Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Veterinary Immunology and Immunopathology 174 (2016) 50–63

Contents lists available at ScienceDirect

Veterinary Immunology and Immunopathology

journal homepage: www.elsevier.com/locate/vetimm

Review paper

Passive immunisation, an old idea revisited: Basic principles and application to modern animal production systems

Chris J. Hedegaard*, Peter M.H. Heegaard

National Veterinary Institute, Technical University of Denmark, Section for Immunology and Vaccinology, The innate immunology Group, Denmark

ARTICLE INFO

Article history:
Received 16 December 2015
Received in revised form 11 April 2016
Accepted 13 April 2016

Keywords:
Passive immunisation
Maternal immunity
Lactogenic immunity
Immunoglobulins
Production animals
Agammaglobulinemic
Gastro intestinal tract
Postweaning diarrhoea
Failure of passive transfer
Colostrum
enterotoxigenic *Escherichia coli*
Porcine circo virus type 2
Spray-dried plasma

ABSTRACT

Immunisation by administration of antibodies (immunoglobulins) has been known for more than one hundred years as a very efficient means of obtaining immediate, short-lived protection against infection and/or against the disease-causing effects of toxins from microbial pathogens and from other sources. Thus, due to its rapid action, passive immunisation is often used to treat disease caused by infection and/or toxin exposure. However immunoglobulins may also be administered prior to exposure to infection and/or toxin, although they will not provide long-lasting protection as is seen with active immunisation (vaccination) in which an immunological memory is established by controlled exposure of the host to the pathogen in question. With multi-factorial infectious diseases in production animals, especially those that have proven hard to control by vaccination, the potential of passive immunisation remains big. This review highlights a number of examples on the use of passive immunisation for the control of infectious disease in the modern production of a range of animals, including pigs, cattle, sheep, goat, poultry and fish. Special emphasis is given on the enablement of passive immunisation strategies in these production systems through low cost and ease of use as well as on the sources, composition and purity of immunoglobulin preparations used and their benefits as compared to current measures, including vaccination (also comprising maternal vaccination), antibiotics and feed additives such as spray-dried plasma. It is concluded that provided highly efficient, relatively low-price immunoglobulin products are available, passive immunisation has a clear role in the modern animal production sector as a means of controlling infectious diseases, importantly with a very low risk of causing development of bacterial resistance, thus constituting a real and widely applicable alternative to antibiotics.

Contents

Abbreviations: ETEC, enterotoxigenic *Escherichia coli*; EPEC, enteropathogenic Escherichia coli; FMD, foot and mouth disease; FPT, failure of passive transfer; IVIG, intravenous immunoglobulin; PCV2, porcine circovirus type 2; PEDV, porcine epidemic diarrhoea virus; PWD, post-weaning diarrhoea; SDP, spray-dried plasma.

* Corresponding author at: Technical University of Denmark, National Veterinary Institute, Bülowsvej 27, DK-1870 Frederiksberg C, Denmark.
E-mail address: cjhe@vet.dtu.dk (C.J. Hedegaard).

http://dx.doi.org/10.1016/j.vetimm.2016.04.007
0165-2427/

1. Introduction

Passive immunisation, i.e. the administration of antibodies (immunoglobulins) in order to protect against infection and/or disease was first demonstrated experimentally more than 100 years ago by, among others Albert Calmette who protected rabbits against a lethal dose of cobra venom by giving antibodies in the form of antiserum parenterally prior to or within one hour of venom injection (Calmette, 1896). Since its discovery the principle of passive immunisation has been used extensively for treating and preventing diseases in animals and humans (Baxter, 2007; Eibl, 2008; Hsu and Safdar, 2011), supplementing active immunisation, i.e. vaccination. In contrast to vaccination, administration of immunoglobulin establishes instant immunity and provides short term protection with no induction of immunological memory. For most applications it works across species, i.e. the species origin of the immunoglobulins is less important. Also, in contrast to active immunisation, existing antibodies (e.g. maternally derived) do not interfere with passive immunity provided by administration of immunoglobulins. The main drawbacks of passive immunisation include the risk of adverse reactions to the administered immunoglobulins, especially if given repeatedly and if given as a non-purified preparation.

In animal production systems both active and passive immunisation may be considered alternatives to the use of antibiotics, as none of these normally lead to the development of antibiotics resistance problems or to microbial resistance generally; the exception being creation of escape mutants of viruses with high mutation rates. Thus in the present era of increasing problems with antibiotics resistance development (see below), immunisation methods are becoming attractive for wider application to the treatment and prevention of infectious diseases in production animals. However, a main prerequisite for this use is their cost-effectiveness compared to antibiotics which are presently used very extensively as inexpensive and highly efficient means for reducing animal morbidity and mortality, boosting food conversion, animal welfare and growth (De Briyne et al., 2014; Garcia-Migura et al., 2014). The possible role of the wide use of antibiotics in the surge of microbial antibiotics resistance experienced during the last few decades is discussed in (Barton, 2000; Bester and Essack, 2012; Garcia et al., 2011; Hong et al., 2007; Mendez Arancibia et al., 2009). The situation threatens to become a major problem for treating infectious diseases in humans (Barton, 2000; Fairbrother et al., 2005) and, generally, increased human mortality associated with antibiotics resistant bacteria has been predicted (CDC, 2013; de Kraker et al., 2011; ECDC/EMEA, 2009; WHO, 2012).

Enteric infections are often encountered in animal production and constitute the main target for antibiotics intervention; this group of infections constitute a specific challenge for traditional active immunisation methods as efficient mucosal immunity is generally not easily achieved by vaccination (Rhee et al., 2012), and as vaccines against enteric infections often need to be directed against a broad spectrum of bacterial and possibly also viral pathogens in order to provide complete protection against disease (Qadri et al., 2013). However, as discussed extensively below, passive immunisation in the form of orally administered immunoglobulins represents an easily applied and affordable solution for immediate treatment of and short term protection against enteral infections, having the potential for being a real alternative to the use of antibiotics in the animal production, especially for intervention at specific time periods in the production in which animals are particularly exposed to enteric infectious disease such as at birth and at weaning. In addition, passive immunisation can be and are currently used for other types of infectious diseases in production animals using a range of different administration routes (see below).

Table 1
Immunoglobulin half-life.

Species	Half-life (days)[a]	References
Pig	14	(Curtis and Bourne, 1973)
Cow	29	(Murphy et al., 2014)
Sheep	12–24[b]	(Watson, 1992)
Horse	27–39[b]	(Wilson et al., 2001)
Poultry (turkey)	4–6[b]	(Dohms et al., 1978a,b)
Fish (salmon)	2	(Voss et al., 1980)
Man	21[c]	(Vidarsson et al., 2014)
Mouse	3–5	(Fahey and Sell, 1965)

[a] Pig, cow, sheep, horse, mouse and man; IgG. Poultry; IgY. Fish; tetrameric IgM.
[b] Half-life changes from neonate to adult and varies between IgG subtypes.
[c] Certain allotypes of IgG3 can have much shorter half-lives.

2. Natural and passive immunity: maternal antibodies and lactogenic immunity

2.1. Natural passive immunity

Passive immunisation is widely used in Nature to protect offspring against disease at birth and during lactation (mammals) or *in ovo* (birds and fish). This is achieved by transfer of immunoglobulins from mother to progeny, in some species transported by blood through the placenta or yolk sack at the foetal stage and during lactation in mammals by the oral route through ingestion of colostrum and/or milk (oro-gastric or lactogenic immunity) (Hurley and Theil, 2011; Palmeira et al., 2012).

Evolutionarily, transfer of maternal immunoglobulins to offspring can be traced as far back as 450 million years ago, being found in primitive fish like the nurse shark (Haines et al., 2005). In some mammals, including primates and rabbits, the foetus obtains immunoglobulin (Ig) G over the placenta (Hurley and Theil, 2011; Palmeira et al., 2012) and the new-born is thus born with circulating mammalian IgG, persisting in the systemic circulation for some months after birth. The half-life of circulatory IgG in man is around 3 weeks (see below, Table 1), thus it has been observed that maternal antibodies are detectable in children 2–3

months after birth as seen in a study on circulating maternal anti-*Neisseria meningitidis* IgG (Shahid et al., 2002). This is supplemented during lactation by the intake of maternal IgA-type immunoglobulin through the milk building up local immunity in the gastrointestinal tract (Malek, 2013). In other mammals such as pigs and ruminants, placental immunoglobulin transfer does not take place and consequently the neonate is born agammaglobulinemic (without immunoglobulin), having neither received maternal immunoglobulin nor initiated their own production of immunoglobulins. Instead, these species are born with an 'open gut' allowing Fc-receptor-mediated immunoglobulin transfer from the gut to the circulation for the first approximately 24 h after birth assuring the very quick establishment of the necessary circulating levels of maternal immunoglobulins through ingestion of colostrum which in these species contains high concentrations of IgG (Cervenak and Kacskovics, 2009). Notably in pigs, colostral IgG concentrations decrease by 80% within 24 h of parturition (Foisnet et al., 2010). A variation of this is seen in rodents and some other species, including mink, where the neonate is born with a certain level of circulating maternal immunoglobulins and has its gut open for transfer of immunoglobulin from the milk for 2–3 weeks postnatally (Brambell, 1966; Kim et al., 2009). In chickens, the prehatching chick receives maternal immunoglobulin through the yolk sac of the egg and therefore is 'born' with maternal immunoglobulin at hatching (Kowalczyk et al., 1985).

Once maternal circulatory IgG is no longer replenished, i.e. after parturition and gut closure the half-life of IgG is around 2–3 weeks in larger mammals (Table 1). In small mammals such as mice the half-life of IgG in the circulation is only a few days which is also the case for immunoglobulin Y (IgY) in birds, and tetrameric IgM in fish (Table 1). Other circulatory immunoglobulins, such IgA, IgD, IgE, and IgM have much shorter half-lives than IgG in humans (Vidarsson et al., 2014), pigs (Curtis and Bourne, 1973) and mice (Fahey and Sell, 1965; Hirano et al., 1983).

Immunoglobulins of human milk and colostrum are largely dimeric IgA (Hurley and Theil, 2011) produced by the mucosal lymphoid tissue of the breastfeeding mother (Brandtzaeg, 2010) and, as they are not taken up by the intestine (Brandtzaeg, 2010), provide oro-gastric protection only, whereas colostrum from lactating cows and pigs contains a very high content of IgG originating from stimulated B cells/plasma cells of the dam's blood (Larson et al., 1980; Quigley, 2002) destined for the circulation of the offspring by intestinal uptake perinatally as detailed above.

Colostrum also contains leukocytes and antimicrobial proteins (such as Complement C3, lactoferrin, lactoperoxidase, and lysozyme) (Hernandez-Castellano et al., 2015; Smolenski et al., 2007). Colostral leukocytes are believed to participate in oro-gastric protection together with maternal immunoglobulins (Goldman, 1977; Morgan et al., 1984), and may enter circulation by intestinal absorption promoting neonatal cellular immunity (Liebler-Tenorio et al., 2002; Salmon et al., 2009; Tuboly and Bernath, 2002).

Thus, the principle of passive immunisation by transfer of immunoglobulin is well-known in Nature, both for providing oro-gastric immunity against pathogens during the suckling period (lactogenic immunity based on locally residing immunoglobulins from mother's milk and colostrum), and for providing systemic immunity either by foetal transfer (primates) or by perinatal transfer from the colostrum (pigs, ruminants) and milk (rodents and mink), boosting circulating (IgG-like) immunoglobulin levels before onset of the offspring's own immunoglobulin production.

2.2. Maternal immunisation to increase off-spring passive immunity

The natural transfer of maternal immunity has to some extent been exploited to passively immunize offspring by maternal vaccination. For example, prevention of rotavirus infection, which has a great economic impact in husbandry, especially in cattle- and hog production (Saif and Fernandez, 1996), can be obtained by vaccination of lactating cows against rotavirus resulting in subsequent passive immunity-mediated protection in calves receiving colostrum from the vaccinated cows (Le Rousic et al., 2000; Parreno et al., 2004; Saif and Fernandez, 1996; Tsunemitsu et al., 1989). Similar observations on lactogenic immunity against rotavirus have been made in pigs (Fu et al., 1990). Likewise, neonate offspring from cows vaccinated with an extract of ETEC (enterotoxigenic *Escherichia coli*) O101:K99 were protected against enteral colibacilliosis (otherwise causing fatal diarrhoea in calves) (Nagy, 1980), and moreover protection against *Salmonella Typhimurium* was obtained by vaccinating dams with formalin-fixed *Salmonella Typhimurium* (Jones et al., 1988) after experimental challenge. Furthermore, a combined vaccination of pregnant cows against *E. coli* and rotavirus is an efficient means of protecting against calf diarrhoea (Combs et al., 1993; Snodgrass et al., 1982). Lactogenic immunity against larval cestodes and metacestodes has also been reported (Larsh, 1942; Lloyd and Soulsby, 1976). For lactogenic immunity to be efficient, it was show that the vaccine had to be administered to the dams at least two weeks before parturition to allow enough time for adequate antibody titres to develop (Haggard et al., 1982). Oro-gastric immunity has been demonstrated in piglets provided with milk from immuno-competent lactating sows as seen by a decrease in faecal shedding of haemolytic *E. coli* by suckling piglets whereas milk from non-immune sources did not reduce shedding (Deprez et al., 1986). Passive immunisation of piglets by immunisation of the pregnant sow a few weeks before parturition has also been demonstrated in a porcine epidemic diarrhoea virus (PEDV) infection model; intramuscular injection of the sow with live attenuated PEDV 2–4 weeks before farrowing conferred significant protection to the suckling piglets (Kweon et al., 1999).

