The Use of Whey or Skimmed Milk Powder in Fortified Blended Foods for Vulnerable Groups¹,²

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Abstract

Fortified blended foods (FBF), especially corn soy blend, are used as food aid for millions of people worldwide, especially malnourished individuals and vulnerable groups. There are only a few studies evaluating the effect of FBF on health outcomes, and the potential negative effect of antinutrients has not been examined. Different lines of evidence suggest that dairy proteins have beneficial effects on vulnerable groups. Here we review the evidence on the effects of adding whey or skimmed milk powder to FBF used for malnourished infants and young children or people living with HIV or AIDS. Adding whey or skimmed milk powder to FBF improves the protein quality, allowing a reduction in total amount of protein, which could have potential metabolic advantages. It also allows for a reduced content of soy and cereal and thereby a reduction of potential antinutrients. It is possible that adding milk could improve weight gain, linear growth, and recovery from malnutrition, but this needs to be confirmed. Bioactive factors in whey might have beneficial effects on the immune system and muscle synthesis, but evidence from vulnerable groups is lacking. Milk proteins will improve flavor, which is important for acceptability in vulnerable groups. The most important disadvantage is a considerable increase in price. Adding 10–15% milk powder would double the price, which means that such a product should be used only in well-defined vulnerable groups with special needs. The potential beneficial effects of adding milk protein and lack of evidence in vulnerable groups call for randomized intervention studies. J. Nutr. 138: 145S–161S, 2008.

Introduction

This article is one component of a Food Aid Quality Enhancement Project to enhance product quality and improve nutrient delivery to recipients of U.S. food aid commodities. The project is coordinated by SUSTAIN, a U.S. nongovernmental organization that uses science and technology to improve nutrition in developing countries. The article will assess the value of adding whey protein (WPRO)³ to fortified-blended foods (FBF) to improve their nutritional value. The potential impact of using other dairy products, especially skimmed milk powder (SMP), will also be evaluated, as it has been used in many other food aid products and is widely available.

FBF is used on a very large scale to feed populations in low income countries, especially malnourished individuals and vulnerable groups. The most common FBF are corn soy blend (CSB) and wheat soy blend (WSB). They are made from wheat or corn as the main staple, soy flour to improve the protein quality, a vegetable oil source, and a mix with mineral-vitamins to fortify the blend. Most of the FBF is donated by the United States and delivered by the World Food Program (WFP).

The recipes are developed to provide a balanced intake of essential nutrients for growth and development of young children and for malnourished individuals. They were originally developed by the U.S. Agency for International Development in the 1960s. They are designed to be energy and nutrient dense, and, as they are precooked, they are easily prepared into an energy-dense porridge that is easy for children to eat. However, very few studies have evaluated the effect of FBF in malnourished and vulnerable groups. Raw soy contains considerable

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³ Abbreviations used: AA, amino acid; BCM, body cell mass; β-LG, β-lactoglobulin; BMD, bone mineral density; CSB, corn soy blend; DSM, corn soy milk; DSM, dried skim milk, same as NDM and SMP; F-100, therapeutic milk; FBF, fortified blended food; GMP, glycomacropeptide; GSH, glutathione; IGF, insulin-like growth factor; IOM, Institute of Medicine; MT, metric ton; NDM, nonfat dry milk, same as DSM and SMP; PDCAAS, protein digestibility-corrected amino acid score; PE%, protein energy percentage; PLWHA, people living with HIV and AIDS; RUTF, ready-to-use therapeutic food; SMP, skimmed milk powder, same as DSM and NDM; WFP, World Food Programme; WP, whey powder; WPC, whey protein concentrate; WPI, whey protein isolate; WPRO, whey protein; WSB, wheat soy blend, WSM, wheat soy milk.

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amounts of antinutrients (such as antitrypsin) that potentially interfere with protein digestibility and mineral absorption. The processing of FBF is designed to reduce antinutritional factors, but the actual decrease in antinutritional factors has not been documented clearly. The efficacy of cereal- and legume-based supplementary feeding in large-scale programs has not been conclusively demonstrated (1–3).

WFP held a technical review on its FBF in Rome in July 2005, which also dealt with the potential use of milk or milk products in FBF. The objective was to review the appropriateness of the product specifications vis-à-vis nutritional requirements of specific target groups, including protein content and qualities, keeping the overall cost of the products in mind. One point of discussion was a number of recent studies highlighting the role of foods of animal origin in ensuring child growth and development. The level of antinutritional factors in the blends was also discussed. One conclusion was the need to develop special “convalescent” foods for moderately undernourished children. Also, it was concluded that the benefits of including SMP in FBF and in new foods for malnourished children should be reviewed.

In terms of formulation, it was recommended that FBF form 25% of the total ration/diet, and it was suggested that a convalescent food should supply a minimum of 50% of energy intake during an initial phase of 1–6 wk.

The main aim of this review is to evaluate whether or not there is research to support substituting some of the vegetable or legume protein in the blends with dairy protein. Two central areas are covered. One is to evaluate data on the potential effects of improved protein quality on health outcomes, and the other is to assess evidence on potential positive health effects of biologically active compounds in milk, especially whey.

The review focuses on 2 important vulnerable groups, namely people living with HIV and AIDS (PLWHA) and malnourished infants and young children. Both groups have increased nutritional needs because of infections and different degrees of malabsorption, have a low muscle mass and thereby increased nutritional needs for catch-up growth, and also often have poor appetites.

A spectrum of nutritional conditions pertain to the populations receiving food aid, including nonmalnourished individuals in need of food, vulnerable groups and individuals with moderate malnutrition, and those with severe malnutrition. FBF without any animal foods will be sufficient to support those without malnutrition. SUSTAIN is currently assessing their suitability as complementary foods for nonmalnourished and moderately malnourished infants, and preliminary findings suggest that dilution of the cooked FBF may negatively impact energy and nutrient density and infants’ ability to consume adequate quantities based on their average stomach capacity. During the last decade, a special diet (therapeutic foods, F-100, produced by several manufacturers) in which the only protein source is milk has proven to be very effective in hospital-based treatment of severely malnourished children and has reduced mortality considerably (4). Recently, a new kind of therapeutic food, ready-to-use therapeutic food (RUTF), has been used in home-based treatment programs of both severely and moderately malnourished children (5–7). Most of the RUTF contains a considerable amount of milk powder. If FBF fortified with dairy protein is introduced as a special food or a “convalescent” food to selected vulnerable groups, it may fill a gap between plant-based FBF and RUTF wherein about half of the protein or more is dairy protein. Consequently, this review also briefly summarizes the composition and main results obtained using therapeutic foods including RUTF.

### FBF

FBF consist of a mixture of cereals, pulses, fats, vitamins, and minerals intended to provide a balanced intake of essential nutrients for vulnerable groups. These comprise the original FBF, namely corn soy blend (CSB) and wheat soy blend (WSB). However, other types of FBF exist based on sorghum and soy, bulgur, wheat and soy, or combinations of cereals with heat-treated soy in its full fat form or as defatted flour. There are also FBF that contain milk, corn soy milk (CSM) and wheat soy milk (WSM), described in more detail below, but they are not widely used, mainly because of the higher cost. WFP has also supported the manufacture of locally designed and produced FBF including Unimix in Kenya, Famix in Ethiopia, Likin Phali in Malawi, and Indiamix in India.

WFP distributed almost 300,000 metric tons (MT) FBF in 2006: >207,000 MT was bought in Italy, Belgium, and developing countries, and 88,000 MT was received as in-kind donations, mainly from the United States (WFP, personal communication). Assuming that FBF provided ~25% of the energy intake [500 kcal (2.1 MJ)] of those receiving it, the amount would be sufficient to supply ~6.5 million people for a whole year.

The nutritional quality of FBF is improved through the addition of soy, and the product is fortified with essential micro-nutrients. Because they are precooked and distributed as flour, they require only limited amounts of fuel for cooking and are simple to prepare and microbiologically safe. Furthermore, they can be produced relatively inexpensively. However, WFP is at present reconsidering the formulation to upgrade the nutritional value.

