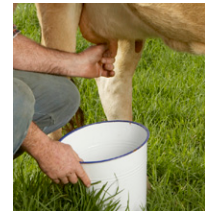


The effects of milk and colostrum on allergy and infection: Mechanisms and implications



R.J.J. van Neerven*†

*FrieslandCampina, Amersfoort, The Netherlands

†Cell Biology and Immunology, Wageningen University, Wageningen, The Netherlands

Implications

- Children that grow up on farms have fewer allergies than children growing up in city environments. This protection against the development of allergy is associated with the consumption of raw farm milk. Heated farm milk does not have this effect, indicating that (non-denatured) milk proteins are responsible for this effect.
- The consumption of normal bovine colostrum protects immunocompromised people against infections.
- *Bovine* milk proteins have immunological effects on *human* cells.
- Currently, raw milk is not commercially available and cannot be used for controlled intervention studies because of the potential presence of pathogenic microorganisms. Alternative milk-processing technologies are needed to preserve immune active milk proteins that can improve immunity in children.

Key words: allergy, immune function, infection, milk, processing

Milk Consumption and Immunity: Effects on Allergy and Infection

The two main functions of milk are to provide tailor-made nutrition as well as protection to the offspring. Infants and calves do not have a fully developed immune system yet, and not surprisingly, many of the milk components are linked to (mucosal) immune function. Like breast milk, the importance of colostrum and milk for protection of calves against infection-related mortality has been recognized for a long time. Calves that do not receive colostrum often develop serious infections, in many cases leading to death (Godden, 2008). Similarly, breast milk consumption by infants has been linked to protection against infection and allergy (Sachdev et al., 1991; Gdalevich et al., 2001; Koch et al., 2003; van Oudijk et al., 2003; Black et al., 2008) although the effect on allergy is still under discussion (Matheson et al., 2012), and may depend on the concentrations of certain components such as transforming growth-factor β (TGF- β) in the breast milk (Oddy and Rosales, 2010).

The composition of bovine and human milk is generally quite comparable, but there are also differences in composition and concentration

of some components. The main difference is in the oligosaccharide composition. Mature human milk contains much higher concentrations and diversity of these oligosaccharides than bovine milk. However, in respect to immunologically active milk proteins, human and bovine milk are quite similar. For example, immunoglobulins, lactoferrin, and TGF- β are all present in human as well as bovine milk, even though their concentrations and amino acid sequences differ (Jensen, 1995; Heck et al., 2009; Hettinga et al., 2011; van Neerven et al., 2012).

Despite these differences, the literature on immunological effects of bovine milk consumption on humans is growing. Multiple epidemiological studies performed in several countries have linked the ingestion of farm milk to the reduced occurrence of allergy in children growing up on farms (Riedler et al., 2001; Perkin and Strachan, 2006; Ege et al., 2007; Waser et al., 2007; von Mutius and Vercelli, 2010; Loss et al., 2011; Sozanska et al., 2013). These studies have been corrected for a series of potentially confounding factors that are linked to a farming environment. Interestingly, the effect of unpasteurized milk on allergy development appears to be larger in towns than in villages (Sozanska et al., 2013), which may be explained by the fact that additional farming-related environmental factors that also contribute to fewer allergy incidences are absent in town environments.

As many, but not all, of the children growing up on farms consume raw milk, Loss et al. (2011) studied the effect of heating farm milk on the prevalence of allergies and demonstrated that the effect on asthma was only seen in children that consumed unheated farm milk and not in children consuming heated farm milk. In addition, the amount of non-denatured proteins in the milk as measured by ELISA was negatively correlated in a dose-dependent fashion with the effect on asthma prevalence, indicating an important role for intact milk proteins.

Although it has been suggested that the effect of raw milk on the development of allergies may be explained by the absence of homogenization (Miller, 2013), children consuming heated farm milk, that is not homogenized on the farm, have a relative risk to develop allergies similar to those consuming ultra-high temperature pasteurized (UHT) milk (Loss et al., 2011). Therefore, homogenization is not critically relevant for the effects observed with raw milk consumption.

Furthermore, as these studies compared the consumption of UHT milk with raw milk consumption, one can hypothesize that consumption of processed milk can be associated with an increased frequency of allergies, rather than raw milk conferring protection against development of allergies. Several recent research works have studied whether early introduction of normal dietary ingredients is linked to the development of allergies (Wijga et al., 2003; Rodriguez-Rodriguez et al., 2010; Suarez-Varela et al., 2010;

Willers et al., 2011). None of these studies reported increases in allergic diseases in relation to regular shop milk (UHT/pasteurized) consumption, and the study by Wijga et al. (2003) even showed an association between milk fat and a reduced risk to develop asthma. These studies indicate that the effect of raw farm milk as compared with UHT milk is a protective effect, rather than a reversal of an allergy-inducing effect of heated milk.

Interestingly, similar effects of heating human breast milk on immune function have also been described. Breast milk is collected by donor milk banks to feed premature infants that cannot receive breastmilk from their mothers. This milk is pasteurized to prevent the transmission of infectious diseases. Infants receiving heat-treated breast milk develop more often enteric infections than infants fed untreated donor milk (Narayanan et al., 1984). Pasteurization of breast milk has also been reported to increase the relative risk of developing sepsis in preterm infants (Cossey et al., 2013). Pasteurization of breast milk reduces the content of immune active components (Ford et al., 1977), as well as its antimicrobial activity (van Gysel et al., 2012).

Although many studies have documented that bacterial contaminants in raw milk can cause diarrhea (reviewed in Claeys et al., 2013; Baars, 2013), limited information is available on the effects of (raw) milk consumption on *prevention* of infections. Most studies on a possible preventive effect of milk on infection have focused on colostrum and purified milk proteins. In these studies, the isolation process is combined with mild heat treatments to preserve the functionality of the studied proteins. Bovine milk and colostrum contain immunoglobulins that are specific for a wide range of potentially pathogenic microorganisms, viruses (Yolken et al., 1985; Stephan et al., 1990; Rump et al., 1992; Lissner et al., 1996, 1998; Kelly, 2003), and even aeroallergens (Collins et al., 1991). Colostrum is a much richer source of bovine immunoglobulins (mainly IgG1) than milk. Raw cow milk contains around 200 to 300 µg/mL IgG1 whereas bovine colostrum contains extremely high levels of immunoglobulins, up to 50 to 100 mg/mL.