One important point to bear in mind is that maternal antibodies present in the offspring may potentially interfere with active immunisation (i.e. vaccination) of the offspring by binding to the vaccination antigen(s) and thereby inhibiting them from activating the offspring's immune system. This becomes critical in situations in which vulnerability to infection is present at the same time as colostrum derived antibodies. As an example anti-hepatitis A virus specific antibodies passed on from mother to infant persists for up to 6 months in the new-born preventing vaccination of infants against hepatitis A virus in this period (Vidor, 2007). Also, vaccinating pregnant sows at the right time before farrowing can protect piglets against Foot-and Mouth Disease (FMD) through colostrum derived maternal antibodies (Francis and Black, 1984a,b) for a limited period of time after birth. However maternal antibodies are capable of inhibiting subsequent active immunisation against FMD in the piglets even at around 8 weeks after parturition (Kitching and Salt, 1995). Interfering maternal antibodies have also been observed in poultry, inhibiting vaccination against H5N2 influenza virus (Forrest et al., 2013). As dealt with in the rest of the review, other ways of creating antibody based passive immunity is to administer immunoglobulins orally or by injection, thereby controlling the location and the timing of immunoglobulins more precisely.

3. Protection and prevention of infection by passive immunisation of humans

A wide range of immunoglobulin products are currently commercially available for treating or preventing various infections and/or toxin-mediated diseases in humans by parenteral administration, including those listed in Table 2. In addition to maternal vaccination sometimes being useful for protecting the new-born

Table 2
Licensed[a] immunoglobulin products for human passive immunisation.

Disease/pathogen source		Immunoglobulin product
Allograft rejection		Equine or rabbit anti-thymocyte IgG
Anthrax		Monoclonal antibody (Raxibacumab and Obiltoxaximab), immune human Ig (Anthrivig™)
Snakebite	Black widow spider	Equine Ig
	Scorpion	Equine $F(ab')_2$[b]
	Rattlesnake[c]	Ovine Fab[b]
Botulism	Type A and B	Human Ig
	Type A-G	Equine Ig
Chickenpox, shingles (Varicella-Zoster virus)		Immune human Ig[d]
Cytomegalovirus		Immune human Ig
Digoxin toxicity or overdose		Ovine Fab[b]
Diphtheria		Specific equine Ig
Hepatitis A, measles		Pooled human Ig
Hepatitis B		Immune human Ig
Primary Humoral Immunodeficiency, Immune Thrombocytopenic Purpura, (prevention of) allogeneic bone marrow transplantation rejection, Guillain Barré syndrome, Kawasaki disease		Pooled human IgG[d]
Rabies		Immune human Ig
Respiratory syncytial virus induced disease		Monoclonal antibody (Palivizumab)
Smallpox (Vaccinia virus)		Immune human Ig
Tetanus		Immune human Ig[d]

[a] Licensed by either FDA or EMEA.
[b] $Fab/F(ab')_2$ denotes products of IgG molecules after enzymatic digestion still capable of binding to antigen in question.
[c] Rattlesnake antivenom covers following species: North American snake venoms: Crotalus atrox (Western Diamondback rattlesnake), Crotalus adamanteus (Eastern Diamondback rattlesnake), Crotalus scutulatus (Mojave rattlesnake), and Agkistrodon piscivorus (Cottonmouth or Water Moccasin).
[d] Pooled human IgG (i.e. IVIG) can also be used.

by maternal antibody transfer as mentioned above a number of other passive immunisation strategies have been studied in humans and/or in models of human diseases (Keller and Stiehm, 2000; Zeitlin et al., 1999). This includes parenteral administration of immunoglobulin preparations for treating and/or preventing influenza (Mancini et al., 2011), plague caused by *Yersinia pestis* (Froude et al., 2011) and viral haemorrhagic fevers (such as Ebola (Qiu et al., 2014)). Passive immunisation is also used to protect against a number of toxins from venomous animals, and bioterror-related toxins (reviewed in (Froude et al., 2011)).

Oral intake of immunoglobulins for oro-gastric protection against enteric infections is well-known in Nature (see above) and this principle has been applied in human medicine for preventing and treating enteric infectious disease. For example, healthy human volunteers given orally colostrum from cows immunised with several *E. coli* serotypes, fimbria types, *E. coli* heat-labile enterotoxin, and cholera toxin, were all protected against diarrhoea when challenged with *E. coli* O78:H11 in contrast to 9/10 in a control group receiving non-immune bovine colostrum (Tacket et al., 1988). Although bovine milk contains some antibody reactivity against human rotavirus (Yolken et al., 1985) it appears that hyper-immune colostrum from immunised cows is needed to alleviate disease symptoms in children with rotavirus-induced diarrhoea (Ylitalo et al., 1998). Moreover children diagnosed with rotavirus induced diarrhoea treated with hyper-immune colostrum were less dehydrated and showed better virus clearance than when receiving non-hyper-immune colostrum (Davidson et al., 1989; Sarker et al., 1998). Likewise, HIV patients with *Cryptosporidium parvum* induced diarrhoea were successfully treated by oral administration of a bovine immunoglobulin concentrate derived from *C. parvum* immunised cows (Greenberg and Cello, 1996). A general concern associated with oral administration of immunoglobulins is that the protein degrading conditions of the gut may greatly reduce immunoglobulin activity (Jasion and Burnett, 2015). Indeed, the combined action of low pH and proteolytic enzymes has been shown to reduce the virus-neutralising capacity of bovine colostrum immunoglobulins (Petschow and Talbott, 1994). Human milk IgA and IgM appear to be more resistant to proteolysis than IgG as shown e.g. by mass spectrometry (Zhang et al., 2014). The general observation in humans is that up to 25% of IgG passing though the digestive system can afterwards be found intact in stool (Jasion and Burnett, 2015). In study in rabbits that were fed bovine immunoglobulins from *Cholera* enterotoxin-immunised cows, and the rabbit cecal extract was shown to possess *Cholera* enterotoxin neutralization ability in vivo (McClead and Gregory, 1984). Intact, non-denatured IgG could also be found throughout the digestive system after oral administration of ovine IgG to rats (Balan et al., 2014). It should be noted that colostrum contains protease inhibitors, such as inter-alpha-trypsin inhibitor and alpha-1-antichymotrypsin (Danielsen et al., 2011; Hernandez-Castellano et al., 2015). Also, the pH in the stomach of weaned piglets is never below 2.5 (Snoeck et al., 2004), both of which contribute to sustain immunoglobulin stability upon oral administration

4. Passive immunisation of production animals

4.1. Pigs

A number of difficult to control diseases with infectious aetiology, such as post weaning diarrhoea (PWD), porcine epidemic diarrhoea, porcine circovirus associated diseases, and new neonatal porcine diarrhoea syndrome, occur with a significant incidence in the modern pig production worldwide. Vaccines are available for some of them including a number of viral infections (see below) and others can be prevented or treated by antibiotics, but products for passive immunisation of pigs are quite limited in type and scope (see Table 4), and none are currently available for protecting against these diseases.

Most pigs in North America and Europe are presently infected with type 2 porcine circovirus (PCV2)(Madec et al., 2008). Several PCV2-vaccines have been developed after the millennium and

Table 3
Licensed Products for induction of maternal immunity for passive immunisation of progeny[a].

Product	Animal	Disease/pathogen prevention
Equine Rotavirus Vaccine	Horse	Rotaviral diarhhoea
Strep-Vax II[b], Pinnacle® I.N.	Horse	Strangles
Equivac® 2in 1[b]	Horse	Tetanus, Strangles
Botvax B	Horse	Butolism
Prestige®V + WNV[b]	Horse	Eastern and Western Encephalomyelitis, Tetanus, Influenza, equine herpesvirus and West Nile virus
Eryvac®[b]	Sheep	Erysipelas polyarthritis
Glanvac® 6[b]	Sheep + Goat	Cheesy Gland, malignant oedema, lamb dysentery, pulpy kidney, struck, tetanus, braxy, blackleg, black disease and clostridial metritis [c]Clostridium perfringens type A; C. perfringens type B; C. perfringens type C; C. perfringens type D; C. chauvoei; C. novyi type B; C. septicum; C. sordellii; C. haemolyticum, and C. tetani
Hepatavac P Plus[b]	Sheep	
Bravoxin 10, Ultravac® 5in1[b]	Cattle + Sheep	
BoviShot® PneumoGuard4	Cattle	Pneumonic Pasteurellosis
Rotagal, Rotavec,	Cattle	Scours (rota –, coronavirus and *E. coli*)
BoviShot® ROCO	Cattle	Scours (rota –, coronavirus)
NeoVac®	Swine	Scours/Colibacillosis (E. coli)
Porcilis Ery[b]	Swine	Erysipelas (*Erysipelothrix rhusiopathiae*)
Lepto-Eryvac®[b]	Swine	Erysipelas and Leptospirosis
Rhini Shield® TX4[b]	Swine	Atrophic rhinitis, Erysipelas and Pneumonic Pasteurellosis
LitterGuard® LT-C	Swine	Enterotoxemia and Colibacillosis
ProSystem® TREC	Swine	Rotaviral diarrhoea, Transmissible gastroenteritis, Enterotoxemia and Colibacillosis
Prefarrow Strep Shield[b]	Swine	Meningitis, Septicemia and Streptococcosis
CircoVac[b]	Swine	PCVAD (Porcine circo virus type 2)
SuiShot® Aujeszkey[b]	Swine	Aujeszkey disease
SuiShot® PT-100	Swine	Porcine epidemic diarrhoea and Transmissible gastroenteritis
SuiShot® AR-DT	Swine	Pneumonic Pasteurellosis
SuiShot® Allres[b]	Swine	Glasser's disease, Enzootic Pneumonia (Mycoplasma hyopneumoniae), Pneumonic Pasteurellosis, Pleuropneumonia (Actinobacillus pleuropneumoniae), Streptococcosis, and Atrophic rhinitis
Gripovac 3	Swine	Swine influenza (H1N1, H1N2, H3N2)

[a] Active vaccines intended for providing the offspring with immunity through colostrum.
[b] Can be administered for active immunisation for the offspring when initial protection has waned.
[c] Pathogens that cause the above-mentioned diseases.

Table 4
Licensed products for passive immunisation of ruminants, horses and pigs.

Product type	Animal	Disease prevention/targeted pathogens	Immunoglobulin type/origin	Administration (Oral/parenteral)
E. coli specific antibodies	Calves	Scour	Bovine colostrum IgG/IgY	Oral
Antibacterial bovine serum antibodies	Cattle Calves Sheep	*Arcanobacterium pyogenes* *E. coli* *Mannheimia haemolytica* *Pasteurella multocida* *Salmonella Typhimurium*	Bovine serum	Parenteral
Clostridial antitoxins	Cattle Calves Goat Sheep Swine Horses	*Clostridium perfringens* C&D *Clostridium Botulinium C&B*	Equine Ig	Parenteral (sc and iv)
Tetanus Antitoxin	Horses Cattle Sheep Swine Goats	Tetanus	Equine serum	Parenteral
Anti-West Nile Virus Antibodies	Horses	West Nile Virus	Equine Ig	Parenteral
Anti-endotoxin antibodies	Horses	Septicaemia	Equine plasma from hyper-immune horses	Parenteral
Antibacterial plasma antibodies	Horses	*Rhodococcus equi* *E. coli* J-5	Equine plasma from hyper-immune horses	Parenteral
Equine plasma	Horses	Failure of Passive Transfer	Equine plasma	Both

have proved useful for controlling PCV2-associated diseases (Chae, 2012; Kristensen et al., 2011). As it is costly and time-consuming to vaccinate all piglets against PCV2 it would be highly preferable to vaccinate the sows only, i.e. to rely on passive immunity for protection of the piglets. It has indeed been observed that clinical signs of PCV2-infection are reduced in the offspring of vaccinated sows

provided maternal anti-PCV2 titres are adequate (Fort et al., 2008; McKeown et al., 2005; Opriessnig et al., 2008), and one commercial sow vaccine has been reported to provide passive immunity in piglets by maternally derived antibodies and lymphocytes (Table 3) (Fort et al., 2008; Fort et al., 2009; Oh et al., 2012). On the other hand, vertical transmission of PCV2 may occur even in the face of maternal vaccination (i.e. PCV2 transmitting through milk) (Dvorak et al., 2013; Gerber et al., 2012; Madson et al., 2009; Shibata et al., 2006), and maternal antibodies can potentially impede the piglet immune response to vaccination as seen in a study on oral vaccine against F4+ ETEC (Snoeck et al., 2003). Collectively, it does appear that neither active immunisation nor lactogenic passive immunisation provided by maternal antibody transfer can prevent PCV2 infection even though disease signs are reduced.

