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4 Review paper

5 Passive immunisation, an old idea revisited: Basic principles and 6 application to modern animal production systems

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12

13 **Abstract**

14 Immunisation by administration of antibodies (immunoglobulins) has been known for
15 more than one hundred years as a very efficient means of obtaining immediate, short-
16 lived protection against infection and/or against the disease-causing effects of toxins
17 from microbial pathogens and from other sources. Thus, due to its rapid action, passive
18 immunisation is often used to treat disease caused by infection and/or toxin exposure.
19 However immunoglobulins may also be administered prior to exposure to infection
20 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.

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

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

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 and 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 and 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 and Mendez Arancibia et al., 2009). The situation threatens to become a major problem for treating infectious diseases in humans (Barton, 2000 and 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 and 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

92 solution for immediate treatment of and short term protection against enteral
93 infections, having the potential for being a real alternative to the use of antibiotics in the
94 animal production, especially for intervention at specific time periods in the production
95 in which animals are particularly exposed to enteric infectious disease such as at birth
96 and at weaning. In addition, passive immunisation can be and are currently used for
97 other types of infectious diseases in production animals using a range of different
98 administration routes (see below).

99

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

101 2.1. Natural passive immunity

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

108 Evolutionarily, transfer of maternal immunoglobulins to offspring can be traced as far
109 back as 450 million years ago, being found in primitive fish like the nurse shark (Haines
110 et al., 2005). In some mammals, including primates and rabbits, the foetus obtains
111 immunoglobulin (Ig) G over the placenta (Hurley and Theil, 2011 and Palmeira et al.,
112 2012) and the new-born is thus born with circulating mammalian IgG, persisting in the
113 systemic circulation for some months after birth. The half-life of circulatory IgG in man is
114 around 3 weeks (see below, Table 1), thus it has been observed that maternal antibodies

115 are detectable in children 2–3 months after birth as seen in a study on circulating
116 maternal anti-Neisseria meningitidis IgG (Shahid et al., 2002). This is supplemented
117 during lactation by the intake of maternal IgA-type immunoglobulin through the milk
118 building up local immunity in the gastrointestinal tract (Malek, 2013). In other mammals
119 such as pigs and ruminants, placental immunoglobulin transfer does not take place and
120 consequently the neonate is born agammaglobulinemic (without immunoglobulin),
121 having neither received maternal immunoglobulin nor initiated their own production of
122 immunoglobulins. Instead, these species are born with an 'open gut' allowing Fc-
123 receptor-mediated immunoglobulin transfer from the gut to the circulation for the first
124 approximately 24 h after birth assuring the very quick establishment of the necessary
125 circulating levels of maternal immunoglobulins through ingestion of colostrum which in
126 these species contains high concentrations of IgG (Cervenak and Kacskovics, 2009).
127 Notably in pigs, colostral IgG concentrations decrease by 80% within 24 h of parturition
128 (Foisnet et al., 2010). A variation of this is seen in rodents and some other species,
129 including mink, where the neonate is born with a certain level of circulating maternal
130 immunoglobulins and has its gut open for transfer of immunoglobulin from the milk for
131 2–3 weeks postnatally (Brambell, 1966 and Kim et al., 2009). In chickens, the pre-
132 hatching chick receives maternal immunoglobulin through the yolk sac of the egg and
133 therefore is 'born' with maternal immunoglobulin at hatching (Kowalczyk et al., 1985).

134 Once maternal circulatory IgG is no longer replenished, i.e. after parturition and gut
135 closure the half-life of IgG is around 2–3 weeks in larger mammals (Table 1). In small
136 mammals such as mice the half-life of IgG in the circulation is only a few days which is
137 also the case for immunoglobulin Y (IgY) in birds, and tetrameric IgM in fish (Table 1).
138 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 and 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 and 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 and Smolenski et al., 2007). Colostral leukocytes are believed to participate in oro-gastric protection together with maternal immunoglobulins (Goldman, 1977 and Morgan et al., 1984), and may enter circulation by intestinal absorption promoting neonatal cellular immunity (Liebler-Tenorio et al., 2002, Salmon et al., 2009 and 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 and 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 and Snodgrass et al., 1982). Lactogenic immunity against larval cestodes and metacestodes has also been reported (Larsh, 1942 and 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 and Francis and Black, 1984b) 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 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 and 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 and 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 and 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 have proved useful for controlling PCV2-associated diseases (Chae, 2012 and 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 and 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 and 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 and 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

284 lactogenic passive immunisation provided by maternal antibody transfer can prevent
285 PCV2 infection even though disease signs are reduced.

