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Review paper

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

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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.

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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.

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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