Infection with diarrhoeagenic ETEC affects newly weaned piglets causing post weaning diarrhoea (PWD), which is a very widespread problem in modern pig production systems (Fleckenstein et al., 2010; Gyles, 1994; Hong et al., 2006). The key step in the pathogenesis of PWD is the fimbria-receptor interaction necessary for the colonisation by ETEC of the small intestine (Gaastra and Svennerholm, 1996; Zhou et al., 2013). An orally provided F4 fimbria subunit vaccine was shown to be able to induce protection against F4 positive ETEC in an experimental model of PWD (Van den Broeck et al., 1999a,b). One commercial vaccine (Coliprotec®) for oral use against PWD, containing live avirulent *E. coli* F4+ strain, has been marketed in Canada for some years (Melkebeek et al., 2013) and was approved for the European market in 2015 as well (EMEA, 2015). Efficacy data for this vaccine do not seem to be available. However, the use of oral vaccines based on live bacteria for oro-gastric protection has several limitations, including (1) in nursing piglets interfering lactogenic maternal antibodies may inhibit induction of active immunity as intestinal colonisation by the bacteria is inhibited, (2) oral vaccination only works fully if the weaners are able to mount a full immune response, which is not the case at four weeks of age (Levast et al., 2014), (3) the vaccine cannot be provided in combination with antibiotics as these will kill the live bacteria of the vaccine, and (4) if the vaccine only provides protection against specific antigens (e.g. F4 fimbriae) it will not work in geographical regions where other bacterial strains prevail (e.g. *E. coli* F18+). However, passive immunisation was shown to protect new-born piglets against otherwise fatal diarrhoea caused by ETEC F4+ by oral administration of a combination of several monoclonal antibodies targeting different F4 fimbria subunits (25 mg/ml in ascites fluid) (Foged et al., 1986). Notably, one oral dose (1 ml) of this monoclonal antibody mixture provided 1 h prior to challenge did not provide protection, however combining administration before challenge with administration at 8, 24 and 32 h after challenge provided complete protection against mortality and disease. Ten days of feeding genetically engineered *Arabidopsis* plant seeds expressing F4-specific llama-derived immunoglobulin was reported by Virdi et al., 2013 to reduce excretion of F4 positive ETEC (experimental challenge at day 6) and to increase the weight gain in pigs (Virdi et al., 2013). Antibodies from hens' eggs (also known as IgY, see below) have also been investigated for their ability to provide passive protection against enteric infections in pigs, however results have been ambiguous (see below). Thus, a study on *E. coli* F18+-specific IgY-containing egg yolk fed to weaning pigs that had been challenged with virulent *E. coli* F18+ showed that growth was significantly improved, and both diarrhoea incidence and *E. coli* colonisation reduced compared to the control groups (Yokoyama et al., 1997). This finding was confirmed in an independent study feeding either egg powder or eggs from fimbria F18-immunised hens to weaning piglets which led to significantly less shedding of the *E. coli* F18+ challenge strain, reduced incidence of diarrhoea, and reduced mortality compared to weaner piglets fed eggs or egg powder from non-immunised hens (Imberechts et al., 1997). Also, a feed supplement of egg yolk powder from eggs of *E. coli* F4+-immunised hens decreased the frequency of diarrhoea and mortality in early-weaned piglets to almost zero as compared to a control group not receiving egg yolk feed supplementation (Marquardt et al., 1999; Owusu-Asiedu et al., 2002). On the other hand, other studies failed to demonstrate any effect on experimental *E. coli* induced diarrhoea incidence after feeding IgY with specificity against the challenge strain (Owusu-Asiedu et al., 2003a; Owusu-Asiedu et al., 2003b) and a field trial on the efficacy of anti-ETEC IgY did not show any effect on diarrhoea and mortality (Chernysheva et al., 2003).

In summary, there are clear indications that orally administered immunoglobulins can aid piglets in handling enteric infections, both when used prophylactically and therapeutically, however dose and timing need to be optimized carefully.

4.2. Cows

Bovine colostrum and milk contains IgG antibodies against many bacteria and yeast (Kelly, 2003; McConnell et al., 2001), and as is the case with piglets, calves are born agammaglobulinemic and thus are highly dependent on efficient enteral uptake of maternal IgG from colostrum in which IgG is the dominating protein at around 70 mg/ml (Matte et al., 1982). However, up to 40% of new-born calves suffer from 'Failure of Passive Transfer' (FPT), defined as failure to attain a serum concentration of IgG of at least 10 g/L within 24–28 h after birth (Godden, 2008; Weaver et al., 2000). Poor quality colostrum (low IgG concentration) and inadequate enteral uptake of IgG are the main causes of FPT (Godden, 2008; Quigley, 2002). Calves suffering from FPT show a reduced average daily weight gain and also have an increased risk of mortality within the first 3 months of life (Robison et al., 1988; Wittum and Perino, 1995). In order to prevent FPT, colostrum replacer may be given to the calf just after birth, and several currently marketed products for ruminants apply the passive immunisation principle (Table 4) for helping new-born calves achieve adequate concentrations of circulating immunoglobulins within the first 24 h after birth. E.g. colostrum replacers contain IgG purified from colostrum or plasma in addition to other proteins, fat, vitamins and minerals and provide 100–150 g IgG per 1.5–2 l dose (Jones and Heinrichs, 2005) and colostrum replacers can thus prevent FPT.

In an experimental setting, Sherman et al. administered ascites fluid containing monoclonal antibodies against K99 bacterial antigen orally to calves before oral challenge with ETEC O9:K30:K99:F34; 82% of the untreated control calves died in comparison to only 29% of the passively immunised calves (Sherman et al., 1983). This demonstrates proof-of-principle for passive immunisation mediated protection against this *E. coli* infection; however monoclonal antibodies are not generally available or applicable for passive immunisation of production animals as they are prohibitively expensive. They may have interest as drugs for treating and/or preventing infections in very high price animals, though (thoroughbred and dressage horses, koi carps,—see below). On the other hand, avian immunoglobulin (IgY, see below), in the form of the water-soluble fraction of yolk from eggs of immunised birds has been demonstrated to efficiently reduce ETEC infection in calves as well as in pigs and rabbits (reviewed in (Chalghoumi et al., 2009)), and to provide protection against rotavirus induced diarrhoea in new-born calves (Sarker et al., 2007; Vega et al., 2011) by the enteral route. Also, a number of IgY based calf feed supplements are commercially available (see Table 4).

4.3. Sheep

Infection with enteropathogenic *Escherichia coli* (EPEC) and *Salmonella enterica* Typhimurium is common in lambs. Passive immunity obtained by transfer of maternal antibodies in colostrum

from ewes vaccinated with extracts of K99 pili from EPEC and with live attenuated *Salmonella*, respectively has been demonstrated in lambs (Altmann and Mukkur, 1983; Mukkur et al., 1998). Lactogenic immunity against enteric infections with the tapeworm *Taenis ovis* can also be achieved by vaccination of ewes against the larvae (Rickard et al., 1977). Commercial products using similar maternal vaccination approaches, vaccinating ewes three to four weeks before lambing are available for protection against *Clostridium perfringens* types C and D infections, lockjaw, lamb dysentery, pulpy kidney, and pasteurellosis (see Table 3). Several of these vaccines can be administered for active immunisation for the offspring as well when the initial, passively mediated protection has waned. Products for direct administration of immunoglobulins for providing passive immunity in sheep against especially Clostridial diseases, but also Tetanus, are listed in Table 4. Collectively, licensed products are typically combination products, targeting a number of different diseases at the same time, increasing cost effectiveness of the invention.

4.4. Horses

Just like ruminant neonates, foals acquire immunoglobulins from the dam's colostrum by enteric uptake during a limited 'open gut' period just after birth as for example illustrated by passive transfer of immunity against West Nile Virus and rotavirus from dam to foal (Sheoran et al., 2000; Wilkins et al., 2006), and indeed several licensed vaccines for horses are available (Wilson, 1999) providing maternal passive immunity for foals against many diseases (see Table 3). The foal are usually re-vaccinated four months after parturition (Wilson, 1999). FPT can also occur in foals with adverse consequences on infections rates, disease and mortality (McGuire et al., 1977). It is well established in horses to use plasma transfusion as well as colostrum supplementation in foals to overcome FPT (Nath et al., 2010), and other immunodeficiency diseases (Crisman and Scarratt, 2008; Tennent-Brown, 2011) (also see Table 4).

4.5. Poultry

Young chicks have an increased susceptibility to pathogens during the first few weeks after hatching, since their immune system is not fully developed and as maternal immunity is insufficient in providing full protection against certain pathogens. Passive immunity has been investigated extensively in poultry (see Table 5), and a number of studies provide positive indications that passive immunisation by the enteral route can be used to prevent and even treat infectious diseases in poultry. The main avian immunoglobulin isotype is IgY and when hatching, the majority of circulating immunoglobulin is constituted by maternal IgY, while in the alimentary tract of the chicken maternal IgA and IgM dominate (Hamal et al., 2006). IgY is functionally similar to mammalian IgG however has four constant domains and no hinge region (reviewed in (Kovacs-Nolan and Mine, 2012)). IgY is transferred from the dam to the yolk of the developing egg through the ovarian follicular epithelium (Morrison et al., 2002; Tesar et al., 2008) while avian IgA and IgM are mainly found in the egg white (albumen) transferred in the oviduct through the mucosal secretion (Rose et al., 1974). The amount of IgY transferred to the progeny from the dam is proportional to the IgY serum concentration in the dam; at day 3 the circulatory IgY concentration of the progeny is approximately 30% of that of the dam (Hamal et al., 2006). The level of protection provided by maternally derived IgY varies in different disease models (Table 5, Maternal Protection); in some cases, even though pathogen-reactive IgY was present in both yolk and serum of the hatchling it was still susceptible to experimental infection (Glavits et al., 1991; Le Roy et al., 1995; Lin and Kleven, 1984). On the other hand eight out of ten studies on immunoglobulin transfer in poultry (Table 5, passive transfer) show that antibodies induced by active immunisation of adult birds and then given in the form of antiserum to newly hatched birds protected the recipient birds when challenged by infection.

Also, a number of studies provide positive indications that passive immunisation by the enteral route; using hyper-immune IgY prevented and even treated infectious diseases in poultry (see Table 5, egg yolk immunoglobulins). The two studies that showed no protection against the pathogenic challenge by passive transfer (Table 5, passive transfer) indicate that protection against infections by antibodies may, as in other species is insufficient against certain avian pathogens such as *Histomonas meleagridis* and Avian metapneumovirus. In addition, and in contrast to neonates and young off-spring of mammals the newly hatched bird does not have natural access to maternal immunoglobulin.

4.6. Fish

Similar to poultry natural passive immunity is provided to fish embryos by transfer of maternal antibodies to the embryos' yolk sack (Swain et al., 2006). The main circulating form of immunoglobulin in fish is tetrameric IgM (Rauta et al., 2012; Salinas et al., 2011), and monomeric IgT seems to constitute the equivalent of mammalian IgA as secretory immunoglobulin associated with mucosal surfaces in fish (Salinas, 2015). Passive immunisation with immunoglobulins from other animal classes has been investigated in various infection models in fish (see Table 6). For example, complete protection of Channel catfish (*Ictalurus punctatus*) against the freshwater protozoan parasite *Ichthyophthirius multifiliis* using murine monoclonal immunoglobulins injected intraperitoneally was reported in the study by (Lin et al., 1996) and correlated with circulating murine monoclonal antibody titres against the parasite. As noted below, however, high-value antibodies such as monoclonal antibodies will probably be too expensive to find their way into use in low-cost production animals such as fish.

In other studies on passive transfer of immunity in catfish (Pasnik et al., 2011; Shelby et al., 2007), Nile tilapia (*Oreochromis niloticus*) (Pasnik et al., 2006), and Pacific herring (*Clupea pallasii*) (Hershberger et al., 2011) only partial protection was achieved by intraperitoneal administration of fish antiserum/plasma against challenge infections with a range of bacterial and viral pathogens. In other studies passive transfer of immunoglobulin to *Oncorhynchus mykiss* (rainbow trout), failed to provide protection by injection in naïve trout, receiving serum from immune donor trout, against both *Yersenia ruckeri* (Raida and Buchmann, 2008) and the parasite *Gyrodactylus derjavini* (Lindenstrom and Buchmann, 2000). This indicates that in order to achieve protection against these pathogens in teleost fish humoral immunity needs to be supplemented by other types of immunity e.g. cell mediated immunity.

Oral administration of pathogen-specific IgY to fish has also been investigated. Protection against Paracolo Disease and Vibriosis was obtained in Japanese eels (Gutierrez et al., 1993) and in *Plecoglossus altivelis* (Ayu) (Li et al., 2014), respectively by oral administration of purified IgY prophylactically in models of these two diseases. On the other hand, studies in *Oncorhynchus mykiss* (rainbow trout) provided orally with pathogen-specific IgY in the form of the water-soluble fraction of egg yolk formulated as pellets did not demonstrate full protection against disease in models for Vibriosis and *Y. ruckeri* infections (Arasteh et al., 2004; Lee et al., 2000). However, full protection was acquired if the *Y. ruckeri*-specific IgY was provided parenterally (egg yolk) intraperitoneally (Lee et al., 2000), in contrast to the failure of whole antiserum from immune donor fishes to provide protection in the same infection model (see above, (Raida and Buchmann, 2008)). Highly priced ornamental fish (Koi carps) have also been successfully treated with

Table 5
Studies on passive immunisation of birds.