286 Infection with diarrhoeagenic ETEC affects newly weaned piglets causing post weaning
287 diarrhoea (PWD), which is a very widespread problem in modern pig production systems
288 (Fleckenstein et al., 2010, Gyles, 1994 and Hong et al., 2006). The key step in the
289 pathogenesis of PWD is the fimbria-receptor interaction necessary for the colonisation
290 by ETEC of the small intestine (Gaastra and Svennerholm, 1996 and Zhou et al., 2013).
291 An orally provided F4 fimbria subunit vaccine was shown to be able to induce protection
292 against F4 positive ETEC in an experimental model of PWD (Van den Broeck et al., 1999a
293 and Van den Broeck et al., 1999b). One commercial vaccine (Coliprotec®) for oral use
294 against PWD, containing live avirulent E. coli F4+ strain, has been marketed in Canada
295 for some years (Melkebeek et al., 2013) and was approved for the European market in
296 2015 as well (EMEA, 2015). Efficacy data for this vaccine do not seem to be available.
297 However, the use of oral vaccines based on live bacteria for oro-gastric protection has
298 several limitations, including (1) in nursing piglets interfering lactogenic maternal
299 antibodies may inhibit induction of active immunity as intestinal colonisation by the
300 bacteria is inhibited, (2) oral vaccination only works fully if the weaners are able to
301 mount a full immune response, which is not the case at four weeks of age (Levast et al.,
302 2014), (3) the vaccine cannot be provided in combination with antibiotics as these will
303 kill the live bacteria of the vaccine, and (4) if the vaccine only provides protection against
304 specific antigens (e.g. F4 fimbriae) it will not work in geographical regions where other
305 bacterial strains prevail (e.g. E. coli F18+). However, passive immunisation was shown to
306 protect new-born piglets against otherwise fatal diarrhoea caused by ETEC F4+ by oral
307 administration of a combination of several monoclonal antibodies targeting different F4
308 fimbria subunits (25 mg/ml in ascites fluid) (Foged et al., 1986). Notably, one oral dose

309 (1 ml) of this monoclonal antibody mixture provided 1 h prior to challenge did not
310 provide protection, however combining administration before challenge with
311 administration at 8, 24 and 32 h after challenge provided complete protection against
312 mortality and disease. Ten days of feeding genetically engineered Arabidopsis plant
313 seeds expressing F4-specific llama-derived immunoglobulin was reported by Virdi et al.,
314 2013 to reduce excretion of F4 positive ETEC (experimental challenge at day 6) and to
315 increase the weight gain in pigs (Virdi et al., 2013). Antibodies from hens' eggs (also
316 known as IgY, see below) have also been investigated for their ability to provide passive
317 protection against enteric infections in pigs, however results have been ambiguous (see
318 below). Thus, a study on E. coli F18+-specific IgY-containing egg yolk fed to weaning pigs
319 that had been challenged with virulent E. coli F18+ showed that growth was significantly
320 improved, and both diarrhoea incidence and E. coli colonisation reduced compared to
321 the control groups (Yokoyama et al., 1997). This finding was confirmed in an
322 independent study feeding either egg powder or eggs from fimbria F18-immunised hens
323 to weaning piglets which led to significantly less shedding of the E. coli F18+ challenge
324 strain, reduced incidence of diarrhoea, and reduced mortality compared to weaner
325 piglets fed eggs or egg powder from non-immunised hens (Imberechts et al., 1997).
326 Also, a feed supplement of egg yolk powder from eggs of E. coli F4+-immunised hens
327 decreased the frequency of diarrhoea and mortality in early-weaned piglets to almost
328 zero as compared to a control group not receiving egg yolk feed supplementation (
329 Marquardt et al., 1999 and Owusu-Asiedu et al., 2002). On the other hand, other studies
330 failed to demonstrate any effect on experimental E. coli induced diarrhoea incidence
331 after feeding IgY with specificity against the challenge strain (Owusu-Asiedu et al.,
332 2003a and Owusu-Asiedu et al., 2003b) and a field trial on the efficacy of anti-ETEC IgY
333 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 and 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 and Weaver et al., 2000). Poor quality colostrum (low IgG concentration) and inadequate enteral uptake of IgG are the main causes of FPT (Godden, 2008 and 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 and 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 and 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 and 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 and 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 and 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 and 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 and 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 and 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 and 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 and 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 immunoglobulins. Thus, two Nishiki carps diagnosed with a mixed Aeromonas salmonicida and A. hydrophila infection were successfully treated by

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

486 The use of IgY for treating other marine animals has also been studied: In a model for
487 Vibrio alginolyticus infection of shellfish Haliotis diversicolor supertexta (small abalone),
488 Vibrio alginolyticus-specific IgY was provided orally and increased survival from 0% to
489 more than 65% after challenge (Wu et al., 2011). Metapenaeus ensis (greasyback
490 shrimps) challenged with White spot syndrome virus had 73% and 33% survival, after
491 subsequent passive immunisation (IgY) and active immunisation, respectively (Lu et al.,
492 2008).

