cells to IgY, using lipopolysaccharide as a positive control and phosphate-buffered saline as a negative control. Treatments also included exposure to human and goat IgG, and exposure lasted 24 hours for all treatments. The researchers found that the levels of pro-inflammatory cytokines tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, and granulocyte-macrophage colony-stimulating factor (GM-CSF) were very low in cell cultures treated with IgY compared with the high levels of TNF-α and GM-CSF in cells treated with lipopolysaccharides, indicating that IgYs do not cause inflammatory responses in lung cells and can thus be safely used for prevention of airway infections (Kubickova et al., 2014). Additionally, oral IgY antibodies have been applied to treat rotavirus infections in humans (Sarker et al., 2001; Rahman et al., 2012; Thu et al., 2017) and to treat pulmonary Pseudomonas aeruginosa infections, and no negative side effects of IgY treatment have been observed in up to 10 years of use (Nilsson et al., 2007b).

Being an ingredient in our regular diet, poultry eggs are considered generally safe. As natural components of eggs, the IgY antibodies tend to be nontoxic. IgY antibodies are not deposited in meat, hence avoiding potential violations of regulations in countries that forbid the use of antibiotics for poultry and livestock (Li et al., 2015). Allergic reactions may occur upon ingestion of egg-derived components particularly those that contain appreciable amount of egg white. However, the water-soluble IgY materials purified from egg yolk (delipidated) are not usually associated with allergic reactions. The risk of allergy is lower when administering the antibodies orally than by other routes (Russo et al., 2001). Moreover, oral administration of egg protein (mainly ovalbumin) has been shown to induce systemic tolerance (Matsunaga et al., 2000).

Generally Recognized as Safe (GRAS) status from both the U.S. Department of Agriculture (USDA) and the Food and Drug Administration (FDA) for IgY is being tried to obtain. Approval of individual products by the FDA for using egg antibodies in human patients is relatively easy. Since the activity of IgY was well preserved and easy to apply for human patients, some companies (e.g., EW Nutrition Japan) (Table 27.4) have started to develop various food products with this IgY like tablets, lozenge, candy, pastilles, sachets, yoghurt (regular, drinking) and baby milk etc. (Table 27.5) (Thu et al., 2017). This would be easier to handle, both for the patients and for the pharmacy or hospital, due to the ease of storing IgY at room temperature.

27.5 Production of IgY

The major choice of animal for IgY production is the avian species chicken. IgY production steps include (1) antigen of interest; (2) antigen + adjuvant mixture, emulsion; (3) immunization; (4) immunization routes; (4) hyperimmunized egg collection; (5) egg breaking; (6) pasteurization of egg liquid; (7) spray-drying; and (8) IgY powder production. IgY production results from immunization, but its production and immunization are not very predictable. Parameters that may influence the immune response of the immunized chicken include the antigen nature and dose, the type of adjuvant used, the route of administration, characteristics of chicken (such as keeping conditions, age, breed, effect on egg laying capacity), and overall immunization schedule. Different type of antigens is being used to produce IgY, such as nucleic acid (Bachtiar et al., 2016), protein (Lee et al., 2016), lipid, and carbohydrates (Zhen et al., 2011). In addition, an immune humoral response must be elicited by immunization with recombinant proteins (Nasiri et al., 2016) or peptides (Hodek et al., 2015). Both, complex antigens, e.g., whole viruses, bacteria, and parasites (Grando et al., 2017; Amro et al., 2018; Lopes et al., 2019; de Faria et al., 2019; Silva et al., 2020) and individual biomolecules, e.g., large proteins (Skottrup et al., 2019; Lu et al., 2020), or small peptides conjugated to a suitable carrier protein, such as keyhole limpet hemocyanin (KLH) (Grzywa et al., 2014; Łupicka-Słowik et al., 2014), have been used to stimulate the

TABLE 27.4

Summary of IgY Purification

Step	Method	Reference
1. De-lipidation		Schade et al. (2005); Pereira et al. (2019)
	a) Freeze and thaw at neutral pH	Jensenius et al. (1981)
	b) Water dilution method	Akita and Nakai (1993); Losonczy et al. (1999); IGY Life Sciences (2021)
	c) Organic solvents (chloroform, acetone, isopropanol)	Bade and Stegemann (1984); Chung and Ferrier (1991); Bizhanov and Vyshniauskis (2000)
	d) Organic acids (caprylic acid, trichloroacetic acid)	Araújo et al. (2010)
	e) Natural gums (polyanionic polysaccharides, e.g., xanthans)	Hatta et al. (1990)
	f) Supercritical carbon dioxide extraction (SCE) delipidation.	Hiidenhovi et al. (2005); Aro et al. (2009)
	g) Polysaccharides (e.g., pectin, λ-carrageenan, carboxymethylcellulose, methylcellulose, dextran sulfate)	Chang et.al. (2000); Tong et al. (2015)
2. Precipitation	a) 3.5% polyethylene glycol (PEG)	Polson et al. (1980, 1985); Svendsen et al. (1995); Meulenaer et al. (2001)
	b) Caprylic acid followed by ultrafiltration at pH 9.0.	Redwan et al. (2021)
	c) Dextran sulphate and calcium chloride	Jensenius et al. (1981)
	d) Phosphotungstic acid and magnesium chloride	Vieira et al. (1984)
	e) Saturated sodium sulphate	Jensenius et al. (1981)
	f) Saturated ammonium sulphate	Ambrosius and Hadge (1987); Garvey et al. (1977)
	g) Precipitation using 12% PEG	Polson et al. (1980); Polson et al. (1985)
3. Purification		
A. Chromatographic Method	a) Size-exclusion chromatography (Sephadex 100G)	Pour Amir & Rasaei (2001)
	b) Low-pressure chromatography	Amro et al. (2018)
	c) Ion exchange (Anion, DEAE-Sephacel) and Cation (CM-Cellulose) chromatography	Akita and Nakai (1993); Ko and Ahn (2007)
	d) Higher solution chromatography through multicolumn systems	Constantin et al. (2020)
	e) Hydrophobic interaction chromatography	Hassl and Aspöck (1988)
	f) Thiophylic interaction chromatography	Hansen et al. (1998)
	g) Gel-filtration chromatography	Pour Amir & Rasaei (2001)
	h) Affinity chromatography	Verdoliva et al. (2000); Behn et al. (2001); Chen et al. (2002); Constantinoiu et al. (2007); Dong et al. (2008); Sui et al. (2011); Jiang et al. (2016a)
B. Filtration	Gel filtration, funnel filtration, and ultrafiltration	Akita & Nakai (1993); Kim & Nakai (1998); Meulenaer et al. (2001); Hernández-Campos et al. (2010)

development of specific IgYs in hens. The antigen dose may be critical since too much or too little antigen can lead to an undesirable immune response (Schade et al., 2001).

27.5.1 Processing of Hyperimmunized Eggs into Egg (IgY) Products

Eggs processing can start with egg washing. Eggs are then individually broken with machines making also white and yolk separation, as well as eggshell removal. Immediately after breaking and separation, yolk and whole egg are filtered and cooled before transfer into pasteurization tanks. After that, these two fractions can be pasteurized before packaging, to obtain liquid egg products, but they can also be spray-dried for marketing as powders. In that case, yolk and whole egg are pasteurized before spray-drying described. Snapshots of different processing steps of hyperimmunized eggs into egg (IgY) products are shown in Figure 27.9.

Different drying technologies have been applicable for producing a whole egg, egg yolk, and egg white powder products. Some of them like foam-mat drying (Kudra & Ratti, 2006; Thirupathi et al., 2008), pan drying, belt drying, and spray drying (Patel et al., 2009; Nandiyanto & Okuyama, 2011; Anandharamakrishnan & Ishwarya, 2015), freeze-drying (Jaekel et al., 2008), and hot air (oven) (Ratti, 2001) was applied within their specific criteria and their limitations.

Spray drying is a unit operation technology widely used in foods (Loh et al., 2005), pharmaceuticals, encapsulation,

TABLE 27.5

IgY Administration Route and Dosage Form for Animal and Human Health Application

Category	Administration Route	
Animal:	**Enteral (Oral) Dosage form**	**Topical (Local) Dosage form**
Feed	Whole egg powder	
Additive	Top dressing	
	Pellet	
Premix	Oil-coated pellet	Lotions
	Tablet	Eye drops
	Enteric tablet	Nasal drops
	Kibble	Spray
	Dental biscuit	Toothpaste
	Dental rope	Wet tissue/paper
	Dental gum	Dental soluble film
	Paste in bottle	Inhalers
	Paste in syringe	
Human:	Egg yolk powder	
	Sachet	Lotions
Food	Troche	Eye drops
	Tablet/coated tablet	
	Candy	
	Lozenges	
	Lollipop	Nasal drops
	Capsule	
Supplement	Chewing gum	Spray
	Oral saline sachet	Toothpaste
	Baby milk powder	Mouth wash
	Drinking yoghurt	Wet tissue/paper
	Regular yoghurt	Dental soluble film
	Shell egg	Face mask
		Air filter
		Inhalers
		Bath salt (nyokuzai)

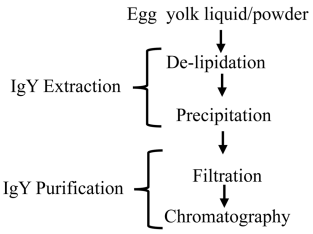

FIGURE 27.10 Flow diagram of IgY purification steps.

plastic resins, paint pigments, ceramic materials, and catalyst supports, for use with microalgae and the chemical industry. The various flow types manufactured in spray dryers include (1) co-current flow dryer, (2) counter-current flow dryer, (3) mixed flow dryer, (4) open cycle dryer, (5) closed cycle dryer, (6) semi-closed cycle dryer, (7) single stage dryer, (8) two-stage dryer, (9) vertical dryer, and (10) horizontal dryer. Most vertical chambers are cylindrical, ending with an inverted cone on their base. (Cal & Sollohub, 2010).

27.6 Purification of IgY

Purification of IgY (Figure 27.10) mainly consists of 2 steps: IgY extraction and purification. The major components of egg yolk are lipids (32%), proteins (16%), and water (50%). About one-third of the lipids are phospholipids, mainly phosphatidylcholine (about 80%) (Figure 27.11). The high concentration of lipids and lipoproteins is one of the major barriers to IgY extraction from egg yolk (Verdoliva et al., 2000, Schade et al., 2005). Therefore, in most cases, IgY isolation involves the removal of lipids ("de-lipidation" step). Various IgY extraction methods were reviewed in detail by De Meulenaer & Huyghebaert (Hatta et al., 1990; Akita & Nakai, 1992; Akita & Nakai, 1994; Fischer et al., 1996; De Meulenaer & Huyghebaert 2001). These methods can be divided into two steps: de-lipidation and precipitation, followed by purification.

IgY purification is summarized in Table 27.4.

It is reported that a combination of the methods mentioned above, e.g., a combination of PEG precipitation with affinity

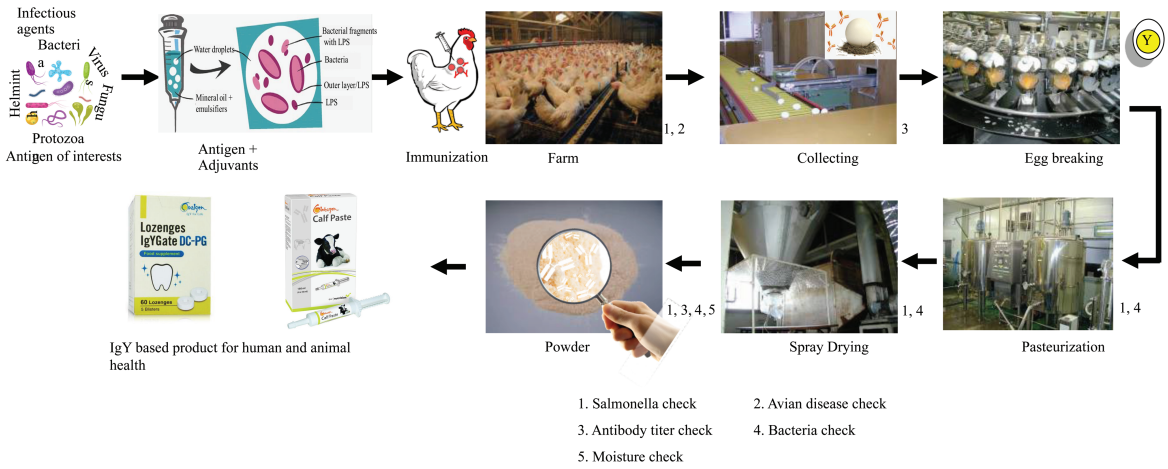

FIGURE 27.9 Snapshots of processing steps of hyperimmunized eggs into IgY products.

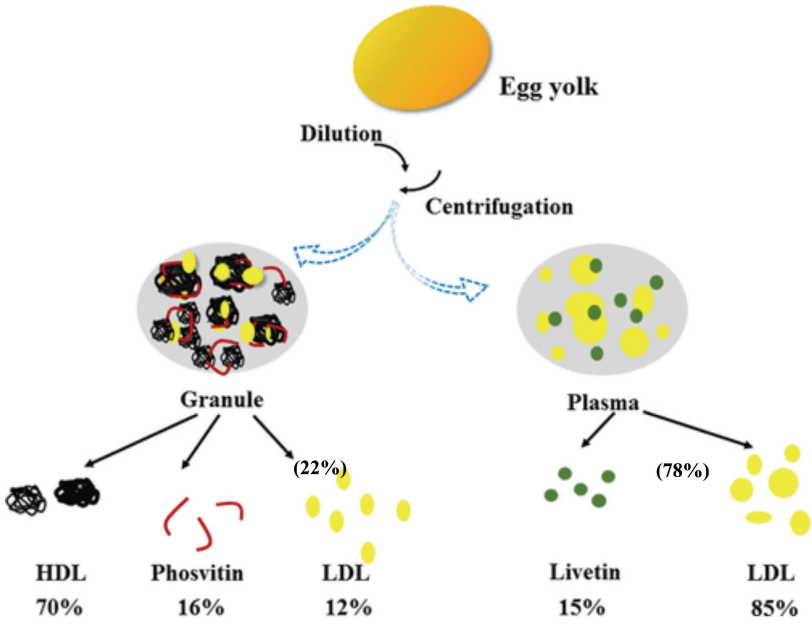

FIGURE 27.11 Constituents of plasma and granules from hen egg yolk (LDL, low-density lipoprotein; HDL, high-density lipoprotein). (Adapted from Xiao et al., 2020.)

chromatography (Pauly et al., 2011) or ammonium sulfate precipitation with ion exchange chromatography (Ko & Ahn, 2007), can further increase the purity of the IgY preparation. Moreover, sequential precipitation with 31% ammonium sulfate and 12% PEG resulted in IgY antibodies of more than 95% purity without any loss in immunoreactivity (Constantin et al., 2020). Despite the numerous protocols described in the literature, the most popular isolation strategy of IgYs from immune eggs involves a de-lipidation step, in which IgY is extracted in the supernatant after treating the egg yolk with 10 volumes of acidic water and a subsequent precipitation step, in which IgY precipitates with ammonium sulfate or PEG, at suitable concentrations (Amro et al., 2018). Purity level is checked by SDS-PAGE and Western blotting (Redwan et al., 2021). Various types of commercial IgY extraction kits are available in the market. Trouble-shooting advice and protocols for other IgY purification methods can be found in the IgY manual (Staak et al., 2000).

In conclusion, IgY extraction methods require an initial delipidation step before extraction of insoluble lipids and lipoproteins. The water dilution method was most efficient for extracting IgY from the water-soluble protein fraction. Further purification of IgY after crude extraction can be achieved by selective precipitation. The precipitation with sodium or ammonium sulfate, sodium chloride as well as polyethylene glycol offers a cheap and easy methodology and can be used in laboratory practice. Column chromatography and ultrafiltration are expensive and impractical for the large-scale production of antibodies.

Large-scale production is continuously improving to achieve a sustainable turnover for industries. Bioactive peptides of egg components like lysozyme, avidin, and IgY antibodies are currently under industrial production using standardized purification protocols, is feasible with different techniques involving supercritical fluid technology, magnetic particles for separation of specific egg compounds by immune magnetic separation (Huopalahti et al., 2007), and enzymatic hydrolysis of egg white albumin and yolk followed by ultrafiltration to obtain low-molecular-weight peptides combined with chromatographic techniques (Nimalaratne & Wu, 2015). The choice of a suitable method depends on the yield and purity desired, final application of the IgY as well as material cost, technology, labor skills, and scale of extraction.

27.7 IgY Administration Route and Dosage Form

IgY has been extensively used in human and veterinary health (Rahman et al., 2013). But the IgY activities are in question when used in different forms. IgY is a protein in nature, may be structural alterations happened due to the digestive enzyme activity and gastrointestinal acidity. At the same time, they pass through the gastrointestinal tract and their biological activity is at risk. To overcome these situations of IgY activity and to improve IgY delivery as well, different types of coating materials (e.g., chitosan-alginate microcapsules, hydrogels containing acrylamide and acrylic, acid methacrylic acid copolymers, liposomes, polymeric microspheres and multiple emulsification) and conventional dosage forms have been developed for different gastrointestinal and topical administrations (Table 27.5). These above coating materials are commonly used to encapsulate and thus protect IgY from digestive degradation (Holser, 2013; Paul et al., 2014; Soumaila Garba et al., 2019). The study of IgY delivery and dosage form design is still at an early stage of development. Some delivery methods reported such as microneedle-based transdermal, transdermal patch, inhalation, aerosol, film-based buccal targeting on oral

mucosal surface, nasal sprays, and self-administration allowed subcutaneous delivery, such as NanoPass MicronJet technology and iontophoresis technology (Anselmo et al., 2019).

27.8 Chicken Monoclonal IgY Antibodies

Monoclonal antibodies are clones of just one antibody, and they bind to one antigen only. Polyclonal antibodies come from several different types of immune cells and will bind to more than one antigen. Monoclonal IgY (mIgY) is a new antibody development that combines the advantages of IgY and Monoclonal antibodies (mAbs). Table 27.6 shows the difference between monoclonal and polyclonal antibodies.

Different types of functional chicken antibodies are reported with variable degrees of immunogenicity. As chicken antibodies are immunogenic in mammals, their clinical applications are limited (Tateishi et al., 2008). In particular, the constant region contributes a significant component to immunogenicity (Morrison et al., 1984). To overcome this problem, genetic engineering techniques have been applied to produce chimeric (Andris-Widhopf et al., 2000; Nishibori et al., 2004), humanized (Jones et al., 1986; Foote & Winter, 1992; Studnicka et al., 1994), and recombinant antibody (Bird et al., 1988; Nakamura et al., 2000) formats of chicken antibodies.

Methods for monoclonal IgY production include (1) Hybridoma Technology (Pink, 1986; Nishinaka et al., 1989; Nishinaka et al., 1991; Nishinaka et al., 1996; Matsushita et al., 1998; Matsuda et al., 1999; Nakamura et al., 2000); (2) DT40 Cell Line, a chicken lymphoma cell line (Cumbers et al., 2002; Seo et al., 2005; Seo et al., 2006); and (3) Antibody Display Technologies: Phage Display (Smith, 1985; Andris-Widhopf et al., 2000), Yeast Surface Display (Boder & Wittrup, 1997; Bogen et al., 2020), and Ribosomal Display (Hanes & Plückthun, 1997; Hanes et al., 1998; He & Taussig, 2007; Qi et al., 2009; Plückthun, 2012).

The hybridoma technology is difficult in the chicken system due to the lack of a robust fusion partner. The simplest, easier, and more efficient way of mIgY production by using phage display library selection for scFv gene constructs with higher affinity against targeted pathogens (Kyung et al., 2005; Finlay et al., 2006). mIgY can be developed into small molecular weight antibody fragments (particularly scFv), chimeric, and humanized antibodies to address the many challenges ahead to developing mAb for various biomedical applications, especially those for which conventional antibodies are ineffective. Table 27.7 shows the overview of mIgY preparations using different antibody engineering technology and selection methods. mIgY has potential applications for immunological detection and diagnosis, for screening and validating biomarkers and drug targets, and to produce antibodies against conserved

TABLE 27.6

Difference between Polyclonal and Monoclonal Antibodies

Parameter	Monoclonal Antibodies	Polyclonal Antibodies
Animal	Rat, mouse, chicken, rabbit, human, etc.	Rabbit, guinea pig, goat, sheep, rat, mouse, chicken, etc.
Form	Hybridoma	Antiserum
Production:		
- Time	Long (up to a year)	Short (3–4 months)
- Cost	Moderate	Low
- Ease	Difficult	Very Easy
Class, subclass	Single Class	Mixed Classes
Epitope	React to a single epitope	React to multiple epitopes
Targets	Immunogenic targets	Immunogenic targets
Binding site	Single specific site	Different areas of target molcules
Specificity	High if good quality antibodies are selected	Moderate. Lower than monoclonal antibodies because multiple types of antibodies are present
Sensitivity	Moderate to high	Variable
Engineering	Only after converting to rAb	Not possible
Antibody nature	Single antibody species	Mixed population of antibodies
Reproducibility	The same antibodies are produced indefinitely	Variable among lots
Stability	Moderate. Binding ability may be lost if the epitope is lost by fixation/denaturation of the antigen, because monoclonal antibodies are homogeneous.	High. Binding ability tends to be unaffected by fixation/denaturation of the antigen, because multiple different antibody molecules are present.
	Tend to be sensitive to modifications, such as labeling and removal of the Fc region	Tolerate modifications, such as labeling and removal of the Fc region
Tolerance	May only recognize a particular protein form (phosphorylation, dimersied) Infinitely renewable	Tolerant of small changes in protein structure (denaturation, dimerization, phospholyration)
Reproducibility	Virtually reproducible	Limited
Availability	Commercially available	Commercially available

Source: Modified and adapted from Frenzel et al. (2013).