The pathogens that cows are exposed to, especially bacterial pathogens, resemble the bacteria humans are exposed to, and cows are also susceptible to the bovine version of several viruses that are pathogenic to humans. As a result, it can be expected that bovine immunoglobulins would react with human pathogens and thus would also offer protection to humans, especially in immunocompromised patients, infants, and elderly people, all of those having a less efficient immune system.

Many studies have been performed with colostrum of cows that have been vaccinated with human pathogens, such as rotavirus and showed that hyperimmune colostrum can protect against rotavirus infections (Hilpert et al., 1987; Mita et al., 1995; Sarker et al., 1998). Even if these studies show that orally delivered bovine IgG can protect against infections in humans, they are out of scope in this paper and will not be discussed in further details. All colostrum studies mentioned below are studies that were performed with normal colostrum obtained from non-immunized cows.

Patients with HIV are severely immunocompromised as a result of the depletion of CD4+ T cells, they are not able to resist infections and are



highly susceptible to diarrhea, especially induced by *Cryptosporidium*, *Amoebae*, and *Campylobacter*. For this reason, several studies have evaluated the effect of normal colostrum for the treatment of HIV-associated diarrhea (Rump et al., 1992; Plettenberg et al., 1993; Shield et al., 1993; Floren et al., 2006). Supplementation with colostrum led to a greater than threefold decrease in stool frequencies. Nevertheless, because HIV patients are currently managed much better by new combination therapies, the need for colostrum preparations for these patients is greatly reduced in Western countries. These studies do, however, clearly demonstrate that the administration of passive immunity in the form of bovine immunoglobulins can protect against a range of pathogens and are especially effective in immunocompromised individuals. Infants in developing countries where HIV infections are not treated efficiently (Africa and Asia) may therefore benefit from this approach.

Knowledge on the effects of bovine colostrum for treatment and prevention of infections in healthy adults and children is more limited. In a single published placebo-controlled study, children affected by diarrhea caused by shiga toxin-producing *E.coli* were treated with an immunoglobulin preparation extracted from normal colostrum and containing more than 65% immunoglobulin (Huppertz et al., 1999). This study showed that the colostrum treatment significantly reduced stool frequency, but no effects were observed on pathogen numbers or complications of infection.

Uchida et al. (2010) demonstrated that ingestion of late colostrum (6 to 7 days postpartum) significantly reduces the mean frequency of upper airway infections and days of illness with fever in 3- to 6-year-old children compared with the placebo group. Likewise, a reduced severity of viral upper respiratory tract infections was reported in children with IgA deficiency receiving a colostrum supplement (Patiroglu and Kondolot, 2013). Patel and Rana (2006) also reported significant decreases in self-reported diarrhea and upper respiratory tract infection episodes in Indian children receiving an oral colostrum preparation for 12 weeks. The study was, however, open and uncontrolled, and the comparison before and after therapy may also be biased by seasonal variations. Two studies reported significantly reduced symptoms of upper respiratory tract infection after colostrum consumption (Brinkworth and Buckley, 2003; Jones et al., 2014), and nonsignificant trends towards reduced upper respiratory

Table 1. Human studies with milk and colostrum: Effects on allergy and infection.

Milk Type	Functional effect	Type of study	Key references
Milk	Consumption of farm milk associated with fewer allergies	Multiple independent epidemiological studies	Ege et al., 2007; Riedler et al., 2001; Loss et al., 2011; Waser et al., 2007; von Mutius and Vercelli, 2010; Perkin and Strachan, 2006; Sozanska et al., 2013
	Consumption of whole milk associated with fewer diarrhea episodes in children as compared to children consuming low fat milk	Epidemiological study	Koopman et al., 1984
Normal colostrum	Bovine late colostrum reduced the mean frequency of upper respiratory tract infections, and decrease the duration of sick days with fever	Double blind, randomized, placebo controlled study (n=195)	Uchida et al., 2010
	Supplements of bovine colostrum to children with recurrent episodes of upper respiratory tract infections or diarrhea decreased the number of episodes of upper respiratory tract infections and diarrhea	Open, uncontrolled study (n=605)	Patel and Rana, 2006
	Bovine colostrum supplementation lowered the infection severity score in IgA-deficient children with viral upper airway infections	Double blind, randomized, placebo controlled study (n=31)	Patiroglu and Kondolot, 2013
	Colostrum supplementation in HIV-associated diarrhea resulted in a decrease in stool evacuations per day	Open-label, non-randomized study (n=30)	Floren et al., 2006
	Colostrum supplementation for 7 days during oral salmonella vaccination was associated with a non-significant trend towards greater increase in specific IgA, but not IgG or IgM	Randomized, placebo controlled vaccination study (n=18)	He et al., 2001
	Oral colostrum supplementation for 6 weeks had no effect on oral vaccination response (typhoid) and subcutaneous vaccination (Tetanus)	Double blind, randomized, placebo-controlled study (n=138)	Wolvers et al., 2006
	Bovine colostrum supplementation for 8 weeks decreased upper respiratory tract infections (self reported)	Retrospective analysis of double-blind, placebo controlled study (n=174);	Brinkworth and Buckley, 2003
	Colostrum supplementation decreased upper respiratory sickdays and episodes in athletes compared to the placebo group	Double blind, randomized, placebo controlled study (n=53)	Jones et al., 2013
	Bovine colostrum for 8 weeks resulted in fewer influenza episodes compared to the control group	Controlled study (n=144)	Cesarone et al., 2007
	Increased levels of salivary sIgA levels in athletes	Open, uncontrolled studies (n=35 and n=30 respectively)	Crooks et al., 2006; Mero et al., 2002

tract infections in highly trained cyclists and swimmers were observed in two other studies (Shing et al., 2007; Crooks et al., 2010). In addition to decreased upper airway infections, concentration of sIgA in saliva of athletes was enhanced after taking colostrum supplements (Mero et al., 2002; Crooks et al., 2006).