The ingredients (cereals and legumes) are heat treated before milling to improve digestibility and to reduce levels of antinutrients and cooking times. The FBF is fortified with a vitamin and mineral mix.

### Types of FBF

CSB and WSB are by far the most widely used FBF. They contain cornmeal or wheat flour, soybeans, and a mineral-vitamin mix. CSB consists of ~80% maize and 20% soy, and WSB consists of ~75% wheat and 25% soy. WFP has given specifications for the energy, protein, and fat content of the blends (Table 1). However, according to the U.S. specifications (8), the energy content is somewhat lower [CSB 376 kcal/100 g (1.57 MJ/100 g) and WSB 355 kcal/100 g (1.49 MJ/100 g)], and the protein content also differs (CSB 16.0 g/100 g and WSB 21.5 g/100 g). In recipes for CSB and WSB, the content of soy flour (defatted) is 22 and 20%, respectively (9).

### TABLE 1

| Nutritional value of commonly used food-aid commodities according to WFP¹ |
|-------------------------------|-------------|-------------|-----------------|----------------|
| **Energy** & **Fat** | **Protein** & **Fat** |
| kcal/100 g | MJ/100 g | % | g/100 g | % |
| FBF | | | | |
| CSB | 380 | 1.50 | 14.2 | 18.0 | 18.9 |
| WSB | 370 | 1.55 | 14.6 | 20.0 | 21.2 |
| CSM | 380 | 1.60 | 14.2 | 20.0 | 21.1 |
| **Ingredients** | | | | |
| Wheat (cereal) | 330 | 1.39 | 4.1 | 12.3 | 14.9 |
| Corn (meal) | 360 | 1.51 | 8.8 | 9.0 | 10.0 |
| Soy (flour, full fat) | 380 | 2.00 | 41.6 | 37.2 | 31.0 |
| **Dairy products** | | | | |
| SMP | 360 | 2.10 | 24.6 | 25.0 | 20.0 |

¹ Adapted from (150).
FBJ with milk as SMP are available but have not been used very much, mainly because of the price. Recipes for both CSM and WSM have been developed. Both of these have 15% (wt:wt) SMP. In both recipes, the amount of soy has been reduced by ~4–5% to compensate for the higher protein content. We have not been able to find any studies evaluating the effects on growth or recovery from malnutrition with these milk blends or studies that have compared effects of CSM or WSM with FBF with no milk.

Therapeutic foods
Therapeutic foods are mainly intended for the treatment of severe malnutrition in children and are outside the scope of this article. They will, however, be described briefly, as the protein source in these products is either 100% milk protein (therapeutic milk or F-100) or mainly based on milk protein (RUTF). F-100 consists of 42% milk powder (SMP), equivalent to 11% of energy from proteins. Thus, all protein is milk protein. RUTF nutritional composition is quite close to that of the F-100 therapeutic milk, but the major difference is that F-100 is given as a milk with an energy density of ~1 kcal/g (4.2 kJ/g), whereas RUTF is fat-based pastes with a very low water content and an energy density that is ~5 times as high (5 kcal/g (21 kJ/g)). Some manufacturers add whey powder (WP) to RUTF together with SMP. The rationale for adding WP is not the potential biological effects of whey but rather that WP is less expensive than SMP, has a better protein quality, and might have some technological advantages. Therapeutic milk/F-100 and RUTF have been very successful in supporting growth and reducing mortality in severely malnourished children, and it is plausible that part of this effect could be related to the high milk content, as discussed later.

Milk and powdered dairy products
Milk is an excellent source of a number of nutrients, and its proteins are easily obtained and used in various contexts, which positions them among the best-characterized proteins chemically, physically, and genetically. Mature bovine milk contains ~3.5% protein (10,11). The main protein fractions of bovine milk are casein and whey, which account for ~80% and 20%, respectively. The major casein products are α₁, α₂, β, and κ-casein. The major WPRO include β-lactoglobulin (β-Lg), α-lactalbumin, immunoglobulins (Ig), serum albumin, and lactoferrin, all of which possess specific biological activity (11,12). There are also several minor proteins with specific biological activities.

Whole milk powder. The main difference between whole milk powder and the other powdered products is the fat content. An important reason that whole milk powder is not used much in food aid is the short shelf life because the fat gets rancid easily. The alternative to milk fat, vegetable oil, has a longer shelf life and is less expensive.

SMP. SMP, which is also called nonfat dry milk (NDM) or dried skim milk (DSM), is characterized by having a low fat (0.8 g/100 g) content. SMP has a high nutritional value and is a source of high-quality animal protein (36 g/100 g). SMP has a carbohydrate content of 52 g/100 g, which is predominantly lactose. When stored in cool conditions with low humidity, it has an average shelf life of 3 y.

Whey. Whey is a collective term referring to the serum or liquid part of milk that remains dissolved in the aqueous portion after the coagulation of casein into curd during the manufacture of cheese, where most of the fat and casein have been used in the cheese-making process. The remnant whey is high in both lactose and minerals (13). Currently there are 2 major basic types of whey available, sweet and acid (sour) (14). Acid whey is obtained during the production of acid-coagulated cheeses such as cottage and cream cheese, and sweet whey originates from the manufacture of rennet-coagulated and hard cheese. The biologically active casein glycomacropeptide is present only in sweet whey (14). The concentration of calcium in acid whey is ~2-fold higher than that in sweet whey.

Whey powder, concentrates, and isolates. WP, which is dried whey, has a typical protein content of 11–14.5% and a lactose content of 63–75%. WPRO is, however, processed into whey protein concentrate (WPC) with different concentrations, usually ranging from 34–80%, and as whey protein isolate (WPI) containing at least 90% protein.

Protein quality
One of the main arguments for adding whey or SMP to FBF is to improve the protein quality. Improved protein quality allows for a reduction of the total amount of protein needed, which is beneficial both for economic reasons, as the amount of soy might be reduced, and for metabolic reasons, as metabolizing surplus nitrogen is not efficient.

Protein quality indexes. High protein quality is defined as protein that supports maximal growth. The various protein quality indexes include 1 or more factors related to the AA profile, digestibility, and the presence of inhibiting or biologically active components in the food ingested.

Until recently, protein efficiency ratio was the most widely used index for evaluating protein quality. It is defined as body weight gain divided by the amount of test protein consumed by a young growing rat. Consequently, different growth patterns between rats and humans are a concern when protein efficiency ratio is used (15).

Protein digestibility-corrected amino acid score (PDCAAS) is a more recent evaluation method of protein quality and has been adopted by FAO and WHO (16) as the preferred method of evaluating protein quality in human nutrition.

PDCAAS represents the AA available after protein digestion, that is, the content of the first limiting essential AA in a test protein divided by the content of the same AA in a reference pattern of essential AA (17). The index further includes true digestibility defined as the true digestibility of the test protein, measured in a rat assay, thereby taking into consideration factors influencing the digestion of the protein (15). The maximum PDCAAS value is 1.0, meaning that 100% or more of the requirement of essential AA is achieved. A score above 1.0 is rounded down to 1.0. However, several limitations must be considered when PDCAAS is used: the validity of using the protein requirement of children in a reference AA pattern and the validity of using true digestibility and the truncation of values above 100%, which limits the information provided about the potency of a specific protein source to counteract and balance inferior proteins in mixed diets (17).

Protein quality of FBF and ingredients. Plant protein sources provide 65% of the world’s supply of edible protein, with the main contributors being cereal, especially wheat, rice, and corn. Soy is also used as a source of protein in blends designed for food aid programs, such as WSB and CSB, because of its favorable content and constitution of AA. Although plant products are a good source of protein and certain plant products contain much
higher levels of some AA than animal sources, no plant source provides optimal levels of all 9 essential AA. When the AA profiles of the major plant staple food sources are compared with human muscle tissue, it appears that the limiting AA of corn is tryptophan, and in soy the sulfur-containing AA methionine and cysteine. Further, all plant sources with the exception of soy have a uniformly lower lysine content. In low-income countries, problems with satisfying AA needs are mainly related to mono-tonous diets. However, for mixed diets based on, for example, both cereals and legumes, requirements are often fully achieved because the products complement each other and compensate for the insufficient protein quality (18).