493 In general, it appears that immunity against infectious pathogens in fish can be passively
494 transferred by parenteral routes (intraperitoneally in most cases) whereas protection by
495 feeding specific immunoglobulins, being much more attractive from a practical point of
496 view, seems to be more challenging. This may be due to the presence of other easily
497 accessible entry points for infectious agent in fish, such as the gills and the fact that the
498 whole body of the fish is constantly challenged.

499

500

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 and 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 and 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

549 borne pathogens, including viruses, such as PCV2 and porcine epidemic diarrhoea virus
550 (PEDV).

551

552 5.2. Egg yolk immunoglobulins

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

565

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

572

573 5.3. Milk and whey

574 As discussed extensively above colostrum and milk provide natural oro-gastric
575 protection against enteric infection in suckling off-spring. The major immunoglobulin
576 type in bovine milk and colostrum is IgG (0.5–1 mg/ml and 60–70 mg/ml, respectively)
577 (El-Loly, 2007 and Hurley and Theil, 2011). Precipitating casein from milk, as done in
578 cheese manufacturing, removes the bulk of protein from the milk, leaving the by-
579 product whey, containing around 0.5 mg/ml IgG, constituting approx. 10% of the protein
580 fraction (Siso, 1996). In cattle, a marketed whey-product (Colostrx) is claimed to protect
581 similarly to colostrum against ETEC in a E. coli K99-challenge model (Harman et al.,
582 1991). Although whey is claimed to have a range of dietary benefits in humans (
583 Marshall, 2004 and Patel, 2015) and pigs (Vanavichial, 1998), and it is a cheaper source
584 of immunoglobulins than milk, it however does not seem that whey is used to any
585 discernible degree for production of purified immunoglobulin preparations. This may be
586 due to the relatively low concentration of IgG in whey (<1 mg/ml) necessitating large
587 volumes to be handled during purification thereby compromising economic feasibility
588 compared to e.g. blood serum (containing around 10 mg/ml).

589

590 **6. Challenges and perspectives**

591 Intensive animal production systems generally face challenges in the shape of infections
592 compromising productivity, economy and animal welfare, and causing extensive use of
593 antibiotics. Active immunisation (vaccination) is a very useful alternative and
594 supplement to antibiotics for protecting against infectious pathogens as it can be used

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

611 However, passive transfer of immunity at large scale in huge animal production facilities
612 is not always feasible and while the use of passive immunisation with immunoglobulins
613 for specific purposes like e.g. oedema disease in pigs is well-known (Johansen et al.,
614 2000), as is the principle of maternal vaccination, immunizing the offspring through a
615 natural passive immunisation process (Oanh et al., 2012), the general application of the
616 principle for the broad group of production related diseases mentioned above is
617 critically dependent upon the large-scale availability of low cost immunoglobulins e.g.
618 for supplementing the feed with immunoglobulins during challenging periods in the
619 animals' lifetime. Although a range of advanced methods for producing

620 immunoglobulins including monoclonal antibody protocols and recombinant antibody
621 expression exist, such types of immunoglobulins are not expected to be prime
622 candidates for large scale use in intensive animal production systems. Also, in practical
623 terms easy administration of immunoglobulins is a must. For example, instead of
624 injecting all fry in a fish production unit it would be much more practical to provide
625 antibodies in the fry feed. Another example is the administration of colostrum feed
626 supplements in which antibodies derived from the dam provide protection against
627 infectious agents in the suckling offspring (see Table 4), and the provision of
628 immunoglobulin-containing egg yolk powder as a feed supplement to reduce enteric
629 infections e.g. in weaner piglets.

630

631 **7. Conclusion**

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

640

641 **Conflict of interest: None.**

642

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.

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Appendix A. Supplementary data

The following are Supplementary data to this article:

Unlabelled electronic file

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Tables

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.

1744 **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

1762 **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)

1763 [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

1783 **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	Tetanus	Equine serum	Parenteral

	Sheep Swine Goats			
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

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1800 **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 *In ovo*	*Salmonella* Enteritidis Infectious bursal disease virus	Chicken Chicken	(Rahimi et al., 2007) (Eterradossi et al., 1997)
Passive transfer [b]	Intraperitoneal Intravenous Subcutaneous n/a Intraperitoneal Subcutaneous Intravenous Intramuscular Subcutaneous	Newcastle disease Avian Influenza Virus, H7N3 Histomonosis (blackhead) Stunting syndrome Avian metapneumovirus Duck enteritis virus *Mycoplasma*	Chicken Chicken Turkey Turkey Turkey Duck Chicken	(Lardinois et al., 2014) (Umino et al., 1987) (Reynolds and Maraqa, 2000) (Shahzad et al., 2008) [c] (Bleyen et al., 2009) (Reynolds et al., 2000) [c] (Rubbenstroth and Rautenschlein, 2009) (Lin et al., 1984) (Lin and