Likewise, Cesarone et al. (2007) reported that colostrum may be more effective in influenza prophylaxis in elderly people than vaccination. Colostrum consumption in an oral *Salmonella* vaccination study showed a nonsignificant trend towards increased *Salmonella*-specific IgA levels (He et al., 2001). A similar immune-enhancing effect of bovine colostrum on oral typhoid and systemic tetanus vaccination could not be demonstrated in another well-controlled study (Wolvers et al., 2006).

These findings, although not supported by many well-controlled trials, suggest, nevertheless, that colostrum may enhance mucosal immunity and play a role in preventing upper respiratory tract infections.

Effects of Milk Components on Immune Function

Bovine as well as human milks contain many components that can have an effect on immune function, such as pathogen- and allergen-specific

immunoglobulins, antimicrobial proteins, oligosaccharides, and growth factors like TGF- β and interleukin 10 (IL-10).

These effects have been reviewed recently by van Neerven et al. (2012) and Verhasselt (2010). The functional effects of bovine milk, colostrum, and their components on immune function and infection are summarized in Tables 1 and 2. Three of these components, bovine immunoglobulins (IgG), lactoferrin, and TGF- β , have been directly linked to the functional effects on immunity and have also been tested as bioactive ingredients in human studies.

Immunoglobulins

Bovine IgG from non-immunized cows can bind to a wide range of pathogenic bacteria, viruses, and inhalation allergens. Importantly, recent experiments showed that bovine IgG can bind to human Fc γ receptors (Fc γ R), which suggests that they may be able to enhance antigen presentation to T cells, as well as phagocytosis and killing by phagocytes (Kramski et al., 2012). In relation to allergy, maternal transfer of IgG-allergen immune complexes in breast milk prevents subsequent sensitization in the offspring (Mosconi et al., 2010), which may contribute to the protective effect of raw milk on asthma (van Neerven et al., 2012). These data suggest that oral ingestion of immunoglobulins modulates immune function in the airways, which is supported by recent findings reporting that oral ingestion of serum-

Table 2. Human studies with milk and colostrum: Effects on allergy and infection.

Milk component	Functional effect	Type of study	Subjects	Key references
Immunoglobulin G (IgG)	IgG preparation from normal colostrum (65% IgG) reduces diarrhea in HIV patients with recurrent diarrhea	Multi-center uncontrolled pilot study (Rump); Case study (Shield); Prospective, open, uncontrolled study (Plettenberg)	HIV patients with recurrent diarrhea (n=37, Rump; n=1 Shield; n=25 Plettenberg)	Rump et al., 1992; Shield et al., 1993; Plettenberg et al., 1993
	IgG preparation from normal colostrum (65% IgG): lowered frequency of loose stools and decreased median stool frequency in children with E.coli positive diarrhea.	Placebo controlled exploratory study	Children (0-18 yr) with diarrhea caused by infection with <i>Escherichia coli</i> (n=27)	Huppertz et al., 1999
	Children with rotavirus diarrhea receiving IgG isolated from hyperimmune colostrum had decreased stool output and stool frequency, required a smaller amount of oral rehydration solution, and cleared rotavirus quicker than children in the placebo group.	Randomized, double blind, placebo-controlled trial	4-24 month old children with rotavirus diarrhea (n=80)	Sarker et al., 1998
	Infants receiving hyperimmune bovine Ig concentrate with high titer antibodies to E.coli enriched formula had a lower incidence and a shorter duration of diarrhea compared to children in the control group.	Randomized, double-blind, controlled field trial	Healthy 3-6 month old infants (n=107)	Tawfeek et al., 2003
Lactoferrine (LF)	Compared with placebo, bovine LF supplementation alone or in combination with lactoglobulin reduced the incidence of a first episode of late-onset sepsis in very low birth weight neonates.	Prospective, multicenter, double-blind, placebo controlled, randomized trial	Very low birthweight infants (n=472)	Manzoni et al., 2009; Manzoni et al., 2012
	Decreased frequency and duration of vomiting and diarrhea in rotaviral gastroenteritis. No effect on incidence.	Placebo controlled, non-randomized study	0-4 year old children (n=234)	Egashira et al., 2007
	Infants receiving lactoferrin-supplemented formula had a lower incidence of lower respiratory tract infections compared to children receiving control formula.	Randomized, placebo-controlled, double-blind study	0-4 week old children (n=52)	King et al., 2007
	Impact of lactoferrin supplementation on growth and prevalence of <i>Giardia</i> colonization in children. No effect on diarrhea.	Randomized, double-blind, placebo-controlled trial	1-3 year old children (n=320)	Ochoa et al., 2008
Transforming growth factor- β (TGF-beta)	Induction of clinical remission and improved quality of life after 8 weeks of enteral nutrition containing TGF-beta.	Prospective cohort study	8-17 year old children with Crohn's disease (n=26)	Afzal et al., 2004
	TGF-beta rich formulas induced clinical remission associated with mucosal healing in Crohn's disease patients	Open, uncontrolled study	Children with Crohn's disease (n=29)	Fell et al., 2000

derived immunoglobulin prevents inflammatory tissue damage in acute lung inflammation in mice (Maijo et al., 2012a,b).

In addition to the studies discussed above and those performed with colostrum, several nutritional studies on the effect of bovine IgG on infections have been performed (Rump et al., 1992; Plettenberg et al., 1993; Shield et al., 1993; Sarker et al., 1998; Huppertz et al., 1999). These studies used isolated IgG preparations or preparations strongly enriched in bovine IgG. Preparations of IgG isolated from normal colostrum and containing more than 65% IgG strongly reduced the severity and occurrence of HIV-associated diarrhea in several studies (Rump et al., 1992; Shield et al., 1993; Plettenberg et al., 1993). Huppertz et al. (1999) reported that the IgG preparation reduced the frequency of loose stools and the median stool frequency in patients hospitalized with diarrhea caused by diarrheagenic *E. coli*.