The PDCAAS of corn, wheat, and soy are 0.35, 0.37, and 0.93, respectively (Table 2). However, in the blended foods, the AA patterns of the ingredients complement each other, resulting in relatively better PDCAAS values, e.g., the PDCAAS of CSB and WSB are 0.65 and 0.64, respectively. If milk is added, as in CSM and WSM, the PDCAAS increases to 0.81 and 0.76, respectively. Digestibility of protein in traditional diets from low-income countries is considerably lower than that of a typical Western diet. This is a result of the presence of less refined cereal and grain legumes, which contain less digestible protein fractions and high levels of insoluble fiber.

The influence of adding whey or SMP to FBF on protein quality. To evaluate the potential effects of adding powdered milk to protein quality, we calculated the quality (PDCAAS) and amount of protein of theoretical blends of FBF where the cereals or soy has been replaced by different amounts of either whey or SMP (Table 3).

PDCAAS is partly based on the content of the first limiting AA, as previously discussed. In accordance with the general knowledge that limited lysine can pose a problem in vegetable-based food sources, the first limiting AA of blends in Table 3 is generally lysine because of the low lysine content in either corn or wheat. There is, however, an exception in 2 blends (see footnote 5 of Table 3), where the first limiting AA is tryptophan, which is a consequence of the content of fairly concentrated whey, which balances out the lack of lysine.

In general, CSB has a slightly higher PDCAAS than WSB. Also, blends with reduced soy content have a lower PDCAAS than blends in which soy is not reduced. It is not surprising that products adding the same amount of WPC80% as WPC34% have considerably higher PDCAAS, as it contains more than double the amount of protein. The lower PDCAAS of blends containing SMP in comparison with whey-containing blends is explained by a lower content of lysine in SMP.

The addition of the milk powders results in considerable increases in protein energy percentages as expected, from the level of 17.2–21% in CSB and WSB in blends with no milk up to levels ~20–25% when 5–20% milk powder is added. Furthermore, when milk is a considerable part of the protein, the digestibility and, thereby, the bioavailability of the protein will be higher as reflected in the higher PDCAAS.

In general, blends containing 10% WPC80% possess slightly higher PDCAAS than blends containing 20% WPC34% as 10% WPC80% contain slightly more protein than 20% WPC34%.

Soy flour has approximately the same protein content as SMP and WPC34%. Thus, exchanging soy for 1 of the 2 milk powders will result in approximately the same protein energy percentage (PE%), but the protein quality will increase from the higher PDCAAS of milk products.

It is beyond the scope of this article to develop detailed recipes. This can be done by linear programming where protein energy percentage, protein quality (PDCAAS), fraction of protein that should be milk protein, lactose content, and fat energy percentage should be taken into consideration.

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### Antinutritional factors.
Antinutritional factors are mainly present in pulses, grain, and legumes and can impair intake, uptake, or utilization of other food and feed components (19). These factors can be difficult to measure, and the Codex Commission has not yet set standards for these factors. Important antinutrients include lectin, hemagglutinins, saponins, antitryptsin, antichymotrypsin, thiame, and phytate.

Raw soy is the most concentrated source of trypsin inhibitors. Trypsin inhibitors are not restricted to their effect on trypsin but may also inhibit other proteases that contain serine in the active site. Tannins are present in various plants, including cereal grains and legume seeds and possess the ability to precipitate proteins in aqueous solutions, making them less available for digestion and absorption. Phytates are found primarily in seeds, nuts, and grains and interfere with zinc and iron absorption as well as the bioavailability of other essential mineral nutrients. Furthermore, phytates are able to bind proteins in the gastrointestinal tract and negatively influence the activity of digestive enzymes.

Although it has often been mentioned that soy contains high levels of antinutrients, we have not been able to identify studies with FBF that have clearly demonstrated a negative effect of such antinutrients. Studies on infant formula based on soy protein show that there are no major differences in growth compared with cow’s milk-based formula (20). However, soy-based infant formulas contain soy protein isolates that have a low content of phytate (1–2%), which is considerably lower than that in FBF using crude toasted soy. In a recent comment from the ESPGHAN Committee on Nutrition, it was recommended that soy formulas be used for specific reasons only, as they may have nutritional disadvantages and contain high levels of phytate and phytoestrogens with unknown long-term effects (20). Additionally, in piglets, WPRO stimulate small intestinal and body growth relative to a corresponding isocaloric and isoproteinous diet with soy hydrolysate (21).

<table>
<thead>
<tr>
<th>Amino acids</th>
<th>WPI &gt; 90% (151)</th>
<th>WPC80% (152)</th>
<th>WPC34% (151)</th>
<th>SMP (151)</th>
<th>F-100 (153)</th>
<th>CSM (153,154)</th>
<th>WSM (153,154)</th>
<th>CSB (153,154)</th>
<th>WSB (153,154)</th>
<th>Soy flour (raw) (153)</th>
<th>Cornmeal (153,154)</th>
<th>Wheat flour (153)</th>
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<tr>
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<td>46.33</td>
<td>48.43</td>
<td>44.22</td>
<td>44.21</td>
<td>39.71</td>
<td>36.91</td>
<td>37.87</td>
<td>34.17</td>
<td>37.52</td>
<td>38.35</td>
<td>30.05</td>
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<tr>
<td>Total BCAA</td>
<td>22.82</td>
<td>21.69</td>
<td>22.51</td>
<td>21.46</td>
<td>21.48</td>
<td>19.38</td>
<td>17.51</td>
<td>18.47</td>
<td>15.98</td>
<td>17.00</td>
<td>20.97</td>
<td>15.12</td>
</tr>
<tr>
<td>Total sulfur-containing AA</td>
<td>5.07</td>
<td>5.41</td>
<td>4.23</td>
<td>3.27</td>
<td>3.26</td>
<td>3.20</td>
<td>3.35</td>
<td>3.21</td>
<td>3.15</td>
<td>2.92</td>
<td>3.92</td>
<td>4.04</td>
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<tr>
<td>Protein, g/100 g protein</td>
<td>100</td>
<td>79.89</td>
<td>35.00</td>
<td>33.50</td>
<td>15.97</td>
<td>19.97</td>
<td>20.62</td>
<td>17.43</td>
<td>20.02</td>
<td>36.54</td>
<td>9.44</td>
<td>10.65</td>
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<tr>
<td>Protein indices (PDCAAS) (17)</td>
<td>1.14–1.67</td>
<td>1.14–1.61</td>
<td>1.14–1.49</td>
<td>1.24</td>
<td>1.24</td>
<td>0.81</td>
<td>0.76</td>
<td>0.65</td>
<td>0.64</td>
<td>0.93</td>
<td>0.35</td>
<td>0.25–0.37</td>
</tr>
</tbody>
</table>
TABLE 3  PDCAAS of different blends with and without milk powder

<table>
<thead>
<tr>
<th></th>
<th>Blends with reduced cereal content</th>
<th>Blends with reduced soy content</th>
<th>Blends with no soy content</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CSB</td>
<td>WSB</td>
<td>CSB</td>
</tr>
<tr>
<td>PDCAAS (PE%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basic blend</td>
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<td></td>
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<tr>
<td>5% WPC34%</td>
<td>0.65 (17.2)</td>
<td>0.64 (21.0)</td>
<td>0.65 (17.2)</td>
</tr>
<tr>
<td>10% WPC34%</td>
<td>0.73 (18.5)</td>
<td>0.71 (22.0)</td>
<td>0.69 (16.5)</td>
</tr>
<tr>
<td>20% WPC34%</td>
<td>0.80 (19.7)</td>
<td>0.77 (23.1)</td>
<td>0.73 (15.8)</td>
</tr>
<tr>
<td>5% WPC80%</td>
<td>0.92 (22.2)</td>
<td>0.89 (25.2)</td>
<td>0.82 (14.5)</td>
</tr>
<tr>
<td>10% WPC80%</td>
<td>0.92 (22.4)</td>
<td>0.92 (27.3)</td>
<td>0.80 (18.9)</td>
</tr>
<tr>
<td>5% SMP</td>
<td>0.71 (18.4)</td>
<td>0.69 (22.0)</td>
<td>0.67 (16.6)</td>
</tr>
<tr>
<td>10% SMP</td>
<td>0.76 (19.6)</td>
<td>0.74 (23.1)</td>
<td>0.68 (15.8)</td>
</tr>
<tr>
<td>20% SMP</td>
<td>0.85 (22.1)</td>
<td>0.82 (25.1)</td>
<td>0.72 (14.4)</td>
</tr>
</tbody>
</table>

1 The amount of dairy powder (WPC or SMP) added to the blend replaced by the same amount of soy, whereas the amount of soy is unchanged.
2 The amount of dairy powder (WPC or SMP) added to the blend replaced by the same amount of cereal (corn in CSB and wheat in WSB), whereas the amount of soy is unchanged.
3 The blends consist only of cereal (corn or wheat) and dairy powder (WPC or SMP) in different ratios.
4 Basic blends: CSB, 80% corn, 20% soy. WSB, 79% wheat, 21% soy.
5 The limiting amino acid is tryptophan. In the other blends lysine is the limiting amino acid.

