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 Odijk 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;
Many studies have been performed with colostrum of cows that have been vaccinated with human pathogens, such as rotavirus and showed that immunoglobulins 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, Amoeba, 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...
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 Fcγ receptors (FcgR), 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>
<thead>
<tr>
<th>Milk Type</th>
<th>Functional effect</th>
<th>Type of study</th>
<th>Key references</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milk</td>
<td>Consumption of farm milk associated with fewer allergies</td>
<td>Multiple independent epidemiological studies</td>
<td>Ege et al., 2007; Riedler et al., 2001; Loss et al., 2011; Waser et al., 2007; von Mutius and Verselli, 2010; Perkin and Strachan, 2006; Szanska et al., 2013</td>
</tr>
<tr>
<td>Normal colostrum</td>
<td>Bovine late colostrum reduced the mean frequency of upper respiratory tract infections, and decrease the duration of sick days with fever</td>
<td>Double blind, randomized, placebo controlled study (n=195)</td>
<td>Uchida et al., 2010</td>
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<tr>
<td>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</td>
<td>Open, uncontrolled study (n=605)</td>
<td>Patel and Rana, 2006</td>
<td></td>
</tr>
<tr>
<td>Bovine colostrum supplementation lowered the infection severity score in IgA-deficient children with viral upper airway infections</td>
<td>Double blind, randomized, placebo controlled study (n=31)</td>
<td>Patiroglu and Kondolot, 2013</td>
<td></td>
</tr>
<tr>
<td>Colostrum supplementation in HIV-associated diarrhea resulted in a decrease in stool evacuations per day</td>
<td>Open-label, non-randomized study (n=30)</td>
<td>Floren et al., 2006</td>
<td></td>
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<tr>
<td>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</td>
<td>Randomized, placebo controlled vaccination study (n=18)</td>
<td>He et al., 2001</td>
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<tr>
<td>Oral colostrum supplementation for 6 weeks had no effect on oral vaccination response (typhoid) and subcutaneous vaccination (Tetanus)</td>
<td>Double blind, randomized, placebo-controlled study (n=138)</td>
<td>Brinkworth and Buckley, 2003</td>
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<tr>
<td>Bovine colostrum supplementation for 8 weeks decreased upper respiratory tract infections (self reported)</td>
<td>Retrospective analysis of double-blind, placebo controlled study (n=174);</td>
<td>Jones et al., 2013</td>
<td></td>
</tr>
<tr>
<td>Colostrum supplementation decreased upper respiratory sickdays and episodes in athletes compared to the placebo group</td>
<td>Double blind, randomized, placebo controlled study (n=53)</td>
<td>Cesarone et al., 2007</td>
<td></td>
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<tr>
<td>Bovine colostrum for 8 weeks resulted in fewer influenza episodes compared to the control group</td>
<td>Controlled study (n=144)</td>
<td>Cesarone et al., 2007</td>
<td></td>
</tr>
<tr>
<td>Increased levels of salivary sIgA levels in athletes</td>
<td>Open, uncontrolled studies (n=35 and n=30 respectively)</td>
<td>Crooks et al., 2006; Mero et al., 2002</td>
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</tbody>
</table>
Table 2. Human studies with milk and colostrum: Effects on allergy and infection.

<table>
<thead>
<tr>
<th>Milk component</th>
<th>Functional effect</th>
<th>Type of study</th>
<th>Subjects</th>
<th>Key references</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunoglobulin G (IgG)</td>
<td>IgG preparation from normal colostrum (65% IgG) reduces diarrhea in HIV patients with recurrent diarrhea</td>
<td>Multi-center uncontrolled pilot study (Rump); Case study (Shield); Prospective, open, uncontrolled study (Plettenberg)</td>
<td>HIV patients with recurrent diarrhea (n=37, Rump; n=1 Shield; n=25 Plettenberg)</td>
<td>Rump et al., 1992; Shield et al., 1993; Plettenberg et al., 1993</td>
</tr>
<tr>
<td>IgG preparation from normal colostrum (65% IgG): lowered frequency of loose stools and decreased median stool frequency in children with E.coli positive diarrhea.</td>
<td>Placebo controlled exploratory study</td>
<td>Children (0-18 yr) with diarrhea caused by infection with Escherichia coli (n=27)</td>
<td>Huppertz et al., 1999</td>
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<td>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.</td>
<td>Randomized, double blind, placebo-controlled trial</td>
<td>4-24 month old children with rotavirus diarrhea (n=80)</td>
<td>Sarker et al., 1998</td>
<td></td>
</tr>
<tr>
<td>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.</td>
<td>Randomized, double-blind, controlled field trial</td>
<td>Healthy 3-6 month old infants (n=107)</td>
<td>Tawfeek et al., 2003</td>
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<td>Lactoferrine (LF)</td>
<td>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.</td>
<td>Prospective, multicenter, double-blind, placebo controlled, randomized trial</td>
<td>Very low birthweight infants (n=472)</td>
<td>Manzoni et al., 2009; Manzoni et al., 2012</td>
</tr>
<tr>
<td>Decreased frequency and duration of vomiting and diarrhea in rotaviral gastroenteritis. No effect on incidence.</td>
<td>Placebo controlled, non-randomized study</td>
<td>0-4 year old children (n=234)</td>
<td>Egashira et al., 2007</td>
<td></td>
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<tr>
<td>Infants receiving lactoferrin-supplemented formula had a lower incidence of lower respiratory tract infections compared to children receiving control formula.</td>
<td>Randomized, placebo-controlled, double-blind study</td>
<td>0-4 week old children (n=52)</td>
<td>King et al., 2007</td>
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<tr>
<td>Impact of lactoferrin supplementation on growth and prevalence of Giardia colonization in children. No effect on diarrhea.</td>
<td>Randomized, double-blind, placebo-controlled trial</td>
<td>1-3 year old children (n=320)</td>
<td>Ochoa et al., 2008</td>
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<tr>
<td>Transforming growth factor-β (TGF-beta)</td>
<td>Induction of clinical remission and improved quality of life after 8 weeks of enteral nutrition containing TGF-beta.</td>
<td>Prospective cohort study</td>
<td>8-17 year old children with Crohn’s disease (n=26)</td>
<td>Afzal et al., 2004</td>
</tr>
<tr>
<td>TGF-beta rich formulas induced clinical remission associated with mucosal healing in Crohn’s disease patients</td>
<td>Open, uncontrolled study</td>
<td>Children with Crohn’s disease Fell et al., 2000 (n=29)</td>
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derived immunoglobulin prevents inflammatory tissue damage in acute lung inflammation in mice (Majjo 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-β2 and TGF-β1. 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-β1 and TGF-β2 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 *vitro* assays (Grover et al., 1997). In addition to this antimicrobial function, lactoferrin can also have immunomodulatory activities (Lomberdal, 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-β1 in the intestinal epithelial cell line Caco-
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 Manzoni 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 that 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 Claeyys 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 (e.g., 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.

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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

22

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