Immunoglobulin type	Method of delivery	Model (disease/pathogen)	Species	References
Polyclonal antibody[a]	Enteral (milk)	*Campylobacter* jejuni	Chicken	(Tsubokura et al., 1997)
Egg yolk immunoglobulins	Enteral	Avian coccidiosis	Chicken	(Lee et al., 2009a,b)
	Intramuscular	*Escherichia coli* spp.	Chicken	(Kariyawasam et al., 2004)
	Intraperitoneal	Infectious bursal disease (Birnavirus)	Chicken	(Malik et al., 2006)
	Enteral	*Campylobacter* jejuni	Chicken	(Tsubokura et al., 1997)
	Enteral	Salmonella Enteritidis	Chicken	(Rahimi et al., 2007)
	In ovo	Infectious bursal disease virus	Chicken	(Eterradossi et al., 1997)
Passive transfer[b]	Intraperitoneal Intravenous Subcutaneous	Newcastle disease	Chicken	(Lardinois et al., 2014) (Umino et al., 1987) (Reynolds and Maraqa, 2000)
	n/a	Avian Influenza Virus, H7N3	Chicken	(Shahzad et al., 2008)
	Intraperitoneal	Histomonosis (blackhead)	Turkey	[c](Bleyen et al., 2009)
	Subcutaneous	Stunting syndrome	Turkey	(Reynolds et al., 2000)
	Intravenous	Avian metapneumovirus	Turkey	[c](Rubbenstroth and Rautenschlein, 2009)
	Intramuscular	Duck enteritis virus	Duck	(Lin et al., 1984)
	Subcutaneous	Mycoplasma gallisepticum	Chicken	(Lin and Kleven, 1984)
	Intravenous	Ornithobacterium rhinotracheale	Chicken	(Schuijffel et al., 2005)
Maternal protection[d]		Salmonella spp.	Chicken	(Barman et al., 2005; Gomez-Verduzco et al., 2010; Inoue et al., 2008; Si et al., 2014)
		Eimeria tenella	Chicken	(Smith et al., 1994)
		Newcastle disease	Chicken	(Umino et al., 1987)
		Derzsy's disease virus	Goose	[c](Glavits et al., 1991)
		Mycoplasma gallisepticum	Chicken	[c](Lin and Kleven, 1984)
		E. coli MT78	Chicken	[c](Le Roy et al., 1995)
		West Nile virus	Chicken	(Nemeth and Bowen, 2007)

[a] Transfer/delivery of antibodies/antiserum from other species (e.g. mouse to chicken).
[b] Transfer/delivery of antibodies/antiserum from same species (e.g. chicken to chicken).
[c] Indication of passive immunity/protection was negative.
[d] No transfer of antibodies/antisera other than from mother to egg.

Table 6
Studies on passive immunisation of fish.

Immunoglobulin type	Model (disease/pathogen)	References
Monoclonal antibody	White spot disease (*Ichtyopthirius multifiliis*)	(Lin et al., 1996)
	Viral haemorrhagic septicaemia virus	(Lorenzen et al., 1990)
Egg yolk immunoglobulins (IgY)	*Vibrosis (Vibrio anguillarum)*	(Arasteh et al., 2004)
	Redmouth disease (*Yersinia ruckeri*)	(Lee et al., 2000)
Passive transfer (serum/plasma)	Redmouth disease (*Yersinia ruckeri*)	(Raida and Buchmann, 2008)
	Columnaris disease (*Flavobacterium columnare*)	(Shelby et al., 2007)
	Gyrodactylus derjavini	(Lindenstrom and Buchmann, 2000)
	Streptococcus ssp.	(Pasnik et al., 2006, 2011)
	Rainbow trout fry syndrome (*Flavobacterium psychrophilum*)	(LaFrentz et al., 2003)
	Viral haemorrhagic septicaemia virus	(Corbeil et al., 1999; Hershberger et al., 2011; Kurath et al., 2006; Traxler et al., 1999)

immunoglobulins. Thus, two Nishiki carps diagnosed with a mixed *Aeromonas salmonicida* and *A. hydrophila* infection were successfully treated by intramuscular injection with goat antiserum raised against these pathogens three times over three weeks, clearing the infection (Prof. Sasaki Takeji, personal communication), and it was recently published that simply immersing Koi carps in anti—*A. salmonicida* IgY containing rearing water at 12.5 μg/ml protected them against skin ulcers and mortality caused by subsequent exposure to this bacterium (Gan et al., 2015), probably by coating the skin of the fish with the IgY antibodies. The fish IgA equivalent IgT could be speculated to be useful for protecting mucosal surfaces and maybe the skin of fish, however no such applications of IgT seem to be reported.

The use of IgY for treating other marine animals has also been studied: In a model for *Vibrio alginolyticus* infection of shellfish *Haliotis diversicolor supertexta* (small abalone), *Vibrio alginolyticus*-specific IgY was provided orally and increased survival from 0% to more than 65% after challenge (Wu et al., 2011). *Metapenaeus ensis* (greasyback shrimps) challenged with White spot syndrome virus had 73% and 33% survival, after subsequent passive immunisation (IgY) and active immunisation, respectively (Lu et al., 2008).

In general, it appears that immunity against infectious pathogens in fish can be passively transferred by parenteral routes

(intraperitoneally in most cases) whereas protection by feeding specific immunoglobulins, being much more attractive from a practical point of view, seems to be more challenging. This may be due to the presence of other easily accessible entry points for infectious agent in fish, such as the gills and the fact that the whole body of the fish is constantly challenged.

5. Immunoglobulin sources

In contrast to human medicine, the implementation of passive immunisation strategies for prevention and treatment of infectious diseases in production animals like pigs, fish, poultry and dairy cattle is massively dependent on the large scale availability of low cost, highly efficient immunoglobulin products. That is, the immunoglobulin product needs to be available to the farmer at a price that can compete with existing solutions including antibiotics and vaccines (see above). In addition, ease of use and broad applicability are pivotal, as are consistent quality, reliable high volume supplies and compatibility with existing vaccine and diagnostic management schemes. Conventional methods for producing antibodies, such as rodent- and/or cell culture derived poly- and monoclonal antibodies, as used for laboratory, biotechnology and clinical and diagnostic uses in humans and high value animals, are generally less useful for production of large amounts of low cost immunoglobulin. This is also the case for phage-derived, and/or engineered and/or recombinantly expressed immunoglobulins. Below, a number of examples on alternative low cost readily available sources of immunoglobulins enabling the general use of passive immunisation strategies in production animals are described.

5.1. Blood plasma

Spray-dried blood plasma (SDP) contains a high concentration of immunoglobulins and is widely used as a feed additive to promote health and growth, especially in the pig production (see Table S1). Documented effects in pigs include increased daily weight gain, improved intestinal health and morphology and improved resistance towards various pathogens (e.g. F4+ ETEC and PCV2) (see Supplementary Table 1) (Bhandari et al., 2008; Hunt et al., 2002; Niewold et al., 2007; Perez-Bosque et al., 2006; Pierce et al., 2005; Quigley and Drew, 2000). It has also been demonstrated in pigs that SDP can protect against experimentally established *E. coli* colonisation using large amounts of SDP in just weaned pigs, significantly decreasing shedding of the challenge *E.coli* strain (Nollet et al., 1999). Approximately 20% of SDP dry matter is constituted by immunoglobulin (Pierce et al., 2005; Quigley and Drew, 2000) and it is generally accepted that the beneficial effects of SDP is due to its copious immunoglobulin content. For example, in a study on the effect of different SDP fractions on the performance of early weaned pigs Pierce et al. (2005) demonstrated that the growth promoting effect of SDP resided in the immunoglobulin rich fraction (Pierce et al., 2005). Also, hyperimmune SDP from pigs vaccinated against F4+ ETEC more efficiently reduced shedding of F4+ ETEC in an experimental model of PWD than SDP from non-immunised animals (Niewold et al., 2007). As methods are now in place to efficiently purify immunoglobulin from slaughterhouse pig plasma by very cost-efficient methods (Lihme et al., 2010) it would be attractive to use the purified immunoglobulin fraction itself instead of SDP, and the anti-bacterial effect in experimentally challenged weaning piglets of such a purified immunoglobulin fraction purified in bulk from slaughterhouse blood was demonstrated recently by us (Hedegaard et al., 2016). The slaughterhouse pig plasma was shown to contain 'natural' antibody activity against both *E. coli* and *Salmonella enterica* spp (Hedegaard et al., 2016). Unfractionated blood products, such as SPD may harbour viral pathogens. For example, PEDV has been suggested to be present in porcine SDP (Pasick et al., 2014) although the heat treatment which is part of the spray-drying process may partly inactivate it (Gerber et al., 2014). Also, porcine parvovirus in liquid plasma has been shown to be inactivated by ultraviolet light irradiation (Polo et al., 2015). Anyhow, purification of immunoglobulin has the added benefit of allowing the removal of blood borne pathogens, including viruses, such as PCV2 and porcine epidemic diarrhoea virus (PEDV).

5.2. Egg yolk immunoglobulins

A single chicken egg contains between 100 and 250 mg IgY (Schade et al., 2005), corresponding to an annual production per egg-laying hen of 20–50 g IgY (Carlander et al., 2000; Michael et al., 2010). IgY with specific binding activity can be obtained by vaccination of egg-laying hens which will then deliver eggs with high antibody titres against the target antigen (Kovacs-Nolan and Mine, 2012). Such IgY antibodies have shown potential for treating/preventing diseases in both humans and animals (reviewed in (Chalghoumi et al., 2009; Diraviyam et al., 2014; Kovacs-Nolan and Mine, 2012), also see above). Notably, IgY does not bind mammalian complement factors and Fc-receptors making its use in mammals relatively uncomplicated (Inoue et al., 2015; Larsson et al., 1991). As expected, if IgY was provided parenterally to mammals a host immune response towards IgY was observed (Diaz et al., 2014). However, such problems have not been reported when administering IgY enterally (Michael et al., 2010).

As IgY is generally obtained from high-value human food items (eggs) from hens specifically immunised against the pathogen in question this approach is *per se* more costly than the use of immunoglobulin obtained from otherwise largely untapped slaughterhouse waste products such as blood. On the other hand, IgY could potentially also be purified from waste blood from broiler slaughterhouses presumably harbouring reactivity against common infectious pathogens such as *Campylobacter* spp.

5.3. Milk and whey

As discussed extensively above colostrum and milk provide natural oro-gastric protection against enteric infection in suckling off-spring. The major immunoglobulin type in bovine milk and colostrum is IgG (0.5–1 mg/ml and 60–70 mg/ml, respectively) (El-Loly, 2007; Hurley and Theil, 2011). Precipitating casein from milk, as done in cheese manufacturing, removes the bulk of protein from the milk, leaving the by-product whey, containing around 0.5 mg/ml IgG, constituting approx. 10% of the protein fraction (Siso, 1996). In cattle, a marketed whey-product (Colostrx) is claimed to protect similarly to colostrum against ETEC in a *E. coli* K99-challenge model (Harman et al., 1991). Although whey is claimed to have a range of dietary benefits in humans (Marshall, 2004; Patel, 2015) and pigs (Vanavichial, 1998), and it is a cheaper source of immunoglobulins than milk, it however does not seem that whey is used to any discernible degree for production of purified immunoglobulin preparations. This may be due to the relatively low concentration of IgG in whey (<1 mg/ml) necessitating large volumes to be handled during purification thereby compromising economic feasibility compared to e.g. blood serum (containing around 10 mg/ml).

6. Challenges and perspectives

Intensive animal production systems generally face challenges in the shape of infections compromising productivity, economy and animal welfare, and causing extensive use of antibiotics. Active

immunisation (vaccination) is a very useful alternative and supplement to antibiotics for protecting against infectious pathogens as it can be used to target different types of pathogens (bacteria, viruses, parasites) and as problems of microbial resistance is rarely a problem. However vaccines come with their own set of challenges, including their cost, and lack of efficiency in very young animals with a less developed immune system, with enteric infections and with multifactorial infectious disease, all of which characterize some of the most common infection related diseases in production animals. This among others include weaning diarrhoea and neonatal diarrhoea in pigs, diarrhoea in young calves, and a host of bacterial infections in fish fry as well as the more specialized example of skin infections in high price Koi carps especially associated with transport and co-mingling stress. As described in this review the passive immunisation principle lends itself to meet the specific need for efficient, inexpensive and non-antibiotics based intervention against these types of disease problems. Numerous examples in all of the common production animals on the efficiency of administered antibodies to combat or prevent infections are found in the scientific literature (see above), underlining the fact that immunoglobulins, administered in numerous ways and not very dependent on their source can provide short term 'traceless' protection against infection.

However, passive transfer of immunity at large scale in huge animal production facilities is not always feasible and while the use of passive immunisation with immunoglobulins for specific purposes like e.g. oedema disease in pigs is well-known (Johansen et al., 2000), as is the principle of maternal vaccination, immunizing the offspring through a natural passive immunisation process (Oanh et al., 2012), the general application of the principle for the broad group of production related diseases mentioned above is critically dependent upon the large-scale availability of low cost immunoglobulins e.g. for supplementing the feed with immunoglobulins during challenging periods in the animals' lifetime. Although a range of advanced methods for producing immunoglobulins including monoclonal antibody protocols and recombinant antibody expression exist, such types of immunoglobulins are not expected to be prime candidates for large scale use in intensive animal production systems. Also, in practical terms easy administration of immunoglobulins is a must. For example, instead of injecting all fry in a fish production unit it would be much more practical to provide antibodies in the fry feed. Another example is the administration of colostrum feed supplements in which antibodies derived from the dam provide protection against infectious agents in the suckling offspring (see Table 4), and the provision of immunoglobulin-containing egg yolk powder as a feed supplement to reduce enteric infections e.g. in weaner piglets.