TABLE 27.7

Overview of mIgY Preparations Using Different Antibody Engineering Technology and/or Selection Methods

mIgY Type	Antigen	Use	Eng./Sel.Method	Reference
Chicken/ human chimeric fab	Recombinant hemagglutinin protein	H5N1 diagnostic testing	Phage display	Pitaksajjakul et al. (2010)
scFv	Gentamicin	Antibiotic detection	Phage display	Li et al. (2016a)
scFv	Salbutamol	Sensitive assay (detection)	Phage display	Lee et al. (2018a)
scFv	Inactivated cobra venom proteins	Diagnosis of snakebites and antibody affinity test	Phage display	Lee et al. (2018b)
scFv	Epidermal growth factor receptor (EGFR)	Detection	Yeast surface display	Bogen et al. (2020)

Source: Adapted from Leow et al. (2021).

mammalian proteins. In addition, the production of antibody fragments and chimeric antibodies make mIgY more widely clinical applicable. We believe that mIgY have enormous prospects in the development of new antibody platforms. New technologies and new types of antibodies are likely to broaden the application of antibodies. As a molecular-targeted drug, monoclonal antibodies that could not be obtained in mammals rather it will be obtained by utilizing the antibody production of chickens of different species. We hope humanized antibody drugs based on monoclonal IgY antibodies will be developed. In the future, chicken mIgY's are likely to play a more important role in disease diagnosis and treatment, and in basic and applied antibody research (Table 27.8).

27.9 Production of IgY in Transgenic Chickens

Transgenic animal refers to an animal in which there has been a deliberate modification of the genome - the material responsible for inherited characteristics - in contrast to spontaneous mutation. Genetically modified animals have significantly contributed to our understanding of different aspects related to immunity, infectious diseases, neurology, behavior, and developmental biology (Yeh et al., 2002; Lyall et al., 2011; Lalonde et al., 2012; Pinkert, 2014; Park et al., 2017). While mice were the first animals to be genetically modified (Costantini & Lacy, 1981; Gordon & Ruddle, 1981). Significant progress was made in generating recombinant proteins, including mAbs for therapeutic applications, in genetically modified chickens over the last decades (Bahrami et al., 2020; Park et al., 2020). Schematic representation of the original immunoglobulin Y technology, Monoclonal IgY and IgY in Transgenic chickens and are also shown (periphery, left and right) in Figure 27.12 (Karachaliou et al., 2021).

TABLE 27.8

Examples of Monoclonal Antibody Treatments Approved by the Food and Drug Administration

Name	Target	mAb Type	Approval Date
Butuximab	CD30	Chimeric	2011.08.19
Dituximab	GD2	Chimeric	2015.03.10
Basiliximab	CD25	Chimeric	1999.03.09
Patoizumab	HER-2	Humanized	2012.06.08
Otozumab	CD20	Humanized	2013.11.01
Perizumab	PD-1	Humanized	2014.09.04
Daremumab	CD38	Humanized	2015.11.06
Elotuzumab	SLAMF7	Humanized	2015.11.30
Nesimumab	EGFR	Recombinant human	2015.11.24
Olarezumab	PDGFR-α	Human	2016.10.19
Avelumab	PD-L1	Human	2017.03.23

Source: Adapted from Leow et al. (2021).

To successfully generate genetically modified chickens, the following methods have been used such as (a) development of in vitro culture system for chickens, (b) utilization of primordial germ cells and genome editing in chickens, (c) creation of chicken embryonic stem (ES) cells and their utilization, and (d) search for leukemia inhibitory factor (LIF) that maintains totipotency of chicken ES cells.

The first genetically modified chicken was generated by the insertion of retroviral foreign DNA delivered by the avian leukosis virus that was successfully integrated to the germline (Salter et al., 1987). Since then, various viral vectors have been used to generate transgenic chickens to produce recombinant proteins (Salter et al., 1987; Harvey et al., 2002; Kamihira et al., 2005), including mAbs (Kamihira et al., 2009).

One of the most effective approaches to producing transgenic chickens is the in vitro transfection of avian cell lines, such as primordial germ cells (PGCs) and embryonic stem cells (ES), the clonal selection and reinsertion into the embryo leading to fully transgenic progeny in the next generation (Zhu et al., 2005; van de Lavoir et al., 2006; Kim et al., 2018).

The OmniChicken by Ligand Pharmaceuticals Inc. is a worldwide unique platform to produce human monoclonal antibodies from chickens using the phylogenetic difference between mammals and birds. A study conducted by Oishi and colleagues demonstrated the ability to integrate human interferon beta (hIFN-β) into the chicken ovalbumin locus in order to produce hIFN-β in egg white (Oishi et al., 2018). Authors demonstrated the ability to produce foreign proteins in eggs, which would have industrial and therapeutic applications.

Several advantages are provided by newly invented gene editing technologies, including the simplicity of design and application combined with high efficiency (Chira et al., 2017). Understanding the host cell behavior during host-pathogen interactions may help target pathogen-specific receptors and viral cellular transport (Heaton et al., 2016). Determining new target genes associated with disease susceptibility should fill the research gap and open the door for

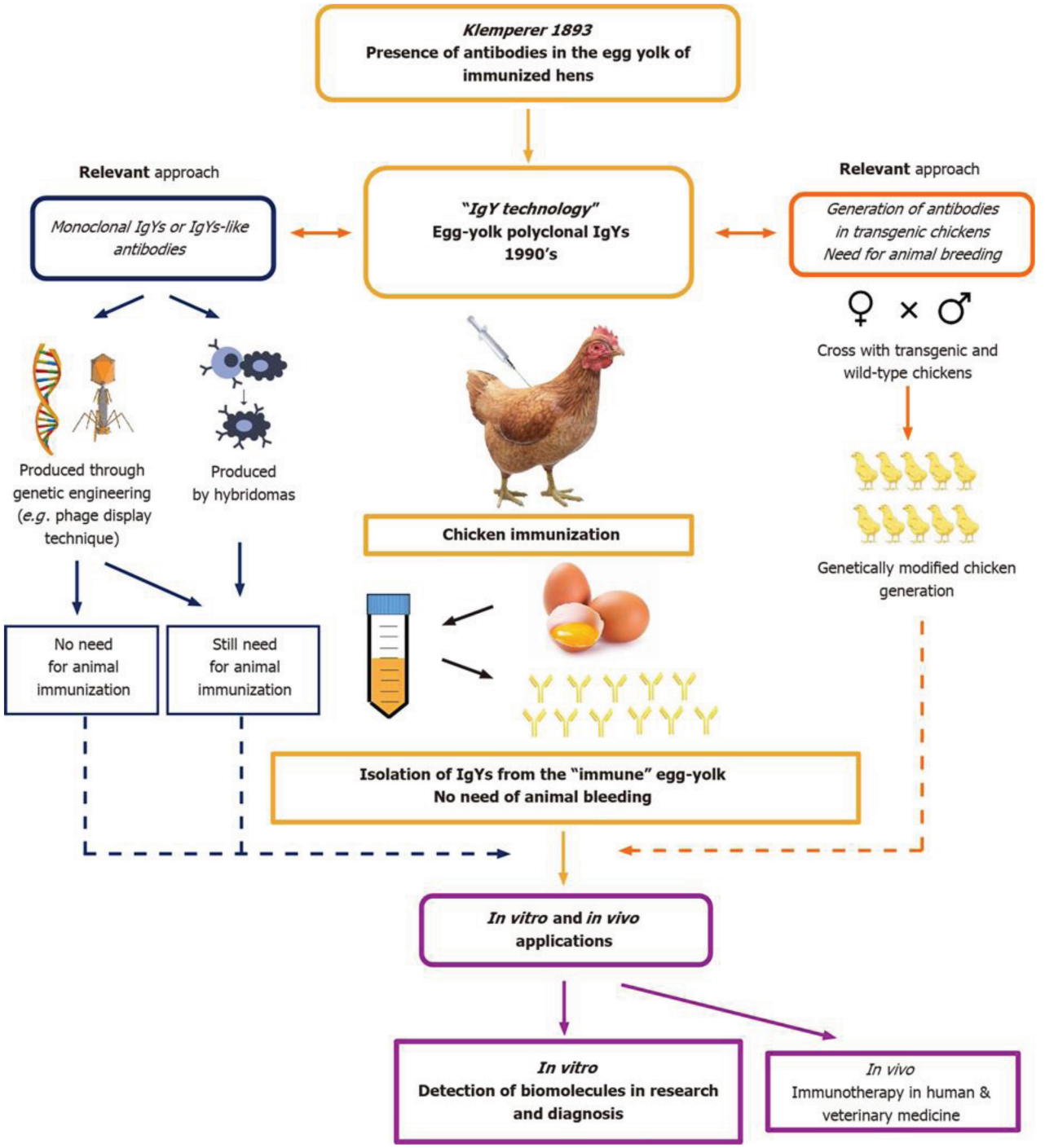

FIGURE 27.12 Schematic representation of the main parts comprising the original immunoglobulin Y technology (central axis); promising relevant approaches are also shown (periphery, left and right). (Adapted from Karachaliou et al., 2021.)

new therapeutical approaches. Although the debate about using genetically modified animals in food production will continue to be stimulated, we may obtain new breeds of chickens in the future that are resistant for specific pathogens. We speculate that spending more efforts connecting gene editing technologies with the prevention of infectious diseases will change the way we use to fight pathogens and will probably improve the animal welfare.

27.10 Use of IgY in Immunoassay and Diagnosis

IgY-based immunoassay is a widespread field to diagnosis biomolecules of interest in biological specimen and infectious diseases pathogen in humans, animals, aquaculture and plants. Enzyme-linked immunosorbent assay (ELISA), western blotting (WB), immunofluorescence (IF), and immunohistochemistry

(IHC) methods are the most common applications for IgY (Behn et al., 2001). Relevant to consider that antigenic target recognition by using antibodies can show some differences according to the method used. Regarding the conformational epitope structure, the performance of antibodies recognizing a given epitope by WB can represent nothing about the same antibody performance in ELISA with the same antigen (Uhlen et al., 2016). IgY antibody shows advantages compared to the mammal IgG use in immunoassay. In this context, the rheumatoid factor (RF) is a major source of interference in many immunoassays using mammalian polyclonal or monoclonal antibodies by interacting with IgG and causing false-positive results. IgY antibodies do not react with RF avoiding false-positive results in ELISA (Larsson et al., 1991). Because of this advantage conferred by IgY's structure, the use of IgY antibodies in immunoassays may result in less background noise, fewer false positives, and decreased aggregation of antibodies, which are common issues observed with both monoclonal and polyclonal mammalian antibodies. Furthermore, IgY antibodies have also shown high binding specificity and low cross-reactivity with other antigens comparable to current industry standards and may have value in a variety of applications to detect pathogens.

27.10.1 IgY in Immunoassay

Use of IgY has been extensively studied in various immunoassay such as:

a. ELSIA (Enzyme-linked immunosorbent assay): IgY-based ELISA does not demand expressive modifications from the most common procedures and reagents used to carry out this protocol (Ferreira Júnior et al., 2012; da Silva et al., 2016). Egg yolk IgY can be labeled with horseradish peroxidase for use in immunoenzymatic assays (Ruan et al., 2007). Some possibilities for application of yolk antibodies-based ELISA are: screening molecules related to drug-drug interactions (Jiang et al., 2016b); sandwich ELISA to capture bacterial toxins (Nagaraj et al., 2016); screening animal diseases by using recombinant antigens (Zhang et al., 2016b); characterization of maternal IgY transferred to egg yolk (Murai et al., 2016); coproantigen to capture ELISA for intestine human parasite (Teimoori et al., 2016); screening antibiotic residues in food samples (He et al., 2016); detection of blood circulating helminth antigens by immunomagnetic bead ELISA (Nie et al., 2014); potential for clinical application diagnosing cancer antigen (Grzywa et al., 2014);
b. Immunofluorescence assay: Specific IgY was used in an indirect immunofluorescence assay to detect microbial antigens in biological specimens (Camenisch et al., 1999; Cipoll al., 2001; Sesarman et al., 2008; Shin et al., 2009; Bentes et al., 2015);
c. Flow cytometry assay: (Santoro et al., 2004). IgY antibodies are suitable reagents for flow cytometry and as well as certain monoclonal antibodies, for example, to study human and rabbit platelet physiology (Santoro et al., 2004). When using phage display-based single chain variable fragments (scFvs), polyclonal IgY production and further the flow cytometry assays it is possible to develop immunoreagents for the isolation and characterization of stem cells, molecular diagnostics and therapeutics of lung cancers (Leu et al., 2010; Bowes et al., 2011);
d. Immunochromatographic assay: The immunochromatographic assay (ICA) requires no instruments and has a detection time of less than 10 min and it is portable and easy to perform in the field. The development of IgY-based strip could be a promising on-site tool for screening infection or disease outbreaks. IgY-gold complexes depositing onto the conjugate pad as detector reagents showed high specificity (He et al., 2015; Zhang et al., 2015a);
e. In diagnostic and analytical applications: IgY antibodies serve as essential components in a variety of diagnostic assays used for the qualitative and quantitative determination of a wide range of substances (Cakir-Koc et al., 2020; Kota et al., 2020; Porte et al., 2020); and
f. As an immunoaffinity ligand and Proteomic: Separation of complex protein mixtures that have a wide dynamic range of concentration, such as plasma or serum, is a challenge for proteomic analysis. Sample preparation to remove high-abundant proteins is essential for proteomics analysis. Immunoglobulin yolk (IgY) antibodies have unique and advantageous features that enable specific protein removal to aid in the detection of low-abundant proteins and biomarker discovery. (Huang et al., 2005; Fang & Zhang, 2008; Nilsson et al., 2008; Qian et al., 2008; Rajic et al., 2009; Polaskova et al., 2010; Magagnotti et al., 2010; Manhani et al., 2011; Kovacs-Nolan & Mine, 2011).

27.10.2 IgY in Diagnosis

a. Viral infections diagnosis: In the detection of canine parvovirus (He et al., 2015), bovine viral diarrhea virus (BVDV) (Zhang et al., 2016), *rhesus* monkeys hepatitis A virus (HAV) (Silva et al., 2012), soft-shelled turtle systemic septicemia spherical virus (STSSSV) (Zhang et al., 2015b), acute respiratory syndrome associated to coronavirus (SARS-CoV) (Palaniyappan et al., 2012), dengue virus 2 (DENV2) (Figueiredo et al., 2015).
b. Bacterial infections diagnosis: In the diagnosis of *Staphylococcus aureus* (Richman et al., 1982; Walczak et al., 2015), staphylococcal enterotoxin A (SEA), B (SEB) C (SEC), toxic shock syndrome toxin (TSST) and α-hemolysin of *S. aureus* (Reddy et al., 2013; Mudili et al., 2015) methicillin resistant *S. aureus* (MRSA) strains (Yamada et al., 2013).
c. Parasitic infections diagnosis: in detecting the protozoan *Toxoplasma gondii* (Cakir-Koc, 2016; Sert et al., 2017), the helminth *Opisthorchirs viverrini, Taenia* spp., *Echinostoma* spp. and *Minute Intestinal Fluke* (MIF) (Teimoori et al., 2017). Miura et al.

produced IgY against the GP60 protein, from the *Cryptosporidium hominis* protozoan. These IgY bound to GP60 in Western blot and to *C. parvum* sporozoites in fecal samples by indirect immunofluorescence, suggesting that anti-GP60 IgY could be used in the diagnosis of cryptosporidiosis caused by both *C. hominis* and *C. parvum* (Miura et al., 2017).

d. Tumors diagnosis: IgY against the peptide antigen CA 15-3, a commonly used breast cancer marker, was used as secondary antibody in a sandwich ELISA aiming to detect CA 15-3, showing potential for clinical use (Grzywa et al., 2014). Sun et al. produced IgY against two portions of the transmembrane glycoprotein HER2, is promising for use in breast cancer diagnosis (Sun et al., 2015). In another study, Łupicka-Słowik et al. developed a direct ELISA test using a lysate of human malignant tumor cells and IgY against bovine adenosine deaminase (c-ADA) for the detection and quantification of ADA for pleural tuberculosis diagnosis (Łupicka-Słowik et al., 2018). IgY developed to detect prostatic specific antigen (PSA) and two peptide fragments of this protein demonstrated specificity (Łupicka-Słowik et al., 2014).
e. Hematological tests: Hens immunized with umbilical cord sera produced specific IgY against IgG and the complement fractions C3b and C3d. These antibodies did not react with the C4b fraction — which configures a higher specificity, since anti-C4b antibodies often cross-reacts with the antigens of Chido/Rodgers RBC group — nor with erythrocyte antigens from ABO group. These antibodies are, therefore, promising as a reagent for Coombs test (Calzado et al., 2017).
f. Enzyme detection: IgY immunoassays were used to detect the hepatic expression of Cytochrome P450 2E1 (CYP2E1) in mice treated with medicinal herbs and products derived from plants rich in flavonoids. Anti-CYP2E1 IgY was specific, without reacting with other cytochromes, and was able to detect the reduction of hepatic CYPE2E1 expression due to the ingestion of natural products with hepatoprotective effects (Jiang et al., 2016b).
g. Harmful substances identification: The ability of IgY in identifying harmful substances in consumer products has been evaluated. An ELISA test was developed to detect the staphylococcal enterotoxin G (SEG), using specific IgY, and showed satisfactory sensitivity and specificity, reducing the interference of protein A that occurs in IgG tests. This test was successfully used to detect SEG in milk and dairy products samples and could therefore be used to identify the toxin in food (Nagaraj et al., 2016). Bittner et al. used IgY in ELISA to detect potentially allergenic proteins in commercially available latex gloves. This assay presented similar results to that of the gold standard test, which uses mammalian IgG (Bittner et al., 2016).
h. Antibiotic residues identification: IgY can also be used in assays to identify antibiotic residues in food products of animal origin, as demonstrated in a study by He et al., in which produced anti-gentamycin IgY specifically detected the target antibiotic present in animal origin products (He et al., 2016). Following this rationale, Li et al. used specific IgY to detect kanamycin and gentamycin residues in milk and meat samples by means of competition ELISA and FPIA (fluorescence polarization immunoassay) (Li et al., 2017).
i. Toxin substance identification: The potential of IgY in identifying substances has also been used to evaluate the toxicity of a natural product employed in the alternative medicine. IgY labeled with Quantum dot were successfully used in a lateral flow assay for the detection of rhein; a toxic substance found in the plant *Rheum officinale*, widely used in Chinese traditional medicine; in plant samples and serum from users (Zhang et al., 2018).

In general, these findings suggest that the phylogenetic distance between birds and mammals, that ensures a stronger immune response against mammalian antigens by birds than by other mammals (Gassmann et al., 1990), makes the production of IgY against various substances, advantageous for usage in several types of immunoassays and diagnoses. Thus development of polyclonal or monoclonal IgY based immunoassays could be a promising alternative to mammalian antibodies. Use of IgYs in Immuno-assay and diagnosis has been summarized in Table 27.9.

27.11 Use of IgY in Animal Health

Oral administration of chicken egg yolk antibody (IgY) is a promising nutritional strategy to control pathogen infections. Oral passive immunization using IgY has been focused on as an alternative to antibiotics for the treatment and control of diseases in animals. This section was focused to determine the effect of IgY in controlling and preventing various diseases in domesticated animals, including Bovine, Swine, Poultry, and Pets, (Wani et al., 2022) which have been studied during the last three decades (1980~2022) and are summarized in Table 27.10.

