Invited review: Bovine colostrum, a promising ingredient for humans and animals—Properties, processing technologies, and uses

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ABSTRACT

Mammalian colostrum, known as "liquid gold," is considered a valuable source of essential nutrients, growth factors, probiotics, prebiotics, antibodies, and other bioactive compounds. Precisely for this reason,, bovine colostrum (BC) is an emerging ingredient for the feed, food, and pharmaceutical industries, being nowadays commercially available in a variety of forms in several countries. Moreover, quite a large number of functional foods and supplements for athletes, human medicines, pet nutrition plans, and complementary feed for some livestock categories, such as piglets and calves, contain BC. The amount of BC yielded by a cow after calving represents approximately 0.5% of the yearly output in dairy breeds. For its nutritional properties and low availability, BC is characterized by a greater market value and an increasing demand compared with other by-products of the dairy sector. However, information regarding the market size of BC for the food and pharmaceutical industries, as well as future developments and perspectives, is scarcely available in the scientific literature. This lack can be attributed to industrial secrecy as well as to the relatively small scale of the BC business when compared with other dairy products, which makes the BC market limited, specific, and intended for a restricted audience. From a legal perspective, regulations assign BC to the large family of milk-derived powders; thus, collecting specific production data, as well as import-export trend information, is not straightforward and can result in unprecise estimates. Given that the interest in BC is increasing in different fields, it is important to have an overview of the production steps and of pros and cons of this emerging ingredient. The present narrative review discloses why BC has started to be considered a product rather than a by-product of the dairy industry. Moreover, the present document aims to summarize the existing methodologies used to assess BC quality in terms of immunoglobulin concentration, the different applications of BC in the industry, and the BC processing technologies. Finally, a panoramic view of the current international market is provided for the first time for this dairy product.
Key words: colostrum, cattle, dairy industry, immunoglobulin

INTRODUCTION

Colostrum obtained from dairy species is a commercially valuable product available for human and animal purposes. It is a nutraceutical biological matrix that provides nutrients, growth factors, probiotics, prebiotics, antibodies, and other bioactive compounds (Borad and Singh, 2018; Borad et al., 2021). Cow, buffalo, and goat colostrums are purchased and used by different companies to manufacture a wide range of preparations in forms like powder, tablet, capsule, and liquid (Scammell, 2001; Tripathi and Vashishtha, 2006; Godhia and Patel, 2013; Bagwe et al., 2015). According to Scammell (2001) and Boland (2003), the market price and the demand of bovine colostrum (**BC**) started to increase in 2000, with 9 companies actively playing in the market. In 2001 the BC market at retail level was estimated to be approximately US$100 million. This value has certainly increased since then, and potentially there could be reasonable profit margins for both farmers and manufacturers (Scammell, 2001; Boland, 2003). Due to the industrial secrecy of dairy companies and current trading classification of BC, it is rather difficult to obtain detailed market information about this

product as well as to retrieve the identity of major suppliers and buyers, detailed production technologies, and manufacturing costs. In the market jargon, powdered colostrum of dairy species belongs to the wider family of milk-derived powders, resulting in challenging situations where it is impossible to understand whether the imported or exported item contains BC and in what amount (Playford et al., 2020). It is more than evident that having publicly available data on the BC market is a challenge. Only through Playford et al. (2020), who collected BC from various brands to assess differences in the bioactivity, has it been possible to retrieve a list of major international producers. These were located in the United States and the United Kingdom at that time and only a few suppliers could be found in New Zealand, Germany, and the Netherlands.

The interest of the dairy industry and scientific communities in the beneficial properties of BC is constantly increasing, with focuses on various species and multiple research fields (Table 1, Figure 1). For example, in 2021 most of the papers on BC were published in the *Journal of Dairy Science* (15%), followed by *Animals* (13%), *Nutrients* (4%), and *Frontiers in Veterinary Science*

(3%; Table 1). In 2022, the *Journal of Dairy Science* again ranked first with 16% of papers, followed by *Animals* (9%) and *Nutrients* (3%). In the papers dealing with BC published in the last 12 years (Figure 1), the most popular key words are "colostrum," "calf," and "immunoglobulin" with an occurrence of 402, 104, and 63, respectively.

Strategies aimed at improving both the quality and the offers of BC could thereby interest some farmers, e.g., large and well-managed farms with either a temporary or a permanent excess of BC. At the same time, interested stakeholders may promote BC commercialization and use by valorizing its properties (McGrath et al., 2016; Oliveira et al., 2019). Although BC yield accounts for only 0.5% of the annual output (kg) of a dairy cow and should be primarily intended for newborn calf feeding, surplus of BC may occur. This could happen especially in farms where banking is performed and when the internal colostrum bank is saturated. It is worth mentioning that while researchers and farmers distinguish BC from transition milk, within the dairy supply chain this distinction is infrequent. In fact, mammary gland secretions produced until the fifth day

Table 1. Target journals of papers (invited reviews + original articles) published between 2010 and 2022[1] where "cow" and "colostrum" or "bovine" and "colostrum" appear in the title or among the authors' key words (source: Scopus, www.scopus.com)

| Year	n	Journals with ≥2 papers
2010	44	Biosci Biotechnol Biochem; Int Dairy J; J Am Vet Med A; Vet Immunol Immunopathol
2011	51	Berl Munch Tierarztl Wochenschr; J Agric Food Chem; J Nutr; J Proteome Res; Vet Immunol Immunopathol; Vet Microbiol
2012	54	BMC Res Notes; J Dairy Sci; Livest Sci; Prev Med; Vaccine; Vet Immunol Immunopathol; Vet Microbiol
2013	63	Anim Sci J; Br J Nutr; Cell Mol Biol; Czech J Anim Sci; J Dairy Sci; J Vet Diagn Invest; PLOS ONE; Vet J
2014	97	Anim Sci J; BMC Vet Res; Czech J Anim Sci; Int Dairy J; J Anim Physiol Anim Nutr; J Dairy Res; J Dairy Sci; PLOS ONE; Vaccine; Vet Immunol Immunopathol
2015	101	Animal; Biotechnol Prog; Br J Nutr; J Anim Physiol Anim Nutr; J Dairy Sci; J Nutr; J Vet Intern Med; PLOS ONE; Prev Vet Med; Vet Microbiol
2016	102	Am J Physiol Gastrointest Liver Physiol; Anim Health Res Rev; Aquacult Res; Food Chem; J Anim Sci; J Dairy Res; J Dairy Sci; J Pediatr Gastroenterol Nutr; J Vet Diagn Invest; PLOS ONE; Semin Cienc Agrar; Tierarztl Prax Ausg G Grosstiere Nutztiere; Vaccine; Vet Immunol Immunopathol; Vet Rec
2017	119	Animal; Anim Sci J; Aust Vet J; Comp Immunol Microbiol Infect Dis; Eur J Appl Physiol; J Agric Food Chem; J Dairy Sci; J Am Vet Med Assoc; N Z Vet J; PLOS ONE; Res Vet Sci; Tierarztl Prax Ausg G Grosstiere Nutztiere; Trop Anim Health Pro; Vet Res
2018	121	Arq Bras Med Vet Zootec; Aust Vet J; Can Vet J; Front Immunol; Front Vet Sci; J Anim Physiol Anim Nutr; J Anim Sci; J Dairy Sci; J Vet Intern Med; J Sci Food Agr; N Z Vet J; PLOS ONE; Res Vet Sci; Transbound Emerg Dis; Vaccine
2019	162	Acta Sci Vet; Acta Vet Scand; Animal; Animals; BMC Vet Res; Buffalo Bull; Can J Anim Sci; Eur J Nutr; J Agric Food Chem; J Anim Sci; J Dairy Res; J Dairy Sci; J Vet Intern Med; Nutrients; PLOS ONE; Prev Vet Med; Punjab Univ J Zool; Schweiz Arch Tierheilkd; Tierarztl Prax Ausg G Grosstiere Nutztiere; Turkish J Vet Anim Sci; Vet Clin North Am Food Anim Pract; Vet Immunol Immunopathol; Vet Microbiol; Vet Rec Open
2020	184	Animal; Animals; BMC Vet Res; Buffalo Bull; Front Immunol; Indian J Anim Sci; Int Dairy J; J Agric Food Chem; J Anim Sci; J Dairy Res; J Dairy Sci; J Parenter Enter Nutr; Livest Sci; Nutrients; Pathogens; PLOS ONE; Prev Vet Med; Rev Bras Parasitol Vet; Tierarztl Prax Ausg G Grosstiere Nutztiere; Vet Clin North Am Small Anim Pract; Vet World
2021	231	Animal; Animals; BMC Vet Res; Front Nutr; Front Vet Sci; Int Dairy J; Int J Mol Sci; J Anim Sci; J Anim Sci Tech; J Dairy Res; J Dairy Sci; J Am Vet Med Assoc; J Vet Med Sci; Livest Sci; Nutrients; Pathogens; PLOS ONE; Protein J; Res Vet Sci; Transbound Emerg Dis; Trop Anim Health Prod; Trop Anim Sci; Vet World
2022	192	Animal; Animals; Antibiotics; BMC Vet Res; Can J Vet Res; Food Chem; Front Immunol; Front Microbiol; Front Pharmacol; Front Vet Sci; Genet Sel Evol; Indian J Anim Sci; J Anim Sci; J Dairy Sci; J Reprod Immunol; J Vet Med Sci; Kafkas Univ Vet Fak Derg; Lect Notes Netw Syst; Metabolites; N Z Vet J; Nutrients; PLOS ONE; Prev Vet Med; Probiotics Antimicrob Proteins; Sh Kexue/Food Sci; Vet Clin North Am Food Anim; Vet Immunol Immunopathol; Vet J; Vet Rec; Vet World