Transforming growth factor- β

Transforming growth factor- β is an anti-inflammatory cytokine that modulates immune function and is also involved in the regulation of epithelial differentiation and barrier function in the intestine. Milk contains relatively high levels of TGF- β 2 and TGF- β 1. The functional effects of milk-derived TGF- β has been studied in many immunological animal models reviewed by Oddy and McMahon (2011), showing that TGF- β

promotes mucosal immune development and reduces allergic disease as well as intestinal inflammation. Concentration of TGF- β in breast milk is inversely correlated with the development of allergies (Oddy and Rosales, 2010), and the presence of TGF- β in murine milk is required for the induction of oral tolerance to allergens, which will protect against the development of allergies later in life (Verhasselt et al., 2008).

The high level of cross-species conservation of TGF- β 1 and TGF- β 2 sequences suggests that bovine milk TGF- β can be functionally active in humans. Studies on the effects of TGF- β containing formulas on inflammatory bowel disease demonstrated that TGF- β supplemented formulas may induce clinical remission associated with mucosal healing (Fell et al., 2000; Afzal et al., 2004).

Lactoferrin

Lactoferrin is an iron-scavenging antimicrobial protein that inhibits the growth of iron-dependent pathogens (Ochoa and Cleary, 2009) and also displays antiviral activity in *in vitro* assays (Grover et al., 1997). In addition to this antimicrobial function, lactoferrin can also have immunomodulatory activities (Lonnerdal, 2009).

Lactoferrin downregulates toll-like receptor signaling in monocytes and dendritic cells, preventing their activation (Haversen et al., 2002; Puddu et al., 2011). Lactoferrin also induces transcription of the anti-inflammatory cytokine TGF- β 1 in the intestinal epithelial cell line Caco-



Thinkstock/Jupiterimages

2 (Lonnerdal et al., 2011). As TGF- β is an important factor that regulates epithelial cell differentiation and barrier function, lactoferrin supplementation may also positively affect barrier function in the intestine.

Bovine milk-derived lactoferrin has been developed as food supplement, and human studies have been performed to study its effect on enterocolitis in preterm infants, diarrhea, and airway infection (Ochoa et al., 2012). In two studies by Manzonei et al. (2009, 2012), lactoferrin supplementation was shown to reduce the incidence of sepsis in very low birth weight infants. In a study by King et al. (2007), lactoferrin supplementation did not have a significant effect on diarrhea but significantly reduced the occurrence of lower respiratory tract infections. A daily supplement of 100 mg bovine lactoferrin for three months did not reduce rotavirus incidence but diminished the frequency and duration of vomiting and diarrhea episodes (Egashira et al., 2007). However, no effect on diarrhea was noted in a study by Ochoa et al. (2008), but lactoferrin supplementation significantly improved the growth of children and decreased the prevalence of *Giardia* colonization (Ochoa et al., 2008).

Impact on Future Research

As discussed above, all these studies with raw milk, colostrum, and isolated milk proteins indicate that preserving not only their nutritional value, but also the immune functionality of milk proteins, may be important for human health.

Even if findings from farm milk studies are based on several epidemiological studies performed in several countries, and that the contribution of many confounding factors has been excluded, placebo-controlled studies on raw milk are needed to confirm the effects on allergy development. This is currently not possible because regulatory guidelines and legislation prescribe heat treatment of milk and milk products for human consumption and absence of detectable levels of alkaline phosphatase is used as a measure of microbiological safety. These guidelines and legislation are based on the observation that raw milk can contain diarrhea-causing pathogens like *Salmonella*, *Listeria*, *Mycobacterium bovis*, *Campylobacter*, and other pathogens reviewed by Claeys et al. (2013) and Baars (2013). Consequently, raw milk is not recognized as safe enough to perform these studies.

To guarantee food safety and consumer convenience, milk has to be processed before it is sold. In the past, processing was done primarily to

ensure milk safety to protect consumers. To this aim, milk must be heated to reduce the number of pathogens in the milk. For convenience, milk can also be sterilized or even dried; the shelf life of sterilized milk can be more than one year at ambient temperatures. Therefore, current milk-processing technology heavily relies on heat treatments that denature these functional proteins. While these technologies do not alter the nutritional value of milk, heat processing clearly has an impact on the bioactivity of milk proteins. Therefore, this calls for the use of novel technologies to produce microbiologically safe milk products, in which milk proteins will not be inactivated by heat treatment. Microbiological safety of milk products should be a leading factor in this, not the mere height of the temperature to which the milk has been exposed.

Mild heat treatment (eg., low-temperature pasteurization), can be done, but results in a much shorter shelf life of around 5 days. New, so-called mild technologies, are becoming available. These techniques, like bactifugation (centrifuging out the microbes and spores), or membrane filtration (filtering off the spores and microbes), are technologies currently used for specialty products and do not result in inactivation or denaturation of bioactive proteins. It is to be foreseen that these technologies, even though they are more expensive, will become more and more important for the production of safe dairy products containing functionally active milk proteins that can contribute to improved immune function.

Acknowledgements

I like to thank A. van der Padt and L. Ulfman for helpful discussions and reviewing the manuscript.

Literature Cited

- Afzal, N.A., H.J. Van Der Zaag-Loonen, F. Arnaud-Battandier, S. Davies, S. Murch, B. Derkx, R. Heuschkel, and J.M. Fell. 2004. Improvement in quality of life of children with acute Crohn's disease does not parallel mucosal healing after treatment with exclusive enteral nutrition. *Aliment. Pharmacol. Ther.* 20:167–172.
- Baars, T. 2013. Milk consumption, raw and general, in the discussion on health or hazard. *J. Nutr. Ecol. Food Res.* 1:91–107.
- Black, R.E., L.H. Allen, Z. Bhutta, L.E. Caulfield, M. de Onis, M. Ezzati, C. Mathers, and J. Rivera. 2008. Maternal and child undernutrition: Global and regional exposures and health consequences. *Lancet* 371:243–260.