Cost of milk, types of whey, FBF, and FBF components

The price of commodities used for FBF and relief feeding is an essential factor in deciding the composition of blends and rations. Table 4 presents typical prices of milk products, FBF, cereals, and legumes as of March 2007. In recent years there have been considerable fluctuations of the world market prices on dairy products, and during the first half of 2007, there have been marked increases. Whey has traditionally been an inexpensive surplus product from cheese production and has been used to feed pigs. Other whey types are more expensive per kilogram protein, and unprocessed WP with 13% protein is more expensive than SMP when compared as price per kilogram protein.

Based on a simple calculation of the amounts, not taking extra costs of mixing and other technical aspects into account, adding for example 10% SMP or WPC34% to CSB will increase the price of the product by about two-thirds to US$0.58/kg and US$0.60/kg.

Vulnerable groups

In many low-income countries, large proportions of the population are nutritionally vulnerable, and food aid is often aimed mainly at vulnerable groups. Traditionally, infants and young children, pregnant and lactating women, and the elderly are regarded as nutritionally vulnerable. Other groups are patients with recurrent acute or chronic infections such as those with TB and HIV/AIDS. During the last few decades, the number of PLWHA has increased dramatically, and it has been realized that this group has considerable nutritional problems.

PLWHA. According to United Nations Programme on HIV/AIDS (22), as many as 4.1 million people became newly infected with HIV during 2005, bringing the total number of people living with HIV to 38.6 million. With >23 million AIDS deaths so far, and many more weakened by HIV infection, the epidemic has consequences that are already brutally felt in most families and communities in the hardest-hit countries and has a devastating impact on social and economic development.

Based on considerable animal and human data, conceptual frameworks describing possible 2-way relations between nutrition and specific infectious diseases have been developed. In brief, most infectious diseases may impair nutritional status, and impaired nutritional status or decreased intake may affect the risk and severity of infectious diseases (23).

The conceptual framework also applies to various nutrients and HIV infection. However, because it has become clear that oxidative stress—an effect of the infection in the absence of adequate intake of antioxidants—directly leads to increased replication of HIV in the cells, HIV-specific conceptual frameworks have been developed, and the current data on the relation between nutrition and HIV have been reviewed (24).

HIV infection may affect the nutritional status of individuals in various ways. It may have a direct biological effect on nutritional status, and it may have indirect effects that are mediated through reduced food production or cash income, and, hence, reduced access to food. The biological effects result from HIV disease causing an acute-phase response or local lesions, which may reduce intake and absorption and increase utilization and loss of nutrients. There is evidence to suggest that even early asymptomatic HIV infection affects absorption of nutrients and also increases resting energy expenditure.

Based on a WHO consultation, it is recommended that asymptomatic HIV-infected individuals increase their energy intake by 10% and that those with symptomatic disease increase their intake by 20–30%. However, regarding proteins, the WHO consultation concluded (25):
There are insufficient data at present to support an increase in protein intake for PLWHAs above normal requirements for health, i.e., 12% to 15% of total energy intake. Participants were aware of the published nutritional guidance suggesting increased protein intake during HIV infection, but they concluded that these recommendations were not based on rigorously conducted studies (25).

Similarly, there are no recommendations regarding quality of the protein.

It is likely that even early HIV infection leads to changes in the structure and function of the intestinal tract, which is accompanied by malabsorption of nutrients. An HIV enteropathy has been described, characterized by villous atrophy and crypt hyperplasia (26). With more advanced disease and frequent episodes of diarrhea, malabsorption becomes increasingly common and contributes to wasting.

**Infants and young children.** Infants and young children are especially vulnerable to malnutrition because of their high growth velocities and consequent high energy and nutrient needs.

According to UNICEF, 31% of children under 5 y suffer from moderate or severe stunting, with 42% in the least-developed countries (27). About 10% of the children in low-income countries have moderate or severe wasting, with 42% in the least-developed countries (27). About 10% of the children in low-income countries die each year in low-income countries before they reach the age of 5 y, equivalent to 7 of every 100 children (27). It has been estimated that in more than half of the deaths, malnutrition is a contributing factor to mortality.

The ages up to ~18 mo are specifically vulnerable. There is a dramatic decline in nutritional status from birth up to ~18 mo in weight for age (underweight), length for age (stunting), and weight for length (wasting) (Fig. 1). Thereafter, there is no further decline, indicating that the children grow at a velocity at the same level as the reference population.

A very common complication to malnutrition in young children is recurrent or persistent diarrhea. Long periods of gastrointestinal infections will affect the mucosa of the intestine, resulting in atrophic mucosa and thereby malabsorption of nutrients, in a further deterioration of the nutritional status. Young children are also more sensitive to the effects of anti-nutrients, e.g., phytate, in that absorption of several minerals, such as iron and zinc, is impaired.

*FIGURE 1* The nutritional status of children under 5 y in the world, expressed as SD scores (Z-scores) relative to the WHO growth reference that was used up to 2006 (158). Reproduced with permission from Pediatrics, American Academy of Pediatrics (158).

<table>
<thead>
<tr>
<th>Age (months)</th>
<th>Global Mean W/A, L/A and W/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>0.97</td>
</tr>
<tr>
<td>2</td>
<td>0.91</td>
</tr>
<tr>
<td>3</td>
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<tr>
<td>4</td>
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<tr>
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<tr>
<td>6</td>
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<td>7</td>
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<tr>
<td>8</td>
<td>0.69</td>
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<tr>
<td>9</td>
<td>0.66</td>
</tr>
<tr>
<td>10</td>
<td>0.63</td>
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</tbody>
</table>

**TABLE 5** Safe level of protein intake for weaned infants, children, and adolescents per kilogram body weight

<table>
<thead>
<tr>
<th>Age</th>
<th>Girls</th>
<th>Boys</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safe levels</td>
<td>Safe levels</td>
<td>Safe levels</td>
</tr>
<tr>
<td>g/kg d</td>
<td>g/kg d</td>
<td>g/kg d</td>
</tr>
<tr>
<td>0.5</td>
<td>1.31</td>
<td>1.06</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>1.14</td>
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<td>1.03</td>
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<tr>
<td>2</td>
<td>0.97</td>
<td>1.14</td>
</tr>
<tr>
<td>3</td>
<td>0.90</td>
<td>1.18</td>
</tr>
<tr>
<td>4</td>
<td>0.86</td>
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<tr>
<td>5</td>
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<td>1.30</td>
</tr>
<tr>
<td>6</td>
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<td>1.40</td>
</tr>
<tr>
<td>7</td>
<td>0.72</td>
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</tr>
<tr>
<td>8</td>
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<td>1.50</td>
</tr>
<tr>
<td>9</td>
<td>0.66</td>
<td>1.50</td>
</tr>
</tbody>
</table>

1 Adapted from (16).
2 The safe level of protein intake is calculated as the mean requirement + 1.96 SD.

**Recommended protein intake for vulnerable groups.** There are 2 main methods of expressing recommendations for protein intake: as safe level of protein intake expressed as grams per kilogram body weight per day or as a safe range of PE% in the diet. The safe levels of protein intake according to the new WHO/FAO report on protein requirement (16) are given in Table 5.