[1]As of December 29, 2022.
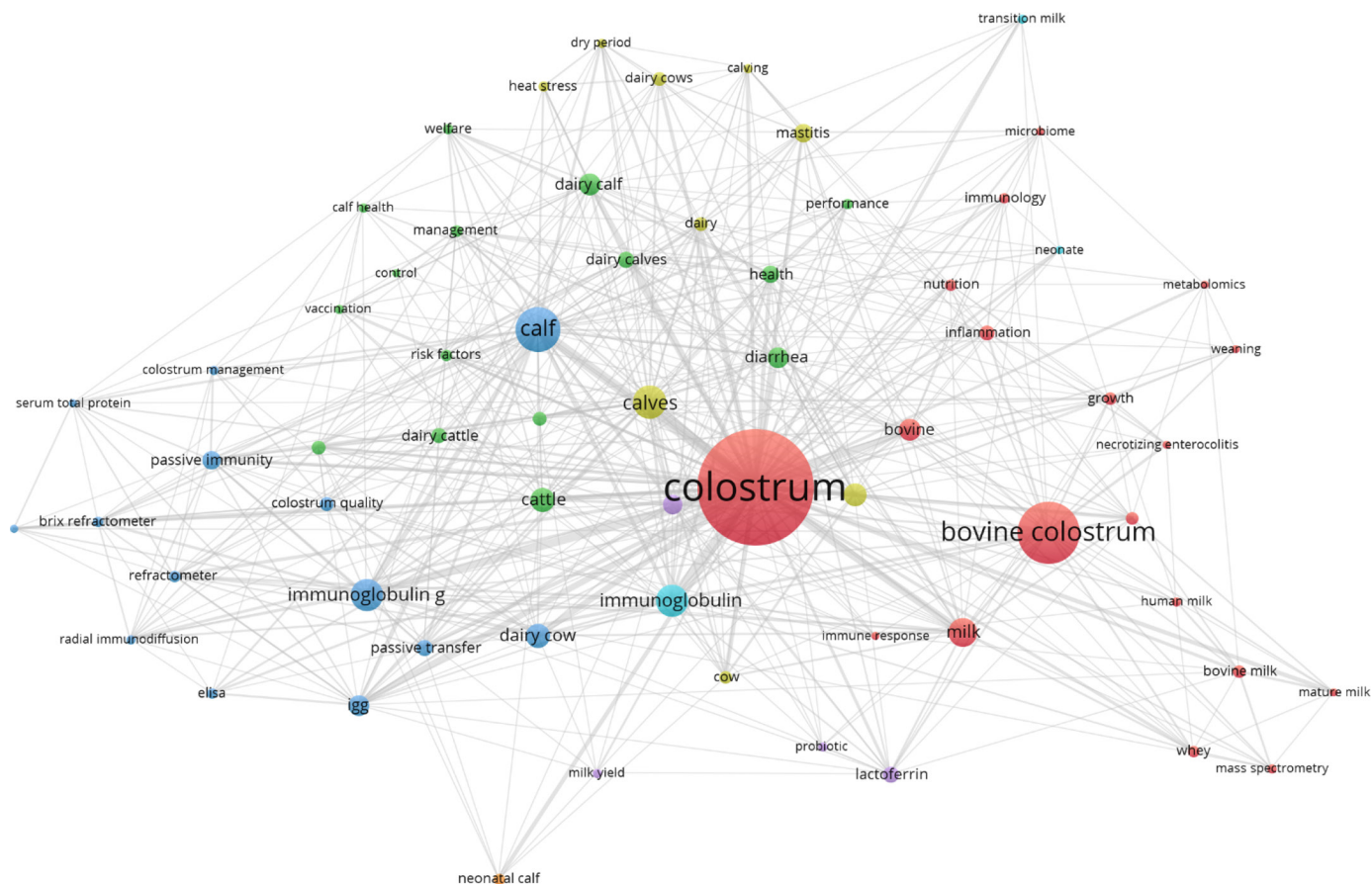
Figure 1. Network analysis based on bibliographic information of 1,517 papers published between 2010 and 2022 where "cow" and "colostrum" or "bovine" and "colostrum" appear in the title or among the authors' key words for the 65 authors' key words with occurrence ≥10. Papers included invited reviews and original articles as of December 29, 2022 (source: Scopus, www.scopus.com). Thickness of gray lines indicates co-occurrence between the key words (van Eck and Waltman, 2009).

after calving are not delivered to milk collectors and therefore are not paid to the farmers. In the practice, both BC and transition milk are generally used for the young stock feeding directly on the farm.

COLOSTRUM QUALITY

Although the quality of BC is mostly assessed via the evaluation of IgG concentration in commercial farms, at the industry level the situation is different. In fact, BC is commonly present as powdered BC (**PBC**) and is an ingredient for animal and human use, which undergoes a wide range of qualitative inspections before and after manufacturing treatments. It therefore appears appropriate to talk about "quality" in the narrower sense if only IgG is accounted for in the evaluation. Supporting this, it is well known that BC contains bioactive compounds other than antibodies whose activity is not species-specific. According to Playford et al. (2000) and Mihic et al. (2016), colostrum of different

mammals can stimulate cellular growth in multiple species, including humans. Overall, the energy content of BC is estimated to be around 130 kcal/100 mL, and compounds with potential bioactive properties include growth factors, insulin-like growth factor-1, lactoferrin, lactoperoxidase, bovine serum albumin, α-lactalbumin, and β-lactoglobulin (Chatterton et al., 2020; Playford et al., 2020), whose importance for neonates, commercial uses (e.g., human foodstuffs or supplements), and phenotypic variability have been extensively reviewed by Godhia and Patel (2013), Arslan et al. (2021), and Kaplan et al. (2022). For commercial purposes, BC payment systems and marketing should rely upon a specific "quality," i.e., concentration of total protein, IgG, or total immunoglobulins. Nevertheless, other fundamental elements like cytokines, peptides, and immune factors (Playford et al., 2020; Playford and Weiser, 2021) may vary regardless of the IgG level. In addition, the BC abilities/properties such as the proreparative activity can differ between samples whose

protein content and IgG concentration appear similar. This is pivotal to consider when considering BC as a supplement or for medical purposes.

Although BC differs from human colostrum in composition, it is well tolerated by children and adults. The compositional differences between the 2 species are partly due to physiological reasons. In fact, the transfer of immunity between the mother and the fetus takes place during gestation in humans, somehow justifying the lower concentration of immunoglobulins and other components in the colostrum compared with cattle. Kehoe et al. (2007), Stelwagen et al. (2009), and Godhia and Patel (2013) reported that human colostrum typically shows lower levels of energy (∼58 kcal/100 mL), IgG (∼0.43 g/L), IgM (∼1.59 g/L), fat (∼2.9%), and protein (∼3.7%), and greater IgA (∼17.35 g/L), lactose (∼5.3%), and lactoferrin (∼800 mg/mL) than BC.

Immunoglobulins

From a calf perspective, the quality of BC in a narrow sense relies on the concentration of immunoglobulins, particularly the isotype G. This is the major fraction, accounting for more than 75% of total immunoglobulins, followed by IgA and IgM fractions (Godden, 2008). With a general consensus among scientists, veterinarians, technicians, and farmers, the threshold that differentiates good- from poor-quality BC is 50 g of IgG per liter. Especially when administered to newborn calves, BC must therefore present at least 50 g/L of IgG to ensure an optimal passive transfer of immunity. In the first 6 h after parturition, more than 80% of total proteins of BC are composed of immunoglobulins, but the composition of BC changes dramatically in the first 24 h together with the newborn calf's gut permeability. In Holstein cows, IgG concentration of colostrum collected within the first 6 h after calving averages 91.31 g/L, whereas isotypes A and M are present in concentrations of approximately 5 g/L (Costa et al., 2021b). The phenotypic correlations between the 3 immunoglobulin fractions are moderate to strong, ranging from 0.51 to 0.61 (Costa et al., 2021b).

Irrespective of the form in which BC is sold (liquid, powder, tablet, or other), the commercial quality mainly depends on immunoglobulins. This implies that the market price of BC should depend on the declared concentration of total immunoglobulin or IgG or, at least, total protein. According to Playford et al. (2020), human products containing BC such as infant formula and supplements have a protein content between 55 and 88 g/100 g, whereas their IgG content can vary from 5 to 40 g/100 g. Twenty years ago, Kelly (2003) reviewed clinical uses of BC in humans and observed that different supplements all contained variable levels

of protein or immunoglobulins. For example, products were labeled as "75% protein with 15% IgG," "80% protein," "43% IgG," or "80% protein with 65% IgG." In companion animals, Torre et al. (2006) used PBC with protein content between 85 and 90% and with a declared IgG proportion of 85%. Colostrum contains other relevant compounds useful to a broad-sense quality evaluation, such as fatty acids, essential amino acids, oligosaccharides, vitamins, minerals, and other minor substances with immune-stimulating or repair-enhancing properties (Stelwagen et al., 2009; Gomes et al., 2021).