7. Conclusion

With the availability of efficient large scale methods for production of purified immunoglobulins from natural sources with certified absence of pathogenic agents the use of passive immunisation for controlling production related infectious disease problems in intensive animal production systems is likely to become relevant and feasible in the near future. In addition to offering a real and broadly applicable alternative to antibiotics with no anticipated resistance development problems, this will also allow the exploitation of largely untapped, low value side streams in the animal production sector, such as slaughterhouse blood and whey from cheese production.

Conflict of interest

None.

Authors' contributions

pH conceived the idea. CJH compiled the information and drafted the paper including the figure and tables. pH critically reviewed and revised the paper and together with CJH drafted the final version. Both authors agreed to the final version of the manuscript.

Acknowledgement

The project was supported by Green Development and Demonstration Programme (Ministry of Food, Agriculture and Fisheries, The Danish AgriFish Agency, Journal number: 34009-12-0471). The funder provided support in the form of salaries for the author CJH, but did not have any additional role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vetimm.2016.04.007.

References

Altmann, K., Mukkur, T.K., 1983. Passive immunisation of neonatal lambs against infection with enteropathogenic *Escherichia coli* via colostrum of ewes immunised with crude and purified K99 pili. Res. Vet. Sci. 35, 234–239.
Arasteh, N., Aminirissehei, A.H., Yousif, A., Albright, L.J., Durance, T.D., 2004. Passive immunization of rainbow trout (*Oncorhynchus mykiss*) with chicken egg yolk immunoglobulins (IgY). Aquaculture 231, 23–36.
Balan, P., Han, K.S., Dukkipati, V.S., Moughan, P.J., 2014. Recovery of intact IgG in the gastrointestinal tract of the growing rat following ingestion of an ovine serum immunoglobulin. J. Anim. Physiol. Anim. Nutr. 98, 209–214.
Barman, T.K., Sharma, V.D., Kumar, S., 2005. Protective efficacy of maternal antibodies induced by *Salmonella* toxoid (vaccine). Indian J. Exp. Biol. 43, 163–166.
Barton, M.D., 2000. Antibiotics use in animals feed and its impact on human health. Nutr. Res. Rev. 13, 279–299.
Baxter, D., 2007. Active and passive immunity vaccine types, excipients and licensing. Occup. Med. (Lond.) 57, 552–556.
Bester, L.A., Essack, S.Y., 2012. Observational study of the prevalence and antibiotic resistance of *Campylobacter* spp. from different poultry production systems in KwaZulu-Natal, South Africa. J. Food Prot. 75, 154–159.
Bhandari, S.K., Xu, B., Nyachoti, C.M., Giesting, D.W., Krause, D.O., 2008. Evaluation of alternatives to antibiotics using an *Escherichia coli* K88+ model of piglet diarrhea: effects on gut microbial ecology. J. Anim. Sci. 86, 836–847.
Bleyen, N., Ons, E., De Gussem, M., Goddeeris, B., 2009. Passive immunization against *Histomonas meleagridis* does not protect turkeys from an experimental infection. Avian Pathol. 38, 71–76.
Brambell, F.W., 1966. The transmission of immunity from mother to young and the catabolism of immunoglobulins. Lancet 2, 1087–1093.
Brandtzaeg, P., 2010. The mucosal immune system and its integration with the mammary glands. J. Pediatr. 156, S8–15.
CDC, 2013. Antibiotic Resistance Threats in the United States. Center of Disease Control.
Calmette, A., 1896. The treatment of animals poisoned with snake venom by the injection of antivenomous serum. Br. Med. J. 2, 399–400.
Carlander, D., Kollberg, H., Wejaker, P.E., Larsson, A., 2000. Peroral immunotherapy with yolk antibodies for the prevention and treatment of enteric infections. Immunol. Res. 21, 1–6.
Cervenak, J., Kacskovics, I., 2009. The neonatal Fc receptor plays a crucial role in the metabolism of IgG in livestock animals. Vet. Immunol. Immunopathol. 128, 171–177.
Chae, C., 2012. Commercial porcine circovirus type 2 vaccines: efficacy and clinical application. Vet. J. 194, 151–157.
Chalghoumi, R., Beckers, Y., Portetelle, D., Thewis, A., 2009. Hen egg yolk antibodies (IgY), production and use for passive immunization against bacterial enteric infections in chicken: a review. Biotechnol. Agron. Soc. 13, 295–308.
Chernysheva, L.V., Friendship, R.M., Gyles, C.L., Dewey, C.E., 2003. Field trial assessment of the efficacy of specific egg-yolk antibody product for control of postweaning *E. coli* diarrhea. Veterinary therapeutics: research in applied veterinary medicine 4, 279–284.
Combs, D.K., Crabb, J.H., Bringe, A.N., Ruch, F.E., Lopez, J.W., 1993. Protection of neonatal calves against K99-*E-Coli* and Coronavirus using a colostrum-derived immunoglobul in preparation. Agri-Practice 14, 13–16.

Corbeil, S., LaPatra, S.E., Anderson, E.D., Jones, J., Vincent, B., Hsu, Y.L., Kurath, G., 1999. Evaluation of the protective immunogenicity of the N, P, M, NV and G proteins of infectious hematopoietic necrosis virus in rainbow trout *Oncorhynchus mykiss* using DNA vaccines. Dis. Aquat. Organ. 39, 29–36.
Crisman, M.V., Scarratt, W.K., 2008. Immunodeficiency disorders in horses. Vet. Clin. North Am. Equine Pract. 24, 299–310, vi.
Curtis, J., Bourne, F.J., 1973. Half-lives of immunoglobulins IgG, IgA and IgM in the serum of new-born pigs. Immunology 24, 147–155.
Danielsen, M., Pedersen, L.J., Bendixen, E., 2011. An in vivo characterization of colostrum protein uptake in porcine gut during early lactation. J. Proteomics 74, 101–109.
Davidson, G.P., Whyte, P.B., Daniels, E., Franklin, K., Nunan, H., McCloud, P.I., Moore, A.G., Moore, D.J., 1989. Passive immunisation of children with bovine colostrum containing antibodies to human rotavirus. Lancet 2, 709–712.
de Kraker, M.E., Davey, P.G., Grundmann, H., group, B.s., 2011. Mortality and hospital stay associated with resistant Staphylococcus aureus and *Escherichia coli* bacteremia: estimating the burden of antibiotic resistance in Europe. PLoS Med. 8, e1001104.
De Briyne, N., Atkinson, J., Pokludova, L., Borriello, S.P., 2014. Antibiotics used most commonly to treat animals in Europe. Vet. Rec. 175, 325.
Deprez, P., Van den Hende, C., Muylle, E., Oyaert, W., 1986. The influence of the administration of sow's milk on the post-weaning excretion of hemolytic E. coli in the pig. Vet. Res. Commun. 10, 469–478.
Diaz, P., Malave, C., Zerpa, N., Vazquez, H., D'Suze, G., Montero, Y., Castillo, C., Alagon, A., Sevcik, C., 2014. IgY pharmacokinetics in rabbits: implications for IgY use as antivenoms. Toxicon 90, 124–133.
Diraviyam, T., Zhao, B., Wang, Y., Schade, R., Michael, A., Zhang, X., 2014. Effect of chicken egg yolk antibodies (IgY) against diarrhea in domesticated animals: a systematic review and meta-analysis. PLoS One 9, e97716.
Dohms, J.E., Saif, Y.M., Bacon, W.L., 1978a. Metabolism and passive transfer of immunoglobulins in the turkey hen. Am. J. Vet. Res. 39, 1472–1481.
Dohms, J.E., Saif, Y.M., Bacon, W.L., 1978b. Studies on metabolism and concentrations of immunoglobulin G in the newly hatched turkey poult. Am. J. Vet. Res. 39, 1466–1471.
Dvorak, C.M., Lilla, M.P., Baker, S.R., Murtaugh, M.P., 2013. Multiple routes of porcine circovirus type 2 transmission to piglets in the presence of maternal immunity. Vet. Microbiol. 166, 365–374.
ECDC/EMEA, 2009. The bacterial challenge: time to react. 54.
EMEA, 2015. Coliprotec F4 *E. coli* O8:K87 Vaccine (live). European Medicines Agency.
Eibl, M.M., 2008. History of immunoglobulin replacement. Immunol. Allergy Clin. North Am. 28, 737–764.
El-Loly, M.M., 2007. Bovine milk immunoglobulins in relation to human health. Int. J. Dairy Sci. 2, 183–195.
Eterradossi, N., Toquin, D., Abbassi, H., Rivallan, G., Cotte, J.P., Guittet, M., 1997. Passive protection of specific pathogen free chicks against infectious bursal disease by in-ovo injection of semi-purified egg-yolk antiviral immunoglobulins. Zentralbl Veterinarmed B 44, 371–383.
Fahey, J.L., Sell, S., 1965. The immunoglobulins of mice. V. The metabolic (Catabolic) properties of five immunoglobulin classes. J. Exp. Med. 122, 41–58.
Fairbrother, J.M., Nadeau, E., Gyles, C.L., 2005. *Escherichia coli* in postweaning diarrhea in pigs: an update on bacterial types, pathogenesis, and prevention strategies. Anim. Health Res. Rev. 6, 17–39.
Fleckenstein, J.M., Hardwidge, P.R., Munson, G.P., Rasko, D.A., Sommerfelt, H., Steinsland, H., 2010. Molecular mechanisms of enterotoxigenic *Escherichia coli* infection. Microbes Infect. 12, 89–98.
Foged, N.T., Klemm, P., Elling, F., Jorsal, S.E., Zeuthen, J., 1986. Monoclonal antibodies to K88ab, K88ac and K88ad fimbriae from enterotoxigenic *Escherichia coli*. Microb. Pathog. 1, 57–69.
Foisnet, A., Farmer, C., David, C., Quesnel, H., 2010. Relationships between colostrum production by primiparous sows and sow physiology around parturition. J. Anim. Sci. 88, 1672–1683.
Forrest, H.L., Garcia, A., Danner, A., Seiler, J.P., Friedman, K., Webster, R.G., Jones, J.C., 2013. Effect of passive immunization on immunogenicity and protective efficacy of vaccination against a Mexican low-pathogenic avian H5N2 influenza virus. Influenza Other Respir. Viruses 7, 1194–1201.
Fort, M., Sibila, M., Allepuz, A., Mateu, E., Roerink, F., Segales, J., 2008. Porcine circovirus type 2 (PCV2) vaccination of conventional pigs prevents viremia against PCV2 isolates of different genotypes and geographic origins. Vaccine 26, 1063–1071.
Fort, M., Sibila, M., Perez-Martin, E., Nofrarias, M., Mateu, E., Segales, J., 2009. One dose of a porcine circovirus 2 (PCV2) sub-unit vaccine administered to 3-week-old conventional piglets elicits cell-mediated immunity and significantly reduces PCV2 viremia in an experimental model. Vaccine 27, 4031–4037.
Francis, M.J., Black, L., 1984a. Effect of the sow vaccination regimen on the decay rate of maternally derived foot-and-mouth disease antibodies in piglets. Res. Vet. Sci. 37, 72–76.
Francis, M.J., Black, L., 1984b. The effect of vaccination regimen on the transfer of foot and mouth disease antibodies from the sow to her piglets. J. Hyg. 93, 123–131.
Froude, J.W., Stiles, B., Pelat, T., Thullier, P., 2011. Antibodies for biodefense. mAbs 3, 517–527.
Fu, Z.F., Hampson, D.J., Wilks, C.R., 1990. Transfer of maternal antibody against group A rotavirus from sows to piglets and serological responses following natural infection. Res. Vet. Sci. 48, 365–373.
Gaastra, W., Svennerholm, A.M., 1996. Colonization factors of human enterotoxigenic *Escherichia coli* (ETEC). Trends Microbiol. 4, 444–452.
Gan, H., He, H., Sato, A., Hatta, H., Nakao, M., Somamoto, T., 2015. Ulcer disease prophylaxis in koi carp by bath immersion with chicken egg yolk containing anti-*Aeromonas salmonicida* IgY. Res. Vet. Sci. 99, 82–86.
Garcia, P.G., Silva, V.L., Diniz, C.G., 2011. Occurrence and antimicrobial drug susceptibility patterns of commensal and diarrheagenic *Escherichia coli* in fecal microbiota from children with and without acute diarrhea. J. Microbiol. 49, 46–52.
Garcia-Migura, L., Hendriksen, R.S., Fraile, L., Aarestrup, F.M., 2014. Antimicrobial resistance of zoonotic and commensal bacteria in Europe: the missing link between consumption and resistance in veterinary medicine. Vet. Microbiol. 170, 1–9.
Gerber, P.F., Garrocho, F.M., Lana, A.M., Lobato, Z.I., 2012. Fetal infections and antibody profiles in pigs naturally infected with porcine circovirus type 2 (PCV2). Can. J. Vet. Res. 76, 38–44.
Gerber, P.F., Xiao, C.T., Chen, Q., Zhang, J., Halbur, P.G., Opriessnig, T., 2014. The spray-drying process is sufficient to inactivate infectious porcine epidemic diarrhea virus in plasma. Vet. Microbiol. 174, 86–92.
Glavits, R., Ratz, F., Palya, V., Molnar, E., Nemesi, M., 1991. Pathological and immunological study of goose embryos and goslings inoculated with an attenuated strain of Derzsy's disease virus. Acta Vet. Hung. 39, 39–47.
Godden, S., 2008. Colostrum management for dairy calves. Vet. Clin. North Am: Food Anim. Pract. 24, 19–39.
Goldman, A.S., 1977. Human milk, leukocytes, and immunity. J. Pediatr. 90, 167–168.
Gomez-Verduzco, G., Tellez, G., Quintana, A.L., Isibasi, A., Ortiz-Navarrete, V., 2010. Humoral immune response in breeding hens and protective immunity provided by administration of purified *Salmonella* Gallinarum porins. Poult. Sci. 89, 495–500.
Greenberg, P.D., Cello, J.P., 1996. Treatment of severe diarrhea caused by *Cryptosporidium parvum* with oral bovine immunoglobulin concentrate in patients with AIDS. J. Acquir. Immune Defic. Syndr. Hum. Retrovirol. 13, 348–354.
Gutierrez, M.A., Miyazaki, T., Hatta, H., Kim, M., 1993. Protective properties of egg-Yolk Igy containing anti-Edwardsiella-Tarda antibody against Paracolo disease in the Japanese eel, *Anguilla-Japonica* temminck and schlegel. J. Fish Dis. 16, 113–122.
Gyles, C.L., 1994. *Escherichia Coli* in Domestic Animals and Humans. CAB International, Wallingford.
Haggard, D.L., Springer, J.A., Vosdingh, R.A., 1982. Efficacy of a single annual booster inoculation of cows with *Escherichia-Coli* bacterin for preventing enteric colibacillosis in neonatal calves. Vet. Med. Sm. Anim. Clin. 77, 1525–1527.
Haines, A.N., Flajnik, M.F., Rumfelt, L.L., Wourms, J.P., 2005. Immunoglobulins in the eggs of the nurse shark, *Ginglymostoma cirratum*. Dev. Comp. Immunol. 29, 417–430.
Hamal, K.R., Burgess, S.C., Pevzner, I.Y., Erf, G.F., 2006. Maternal antibody transfer from dams to their egg yolks, egg whites, and chicks in meat lines of chickens. Poult. Sci. 85, 1364–1372.
Harman, R.J., Doherty, T.V., Mccloskey, M.J., 1991. Colostrx supplement protects against challenge with enterotoxigenic *Escherichia-Coli* in neonatal dairy calves. Agri-Practice 12, 41-&.
Hedegaard, C.J., Strube, M.L., Hansen, M.B., Lindved, B.K., Lihme, A., Boye, M., Heegaard, P.M., 2016. Natural pig plasma immunoglobulins have anti-bacterial effects: potential for use as feed supplement for treatment of intestinal infections in pigs. PLoS One 11, e0147373.
Hernandez-Castellano, L.E., Arguello, A., Almeida, A.M., Castro, N., Bendixen, E., 2015. Colostrum protein uptake in neonatal lambs examined by descriptive and quantitative liquid chromatography-tandem mass spectrometry. J. Dairy Sci. 98, 135–147.
Hershberger, P.K., Gregg, J.L., Grady, C.A., LaPatra, S.E., Winton, J.R., 2011. Passive immunization of pacific herring against viral hemorrhagic septicemia. J. Aquat. Anim. Health 23, 140–147.
Hirano, T., Hom, C., Ovary, Z., 1983. Half-life of murine IgE antibodies in the mouse. Int. Arch. Allergy Appl. Immunol. 71, 182–184.
Hong, T.T.T., Linh, N.Q., Ogle, B., Lindberg, J.E., 2006. Survey on the prevalence of diarrhoea in pre-weaning piglets and on feeding systems as contributing risk factors in smallholdings in Central Vietnam. Trop. Anim. Health Prod. 38, 397–405.
Hong, J., Kim, J.M., Jung, W.K., Kim, S.H., Bae, W., Koo, H.C., Gil, J., Kim, M., Ser, J., Park, Y.H., 2007. Prevalence and antibiotic resistance of *Campylobacter* spp. isolated from chicken meat, pork, and beef in Korea, from 2001 to 2006. J. Food Prot. 70, 860–866.
Hsu, J.L., Safdar, N., 2011. Polyclonal immunoglobulins and hyperimmune globulins in prevention and management of infectious diseases. Infect. Dis. Clin. North Am. 25, 773–788.
Hunt, E., Fu, Q., Armstrong, M.U., Rennix, D.K., Webster, D.W., Galanko, J.A., Chen, W., Weaver, E.M., Argenzio, R.A., Rhoads, J.M., 2002. Oral bovine serum concentrate improves cryptosporidial enteritis in calves. Pediatr. Res. 51, 370–376.
Hurley, W.L., Theil, P.K., 2011. Perspectives on immunoglobulins in colostrum and milk. Nutrients 3, 442–474.
Imberechts, H., Deprez, P., Van Driessche, E., Pohl, P., 1997. Chicken egg yolk antibodies against F18ab fimbriae of *Escherichia coli* inhibit shedding of F18 positive *E. coli* by experimentally infected pigs. Vet. Microbiol. 54, 329–341.