27.11.1 Use of IgY in Bovine

27.11.1.1 Bovine Mastitis

Worldwide bovine mastitis continues to be a costly disease for the dairy industry (Zhen et al., 2008a; Zhen et al., 2008b; Zhen et al., 2009). Numerous pathogens can cause mastitis and these can be classified into contagious pathogens (primary Staphylococcus aureus and Streptococcus agalactiae) or environmental pathogens (primary *E. coli*) (Riffon et al., 2001). *S. aureus* is implicated in ruminant mastitis, which affects the quality and quantity of milk produced, as well as the health of infected animals (Baselga et al., 1994). Although there are antibiotic treatments and vaccines available, they are not fully effective and *S. aureus*-associated

TABLE 27.9

Use of IgYs in Immuno-Assay and Diagnosis

Category of Use	IgY Using Area Covered	Reference
A. Immuno-assay		
ELISA	IgY-based ELISA modifications from the most common procedures and reagents	da Silva et al. (2016)
	Labeled IgY with horseradish peroxidase for use in immunoenzymatic assays	Ruan et al. (2007)
	Screening molecules related to drug-drug interactions	Jiang et al. (2016b)
	Sandwich ELISA to capture bacterial toxins	Nagaraj et al. (2016)
	Screening animal diseases by using recombinant antigens	Zhang et al. (2016b)
	Characterization of maternal IgY transferred to egg yolk	Murai et al. (2016)
	Coproantigen to capture ELISA for intestine human parasite	Teimoori et al. (2016, 2017)
	Screening antibiotic residues in food samples	He et al. (2016)
	Detection of blood circulating helminth antigens by immunomagnetic bead ELISA	Nie et al. (2014)
	Clinical diagnosing cancer antigen	Grzywa et al. (2014)
	Evaluation of ADA as a cancer biomarker	Łupicka-Słowik et al. (2018)
	Diagnosis of human strongyloidiasis	de Faria et al. (2019)
	Detection of neurocysticercosis	Silva et al. (2020)
	Diagnosis of Hookworm infection	Souza et al. (2020)
	Diagnosis of human ascariasis	Lopes et al. (2019)
	Diagnosis of human prostate cancer	Łupicka-Słowik et al. (2019)
	Detection of *Fusarium verticillioides* (and prediction of fumonisin contamination) in poultry feed	Omori et al. (2019)
	Evaluation of karilysin (i.e., an enzyme secreted by the periontopathogen *Tannerella forsythia*) as a biomarker for the diagnosis of periodontitis	Skottrup et al. (2019)
ELISA, FPIA	Detection of veterinary drug residues (SMZ) in milk	Liang et al. (2018)
Immunofluorescence	Detection of antigenic targets on cells and tissues samples	Camenisch et al. (1999)
	To clarify the pathogeny of mammalian autoimmune diseases	Sesarman et al. (2008)
	To detect mycobacterium avium subsp. paratuberculosis pathogen inside the cytoplasm of infected macrophages	Shin et al. (2009)
	Detection of hepatitis A virus in frozen liver sections	Bentes et al. (2015)
Fluorescence sensor assay	Diagnosis of hand-foot-and-mouth disease caused by enterovirus 71 infection	Nie et al. (2019)
Fluorescence immunochromatographic rapid-antigen test	Diagnosis of COVID-19	Porte et al. (2020)
In vitro immunochemicaltechniques	Diagnosis of infection with *Salmonella typhimurium* and *Salmonella enteritidis*	Esmailnejad et al. (2019)
Tissue indirect immunofluorescence assay	Diagnosis of human ascariasis	Lopes et al. (2019)
Immunocapture PCR assay	Detection of *Staphylococcus aureus* in food samples, skin and nasal swabs	Kota et al. (2020)
Flow cytometry	To study human and rabbit platelet physiology	Santoro et al. (2004)
	For the isolation and characterization of stem cell	Leu et al. (2010)
	Molecular diagnostics and therapeutics of lung cancers	Bowes et al. (2011)
Immunochromatographic assay (ICA)	IC strip to detect swimming crab Portunus trituberculatus reovirus	Zhang et al. (2015a)
	For canine parvovirus detection	He et al. (2015)
Immunocytochemistry, Immunohistochemistry	Diagnosis of infection with influenza A virus	da Silva et al. (2018)
Lateral flow immunoassay	Detection of fumonisin B1 and fumonisin B2 in maize	Tran et al. (2019)
Immuno-dot blot assay (with the use of IgY-colloidal gold nanoparticles conjugates)	Detection of indoor dust mite allergens	Egea et al. (2019)

(Continued)

TABLE 27.9 ***(Continued)***

Use of IgYs in Immuno-Assay and Diagnosis

Category of Use	IgY Using Area Covered	Reference
Paper-based microfluidic immunochromatographic test	Differential diagnosis of Russell's viper envenomation	Lin et al. (2020)
Latex agglutination assay	Diagnosis of Toxoplasmosis	Cakir-Koc et al. (2020)
Latex agglutination assay	Diagnosis of infection with influenza A virus	Budama-Kilinc et al. (2018)
B. Diagnosis		
Viral infections diagnosis	Canine parvovirus detection	He et al. (2015)
	Bovine viral diarrhea virus (BVDV)	Zhang et al. (2016b)
	Hepatitis A virus (HAV)	Silva et al. (2012)
	Detection of hepatitis A virus in frozen liver sections	Bentes et al. (2015)
	Soft-shelled turtle systemic septicemia spherical virus (STSSSV) in serum and feces samples of infected turtles	Zhang et al. (2015a)
	Nucleocapsid protein (NP) of coronavirus (CoV)	Palaniyappan et al. (2012)
	Severe acute respiratory syndrome-associated coronavirus (SARS-CoV)	
	Non-structural protein 1 (NS1) of dengue virus 2 (DENV2)	Figueiredo et al. (2015)
Bacterial infections diagnosis	Diagnosis of *Staphylococcus aureus* infection	Walczak et al. (2015)
	Detection of α-hemolysin of *S. aureus* on food and clinical samples	Mudili et al. (2015)
	Detection of α-hemolysin of *S. aureus*	Reddy et al. (2013)
	Detection of methicillin-resistant *Staphylococcus aureus*	Yamada et al. (2013)
Parasitic infections diagnosis	Detection of the protozoan *Toxoplasma gondii*	Cakir-Koc (2016)
	FITC-labeled IgY antibody: fluorescence imaging *Toxoplasma gondii*	Sert et al. (2017)
	IgY-based coproantigen capture ELISA for diagnosis of human opisthorchiasis (*Opisthorchirs viverrine*)	Teimoori et al. (2017)
	Diagnosis of cryptosporidiosis caused by both *C. hominis* and *C. parvum*	Miura et al. (2017)
Diagnosis of tumors	Cancer antigen 15-3	Grzywa et al. (2014)
	Detection of cancer antigen human epidermal growth factor receptor 2 (HER2) in breast cancer diagnosis	Sun et al. (2015)
	IgY against bovine adenosine deaminase (c-ADA) in detecting human adenosine deaminase (h-ADA) present in the tumor cells lysate	Łupicka-Słowik et al. (2018)
	Anti-prostate-specific antigen (PSA) IgY for prostate cancer diagnostics.	Łupicka-Słowik et al. (2014)
In proteomics	Efficacy in removing high-abundant proteins (HAP) from plasma, serum, CSF, urine, and other body fluid or cellular sources	Huang et al. (2005)
	Specific phage-display peptides discriminate diferente forms of neurocysticercosis by antibody detection in the serum samples	Manhani et al. (2011)
	Detection of low abundance human plasma proteins using a tandem IgY12-SuperMix immunoaffinity separation strategy	Qian et al. (2008)
	Human protein depletion	Rajic et al. (2009)
	Human plasma biomarker discovery	Polaskova et al. (2010)
Hematological tests	As a polyspecific reagent for coombs test	Calzado et al. (2017)
Enzyme detection	To detect the hepatic expression of Cytochrome P450 2E1 (CYP2E1)	Jiang et al. (2016b)
Identification of substances	Detection of staphylococcal enterotoxin G (SEG) in milk and dairy products	Nagaraj et al. (2016)
	Detection allergenic proteins in commercially available latex gloves	Bittner et al. (2016)
	Identification of antibiotic gentamicin residues in food products of animal origin	He et al. (2016)
	Detection of kanamycin and gentamicin residues in animal-derived food	Li et al. (2017)
	Evaluation of the toxicity of a natural product employed in the alternative medicine	Zhang et al. (2018)

Source: Modified and adapted from Karachaliou et al. (2021).

TABLE 27.10

Use of IgY to Control Diseases in Animals

Animal Spp	Pathogen	IgY Outcome	Reference
A. Bovine			
Mastitis	*Staphylococcus aureus* and *Streptococcus agalactiae, E. coli*	Prevented bacterial infection	Riffon et al. (2001)
			Zhen et al. (2008a, 2008b, 2009)
			Wang et al. (2011)
Diarrhea	Rotavrus A	Inactivate virus/bacteria in vivo	Kuroki et al. (1994)
	Enterotoxigenic *E. coli* (ETEC)		Ikemori et al. (1992)
	Corona virus		Ikemori et al. (1997)
Pneumonia	Respiratory syncytial virus, pneumovirus	Neutralize virus in vitro	Ferella et al. (2012)
Enzootic bovine leukosis	Leukemia virus	Bound to BLV particles	Martínez et al. (2014)
B. Swine			
Diarrhea			
	Enterotoxigenic *E. coli* (ETEC)	Prevented K88+, K99+, 987P+ ETEC infection	Yokoyama et al. (1992)
		Inhibits the adhesion of K88+ ETEC to piglet intestinal mucosa	Jin et al. (1998)
		Prevention of K88+ ETEC infection in neonatal and early weaned piglets	Marquardt et al. (1999)
		Fast protection from diarrhea in piglets orally treated with anti-K88+ ETEC IgY encapsulated on chitosan-alginate microparticles	Li et al. (2007)
		Protection of ETEC infected piglets from diarrhea with IgY delivered in hydrogel-carbon nanotubes composites	Alustiza et al. (2016)
		Neutralize the activity of heat-stable enterotoxins (ST) and heat-labile enterotoxin (LT)	You et al. (2011)
Diarrhea	Porcine Epidemic Diarrhea virus (PEDV)	Partial protection of piglets against PEDV associated mortality	Kweon et al. (2000)
		Protected of neonatal piglets against PEDV	Lee et al. (2015)
Diarrhea	Porcine transmissible gastroenteritis virus (TGEV)	Prophylactic administration: Increase in piglets' survival rate after challenge	Zuo et al. (2009)
		Therapeutic administration: Reduction in mortality	
Diarrhea	Rotavirus group A (RVA)	Protection of gnotobiotic piglets from human RVA-associated diarrhoea	Vega et al. (2012)
C. Poultry			
Lesion	*E. coli*	Protection from homologous challenge by *E. coli* 078	Kariyawasam et al. (2004)
		Reduced symptoms, lesions	Tamilzarasan et al. (2009)
		Decreased ileal *E. coli* counts and the circulating	Mahdavi et al. (2010a, 2010b)
Campylobacteriosis	*Campylobacter jejuni*	Prophylactic (99%) and therapeutic treatments (80%–95%) reduction in bacteria	Tsubokura et al. (1997)
	C. Jejuni	Significantly reduced bacterial cell counts	Hermans et al. (2014)
	C. Jejuni	Significantly reduced bacterial cell counts	Vandeputte et al. (2019)
Salmonellosis	*Salmonella enteritidis* or *S. typhimurium*		Lee et al. (2002)
	S. enteritidis		Rahimi et al. (2007); Tellez et al. (2001)
	S. enteritidis	*Salmonella* contamination of eggs	Gürtler et al. (2004)
	S. enteritidis and S. typhimurium		Chalghoumi et al. (2009)

(Continued)

TABLE 27.10 ***(Continued)***

Use of IgY to Control Diseases in Animals

Animal Spp	Pathogen	IgY Outcome	Reference
	S. enteritidis		Fulton et al. (2002)
	Gallibacterium anatis		Zhang et al. (2019)
Infectious bursal disease (IBD)	IBD virus	Protection of chickens against IBD virud	Muhammad et al. (2001); Malik et al. (2006); El-Ghany (2011) ; Farooq et al. (2012)
Newcastle disease		Protection of chickens against Newcastle disease	Wills and Luginbuhl (1963); Box et al. (1969)
Duck hepatitis	Duck hepatitis virus	Protection of ducklings against duck hepatitis	Gui-rong & Yun-ying (2011)
Arthritis	Reovirus	Diagnostic with high consistency	Zhang et al. (2015a)
Coccidiosis	Genus Eimeria (coccidia)	Diagnostic and therapeutic treatment	Thirumalai et al. (2019)
	E. acervuline, E. maxima, E. tenella, E. praecox and *E. necatrix*		
D. Pet			
Canin (Dog) Periodontitis	*Porphyromonas gingivalis* and *P. gulae*	Reduced bacterial cell counts and protection against periodontitis dose dependently	Shofiqur et al. (2011)
Canin Diarrhea	Canine parvovirus type 2 (CPV-2)	Dose dependently minimized the excretion of virus from stool samples	Van Nguyen et al. (2006)
	Canine parvovirus field isolates	Intravenous IgY immunotherapy was effective in dogs after oral challenge with a highly pathogenic CPV isolate Kinetics of anti CPV IgY antibodies was studied by regression analysis to determine the level of IgY in serum from the time of injection To detect canine parvovirus in feces by indirect ELISA.	Suartini et al. (2014) Suartini et al. (2016) Guimaraes et al. (2008)
Canin cold, bronchitis, pneumonia, and gastroenteritis	Canine morbillivirus (formerly termed Canine distemper virus, CDV)	Protection against Canin cold, bronchitis, pneumonia, and gastroenteritis in pets	Guimaraes et al. (2009a)
Allergies to cats (Human allergy)	Cat allergen protein Fel d 1	Neutralized salival Fel d 1 protein in cat	Satyaraj et al. (2019)
Rabbit hemorrhagic disease (RHD)	Rabbit hemorrhagic virus	Significant reduction in onset, duration and severity of RHD infection	Li et al. (2014)

infections often recur (Hwang et al., 2000). The control of this disease is necessary to ensure the sustainability of dairy farming and the production of milk which meets high quality global standards (Ruegg, 2017). At present, antibiotics are primarily used for therapy of mastitis, although milk-containing antibiotics must be discarded (Nair et al., 2005). Staphylococcus aureus, the primary pathogen causing bovine mastitis, is increasingly resistant to antibiotic treatment and has a propensity to recur chronically (Gill et al., 2006). As a result, alternative therapies for mastitis are needed. IgY as an inexpensive and easily produced antibody has received much attention and was found to efficiently prevent or control pathogen infections in animals (Peralta et al., 1994; Erhard et al., 1996; Kuroki et al., 1997; Jin et al., 1998; Carlander et al., 2000; Sugita-Konishi et al., 2000; Gürtler et al., 2004). IgY produced against *S. aureus* was highly specific to mastitis-causing strains, enhanced the phagocytic activity of milk macrophages (Zhen et al., 2008a), and reduced bacterial growth in culture (Mahenthiran et al., 2013). In addition, specific IgY blocked the internalization and infection of bovine mammary epithelial cells by *S.aureus in vitro* (Wang et al., 2011). Wang et al. reported that specific IgY against encapsulated type 5 (IgY-T5) and type 8 (IgY-T8) and non-encapsulated type 336 (IgY-T336) S. aureus strains (at 5 mg/mL) significantly blocked the internalization of their homologous strains by bovine mammary epithelial cells (MAC-T cells) within 6 hour (Wang et al., 2011). At a concentration of 20 mg/mL, IgY anti-*S.aureus* infused by insertion into the teat canal decreased somatic cell and bacterial counts, while curing most experimentally challenged lactating cows (Zhen et al., 2009). Similar cure rates were also observed in challenged buffaloes with mastitis, and specific IgY administered through intramammary infusions at a dose rate of 20 mg/mL improved milk yield (Iqbal et al., 2013). It was reported that polyclonal IgY against Streptococcus agalactiae and *S. aureus* was effective in reducing somatic cell count (SCC) in

dairy cows (Coleman, 1996). These results suggest that IgY acts to control mastitis by prevention of uptake rather than by impacting on growth of the pathogen.

27.11.1.2 Bovine Diarrhea

Neonatal calf diarrhea is a common disease affecting newborn calves and is the leading cause of calf mortality before weaning in both beef and dairy calves (Cho & Yoon, 2014). Diarrhea is more common between 1 and 21 days of age, with a peak incidence at 2 weeks, but it can extend up to 30–45 days of age (Bartels et al., 2010). Diarrhea is caused by a combination of agents which may result in more severe disease than a single agent alone (Hoet et al., 2003; Izzo et al., 2011; Cho et al., 2013; Ferragut et al., 2016). Historically, calf diarrhoea has been attributed to bovine rotavirus group A (RVA), bovine coronavirus (BCoV), Salmonella spp., *Escherichia coli* strains with virulent factors and Cryptosporidium parvum as the main aetiological agents (Foster & Smith, 2009; Heller & Chigerwe, 2018; Brunauer et al., 2021)

Antibodies from bovine colostrum protect against RVA-associated diarrhea in calves (Parreño et al., 2004; Parreño et al., 2010). However, this strategy is industrially unfeasible at a large scale and several bovine infectious agents could be spread as adventitious virus/bacteria, like bovine leukemia virus. It has been shown that IgY antibodies can resist digestion in the gastrointestinal tract of calves, remaining biologically active (Vega et al., 2011). The therapeutic value and safety of using oral anti-rotavirus IgY in animals is now well-established after extensive studies over the past decades (Vega et al., 2015). In a review of the effect of IgY in the treatment of rotavirus infection (Thu et al., 2017), it is speculated that its mode of action involves either blocking the entry of the rotavirus into the host cells and/or minimizing the cell to cell spread of the virus. The oral administration of egg-derived preparations to new born calves has not only shown protection against diarrhea but also an increase in weight gain and an improvement in growth performance (DiLorenzo et al., 2006; Vega et al., 2015).

The passive protective effects of using anti-ETEC IgY administration on fatal enteric colibacillosis in neonatal calves have been studied (Ikemori et al., 1992). Calves fed milk containing IgY had only transient diarrhea, 100% survival and exhibited good body weight gains during the course of the study. In contrast, the controls which received no antibody had severe diarrhea and all died within 6 days of infection. The effect of IgY in controlling and preventing diarrhea (including rotaviral diarrhea) in domesticated animals from 1994 to 2015 has been a subject of critical review by Diraviyam T et al. (Diraviyam et al., 2014). The authors pooled accumulated data from 49 studies of 4 different animal species (piglets, mice, poultry and calves) that revealed that IgY significantly reduced the risk of diarrhea in treatment groups when compared to corresponding placebo groups. This general observation based on data from 49 studies supports the view that IgY is a useful tool for prophylaxis and treatment of diarrhea in animals. A promising, economically feasible and practical strategy which has been explored is the supplementation of the milk diet of calves with specific IgY antibodies from egg yolk (Kuroki et al., 1994, 1997; Mine & Kovacs-Nolan, 2002; Vega et al., 2011, 2015).

27.11.1.3 Bovine Pneumonia

Bovine respiratory syncytial virus is a pneumovirus in the Paramyxovirus family that afflicts young calves and is difficult to diagnose and treat due to its lability and poor growth in cell culture (Larsen, 2000). However, IgY against bovine respiratory syncytial virus specifically recognized and neutralized the virus *in vitro* when analyzed in dot blot and virus neutralization assays (Ferella et al., 2012). Because of the success of IgY production and activity *in vitro*, IgY may be a novel prophylactic treatment to combat bovine respiratory disease in infected calves.

27.11.1.4 Bovine Leukemia

Bovine leukemia virus (BLV) is a retrovirus that causes enzootic bovine leukosis, a chronic and slow-developing disease in cattle (Ghysdael et al., 1984). BLV can easily be transmitted through birth and contaminated colostrum, milk, blood, exudates, and tissue (Hopkins & DiGiacomo, 1997). Currently, methods to minimize BLV transmission include careful herd management given the unavailability of effective antiviral drugs and vaccines (Martínez et al., 2014). IgY antibodies generated against the whole virus or the p24 core protein specifically bound to BLV particles (in an infected cell line), purified p24, and supernatants from *ex vivo* cultures of peripheral blood mononuclear cells from naturally infected animals. IgY against BLV may warrant evaluation as a passive immunization against this virus for enzootic bovine leukosis.

27.11.2 Swine

27.11.2.1 Swine Diarrhea

Swine diarrhea, especially neonatal porcine diarrhea (NPD), was recognized as a serious problem in the late 1950s and 1960s with the emergence of the modern pig industry. Over the years, various aetiological agents have been described. Going forward, neonatal diarrhea not related to enterotoxigenic *E. coli* (ETEC), *C. perfringens* type C, TGE, or coccidiosis, was reported. Several potentially pathogenic, causative agents have been suggested, including C. perfringens type A, *Clostridioides (C.) difficile*, previously largely overlooked *E. coli* strains such as enteropathogenic *E. coli* (EPEC), rotavirus, and members of the Enterococcus (E.) faecium species group (*E. durans, E. hirae, E. villorum*). NPD has been given various names: neonatal diarrhea neonatal colibacillosis, baby pig scours, enterotoxemia in baby pigs, infectious gastroenteritis of suckling pigs, neonatal hemorrhagic and necrotic enteritis, necrotizing enteritis, neonatal necrotic enterotyphlocolitis (Uzal & Songer, 2019), epidemic diarrhoea type II, transmissible gastroenteritis, or new neonatal porcine diarrhoea (NNPD) (Jacobson, 2022).

The most common cause of enteric colibacillosis is Enterotoxigenic *E. coli* (ETEC) in neonatal (Alexander, 1994) and post-weaned pigs (Yokoyama et al., 1992). The strains of *E. coli* associated with intestinal colonization which cause

severe diarrhea are the K88, K99 and 987P fimbrial adhesins. Among the ETEC, those expressing the K88+ fimbrial antigen are the most prevalent forms causing *E. coli* infection worldwide (Rapacz & Hasler-Rapacz, 1986). It has been estimated that K88+ ETEC are responsible for more than half of the piglet mortality which occurs each year (Waters & Sellwood, 1982), causing significant economic loss for the pig industry.

IgY is recognized as an alternative source of antibodies for the prevention of ETEC coli infection because it has been found to inhibit binding of *E. coli* to the intestinal mucosa (Jin et al., 1998). IgY has been orally administered to piglets and offers a potential prophylactic and therapeutic approach for controlling *E. coli*-induced diarrhea. Yokoyama et al. showed that orally administered IgY generated against *E. coli* K88, K99, or 987P fimbriae was protective against infection from each of the three homologous strains of *E. coli* in a dose-dependent manner. *E. coli* K88, K99, and 987P strains adhered equally to porcine epithelial cells from the duodenum and ileum but failed to so in the presence of homologous antifimbrial IgY (Yokoyama et al., 1992). A group of researchers at the University of Manitoba (Winnipeg, Canada) have carried out some excellent studies on the passive protective effect of IgY against ETEC K88 fimbriae in the control of neonatal and early-weaned piglets in vitro and in vivo (Jin et al., 1998; Marquardt et al., 1999).