Variability

Due to physiological reasons, in ruminants a dramatic change in the composition of colostrum can be observed in the first few hours after calving. In fact, gut permeability of the newborn is maximal at birth and immediately starts to decline thereafter, reaching total closure at around 36 h of age (Godden, 2008). Therefore, nutrients and antibodies must be provided as soon as possible through BC at the first meal (Godden, 2008). In cattle, at least 4 L of BC with IgG concentration greater than 50 g/L should be administered to calves within 12 h after calving to reduce the risk of failure of passive transfer of immunity and ensure protection. Insufficient amounts of IgG expose the calf to a greater susceptibility to diseases in early life with negative consequences in the medium to long term. Through pinocytosis, nonselective enterocytes in the first hours of life are able to absorb various substances, including immunoglobulins (Godden, 2008). Following the progressive closure of the gut, the concentration of immunoglobulins in BC peaks immediately after parturition and gradually decreases afterward (Scammell, 2001; Elfstrand et al., 2002; Dunn et al., 2017). Using data of BC collected at first milking (0–6 h after calving) in Holsteins, Costa et al. (2021b) calculated high coefficients of variation: 39.56, 63.42, and 48.52% for IgG, IgA, and IgM, respectively. Colostral IgG concentration ranged from 4 to 235 g/L in Norwegian dairy cows (Gulliksen et al., 2008), with median and 10th, 25th, 75th, and 90th percentiles of 45.0, 23.1, 31.4, 63.6, and 91.6 g/L, respectively. Overall, according to the review of McGrath et al. (2016), the total immunoglobulin concentration in BC can vary considerably postpartum, from 30 to 200 g/L.

It is not news that the cow's parity affects the IgG concentration of BC (Dunn et al., 2017; Costa et al., 2021b; Cordero-Solórzano et al., 2022), with BC from multiparous cows having greater immunoglobulin content than primiparous cows (Table 2). In this regard, Bielmann et al. (2010) observed a greater frequency

Table 2. Concentrations (g/L) of IgG and, when available, IgA and IgM in bovine colostrum across parities

Reference	Breed	n. cows	Item	Parity	IgG	IgA	IgM
Silva-del-Río et al. (2017)	Jersey	134	Raw means	2	77.3		
				3	74.9		
				≥4	98.4		
Dunn et al. (2017)	Various	1,239	LSM	1	49.3		
				2	50.1		
				3	54.3		
				4	55.5		
				≥5	65.9		
Johnsen et al. (2019)	Norwegian Red	167	Raw means	1	41.5		
				2	34.1		
				3	40.8		
				≥4	47.9		
Costa et al. (2021b)	Holstein	678	LSM	1	74.36	3.02	4.36
				2	81.72	4.63	4.63
				3	95.98	6.23	5.67
				4	97.58	5.66	5.17
				5 to 8	107.12[1]	6.69	5.36

[1]Presence of an important number of samples with IgG greater than 10% solids (>100 g/L).

of poor-quality samples (IgG <50 g/L) in primiparous than in multiparous cows. Costa et al. (2021b) did not observe differences in terms of IgG concentration between first- and second-parity cows; however, these differed significantly from cows in subsequent lactations. In the same study, BC of cows in parity greater than 2 often presented IgG greater than 10% solids, which is to say, >100 g/L (Table 2). In line with this, Shivley et al. (2018) reported a similar IgG concentration in BC sampled from first- and second-parity cows, lower than the concentration of cows from third lactation onward. The positive association between IgG and parity has been attributed to the greater exposure of the immune system of older cows compared with heifers (Costa et al., 2021b; Cordero-Solórzano et al., 2022). However, even dilution can be partly responsible for such a trend, as the BC density from the third parity onward is greater (1,068 vs. 1,059 kg/m^3) compared with younger cows (Strekozov et al., 2008; McGrath et al., 2016).

The effects of seasonality on BC IgG are less clear. Although some authors did not detect a significant effect of calving season, Costa et al. (2021b) recently observed greater concentrations of immunoglobulin in cows that calved between late summer and early autumn. Strekozov et al. (2008) observed that the BC density was maximal in autumn regardless of the parity, and the greatest proportion of samples with high IgG concentrations (>100 g/L) were collected in this period. In general, it seems that quality tends to be greater in cows calving in autumn and winter (temperate zone) for reasons related to the photoperiod and physiology. The IgG concentration, in fact, is expected to be subject to a concentration or dilution effect, decreasing in the presence of longer hours of darkness, i.e.,

when the amount of BC produced is generally higher (Gavin et al., 2018).

As regards the farm effect on IgG, literature teaches that management practices during the dry period can affect colostral quality. As an example, the feed composition administered before calving is a source of variability for BC quality (Mann et al., 2016) and the omission of the dry period can reduce immunoglobulin concentration by 50% (Verweij et al., 2014). Hyperimmune BC can be obtained from cows immunized before calving, as during the dry period. Most popular vaccines available against etiological agents like rotavirus and coronavirus (Kelly, 2003; Kramski et al., 2012) provide exogenous antibodies to the cow and cause a non-innate increase of plasma immunoglobulins. Hyperimmune BC, interesting for human experimental therapies, trials, and curative purposes, (Kramski et al., 2012; Batista da Silva Galdino et al., 2021), is obtained from cows purposely vaccinated to generate it, as in the case of the "Stolle milk" (Stolle and Beck, 1989). Boosting the concentrations of immunoglobulins can be viewed as a way to naturally obtain preparations rich in IgG to be incorporated in foodstuffs and pharmaceutical items.

Therefore, the concentration of immunoglobulins in BC depends on both the acquired and the innate immune systems of cows and shows phenotypic variability and differences among herds and among cows. The presence of genetic variability indicates that to a certain extent BC quality can be manipulated through breeding. A limited number of studies have explored genetic aspects of BC composition traits so far. By using BC produced within 6 h from calving, Costa et al. (2021a) estimated heritability of IgG, IgA, and IgM

concentrations measured via radial immunodiffusion (**RID**) as well as their genetic correlations in Holstein cattle. The IgM showed the greatest heritability (from 0.216 to 0.249), whereas IgG (0.060 to 0.172) and IgA (0.078 to 0.178) were less heritable. Even if estimates were characterized by some uncertainty—large standard errors—due to the sample size, the study showed that the fractions are positively genetically correlated (Costa et al., 2021a). The strongest genetic correlation was the one between IgG and IgM (0.401), and the lowest between IgA and IgM (0.144). The association between IgG and IgA was characterized by an intermediate magnitude (0.220).

In Charolais breed cattle, heritabilities of colostral IgG as determined according to RID and via an alternative method (ELISA) were 0.28 and 0.08, respectively (Martin et al., 2021). In the same study, heritability of serum IgG in calves was 0.36. In Sweden, Cordero-Solórzano et al. (2022) estimated a heritability of 0.20 for IgG measured with ELISA. In addition, Lin et al. (2022) discovered genomic regions associated with serum and colostral ELISA immunoglobulins in Chinese Holstein. In this population heritabilities of 0.235 and 0.141 were estimated for IgG in BC and serum, respectively. Both IgA and IgM were more heritable than IgG in both fluids. It is reasonable to assume that differences in the heritability and genetic variability of immunoglobulin fractions can be attributed to the quantification method rather than to sampling protocol, breed, and model used (Martin et al., 2021). Although based on a limited number of animals, the genome-wide association study of Lin et al. (2022) highlighted that colostral and serum immunoglobulins are affected by several regions throughout the *Bos taurus* genome, which are within or nearby 14 known genes. Some of the target genes identified, namely *FGFR2*, *FGFR4*, *NCF1*, *IKBKG*, *SORBS3*, *KIT*, and *PTGS2*, have generally been related to inflammatory response and white blood cell activity (Lin et al., 2022). Similarly, genes with significant effects on serum immunoglobulins and with known immune-related functions were *ICAM1*, *RAC3*, *TGFB1*, *BAX*, *GRB2*, and *TAOK1*. All of the aforementioned genes play a role during and after inflammation, with an effect on neutrophil activation and immune-related processes (Lin et al., 2022).

Considering the high cost of reference methods for BC immunoglobulin phenotyping, most large-scale studies have dealt with indirect measurements of quality. As an example, genetic parameters of BC refractive index expressed on a Brix scale (%) have been reported by Soufleri et al. (2019) together with other traits of interest such as the BC yield, the fat, protein, and lactose content, and the energy content. The experimental protocol of Soufleri et al. (2019) allowed samples to be collected in a wide temporal window, from 10 min to 16 h from parturition. In that study, the Brix % was considered as an indirect proxy of the total solids content of BC, which in turn affects the IgG level. In terms of heritability, the greatest and the lowest estimates were reported for Brix % (0.27) and BC yield (0.04). These traits were genetically correlated with each other (0.49), and the correlation between Brix % and total protein content was close to unity (0.97), indicating that the BC total solids in the first 24 h after calving mostly consist of proteins. Evaluation of BC quality through Brix % can be of particular interest in contexts with no access to laboratory equipment for immunoglobulin determination. Moreover, because in most countries a punctual, rapid, and accurate quantification of BC immunoglobulins is not currently feasible on a large scale, acquisition of indirect quality phenotypes can temporarily rely on refractometers (Costa et al., 2022c; Franzoi et al., 2022).

COLOSTRUM YIELD

Previous studies have observed that the quantity of BC administered, rather than quality, is essential to consider for efficient passive transfer of immunity in calves. In the first 12 h of life, the BC intake should be equal to or greater than 4 L (Godden et al., 2019). However, there is the concrete risk that cows, especially dairy breeds, yield less than needed in some circumstances (Gavin et al., 2018). A deficient BC production impairs the health and survival rates of newborn calves if no additional BC is provided.

The BC yield is difficult to measure individually, especially in nonexperimental conditions. On commercial farms, the newborn calf is often left with the dam after birth, allowing for direct suckling at first meal. Moreover, the BC yield at first milking may not be representative of the real expression of the production of the cow. For example, massive variability, from 0.5 to 39.7 kg, was reported for first-milking BC yield recorded in 9 US farms (Cabral et al., 2016), but the time window allowed for the collection was generous: from 1 to 14.5 h after calving (Cabral et al., 2016). Only a few studies have investigated BC yield on a large number of animals, through specific sampling and recording protocols.