Safe ranges for protein energy percentage are given by the U.S. Institute of Medicine (IOM) (28). The ranges [acceptable macronutrient distribution ranges (AMDR)] are 5–20 PE% for children of 1–3 y, 10–30 PE% for children of 4–18 y, and 10–35 PE% for adults. The recommendations are developed for healthy individuals living in industrialized countries. There is considerable uncertainty in the lower values of these safe ranges. A PE% based on the recommended protein intake, which should be regarded as a minimum PE% in the diet, may be calculated from the recommended protein intake and the mean energy requirements per kilogram body weight (29). The value is 3.3 PE% at 6 mo, gradually falls to 4.3 PE% at 2 y, and then increases gradually again to 8.7 PE% at 17 y.

A basic assumption for recommendations on protein intake is that the energy requirement is met. Otherwise, some of the protein will be oxidized to provide energy. In a situation in which the total diet remains unknown, as when planning special foods for vulnerable groups, it makes more sense to give recommendations on protein content of diets as PE%. This is in accord with the approach suggested by Waterlow in 1992 (30). Waterlow also calculated the PE% needed for catch-up growth assuming different rates of catch-up. A young child who needed a diet with 8 PE% for a catch-up of 5 g · kg⁻¹ · d⁻¹ and 10.4 PE% for a catch-up of 10 g · kg⁻¹ · d⁻¹. In the new WHO/FAO report on protein requirements (16), the corresponding values are somewhat lower; 6.9 PE% for a catch-up of 5 g · kg⁻¹ · d⁻¹ and 8.9 PE% for a catch-up of 10 g · kg⁻¹ · d⁻¹. For comparison, F-100, which is intended for treatment of severely malnourished children, has a PE% of 11 with a PDCAAS of 1.24. In several studies (31), it has been shown that it is possible to obtain mean weight gain ~10–15 g · kg⁻¹ · d⁻¹ in severely malnourished children using F-100.

An important consideration regarding protein requirements to vulnerable groups is the fact that infections are common. According to the new WHO/FAO report on protein requirements...
potential for interventions with whey could be caused by the general characteristics of an animal food source, e.g., the AA pattern or the minerals. Therefore, it is relevant to discuss the general aspects of feeding animal foods to malnourished individuals.

A number of studies have examined the association between intake of animal-source foods and growth and development (physical and mental), morbidity (including nutritional anemia), and immune function (3,32–36). In an observational study from Kenya, Mexico, and Egypt, positive associations between intake of animal-source foods and growth in weight and length were found, even after controlling for socioeconomic factors (37). Similar findings have been obtained in Peru (38), in New Guinea (39), and in Central America (40). Iron, zinc, and vitamin B-12 contents of animal-source foods in addition to good protein quality may contribute to these findings.

In a study in Kenya, the effect of meat and milk on growth was examined in schoolchildren who were randomized to a meat, milk, or energy supplement compared with a control group without a supplement (41). Children in each of the supplemented groups gained ~0.4 kg (10%) as compared with children in the control group, but only those receiving the animal foods gained more lean body mass. In the subgroup of children with a lower baseline height-for-age z-score (≤1.4), a positive effect of milk supplements on height gain was shown, suggesting that the effect of milk on linear growth may be superior to that of other animal-source foods.

Potential effects of milk on vulnerable groups

Animal-source foods in malnutrition. Whey is an animal protein, and potential effects of interventions with whey could be caused by the general characteristics of an animal food source, e.g., the AA pattern or the minerals. Therefore, it is relevant to discuss the general aspects of feeding animal foods to malnourished individuals.

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Potential effects of milk protein constituents. The biological activities of several bioactive proteins and peptides obtained from milk proteins and their physiological roles have been examined in animal studies and in a limited number of intervention studies in humans. Proposed functions of WPRO are mainly related to the immune or digestive system (42). It has been speculated that some of the effects of whey or other milk proteins could be caused by peptides formed after digestion in the gastrointestinal tract (43–47). There is an extensive interest in the potential use of bioactive milk components, such as β-lactoglobulin, α-lactalbumin, lactoferrin, and glycomacropeptide, in infant formula, clinical nutrition, and functional foods. Using specific bioactive milk components in FBF or other foods used in relief feeding is at present not realistic because of the cost issue.

Lactose maldigestion and intolerance. The lactose content of both SMP and low whey concentrates (WPC34%) is ~50% as opposed to the more concentrated isolates (WPI90%), where it is ~1%. In WPC80% it is ~10%. Because the WPI are much more expensive than WPC and therefore not relevant for low-cost food aid products, it is appropriate to consider to what degree lactose maldigestion and intolerance are relevant problems for feeding malnourished patients with high-lactose-content milk components.

Lactose maldigestion and intolerance develop after early childhood, at about age 3–5 y in many populations. It is estimated that lactose maldigestion is present in 75% of the world’s population (48). Lactose intolerance is characterized by symptoms that are primarily gastrointestinal and include flatulence, cramping, abdominal pain, nausea, distention, bloating, and diarrhea.

Solomons et al. (49) assessed the effect of using lactose-containing and lactose-hydrolyzed formulas based on cow’s milk in the rehabilitation of severely malnourished children. More diarrheas were experienced by the group receiving the lactose-containing formula, but the overall recovery was satisfactory in both cohorts, and there were no differences in rates of growth, body protein repletion, restoration of energy reserves, or intestinal functions. In a meta-analysis of studies treating children with diarrhea with either lactose-containing or lactose-free diets, it was concluded that most children with acute diarrhea can safely be treated with undiluted lactose-containing milks. It was further stated that children should be fed continuously during illness with their usual diets (50).

Miller et al. (51) observed that lactose malabsorption was a common finding in HIV-infected children and was less common in an age-matched group of control children. However, lactose malabsorption was not associated with higher rates of diarrhea or growth failure.

F-100 is used extensively in the treatment of severe malnutrition, a condition in which diarrhea is frequent and likely to cause considerable intestinal atrophy and therefore low lactase. Although it has not been strictly documented, there is a general impression that lactase intolerance is not a major problem in rehabilitation of severely malnourished children (52). F-100 contains 42% SMP, and with a lactose content of ~50% in SMP, ~20% of the dry matter and 15% of the energy content in this diet comes from lactose. Thus, it seems that a reduction of the lactose content in milk-based diets for severe malnutrition offers no appreciable advantages, and the use of milk as the protein source for rehabilitation is not contraindicated (31,49,53). This is supported by the conclusion of a recent meta-analysis (34). It should be kept in mind that ~40% of the energy in human milk comes from lactose, about twice as much as in cow’s milk, and that human milk is considered an ideal food, even during periods of diarrhea.

Some studies in piglets have shown a positive effect on growth of adding lactose to a cereal-based diet, most likely because lactose is a carbohydrate with high bioavailability (55).

In conclusion, the lactose content of FBF is not likely to be a problem. There is ~50% lactose in WPC34% or SMP, but the amount of milk in FBF will be small, perhaps 10–20%, and the FBF will constitute only a part of the energy intake, perhaps 25–50%. Furthermore, such blends will not be intended for severely malnourished individuals, who have low levels of lactase.

Bone. Adding SMP or whey to the diet of vulnerable groups living mainly on a vegetarian diet may have positive effects on bone mineralization.

It has been shown that very low calcium intake in some areas, especially in Africa, can be the main reason for bone diseases.
such as rickets despite high sun exposure and normal vitamin D status (56–61). Furthermore, supplementing with calcium can eliminate symptoms such as leg pain and radiological signs of rickets (57). It may, therefore, be especially important to ensure a sufficient calcium intake during periods with nutritional rehabilitation. Protein supplements for rehabilitation should, therefore, normally also contain calcium. However, the FBF is enriched with calcium as part of the mineral mix.

It was earlier believed that high animal protein intake had a negative influence on calcium balance because individuals with high nondairy animal protein intake usually have higher urine calcium excretion (62). However, newer studies have shown that animal protein also seems to have a stimulating influence on calcium absorption, so the overall effect on calcium balance normally will be neutral (63). Furthermore, in the elderly, with the appropriate intakes of vitamin D and calcium, giving protein supplements to correct an inadequate protein intake increases circulating insulin-like growth factor (IGF)-1 levels, improves clinical outcomes after hip fracture, and prevents bone mineral density (BMD) loss at the proximal femur (64).