- Brinkworth, G.D., and J.D. Buckley. 2003. Concentrated bovine colostrum protein supplementation reduces the incidence of self-reported symptoms of upper respiratory tract infection in adult males. *Eur. J. Nutr.* 42:228–232.
- Cesarone, M.R., G. Belcaro, R.A. Di, M. Dugall, M. Cacchio, I. Ruffini, L. Pellegrini, B.G. Del, F. Fano, A. Ledda, A. Bottari, A. Ricci, S. Stuard, and G. Vinciguerra. 2007. Prevention of influenza episodes with colostrum compared with vaccination in healthy and high-risk cardiovascular subjects: The epidemiologic study in San Valentino. *Clin. Appl. Thromb. Hemost.* 13:130–136.
- Claeys, W.L., S. Cardoen, G.H. Daube, J. De Block, K. Dewettinck, K. Dierick, L. De Zutter, A. Huyghebaert, H. Imberechts, P. Thiange, Y. Vandenplas, and L. Herman. 2013. Raw or heated cow milk consumption: Review of risks and benefits. *Food Contr.* 31:251–262.
- Collins, A.M., D.M. Robertson, C.S. Hosking, and G.R. Flannery. 1991. Bovine milk, including pasteurised milk, contains antibodies directed against allergens of clinical importance to man. *Int. Arch. Allergy Appl. Immunol.* 96:362–367.
- Cossey, V., C. Vanhole, A. Eerdeken, M. Rayyan, S. Fieus, and A. Schuermans. 2013. Pasteurization of mother's own milk for preterm infants does not reduce the incidence of late-onset sepsis. *Neonatology* 103:170–176.
- Crooks, C., M.L. Cross, C. Wall, and A. Ali. 2010. Effect of bovine colostrum supplementation on respiratory tract mucosal defenses in swimmers. *Int. J. Sport Nutr. Exerc. Metab.* 20:224–235.
- Crooks, C.V., C.R. Wall, M.L. Cross, and K.J. Rutherford-Markwick. 2006. The effect of bovine colostrum supplementation on salivary IgA in distance runners. *Int. J. Sport Nutr. Exerc. Metab.* 16:47–64.
- Egashira, M., T. Takayanagi, M. Moriuchi, and H. Moriuchi. 2007. Does daily intake of bovine lactoferrin-containing products ameliorate rotaviral gastroenteritis? *Acta Paediatr.* 96:1242–1244.
- Ege, M.J., R. Frei, C. Bieli, D. Schram-Bijkerk, M. Waser, M.R. Benz, G. Weiss, F. Nyberg, M. Van Hage, G. Pershagen, B. Brunekreef, J. Riedler, R. Lauener, C. Braun-Fahrlander, and E. Von Mutius. 2007. Not all farming environments protect against the development of asthma and wheeze in children. *J. Allergy Clin. Immunol.* 119:1140–1147.
- Fell, J.M., M. Paintin, F. Arnaud-Battandier, R.M. Beattie, A. Hollis, P. Kitching, A. Donnet-Hughes, T.T. MacDonald, and J.A. Walker-Smith. 2000. Mucosal healing and a fall in mucosal pro-inflammatory cytokine mRNA induced by a specific oral polymeric diet in paediatric Crohn's disease. *Aliment. Pharmacol. Ther.* 14:281–289.
- Floren, C.H., S. Chinenye, L. Elfstrand, C. Hagman, and I. Ihse. 2006. ColoPlus, a new product based on bovine colostrum, alleviates HIV-associated diarrhoea. *Scand. J. Gastroenterol.* 41:682–686.
- Ford, J.E., B.A. Law, V.M. Marshall, and B. Reiter. 1977. Influence of the heat treatment of human milk on some of its protective constituents. *J. Pediatr.* 90:29–35.
- Gdalevich, M., D. Mimouni, and M. Mimouni. 2001. Breast-feeding and the risk of bronchial asthma in childhood: A systematic review with meta-analysis of prospective studies. *J. Pediatr.* 139:261–266.
- Godsen, S. 2008. Colostrum management for dairy calves. *Vet. Clin. North Am. Food Anim. Pract.* 24:19–39.
- Grover, M., O. Giouzeppos, R.D. Schnagl, and J.T. May. 1997. Effect of human milk prostaglandins and lactoferrin on respiratory syncytial virus and rotavirus. *Acta Paediatr.* 86:315–316.
- Haversen, L., B.G. Ohlsson, M. Hahn-Zoric, L.A. Hanson, and I. Mattsby-Baltzer. 2002. Lactoferrin down-regulates the LPS-induced cytokine production in monocyte cells via NF-kappa B. *Cell. Immunol.* 220:83–95.
- He, F., E. Tuomola, H. Arvilommi, and S. Salminen. 2001. Modulation of human humoral immune response through orally administered bovine colostrum. *FEMS Immunol. Med. Microbiol.* 31:93–96.
- Heck, J.M.L., H.J.F. van valenberg, J. Dijkstra, and A.C.M. van Hooijdonk. 2009. Seasonal variation in the Dutch bovine raw milk composition. *J. Dairy Sci.* 92:4745–4755.
- Hettinga, K., H. van Valenberg, S. de Vries, S. Boeren, T. van Hooijdonk, J. van Arendonk, and J. Vervoort. 2011. The host defense proteome of human and bovine milk. *PLoS ONE* 6:e19433. doi: 10.1371.
- Hilpert, H., H. Brussow, C. Mietens, J. Sidoti, L. Lerner, and H. Werschau. 1987. Use of bovine milk concentrate containing antibody to rotavirus to treat rotavirus gastroenteritis in infants. *J. Infect. Dis.* 156:158–166.
- Huppertz, H.I., S. Rutkowski, D.H. Busch, R. Eisebit, R. Lissner, and H. Karch. 1999. Bovine colostrum ameliorates diarrhea in infection with diarrheagenic *Escherichia coli*, Shiga toxin-producing *E. coli*, and *E. coli* expressing intimin and hemolysin. *J. Pediatr. Gastroenterol. Nutr.* 29:452–456.