Gavin et al. (2018) observed that insufficient BC production is more frequent in cows that calved during the winter season in the northern hemisphere. According to other authors, BC yield tends to be lower in cows calving in autumn than in spring and summer (Conneely et al., 2013; Godden et al., 2019).

The effect of season on BC production in cows is related to physiological changes and hormonal regula-

Table 3. Overview of pros and cons of methodologies available for the determination of colostral IgG

Method[1]	Cost per sample	Time for analysis	Repeatability	Feasibility of routine use	Need of expert laboratory personnel	Accuracy	Correlation with gold standards	Output
Gold standard								
RID	+ + +	+ + +	+ + +	+	+ + +	+ + +		IgG concentration
ELISA	+ + +	+ + +	+ + +	+	+ + +	+ + +		IgG concentration
Indirect								
Colostrometer	+	+	+ +	+ + +	+	+	Moderate–strong	Specific gravity
Refractometer	+	+	+ +	+ + +	+	+ +	Moderate–strong	Refractive index
NIRS	+	+	+ + +	+ + +	+ +	+ +	Strong	IgG concentration
MIRS	+	+	+ + +	+ + +	+ +	+ +	Strong	IgG concentration

[1]RID = radial immunodiffusion assay; NIRS = near-infrared spectroscopy machine (not portable or pocket devices); MIRS = mid-infrared spectroscopy machine (not portable or pocket devices).

tion in different photoperiods. In a study carried out on US Jersey cattle (Gavin et al., 2018), BC yield was apparently strongly correlated with the number of light hours 1 mo before parturition and at parturition. In particular, greater BC volume and lower concentration of immunoglobulins were observed with increasing light hours; that is, in the period from spring to summer. The same authors demonstrated that production of BC followed the photoperiod, since the volume yielded was the lowest when the number of light hours was minimum (Gavin et al., 2018). In certain periods of the year, a considerable percentage of US Jersey cows did not produce enough BC at calving. This demonstrates how banking is important and highly recommended to cover critical periods, in Jersey farms in particular.

Cabral et al. (2016) reported a negative correlation between BC yield and number of days before calving with a maximum temperature exceeding 23°C. The photoperiod affects several hormonal functions and regulations in livestock to a species-specific extent; for example, fertility is strongly affected by season in buffaloes and goats, and cows' plasma melatonin levels are higher in periods with longer hours of darkness. In a similar manner, the lactogenesis in cattle is affected by calving season (Dahl et al., 2000), and greater BC production is expected with increasing photoperiod (Zarei et al., 2017). The surge in prolactin, the hormone responsible for lactogenesis, is affected by photoperiod and is reported to have an influence on colostrogenesis in cows (Gavin et al., 2018). In general, the reduction in BC yield in autumn and winter calvings is more evident in multiparous than in primiparous cows. In addition, the incidence of the so-called "colostrum production deficiency syndrome" has been found to be maximal in December and was greater in multiparous cows (Gavin et al., 2018).

Gross et al. (2016) observed that rear quarters tend to yield more and to deliver BC with greater IgG, regardless of the parity. Authors concluded that a strong correlation exists between BC yields at different pari-

ties. In other words, the highest-producing quarter(s) of a primiparous cow is likely to be the most productive in all the subsequent lactations compared with the other quarters (Gross et al., 2016).

There is potential to include BC yield and immunoglobulin concentration as indicators of traits for selective breeding in cattle (Gavin et al., 2018; Soufleri et al., 2019). Soufleri et al. (2019) estimated heritability of BC yield (0.04) in addition to Brix % (0.27), and figured out that the traits are correlated in the Greek Holstein population. The genetic and phenotypic correlations were 0.49 and 0.10, respectively. The positive genetic correlation indicated that improvements in yield and quality of BC is achievable if a proper emphasis is given to the features. Preliminary results of Costa et al. (2022c) suggest that the Brix % measured on first colostrum is not correlated with milk protein content and milk yield recorded in the early lactation at the first official test-day (5–75 DIM).

In perspective, this overview indicates that robust data and BC-specific recording systems are necessary to make robust simulations and assumptions on the possibility to genetically select for BC yield and quality.

NARROW SENSE QUALITY ASSESSMENT

A list of methods available to measure the IgG concentration, the main proxy of the BC quality, is provided in Table 3, with indications of their advantages and disadvantages. While some methods provide a punctual determination of the IgG concentration in grams per liter, others, like the refractive index, are a proxy of the real concentration of antibodies (Table 3).

Direct Methods

The gold standard for the determination of immunoglobulins in serum and colostrum is the RID assay, a method characterized by good repeatability and reproducibility (Pechova et al., 2019; Gamsjäger et al., 2020).

Costa et al. (2021b) reported a cost of US$100 for the analysis of 21 samples, excluding personnel labor.

Most published literature on colostrum and calves' blood immunoglobulins is based on RID determinations on diluted colostrum; nevertheless, ELISA kits have also been used (Taniguchi et al., 2016; Dunn et al., 2017; Cordero-Solórzano et al., 2022). The 2 methods differ in terms of sensitivity, specificity, repeatability, and reproducibility. Therefore, comparing results obtained from RID and ELISA is not recommended (Gapper et al., 2007). Martin et al. (2021) reported IgG to average 84.07 g/L (SD = 45.20 g/L) when RID was used to determine the concentration, whereas, under ELISA, the average in the same samples increased to 158.44 g/L (SD = 88.61 g/L). Furthermore, the correlation between the 2 was found to be very weak (0.10). According to the explanation given by Martin et al. (2021), this was due to the high viscosity of some samples, which compromised dilution and pipetting for the ELISA test and impaired their accuracy. Gelsinger et al. (2014), instead, reported that differences between the 2 methods may be due to heating (or thawing) of the target matrix. In fact, Gelsinger et al. (2014) observed no correlation between IgG measured through RID and ELISA in heat-treated colostrum samples; in addition, the correlation was weak in the cases of plasma and unheated colostrum. Gelsinger et al. (2014) concluded that the ELISA-determined immunoglobulin concentration tends to be lower compared with that determined via RID in unheated and heated colostrum. The same authors affirmed that RID is the most reliable and accurate method available for quantification of immunoglobulins in calf and cow plasma and in BC.

In general, the direct determination of immunoglobulins is demanding in terms of cost, labor, and time, making routine implementation rather unfeasible on commercial farms or in manufacturing plants of dairy, food, or pharmaceutical industries. However, gold-standard methodologies are still needed to calibrate, validate, and standardize indirect techniques (Bartier et al., 2015; Spina et al., 2021; Costa et al., 2022b; Franzoi et al., 2022).

Indirect Measurement on Farm

Individual or pooled BC can be stored for internal use on dairy farms (Bartier et al., 2015; Soufleri et al., 2019; Costa et al., 2021a). Banking is considered one of the best management practices related to young stock management and is recommended to limit incidence of mortality and disease. In herds where banking occurs, BC of parturient cows in excess of calf demand can be frozen and subsequently administered to calves when (i) BC production is scarce, (ii) BC quality is subop-timal (IgG under the recommended threshold), or (iii) the newborn calf is a female intended for future herd replacement.

The quality of BC samples to store is usually evaluated indirectly through easy-to-handle portable tools, such as colostrometers and refractometers (Bielmann et al., 2010; Quigley et al., 2013; Bartier et al., 2015; Buczinski and Vandeweerd, 2016). Both instruments estimate densities and solid concentrations of BC, and an approximation of the IgG concentration can be derived using manufacturers' instructions. Colostrometers provide easy-to-interpret results, with a colored scale where green, yellow, and red indicate good, moderate, and low quality, respectively. On the other hand, refractometers tend to be more accurate and more popular among dairy farmers. Colostrometers require a small BC volume to be injected in the cylinder and—starting from the measure of specific gravity—provide an approximation of the IgG level (e.g., mg/mL or g/L according to the brand). Practically, BC falling in the red, yellow, and green areas of the scale is expected to contain ≤ 20, 21–50, and ≥ 51 mg/mL of total immunoglobulins, respectively. As regards refractometers, both analogic/optical and digital devices are commercially available, with no significant difference in terms of sensitivity and specificity between them in either fresh or thawed colostrum (Bielmann et al., 2010).

The Brix % is used in the field to monitor colostral quality in various species, including small ruminants, buffaloes, and horses (Bielmann et al., 2010; Quigley et al., 2013; Soufleri et al., 2019; Giammarco et al., 2021). In cattle, the diagnostic accuracy of refractometer has been extensively evaluated in the past. For example, it has been suggested that good-quality BC might be characterized by Brix % equal to or greater than 22.0 (Bielmann et al., 2010; calculated using data from 288 Holstein cows) and 20.2 (Costa et al., 2022c; calculated using data from 548 Holstein cows). Quigley et al. (2013) reported that the correlation between the Brix % and RID IgG ranges from 0.54 to 0.89 in bovines and is affected by sampling protocol and collection time. In Sweden, Cordero-Solórzano et al. (2022) estimated a phenotypic correlation of 0.70 between Brix % and ELISA-measured IgG level.

By using BC samples collected in 13 Canadian dairy farms, Bartier et al. (2015) determined the main quality parameter, IgG, via RID, colostrometer, and refractometer. The concentrations of IgG estimated with the 2 indirect methods were strongly correlated with the gold-standard RID, with a coefficient of 0.77 in the case of the colostrometer and 0.64 in the case of the refractometer (Bartier et al., 2015).