Porcine epidemic diarrhea virus (PEDV) is a highly contagious enteric pathogen of swine causing high mortality rates in piglets. PEDV outbreaks have occurred in most swine-producing countries globally and leading to large economic losses for pig industries (Kikuti et al., 2022). Oral administration of anti-PEDV IgY efficiently protects neonatal piglets against PEDV, suggesting its potential as a prophylactic or therapeutic agent against acute PEDV infection (Kweon et al., 2000; Lee et al., 2015; Umeda et al., 2019).

27.11.3 Avian (Poultry)

27.11.3.1 Salmonellosis

Salmonella infections are thought to be responsible for a variety of acute and chronic diseases of poultry. It has been shown that specific IgY against *Salmonella enteritidis* or *Salmonella typhimurium* inhibits bacterial growth in vitro (Lee et al., 2002) and reduces the colonization of *Salmonella* in market-aged broilers (Rahimi et al., 2007b, Tellez et al., 2001). The use of whole egg powder (containing antibody) as a feed additive may be an alternative way to reduce the rate of *Salmonella* contamination of eggs (Gürtler et al., 2004).

27.11.3.2 Campylobacteriosis

Campylobacter jejuni has become a major concern to the commercial broiler, turkey and commercial egg-producing flocks in all countries. Tsubokura et al. used egg yolk antibodies for prophylactic and therapeutic applications in *Campylobacter*-infected chickens. In a prophylaxis experiment, it was found that these antibodies caused a 99% decrease in the number of *Campylobacter* observed, whereas in a therapy trial (antibodies were given after establishment of the infection), the number of bacteria in the feces was 80–95% lower (Tsubokura et al., 1997).

27.11.3.3 Infectious Bursal Disease

Infectious bursal disease (IBD) is an acute, highly contagious immunosuppressive disease of young chickens caused by IBD virus (Chettle et al., 1989; Qin & Zheng, 2017; Dey et al., 2019). Antibiotic therapy is the most readily available approach for controlling IBD-induced secondary bacterial infections in affected flocks. It has been shown that specific IgY has a great potential as an alternative to antibiotics for IBD. Muhammad et al. demonstrated that yolks from hyperimmunized hens can be used to control IBD in commercial laying hens (Muhammad et al., 2001).

27.11.3.4 Newcastle Disease

Newcastle disease is a severe viral infection causing a respiratory nervous disorder in several species of poultry. This disease is endemic in commercial poultry from many countries and can cause great economic loss due to high mortality rates (Lancaster, 1976). Vaccination has been used to prevent this disease in endemic areas, but vaccines are not always effective and vaccinated flocks may still be infected. It has been shown that egg yolk antibodies conferred protection in chickens against Newcastle disease (Wills & Luginbuhl, 1963; Box et al., 1969). Wills and Luginbuhl have found that subcutaneous administration of egg yolk containing high levels of IgY antibody specific to Newcastle disease protected 80% of the birds during a four-week study period (Wills & Luginbuhl, 1963).

27.11.3.5 Hepatitis Virus

Numerous studies have been carried out to develop IgY preparations against duck hepatitis virus. A related veterinary drug has been licenced in China for protection of ducklings against duck hepatitis by prophylactic subcutaneous or intramuscular injection (Gui-rong & Yun-ying, 2011).

27.11.3.6 Coccidiosis

Avian coccidiosis is an intestinal disease caused by infection with a protozoan parasite of the genus Eimeria (coccidia). There are several distinct species that infect chickens, including *E. acervuline, E. maxima, E. tenella, E. praecox*, and *E. necatrix*. The reader is referred to a review of the use of IgY as both a diagnostic and therapeutic treatment of parasitic infections (Thirumalai et al., 2019).

27.11.3.7 Arthritis Reovirus

Most frequent reovirus-associated disease in poultry is arthritis with malabsorption syndrome, immunosuppression, pericarditis, myocarditis, and osteoporosis as other common features (Fahey & Crawley, 1954; Jones, 2013). Although several commercial vaccines have been developed against avian reovirus, it is difficult to detect and treat infected flocks with multiple or novel strains of circulating reovirus (Sellers, 2017). Specific IgY

against avian reovirus in infected birds displayed a high sensitivity to the virus, detected the presence of the virus in contaminated tissue, and neutralized the virus in BHK-21 cells without binding to heterologous viral strains (Jung et al., 2014).

27.11.4 Pet

27.11.4.1 Canin Periodontitis

Porphyromonas gulae is one of the key microorganisms in biofilm dysbiosis that leads to periodontal disease, a prevalent disease in pet (e.g., dog and cat). Gingipains are proteases secreted that promote the disruption of cell adhesion and the differentiation of osteoclasts. The use of anti-gingipain immunoglobulin Y (IgY-GP) has emerged as a promising alternative to conventional prevention and treatment methods. The consumption of IgY-GP reduces plaque accumulation, which may lead to an improvement in the oral health of adult dogs (Rahman et al., 2011) and cats (Oba et al., 2018).

27.11.4.2 Canine Parvovirus

Canine parvovirus (CPV) infection is a fatal disease of dogs, believed to have originated from cats and parvoviruses of carnivores, including bush dogs, cats, coyotes, bears and wolves, causes hemorrhagic diarrhea and myocarditis resulting from severe gastroenteritis. The aetiological agent is Canine parvovirus type 2 (CPV-2). IgY antibodies have been used for the diagnosis, prophylaxis and treatment of diseases of dogs. Oral passive immunization with IgY antibodies specific to CPV-2 virus, administered as an egg yolk powder to dogs challenged orally with a CPV-2 viral strain for 7 days controlled the infection to a great extent (Van Nguyen et al., 2006). Animal groups treated with 2 g of IgY antibodies in powdered form for 16 days post challenge showed significant weight gain and shorter duration of virus shedding than the control group. Apart from oral administration of antibodies, an intravenous route of anti CPV-2 IgY treatment has been used to protect dogs from CPV infection. Experimental infection induced by an oral challenge of dogs with CPV, after treatment with 1,000 and 10,000 PD (Protective Doses) of Anti CPV IgY antibodies showed recovery rates of 25% and 100%, respectively. Higher doses produce increased antibody titres which suppressed the viral load and minimized the excretion of virus from stool samples (Suartini et al., 2014). Therefore, in addition to oral therapy, intravenous immunization with antibodies also proves to be an efficient passive therapy method. The kinetics of anti CPV IgY antibodies was studied by regression analysis to determine the level of IgY in serum from the time of injection (Suartini et al., 2016). The use of monoclonal IgY antibodies and scFv to treat disease has become more prominent, including the treatment of CPV. Oral passive immunotherapy can be extended to the development of supplementary oral products to protect dogs from parvoviral infections

27.11.4.3 Canine Morbillivirus

Canine morbillivirus (formerly termed Canine distemper virus, CDV) is an extremely contagious immunosuppressive disease that affects dogs. Morbilliviruses belong to the family Paramyxoviridae and the genus Morbillivirus and cause moderate to severe immunosuppressive, respiratory, gastrointestinal and neurological diseases in a variety of hosts from humans (measles) to canines; and present an interesting model to research inter-species jumping (Quintero-Gil et al., 2019). The early symptoms are similar to a cold, followed by bronchitis, catarrhal pneumonia, and gastroenteritis. In the later stages of the disease, there are neurological symptoms such as convulsions. In some cases, there may be a high degree of keratosis of the nose and hardening of the skin of the footpads of the paws (hard pad disease). Dogs are vaccinated to protect from the disease, but there are geographical genetic variations in the virus (Pratelli, 2011).

Due to the broad clinical symptoms, laboratory tests are required to confirm the disease and a range of biological samples have been used to measure the virus, mainly by PCR but also by immunochromatography, immunofluorescence and ELISA (Costa et al., 2019). Currently, there is no specific drug for the treatment of this disease. Antibody based therapy has been considered as a relatively efficient intervention. IgY antibodies have been generated by immunizing laying hens with CDV (Guimaraes et al., 2008; Guimaraes et al., 2009a).

27.11.4.4 Rabbit Hemorrhagic Virus

Global rabbit production has been estimated at more than one million tonnes per year, according to the FAO (FAOSTAT 2012 ; Alexandratos & Bruinsma, 2012) and therefore infections of rabbits need to be controlled. Rabbit hemorrhagic disease (RHD) is a contagious and highly lethal viral disease of rabbits. Hens were immunized with the N-terminal of the viral VP-60 capsid protein and IgY treated rabbits showed a significant reduction in the onset, duration and severity of RHD infection (Li et al., 2014).

27.11.4.5 Cat Allergen Fel d 1

Allergies to cats are the most common human allergy of animal origin; the major cat allergen is Fel d 1 (Satyaraj et al., 2019). Hens were immunized with this allergen and allergen specific IgY fed to cats was shown to neutralize Fel d 1 after its production and lessen the release into the environment thus decreasing the allergic response of the owners.

27.12 Fish Health (Aquaculture)

Globally fish production has been estimated to be about 179 million tonnes in 2018, of which aquaculture accounted for 46% (82 million tonnes); aquaculture production is projected to reach 109 million tonnes in 2030 (FAO, 2020). The leading producers of farmed fish are China, Egypt, Chile, India, Indonesia, Viet Nam, Bangladesh, and Norway. Of the major finfish species produced in 2018, carp accounted for 33%, salmon for 4.5%, and rainbow trout for 1.6% of the total production; of the world production of crustaceans, white shrimp accounted for 53% (FAO, 2020). One of the major factors impacting the productivity of the aquaculture sector is the outbreak of diseases;

the widespread use of antimicrobials is problematic and can lead to the development of antibiotic resistance. While finfish have innated and adaptive immune systems, crustaceans depend completely on the innate immune system for defense and thus vaccination is ineffective (Vazquez et al., 2009). Oral administration of specific IgY antibodies is effective against various intestinal pathogen (Mine & Kovacs-Nolan, 2002). This section presents an overview of the potential to use immunotherapy with specific IgY for the prevention and treatment of fish diseases. Oral intubation and feeding of anti-fish pathogens IgY resulted in different levels of protection against various fish diseases are summarized in Table 27.11.

The IgY-coated diets helped to reduce the pathogen load and boosted the immune system in fish against both pathogens challenge. The oral administration of specific IgY against fish pathogens could provide an alternative method to antibiotics and chemotherapy for the prevention of microbial diseases of fish in a fish farm.

The use of passive immunization in aquaculture poses a number of specific challenges which need to be considered. For routine application of antibodies oral administration would be preferred but may be species specific. Administration of IgY through oral and anal routes was not detectable in gastric rainbow trout probably impacted by pepsin activity in the gut (Winkelbach et al., 2015a, 2015b); in contrast uptake in the gastric carp (lacking acidic stomach enzymes) demonstrated an efficient uptake of IgY (Winkelbach et al., 2015a, 2015b) and probably increased IgY transcytosis in carp compared to

TABLE 27.11

IgY on Fish Health

Pathogen	Fish Species	IgY Form	IgY Outcome	Reference
Edwardsiella tarda	Japanese eels (*Anguilla japonica*	Oral	Non-treated infected eels died within 15 days whereas the eels receiving IgY survived and no disease symptoms were observed	Gutierrez et al. (1993); Hatta et al. (1994)
White spot syndrome virus (WSSV)	Shrimp	Injected IM	0.01 mg/10 μL, 0.1 and 0.5 mg/μL exhibited a survival rate of 50%, 85%, and 83%	Kim et al. (2004)
White spot syndrome virus (WSSV)	Shrimp	Injected IM	When challenged with virus, 73% survival when IgY prepared with inactivated virus; 33% with IgY prepared from WSSV-DNA	Lu et al. (2008)
WSSV	Crayfish	Injected IM, oral, immersion	IgY from inactivated WSSV and DNA vaccine were, respectively, 20% and 80% mortality. Diet added 10% egg yolk powder and 1% IgY power showed 53.3% and 67.7% mortality, respectively, and the immersion showed 46.7% mortality	Lu et al. (2009)
White spot syndrome virus	Shrimp	IgY in feed	Highly resistanttTo WSSV challenge	Kumaran et al. (2010)
White spot syndrome virus (WSSV)	Crayfish	Injected IM, feed or immersion in IgY solution	All methods provided some protection of crayfish against infection	Lu et al. (2009)
V. harveyi and V. parahaemolyticus	Shrimp	β-Cyclodextrin encapsulated egg yolk powder	Protected from infection	Gao et al. (2016a); Gao et al. (2016b)
Vibrio parahaemolyticus	Shrimp	Whole egg powder with specific IgY fed at 20%	Survival of 86% when treated with recombinant PirA- like toxin induced IgY	Nakamura et al. (2019)
Yersinia ruckeri	Rainbow trout	Microencapsulated IgY	Lower mortalities than control fish	Lee et al. (2000)
Piscirickettsia salmonis	Salmon	Chitosan-alginate micro encapsulated IgY	Encapsulated IgY can resist degradation and is absorbed into the bloodstream	Oliver et al. (2015)
Reovirus	Swimming crabs	Rapid immunochromatographic test strip	Anti-swimming crab reovirus IgY effectively detected the virus in contaminated samples with high consistency	Zhang et al. (2015a)
Vibrio anguillarum	Rainbow trout	Intraperitoneal(IP) injection, oral intubation, or feeding	Injection conferred protection for 14 days. Oral intubation and feeding gave comparable results in some cases	Arasteh et al. (2004)
Edwardsiella tarda	Turbot	Chitosan-alginate encapsulated IgY at 1%, 3%, and 5% in feed	Survival rates of the1%, 3% and 5% micro-encapsulated specific IgY groups were 20%, 56.7% 63.3%, on the tenth day post infection with 10^7 CFU *E. tarda*	Xu et al. (2020)

(Continued)

TABLE 27.11 ***(Continued)***

IgY on Fish Health

Pathogen	Fish Species	IgY Form	IgY Outcome	Reference
V. alginolyticus	Abalone	5% or 10% alginate encapsulated IgY in feed	Survival rates of fed with 5 or 10% anti-vibrio IgY egg powders ranged from 65–70% 14 days post- *V. alginolyticus* challenge (1×10^6CFU)	Elston & Lockwood (1983); Anguiano-Beltrán et al. (1998); Liu et al. (2000); Wu et al. (2011)
Vibrio	Ayu (*Plecoglossus altivelis*)		Anti-Vibrion IgY supplemented feed, significantly increased the survival of Ayu fish, challenged by *V. alginolyticus.*	Kanno et al. (1989)
Vibrio splendidus	Sea Cucumber (*Apostichopus japonicus*)		Increased the survival of Sea Cucumber, challenged by *V. splendidus*	Li et al. (2016b)
V. anguillarum	Half-smooth tongue sole (*Cynoglossus semilaevi*)	Oral feed	Increased the survival of Half-smooth tongue sole, challenged by *V. anguillarum*	Gao et al. (2016b)
Shewanella marisflavi	Sea cucumber	Oral yolk powder at 25, 5 and 1 mg/mL	25, 5, and 1 mg/mL anti-S. marisflavi AP629 IgY gave77.5%, 50%, and 22.5% survival rates at day 12, respectively, when challenged with 4.2 10^6 CFU *S. marisflavi*	Xu et al. (2019)
Non-O1 Vibrio Cholerae	Carp	Feed additive	Survival rate of carp fed with IgY significantly elevated, when challenged with non-O1 *V. cholerae*.	Gao et al. (2017)
Vibrio harveyi IgY	Indian white shrimp	Feed supplement	Anti-Vibrio harveyi IgY effective against V. harveyi	Kumaran et al. (2018)
Red-spotted grouper nervous necrosis virus (RGNNV)	Marine fish larvae	10% lyophilized egg yolk powder in feed	Protection rates of groupers under treatment after RGNNV infection and continuous feeding during RGNNV infection were 68% and 70%, respectively,	Liu et al. (2021)
Vibrio parahaemolyticus	Pacific white shrimp	IgY fed at a dose of 0, 0.2%, 0.3%, 0.4%, and 0.5%	Reduced mortality rate (25–40%) in contrast to the control group (60%)	Keetanon et al. (2021)

trout. Other considerations are the period of immunization which is most effective for uptake and the duration for which passively transmitted IgY are present in the different fish species; continuous administration may be necessary in some cases (Rajan et al., 2017). Despite these challenges, advances have been made in the use of IgY antibodies for the treatment of fish diseases and these are summarized in Table 27.11.

Some references IgY development for fish health are being discussed here.

Vibrio parahaemolyticus is a pathogen associated with acute hepatopancreatic necrosis disease (AHPND) and can cause up to 100% mortality in post-larvae shrimp. IgY has been shown to confer protection to this infection (Gao et al., 2016a).

Piscirickettsia salmonis causes the disease piscirickettsiosis in salmon, resulting in significant mortality and economic losses in fish (Oliver et al., 2015). Specific IgY was produced by immunizing hens with *P. salmonis* proteins and was effective against the infection in SHK-1 cells; further studies are necessary to show its efficacy in fish.

Vibrio anguillarum is an important pathogen of marine and fresh water fish and alternates to vaccination which can be stressful for fish were sought (Arasteh et al., 2004). Oral treatment is preferable and was shown to be as effective in some cases as intraperitoneal injection.

Edwardsiella tarda, a Gram-negative bacterium belonging to the family Enterobacteriaceae, is considered a common pathogen infecting mainly economically important fish species such as Japanese eel (*Anguilla japonica*), red sea bream (*Pagrus major*), yellowtail (*Seriola quinqueradiata*), channel catfish (*Ictalurus punctatus*), and turbot (*Scophthalmus maximus*) (Park et al., 2012). The use of encapsulated IgY shows promise for the treatment of turbot (Xu et al., 2020).

IgY has been tested against *Vibrio alginolyticus*, which causes infections and high rates of mortality in abalone (marine snails) (Elston & Lockwood, 1983; Casandra et al., 1998; Liu et al., 2000). When incorporated into the feed, IgY anti-*V. alginolyticus* significantly increased the survival of small abalones challenged by *V. alginolyticus* (Wu et al., 2011). Similar results were obtained using IgY against *Vibrio anguillarum* in rainbow trout (Arasteh et al., 2004), ayu fish (Kanno et al., 1989; Li et al., 2016b), half-smooth tongue sole (Gao et al., 2016b), shrimp (Keetanon et al., 2021), and carp (Gao et al., 2017).

Reovirus is a growing problem in aquaculture, causing high mortality rates of swimming crabs. Use of anti-swimming crab reovirus IgY effectively detected the virus in contaminated samples with high consistency, suggesting potential benefit in reovirus-associated disease outbreaks in aquaculture (Zhang et al., 2015a).

Aeromonas is commonly found in aquatic environments. IgY-specific antibodies have been investigated as an alternative method to diagnose *Aeromonas*-diseased aquatic animals. IgY produced against *Aeromonas hydrophila* detected *A. hydrophila* in tissues and phagocytes in infected Nile tilapia (Fernandes et al., 2019a), neutralized bacterial adhesins and toxins released by the bacteria, promoted agglutination, inhibited bacterial growth, and enhanced the phagocytic activity of infected Nile tilapia, blunt snout bream (Qin et al., 2018; Fernandes et al., 2019b), and polyploid gibel carp (Li et al., 2006). When added to rearing water, specific IgY eliminated the development of skin ulcers, as well as transmission of the infection between different fish (Gan et al., 2015).

27.13 Use of IgY in Plant Health

Viruses are one of the major plant pathogens, drastically influencing crop yield and productivity in the whole world (Fraser, 1990; Kang et al., 2005). Although there is no statistical data on crop yield losses due to virus attacks, the damage varies from 50 to 80% and sometimes reaches 100% depending upon the severity of virus spread (Roger, 2009). The history of plant virus infections starts in 1898. There are no natural effective control measures discovered yet except plants' own internal wide range of defense mechanisms to protect themselves against virus infection (Sanseverino et al., 2010). In these circumstances, the production of polyclonal IgY against various etiological agents or viruses of plants may have an important role in immuno-diagnosis in epidemiological studies with the prevention and treatment of plant diseases.

27.13.1 IgY in Immuno-Diagnosis of Plant Viruses

With rapid international expansion of trade, horticultural production of ornamental plants has become a global industry with commercial production of flowers and bulbs in many countries. Various plant viruses infect plants with variable infection frequencies (3% ~100%), followed by great economical loss. There was no efficient method discovered yet to detect the viruses. Detection of viruses in field samples in epidemiological studies can be performed routinely using the IgY. Based on a literature survey, it is reported that IgY has already developed for the diagnosis of fique Furcraea Necrotic Streak Virus-FNSV (Toloza-Moreno et al., 2022), Potato viruses X and Y (PVX, PVY) (Weilbach & Sander, 2000), Lily symptomless virus (LSV), Lily mottle virus (LMoV), Cucumber mosaic virus (CMV) (Yoo & Jung, 2014), orchid Cymbidium mosaic virus (CyMV) (Vejaratpimol et al., 1999), Citrus yellow mosaic virus (CYMV) (Kumar et al., 2018). In conclusion, using this IgY was established for detecting plant viruses. This method can be used for virus surveillance to help reduce economic losses in the natural, agricultural, and ornamental plant industries.

27.13.2 IgY Against Plant Viruses

Chinese sacbrood virus (CSBV) infects Apis cerana larvae, resulting in the inability of the larvae to pupate and their consequent death, which may pose a serious threat to entire colonies (Sun et al., 2018). Apis mellifera Colony Collapse Disorder by Deformed Wing Virus (DWV) is also reported (Nordseth, 2020). As there is no effective medical treatment for CSBV and DWV infections. IgY against CSBV (Sun et al., 2018) and DWV (Nordseth, 2020) has been developed. Experimental results revealed that anti-CSBV IgY and anti-DWV IgY has protection ability against the infection of CSBV infections and DWV, which would significantly reduce the diseases. This technology could have a profound impact on the future of beekeeping – an industry that is key to avoiding a global food sustainability crisis.