- Jensen, R.G. 1995. Handbook of milk composition. Academic press, San Diego CA.
- Jones A.W., S.J. Cameron, R. Thatcher, M.S. Beecroft, L.A. Mur, and G. Davison. 2014. Effects of bovine colostrum supplementation on upper respiratory illness in active males. *Brain, Behav., Immun.* (in press). doi:10.1016/j.bbi.2013.10.032.
- Kelly, G.S. 2003. Bovine colostrums: A review of clinical uses. *Altern. Med. Rev.* 8:378–394.
- King, J.C., Jr., G.E. Cummings, N. Guo, L. Trivedi, B.X. Readmond, V. Keane, S. Feigelman, and R. de Waard. 2007. A double-blind, placebo-controlled, pilot study of bovine lactoferrin supplementation in bottle-fed infants. *J. Pediatr. Gastroenterol. Nutr.* 44:245–251.
- Koch, A., K. Mølbak, P. Homøe, P. Sørensen, T. Hjuler, M.E. Olesen, J. Pejil, F.K. Pedersen, O.R. Olsen, and M. Melbye. 2003. Risk factors for acute respiratory tract infections in young Greenlandic children. *Am. J. Epidemiol.* 158:374–384.
- Koopman, J.S., V.J. Turkisk, A.S. Monto, F.E. Thompson, and R.E. Isaacson. 1984. Milk fat and gastrointestinal illness. *Am. J. Public Health* 74:1371–1373.
- Kramski, M., G.F. Lichtfuss, M. Navis, G. Isitman, L. Wren, G. Rawlin, R.J. Center, A. Jaworowski, S.J. Kent, and D.F.J. Purcell. 2012. Anti-HIV-1 antibody-dependent cellular cytotoxicity mediated by hyperimmune bovine colostrum IgG. *Eur. J. Immunol.* 42:2771–2781.
- Lissner, R., H. Schmitz, and H. Karch. 1996. A standard immunoglobulin preparation produced from bovine colostrum shows antibody reactivity and neutralization activity against Shiga-like toxins and EHEC-hemolysin of *Escherichia coli* O157:H7. *Infection* 24:378–383.
- Lissner, R., P.A. Thurmann, G. Merz, and H. Karch. 1998. Antibody reactivity and fecal recovery of bovine immunoglobulins following oral administration of a colostrum concentrate from cows (Lactobin) to healthy volunteers. *Int. J. Clin. Pharmacol. Ther.* 36:239–245.
- Lonnerdal, B. 2009. Nutritional roles of lactoferrin. *Curr. Opin. Clin. Nutr. Metab. Care* 12:293–297.
- Lonnerdal, B., R. Jiang, and X. Du. 2011. Bovine lactoferrin can be taken up by the human intestinal lactoferrin receptor and exert bioactivities. *J. Pediatr. Gastroenterol. Nutr.* 53:606–614.
- Loss, G., S. Apprich, M. Waser, W. Kneifel, J. Genuneit, G. Büchele, J. Weber, B. Sozanska, H. Danielewicz, E. Horak, R.J.J. Van Neerven, D. Heederik, P. C. Lorenzen, E. Von Mutius, and C. Braun-Fahrlander. 2011. The protective effect of farm milk consumption on childhood asthma and atopy: The GABRIELA study. *J. Allergy Clin. Immunol.* 128:766–773.
- Maijo, M., L. Miro, J. Polo, J. Campbell, L. Russell, J. Crenshaw, E. Weaver, M. Moreto, and A. Perez-Bosque. 2012a. Dietary plasma proteins modulate the adaptive immune response in mice with acute lung inflammation. *J. Nutr.* 142:264–270.
- Maijo, M., L. Miro, J. Polo, J. Campbell, L. Russell, J. Crenshaw, E. Weaver, M. Moreto, and A. Perez-Bosque. 2012b. Dietary plasma proteins attenuate the innate immunity response in a mouse model of acute lung injury. *Br. J. Nutr.* 107:867–875.
- Manzoni, P., M. Rinaldi, S. Cattani, L. Pagni, M.G. Romeo, H. Messner, I. Stolfi, L. Decembrino, N. Laforgia, F. Vagnarelli, L. Memo, L. Bordignon, O.S. Saia, M. Maule, E. Gallo, M. Mostert, C. Magnani, M. Quercia, L. Bollani, R. Pedicino, L. Renzullo, P. Betta, F. Mosca, F. Ferrari, R. Magaldi, M. Stronati, and D. Farina. 2009. Bovine lactoferrin supplementation for prevention of late-onset sepsis in very low-birth-weight neonates: A randomized trial. *JAMA* 302:1421–1428.
- Manzoni, P., I. Stolfi, H. Messner, S. Cattani, N. Laforgia, M.G. Romeo, L. Bollani, M. Rinaldi, E. Gallo, M. Quercia, M. Maule, M. Mostert, L. Decembrino, R. Magaldi, F. Mosca, F. Vagnarelli, L. Memo, P.M. Betta, M. Stronati, and D. Farina. 2012. Bovine lactoferrin prevents invasive fungal infections in very low birth weight infants: A randomized controlled trial. *Pediatrics* 129:116–123.
- Matheson, M.C., K.J. Allen, and M.L. Tang. 2012. Understanding the evidence for and against the role of breastfeeding in allergy prevention. *Clin. Exp. Allergy* 42:827–851.
- Mero, A., J. Kahkonen, T. Nykanen, T. Parviainen, I. Jokinen, T. Takala, T. Nikula, S. Rasi, and J. Leppaluoto. 2002. IGF-I, IgA, and IgG responses to bovine colostrum supplementation during training. *J. Appl. Physiol.* 93:732–739.
- Miller, J.D. 2013. Absence of homogenization might explain the benefits of raw cow's milk. *J. Allergy Clin. Immunol.* 131:927.
- Mita, A.K., D. Mahalanabis, H. Ashraf, L. Unicomb, R. Eeckels, and S. Tzipori. 1995. Hyperimmune cow colostrum reduces diarrhoea due to rotavirus: A double-blind, controlled clinical trial. *Acta Paediatr.* 84:996–1001.
- Mosconi, E., A. Rekima, B. Seitz-Polski, A. Kanda, S. Fleury, E. Tissandier, R. Monteiro, D.D. Dombrowicz, V. Julia, N. Glaichenhaus, and V. Verhasselt.