Finally, the BC testing with refractometers has recently been debated (Lombard et al., 2022; Schalich

and Selvaraj, 2022). Evidence indicates that refractive index of BC can be affected by other solids present in solution, which become confounding variables (Schalich et al., 2021; Schalich and Selvaraj, 2022). Based on the high residuals observed in regression, in fact, Schalich et al. (2021) affirmed that the predictive power for punctual IgG concentration from Brix % is far from being considered sufficiently accurate. At the same time, quality testing via refractometer is a common, easy to perform, and widely accepted practice and has definitely contributed to improving calf conditions and definition of best practices in BC management worldwide. Indeed, it has been demonstrated that Brix % and IgG of BC are strongly genetically and phenotypically correlated (Soufleri et al., 2019; Costa et al., 2022c). This suggests that refractometers are able to generate an exploitable proxy of the IgG, in both low- and high-quality BC samples. In their letter to the editor, Lombard et al. (2022) advised that conclusions derived by Schalich et al. (2021) using data from 27 high-quality BC samples are potentially distorted and can thus generate confusion.

Infrared Spectroscopy

Mid-, VIS, and near-infrared spectroscopy are widely used for rapid and accurate analysis of several matrices, including milk and dairy products. Based on preliminary research carried out by Navrátilová et al. (2006) and Rivero et al. (2012) and, more recently, Franzoi et al. (2022) and Costa et al. (2022a,b), prediction of BC composition traits through infrared spectroscopy is feasible and shows promising accuracy. Franzoi et al. (2022) evaluated the ability of near-infrared spectroscopy (NIRS) to assess IgG, IgA, and IgM in thawed BC individual samples using RID as a reference. Out of the 3 fractions, only the model for IgG reached satisfactory prediction performance, making the calibration suitable and sufficiently accurate for implementation and routine application (Franzoi et al., 2022). Costa et al. (2021a) estimated a genetic correlation of 0.85 and a phenotypic correlation of 0.77 between the RID and the NIRS-predicted IgG (Figure 2). Similarly, correlations between the RID and the NIRS prediction were calculated for the other fractions (Figure 2). These findings suggest that collection of phenotypes on a large scale could rely on infrared spectroscopy devices, allowing for cost-effective, objective, accurate, and rapid BC phenotyping. Preliminary simulations of Costa et al. (2021a) demonstrated that the response to selection achievable with NIRS-predicted IgG is similar to that attainable through RID phenotypes. Research on the ability and potential use of mid-infrared spectroscopy (MIRS) to predict BC immunoglobulins is in progress (Spina

et al., 2021; Costa et al., 2022a,b; Goi et al., 2023). The development and the implementation of specific prediction equations in existing devices used for milk analysis would provide robust and reliable phenotypes to be used for management and breeding purposes. Briefly, Costa et al. (2022b) observed that the total protein content predicted via MIRS is strongly associated with the BC total protein content determined with the Kjeldahl method (0.97) and with RID IgG (0.87) at phenotypic level. In addition, MIRS shows outstanding predictive ability for IgG in colostrum diluted 1:1 in pure water (Goi et al., 2023), with coefficient of determination in cross (n = 383) and external validation (n = 132) of 0.92 and 0.84, respectively. Goi et al. (2023) reported slightly lower root mean square error in cross (9.53 g/L) than in external validation (13.39 g/L). Receiving operating characteristic analyses carried out by Goi et al. (2023) showed that IgG and protein content predicted with MIRS using a model developed specifically for BC can accurately identify BC of insufficient quality. In particular, 3 thresholds of IgG were tested (50, 70, or 90 g/L); briefly, the area under the curve was excellent (0.85) for MIR-predicted protein content when IgG threshold was set at 50 g/L and the cut-off identified was 13.08%. Such recent findings do indicate that milk laboratories equipped with MIRS devices may offer an indirect quality evaluation for laboratories and industries where BC is used as an ingredient, for acquisition of phenotypes with punctual determination of IgG (Table 3), and finally for farmers to support the decision making.

Devices currently in use for official routine milk analysis can be used to perform liquid BC quality assessment. However, specific prediction equations for major BC components are still not commercially available from the NIRS and MIRS device manufacturers (Costa et al., 2021a; Goi et al., 2023). Customized equations may be developed for PBC or pooled BC for a variety of features in addition to IgG. In fact, several components that may be relevant to the food and pharmaceutical industry are independent from the immunoglobulin concentration (Playford et al., 2020).

In addition to the already-widespread use of benchtop infrared instruments, the application of portable spectrometers in the dairy sector has also increased due to the ease of use, along with their low cost, which gives the opportunity for rapid, reliable on-site feedback. Most popular hand-held analyzers are not specifically designed for complex matrices such as dairy products (Pu et al., 2021). Efforts have been made in the past few years to improve their adaptability and prediction ability in the dairy industry, paving the way for discussions on the potential application for BC. Several studies have already demonstrated screening capacity
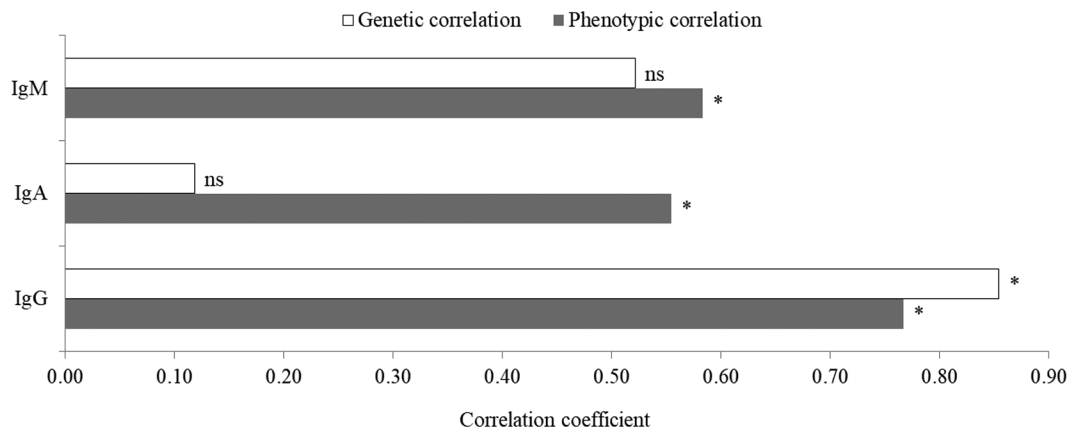
Figure 2. Genetic and phenotypic correlations estimated between the concentrations (g/L) of IgG, IgA, and IgM in bovine colostrum. Significant estimates ($P < 0.05$) are flagged with an asterisk. Estimates retrieved from Costa et al. (2021a).

and discriminant ability of such devices, as in detecting adulterated milk (Santos et al., 2013), organic versus conventional milk (Liu et al., 2018), and presence or absence of lactose (Riu et al., 2020). Gorla et al. (2020) reported an excellent prediction ability of a portable spectrometer for proteins and carbohydrates in milk, which was comparable to results obtained by the benchtop system. Similarly, promising outcomes have been reported by other researchers. A good example is given by Riu et al. (2020), who confirmed optimal results using 2 miniaturized instruments that work at different wavelength ranges in the NIRS region to predict protein and fat content of milk. In perspective, there is potential to adopt infrared spectroscopy for the analysis of solid forms such as PBC. After proper validation, the implementation of such technology will allow further BC quality data acquisition and could help, in the context of farm-level management, to carry out countless control analyses by reducing response times.

PROCESSING

Immune medicaments, infant formula, health beverages, pharmaceuticals, and cosmetics (Tripathi and Vashishtha, 2006; Borad and Singh, 2018; Playford et al., 2020) can contain BC. At the international level, PBC is the most traded form, intended as an ingredient for products used for both animals and humans (Gomes et al., 2021). The industrial processing of fresh or thawed colostrum to obtain PBC is challenging, as BC is a complex matrix characterized by very large variations in terms of water, protein, and fat contents. Moreover, apart from the gross composition, the IgG concentration rapidly decreases in the first 72 h postpartum (Kelly, 2003; Godden, 2008). As a consequence, efforts to establish standardized industrial protocols for

BC handling and processing, and for PBC production, have been met with practical difficulties by dairy plants.

Overall, processing technologies aim at standardizing the matrix of origin, maximizing shelf life, and facilitating logistics of PBC while maintaining its intrinsic beneficial properties (Hurley and Theil, 2011). Processing procedures should seek to protect and preserve the important bioactive factors of BC, to maintain its beneficial effects. Nevertheless, a standardization method does not exist currently due to the variability of delivered supplies, e.g., density and solids content (Scammell, 2001). Conventionally, BC intended for PBC manufacturing should meet some general physical and composition criteria regarding density, color, odor, IgG concentration, and presence of foreign material and residues of antibiotics or pesticides.

Heat Treatment

Temperature and duration of heat treatments can differ according to the dairy industry and product purpose, but generally they aim at reducing pathogen concentrations and proliferation. Colostrum is pasteurized at 72°C for 15 s prior PBC manufacturing to limit undesired changes in terms of quality (e.g., IgG, IgA, IgM, lactoferrin, lysozyme, growth factors). Immunoglobulins, in fact, are thermolabile, and denaturation initiates at operating temperatures >65°C (Borad and Singh, 2018). A 100% protein denaturation was observed by Li-Chan et al. (1995) after ultra-high temperature heating (138°C for 4 s). Godden et al. (2003) observed immunoglobulin loss after pasteurization of 26.2% in BC intended for calf feeding. The same authors stated that the loss extent depends on the batch size. For example, 95-L and 57-L batches showed losses of 58.5 and 23.6%, respectively. Findings of Godden et al.