Inoue, A.Y., Berchieri Jr., A., Bernardino, A., Paiva, J.B., Sterzo, E.V., 2008. Passive immunity of progeny from broiler breeders vaccinated with oil-emulsion bacterin against Salmonella enteritidis. Avian Dis. 52, 567–571.
Inoue, S., Park, C., Hatta, H., 2015. Production of polyclonal rabies virus antibodies in birds. In: Rupprecth, C., Nagarajan, T. (Eds.), Current Laboratory Techniques in Rabies Diagnosis, Research and Prevention. Academic Press (Elsevier).
Jasion, V.S., Burnett, B.P., 2015. Survival and digestibility of orally-administered immunoglobulin preparations containing IgG through the gastrointestinal tract in humans. Nutr. J. 14.
Johansen, M., Andresen, L.O., Thomsen, L.K., Busch, M.E., Wachmann, H., Jorsal, S.E., Gyles, C.L., 2000. Prevention of edema disease in pigs by passive immunization. Can. K. Vet. Res. 64, 9–14.
Jones, C., Heinrichs, J., 2005. Colostrum Supplements and Replacer Penn State. http://extension.psu.edu/animals/dairy/nutrition/calves/colostrum/das-11-180.
Jones, P.W., Collins, P., Aitken, M.M., 1988. Passive protection of calves against experimental-Infection with *Salmonella-Typhimurium*. Vet. Rec. 123, 536–541.
Kariyawasam, S., Wilkie, B.N., Gyles, C.L., 2004. Resistance of broiler chickens to *Escherichia coli* respiratory tract infection induced by passively transferred egg-yolk antibodies. Vet. Microbiol. 98, 273–284.
Keller, M.A., Stiehm, E.R., 2000. Passive immunity in prevention and treatment of infectious diseases. Clin. Microbiol. Rev. 13, 602–614.
Kelly, G.S., 2003. Bovine colostrums: a review of clinical uses. Altern. Med. Rev. 8, 378–394.
Kim, J., Mohanty, S., Ganesan, L.P., Hua, K., Jarjoura, D., Hayton, W.L., Robinson, J.M., Anderson, C.L., 2009. FcRn in the yolk sac endoderm of mouse is required for IgG transport to fetus. J. Immunol. 182, 2583–2589.
Kitching, R.P., Salt, J.S., 1995. The interference by maternally-derived antibody with active immunization of farm animals against foot-and-mouth disease. Brit. Vet. J. 151, 379–389.
Kovacs-Nolan, J., Mine, Y., 2012. Egg yolk antibodies for passive immunity. Ann. Rev. Food Sci. Technol. 3, 163–182.
Kowalczyk, K., Daiss, J., Halpern, J., Roth, T.F., 1985. Quantitation of maternal-fetal IgG transport in the chicken. Immunology 54, 755–762.
Kristensen, C.S., Baadsgaard, N.P., Toft, N., 2011. A meta-analysis comparing the effect of PCV2 vaccines on average daily weight gain and mortality rate in pigs from weaning to slaughter. Prev. Vet. Med. 98, 250–258.
Kurath, G., Garver, K.A., Corbeil, S., Elliott, D.G., Anderson, E.D., LaPatra, S.E., 2006. Protective immunity and lack of histopathological damage two years after DNA vaccination against infectious hematopoietic necrosis virus in trout. Vaccine 24, 345–354.
Kweon, C.H., Kwon, B.J., Lee, J.G., Kwon, G.O., Kang, Y.B., 1999. Derivation of attenuated porcine epidemic diarrhea virus (PEDV) as vaccine candidate. Vaccine 17, 2546–2553.
LaFrentz, B.R., LaPatra, S.E., Jones, G.R., Cain, K.D., 2003. Passive immunization of rainbow trout, *Oncorhynchus mykiss* (Walbaum), against *Flavobacterium psychrophilum*, the causative agent of bacterial coldwater disease and rainbow trout fry syndrome. J. Fish Dis. 26, 377–384.
Lardinois, A., van den Berg, T., Lambrecht, B., Steensels, M., 2014. A model for the transfer of passive immunity against Newcastle disease and avian influenza in specific pathogen free chickens. Avian Pathol. 43, 118–124.
Larsh, J.E., 1942. Transmission from mother to offspring of immunity against the mouse cestode, Hymenolepis nana var fraterna. Am. J. Hyg. 36, 187–194.
Larson, B.L., Heary Jr., H.L., Devery, J.E., 1980. Immunoglobulin production and transport by the mammary gland. J. Dairy Sci. 63, 665–671.
Larsson, A., Karlssonparra, A., Sjoquist, J., 1991. Use of chicken antibodies in enzyme immunoassays to avoid interference by rheumatoid factors. Clin. Chem. 37, 411–414.
Le Rousic, S., Klein, N., Houghton, S., Charleston, B., 2000. Use of colostrum from rotavirus-immunised cows as a single feed to prevent rotavirus-induced diarrhoea in calves. Vet. Rec. 147, 160–161.
Le Roy, D., Crouzier, C., Dho-Moulin, M., Dumont, A.S., Bouchet, A., Lafont, J.P., Andremont, A., 1995. Results of passive and active immunization directed against ferric aerobactin in experimental enterobacterial infections in mice and chickens. Res. Microbiol. 146, 167–174.
Lee, S.B., Mine, Y., Stevenson, R.M., 2000. Effects of hen egg yolk immunoglobulin in passive protection of rainbow trout against *Yersinia ruckeri*. J. Agric. Food Chem. 48, 110–115.
Lee, S.H., Lillehoj, H.S., Park, D.W., Jang, S.I., Morales, A., Garcia, D., Lucio, E., Larios, R., Victoria, G., Marrufo, D., Lillehoj, E.P., 2009a. Induction of passive immunity in broiler chickens against *Eimeria acervulina* by hyperimmune egg yolk immunoglobulin Y. Poult. Sci. 88, 562–566.
Lee, S.H., Lillehoj, H.S., Park, D.W., Jang, S.I., Morales, A., Garcia, D., Lucio, E., Larios, R., Victoria, G., Marrufo, D., Lillehoj, E.P., 2009b. Protective effect of hyperimmune egg yolk IgY antibodies against *Eimeria tenella* and *Eimeria maxima* infections. Vet. Parasitol. 163, 123–126.
Levast, B., Berri, M., Wilson, H.L., Meurens, F., Salmon, H., 2014. Development of gut immunoglobulin A production in piglet in response to innate and environmental factors. Dev. Comp. Immunol. 44, 235–244.
Li, C.H., Lu, X.J., Li, D.F., Chen, J., 2014. Passive protective effect of chicken egg yolk immunoglobulins against experimental Vibrio anguillarum infection in ayu (*Plecoglossus altivelis*). Fish Shellfish Immunol. 37, 108–114.
Liebler-Tenorio, E.M., Riedel-Caspari, G., Pohlenz, J.F., 2002. Uptake of colostral leukocytes in the intestinal tract of newborn calves. Vet. Immunol. Immunopathol. 85, 33–40.
Lihme, A., Hansen, M.B., Andersen, I.V., Burnouf, T., 2010. A novel core fractionation process of human plasma by expanded bed adsorption chromatography. Anal. Biochem. 399, 102–109.
Lin, M.Y., Kleven, S.H., 1984. Transferred humoral immunity in chickens to *Mycoplasma gallisepticum*. Avian Dis. 28, 79–87.
Lin, W.Q., Lam, K.M., Clark, W.E., 1984. Active and passive immunization of ducks against duck viral enteritis. Avian Dis. 28, 968–973.
Lin, T.L., Clark, T.G., Dickerson, H., 1996. Passive immunization of channel catfish (*Ictalurus punctatus*) against the ciliated protozoan parasite *Ichthyophthirius multifiliis* by use of murine monoclonal antibodies. Infect. Immunol. 64, 4085–4090.
Lindenstrom, T., Buchmann, K., 2000. Acquired resistance in rainbow trout against *Gyrodactylus derjavini*. J. Helminthol. 74, 155–160.
Lloyd, S., Soulsby, E.J.L., 1976. Passive transfer of immunity to neonatal calves against metacestodes of *Taenia-Saginata*. Vet. Parasitol. 2, 355–362.
Lorenzen, N., Olesen, N.J., Jorgensen, P.E., 1990. Neutralization of Egtved virus pathogenicity to cell cultures and fish by monoclonal antibodies to the viral G protein. J. Gen. Virol. 71 (Pt. 3), 561–567.
Lu, Y.N., Liu, J.J., Jin, L.J., Li, X.Y., Zhen, Y.H., Xue, H.Y., You, J.S., Xu, Y.P., 2008. Passive protection of shrimp against white spot syndrome virus (WSSV) using specific antibody from egg yolk of chickens immunized with inactivated virus or a WSSV-DNA vaccine. Fish Shellfish Immunol. 25, 604–610.
Madec, F., Rose, N., Grasland, B., Cariolet, R., Jestin, A., 2008. Post-weaning multisystemic wasting syndrome and other PCV2-related problems in pigs: a 12-year experience. Transbound. Emerg. Dis. 55, 273–283.
Madson, D.M., Patterson, A.R., Ramamoorthy, S., Pal, N., Meng, X.J., Opriessnig, T., 2009. Effect of porcine circovirus type 2 (PCV2) vaccination of the dam on PCV2 replication in utero. Clin. Vacc. Immunol: CVI 16, 830–834.
Malek, A., 2013. Role of IgG antibodies in association with placental function and immunologic diseases in human pregnancy. Expert Rev. Clin. Immunol. 9, 235–249.
Malik, M.W., Ayub, N., Qureshi, I.Z., 2006. Passive immunization using purified IgYs against infectious bursal disease of chickens in Pakistan. J. Vet. Sci. 7, 43–46.
Mancini, N., Solforosi, L., Clementi, N., De Marco, D., Clementi, M., Burioni, R., 2011. A potential role for monoclonal antibodies in prophylactic and therapeutic treatment of influenza. Antiviral Res. 92, 15–26.
Marquardt, R.R., Jin, L.Z., Kim, J.W., Fang, L., Frohlich, A.A., Baidoo, S.K., 1999. Passive protective effect of egg-yolk antibodies against enterotoxigenic *Escherichia coli* K88+ infection in neonatal and early-weaned piglets. FEMS Immunol. Med. Microbiol. 23, 283–288.
Marshall, K., 2004. Therapeutic applications of whey protein. Altern. Med. Rev. 9, 136–156.
Matte, J.J., Girard, C.L., Seoane, J.R., Brisson, G.J., 1982. Absorption of colostral immunoglobulin G in the newborn dairy calf. J. Dairy Sci. 65, 1765–1770.
McClead, R.E., Gregory, S.A., 1984. Resistance of bovine colostral anti-cholera toxin antibody to in vitro and in vivo proteolysis. Infect. Immun. 44, 474–478.
McConnell, M.A., Buchan, G., Borissenko, M.V., Brooks, H.J.L., 2001. A comparison of IgG and IgG1 activity in an early milk concentrate from non-immunised cows and a milk from hyperimmunised animals. Food Res. Int. 34, 255–261.
McGuire, T.C., Crawford, T.B., Hallowell, A.L., Macomber, L.E., 1977. Failure of colostral immunoglobulin transfer as an explanation for most infections and deaths of neonatal foals. J. Am. Vet. Med. Assoc. 170, 1302–1304.
McKeown, N.E., Opriessnig, T., Thomas, P., Guenette, D.K., Elvinger, F., Fenaux, M., Halbur, P.G., Meng, X.J., 2005. Effects of porcine circovirus type 2 (PCV2) maternal antibodies on experimental infection of piglets with PCV2. Clin. Diagn. Lab. Immunol. 12, 1347–1351.
Melkebeek, V., Goddeeris, B.M., Cox, E., 2013. ETEC vaccination in pigs. Vet. Immunol. Immunopathol. 152, 37–42.
Mendez Arancibia, E., Pitart, C., Ruiz, J., Marco, F., Gascon, J., Vila, J., 2009. Evolution of antimicrobial resistance in enteroaggregative *Escherichia coli* and enterotoxigenic *Escherichia coli* causing traveller's diarrhoea. J. Antimicrob. Chemother. 64, 343–347.
Michael, A., Meenatchisundaram, S., Parameswari, G., Subbraj, T., Selvakumaran, R., Ramalingam, S., 2010. Chicken egg yolk antibodies (IgY) as an alternative to mammalian antibodies. Ind. J. Sci. Technol. 3, 468–474.
Morgan, D.R., DuPont, H.L., Gonik, B., Kohl, S., 1984. Cytotoxicity of human peripheral blood and colostral leukocytes against Shigella species. Infect. Immun. 46, 25–33.
Morrison, S.L., Mohammed, M.S., Wims, L.A., Trinh, R., Etches, R., 2002. Sequences in antibody molecules important forreceptor-mediated transport into the chicken egg yolk. Mol. Immunol. 38, 619–625.
Mukkur, T.K., Walker, K.H., McDowell, G.H., 1998. Passive immunisation of neonatal lambs via colostrum and milk of ewes previously immunised with live attenuated *Salmonella typhimurium* protects neonatal lambs from experimental salmonellosis. Comp. Immunol. Microbiol. Infect. Dis. 21, 327–336.
Murphy, J.M., Hagey, J.V., Chigerwe, M., 2014. Comparison of serum immunoglobulin G half-life in dairy calves fed colostrum, colostrum replacer or administered with intravenous bovine plasma. Vet. Immunol. Immunopathol. 158, 233–237.
Nagy, B., 1980. Vaccination of cows with a K99 extract to protect newborn calves against experimental enterotoxic colibacillosis. Infect. Immun. 27, 21–24.
Nath, L.C., Anderson, G.A., Savage, C.J., McKinnon, A.O., 2010. Use of stored equine colostrum for the treatment of foals perceived to be at risk for failure of transfer of passive immunity. Javma-J. Am. Vet. Med. A 236, 1085–1090.