27.14 Use of IgY in Environmental Health (Historical World Pandemic)

Cholera, influenza, and SARS-CoV-2 are some of the most brutal killers in human history. Outbreaks of these diseases across international borders are properly defined as a pandemic. IgY may be useful to control such pandemic diseases. The use of IgY in environmental health is summarized in Table 27.12.

TABLE 27.12

Use of IgY in Environmental Health/World Pandemic

World Pandemic Disease	Pathogen	IgY Studied Based on	Reference
Cholera	*Vibrio cholerae* (Cholera Toxin B Subunit)	In vitro and in vivo mouse	Hirai et al. (2010); Barati et al. (2018)
	Vibrio cholerae Lipopolysaccharide (LPS)	In vitro and in vivo mouse	Akbari et al. (2018)
Influenza	Influenza virus A/H1N1 2009	In vitro	Adachi et al. (2011); Tsukamoto et al. (2011); Yang et al. (2014)
	Influenza Virus H5N1 and H1N1	In vitro and in vivo Mice	Nguyen et al. (2010); Wallach et al. (2011)
	Influenza B Virus	In vitro and in vivo mice	Wen et al. (2012)
COVID-19	Severe acute respiratorysyndrome coronavirus 2 (SARS-CoV-2) infection	Review	Constantin et al. (2020)
		In vitro	Lu et al. (2020); Shen et al. (2021); Wei et al. (2021)

Based on these data, IgY may be inexpensive and rapid prophylaxis that can be given *via* orally after mixing them into dairy products, powdered milk, foods, water, or ORS to prevent or treat cholera in humans, because they can supply water and nutrition in addition to antibody activity. IgY-supplemented tablet, lozenge, face mask intranasal spray, or drops are also applied to prevent or treat influenza and SARS-CoV-2 infection to bind to numerous epitopes on the virus and thus prevent viral entry into the body (Yang et al., 2014). This approach may be practical for those where vaccination is unavailable or as a temporary measure (such as during travel) before or to supplement vaccination. IgY can be easily given to people of all ages, from babies to the elderly, even under serious or miserable conditions such as those occurring after a natural disaster.

27.15 Use of IgY in Human Health

Acute microbial gastrointestinal infections destroy the body's first line of defense in the alimentary tract, which includes the innate component of the immune response, particularly the epithelial barriers, as well as the adaptive mucosal immunity resulting in the development of severe and complicated forms of the infectious disease. Gastrointestinal infections with various pathogens are mainly treated with antibiotics or antimicrobials. However, a dramatic increase in antibiotic resistance among common bacterial pathogens has impacted negatively impacted the efficacy of antimicrobial chemotherapy (Carlander et al., 2000). It is re-shaping the topography of research for novel and alternative infection control modalities. The past decade or so has seen increasing numbers of studies on and use of IgY in the treatment and prevention of infectious diseases in a variety of animal species (Xu et al., 2011) as well as in the development of functional food for human application (Schade et al., 2007). It has been established that oral administration of antimicrobial immunoglobulins derived from bovine milk (Korhonen et al., 2000) and poultry egg is an effective way to provide protective immunity against a variety of viral or bacterial pathogens (Narat, 2003) which might reduce the clinical use of antibiotics and thereby minimize the risk of bacteria developing antibiotic resistance.

Here we provide a comprehensive overview of previous applications of IgY in humans, including viral, bacterial, fungal, parasitic infections and others.

27.15.1 Viral Infection

27.15.1.1 Hepatitis B Virus

Hepatitis B viruses have a narrow range of host specificity (Maenz et al., 2007). Similar to the human hepatitis B virus (HBV), duck HBV infection can lead to chronic hepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma (Omata et al., 1983). In eggs laid by ducks that were immunized against duck HBV, significant titers of specific IgY were found in the yolk (Abouzid et al., 2006; Rollier et al., 2000). Also, uninfected treated ducks were protected against the virus, and treated carriers had decreased serum and liver levels of duck HBV (Thermet et al., 2004). Despite the availability of an effective vaccine, rates of vaccination in humans are poor and immunotherapies may be unavailable in resource-limited settings, or not tolerated. IgY may also warrant evaluation as a therapeutic for the treatment of postexposure HBV infection in humans where standard treatments are not readily available.

27.15.1.2 Rotavirus

Among the etiologic agents of diarrhea, rotavirus is the most important being responsible for over two million diarrhea episodes among infants with 600,000 deaths annually, mainly in developing countries (Parashar et al., 2003). Although mortality rate from diarrhea have decreased, morbidity rates remain high. Several independent guidelines based on systematic reviews of the best available evidence related to rotavirus vaccination of infants and to the management of acute gastroenteritis among infants and young children were published (Guarino et al., 2012; Szajewska and Dziechciarz, 2010). There is agreement in the scientific community that antimicrobials should not be routinely administered to children with gastroenteritis. The uptrend in the frequency of antibiotic-resistant bacteria, the widespread treatment of diarrhea with antimicrobials that sometimes do not respond to antibiotics, and the increasing number of immuno-compromised individuals has prompted much research into alternative approaches to management of diarrhea. The oral administration of IgY specific for any of the causative agents of diarrhea has proved successful for treatment of a variety of gastrointestinal infections (Rahman et al., 2013).

Rotavirus is the most common cause of severe diarrhea in children and outbreaks can occur in both vaccinated and unvaccinated children (Burke et al., 2018). When administered to pediatric patients who tested positive for rotavirus infection, orally administered treatments of 20% IgY sachets (Rahman et al., 2012) or 4 doses of 10 g of IgY powder (Sarker et al., 2001) significantly reduced the time for viral clearance in the feces, volume and duration of oral rehydration, intravenous fluid administration, duration of diarrhea, and recovery time. Wang et al. (Wang et al., 2019b) conducted a meta-analysis involving 2626 infants with rotavirus diarrhea from 17 randomized clinical trials. Among these infants, 1347 received anti-rotavirus IgY taken orally and 1279 received conventional treatment. Anti-rotavirus IgY treatment was significantly more effective than conventional treatment. These preliminary data demonstrate the utility of IgY as an antiviral therapy for infantile rotavirus enteritis (Wang et al., 2019b).

27.15.1.3 Zika Virus

In 2016, a global health emergency was declared by the World Health Organization after the observation of hundreds of thousands of infections by the Zika virus. Zika virus is transmitted by Aedes mosquitoes (Dick, 1952). The illness is characterized by fever, rash, arthritis (Duffy et al., 2009), and less commonly, Guillain-Barré syndrome (Cao-Lormeau et al., 2016). In pregnant women, Zika virus infection may cause severe birth defects, including microcephaly (Brasil et al., 2016; Rasmussen et al., 2016). There is no effective drug or vaccine

for Zika virus infection in part because of antibody-dependent enhancement, a phenomenon in which prior infection results in virus-specific antibodies enhancing replication of virus into monocytes/macrophages and granulocytic cells through interaction with Fc or complement receptors (Tirado & Yoon, 2003). IgY against the Zika virus was able to neutralize the virus *in vitro* at a concentration of 25 μg/mL (O'Donnell et al., 2019). Furthermore, intraperitoneal injection with 1 mg of specific IgY protected 3-week-old IFNAR–/– mice that received a lethal challenge of Zika virus without inducing antibody-dependent enhancement. Zika virus-specific IgY may warrant further evaluation as passive immunotherapy, with caution for the potential to elicit an allergic response.

27.15.1.4 Dengue Virus

Dengue fever, dengue hemorrhagic fever, and dengue shock syndrome are tropical, mosquito-borne diseases that are caused by infection with one of four dengue virus serotypes (Gubler & Clark, 1995). In the last 50 years, dengue virus-associated diseases have re-emerged, causing millions of infected cases and tens of thousands of deaths annually (Wilder-Smith et al., 2020). Although there is a commercially available vaccine to treat dengue fever, the World Health Organization recommends only vaccinating seropositive individuals who have a history of dengue virus infection, or by age 9 years in areas where the infection is prevalent (WHO, 2018). Currently, IgG-coupled enzyme-linked immunosorbent assays (ELISAs) are used for serological testing for dengue virus infection, suggesting that IgY can also be used in a diagnostic test for this disease.

Specific IgY has been developed against nonstructural protein 1, which is secreted by the dengue virus during infection and is detectable for up to 9 days after infection (Dussart et al., 2006; Lapphra et al., 2008). IgY anti-nonstructural protein 1 that is highly specific can neutralize the virus in immunoassays (Figueiredo et al., 2015; O'Donnell et al., 2017; O'Donnell et al., 2020). Specific IgY generated against dengue virus serotype 2 also demonstrated a similar ability to neutralize the virus (Fink et al., 2017). In vivo, IgY antibodies given at a dose of 150 μg (Figueiredo et al., 2015) or 1 mg through intraperitoneal injection (Fink et al., 2017) protected mice lethally challenged with dengue virus, suggesting that specific IgY may be used as a treatment of dengue virus-associated diseases in humans provided that a severe immune response (e.g., anaphylactic shock) to the IgY will not be generated (Yao et al., 2015). IgY antibodies are not likely to lead to immune amplification of dengue virus infection, unlike IgG where enhanced viral uptake *via* IgG-bound dengue virus enters into monocytes/macrophages *via* Fc receptors (Goncalvez et al., 2007).

27.15.1.5 Hantavirus

Hantavirus Pulmonary Syndrome (HPS) is a rare, severe, and potentially fatal respiratory disease caused by infection with hantaviruses (most commonly, Andes virus) (Zaki et al., 1995; Padula et al., 1998; Lee et al., 2021). Infection is believed to occur primarily through inhalation or ingestion of rodent feces, urine, and saliva, or by rodent bites. Person-to-person transmission is also recognized. The mortality rate is estimated at 38% (CDC, 2021). There are no current immunotherapies, antiviral treatments, or vaccines to treat HPS (Custer et al., 2003). Specific IgY developed after immunization of ducks with Andes virus neutralized the virus *in vitro* (Brocato et al., 2012; Haese et al., 2015) and protected Syrian hamsters administered a dose of 12,000 neutralizing antibody units/kg through intranasal delivery (Brocato et al., 2012) or 20,000 neutralizing antibody units/kg through subcutaneous injection (Haese et al., 2015) after receiving intramuscular and intranasal challenge. This suggests that IgY may warrant evaluation as a treatment following infection with the Andes virus to prevent the onset of HPS, especially in settings of clustering of cases (Lee et al., 2021).

27.15.1.6 Ebola Virus

Ebola virus infection is rare but results in high mortality rates in humans and nonhuman primates. Ebola virus also can persist in survivors and relapse has been documented. In addition to supported care, two monoclonal antibody treatments and a vaccine have been approved (WHO, 2021).

Anti-Ebola virus IgY was harvested from hens immunized with a recombinant vesicular stomatitis virus vector encoding Ebola virus glycoproteins. Anti-Ebola virus IgY was then evaluated in newborn Balb/c mice challenged with a lethal dose of Ebola pseudovirus 2 or 24 hours after infection (Zhang et al., 2021). Animals receiving a high dose of anti-Ebola virus IgY showed complete protection, while the low dose group showed partial protection. All mice receiving naïve IgY (i.e., from hens not immunized with Ebola glycoproteins) died. Zhang et al. note that because Ebola epidemics typically occur in impoverished hot African areas where electricity and cold-chain storage may be limited, advantages of low-cost mass production and avoidance of antibody-dependent enhancement may make anti-Ebola virus IgY an especially novel approach that warrants further investigation (Zhang et al., 2021).

27.15.2 Bacterial Infection

27.15.2.1 Dental Caries

Dental caries is one of the most common infectious diseases among children and adolescents affecting up to 90% of the world's inhabitants. The economic burden of the disease is therefore quite high with dental caries costs alone exceeding the total healthcare budget for children in many low-income countries. *Streptococcus mutans* (*S. mutans*) is the main odontopathogen implicated in the development of dental carries in humans (Loesche, 1986). Although most antibiotic treatments of *S. mutans* are effective, resistance to penicillin, erythromycin, amoxicillin, clindamycin, and lincomycin is common (Al-Shami et al., 2019). IgY developed against *S. mutans* is highly stable and cross-reacts with other serotypes, including *S. salivarum* (Hatta et al., 1997; Chang et al., 1999; Moreno et al., 2011). IgY against *S. mutans* inhibited *in vitro* bacterial growth, biofilm development, and binding to bacterial adhesion proteins, and inducing agglutination of *S. mutans* (Nguyen et al., 2011; Bachtiar et al., 2015). Rats exposed to

S. mutans and fed a caries-inducing diet had reduced dental caries when lyophilized anti-*S. mutans* IgY was incorporated into their feed (Otake et al., 1991; Fan et al., 2003), topical gel (Bachitar et al., 2016b), or chitosan-enriched soy milk (Bachtiar et al., 2015).

The efficacy of anti-*S. mutans* IgY in humans has also been evaluated. IgY anti-*S. mutans* incorporated into a mouth rinse significantly reduced levels of *S. mutans* in saliva within 4 hours, and in plaque within 7 days (Hatta et al., 1997). In comparison to commercial toothpaste, anti-S. *mutans* IgY toothpaste reduced levels of S. *mutans* more quickly and colonization was suppressed as long as 2 weeks after discontinuation (Chi et al., 2004).

In a randomized, double-blind, placebo-controlled clinical trial, Nguyen et al. reported that lozenges containing anti-CA-GTase IgY can significantly and selectively suppress oral colonization by salivary mutans after 5 days (Nguyen et al., 2011. Prior to this, effective local protection against dental caries was achieved with anti-*Streptococcus mutans* IgY in an animal model (Krüger et al., 2004). In this latter trial, a direct correlation was found between a given IgY dose and a reduction in the incidence of dental caries. Hatta et al. evaluated the efficacy of oral IgY anti-*S. mutans* rinses in human volunteers. This IgY inhibited *S. mutans* adherence to saliva-coated hydroxyapatite discs by 59%, while the control IgY from non-immunized hens only gave an 8% inhibition (Hatta et al., 1997). All these results strongly support the efficacy of oral treatments with anti-*S. mutans* IgY as a valid alternative for preventing dental plaque in humans.

27.15.2.2 Periodontitis

Periodontitis is a bacterial biofilm-induced oral disease, mostly caused by *Aggregatibacter actinomycetemcomitans* (*A. actinomycetemcomitans*) (Li et al., 2020), *Porphyromonas gingivalis* (*P. gingivalis*), *Prevotella intermedia, Solobacterium moorei, Fusobacterium nucleatum*. Oral administration of chicken egg yolk antibody (IgY) is a promising nutritional strategy to control pathogen infections.

A review on the effectiveness of mechanical, chemical, and antibiotic plaque removal in subjects with periodontal disease has outlined their various degrees of limitations. While oral care products containing chlorhexidine exert anti-plaque effects as indicated by meta-analyses (Sugano, 2012), IgE antibodies against chlorhexidine have been detected in the majority of sera from a small group of predominantly Japanese individuals showing anaphylactic-type adverse reactions directed against chlorhexidine. The use of chlorhexidine at a concentration effective for oral care has thus been banned in Japan.

Meanwhile, the emergence of antimicrobial resistance is currently posing a major challenge globally, with an increasing number of strains, including commensal and pathogenic oral bacteria, becoming resistant to commonly used antibiotics. Due to these current limitations, new therapeutic approaches for the control of biofilm are clearly required. The search for adjuncts in biofilm control has led to the exploration of oral passive immunotherapy by IgY as a biological plaque controller.

27.15.2.2.1 Porphyromonas gingivalis

Porphyromonas gingivalis (*P. gingivalis*), which causes biofilm on teeth (Costalonga & Herzberg, 2014), is quite resistant to the host immune response and leads to inflammation and bone loss associated with periodontitis (Hajishengallis & Lamont, 2012). Anti-*P. gingivalis* IgY against gingipains, a protein family released by *P. gingivalis*, inhibited attachment of the bacteria in cultured human epithelial cells (Yokoyama et al., 2007a). In addition, IgY against a 40 kDa outer membrane protein prevented the aggregation of *P. gingivalis* with *Streptococcus gordonii*, another bacterial strain implicated in periodontitis (Hamajima et al., 2007). Furthermore, IgY-anti-*P. gingivalis* in dry feed or administered as an ointment in a dog model reduced biofilm formation and inflammation (Rahman et al., 2011). Sublingual application of IgY anti-*P. gingivalis* in five periodontitis patients reduced the levels of the bacteria and gum bleeding (Yokoyama et al., 2007b). A clinical trial using egg yolk antibody against gingipains (IgY-GP) was performed in five patients with chronic periodontitis. IgY-GP containing ointment was administered directly into the periodontal pocket. Scaling and root planning (SRP) combined with the use of IgY-GP reduced the probing depth, bleeding on probing, and levels of *P. gingivalis* at 4 weeks as compared with SRP only (Yokoyama et al., 2007b). Sugano N also investigated the effect of IgY-GP on periodontitis by IgY-GP supplemented tablets in 42 patients after scaling and root planning employing a double-blind placebo-controlled approach (Sugano, 2009). A significant improvement in mean probing depth was noted in the IgY-GP group at 12 weeks after therapy. Parallel to the clinical changes, the number of *P. gingivalis* cells in subgingival plaque from the deepest pocket was significantly reduced. These results indicated that daily administration of tablet containing IgY-GP, in conjunction with scaling and root planning, in patients produced significantly better clinical and microbiological results. Near-infrared (NIR) photo-antimicrobial targeting therapy (PAT) for periodontitis is reported by Maruyama et al. The antimicrobial effect of PG-IgY-PAT is dependent on the NIR-light dose. PG-IgY-PAT significantly reduces the area of ulcers in a mouse model of PG-infected cutaneous ulcers, indicating that PG-IgY-PAT is a new promising therapeutic method for PG infection (Maruyama et al., 2022).

27.15.2.2.2 Prevotella intermedia

Like *Porphyromonas gingivalis*, *Prevotella intermedia* also causes gingivitis and other periodontal diseases (Maeda et al., 1998) and can be associated in humans with systemic diseases such as diabetes mellitus (Schara et al., 2013), respiratory illnesses (Widmer, 2010), cardiovascular disease (Beck et al., 1996, ischemic stroke (Joshipura et al., 2003), osteoporosis (von Wowern et al., 1994), and risk of low birthweight preterm pregnancies (Offenbacher et al., 1996). In rat models challenged with *P. intermedia* on gingivae, IgY anti-*P. intermedia* treatment protected against gingivitis by decreasing gingival index, plaque index, bleeding on probing, white blood cell counts, and local inflammation typically associated with periodontal disease (Hou et al., 2014). Because of the success of anti-*P. intermedia* IgY in rat models, as well as the general challenge due to increased resistance to antibiotics, IgY treatment may provide an alternative in humans.

27.15.2.2.3 Solobacterium moorei

Solobacterium moorei causes oral halitosis, periodontitis, and gingivitis (Haraszthy et al., 2008; Vancauwenberghe et al., 2013). *S. moorei* is susceptible to common antibiotics such as penicillin, vancomycin, and moxifloxacin (Pedersen et al., 2011). Specific IgY inhibited bacterial growth in liquid media and biofilm formation *in vitro* (Li et al., 2012). In a mouse model challenged with *S. moorei*, 20–40 mg/mL of specific IgY decreased bacterial counts in the oral cavities of treated animals (Li et al., 2012). Benefit in humans has not been determined.

27.15.2.2.4 Fusobacterium nucleatum

Fusobacterium nucleatum is one of many pathogenic bacterial strains that contributes to halitosis and periodontitis (Pianotti et al., 1986). Although available treatments include chemical antiseptics, antimicrobials, and mechanical therapy (Wang et al., 2019a), efficacy is limited by poor compliance and the development of antibiotic resistance. IgY anti-*F. nucleatum* has been suggested as an immunotherapeutic alternative to mediating the development of *F. nucleatum* and other bacteria in the oral cavity. In a periodontitis rat model, IgY anti-*F. nucleatum* inhibited the development of volatile sulfurous and odorous compounds and decreased the malodor index, levels of anti-inflammatory cytokines, and alveolar bone loss, while aiding periodontal restoration (Wang et al., 2019a).

27.15.2.3 Gastritis (Helicobacter pylori)

Helicobacter pylori infection may lead to gastric cancer which is the fourth most common cancer and second leading cause of cancer-related deaths worldwide (Herszenyi & Tulassay, 2010). *H. pylori* infects approximately 50% of the world's inhabitants and the number of newly diagnosed cases was calculated as 750,000 persons per year. *H. pylori* is the first bacterium to be classified as a class 1 carcinogen by the World Health Organization. Eradication of *H. pylori* infection both in animal models and in human subjects invariably fails when using an antibiotic as a monotherapeutic regimen even when the organism is susceptible to said antibiotic in vitro. Current first-line treatment regimens generally employ a potent acid-suppressing agent plus two antibiotics (such as amoxicillin, metronidazole, or tetracycline) but this approach is also associated with a variety of problems, including induction of antimicrobial resistance and high cost of treatment. Because of the development of resistance to antibiotics, treatment of *H. pylori* requires the incorporation of multiple antibiotics. *H. pylori* exhibits resistance to metronidazole (78%), levofloxacin (56%), multidrug treatments (53%), and clarithromycin (31%) (Wang et al., 2019d). Thus, orally administered immunoglobulins, and particularly IgY, have been suggested as an alternative approach to treat *H. pylori*-related infections because they limit the development of antibiotic resistance. IgY has been developed against *H. pylori* urease (HPU), a protein likely required for bacterial adhesion to mucin or the surface of epithelial cells in the gastric mucosa (Marcus & Scott, 2001).