(2003) suggested also that immunoglobulin reduction is greater when the initial concentration of immunoglobulins is high. In particular, the IgG concentration before pasteurization was positively correlated (0.46) with the IgG loss after pasteurization, indicating that IgG loss is partly determined by the initial concentration before processing. Therefore, the quality of BC before pasteurization must be high enough to guarantee a sufficient quality (>50 g/L) after heat treatments. Finally, although BC administered to the newborns is often delivered warm (e.g., 63°C for 30 min) to reduce microbial activity, calves' serum IgG concentrations tend to be greater when BC is served as fresh (Godden et al., 2003). As an alternative, high-pressure processing can be used as a preservation technology, as it reduces the BC pathogen loads and prolongs the shelf life. Unlike conventional pasteurization, this technique minimizes loss of bioactive compounds and nutrients (Stratakos et al., 2019).

Powder Processing

Powdered BC has become a common ingredient for enrichment or fortification and can be found in the recipe of various products, including infant formula and cosmetics. As mentioned in the previous section, the production of PBC requires certain treatments but starts with collection (phase I). If the supply is frozen, thawing of bags, bottles, or buckets in a controlled and sterile environment is needed, followed by pooling and mixing in batches to guarantee homogenization. Various critical control points can be identified during the whole process, most of them regarding contamination and cold chain maintenance. The pooling step leads to standardization of solids contents and ratios of constituents to each other. As with milk, raw BC for human use must undergo thermal treatments. In fact, spray drying of any secretion, including BC, into a powder requires a pre-heating step that is often used in conjunction with a pasteurization loop (phase III; Kaplan et al., 2022). This is generally a high-temperature short-time pasteurization, with the fluid reaching 72°C for 15 s, sufficient for the removal of the most common pathogens: *Salmonella*, *Mycobacterium*, *Mycoplasma*, and *Listeria* (Godden et al., 2003; Stabel and Lambertz, 2004; Kaplan et al., 2022).

Once the matrix is pasteurized, it goes through a spray drying process (phase IV), which aims to facilitate long-term storage with minimal loss of functionality (Guiné, 2018). However, as discussed in previous sections, heat can negatively affect the immunoglobulin content of BC: all drying methods cause some form of protein damage (Støy et al., 2016). Freeze drying can be used for the maintenance of bioactive compounds (Elfstrand et al., 2002); however, the throughput is lesser and the cost greater than spray drying, thereby affecting the total volume of BC processable in a given period. Its cost-effectiveness makes spray-drying the preferred option (Chelack et al., 1993). Independent of the method used to dry BC into powder, the final product in all commercialized forms needs to be safe for humans before, during, and after distribution. In particular, to be marketed, PBC is usually tested for one or more components necessary to determine its nutritional value, like IgG, fat, protein, moisture, vitamins, minerals, lactose, and so on. Thereafter, PBC could undergo bacterial testing for both total aerobic plate count and total thermophilic count, followed by testing for pathogenic organisms such as *Cronobacter* spp. and *Salmonella* spp., the major potential pathogens of dairy powders. Testing for these noncompliances is done under standards of the International Organization for Standardization (ISO) and International Dairy Federation guidelines, such as ISO 14461, 17822, 22119, and 22174. The outcome of such testing is provided to the purchasing market or final processor to meet contractual requirement concerning quality.

Properties of the Solid Form

Some standards for PBC can be retrieved, with specific information regarding gross composition, specific weight, and sensorial properties. Solid forms of milk and BC show properties different from those detectable in the raw liquid form. For example, protein digestibility of dairy foods is affected by processing, due to the interactions between protein structure and heat (van Lieshout et al., 2020).

Freeze-dried PBC shows reduction in both IgG and IgA, independent of the processing temperature used before drying (Das and Seth, 2017). As IgG is one of the major components on which PBC is sold, the decrease along the production steps is important to track. A study of available PBC products showed a large spread in the concentrations of IgG regardless of the protein content, with the lowest concentration of 5 g of IgG/100 g observable in an item containing 60 g of total protein per 100 g of product (Playford et al., 2020). The stated IgG concentration varied from 5 to 40 g/100 g when total stated protein ranged from 55 to 88 g/100 g. Lastly, many of the items that were investigated by Playford et al. (2020) stated neither the IgG nor the protein content. In Australia, according to the legal compositional requirements published in 2011 by the Therapeutic Goods Administration (TGA; Australian Government Department of Health and Aged Care), PBC permitted for use in listed medicines must be obtained exclusively from *Bos taurus* and cannot contain

less than 10% wt/wt of IgG (TGA, 2011). The same document also provides specific indications regarding the geographical origin of BC: that is, it must be supplied by Australian herds or herds from bovine spongiform encephalopathy-free countries already registered for milk production for human use (TGA, 2011).

In perspective, considering that NIRS shows promising performance in prediction of IgG concentration in liquid BC (Franzoi et al., 2022) and milk powder (Wu et al., 2008), it cannot be excluded that NIRS may be adopted for the analysis of PBC in the near future.

In some circumstances, PBC can undergo further heat stress, as during transportation or storage or during further manufacturing paths (e.g., biscuits, lozenges, or gummies containing BC). In this regard, the heat stability of PBC has been investigated by Playford et al. (2020), who demonstrated that heating from room temperature up to 60°C can reduce the starting bioactivity but not the concentration of immunoglobulins. Overall, authors concluded that even short exposure of PBC to temperature between 40 and 60°C can impair its bioactivity, which is defined as the ability of a substance to favorably affect the physiological processes of living matter, be it a cell, a tissue, or an organ (Playford et al., 2020).

APPLICATIONS

Historically, BC has rarely been consumed per se, but it is present in traditional local foods of certain European and South Asian areas, such as yogurts, fermented milk, kefir, dessert, cheese, and curd (Scammell, 2001; Silva et al., 2019; Mehra et al., 2021). In the early 1980s, colostrum of dairy species was recognized as a source of important antibodies, and inclusion in infant formula was suggested (Scammell, 2001). The BC began to be sold and purchased as a commercial product in the late 1980s for veterinary use, to limit failure of passive transfer of immunity in newborn progeny of livestock species. In the mid-1990s pharmaceutical human products based on or containing colostrum of dairy species have been patented and produced by a few manufacturers located in Europe, the United States, and Australia. Using rat models, increasing levels of BC supplementation were tested in New Zealand to define the toxicity level of this ingredient in humans (Davis et al., 2007). After the trial (90-d length), no adverse or detrimental effects were observed, but the authors concluded that human-based studies were still necessary to confirm the safety of BC consumption in the long term. Nowadays, hyperimmune BC preparations are suitable for human use and are recommended as promoters of health (Kramski et al., 2012; Batista da Silva Galdino et al., 2021).

Functional Foods and Dietary Supplements

The nutraceutical properties of BC have been extensively studied in the literature (Stelwagen et al., 2009; Bagwe et al., 2015; Lee et al., 2019), and principal functions of major components are summarized in Table 4. Several clinical trials carried out around the year 2000 revealed a positive effect of colostrum on adults' athletic performance, muscle mass, and bone health (Antonio et al., 2001; Mizelman et al., 2017; Silva et al., 2019). In particular, athletes who consumed BC were characterized by greater resistance to fatigue, greater lean mass, lower body fat, healthier gut, boosted immune system, and quickened recovery from injuries (Scammell, 2001; Godhia and Patel, 2013; Bagwe et al., 2015; Silva et al., 2019). Such positive effects are generally attributed to antibodies, antimicrobials, and some growth promoting factors, such as insulin-like growth factor-I and II (Godhia and Patel, 2013), but still the role of each compound remains to be elucidated (Antonio et al., 2001; Arslan et al., 2021). A recent review has underlined limited evidence for effects of BC on body composition and physical performance (Davison, 2021). Early suggestions that supplementation with BC products could increase systemic levels of insulin-like growth factor-I are not supported by the balance of available evidence examining a range of doses over both short- and long-term periods. Therefore, future studies should better investigate the dose-response profile and explore the mechanisms underpinning the efficacy of supplementation (Davison, 2021). In addition, BC contains leptin, a satiety-inductor, and the lipid profile shows that 54% of fatty acids are mono- or polyunsaturated (Antonio et al., 2001; Silva et al., 2019). Therefore, due to interactions of all its bioactive factors, addition of BC to sport and weight loss diets is expected to be beneficial for adults. Powdered whey proteins used in sport environments are typically consumed through drink, shakes, tablets, and bars enriched with PBC, the latter being usually very well tolerated by consumers with almost no collateral effects (Bagwe et al., 2015). As reported by Silva et al. (2019), the incidence of gastrointestinal problems in exercising adults is reduced in presence of BC supplementation, as prolonged or agonistic sports practices often result in immune depression and oxidative stress (Chantler et al., 2022).

Infant Formula

Milk and derivatives, including BC, are frequently used for infant formula production. According to the recipe, various ingredients that have already undergone preliminary quality checks are mixed and processed following standard procedures.

Table 4. Common bioactive compounds[1] of bovine colostrum and indication of their primary roles

Constituent	Main function(s)	Typical concentration[2]
Immunoglobulins	Immune response, including antiviral function and toxins neutralization	30–200 g/L
Lactoferrin	Antiviral, anti-inflammatory, antibacterial, and antioxidant functions	1.5–5 g/L
Vitamins	Antioxidant activity, nutritional role as promotors[3] of growth and health	~11 mg/L
Minerals	Nutritional role as promotors[3] of growth and health	~13.9 g/L
Fatty acids	Nutritional role as promotors[3] of growth and health	~60 g/L
Growth factors	Stimulation of cell/tissue growth via new DNA formation	~1.6 μg/L
Lysozyme	Bactericidal role, immune system boosting	0.14–0.70 mg/L

[1]Sources: Stelwagen et al. (2009); Godhia and Patel (2013); McGrath et al. (2016); Bagwe-Parab et al. (2020); Arslan et al. (2021); Gomes et al. (2021); Playford and Weiser (2021).