Nemeth, N.M., Bowen, R.A., 2007. Dynamics of passive immunity to West Nile virus in domestic chickens (*Gallus gallus domesticus*). Am. J. Trop. Med. Hyg. 76, 310–317.
Niewold, T.A., van Dijk, A.J., Geenen, P.L., Roodink, H., Margry, R., van der Meulen, J., 2007. Dietary specific antibodies in spray-dried immune plasma prevent enterotoxigenic *Escherichia coli* F4 (ETEC) post weaning diarrhoea in piglets. Vet. Microbiol. 124, 362–369.
Nollet, H., Deprez, P., Van Driessche, E., Muylle, E., 1999. Protection of just weaned pigs against infection with F18+ *Escherichia coli* by non-immune plasma powder. Vet. Microbiol. 65, 37–45.
Oanh, T.K., Nguyen, V.K., De Greve, H., Goddeeris, B.M., 2012. Protection of piglets against Edema disease by maternal immunization with Stx2e toxoid. Infect. Immun. 80, 469–473.
Oh, Y., Seo, H.W., Han, K., Park, C., Chae, C., 2012. Protective effect of the maternally derived porcine circovirus type 2 (PCV2)-specific cellular immune response in piglets by dam vaccination against PCV2 challenge. J. Gen. Virol. 93, 1556–1562.
Opriessnig, T., Patterson, A.R., Elsener, J., Meng, X.J., Halbur, P.G., 2008. Influence of maternal antibodies on efficacy of porcine circovirus type 2 (PCV2) vaccination to protect pigs from experimental infection with PCV2. Clin. Vacc. Immunol.: CVI 15, 397–401.
Owusu-Asiedu, A., Baidoot, S.K., Nyachoti, C.M., Marquardt, R.R., 2002. Response of early-weaned pigs to spray-dried porcine or animal plasma-based diets supplemented with egg-yolk antibodies against enterotoxigenic *Escherichia coli*. J. Anim. Sci. 80, 2895–2903.
Owusu-Asiedu, A., Nyachoti, C.M., Baidoo, S.K., Marquardt, R.R., Yang, X., 2003a. Response of early-weaned pigs to an enterotoxigenic *Escherichia coli* (K88) challenge when fed diets containing spray-dried porcine plasma or pea protein isolate plus egg yolk antibody. J. Anim. Sci. 81, 1781–1789.
Owusu-Asiedu, A., Nyachoti, C.M., Marquardt, R.R., 2003b. Response of early-weaned pigs to an enterotoxigenic *Escherichia coli* (K88) challenge when fed diets containing spray-dried porcine plasma or pea protein isolate plus egg yolk antibody, zinc oxide, fumaric acid, or antibiotic. J. Anim. Sci. 81, 1790–1798.
Palmeira, P., Quinello, C., Silveira-Lessa, A.L., Zago, C.A., Carneiro-Sampaio, M., 2012. IgG placental transfer in healthy and pathological pregnancies. Clin. Dev. Immunol. 2012, 985646.
Parreno, V., Bejar, C., Vagnozzi, A., Barrandeguy, M., Costantini, V., Craig, M.I., Yuan, L., Hodgins, D., Saif, L., Fernandez, F., 2004. Modulation by colostrum-acquired maternal antibodies of systemic and mucosal antibody responses to rotavirus in calves experimentally challenged with bovine rotavirus. Vet. Immunol. Immunopathol. 100, 7–24.
Pasick, J., Berhane, Y., Ojkic, D., Maxie, G., Embury-Hyatt, C., Swekla, K., Handel, K., Fairles, J., Alexandersen, S., 2014. Investigation into the role of potentially contaminated feed as a source of the first-detected outbreaks of porcine epidemic diarrhea in Canada. Transbound. Emerg. Dis. 61, 397–410.
Pasnik, D.J., Evans, J.J., Klesius, P.H., 2006. Passive immunization of Nile tilapia (*Oreochromis niloticus*) provides significant protection against Streptococcus agalactiae. Fish Shellfish Immunol. 21, 365–371.
Pasnik, D.J., Evans, J.J., Klesius, P.H., 2011. Specific serum antibody responses in channel catfish (*Ictalurus punctatus*) provide limited protection against Streptococcus ictaluri challenge. Vet. Immunol. Immunopathol. 144, 144–146.
Patel, S., 2015. Emerging trends in nutraceutical applications of whey protein and its derivatives. J. Food Sci. Technol. 52, 6847–6858.
Perez-Bosque, A., Amat, C., Polo, J., Campbell, J.M., Crenshaw, J., Russell, L., Moreto, M., 2006. Spray-dried animal plasma prevents the effects of *Staphylococcus aureus* enterotoxin B on intestinal barrier function in weaned rats. J. Nutr. 136, 2838–2843.
Petschow, B.W., Talbott, R.D., 1994. Reduction in virus-neutralizing activity of a bovine colostrum immunoglobulin concentrate by gastric acid and digestive enzymes. J. Pediatr. Gastroenterol. Nutr. 19, 228–235.
Pierce, J.L., Cromwell, G.L., Lindemann, M.D., Russell, L.E., Weaver, E.M., 2005. Effects of spray-dried animal plasma and immunoglobulins on performance of early weaned pigs. J. Anim. Sci. 83, 2876–2885.
Polo, J., Rodriguez, C., Rodenas, J., Russell, L.E., Campbell, J.M., Crenshaw, J.D., Torrallardona, D., Pujols, J., 2015. Ultraviolet light (UV) inactivation of porcine parvovirus in liquid plasma and effect of UV irradiated spray dried porcine plasma on performance of weaned pigs. PLoS One 10, e0133008.
Qadri, F., Bhuiyan, T.R., Sack, D.A., Svennerholm, A.M., 2013. Immune responses and protection in children in developing countries induced by oral vaccines. Vaccine 31, 452–460.
Qiu, X., Wong, G., Audet, J., Bello, A., Fernando, L., Alimonti, J.B., Fausther-Bovendo, H., Wei, H., Aviles, J., Hiatt, E., Johnson, A., Morton, J., Swope, K., Bohorov, O., Bohorova, N., Goodman, C., Kim, D., Pauly, M.H., Velasco, J., Pettitt, J., Olinger, G.G., Whaley, K., Xu, B., Strong, J.E., Zeitlin, L., Kobinger, G.P., 2014. Reversion of advanced Ebola virus disease in nonhuman primates with ZMapp. Nature 514, 47–53.
Quigley, J.D., Drew, M.D., 2000. Effects of oral antibiotics or bovine plasma on survival, health and growth in dairy calves challenged with *Escherichia coli*. Food Agr. Immunol. 12, 311–318.
Quigley, J., 2002. Passive immunity in newborn calves. Adv. Dairy Technol. 14, 273–292.
Rahimi, S., Shiraz, Z.M., Salehi, T.Z., Torshizi, M.A.K., Grimes, J.L., 2007. Prevention of *salmonella* infection in poultry by specific egg-Derived antibody. Int. J. Poult. Sci.
Raida, M.K., Buchmann, K., 2008. Bath vaccination of rainbow trout (*Oncorhynchus mykiss* Walbaum) against *Yersinia ruckeri*: effects of temperature on protection and gene expression. Vaccine 26, 1050–1062.
Rauta, P.R., Nayak, B., Das, S., 2012. Immune system and immune responses in fish and their role in comparative immunity study: a model for higher organisms. Immunol. Lett. 148, 23–33.
Reynolds, D.L., Maraqa, A.D., 2000. Protective immunity against Newcastle disease: the role of antibodies specific to Newcastle disease virus polypeptides. Avian Dis. 44, 138–144.
Reynolds, D., Akinc, S., Ali, A., 2000. Passively administered antibodies alleviate stunting syndrome in turkey poults. Avian Dis. 44, 439–442.
Rhee, J.H., Lee, S.E., Kim, S.Y., 2012. Mucosal vaccine adjuvants update. Clin. Exp. Vacc. Res. 1, 50–63.
Rickard, M.D., Boddington, E.B., McQuade, N., 1977. Vaccination of lambs against *Taenia* ovis infection using antigens collected during in vitro cultivation of larvae: passive protection via colostrum from vaccinated ewes and the duration of immunity from a single vaccination. Res. Vet. Sci. 23, 368–371.
Robison, J.D., Stott, G.H., DeNise, S.K., 1988. Effects of passive immunity on growth and survival in the dairy heifer. J. Dairy Sci. 71, 1283–1287.
Rose, M.E., Orlans, E., Buttress, N., 1974. Immunoglobulin classes in hens egg—their segregation in yolk and white. Eur. J. Immunol. 4, 521–523.
Rubbenstroth, D., Rautenschlein, S., 2009. Investigations on the protective role of passively transferred antibodies against avian metapneumovirus infection in turkeys. Avian Pathol. 38, 427–436.
Saif, L.J., Fernandez, F.M., 1996. Group A rotavirus veterinary vaccines. J. Infect. Dis. 174 (Suppl. 1), S98–106.
Salinas, I., Zhang, Y.A., Sunyer, J.O., 2011. Mucosal immunoglobulins and B cells of teleost fish. Dev. Comp. Immunol. 35, 1346–1365.
Salinas, I., 2015. The mucosal immune system of Teleost fish. Biology (Basel) 4, 525–539.
Salmon, H., Berri, M., Gerdts, V., Meurens, F., 2009. Humoral and cellular factors of maternal immunity in swine. Dev. Comp. Immunol. 33, 384–393.
Sarker, S.A., Casswall, T.H., Mahalanabis, D., Alam, N.H., Albert, M.J., Brussow, H., Fuchs, G.J., Hammerstrom, L., 1998. Successful treatment of rotavirus diarrhea in children with immunoglobulin from immunized bovine colostrum. Pediatr. Infect. Dis. J. 17, 1149–1154.
Sarker, S.A., Pant, N., Juneja, L.R., Hammarstrom, L., 2007. Successful treatment of rotavirus-induced diarrhoea in suckling mice with egg yolk immunoglobulin. J. Health Popul. Nutr. 25, 465–468.
Schade, K., Calzado, E.G., Sarmiento, R., Chacana, P.A., Porankiewicz-Asplund, J., Terzolo, H.R., 2005. Chicken egg yolk antibodies (IgY-technology): A review of progress in production and use in research and human and veterinary medicine. Atla-Altern Lab. Anim. 33, 129–154.
Schuijffel, D.F., van Empel, P.C., Pennings, A.M., van Putten, J.P., Nuijten, P.J., 2005. Passive immunization of immune-suppressed animals: chicken antibodies protect against *Ornithobacterium rhinotracheale* infection. Vaccine 23, 3404–3411.
Shahid, N.S., Steinhoff, M.C., Roy, E., Begum, T., Thompson, C.M., Siber, G.R., 2002. Placental and breast transfer of antibodies after maternal immunization with polysaccharide meningococcal vaccine: a randomized, controlled evaluation. Vaccine 20, 2404–2409.
Shahzad, M.I., Naeem, K., Mukhtar, M., Khanum, A., 2008. Passive immunization against highly pathogenic Avian Influenza Virus (AIV) strain H7N3 with antiserum generated from viral polypeptides protect poultry birds from lethal viral infection. Virol. J. 5, 144.
Shelby, R.A., Shoemaker, C.A., Klesius, P.H., 2007. Passive immunization of channel catfish *Ictalurus punctatus* with anti-Flavobacterium columnare sera. Dis. Aquat. Organ. 77, 143–147.
Sheoran, A.S., Karzenski, S.S., Whalen, J.W., Crisman, M.V., Powell, D.G., Timoney, J.F., 2000. Prepartum equine rotavirus vaccination inducing strong specific IgG in mammary secretions. Vet. Rec. 146, 672–673.
Sherman, D.M., Acres, S.D., Sadowski, P.L., Springer, J.A., Bray, B., Raybould, T.J.G., Muscoplat, C.C., 1983. Protection of calves against fatal enteric colibacillosis by orally-administered *Escherichia-Coli* K99-specific monoclonal-antibody. Infect. Immun. 42, 653–658.
Shibata, I., Okuda, Y., Kitajima, K., Asai, T., 2006. Shedding of porcine circovirus into colostrum of sows. J. Vet. Med. B 53, 278–280.
Si, W., Yu, S., Chen, L., Wang, X., Zhang, W., Liu, S., Li, G., 2014. Passive protection against *Salmonella enterica* serovar Enteritidis infection from maternally derived antibodies of hens vaccinated with a ghost vaccine. Res. Vet. Sci. 97, 191–193.
Siso, M.I.G., 1996. The biotechnological utilization of cheese whey: a review. Bioresour. Technol. 57, 1–11.
Smith, N.C., Wallach, M., Petracca, M., Braun, R., Eckert, J., 1994. Maternal transfer of antibodies induced by infection with *Eimeria maxima* partially protects chickens against challenge with *Eimeria tenella*. Parasitology 109 (Pt 5), 551–557.
Smolenski, G., Haines, S., Kwan, F.Y., Bond, J., Farr, V., Davis, S.R., Stelwagen, K., Wheeler, T.T., 2007. Characterisation of host defence proteins in milk using a proteomic approach. J. Proteome Res. 6, 207–215.
Snodgrass, D.R., Nagy, L.K., Sherwood, D., Campbell, I., 1982. Passive immunity in calf diarrhea: vaccination with K99 antigen of enterotoxigenic *Escherichia coli* and rotavirus. Infect. Immun. 37, 586–591.
Snoeck, V., Huyghebaert, N., Cox, E., Vermeire, A., Vancaeneghem, S., Remon, J.P., Goddeeris, B.M., 2003. Enteric-coated pellets of F4 fimbriae for oral vaccination