IgY have been used successfully to reduce *H. pylori* colonization and diminish the severity of mucosal inflammation in the stomach in a mouse model of infection (Ameri Shah Reza et al., 2012). In animal models, a chow diet containing 25 mg anti-HPU IgY/g and 0.16 mg famotidine/g reduced *H. pylori* activity in infected Mongolian gerbils and prevented colonization of *H. pylori* in the gastrointestinal tracts of uninfected controls (Nomura et al., 2005). In the Mongolian gerbil model, anti- *H. pylori* IgY reduced inflammation, neutrophil and leukocyte infiltration, and gastric mucosal injury by interfering with the adhesion of *H. pylori via* its urease (Shin et al., 2002). A similar anti-inflammatory effect and reduction of *H. pylori* in the gastric mucosa were also observed in C57BL6/j mice treated with 60 mg of anti-*H. pylori* urease C IgY in either powder form or dissolved in phosphate-buffered saline (Malekshahi et al., 2011). Importantly, orally administered IgY (100–500 mg) in male C57BL/6 mice were more efficacious in eliminating *H. pylori* compared to treatment with the commonly used proton pump inhibitor pantoprazole (Yang et al., 2012). IgY against other *H. Pylori* antigens with good efficacy includes IgY against the outer inflammatory protein (Dossumbekova et al., 2006; Franco et al., 2008), the neutrophil-activating protein (Evans et al., 1995), and the native or recombinant VacA protein l (Xun et al., 2010; Xia et al., 2011).

In a clinical trial performed in 16 volunteers and designed to evaluate the protective effect of a yogurt drink fortified with anti-*H. pylori* urease IgY, values of urea breath and *H. pylori* stool antigen (HpSA) among the treatment group decreased significantly (Yamane et al., 2003). Interestingly, the number of volunteers with complaint of gastric pain decreased over the three-month treatment period. Although reduction and not elimination of *H. pylori* load upon oral treatment with IgY against *H. pylori* urease was observed, such reduction may have been enough to improve the quality of life of *H. pylori* infected patients. An egg yolk powder dietary supplement containing IgY anti-HPU administered to a cohort of asymptomatic *H. pylori*-positive patients reduced the levels of *H. pylori* and aided the treatment of *H. pylori*-associated gastritis, with no side effects reported (Suzuki et al., 2004). Another clinical study (Horie et al., 2004) on anti-urease IgY involving 42 volunteers revealed significant reduction in urea breath values among patients in the treated group. Protection by anti-*H. pylori* IgY has also been investigated in animals (Nomura et al., 2005) and humans (Suzuki et al., 2004). In this study of 42 *H. pylori*-positive subjects, drinkable yogurt fortified with anti-HPU IgY significantly suppressed *H. pylori* infection and was well tolerated with no adverse effects (Horie et al., 2004). Some studies on anti-*H. pylori* IgY in animals also demonstrated a prophylactic effect. While IgY does not bring about a total eradication of *H. pylori*, it may serve as an adjunct to standard treatment of *H. pylori* infection.

27.15.2.4 Salmonellosis

The *Salmonella* species, particularly *S. typhimurium* and *S. enteritidis*, are human and chicken pathogens (Haselbeck et al., 2017; Broom & Kogut, 2019). *Salmonella*-specific IgY inhibited bacterial cell growth (Lee et al., 2002) by binding to and structurally altering antigens on the surface of the bacterium or by causing bacterial agglutination (Mine, 1997). In a human epithelial Caco2 cell model, IgY anti-*Salmonella*

antibodies also prevented the adhesion of the bacterium to cells (Chalghoumi et al., 2009).

IgY anti-*S. typhimurium* and IgY anti-*S. enteritidis* exhibited significant cross-reactivity and agglutination (Mine, 1997; Terzolo et al., 1998), which indicates that IgY against a specific *Salmonella* serovar may be useful in treating a broad range of different *Salmonella* strains. IgY anti-*S. typhimurium* reduced immune cell recruitment and cytokine release in a mouse model infected with these bacteria (Li et al., 2016c). A combination treatment of a probiotic with IgY anti-*S. enteritidis* also decreased colonization and fecal shedding in young, market-aged broiler chicks challenged with *S. enteritidis* (Rahimi et al., 2007), indicating the additional potential benefit of using IgY anti-*Salmonella* antibodies in animals consumed as food.

27.15.2.5 Clostridiosis (Clostridium difficile)

Clostridium difficile (CD) is a cause of morbidity due to diarrhea and mortality due to inflammation of the colon, especially in the elderly, immunosuppressed, and after chronic antibiotic use. This serious condition has been increasing in incidence. IgY anti-CD has shown promise for patients based on animal studies (Khanna & Pardi, 2016). For example, 0.5 mg of IgY against the CD's FliD colonization-associated factor administered by gavage prevented the adhesion of CD and significantly enhanced survival rates in CD-challenged Syrian hamsters (Mulvey et al., 2011). Oral gavage treatments of 0.6 mg of anti-CD spore IgY delayed diarrhea onset and reduced spore adhesion to intestinal cells in mouse models, especially when coupled with an existing antibiotics treatment such as vancomycin (Pizarro-Guajardo et al., 2017). IgY anti-CD toxin A and B neutralized toxins and prevented recurrent infections in a hamster model (Kink & Williams, 1998) (209). Delivery of IgY anti-CD toxins to the colon instead of the upper gastrointestinal tract was enhanced when IgY was coated on microbeads (Zhang et al., 2016a) or encapsulated in chitosan-Ca pectinate microbeads (Xing et al., 2017) in a rat model.

27.15.2.6 Tetanus (Clostridium tetani)

Tetanus neurotoxin (TeNT), the product of Clostridium tetani, is the causative agent of the fatal disease tetanus. It is estimated 58,000 neonates and an unknown number of mothers die every year from tetanus (Thwaites et al., 2015). The tetanus bacteria typically enter the body through a cut or puncture wound and release the toxin in increasing amounts. When the neurotoxin reaches the nervous system it triggers increased rigidity of voluntary muscles, mainly those of the face, body, legs, neck, and tail (in animals). The steady and prolonged rigidity of the affected muscles ultimately leads to spasms and death. The neurotoxin is composed by two chains, one of 100 kDa (heavy chain) and another of 50 kDa (light chain), interacting through an interchain disulphide bond. The heavy chain is responsible for binding to polysialogangliosides and nidogen of nerve cell membranes and the light chain has a catalytic function, cleaving VAMP/synaptobrevin and blocking inhibitory synaptic vesicle release. Finally, an imbalance occurs between the inhibitory and excitatory synaptic vesicles on the motor neurons, leading to interruptions in muscle contraction and spastic paralysis (Surana et al., 2018). In a study, Selim et al., investigated the application of IgY both prophylactically and therapeutically for tetanus treatment (Selim et al., 2015). Results showed that all mice in the therapeutic groups as well as a prophylactic groups survived after a challenge with 2 minimum lethal dose (MLD) of *C. tetani*; similar results were obtained in donkeys. These data confirmed that the IgY approach was as effective as the equine IgG approach in tetanus therapy (Selim et al., 2015).

27.15.2.7 Botulism (Clostridium botulinum)

Botulinum neurotoxin (BoNT) is produced by *Clostridium botulinum* under anaerobic conditions and is known as one of the most poisonous substances in the world (Peck, 2009). To date a total of seven different BoNT toxin types are described (A to G). Botulism usually occurs as a food poisoning caused by botulinum neurotoxin produced by *C. botulinum*. BoNT consists of a heavy chain (100 KDa) and a light chain (50 KDa) that interact via a disulphide bond. Just like TeNT, the heavy chain binds to polysialogangliosides on the nerve plasma membrane, to G1b gangliosides, with high specificity and affinity and whole toxin is internalized to the cytoplasm via endocytic vesicles. The light chain has an endopeptidase activity and cleaves the SNARE proteins VAMP/synaptobrevin 1–3 and syntaxin. This phenomena inhibits neurotransmitter (acetylcholine) vesicle release which results in muscle fiber paralysis (Rossetto et al., 2011). In a number of studies, BoNT/A or BoNTB or a combination were used to generate IgY for treatment of mice or birds (Pauly et al., 2009; Li et al., 2013; You et al., 2014a). In all cases IgY showed a protective effect. Another important fact to significantly reduce botulism mortality, is the need for a fast diagnosis of BoNT toxin. Indeed a rapid and accurate test for the botulinum neurotoxin is essential for BoNT prevention and therapy. IgY was developed against either a linear peptide substrate (SNAP25) (Li et al., 2013) or BoNT A/B and D (Doellgast et al., 1997) and both showed robust results for toxin detection applications, namely in food or clinical conditions. Notably, Doellgast et al., develop an enzyme linked immunosorbent assay and an enzyme linked coagulation assay (ELISA-ELCA) for high sensitivity detection of anti-neurotoxin in human sera (Doellgast et al., 1997).

27.15.2.8 Necrotic Enteritis (Clostridium perfringens)

Clostridium perfringens type A is the most common bacterial infection associated with necrotic enteritis (NE). The main toxin produced by *Clostridium perfringens* type A is alpha toxin (CPA), which can have critical roles in pathogenesis of NE. This toxin can induce mucosal damage in chicken intestinal loops and has been associated with NE lesions in germ-free chickens. Anti-CPA serum applications have been shown to effectively neutralize the effects of the toxin (Doellgast et al., 1997). Specific IgY has been shown to be effective in protecting birds lowering the presentation of NE lesions.

27.15.2.9 Gastroenteritis (Campylobacter jejuni)

The *Campylobacter* species, in particular *Campylobacter jejuni*, is the most common cause of gastroenteritis in humans worldwide (WHO, 2021a). Most human *C. jejuni* infections are caused by the consumption of contaminated poultry. However, *C. jejuni* seems to have a commensal relationship with chickens while acting as a pathogen in humans (Young et al., 2007). Because of the use of growth-promoting antibiotics in the meat-producing industry, there is a rise in antibiotic-resistant *Campylobacter* strains (Alfredson & Korolik, 2007). IgY against *C. jejuni* may provide an alternative to antibiotic use (Al-Adwani et al., 2013; Thibodeau et al., 2017). Because of its high specificity and limited cross-reactivity, IgY anti-*C. jejuni* also can provide a highly accurate method to detect food contamination with *C. jejuni* (Hochel et al., 2004; Horak & Hochel, 2005).

To reduce the spread of *C. jejuni* from poultry to humans, IgY has been administered as a passive vaccine to chickens. IgY against *C. jejuni* has prophylactic and therapeutic effects through its ability to decrease overall and fecal bacterial levels in *C. jejuni*-challenged chickens (Tsubokura et al., 1997; Hermans et al., 2014; Nothaft et al., 2016). Similar results were also observed using IgY against *C. jejuni* adhesins and flagellins, which significantly reduced caecal colonization by *C. jejuni* and initiated the production of *C. jejuni* specific antibodies, although these may not play a role in protection (Neal-McKinney et al., 2014; Chintoan-Uta et al., 2016). Administration of anti-*C. jejuni* IgY also resulted in a significant reduction in transmission of *C. jejuni* to non-inoculated birds (Hermans et al., 2014), without altering the microflora of the intestinal tract (Nothaft et al., 2016).

27.15.2.10 Sepsis

27.15.2.10.1 Escherichia coli

Escherichia coli is an integral constituent of the mammalian microflora, with several pathotypes of *E. coli* implicated in the development of enteric and extraintestinal diseases such as diarrhea, sepsis, meningitis, and urinary tract infections (Kaper et al., 2004). Among the enteric *E. coli*-associated diseases, there are at least six different categories: enterotoxigenic *E.coli*, enteropathogenic *E. coli*, enterohemorrhagic *E. coli*, enteroaggregative *E. coli*, enteroinvasive *E. coli*, and diffusely adherent *E. coli* (Nataro & Kaper, 1998). Due to widespread antibiotic resistance of *E.coli* (Sáenz et al., 2004), IgY may serve as an alternative method to neutralize virulent *E. coli* in food, animals, and humans.

The major factor in the pathogenicity of *E. coli* is production of Shiga-like toxin. Numerous assays using IgY have been developed to detect the presence of Shiga-toxin-producing enterohemorrhagic *E.coli*. For instance, an ELISA assay involving IgY against *E.coli* O157:H7 was able to detect as little as 40 CFU/mL of *E. coli* O157:H7, suggesting that such assays can be used for detecting foodborne pathogens (Sunwoo et al., 2006). Furthermore, because Shiga-toxin is uniformly expressed by all enterohemorrhagic *E. coli*, IgY can be used to detect different serotypes and variants of Shiga-toxin-producing *E. coli* (Parma et al., 2012). Similarly, toxin-specific IgY has also been used to detect and neutralize heat-labile toxin produced by enterotoxigenic *E. coli* (Akita et al., 1998). Chicken or ostrich IgY against *E. coli* O157:H7 and O78:K80 inhibited bacterial growth in liquid medium (Sunwoo et al., 2006; Mahdavi et al., 2010a; Meenatchisundaram et al., 2011; Tobias et al., 2012).

A randomized, double-blind, placebo-controlled trial evaluated 301 Guatemalan children (154 intervention and 147 placebo) with acute non-bloody diarrhea who received PTM202 (combined IgY specifically targets rotavirus, enterotoxigenic *E. coli*, Shiga toxin-positive *E. coli*, and salmonella) or placebo for 3 days (Gaensbauer et al., 2017). PTM202 led to a reduction in duration of diarrhea among children whose diarrheal stool at enrollment contained one or more PTM202-targeted organisms. No adverse events were reported.

27.15.2.10.2 Enterohemorrhagic Escherichia coli Infection

Enterohemorrhagic *Escherichia coli* (EHEC) causes a spectrum of human diseases, including diarrhea, hemorrhagic colitis, disordered consciousness, renal failure and hemolytic uremic syndrome (HUS). The bacterium colonizes the large intestine and produces shiga-toxins (Stxs) as a major virulence factors. EHEC produces two types of Stxs, Stx-1, and Stx-2. Stxs released into the intestinal lumen enter the systemic circulation and reach target organs. Stxs are multimeric proteins that consist of an A subunit and a pentamer of B subunits. The B pentamer is responsible for the toxin binding to target cell-surface glycolipid receptors (Linderberg et al., 1987; Lingwood et al., 1987). After binding, the toxin is internalized into the cells by endocytosis, and then a fragment cleaved from A subunit exerts its toxic activity by inhibiting protein synthesis.

Monoclonal antibodies against Stxs have been investigated for the prevention of Stx-mediated diseases (Dowling et al., 2005; López et al., 2010). The antibodies have been designed mostly for parenteral administration to neutralize Stx in the systemic circulation. However, EHEC produces Stx in the intestine, from where the toxin enters the bloodstream to reach the target organ. While we believe that neutralization of Stxs in the intestine by oral treatment is more desirable than neutralization in the vessel for preventing Stx-mediated diseases, oral administration requires greater quantities of antibodies compared with parenteral administration. Recently, oral administration of chicken IgY antibody has been demonstrated to prevent or control several intestinal infections. Chicken IgY is thought to be an economical source to obtain large amounts of antibody that can be given orally (Mine & Kovacs-Nolan, 2002). We focused IgY antibodies against Stxs for oral use to prevent Stx-mediated diseases (Neri et al., 2011; Neri et al., 2012).

In conclusion, immunization with Stx-1 and Stx-2 holotoxins induced IgY antibodies in chickens. Their neutralizing activity against Stxs was exerted through binding activity to polymeric form of Stx B subunit. The oral administration of anti-Stx-2 IgY prevented the death of mice infected intestinally with Stx-2-producing EHEC O157:H7. Immunization with recombinant Stx B subunit also induced neutralizing IgY antibody in chickens. Oral administration of the IgY is thought to be promising

to prevent Stx-mediated diseases. The IgY may have the potential to reduce the risk of HUS due to the use of antibiotics by the combined treatment.

27.15.2.10.3 Staphylococcus aureus

Staphylococcus aureus is a pathogenic bacterial strain that causes food poisoning, toxic shock syndrome, endocarditis, sepsis, soft tissue infections, and in-hospital infections (Lowy, 1998; Henderson and Nimmo, 2018). Although *S. aureus* is normally found in mammals and 30%–50% of humans, it remains a dangerous pathogen due to its endotoxicity, virulence, invasiveness, and antibiotic resistance (Le et al., 2003). *S. aureus* has increasingly displayed resistance to common antibiotic treatments such as methicillin and vancomycin (Smith et al., 1999; Klevens et al., 2007) and antimicrobial-resistant strains are now detected in the community, not just in healthcare settings (Chambers, 2001; Saveli et al., 2011). Stronger measures to contain *S. aureus* infections, as well as alternative and combination treatments, are now promoted to combat increasing antibiotic resistance. In vitro, specific IgY had high binding specificity and inhibited bacterial growth in culture, possibly by interrupting interactions with surface antigens (Guimarães et al., 2009b). IgY generated against *S. aureus* also caused agglutination of the bacterium, and did not show cross-reactivity with other bacterial strains such as *Streptococcus epidermidis*, *Escherichia coli*, and *Pseudomonas aeruginosa* (Jagadeeswari et al., 2015). The anterior nare of the nose is the most frequent carriage site for *S. aureus* (Kluytmans et al., 1997). When the nares are treated topically to eliminate nasal carriage, in most cases the organism also disappears from other body areas. Anti-*S. aureus* IgY given intranasally may be of special interest in the treatment of this pathogen, including for the growing threat of methicillin-resistant *S. aureus* (Jernigan et al., 2020).

27.15.2.10.4 Aeromonas

Aeromonas is found in aquatic environments and the microflora of animals and humans. However, certain strains of *Aeromonas* have been implicated in the development of sepsis and gastroenteritis in humans (Merino et al., 1995), as well as fish, other animals, and environmental reservoirs (Parker & Shaw, 2011). Notably, almost all subspecies of *Aeromonas* express strong resistance to beta-lactam antibiotics such as penicillin, ampicillin, and carbenicillin, which has led to the pursuit of alternative and combination antimicrobial therapies (Altwegg & Geiss, 1989). IgY-specific antibodies have been investigated as an alternative method to diagnose, prevent and treat the *Aeromonas*-diseased aquatic animals (Li et al., 2006; Gan et al., 2015; Qin et al., 2018; Fernandes et al., 2019a).

27.15.2.11 Lung Infections

27.15.2.11.1 Treatment of Pseudomonas aeruginosa in Cystic Fibrosis

Cystic fibrosis is a common, hereditary, and life-threatening disease associated with damage to the lungs, pancreas, and male sex organs (Collins, 1992; Govan & Deretic, 1996). Patients with cystic fibrosis are especially prone to debilitating chronic lung infections caused by bacteria such as *Pseudomonas aeruginosa* (Ulrich et al., 2010). Due to a fear of developing antibiotic-resistant strains, alternative treatments to chronic antibiotic therapy have been studied, including the use of IgY against *P. aeruginosa* as a method of passive immunization. Anti-*P. aeruginosa* IgY significantly increased the neutrophil-mediated respiratory burst and subsequent bacterial killing of *P. aeruginosa in vitro* (Thomsen et al., 2015; Thomsen et al., 2016). Anti-*P. aeruginosa* IgY also inhibited murine pneumonia when administered intranasally as evidenced by reduced bacterial burden, inflammatory cytokines, inflammation of the lung tissue, and clinical symptoms, an effect enhanced by pretreatment with azithromycin 8 (Thomsen et al., 2021). The benefit of specific IgY anti-*P. aeruginosa* is believed to be against the flagellin protein implicated in the motility, adhesion, and inflammation of *P. aeruginosa* (Nilsson et al., 2007a).

In 17 patients with cystic fibrosis, prophylactic continuous oral treatment (solution gargled for 2 min and swallowed in the evening) with specific IgY against *P. aeruginosa* to prevent pulmonary infections for up to 12 years (114 patient-years) showed significant reduction in *P. aeruginosa* infections compared with 23 cystic fibrosis control patients, with no adverse events (Nilsson et al., 2008).

A randomized, double-blind, placebo-controlled Phase 3 trial of 164 patients age 5 and older with cystic fibrosis was conducted at 47 European sites from 2011 to 2015 to evaluate treatment with oral anti-*P. aeruginosa IgY* gargling solution ($n = 83$) vs. placebo ($n = 81$). Study drug was to be gargled and then swallowed once daily in the evening. Study duration (and primary outcome measure) was until the next *P. aeruginosa* infection was diagnosed or two years, whichever came first. There was no significant difference between treatment groups in time to first recurrence of *P. aeruginosa* infection (median, 26.3 months for IgY-treated group) or secondary endpoints of number of exacerbations, number of days of illness, and use of antibiotics (EU Clinical Register, 2021). Despite findings of no efficacy, this study provided an excellent safety database. A total of 1972 adverse events (AEs), mostly mild in severity, were reported, 989 of which were in the placebo group and 980 in the IgY group. The incidence of AEs was also similar between the two groups. The most commonly reported AEs were abdominal pain, vomiting, pyrexia, nasopharyngitis, and upper respiratory tract infection. No deaths occurred. Only 5 AEs in the IgY-treated group and 20 AEs in the placebo group (none serious) were judged to be related to the study drug.

27.15.2.12 Tuberculosis

Mycobacterium tuberculosis (MBTC) is responsible for the development of tuberculosis, a potentially fatal respiratory disease that also can cause extrapulmonary disease (e.g., of the urinary system). MBTC is increasingly becoming more difficult to treat due to antibiotic resistance (Chauhan et al., 2021). In a rat peripheral blood mononuclear cell model, administration of high concentrations of IgY anti-MBTC increased interleukin-2 and interferon expression (Sudjarwo et al., 2017a). IgY against MBTC may warrant evaluation for use in combination with other immunotherapeutic treatments of tuberculosis (Sudjarwo et al., 2017b). In addition, IgY may also be

of interest as a novel treatment of pulmonary nontuberculous mycobacteria, regarded as more challenging to treat because of frequent antimicrobial intolerance, toxicities, resistance, and drug-drug interactions (Shulha et al., 2019).