Some studies, mostly with animals, have examined the effect of WPRO on bone metabolism. In cells it has been shown that WPRO may stimulate osteoblasts (bone-forming cells) (65) and inhibit osteoclasts (bone-resorbing cells) (66). It has also been shown that WPRO may enhance bone strength in both growing (67) and ovariectomized rats (66,68). In ovariectomized rat studies, the control diet protein was casein compared with casein plus some extra WPRO (66,68). Recently, rat studies have shown an antiresorptive effect (69) and bone density-maintaining effect (70) of the acidic protein fractions isolated from bovine milk whey. Only a few human studies examining the effect of whey on bones have been published. In a study from Japan, whey (a special type called the basic protein fraction, MBP) has been shown to increase BMD in adult (71) and menopausal women (72). No studies on the effect of WPRO on BMD in adult men, children, or adolescents have been published.

From the literature it is not possible to state whether milk protein or whey, compared with other protein sources, will have a positive effect on the bones in malnourished individuals. A low calcium intake from a diet with no animal foods could have a negative influence on bones. However, the blends discussed in this review are fortified with a sufficient level of calcium.

**Milk and linear growth.** In a recent article (73) summarizing human observational and intervention studies, it was concluded that cow’s milk seems to have a positive effect on linear growth.

The strongest evidence that cow’s milk stimulates linear growth comes from observational studies in both infants (74,75) and preschool children (32,76–78) and from intervention studies (79–86) in low income countries that show considerable effects. Additionally, observational studies from well-nourished populations show an association between milk intake and growth (87). These results suggest that milk has a growth-stimulating effect even in situations where the nutrient intake is adequate. This effect is supported by studies showing that milk intake stimulates circulating levels of the growth factors insulin (88) and IGF-1 (89,90), which suggests that at least part of the growth-stimulating effects of milk occur through the stimulation of the IGF. Because the biological purpose of milk is to support the newborn during a period of high growth velocity, such an effect seems plausible, and the “milk hypothesis,” put forward by Bogin (91), proposes that a greater consumption of milk during infancy and childhood will result in taller adult stature.

Adding cow’s milk to the diet of stunted children is, therefore, likely to improve linear growth.

Whey stimulates levels of insulin in circulation in both postprandial (92) and fasting (93) states. However, because casein seems to increase circulating IGF-1 (93), it could be speculated that the entire milk protein with both whey and casein is needed to obtain the complete positive effect of milk on linear growth.

**Muscle mass.** PLWHA and malnourished infants and young children have decreased whole-body protein synthesis and net mobilization of proteins into free AA. WPRO are easily digested and have high metabolic efficiency, giving the protein a high biological value compared with other milk proteins. WPRO might influence body cell mass (BCM) in several ways. WPRO contain the highest concentration of BCAA available from any food protein source. BCAA must be present in the muscle cells to promote protein synthesis (14). Circulating BCAA are unique among AA because they are metabolized for energy by muscle rather than by the liver, thus helping to increase carbohydrate availability and counteract muscle protein breakdown. Therefore, BCAA might be exceptional among AA in their ability to provide an energy source during fasting and thus decrease muscle breakdown and aid recovery. However, this theory has, from our knowledge, not been clinically studied.

In addition, during starvation and malnutrition, the levels of insulin are greatly reduced, thus in part mediating the loss of body protein because insulin is known to inhibit proteolysis (94). In a healthy individual, there is a rise in circulating insulin to initiate the response to feeding, which is thought to be a major factor in controlling the retention of absorbed AA (95). Increases in AA concentrations, particularly of the BCAA, induce similar effects to those of insulin. In a healthy subject these 2 factors appear to act synergistically. However, because insulin levels are decreased during starvation and malnutrition, intake of BCAA might be more important for inhibition of body protein breakdown (94). Also, as antiretroviral therapy and especially the group of AIDS retroviral drugs, which are protease inhibitors, cause lipodystrophy and metabolic syndrome (96–98), an increased intake of BCAA may be especially beneficial for PLWHA.

However, because glucagon levels also are decreased in malnourished individuals, the insulin-to-glucagon ratios may be more important than the absolute concentration of either insulin or glucagon (94,99). Although the percentage of AA that stimulate the secretion of insulin is the same in casein and WPRO, the higher proportion of BCAA in whey results in a synergistic effect with insulin on protein metabolism (94). Moreover, the number of AA that stimulate glucagon secretion is substantially lower in WPRO than in casein. Hence, the catabolic effect of glucagon, which counterbalances insulin in the acute control of protein, is less after a whey-protein meal.

WPRO are also rich in arginine and lysine. Arginine and lysine are among the AA thought to possibly stimulate growth hormone, which is an anabolic hormone. AA composition of WPRO is very similar to that of skeletal muscle (100), providing almost all of the AA in approximate proportion to their ratios in muscle. Logically, it can be supposed that this compatibility would position whey as an effective anabolic supplement, although it should be recognized that the nonessential AA contribute little to the overall response (101).

**Immune system and glutathione.** Whey contains a relatively high proportion of sulfur-containing AA, especially cysteine. This might be of particular value in conditions of immune...
activation in that the high cysteine content of whey may spare tissue protein because acute phase proteins, which are produced in response to immune challenge, are inordinately enriched in cysteine.

Infection with HIV results in a progressive impairment of immune function, especially a decline in the amount of the membrane glycoproteins CD4, ultimately leading to opportunistic infections and malignancies of AIDS (102). Impaired antioxidant defense may play a role in the immunopathogenesis of HIV infection (103–105). Also, in severe malnutrition, as in kwashiorkor, an impairment of the antioxidant defense is observed (106–110). Reactive oxygen species and a consequent depletion of antioxidants have been suggested as the etiology of kwashiorkor (111,112). Interestingly, it has been reported that blood levels of glutathione (GSH) are low, as in the case of HIV-positive patients. Based on the antioxidant hypothesis, a recent study from Malawi tested the effect of antioxidant supplementation in children with kwashiorkor in Malawi but did not find an effect (110).

GSH is a cysteine-containing tripeptide (γ-glutamyl-cysteinyl-glycine) that is regarded as the major intracellular redox buffering principle (105,113). Finally, GSH provides reducing power for the maintenance of other antioxidants, e.g., ascorbic acid (vitamin C), vitamin E, and β-carotene (113). HIV patients are often depleted of GSH and other antioxidants (114), and GSH levels are reduced in children with kwashiorkor (106).

WPRO is rich in the AA cysteine, which is the main source of the sulphydryl group of GSH. Therefore, an increased intake of whey may be beneficial in GSH-depleted individuals, such as PLWHA and children suffering from kwashiorkor.

Oxidant/antioxidant imbalance can occur in obstructive airway disease as a result of ongoing inflammation. GSH plays a major role in pulmonary antioxidant protection. A whey-based oral supplement increased whole-blood GSH levels and pulmonary function in 1 patient who had obstructive lung disease and low whole-blood GSH levels (115). The potential for such supplementation in pulmonary inflammatory conditions deserves further study.

Gastrointestinal development and recovery. Malnutrition and HIV infection have detrimental effects on the health of the gastrointestinal tract. In a review by Playford et al. (116), it is mentioned that the growth and development of intestinal cells are positively influenced by components of milk and whey, including growth factors and peptides. Glycomacropeptide exhibits prebiotic activity (117), and lactose can be enzymatically hydrolyzed to form monosaccharides, which are readily utilized by bifido bacteria, thus contributing to better functioning of the digestive tract (42). Glutamine (13% in casein and 4.6% in whey) might be an important fuel source for the small intestine, although results of its therapeutic effects indicate limited efficacy (118,119). Thus, although there is a plausible mechanism whereby an individual with gastrointestinal dysfunction may benefit from whey, this theory has not yet been tested (101).

Evidence from animal studies
Numerous animal studies are available on the effects of bovine milk products on early life growth patterns. Well-controlled animal studies clearly offer a potential to improve our understanding of the mechanisms whereby milk components affect the body during health and disease.