2010. Breast milk immune complexes are potent inducers of oral tolerance in neonates and prevent asthma development. *Mucosal Immunol.* 3:461–474.
- Narayanan, I., K. Prakash, N.S. Murthy, and V.V. Gujral. 1984. Randomised controlled trial of effect of raw and holder pasteurised human milk and of formula supplements on incidence of neonatal infection. *Lancet* 2:1111–1113.
- Ochoa, T.J., E. Chea-Woo, M. Campos, I. Pecho, A. Prada, R. J. McMahon, and T. G. Cleary. 2008. Impact of lactoferrin supplementation on growth and prevalence of *Giardia* colonization in children. 46:1881–1883.
- Ochoa, T.J., and T.G. Cleary. 2009. Effect of lactoferrin on enteric pathogens. *Biochimie* 91:30–34.
- Ochoa, T.J., A. Pezo, K. Cruz, E. Chea-Woo, and T.G. Cleary. 2012. Clinical studies of lactoferrin in children. *Biochem. Cell Biol.* 90:457–467.
- Oddy, W.H., and R.J. McMahon. 2011. Milk-derived or recombinant transforming growth factor-beta has effects on immunological outcomes: A review of evidence from animal experimental studies. *Clin. Exp. Allergy* 41:783–793.
- Oddy, W.H., and F. Rosales. 2010. A systematic review of the importance of milk TGF- β on immunological outcomes in the infant and young child. *Pediatr. Allergy Immunol.* 21:47–59.
- Patel, K., and R. Rana. 2006. Pedimune in recurrent respiratory infection and diarrhoea—the Indian experience—the pride study. *Indian J. Pediatr.* 73:585–591.
- Patioglu, T., and M. Kondolot. 2013. The effect of bovine colostrum on viral upper respiratory tract infections in children with immunoglobulin A deficiency. *Clin. Respir. J.* 7:21–26.
- Perkin, M.R., and D.P. Strachan. 2006. Which aspects of the farming lifestyle explain the inverse association with childhood allergy? *J. Allergy Clin. Immunol.* 117:1374–1381.
- Plettenberg, A., A. Stoehr, H.J. Stellbrink, H. Albrecht, and W. Meigel. 1993. A preparation from bovine colostrum in the treatment of HIV-positive patients with chronic diarrhea. *Clin. Investig.* 71:42–45.
- Puddu, P., D. Latorre, M. Carollo, A. Catizone, G. Ricci, P. Valenti, and S. Gessani. 2011. Bovine lactoferrin counteracts Toll-like receptor mediated activation signals in antigen presenting cells. *PLoS ONE* 6:e22504.
- Riedler, J., C. Braun-Fahrlander, W. Eder, M. Schreuer, M. Waser, S. Maisch, D. Carr, R. Schierl, D. Nowak, and E. Von Mutius. 2001. Exposure to farming in early life and development of asthma and allergy: A cross-sectional survey. *Lancet* 358:1129–1133.
- Rodriguez-Rodriguez, E., J.M. Perea, A.I. Jimenez, P. Rodriguez-Rodriguez, A.M. Lopez-Sobaler, and R.M. Ortega. 2010. Fat intake and asthma in Spanish schoolchildren. *Eur. J. Clin. Nutr.* 64:1065–1071.
- Rump, J.A., R. Arndt, A. Arnold, C. Bendick, H. Dichtelmuller, M. Franke, E.B. Helm, H. Jager, B. Kampmann, P. Kolb, W. Kreuz, R. Lissner, W. Meigel, P. Ostendorf, H.H. Peter, A. Plettenberg, I. Schedel, H.W. Stellbrink, and W. Stephan. 1992. Treatment of diarrhoea in human immunodeficiency virus-infected patients with immunoglobulins from bovine colostrum. *Clin. Investig.* 70:588–594.
- Sachdev, H.P., S. Kumar, K.K. Singh, and R.K. Puri. 1991. Does breastfeeding influence mortality in children hospitalized with diarrhoea? *J. Trop. Pediatr.* 37:275–279.
- Sarker, S.A., T.H. Casswall, D. Mahalanabis, N.H. Alam, M.J. Albert, H. Brusow, G.J. Fuchs, and L. Hammerstrom. 1998. Successful treatment of rotavirus diarrhea in children with immunoglobulin from immunized bovine colostrum. *Pediatr. Infect. Dis. J.* 17:1149–1154.
- Shield, J., C. Melville, V. Novelli, G. Anderson, I. Scheimberg, D. Gibb, and P. Milla. 1993. Bovine colostrum immunoglobulin concentrate for cryptosporidiosis in AIDS. *Arch. Dis. Child.* 69:451–453.
- Shing, C.M., J. Peake, K. Suzuki, M. Okutsu, R. Pereira, L. Stevenson, D.G. Jenkins, and J.S. Coombes. 2007. Effects of bovine colostrum supplementation on immune variables in highly trained cyclists. *J. Appl. Physiol.* 102:1113–1122.
- Sozanska, B., N. Pearce, K. Dudek, and P. Cullinan. 2013. Consumption of unpasteurized milk and its effects on atopy and asthma in children and adult inhabitants in rural Poland. *Allergy* 68:644–650.
- Stephan, W., H. Dichtelmuller, and R. Lissner. 1990. Antibodies from colostrum in oral immunotherapy. *J. Clin. Chem. Clin. Biochem.* 28:19–23.
- Suarez-Varela, M.M., L.G. Alvarez, M.D. Kogan, J.C. Ferreira, G.A. Martinez, O.I. Aguinaga, D.C. Gonzalez, P.A. Arnedo, A.B. Dominguez, R.M. Busquets Monge, Q.A. Blanco, G.J. Batlles, A.N. Garcia de, A.L. Varela, M.A. Garcia, C.N. Gimeno, and G.A. Llopis. 2010. Diet and prevalence of atopic eczema in 6 to 7-year-old schoolchildren in Spain: ISAAC phase III. *J. Investig. Allergol. Clin. Immunol.* 20:469–475.
- Tawfeek, H.I., N.H. Najim, and S. Al-Mashikhi. 2003. Efficacy of an infant formula containing anti-*Escherichia coli* colostral antibodies from hyperimmunized cows in preventing diarrhea in infants and children: A field trial. *Int. J. Infect. Dis.* 7:120–128.
- Uchida, K., H. Yamaguchi, M. Kawasaki, K. Yamashita, and N. Kaji. 2010. Bovine late colostrum (colostrum 6 or 7 days after parturition) supplement reduces symptoms of upper respiratory tract infection in infant. *Japanese J. Clin. Nutr.* 31:122–127.
- van Gysel, M., V. Cossey, S. Fieuws, and A. Schuermans. 2012. Impact of pasteurization on the antibacterial properties of human milk. *Eur. J. Pediatr.* 171:1231–1237.
- van Neerven, R.J., E.F. Knol, J.M. Heck, and H.F. Savelkoul. 2012. Which factors in raw cow's milk contribute to protection against allergies? *J. Allergy Clin. Immunol.* 130:853–858.
- van Odijk, J.V., I. Kull, M.P. Borres, P. Brandtzaeg, U. Edberg, M. Kuitunen, S.F. Olsen, S. Skerfving, J. Sundell, and S. Wille. 2003. Breastfeeding and allergic disease: A multidisciplinary review of the literature (1966 to 2001) on the mode of early feeding in infancy and its impact on later atopic manifestations. *Allergy* 58:833–843.
- Verhasselt, V. 2010. Neonatal tolerance under breastfeeding influence. *Curr. Opin. Immunol.* 22:623–630.
- Verhasselt, V., V. Milcent, J. Cazareth, A. Kanda, S. Fleury, D. Dombrowicz, N. Glaichenhaus, and V. Julia. 2008. Breast milk-mediated transfer of an antigen induces tolerance and protection from allergic asthma. *Nat. Med.* 14:170–175.
- von Mutius, E., and D. Vercelli. 2010. Farm living: Effects on childhood asthma and allergy. *Nat. Rev. Immunol.* 10:861–868.
- Waser, M., K. B. Michels, C. Bieli, H. Floistrup, G. Pershagen, M. E. von, M. Ege, J. Riedler, D. Schram-Bijkerk, B. Brunekreef, H. M. van, R. Lauener, and C. Braun-Fahrlander. 2007. Inverse association of farm milk consumption with asthma and allergy in rural and suburban populations across Europe. *Clin. Exp. Allergy* 37:661–670.
- Wijga, A.H., H.A. Smit, M. Kerkhof, J.C. de Jongste, J. Gerritsen, H.J. Neijens, H.C. Boshuizen, and B. Brunekreef. 2003. Association of consumption of products containing milk fat with reduced asthma risk in pre-school children: The PIAMA birth cohort study. *Thorax* 58:567–572.
- Willers, S.M., A.H. Wijga, B. Brunekreef, S. Scholtens, D.S. Postma, M. Kerkhof, J.C. de Jongste, and H.A. Smit. 2011. Childhood diet and asthma and atopy at 8 years of age: The PIAMA birth cohort study. *Eur. Respir. J.* 37:1060–1067.
- Wolters, D.A., W.M. van Herpen-Broekmans, M.H. Logman, R.P. van der Wielen, and R. Albers. 2006. Effect of a mixture of micronutrients, but not of bovine colostrum concentrate, on immune function parameters in healthy volunteers: A randomized placebo-controlled study. *Nutr. J.* 5:28.
- Yolken, R.H., G.A. Losonsky, and S. Vonderfecht. 1985. Antibody to human rotavirus in cow's milk. *N. Engl. J. Med.* 312:605–610.