27.15.2.13 Nosocomial Infections

Acinetobacter baumannii, a gram-negative bacterium, is the cause of nosocomial infections and outbreaks in hospitals worldwide, such as sepsis, urinary tract infections, pneumonia, or surgical wound infections. Due to its resistance to desiccation and antimicrobial agents, *A. baumannii* is associated with significant mortality, costs, and hospital stays, particularly in vulnerable patients (Fournier & Richet, 2006). Shi et al. produced specific IgY against multi-drug resistant strains of *Acinetobacter baumannii*. In a mouse model of *A. baumannii*-associated pneumonia, intraperitoneal anti-*A. baumannii* IgY specific to pan-drug-resistant strains reduced levels of inflammatory cytokines, lung inflammation, and mortality (Shi et al., 2017). Similar results were also seen with intraperitoneal injections of 40 μg of IgY developed against the inactivated whole-cell or outer membrane proteins of *A. baumannii*, which protected against nasally challenged mice, possibly by inhibiting bacterial adhesion (Jahangiri et al., 2019).

27.15.2.14 Skin-Related Infections

27.15.2.14.1 Propionibacterium

Acne vulgaris is a skin condition that affects most humans at some time and is thought to be caused by multiple factors, including increased sebaceous gland sebum production, hormones, cytokines, nutrition, and bacteria such as *Propionibacterium acnes* (Kurokawa et al., 2009). Because of rising antibiotic resistance, IgY has also been proposed as a cost-effective alternative to antimicrobial treatments of acne. IgY anti-*P. acnes* inhibited growth of *P. acnes* colonies as well as biofilm development by preventing bacterial adhesion (Revathy et al., 2014).

27.15.3 Fungal Infection

27.15.3.1 Candidiasis

Candidiasis is one of the most common oral fungal infections. From over 8.7 million eukaryotic species identified to the current date, the kingdom of fungi has approximately 611,000 species, making up 7% of all eukaryotic species (Mora et al., 2011). At the cellular level, fungi are more related to humans than bacteria and belong to the Eumycota group, as chemoheterotrophic organisms (Khan et al., 2010). However, only 600 species of fungi are able to cause infections in humans (Mora et al., 2011). The genus *Candida* includes about 150 species, but many species are endosymbionts of humans, causing infections mainly in immunosuppressed hosts. Around 80% of infections are caused by *Candida albicans,* although *Candida non-albicans* infections (*Candida glabrata*, *Candida tropicalis*, *Candida krusei*, *Candida dubliniensis*) are becoming more and more frequent (Mark & Roberts, 2016; Ciurea et al., 2020). Candidiasis is one of the most common oral fungal infections in patients with impaired immune system and has a high morbidity with approximately 85% of patients being infected at some point during their illness. As we know that HIV and AIDS patients are susceptible to opportunistic infections. Oral candidiasis or thrush is the primary manifestation of fungal infection in these patients. (Noël de Tilly & Tharmalingam, 2022). In this section, author highlighted the novel treatment options of candidiasis with anti C. albicans IgY added in gel (Takeuchi et al., 2016); denture base (Kamikawa et al., 2016), tablet (Ibrahim et al., 2007), photosensitizing phthalocyanine dye (IRDye700Dx; IR700) (CA-IgY-IR700) (Yasui et al., 2021), including intravenous immunoglobulin antibodies (Pedraza-Sanchez et al., 2018).

A gel preparation for oral use containing IgY against *Candida albicans* was tested by Tekeuchi et al. and caused a reduction in the number of colony-forming units (CFU) on the oral cavity of elderly people, showing promise for prophylactic use against *C. albicans* oral infection (Takeuchi et al., 2016). In other research, specific IgY inhibited the adhesion of *Candida albicans* and *Candida glabrata* to denture base material. Anti-*C. albicans* IgY was more effective against *C. albicans* than anti-*C. glabrata* IgY, while both antibodies were equally effective in preventing the adhesion of *C. glabrata* (Kamikawa et al., 2016).

Treatment of oral candidiasis is relatively simple and effective for the healthy patient. Typically, topical medications are adequate usually involving the use of a commonly prescribed anti-fungal agent, nystatin oral suspension. To be effective, topical medications must be in contact with the organism to eliminate it. Since patients are usually unable to hold liquids in their mouth cavity, antibiotic-supplemented lozenge tablets are used wherein the tablet dissolves slowly allowing the drug to be present for a longer length of time in the oral cavity. From another perspective, development of cross resistance has primarily been a problem with fluconazole in AIDS treatment. Inasmuch as antibiotic resistance correlates with clinical failure, oral passive immunization with IgY for the control of oral candidiasis acquires a special relevance. Toward this end, a clinical trial was performed by our group in two healthy elderly volunteer subjects. A tablet supplemented with egg yolk antibody against *Candida albicans* (CA-IgY) was prescribed for 4 weeks daily and treatment was stopped for 4 weeks. This treatment cycle was repeated three more times with both subjects being examined every week. The patient who received tablets containing anti-CA IgY revealed reduced the number of salivary Candida CFU. With each 4-week pause in treatment, *Candida albicans* count gradually increased to previous level (Ibrahim et al., 2007) indicating that the mode of action was specific for the anti-CA IgY and reduction of Candida CFU is feasible with regular treatment.

Near-Infrared Photo-Antimicrobial Targeting Therapy for Candidiasis is reported by Yasui et al. (Yasui et al., 2021). Near-infrared photoimmunotherapy (NIR-PIT), originally developed as a cancer treatment, specifically kills cancer cells via a photosensitizing phthalocyanine dye (IRDye700Dx; IR700)-conjugated monoclonal antibody, and irradiating NIR light. IgY-photo-antimicrobial targeting therapy (IgY-PAT), exploiting NIR-PIT, is investigated to destroy only microorganisms. IR700 is conjugated with anti-*Candida albicans* IgY

(CA-IgY) to generate CA-IgY-IR700, which specifically binds various *Candida* spp. (and not human skin cells). The antimicrobial effect of CA-IgY-PAT is dependent on the NIR-light dose. CA-IgY-PAT significantly reduces the area of ulcers in a mouse model of CA-infected cutaneous ulcers ($p < 0.0001$), indicating that CA-IgY-PAT is a new promising therapeutic method for CA infection. (Yasui et al., 2021).

These novel forms of therapy are important in consideration of the arms race in successfully treating fungal infections while preventing the evolution of resistant strains. Like bacteria, fungi are constantly evolving and developing resistance to existing treatments and prophylaxis application (Noel de Tilly and Tharmalingam, 2022).

27.15.4 Protozoal Infection

27.15.4.1 Trypanosoma

The protozoan parasite, *Trypanosoma cruzi,* found in mammals and triatomine bugs in the Americas, causes Chagas disease, a zoonotic disease that can be transmitted to humans by insect vectors, blood-sucking triatomine bugs. Chronic infection can lead to heart and gastrointestinal disease that can be life-threatening (Bern et al., 2011; Elliot et al., 2015). Vaccines developed against *T. cruzi* are only partially protective since defined antigens must be used to prevent the occurrence of cryptic infections (Brener, 1973). Furthermore, drugs approved for the treatment of Chagas disease can have toxic, mutagenic, and other adverse side effects (Castro et al., 2006). Since no cytotoxic or proliferative effects were observed on mononuclear and VERO cells *in vitro* when treated with IgY against *T. cruzi*, specific IgY has been considered as a possible therapeutic for Chagas disease (Grando et al., 2017). In a mouse model, anti-*T. cruzi* IgY administered prophylactically at 50 mg/kg reduced parasitemia post-challenge and prevented the development of cardiac lesions by amastigotes. These same effects were also observed with the therapeutic administration of 50 mg/kg of IgY, which also improved the immune response by preventing an increase in activity of E-NTPDase and E- ADA activities in the splenic lymphocytes of the animals (Grando et al., 2018).

Another member of the *Trypanosoma* family, *T. evansi*, infects a wide range of domesticated livestock worldwide (Luckins, 1988), causing anemia (Trail et al., 1990). One case of *T. evansi* infection in humans has also been documented, possibly by blood transmission from an infected animal (Joshi et al., 2005). Current strategies for controlling the dissemination of *T. evansi* include herd culling (Herrera et al., 2004) and chemical therapy of infected animals, although this latter approach has limited use due to high toxicity and the development of drug-resistant strains (Silva et al., 2002). In contrast, no significant cytotoxic or genotypic toxicity was observed when IgY anti-*T. evansi* was used to treat peripheral blood samples, although an increase in cell viability and lymphocyte proliferation was observed when a concentration of 10 mg/mL of specific IgY was used (Sampaio et al., 2014a). In vivo, specific IgY against *T. evansi* administered intraperitoneally at a dose of 10 mg/kg increased the longevity and survival of infected animals (Sampaio et al., 2014b).

27.15.4.2 Cryptosporidiosis

Several members of the *Cryptosporidium* family are implicated in the development of cryptosporidiosis, an intestinal infection that causes diarrhea and, less commonly, pneumonia in humans (Fayer, 1997). There are no therapies to fully treat cryptosporidiosis or prevent the infection in humans and animals (Pinto & Vinayak, 2021) although hydration and passive immunization through the administration of monoclonal antibodies (Perryman et al., 1993), nitazoxanide, or hyperimmune bovine colostrum have limited efficacy (Nord et al., 1990; Ungar et al., 1990). IgY has been explored as a treatment against *Cryptosporidium* infection. In vitro, IgY antibodies generated against *C. parvum* oocyst antigens were highly specific (Hashemzadeh and Shahbazi, 2016), decreased binding of the parasite to Caco-2 cells, and blocked the vitality of *C. parvum* (Kobayashi et al., 2004). However, in a severe combined immunodeficiency mouse model, treatment using feed containing 25% specific IgY powder and a 20% specific IgY solution was only capable of partially reducing oocyst shedding in challenged animals, and was unable to eliminate infection. Similarly, IgY against the P23 protein in *C. parvum* also has high specificity for the parasite (Shahbazi et al., 2009; Omidian et al., 2014). Using a mouse model, the anti-P23 IgY reduced oocyst shedding by 70%. Specific IgY against the GP60 glycoprotein in *Cryptosporidium hominis*, another strain implicated in cryptosporidiosis, was also found to specifically bind to the antigen, as well as the parasite (Miura et al., 2017). The high specificity and protective effectiveness of these antibodies suggest that IgY warrants evaluation as a novel diagnostic test for cryptosporidiosis and a passive immunization treatment in immunocompromised individuals.

27.15.5 Other Important Applications of IgY

27.15.5.1 Antiobesity Activity

IgY raised against porcine pancreatic lipase was used against the enzyme *in vitro* and *in vivo*. Later, mice with obesity induced by high fat diet were orally treated with the antibody, which was given concomitantly with food, and a reduction of adipose tissue and liver fat level was observed, as well as an increase of fecal excretion of triglycerides and their decrease in blood plasma. Anti-lipase IgY inhibited the hydrolysis of diet fat and reduced its intestinal absorption, showing anti-obesity activity (Hirose et al., 2013; Tarigan et al., 2016).

27.15.5.2 Antiallergic Activity

Wei-xu et al. evaluated the antiallergic effect of specific IgY against the pro-inflammatory cytokines IL-β1 and TNF-α in guinea pigs with induced allergic rhinitis. A reduction of the eosinophils number in the blood and in the nasal and bronchial lavages was found, as well as a decrease of eosinophils, neutrophils and lymphocytes infiltration into the nasal mucosa and the lungs of animals treated with anti-IL-β1 and anti-TNF-α IgY, alone or jointly (Wei-xu et al., 2016).

27.15.5.3 Antitumor Activity

The phylogenetic distance between birds and mammals ensures a stronger immune response against mammalian antigens by birds (Gassmann et al., 1990). Such a feature may be advantageous to produce IgY against human tumor antigens. Following this rationale, Amirijavid et al. produced highly specific IgY against a sequence of 21 amino acids present on the ectodomain of the TRAIL (TNF-related apoptosis-inducing ligand) receptor TRAIL-R2 (DR5). The antibodies bound to the amino acid sequence and activated the DR5 receptors in human breast cancer cells MCF7, acting as a TRAIL agonist and inducing apoptosis (Amirijavid et al., 2016). IgY against other receptors, such as the HER2 receptor, was tested coupled to single walled carbon nanotubes (SWNTs) and specifically detected the HER2 receptors on the surface of SK-BR-3 cells. The binding of the complex to the receptors was measured by Raman signals emitted by the nanotubes. SWNT has a near infrared absorption (NIR), which can be used for tumor ablation, and, coupled to anti-HER2 IgY, was able to kill SK-BR-3 cells without needing internalization of the complex by the cell (Xiao et al., 2009). These findings show that IgY produced against tumor antigens is an attractive alternative for a more selective treatment of cancers and its use could, therefore, minimize the side effects of traditional chemotherapy.

27.15.5.4 Anti-Venom Activity

One of the side effects that occur in individuals receiving antivenom serum produced in goats, sheep and horses is due to the presence of serum proteins on the anti-venom serum derived from these animals, in which IgG is not sufficiently purified (Araújo et al., 2010; Sjostrom et al., 1994). One advantage of using IgY in anti-venom serotherapy is that it is easily purified, which would minimize the occurrence of side effects due to nonspecific proteins. Arqo et al. demonstrated this property when specific IgY was produced as anti-venom of the snake genus *Bothrops* sp. These antibodies neutralized a pool of venoms from five *Bothrops* species, with an ED50 of 150 μL/2LD50, showing little to no side effects in mice (Araújo et al., 2010).

Mendoza et al. also produced IgY capable of neutralizing the venom of the peruvian snake *Bothrops atox*. The antivenom IgY showed considerable cross reaction with the venom of *Bothrops brazili* and could be used not only as *B. atox* antivenom, but also as a tool for the research of cross reaction with venoms from different species (Mendoza et al., 2012).

In another elegant work, Andrade et al. produced IgY against a pool of venoms from snakes of the genus *Bothrops* and against the venom from the species *Crotalus durissus terrificus*. Anti-venom IgY extracted from eggs was compared to the horse anti-venom IgG in Western blot. The results showed that specific egg's IgY recognized the same antigens as the equine anti-venom (de Andrade et al., 2013).

IgY against coral snake venom was first produced in response to a pool of venoms from different species of *Micrurus.* These antibodies recognized, by Western blot, venom proteins from several snakes: *M. isozonus*, *M. surinamensis*, *M. f. fulvius*, *Naja kaouthia*, *N. pallida*, *Bothrops colombiensis*, *Crotalus durissus cumanensis,* and *C. vegrandis* and could, therefore, be used as a broad-spectrum snake anti-venom (Aguilar et al., 2014).

Zolfagharian and Dounighi produced IgY by inoculating the *Vipera lebetina* snake venom, inactivated by γ radiation, in hens (Zolfagharian & Dounighi, 2015). These antibodies were effective in neutralizing the crude venom of *Vipera lebetina* in mice.

Anti-venom IgY were also obtained from eggs of hens immunized with the venom of the snake *Trimeresurus albolabris*. These IgY recognized, by Western blot, most of the proteins present in the *T. albolabris* venom and neutralized it in mice in a dose-dependent manner (Duan et al., 2016).

More recently, Liu et al. extracted and purified IgY from eggs of hens inoculated with the venom of the *Deinagkistrodon actus* snake. These antibodies were able to neutralize the lethal effects of the venom, such as bleeding, edema formation and myotoxicity in a dose-dependent manner (Liu et al., 2017).

da Rocha et al. produced IgY against ophidian toxins of *Crotalus durissus terrificus*, *Bothrops jararaca* and *Bitis arietans*. The antibodies were able to bind to specific components of the venoms in Western blot and protected 100% of the intoxicated mice when obtained after the ninth inoculation. The authors recommended the use of a small antigen dose (20 μL) applied in successive inoculations for IgY production, since this dose was enough to genetically alter the V(D)J segments on the naïve cells and to generate immunological memory (da Rocha et al., 2017).

However, IgY raised against the venom of the snake *Oxyuranus scutellatus* was less effective than equine IgG, being unable to neutralize the neurotoxic and coagulant effects of the venom (Navarro et al., 2016). Nonetheless, this result cannot be extended to IgY produced against other venoms.

IgY against the *Tityus caripitensis* scorpion venom, produced by Alvarez et al., neutralized not only the venom of *T. caripitensis*, but also that of other *Tityus* species (*T. quirogae*, *T. discrepans,* and *Tityus gonzalespongai*), and inactivated the hyaluronidase, an enzyme that facilitates the toxin spread in the tissues, present in the *T. serrulatus* venom (Alvarez et al., 2013). Thus, IgY raised against *T. caripitensis* venom could be used as a broad- spectrum anti-scorpionic serum.

27.15.5.5 Prophylaxis of Celiac Disease

Another application of IgY technology, the prophylaxis of Celiac disease, was demonstrated by Gujral et al., who developed powdered egg yolk formula with protective sugars containing antigliadin IgY, among which, the formula with mannitol (EYP-M) retained its activity after being submitted, *in vitro*, to chemical conditions analogous to those of the stomach and small intestine. The formula IgY-EPY-M neutralized *in vitro* both the isolated gliadin and that present in food matrix and inhibited its intestinal absorption in mice, showing promising for the prevention of Celiac disease (Gujral et al., 2012).

27.15.5.6 Prophylaxis of Toxicity

Bobeck et al. used IgY against the human intestinal alkaline phosphatase (hIAP) to assess the influence of IAP on increased bioavailability of phytate phosphate in the presence

of 1α-dihydroxycholecalciferol (vitamin D3) in chickens. Anti-hIAP IgY was ingested by chickens and reduced the absorption of phytate phosphate, which suggests that although it performed less adequately than sevelamer chorhydrate, already used for the same purpose, anti-hIAP IgY can be optimized for the prevention of phytate phosphate toxicity induced by the consumption of the active form of vitamin D (Bobeck et al., 2016).

27.15.5.7 Food Preservation

IgY raised against the bacterium *Listeria monocytogenes* showed a significant inhibitory effect of bacterial growth in liquid medium and in fish samples stored between 0°C and 6°C in a dose-dependent manner, which indicates that anti-*L. monocytogenes* IgY is a potential antimicrobial for use in the food industry (Sui et al., 2011). Taking into consideration the versatility and the range of IgY already tested against several bacteria, this result could be easily apply to other food poisoning bacteria and viruses.

27.15.5.8 Bioterrorism Circumstance

Among the importance of this technology, LeClair et al. demonstrated that IgY produced against the staphylococcal enterotoxin B (SEB), a potential biological weapon, can save individuals exposed to this material. The results with *Rhesus* monkeys showed that animals that received anti-SEB IgY 30 min before or 4 hour after exposure to a le- thal SEB aerosol survived (LeClaire et al., 2002), which indicates that anti-SEB IgY could be used to protect populations in a hypothetical context of bioterrorism involving SEB (Shade & Terzolo, 2006).

Previous applications of IgY in humans, including viral, bacterial, fungal, parasitic infections, and others are summarized in Table 27.13.

It may be mentioned here again the advantages of IgY in controlling animal, plant, fish, human and other diseases are (1) highly effective, (2) cost-effective, (3) egg collection is non-invasive, (4) treatment is safe and live organisms are not used, (5) procedure is environmentally friendly, (6) no toxic residues are produced and there is no development of resistance, and (7) treatment can be used to control many different types of pathogens.

27.16 IgY-Technology in Human Medicine: Patents and Clinical Trials

IgY technology has been successfully used for the development of many potential therapeutics (Pereira et al., 2019) and many of them are being tested in human clinical trials (Leiva et al., 2020). Leiva et al. reviewed the patents and clinical trials of IgY (egg yolk antibodies) in human medicine. This review provided a comprehensive analysis of IgY-based biologicalls for human medicine, including patent applications and clinical trials during the period 2010–2018, and addressed how IgY-technology can lead to innovation in the production of biologicals for the treatment and prophylaxis of a wide range of infectious and non-communicable diseases. Authors also listed IgY patent applications and clinical trials in tabular form (Leiva et al., 2020).

27.17 Utilization of IgY in Feeds and Foods

United States Code of Federal Regulations has granted egg powder, including IgY, as "GRAS generally recognized as safe" for use as food or food ingredients. Avian immunoglobulin is a super-drug (used in more than 250,000 doses of anti-*Pseudomonas* IgY in phase I, II, and III studies on protection for Pseudomonas infection in the lungs of CF patients.) that immediately must be considered in the world's fight against antibiotic resistance (Kollberg, 2017). GI Immune DF is a self-affirmed GRAS supplement that provides IgY immunoglobulins and immunoregulating molecules from a hyperimmune chicken egg. GI-Immune-DFHUGHPA.pdf (naplescfm.com) distributed by Hughes Center for Functional Medicine 800 Goodlette Road North # 270 Naples, FL 34102 239-649-7400.

IgY is gradually moving from feed to functional food to active pharmaceutical ingrédients. The results of all clinical trials (Rahman et al., 2012; Thu et al., 2017) indicate that the use of oral dosage form of anti-rotavirus IgY in a child-friendly carrier (such as infant milk formula or maltitol) is a promising, safe, and effective adjunct to the management of acute diarrhea in pediatric patients. The infant milk formula is particularly attractive as it addresses the nutritional and therapeutic needs of rotavirus-infected children in a user-friendly manner. For diarrhea patients below 5 years of age and who are lactose tolerant, the infant milk formula made available in powder form is an ideal vehicle for oral IgY delivery. It must be noted however that lozenges, tablets, or capsules for older children may also be used as oral delivery systems as had been done for some IgY products with various target infections now being sold in the Japanese and East Asian markets (Table 27.14).