As an omnivorous species with a gastrointestinal tract similar to that in humans, the pig is believed to be 1 of the best animal models for human nutrition and for studies on milk diets in early life (120). At 3–5 wk of age, pigs are generally subjected to abrupt (premature) weaning from mother’s milk onto a vegetable-based diet, often resulting in significant anorexia, gastrointestinal disease (weanling diarrhea), and increased mortality. It is likely that results from weanling pigs reflect the responses in malnourished and growth-stunted infants in the transition phase from milk to solid food.

It is widely recognized that young weanling pigs achieve better growth performance with milk-based diets than with isocaloric diets containing similar amounts of nutrients derived from corn-soy diets (55,121–123). The potential explanation for this positive effect includes a better overall PDCAAS value for milk protein (124), faster stomach emptying (120), lower antinutrient levels, and higher levels of milk bioactive substances leading to better gut health (55,125). Part of the beneficial effect of milk products is also believed to arise specifically from the high digestibility and beneficial luminal effects of milk lactose, which are present not only in the very nutrient-sensitive period just after weaning (55) but also in older and healthier piglets, especially those showing slowest growth postweaning (126).

The milk casein fraction has been shown to affect intestinal structure and function in weanling pigs (127), and this could be via its content of immunomodulatory glycomacropeptides (128). Generally however, casein does not seem to explain the high digestibility and growth performance in weanling pigs reared on milk diets (129,130). More likely, it is the whey fraction that contains bioactive factors to exert improved gut health, digestibility, and growth beyond the effects explained solely by the contents of highly digestible lactose and protein. Hence, spray-dried whey products have become widely used to enhance health and growth performance for weanling pigs. Even better performance and gut health are achieved when colostral protein rather than whey-derived protein is included in weanling diets (131). This probably reflects even higher concentrations of bioactive factors in colostral whey than in milk whey.

The responses seen in weanling pigs may resemble those in malnourished weaning infants but could also be valid during the entire period from birth. In immunocompromised, stunted newborn pigs, WPRO stimulated small intestinal and body growth, relative to a corresponding isocaloric and isoproteinous diet with soy hydrolysate (21). The effects of casein on gut and body growth were intermediate, but it is noteworthy that casein increased bone mineral deposition, whereas WPRO exerted effects mainly on soft tissue growth (organs, muscle, fat). The results confirm not only that milk proteins are clearly superior to vegetable proteins (soy hydrolysate) in supporting growth in sick newborns but also that whey and casein proteins exert differential effects on the different parts of the body.

Because the weanling pig is a very appropriate model for vulnerable infants and young children during the weaning period, and because these studies have been strictly controlled, these results from animal studies are relevant and support the hypothesis that there will be positive effects of adding whey or SMP. However, the growth velocity of piglets is very high, and results seen in piglets may overestimate the effects in humans, underlining the need for strictly controlled relevant studies in humans.

Intervention studies with whey in vulnerable populations
PLWHA. The use of WPRO in vulnerable populations, such as those affected by HIV infection, has been suggested as a means to improve health. If inadequate intake of protein increases the...
progression of HIV infection, increasing the intake or quality of protein, from whey or other sources, may have beneficial effects on HIV infection. However, the question addressed here is whether WPRO has specific effects on the course of HIV infection per se, i.e., effects that are not merely explained by the provision of high-quality proteins. Providing whey to people with inadequate intake of protein may be beneficial whether or not they have HIV infection. However, it may be useful to distinguish between 1) whether effects of whey are over and above the effects of other high-quality proteins, and 2) whether effects are general or HIV-specific, i.e., affecting the course of HIV infection. However, it is complex to distinguish whether effects are general or HIV-specific. As for the latter, an effect on lean body mass is likely to be general, if not explained by HIV-specific effects on CD4 count and viral load.

WPRO is rich in the AA cysteine, which is the main source of the sulfhydryl group of the GSH. HIV patients are often depleted of GSH and other antioxidants (114). When put on antiretroviral treatment, HIV infected patients will experience a pronounced decline in viral load and an increase in CD4 counts, which will be accompanied by an improvement in GSH-redox status and increase in levels of antioxidant vitamins (132). However, if they are not on HIV treatment, the resulting oxidative stress may increase viral replication and hence progression of HIV to AIDS or death. Therefore, it has been suggested that WPRO might increase GSH-levels and thus reduce progression of HIV.

Four studies have examined the effect of whey in PLWHA (Table 6). A pilot study was done on 3 HIV-infected individuals (133). The patients were clinically stable and given a WPC in amounts increasing from 8 to 39 g/d for 3 mo. The blood mononuclear cell GSH content was below normal at baseline but increased in all 3, whereas there were no effects on various serum protein concentrations. However, weight gains were between 2 and 7 kg. According to the authors, this pilot study will serve as a basis for a much larger clinical trial, which apparently has not been conducted or published.

In a study among 30 clinically stable HIV-infected individuals with CD4 counts <300 cells/μL, 45 g of WPRO was given daily for 14 d. Special commercial whey products were used called Protectamin or Immunocal (134). The production processes were distinct, with a lower isolation temperature (<72°C) for Immunocal. The protein content ranged from 75 to 95% with a fat content of 0–6%. Plasma GSH increased significantly in the 15 patients receiving Protectamin but not in the 15 patients receiving Immunocal. The authors claim that the study was a double-blinded clinical trial and that short-term oral supplementation with WPRO increased plasma GSH levels. However, because there was no control group and only before-after comparison, the conclusion does not seem to be valid. All the patients receiving Immunocal were, therefore, openly switched to Protectamin for an additional 5% mo (135). After the full 6 mo of supplementation, the mean plasma GSH was significantly higher than at baseline. Again, because the study was in fact not a randomized, controlled trial, the increase in plasma GSH cannot be attributed to the intervention with whey.

Another small study was done among 30 HIV-infected women with BCM <90% of normal values and the same data published in 2 articles (136,137). The body composition of the patients was thoroughly assessed before and after a 6-wk control period before the intervention, and then the patients were randomized to WPRO, progressive resistance exercise, or both for 14 wk. The authors claim that both interventions had effects on various outcomes. However, there was no proper control group and, although data were not presented, there seemed to be no differences between the intervention groups.

A so-called prospective, double-blind trial was conducted among 18 vertically HIV-infected children on antiretroviral therapy (138). The children were between 12 and 72 mo. Half of the children received a WPC, and the other half received a placebo (maltodextrin, same amount of energy) or nothing. It is not clear how allocation to treatment was done, but the study was apparently not randomized. Also, it is not clear to what extent the groups were comparable at baseline with respect to

### Table 6 Whey intervention studies with PLWHA

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study type</th>
<th>n</th>
<th>Subjects</th>
<th>Study period</th>
<th>Whey type (amount)</th>
<th>Name</th>
<th>Control</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agin et al., 2000</td>
<td>Randomized intervention study</td>
<td>30</td>
<td>Women (28–66 y)</td>
<td>14 wk</td>
<td>Undenatured bovine derived whey protein powder (1.0 g · kg⁻¹ · d⁻¹)</td>
<td>Optimune</td>
<td>1) Exercise</td>
<td>Weight gain as fat (P = 0.002)</td>
</tr>
<tr>
<td>(136,137)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No significant change in BCM, skeletal muscle, strength or QOL</td>
</tr>
<tr>
<td>Bounous et al., 1993</td>
<td>Pilot study (intervention)</td>
<td>3</td>
<td>White men</td>
<td>3 mo</td>
<td>75% WPC (8.4 g/d increasing to 39.2 g/d)</td>
<td>Immunocal</td>
<td>None</td>
<td>Weight gain</td>
</tr>
<tr>
<td>(133)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No change in serum proteins. Increased GSH.</td>
</tr>
<tr>
<td>Micke et al., 2001</td>
<td>Prospective randomized</td>
<td>30</td>
<td>male, 5 female (42 ± 9.8 y)</td>
<td>2 wk</td>
<td>45 g whey/d</td>
<td>Protectamin (P)</td>
<td>Immunocal (I)</td>
<td>Increase in GSH (P = 0.018)</td>
</tr>
<tr>
<td>(134,135)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>GSH levels: Increased in P-group (P = 0.004), no change in I-group. No change in TNF-α, IL-2, and IL-12.</td>
</tr>
<tr>
<td>Moreno et al., 2006</td>
<td>Prospective double-blind clinical trial</td>
<td>18</td>
<td>10 boys, 8 girls (1.98–3.67 y)</td>
<td>4 mo</td>
<td>79% WPC (20% of protein increasing to 50% of protein)</td>
<td>1) Maltodextrin</td>
<td>2) None</td>
<td>Increase in GSH in whey group (P = 0.018). TCD4/CD8 increased nonsignificantly (P = 0.116). Occurrence of co-infections lowered nonsignificantly (P = 0.058).</td>
</tr>
</tbody>
</table>

154S Supplement
relevant risk factors and how double-blinding was maintained. The supplements were given for 4 mo, and the effects on erythrocyte GSH, CD4 counts, and morbidity were assessed. An increase in erythrocyte GSH was observed in the whey-supplemented group but not in the control group. No tests were done to compare the change over time in the 2 intervention groups. There were no effects on CD4 count.