	Intravenous	*gallisepticum* *Ornithobacterium rhinotracheale*	Chicken	Kleven, 1984) (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)

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1802 [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*) Columnaris disease (*Flavobacterium columnare*) *Gyrodactylus derjavini* *Streptococcus ssp.* Rainbow trout fry syndrome (*Flavobacterium psychrophilum*) Viral haemorrhagic septicaemia virus	(Raida and Buchmann, 2008) (Shelby et al., 2007) (Lindenstrom and Buchmann, 2000) (Pasnik et al., 2006, 2011) (LaFrentz et al., 2003) (Corbeil et al., 1999; Hershberger et al., 2011; Kurath et al., 2006; Traxler et al., 1999)

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1822 **Supplementary Table 1**

Effects of SDP[a] meal supplement[d]			
Animal	Disease model	Effect	References
Piglets (6-20 days post weaning)	Experimental induced diarrhoea by *E. coli*	SDP[1] reduced disease in piglets experimentally inoculated with *E. coli* O149K91. Faecal excretion of the *E. coli* was also reduced by SDP originating from *E. coli* O149K91-immunised pigs	(Niewold et al., 2007)
Piglets (7 days post weaning)		Dietary SDP significantly reduced mortality in comparison to the control group but SDP did not provide same level of protection against the *E. coli* inoculate as a group receiving antibiotics.	(Bhandari et al., 2008)
Piglets (7 and 14 days post weaning)	Post weaning diarrhoea (PWD)	Dietary porcine SDP had a positive influence on intestinal barrier function and reduced inflammation and diarrhoea.	(Peace et al., 2011)
Piglets (14 and 28 days post weaning)	The effect of SDP on piglet growth and intestinal morphology	Piglets given SDP had improved ADG [b] for 14 and increased body weight and crypt/villus ratios at day 28 as compared to control piglets.	(Tran et al., 2014)

Piglets	Salmon hydrolysate dietary supplement over SDP	Within the first 7 days, SDP, especially in 1+1 combination with salmon hydrolysate significantly improved ADG [b] and daily feed intake	(Tucker et al., 2011)
Piglets (5 days pre-weaned)	The effect of SDP on stress (weaning and transportation)	SDP provided post-weaned piglets with increased bodyweight and decreased levels of stress markers	(Wittish et al., 2014)
Piglets (28 days post weaning)	The effect of ultraviolet light on SDP	Ultraviolet light inactivated porcine parvovirus in liquid plasma, and SPD derived from ultraviolet radiated plasma improved growth in weaner piglets.	(Polo et al., 2015)
Sows	The effect of SDP on sow productivity: piglet survival to weaning, weaning interval, last lactation day of offspring, number of piglets and weight of litter, and ADG [b] and ADFI [c] of litter.	Dietary SDP had a significant positive effect on productivity in older sows (in parity 4) as compared to younger sows.	(Fruge et al., 2009)

Cattle	The effect of bovine SDP against *E. coli* infection, incl. ADG [b].	SDP resulted in borderline significant decrease in mortality and a significant increase in ADG [b].	(Quigley and Drew, 2000)
Broilers	The effect of SDP on chicken growth	Bovine SDP significantly increased ADG and feed intake for up to 28 days after hatching.	(Campbell et al., 2006)
Chickens (1-28 days old)		Porcine SDP had no effect on body weight after 4 weeks of feeding (in comparison with control group).	(Jamroz et al., 2011)
Chicken (1-30 days old)		Porcine SDP had a significantly positive effect on body weight after 4 weeks of feeding.	(Jamroz et al., 2012)
Isa Brown hens	The effect of SDP on egg composition	The introduction of spray-dried blood by-products did not have any beneficial effects on egg quality, yolk and mineral content.	(Orda et al., 2012)
Wistar-Lewis rats (21 days post weaning)	Experimental induced intestinal inflammation with *Staphylococcus aureus* enterotoxin B.	Dietary SDP (and Ig concentrate) attenuated intestinal inflammation.	(Perez-Bosque et al., 2006; Perez-Bosque et al., 2008, 2010)
Male C57BL/6 mice (19 days old)	Experimental LPS-induced pulmonary	SDP (and Ig concentrate) decreased both the adaptive and	(Maijo et al., 2012a, b)

	inflammation	innate immune response.	
Sparus aurata (Gilthead sea bream) fingerlings	The effect of SDP on fingerling fish growth and intestinal mucosal	SDP improved fish size, weight, and increased density of intestinal goblet cells	(Gisbert et al., 2015)

[a] SDP = Spray-dried plasma

[b] ADG = average daily growth

[c] ADFI = average daily feed intake

[d] Also see (Torrallardona, 2010) for more on the effects in pigs