While all these products are currently classified as food supplements, the forward trend is toward the pharmaceuticalization of IgY, which may only be a few years away in the future. The re-classification of IgY as a drug would provide a fresh breath of air in the field of therapeutics, where the dearth in novel synthetic antimicrobials has cast a pall of uncertainty to the healthcare industry and medicine end-users, especially now that we are facing increasingly resistant populations of pathogenic microorganisms.

27.18 IgY for Life: Holistic Approach

The health of humans, animals, and the environment are inextricably linked. The last decade of the twentieth century and the first decade of the twenty-first century saw the emergence of a plethora of public health challenges at the convergence of human, animal, and environmental health, including bovine spongiform encephalopathy (BSE) and variant Creutzfeldt–Jakob Disease, H5N1 influenza, Nipah virus, West Nile Virus, 9/11 and the threat of bioterrorism, SARS, and the impact of climate change on global food systems. Potential outcomes from the one health approach: (1) more interdisciplinary programs in education, training, research, and established policy;

TABLE 27.13

Use of IgY in Human Health

Pathogen	Disease	IgY Study Based on	Reference
A. Viral origin			
Rotavirus	Diarrhea	Randomized clinical trials	Rahman et al. (2012)
		Randomized clinical trials	Thu et al. (2017)
		Meta-analysis of 17 randomized clinical trials	Wang et al. (2019b)
Hepatitis B viruses (HBV)	Hepatitis	Duck HBV model	Thermet et al. (2004)
Zika virus	Fever, rash, arthritis, and microcephaly	In vitro and in vivo mice model	O'Donnell et al. (2019)
Dengue virus	Dengue fever	In vitro and mice model	Fink et al. (2017)
Hantavirus	Hantavirus pulmonary syndrome (HPS)	In vitro and in vivo Syrian hamsters	Brocato et al. (2012); Haese et al. (2015)
Ebola virus	Ebola virus infection	In vivo mice model	Zhang et al. (2021)
B. Bacterial origin			
Streptococcus mutans	Dental caries	Randomized clinical trials	Nguyen et al. (2011)
	Dental plaque	Human trial	Hatta et al. (1997)
Porphyromonas gingivalis	Periodontitis	Periodontitis patients	Yokoyama et al. (2007b)
	Periodontitis	Randomized clinical trials	Sugano (2009)
	Porphyromonas gingivalis infection	Near-infrared photo-antimicrobial targeting therapy	Maruyama et al. (2022)
Prevotella intermedia	Periodontitis	In vivo rat	Hou et al. (2014)
Solobacterium moorei	Halitosis, periodontitis, and gingivitis	In vitro and in vivo mouse	Li et al. (2012)
Fusobacterium nucleatum	Halitosis and periodontitis	In vivo rat model	Wang et al. (2019a)
Candida albicans	Candidiasis	In vitro, in vivo mouse and human	Ibrahim et al. (2007) (2008); Takeuchi et al. (2016)
	Candida infection	In vitro and Near-Infrared Photo-Antimicrobial Targeting Therapy	Yasui et al. (2021)
Helicobacter pylori	Gastritis		Marcus & Scott (2001)
		In vivo mouse	Malekshahi et al. (2011); Ameri Shah Reza et al. (2012); Yang et al. (2012)
		In vivo Mongolian gerbils	Nomura et al. (2005); Shin et al. (2002)
		In vivo humans	Yamane et al. (2003); Horie et al. (2004); Suzuki et al. (2004)
Salmonella typhimurium and *S. enteritidis*	Salmonellosis	In vitro	Lee et al. (2002); Chalghoumi et al. (2009)
	S. typhimurium infection	In vivo mouse model	Li et al. (2016c)
		In vivo young broiler chicks	Rahimi et al. (2007)
Clostridium difficile	Clostridiosis	In vivo Syrian hamsters	Mulvey et al. (2011)
		in mouse models	Pizarro-Guajardo et al. (2017)
		In vivo hamster model	Kink and Williams (1998)
Clostridium tetani, Tetanus neurotoxin (TeNT)	Tetanus	In vivo mouse models	Selim et al. (2015)
Clostridium botulinum Botulinum neurotoxin (BoNT)	Botulism	In vivo mice or birds	Pauly et al. (2009); Li et al. (2013); You et al. (2014a)
Campylobacter jejuni,	Gastroenteritis	In vivo birds	Hermans et al. (2014)
E. coli O157:H7 and O78:K80	Extraintestinal: sepsis, meningitis, and urinary tract infections	In vitro	Sunwoo et al. (2006); Mahdavi et al. (2010a)
E. coli	Respiratory, enteric, and septicemic diseases	In vivo birds	Kariyawasam et al. (2004)

(Continued)

TABLE 27.13 ***(Continued)***

Use of IgY in Human Health

Pathogen	Disease	IgY Study Based on	Reference
Enterotoxigenic *E. coli K88*	Gastrointestinal infection, Diarrhea	In vivo piglet	Wang et al. (2019c)
Enterohemorrhagic Stx-2-producing *Escherichia coli* (EHEC) O157:H7	Diarrhea, hemorrhagic colitis	In vivo mouse	Neri et al. (2011, 2012)
Enterotoxigenic Shiga toxin-positive *E. coli*	Non-bloody diarrhea	Randomized clinical trials	Gaensbauer et al. (2017)
Staphylococcus aureus	Food poisoning, toxic shock syndrome, endocarditis, and sepsis	In vitro	Guimarães et al. (2009b)
Aeromonas hydrophila	Sepsis and gastroenteritis in humans	In vivo fish	Merino et al. (1995); Fernandes et al. (2019a); Fernandes et al. (2019b)
Aeromonas Salmonicida	Gastroenteritis in humans; skin ulcer in fish	In vivo fish	Gan et al. (2015)
Propionibacterium acnes	Skin infection in human	In vitro	Revathy et al. (2014)
Pseudomonas aeruginosa	Cystic fibrosis, pneumonia	In vitro and In vivo mouse	Thomsen et al. (2016); Thomsen et al. (2021)
		Randomized clinical trials	Nilsson et al. (2008); EU Clinical Trials Register (2021)
Mycobacterium tuberculosis	Tuberculosis	In vivo rat	Sudjarwo et al. (2017a, 2017b)
Acinetobacter baumannii	Nosocomial infections in hospitals	In vivo mouse	Shi et al. (2017); Jahangiri et al. (2019)
Listeria monocytogenes	Food contaminants	In vitro	Sui et al. (2011)
(Food preservation)			
Staphylococcal enterotoxin B (SEB)	Bioterrorism	In vitro and in vivo monkey	LeClaire et al. (2002); Shade and Terzolo (2006)
C. Protozoal origin			
Trypanosoma cruzi	Chagas disease	In vitro and in vivo mouse	Grando et al. (2017, 2018)
Trypanosoma evansi	Anemia	In vitro and in vivo animal	Joshi et al. (2005); Sampaio et al. (2014a, 2014b)
Cryptosporidium parvum	Cryptosporidiosis	In vitro and in vivo mouse	Kobayashi et al. (2004); Hashemzadeh & Shahbazi (2016)
Cryptosporidium hominis	Cryptosporidiosis	In vitro	Miura et al. (2017)
D. Others			
Lipase	Obesity	In vivo mouse	Hirose et al. (2013)
Pro-inflammatory cytokines IL-β1 and TNF-α	Allergic rhinitis	In vivo guinea pigs	Wei-xu et al. (2016)
Human tumor antigens	Tumor, Cancer	In vitro	Xiao et al. (2009); Amirijavid et al. (2016)
Bothrops sp	Sanke Venom toxigenosis	In vitro and in vivo mouse	Araújo et al. (2010); Mendoza et al. (2012)
Crotalus durissus terrificus		In vitro	de Andrade et al. (2013)
Micrurus spp		In vitro	Aguilar et al. (2014)
Vipera lebetina		In vitro and in vivo mouse	Zolfagharian & Dounighi (2015)
Trimeresurus albolabris		In vitro and in vivo mouse	Duan et al. (2016)
Deinagkistrodon actus		In vitro and in vivo mouse	Liu et al. (2017)
Crotalus durissus terrificus,*Bothrops jararaca, Bitis arietans*		In vitro and in vivo mouse	da Rocha et al. (2017)
Tityus caripitensis, can cross neutralize other *Tityus* species (*T. quirogae*, *T. discrepans* and *T. gonzale- spongai*)			Alvarez et al. (2013)
Gliadin in food matrix	Celiac disease	In vitro and in vivo mouse	Gujral et al. (2012)
Intestinal alkaline phosphatase hIAP)	Phytate phosphate toxicity	In vitro and in vivo chick	Bobeck et al. (2016)

TABLE 27.14

IgY Supplemented Food Products Available Commercially in Global Biohealth Market

Product Name	Product Type	Country	Sales Start
Ovalgen HP Anti-*Helicobacter pylori* IgY for gastritis	Drinking yoghurt	Korea	2001.5
	Capsule	Japan	2001.10
	Shell egg	Japan	2003.4
	Tablet	Japan	2003.10
	Regular yoghurt	Japan	2004.7
	Drinking yoghurt	Taiwan	2004.8
	Tablet	Japan	2005.6
	Tablet	Japan	2005.6
	Drinking yoghurt	Japan	2010.7
	Sachet	Viet Nam	2015.2
Ovalgen DC Anti-*Streptococcus mutans* IgY for dental caries	Lozenge	Japan	2005.9
	Drinking yoghurt	Korea	2006.9
	Tablet	Japan	2007.5
	Lozenge	America	2009.8
	Lozenge	Japan	2010.5
	Lozenge	Viet Nam	2013.11
Ovalgen PG Anti-*Porphyromonas gingivalis* IgY for periodontitis/gingivitis	Lozenge	Japan	2005.9
	Lozenge	America	2009.8
	Lozenge	Viet Nam	2013.11
Ovalgen CA Anti-*Candida albicans* IgY for oral thrush or candidiasis	Dental gel	Japan	2012.5
Ovalgen FL Anti-Influenza IgY for seasonal flu	AC filter	Japan	2003.10
	Mask	Japan	2005.10
	Mask	Japan	2006.10
	Tablet	Japan	2008.12
	Lozenge	Viet Nam	2013.10
Ovalgen RV Anti-human rotavirus IgY for rotaviral diarrhea	Baby milk	Korea	2009.6
	Baby milk	Korea	2014.9
Ovalgen CS Anti- *Cronobacter sakazakii* IgY for infant milk formula	Baby milk	Korea	2014.9

Source: Adapted from Thu et al. (2017).

(2) more information sharing related to disease detection, diagnosis, education, and research; (3) more prevention of diseases, both infectious and chronic; and (4) development of new therapies and approaches to treatments

IgY antibodies are a sustainable and efficacious therapeutics for life and Global One Health. Application of egg-derived, supernatural, tailor-made IgY is the God-gifted miracle holistic approach for health. Diseases can be treated with holistic agent biological/medicine with a holistic approach. Many biohealth companies (like EW Nutrition Japan, IGY Life Sciences, NABAS, GenWay Biotech, Creative Biolabs, Aves lab, Creative diagnostics, IFY Inc.Mitacs, Bioinnovo IgY-DNT, Thermo Fisher, Sigma-Aldrich, Charles River laboratories, and so on (Table 27.15)) has optimized the sustainable generation of highly specific and efficacious egg-derived IgY antibodies, for human and animal health. These companies' pipeline includes marketed immune and sports health products, and lead compounds against COVID-19 and African swine fever and are ready upfront to prepare suitable solutions for the upcoming emergence of novel pathogens.

27.19 IgY and Egg Protein Industries and Markets

Some IgY companies in the global market are shown in Table 27.15. Many companies retail products and services based on IgY-derived technologies for research purposes, including R&D antibodies, antibody-based solutions, and diagnostic kits. For reference, these include companies such as Abcore Inc. (US), Agrisera AB (Sweden), Covalab (France), Creative Biolabs Inc. (US), Immuno Reagents Inc. (US), Innovagen AB (Sweden) and OriGene Technologies Inc. (US). To date, there is no systematic report on the IgY antibody markets, so one

TABLE 27.15

Summary of IgY Companies and Industries in the World

Name	Website	Country
AD Biotech Co.	http://adbiotech.com	South Korea
Aves Labs, Inc.	http://www.aveslab.com/	United States
Avianax LLC	https://www.avianax.com/	United States
Bioinnovo	http://bioinnovo.com.ar/	Argentina
Crystal Bioscience[a]	http://www.crystalbioscience.com/	United States
DAN Biotech, Inc.	http://www.danbio.com	South Korea
Davids Biotechnologie GmbH	https://www.davids-bio.de/	Germany
Eggcellent Proteins	https://www.eggcellentproteins.com/	Scotland
EW Nutrition	https://ew-nutrition.com/	Germany
Gallus Immunotech, Inc.[b]	https://www.exalpha.com/	United States
Gentian AS	https://www.gentian.com/	Norway
Good Biotech Corp.	http://www.good-biotech.com/	China
HenBiotech	http://www.henbiotech.com/	Portugal
IgY Immunologix	http://www.igylx.com/	India
IGY Life Sciences, Inc.	http://www.igylifesciences.com/	Canada
IgY Nutrition	https://www.igynutrition.com/	United States
IgYTechnology.com	https://www.igytechnology.com/	Portugal
Immune Biosolutions	https://immunebiosolutions.com/	Canada
NABAS	http://www.nabas.no/	Norway
Ovagen Group Limited	http://www.ovagen.ie/	Ireland

[a] Acquired by Ligand Pharmaceuticals Inc. in 2017 (CA, USA).
[b] Acquired by Exalpha Biologicals, Inc. in 2018 (MA, USA). Working webpages as of September 2022.

can only extrapolate the market value of particular IgY applications in specific market niches, and it is rather challenging and maybe misleading, to combine all of them in a single number reflecting the overall IgY businesses market value.

27.20 Perspective of IgY Technology Study

IgY field is more than 120 years old. Interests in IgY technology span many areas of scientific research, from basic biology to applications for both human and animal welfare (Zhang et al., 2021). Until now, the number of articles, patents, clinical studies, and commercial products on IgY technology has increased significantly. Wu et al. (2022) surveyed 1,029 IgY-related papers, including 981 journal articles and 48 reviews, and reported scientometric analysis of IgY. These Web of Science (WoS) database analyses showed an increasing trend in IgY-related publications over the 4 decades, especially from 2008 to 2021.

IgY is central to our understanding of immunoglobulin evolution across species. A cross-disciplinary approach may enhance our understanding of IgY and promote IgY study and application. IgY is an effective immunologic tool to fight infection involving microbes colonizing the alimentary tract of humans. It is relatively safe being a functional foodstuff found in the daily human diet and can exert its activity within the entire length of the alimentary tract in a predictable fashion. While it (IgY) may not exert total microbial eradication, it may significantly reduce infectious pathogen load to a point where the patient's immunity can finish the job of host protection. A major force that is drawing more and more attention to IgY's reliable and customizable antimicrobial mechanism is the gloomy prospect in the long-term fight against pathogenic microbes whose resistance to many antimicrobials is thwarting current treatment efforts. Together with other developments in recent antimicrobials and chemotherapeutic research, IgY has the potential to play a contributory role in delaying the advent of the dreaded post-antibiotic era. Non- parenterally administered IgY products, such as oral ingestible, nasal sprays, and nasal drops may provide widespread protection against pathogens that can colonize, infect, or damage the gastrointestinal and respiratory tracts. Neutralizing IgY antibodies may also warrant evaluation to target specific pathogens circulating in the bloodstream or localized in a specific area. Because IgY administration before the infection has been demonstrated to have significant protective effects *in vivo* in animal models, evaluating its use as prophylactic therapy in humans may be of special interest. Besides passive immunotherapy, IgY antibodies have also shown promise as a potential therapeutic agent for a wide spectrum of clinical applications. Specific IgY has detected and neutralized both surface and internal pathogenic antigens when administered after infection or consumption in multiple preclinical models. In most of these applications, IgY is not curative and has a greater therapeutic benefit with greater protection when used as a prophylactic treatment or in conjunction to supplement existing standard treatments.

In conclusion, IgY technology has made significant progress in the last 2 decades (during 1988 ~ 2022) (Figure 27.2) and has proven that it can be applied for diagnostic, prophylactic, or treatment purposes. lgY technology is expected to continue developing with the rapid advancements of modern biotechnology and biomedicine. There remains a requirement to standardize the technology components to make it more accessible to new researchers in the field and to broaden its potential value-added applications. In addition, developing laboratory methods and applying the other technologies to this field has led to more maturity of IgY technology toward commercialization.

27.21 Future Directions of IgY Technology (Feed to Food to Pharma)

Future directions of IgY inclined from feed to pharma. Within the biopharmaceutical disciplines, IgY technology constitutes a relatively novel field that started to draw serious attention more than two decades ago (1988 ~ 2022), with pioneering efforts largely coming from Japan. With the availability of IgY products as functional foodstuffs delivered via lozenge tablets or food carriers such as fermented milk products in the past decade in the Japanese and other East Asian markets, the practical impact of IgY for human application has created ripples in the biomedical sphere, with its broad potential only now starting to unfold. The relatively low cost of producing

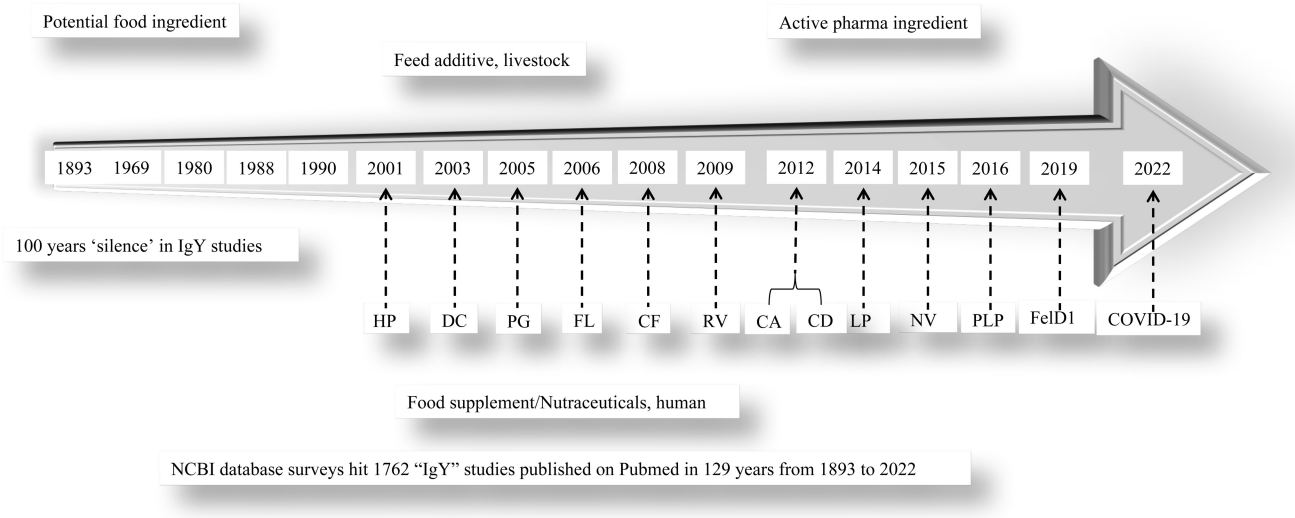

FIGURE 27.13 Future direction of IgY research: The timeline shows 100 years of progression from feed/food additive or health supplement toward nutraceutical and active pharmaceutical ingredient status. HP = Anti-*Helicobacter pylori* IgY for gastritis (2001); DC = Anti-*Streptococcus mutans* IgY for dental caries (2003); PG = Anti-*Porphyromonas gingivalis* IgY for periodontitis (2005); CF = Anti-*Pseudomonas aeruginosa* IgY for cystis fibrosis (2008); RV = Anti-Rotavirus IgY for rotaviral diarrhea (2009); CA = Anti-*Candida albicans* IgY for candidiasis (2012); CD = Anti-Gliadin IgY for celiac diseases (2012); LP = Anti-Lipase IgY for metabolic syndrome (2014); NV = Anti-Norovirus IgY for norovirus infection (2015); PLP = Anti-Phospholipase IgY for pain relieve (2016); FelD1 = Anti-Feld1 IgY for cat allergen (2019); and COVID-19 = Anti-SARS COV-2 IgY for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (2022).

antibodies from poultry eggs is an attractive side of IgY technology. The need for an inexpensive alternative to anti-infectious regimens has become even more urgent with sharply escalating healthcare costs, the prospect of an aging population in many industrialized and newly-developed countries, and scarcity of financial resources among Third World economies. Likewise, the current trend among consumers shifting from synthetics to natural materials to alleviate medical concerns has provided further impetus to the growth of the IgY market. As a functional foodstuff, IgY is well-positioned to expand its niche in both pharmaceutical and dietary supplement areas. With the expected application of advances in drug delivery systems to IgY delivery, IgYs are destined for pharmaceuticalization. They are expected to devolve toward other important clinical targets, including microbial toxins or other high-value targets such as metabolic syndrome (Hirose et al., 2013). Timeline shows 100 years of progression of IgY from functional food ingredient status, feed/food additive, or health supplement toward nutraceutical and active pharmaceutical ingredient status (Figure 27.13).

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