[2]Average values from colostrum sampled in the first days after calving converted by considering a density of 1.068 kg/m^3.

[3]Particularly those belonging to the "essential" family.

Studies carried out in human infants and animals suggest that BC should be supplemented at an optimal age, time, and level to be both safe and effective (Hurley and Theil, 2011; Ulfman et al., 2018; Bagwe-Parab et al., 2020). Feeding exclusively pasteurized BC, or as a supplement to an infant formula, may protect against several gastrointestinal diseases, such as rotaviral diarrhea, necrotizing enterocolitis, sepsis, and chemotherapy-induced mucositis (Gomes et al., 2021). The evidence suggests safe and beneficial effects particularly of hyperimmune BC products directed toward specific pathogens in infants and children (Hurley and Theil, 2011; Ulfman et al., 2018; Bagwe-Parab et al., 2020). However, currently, exclusive BC feeding is not recommended for infants because of nutritional imbalances compared with human milk. Moreover, adverse effects, including allergies and intolerance, appear unlikely when BC is provided as a supplement within normal nutrition guidelines for infants and children. Indeed, immunoglobulins and other bioactive factors in BC may work in synergy, making it critical to preserve bioactivity with gentle processing and pasteurization methods. Accordingly, BC is considered a safe and effective nutritional supplement for several pediatric subpopulations (Sangild et al., 2021). However, it has been suggested that supplementation with BC might only be considered when a mother's own milk or donor human milk is not available or is clearly insufficient in nutrients or protective factors. Inclusion of BC has been proposed to support other therapies such as probiotics, which until recently were considered unsafe for immunocompromised infants and children (Sangild et al., 2021).

Companion and Livestock Animal Nutrition

Colostrum administration to newborn animals is extremely important in mammals whose placenta does not allow direct transfer of antibodies from dam to fetus during gestation or in situations where maternal colostrum quality or quantity is insufficient (Costa et al., 2021b; Rossi et al., 2021). Dam-side aspects such as amount and quality of colostrum produced are important to consider; however, it is also crucial to highlight that the gut's uptake ability in calves can differ due to both genetic and nongenetic sources of variation (Cordero-Solórzano et al., 2022). To the authors' knowledge, no studies have evaluated the heritability of gut permeability in neonatal calves. However, Cordero-Solórzano et al. (2022) demonstrated that serum IgG in calves is a heritable trait (0.25). This suggests that not only BC IgG but also the IgG absorption ability of calves could be increased by means of selective breeding.

On well-managed dairy farms, frozen BC is available to cover emergency situations and to guarantee passive acquisition of immunoglobulins. Seasonal husbandry systems, such as that of New Zealand, provide the ability to pool BC or to use higher-quality fresh BC to cover periods of shortage, as all cows calve within a 9- to 12-wk period. Despite this flush or peak of calving and therefore of BC production in countries like New Zealand, there is limited scope for industrial processing of colostrum for PBC. This is partly due to the welfare implications of supplying high-quality BC for processing, whereas calves may have access to BC with lower IgG concentrations (Coleman et al., 2015). Conversely, some farmers prefer purchasing PBC; this colostrum-based preparation needs to be dissolved in water, mixed, and heated according to the manufacturer's instructions before it can be administered to neonates. Such preparations are not specifically developed for calves, making them useful also for buffalo calves, rabbits, piglets, foals, kids, and lambs (Blum and Hammon, 2000; Castro et al., 2005; Støy et al., 2016). In their review Boudry et al. (2008) reported that BC can be a growth promotor in weaning piglets. Some studies, such as that of Agbokounou et al. (2017), demonstrated an augmented average daily gain and gut health in BC-treated versus control piglets. In addition to young livestock animals, PBC can be administered

at home in case of urgency to puppies and kittens upon veterinarian recommendation (Rossi et al., 2021). In fact, colostrum has been used for several experimental purposes in companion animals, and several favorable clinical effects have been demonstrated: it stimulated canine immune functions (Satyaraj et al., 2013), improved fecal score in puppies (Giffard et al., 2004), and increased proliferation of fibroblasts in dogs (Torre et al., 2006). Overall, literature confirms BC to have the potential for use for regenerative scope and gut health maintenance in pets (Torre et al., 2006; Gore et al., 2021; Rossi et al., 2021).

In fish, Da Cruz et al. (2016) evaluated the effects of lyophilized BC in the intestinal epithelium; inclusion of BC in the measure at 0, 10, or 20% in the diet did not significantly influence the enteric histological characteristics of juveniles (*Salminus brasiliensis*). In contrast, Rodrigues et al. (2010) reported a significant effect of BC on both intestinal epithelial traits in *Pseudoplatystoma fasciatum* juveniles under experimental conditions.

Clinical Use and Pharmaceutical Industry

As reviewed by Rathe et al. (2014), beneficial effects and good tolerability of BC-based products on gut health have been demonstrated in adults in a large number of studies. In particular, the protective role of BC against cardiovascular diseases, colon cancer, and inflammatory bowel disease, and its favorable effect on epithelial growth and repair deserve specific mention (Anderson et al., 2019; Silva et al., 2019). Indeed, BC has been successfully used to treat and prevent gastrointestinal diseases (diarrhea), immune system disorders, bone resorption, and allergies, thanks to the growth factors, nutrients, hormones, and paracrine factors that contribute to mucosal healing (Gomes et al., 2021). As to the specific activity on immune system, BC can modulate the function of subsets of lymphocytes, macrophages, and dendritic cells, and increase regulatory cytokines such as interleukin 10. In animal models, BC benefits nonsteroidal anti-inflammatory drug-induced enteropathy, inflammatory bowel disease, and intestinal failure. In human trials, substantial evidence suggests efficacy of BC in inflammatory bowel diseases and in infectious diarrhea (Chandwe and Kelly, 2021). This has been confirmed by a recent systematic review describing some general benefits of BC on intestinal and respiratory recovery in absence of adverse effects (Guberti et al., 2021). According to the authors, this was achieved due to the BC capacity to promote immune system enhancement and modulation of local and systemic responses in various clinical and nonclinical conditions (Guberti et al., 2021).

In addition, BC has been used to promote topical tissue and mucosa repair and wound healing (Scammell, 2001; Bagwe et al., 2015; Mehra et al., 2021). Insulin-like growth factors, epidermal growth factors, and transforming growth factors are involved in tissue repair and development of the epidermis (Tripathi and Vashishtha, 2006), and, because of their presence in BC, a variety of compositions have been patented. Nowadays various products intended for skin care and regeneration exist, such as antiaging creams, body lotions, and hand moisturizers (Mehra et al., 2021).

Other clinical uses include BC in topical application in a uro-gynecology setting (Stefani et al., 2014; Nappi et al., 2016), as a dietary supplement for healthy older adults (Duff et al., 2014), and as supporting therapy in critically ill patients (Eslamian et al., 2019). Moreover, studies have described the role of BC in increasing neutrophil counts in acute lymphoblastic leukemia patients undergoing chemotherapy (Caysido, 2019), decreasing acute diarrhea in infants after 72 h (Barakat et al., 2019), reducing enteric inflammation in exposed children (Donowitz et al., 2019), and reducing nasal congestion and thereby promoting pulmonary function in children affected by respiratory allergies (Oloroso-Chavez et al., 2017).

Ghosh and Iacucci (2021) reviewed papers about the potential BC effects on human health and underlined the lack of strong evidence, particularly regarding its role as a defense against infections in vulnerable elderly populations and in infants, in the prevention of necrotizing enterocolitis or sepsis. However, those authors explained that changes in the gut microbiome after the administration of BC and lactoferrin mediated antimicrobial and immune effects. This highlights the potential of BC in preventing infections in undernourished children in developing countries and in preventing diseases such as colorectal cancer (Ghosh and Iacucci, 2021). In conclusion, limited data suggest that BC may have promising beneficial effects in both healthy and sick patients, but further well-designed prospective studies are needed to support the administration of BC in adult, pediatric, clinical, and nonclinical settings.

Colostrum and the COVID-19 Pandemic

Hyperimmune BC can be secreted by cows that have been vaccinated before calving (Weiner et al., 1999). In the era of the COVID-19 pandemic and concerns about vaccination, consumers may potentially have access to milk or dairy products naturally enriched in specific antibodies if vaccines containing SARS-CoV-2 are used on lactating cows (Jawhara, 2020a,b). Based on the recent literature on immunology (de Alwis et al., 2020; Fox et al., 2020; Valk et al., 2020), consumption of co-

lostrum or milk with high concentration of specific IgG ensures a short-term protection against SARS-CoV-2 infections, the agent responsible for the COVID-19 pandemic. In the study of Fox et al. (2020), a pool of women who had experienced COVID-19 produced fortified colostrum and milk for their infants; that is, their secretion was characterized by specific immune properties. Muyldermans et al. (2022) reviewed 30 articles investigating the effect of COVID-19 vaccination on lactating women; in all studies, vaccinated nursing women presented SARS-CoV-2-specific antibodies in the breast milk. It is a common misconception that immunoglobulins are entirely absorbed into the bloodstream following BC ingestion in humans. Intake of BC or milk with artificially or naturally increased IgG concentration is not able to boost the circulating IgG itself: antibodies are subjected to proteolysis during digestion and are unlikely to be absorbed intact (Hurley and Theil, 2011). Mechanisms of action remains unknown, but it is likely that immune modulation occurs through other processes after the ingestion of IgG, such as immune complex formation, rather than by absorption into the bloodstream, (Gomes et al., 2021). Moreover, the observed beneficial preventive effects of BC depend on the volume ingested and the processing techniques used for product manufacturing.