About the Author



Joost van Neerven received his Ph.D. in 1995 at the University of Amsterdam, the Netherlands and subsequently worked as a scientist in several biopharmaceutical companies in Denmark and the Netherlands. In 2003, he co-founded Bioceros BV, a contract R&D company in the field of immunology. In 2006, he joined FrieslandCampina, and in 2013, he was appointed as Professor of Mucosal Immunity (endowed chair) at Wageningen University. His research interests are (mucosal) immunology, allergy, nutrition, and

dairy. His current research at Wageningen University is in the field of mucosal immunity, especially in relation to the effects of nutrition on immunity in the respiratory tract. His research at FrieslandCampina Research is focusing on immune functions of bovine milk ingredients. He has published more than 70 papers, book chapters, and patent applications.

Correspondence: joost.vanneerven@frieslandcampina.com



Become a Sustaining Partner of *Animal Frontiers*

There are many benefits to becoming a sustaining partner of *Animal Frontiers* magazine, including:

- 20% off the cost of advertising in our quarterly magazine.
- Complimentary print copies of the magazine.
- Recognition on the *Animal Frontiers* website.
- Recognition on the respective ASAS, CSAS, EAAP, and AMSA websites.
- Recognition in each issue of the *Animal Frontiers* magazine.
- Recognition at the respective ASAS, CSAS, EAAP, and AMSA annual meetings.

Interested in becoming a sustaining partner? Contact Meghan Wulster-Radcliffe at meghanwr@asas.org.

Foundational Sponsors

American Society of Animal Science Foundation
Novus International, Inc.

Sustaining Partners

American Meat Science Association
American Registry of Professional Animal Scientists

American Society of Agronomy
American Society of Animal Science
American Society of Animal Science Foundation
Animal Science Department, California Polytechnic State University
Dairy Science Department, California Polytechnic State University
Canadian Society of Animal Science
Crop Science Society of America
European Federation of Animal Science
Kemin
Poultry Science Association
Purdue University
College of Agriculture and Natural Resources, University of Connecticut
University of Florida
Department of Animal Science, University of Nebraska
Department of Animal Sciences, Washington State University
World Association for Animal Production



Susan Schoenian