of suckling piglets against enterotoxigenic *Escherichia coli* infections. Vet. Immunol. Immunopathol. 96, 219–227.
Snoeck, V., Cox, E., Verdonck, F., Joensuu, J.J., Goddeeris, B.M., 2004. Influence of porcine intestinal pH and gastric digestion on antigenicity of F4 fimbriae for oral immunisation. Vet. Microbiol. 98, 45–53.
Swain, P., Dash, S., Bal, J., Routray, P., Sahoo, P.K., Sahoo, S.K., Saurabh, S., Gupta, S.D., Meher, P.K., 2006. Passive transfer of maternal antibodies and their existence in eggs, larvae and fry of Indian major carp, *Labeo rohita* (Ham.). Fish Shellfish Immunol. 20, 519–527.
Tacket, C.O., Losonsky, G., Link, H., Hoang, Y., Guesry, P., Hilpert, H., Levine, M.M., 1988. Protection by milk immunoglobulin concentrate against oral challenge with enterotoxigenic *Escherichia coli*. N. Engl. J. Med. 318, 1240–1243.
Tennent-Brown, B., 2011. Plasma therapy in foals and adult horses. Compendium 33, E1–4.
Tesar, D.B., Cheung, E.J., Bjorkman, P.J., 2008. The chicken yolk sac IgY receptor, a mammalian mannose receptor family member, transcytoses IgY across polarized epithelial cells. Mol. Biol. Cell 19, 1587–1593.
Traxler, G.S., Anderson, E., LaPatra, S.E., Richard, J., Shewmaker, B., Kurath, G., 1999. Naked DNA vaccination of atlantic salmon salmo salar against IHNV. Dis. Aquat. Organ. 38, 183–190.
Tsubokura, K., Berndtson, E., Bogstedt, A., Kaijser, B., Kim, M., Ozeki, M., Hammarstrom, L., 1997. Oral administration of antibodies as prophylaxis and therapy in *Campylobacter* jejuni-infected chickens. Clin. Exp. Immunol. 108, 451–455.
Tsunemitsu, H., Shimizu, M., Hirai, T., Yonemichi, H., Kudo, T., Mori, K., Onoe, S., 1989. Protection against bovine rotaviruses in newborn calves by continuous feeding of immune colostrum. Jpn. J. Vet. Sci. 51, 300–308.
Tuboly, S., Bernath, S., 2002. Intestinal absorption of colostral lymphoid cells in newborn animals. Adv. Exp. Med. Biol. 503, 107–114.
Umino, Y., Kohama, T., Kohase, M., Sugiura, A., Klenk, H.D., Rott, R., 1987. Protective effect of antibodies to two viral envelope glycoproteins on lethal infection with Newcastle disease virus. Arch. Virol 94, 97–107.
Van den Broeck, W., Cox, E., Goddeeris, B.M., 1999a. Induction of immune responses in pigs following oral administration of purified F4 fimbriae. Vaccine 17, 2020–2029.
Van den Broeck, W., Cox, E., Goddeeris, B.M., 1999b. Receptor-dependent immune responses in pigs after oral immunization with F4 fimbriae. Infect. Immun. 67, 520–526.
Vanavichial, B., 1998. Provision of immunoglobulins to sucking piglets can enhance post-weaning growth performance. In: Department of Animal Science. Massey University, New Zealand.
Vega, C., Bok, M., Chacana, P., Saif, L., Fernandez, F., Parreno, V., 2011. Egg yolk IgY: protection against rotavirus induced diarrhea and modulatory effect on the systemic and mucosal antibody responses in newborn calves. Vet. Immunol. Immunopathol. 142, 156–169.
Vidarsson, G., Dekkers, G., Rispens, T., 2014. IgG subclasses and allotypes: from structure to effector functions. Front. Immunol. 5, 520.
Vidor, E., 2007. 2007: Vaccination of newborns against hepatitis A in the presence of maternally derived antibodies. J. Comp. Pathol. 137 (Suppl. 1), S42–45.
Virdi, V., Coddens, A., De Buck, S., Millet, S., Goddeeris, B.M., Cox, E., De Greve, H., Depicker, A., 2013. Orally fed seeds producing designer IgAs protect weaned piglets against enterotoxigenic *Escherichia coli* infection. Proc. Natl. Acad. Sci. U.S.A. 110, 11809–11814.
Voss Jr., E.W., Groberg Jr., W.J., Fryer, J.L., 1980. Metabolism of coho salmon Ig. Catabolic rate of coho salmon tetrameric Ig in serum. Mol. Immunol. 17, 445–452.
WHO, 2012. The Evolving Threat of Antimicrobial Resistance Options for Action World Health Organisation.
Watson, D.L., 1992. Biological half-life of ovine antibody in neonatal lambs and adult sheep following passive immunization. Vet. Immunol. Immunopathol. 30, 221–232.
Weaver, D.M., Tyler, J.W., VanMetre, D.C., Hostetler, D.E., Barrington, G.M., 2000. Passive transfer of colostral immunoglobulins in calves. J. Vet. Intern. Med. 14, 569–577.
Wilkins, P.A., Glaser, A.L., McDonnell, S.M., 2006. Passive transfer of naturally acquired specific immunity against West Nile Virus to foals in a semi-feral pony herd. J. Vet. Intern. Med. 20, 1045–1047.
Wilson, W.D., Mihalyi, J.E., Hussey, S., Lunn, D.P., 2001. Passive transfer of maternal immunoglobulin isotype antibodies against tetanus and influenza and their effect on the response of foals to vaccination. Equine Vet. J. 33, 644–650.
Wilson, W.D., 1999. Vaccination programs for foals and weanlings. In: Proceedings of the Annual Convention of the AAEP, American Association of Equine Practitioners, Albuquerque (NM), pp. 254–263.
Wittum, T.E., Perino, L.J., 1995. Passive immune status at postpartum hour 24 and long-term health and performance of calves. Am. J. Vet. Res. 56, 1149–1154.
Wu, C.J., Wang, H., Chan, Y.L., Li, T.L., 2011. Passive immune-protection of small abalone against *Vibrio alginolyticus* infection by anti-Vibrio IgY-encapsulated feed. Fish Shellfish Immunol. 30, 1042–1048.
Ylitalo, S., Uhari, M., Rasi, S., Pudas, J., Leppaluoto, J., 1998. Rotaviral antibodies in the treatment of acute rotaviral gastroenteritis. Acta Paediatr. 87, 264–267.
Yokoyama, H., Hashi, T., Umeda, K., Icatlo Jr., F.C., Kuroki, M., Ikemori, Y., Kodama, Y., 1997. Effect of oral egg antibody in experimental F18+ *Escherichia coli* infection in weaned pigs. J. Vet. Intern. Med. 59, 917–921.
Yolken, R.H., Losonsky, G.A., Vonderfecht, S., Leister, F., Wee, S.B., 1985. Antibody to human rotavirus in cow's milk. N. Engl. J. Med. 312, 605–610.
Zeitlin, L., Cone, R.A., Whaley, K.J., 1999. Using monoclonal antibodies to prevent mucosal transmission of epidemic infectious diseases. Emerg. Infect. Dis. 5, 54–64.
Zhang, Q., Cundiff, J.K., Maria, S.D., McMahon, R.J., Wickham, M.S., Faulks, R.M., van Tol, E.A., 2014. Differential digestion of human milk proteins in a simulated stomach model. J. Proteome Res. 13, 1055–1064.
Zhou, M., Duan, Q., Zhu, X., Guo, Z., Li, Y., Hardwidge, P.R., Zhu, G., 2013. Both flagella and F4 fimbriae from F4ac+ enterotoxigenic *Escherichia coli* contribute to attachment to IPEC-J2 cells in vitro. Vet. Res. 44, 30.