TRADING

It is reasonable to think that suppliers of BC are nowadays paid mostly according to the volume delivered. As with milk and other feeds/foodstuffs, colostrum-based preparations usually require ingredients to be standardized to obtain final products of standard quality, as in the form of powder, tablets, gummies, or liquid.

Despite the high number of items available in the market, fewer than 10 companies were commercializing BC in the early 2000s (Scammell, 2001; Boland, 2003). Nowadays this business interests a wider audience, and both the market price and the demand for BC have thus increased. Retrieving detailed information is challenging due to the absence of specific custom codes for BC. In fact, BC could be present in different amounts in all items labeled with specific custom codes: HS 04049021 ("products consisting of natural milk constituents, not containing added sugar or other sweetening matter, of a fat content, by weight, of $\leq 1.5\%$, not elsewhere specified") and HS 04041048 ("whey and modified whey, whether or not concentrated, not containing added sugar or other sweetening matter, of a protein content [nitrogen content $\times$ 6.38], by weight, of $\leq 15\%$ and of a fat content, by weight, of $\leq 1.5\%$ with exclusion of powder, granules or other solid forms") refer to matrices or items containing colostrum, fully or in part (CLAL, Modena, Italy, personal communication).

Playford et al. (2020) summarized the IgG concentration of BC of different brands, of which most of the producers were located in the United States, the United Kingdom, New Zealand, Germany, and the Netherlands. These companies were prevalently producing BC powders and tablets. Because few companies and countries are involved in PBC production and export, it is possible that a single company may be sourcing BC from several sources or countries in various forms to produce mixtures to be used for final products; this phenomenon may mask individual country effects. Similarly, different brands of BC may, in reality, be identical in terms of constituents due to being sourced from the same main producer and simply labeled under a different brand name.

North America is the leading region for BC, followed by Asia and Europe (Scammell, 2001). Through the Google Trends feature (https://trends.google.com/trends), the trends of popular words entered into Google's search engine can be tracked back. In addition, the application can show how frequently a given term is searched in a window of time by mean of the overall interest, expressed in percentage, where 100% indicates the maximum popularity achieved by the term in a given geographic area since 2004, the starting year of Google Search. By exploiting this public information, it has been possible to observe that in the major PBC-producing countries indicated by Playford et al. (2020), the United States and the United Kingdom, general interest in the word "colostrum" has progressively increased in the past 12 years (Figure 3). The same can be said for the worldwide trend. Furthermore, regardless of the geographic area, the maximum interest ever (100%) has been reached in the last 24 mo, suggesting that colostrum is a topic that grabs the attention of the current society. Colostrum is therefore interesting for a wide-ranging audience and not exclusively for people in the industry or in research fields (Table 1; Figure 1). For the year 2010, the number of items associated with the word "colostrum" available in Google engine search can be approximated at 11,000 (https://www.google.com/); 12 years after, in particular from January 1 to October 30, 2022, that number massively increased, to 2,310,000 (https://www.google.com/).

For industrial use, only BC milked from the second or third day after calving is expected to be supplied. In this secretion, the immunoglobulin concentration is greatly lower compared with the first milking (Godden, 2008). Therefore, it is the transition milk that in reality may show potential applications, as it can be considered a dairy farm by-product. Although this aspect could limit applications of BC if products require high IgG
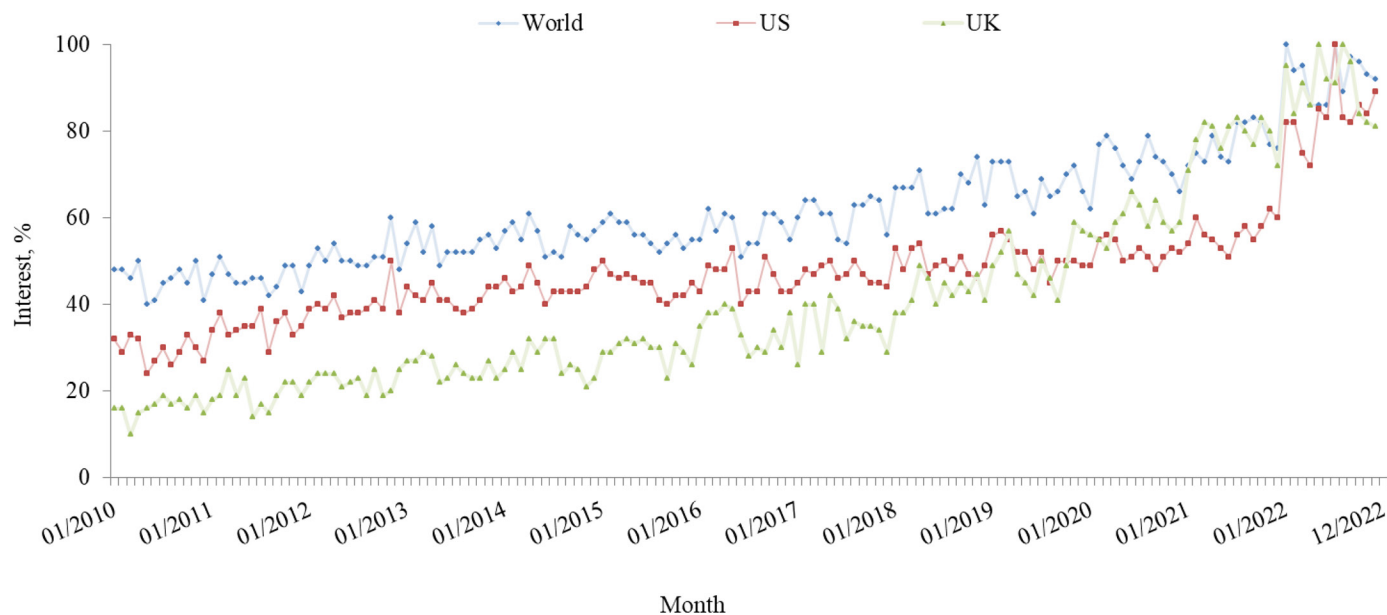
Figure 3. Interest in the term "colostrum" over time from 2010 onward (source: Google Trends, https://trends.google.com/trends/). Data as of December 29, 2022, expressed in percentage, where 100% indicates the maximum popularity achieved by the term in the geographic area.

in the original matrix, it is also common not to declare the specific concentrations in most commercial product labels (Playford et al., 2020).

An additional consideration is needed for some market access requirements, with countries such as Japan prohibiting the sale of any mammary gland secretion (milk or BC) obtained in the first 5 d following parturition (Cairangzhuoma et al., 2013). Furthermore, a particular situation is present in China, where the Ministry of Health in 2012 started to put constraints into inclusion of BC and milk obtained in the first 7 d after calving in infant formulas and infant foodstuffs. Reasons lie in the unknown side effects of prolonged intake of BC in babies and toddlers, and in the potential presence of dangerous substances such as antibiotics and hormones.

Figures related to volume demand and market price trends of PBC are not available, but the global business around colostrum was estimated to be around US$15 million in 2001 (Scammell, 2001), and it is expected to reach US$4 billion in 2027 (Transparency Market Research, 2021).

Due to the large variability of BC chemical composition, standardization of PBC processing is hardly achievable, and further efforts and research are needed to better master and manage the delivered BC. In addition, further important points include consistency of supplies and the welfare implications from a calf welfare and development standpoint. In fact, farmers may not have BC in excess on a regular basis to be sold to the dairy processing industry and it has been

demonstrated that some cattle breeds do not produce enough BC at first milking for the calf (Gavin et al., 2018). Therefore, in some contexts, BC delivery to the factory—but not necessarily the availability of PBC on the market—could suffer from seasonal factors. Furthermore, from an ethical perspective, risk exists that PBC production may start to be seen as an opportunity for business by farmers and other dairy stakeholders. Increased willingness to sell fresh or frozen BC could be unfavorable for the young stock. The best practice for calf rearing is to feed BC with as high an IgG content as possible, meaning that BC obtained at first milking—highly rich in IgG—must be primarily used for newborn calves. Instead, BC with a lower IgG content, such as that yielded from the second or third milking onward, which exceeds the farm's needs, can be treated as a by-product available for other uses. In this view, animal health and welfare implications deserve discussion. With the market price of BC getting progressively higher, there might be a tendency to sell more and more. The practice of collecting BC from farmers can risky for the newborns. Therefore, the rules around the supply of this milk stream would need to be regulated at an international level to ensure that, while quality is maintained, animal welfare is not compromised in any case.

CONCLUSIONS

In dairy species, colostrum is primarily intended for feeding the neonate. In the case of cattle, BC shows

nutraceutical properties and proven benefits that make it a very promising ingredient to be incorporated in foodstuffs and supplements, stimulating the interest of both the food and the pharmaceutical industries. The interest in BC is increasing year on year, particularly from medical science applications for curative purposes. There is room to promote the use of BC in the dairy industry, but, in parallel, research is needed to explore the properties of this matrix and define specific quality standards and sampling protocols. Moreover, indirect assessment of BC quality, including IgG concentration, through infrared tools is feasible considering the promising prediction accuracy. Being able to determine and monitor the BC composition will translate into the possibility to set up a payment system for suppliers in future times. Finally, with the price of colostrum rising, the risk of compromising health and welfare of young stock is not negligible, as the willingness of sell colostrum could take over. The scientific community is invited to discuss the possibility to modulate and monitor the offering of BC, as through a quota-like system. Above all, stakeholders of the dairy chain must cooperate horizontally to ensure proper destination of BC within the farm and to support related decision making.

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
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