In conclusion, there is no convincing evidence that whey has beneficial effects on antioxidant status, immunological parameters, or HIV-specific outcomes. Most studies had not only inadequate power but also flawed design. For example, most trials were based on before-after comparisons, and a beneficial change is, therefore, possibly attributable to the effects of other exposures, e.g., season. Furthermore, details of composition or processing of the supplements are not known. Some of the data suggest that whey may increase GSH levels. If GSH depletion impairs immune function or increases viral load, whey supplements might reduce progression of HIV, but this is speculative. However, if the GSH depletion is secondary to oxidative stress in the background of low dietary intake of antioxidants, then it seems likely that antioxidant supplementation will be equally beneficial and probably less expensive. There is a need for soundly conducted intervention studies of the effect of WPRO on HIV specific outcomes.

Infants and young children. A number of studies have evaluated the effects of adding milk to the diet of vulnerable groups of infants and young children. However, we have not been able to find published studies that have examined the effect of adding whey to the diet, and especially not studies that have compared FBF with and without milk in infants and young children.

It is beyond the scope of this article to go through the literature of the effects of adding milk to the diet. In the previous sections “Animal-Source Foods in Malnutrition” and “Milk and Linear Growth,” we have summarized some of the literature suggesting that there might be specific positive effects of adding milk to diets of infants and young children, especially if their diets are mainly vegetable based. Such effects are likely to be much more pronounced in infants and young children who are not being breast-fed.

It is not possible to evaluate to what degree the effects seen in studies using milk or milk powder result from special effects of the whey fraction, as whey constitutes only ~20% of the protein in milk powder, and milk is often covering only a limited part of the energy intake.

An increasing number of publications have reported that RUTF is very effective in home-based treatment of infants and young children with severe malnutrition. Although this article does not focus on treatment of severe malnutrition, we find it relevant to describe in brief some of the studies that focus on more moderate malnutrition, which is common among vulnerable groups such as infants and young children and HIV patients.

The content of milk is high in most RUTF. Typically >50% of the protein comes from milk. In some of the products part of the milk protein is WP (Plumpy Nut, Nutriset and BP-100, Compact A/S). The reasons for adding whey to these products are basically lower price, better taste (high lactose content), and technological.

Studies in Malawi (5–7), Chad (139), Ethiopia (140), and Senegal (141) have shown that RUTF is readily consumed by severely malnourished children and that they promote weight gain, both during regular nutritional rehabilitation and in refugee conditions. In summary, RUTF, which has a high content of milk, seems to improve weight gain, but whether this is caused by the higher energy density, the fact that RUTF is more convenient, or because of the milk content, is not known.

In hospital-based clinical nutrition in industrialized countries, there has been some interest in the differences in effects of tube-feeding formulas based on whey or casein. Formulas containing only whey or only casein and formulas with different ratios of casein and whey are available in the market. However, most formulas for enteral feeding of children in the European market are made from casein or are casein predominant. We have not been able to find studies with relevant comparison of the effects of these formulas. From discussions with the producers of formulas for enteral feeding, it is our impression that casein has been used traditionally because it was lactose-free. The reason for using whey in some formulas has mainly been the faster gastric emptying. As far as we are aware, it has not been because of other potential effects of WPRO.

In conclusion, there are no studies showing specific effects of WPRO in infants and young children in either well-nourished or malnourished populations. A number of studies show the positive effects of milk and animal foods on growth and development, especially in populations in low-income countries with a diet mainly based on plant-source foods, and there are no studies that have compared weight gain in infants and young children receiving FBF with and without the addition of milk. However, the 5 times higher energy density and the convenience of a RUTF could explain the differences.

Considerations for formulations of FBF with milk

A crucial factor in the discussion of improving FBF is the cost of the product. Adding milk-based powders will increase the cost of the products considerably. Adding 15% WPC34% will double the price of a CSB, based on prices in early 2007 (Table 4). Adding 15% SMP, which has approximately the same amount of protein as WPC34%, will result in a slightly cheaper product. Whey is traditionally a surplus product from cheese production. However, with the increasing interest in using whey in many different technical applications in the food sector, and also with an increasing interest in using whey as a food supplement in the “health food” sector, its cost has gone up. WPC34% was considerably cheaper than SMP, ~25–33% cheaper up to early 2007. Other milk powder products, such as whey concentrates with more protein or whey isolates, are considerably more expensive per kilogram protein than WPC34% and SMP.

The increased price of a FBF with milk protein should be seen in relation to the target groups and the potential beneficial effects. The improved blends are aimed at vulnerable groups that are likely to be moderately malnourished and are at risk of developing severe malnutrition. We find it likely that blends containing SMP or WPC powder will be more effective in improving the nutritional status of the vulnerable children and thereby also protect against development of severe malnutrition, which is associated with considerable morbidity and mortality and is also expensive to treat. However, we acknowledge that there is a need for randomized studies to show whether FBF containing milk protein has beneficial effects compared with FBF without milk.

Amount and type of milk protein. Replacing the 20% (wt:wt) soy in a CSB (almost all the soy) by 20% (wt:wt) WPC34% increases the PDCAAS from 0.65 to 0.82 (Table 3). If SMP is used instead, the PDCAAS would increase less, to 0.72.
Adding SMP or WPC allows for a reduced content of soy or cereal in the blend, which will increase the protein availability. With a higher PDCAAS it is also possible to reduce the amount of protein. First, protein is expensive, and it is thus not feasible to use protein as an energy supply. Second, it might be a strain on the compromised metabolic systems in malnourished individuals or PLWHA if surplus protein had to be metabolized to energy. The nutritional quality of the FBF will, therefore, be improved if SMP or WPC is added, both by an increase in the quality and a decrease in the quantity of protein.

As discussed in an earlier section, a PE% of 8 in a blend to vulnerable groups would be sufficient, if the PDCAAS were 1.0 and the whole diet were covered by the blend. A PE% of 8 would also allow for the extra need for moderate catch-up growth in infants and young children. However, it might be marginal for individuals with infectious diseases (16). Because the whole diet is not supposed to be covered by a fortified blend, a PE% of 10–12 would compensate somewhat for a lower protein content and quality in the remaining diet. Aiming for a PE% of 12 would also allow for a PDCAAS somewhat below 1.0, e.g., 0.80.

The fraction of protein that should come from milk is difficult to determine. The higher the fraction, the more likely it is that there will be a positive effect on weight gain and linear growth, but the price will also increase considerably. If the milk protein is whey, any potential bioactive effect of whey is also likely to be higher if the whey content is higher. However, our literature review has not been able to find documentation for such effects. The higher the milk protein fraction from milk, the lower any potential effects of antinutrient effects from soy and the cereals will be. Again, such effects are not well documented. A suggestion is that one-third to half of the protein should come from milk to make an impact. In trials to test if there is a beneficial effect of adding milk to FBF, it is recommended to start the trials with blends with half of the protein from milk tested against blends with no milk.

A blend with a PE% of 12, a PDCAAS of 0.80, and with one-third to half of the protein from milk seems to be a reasonable compromise to aim for. A blend with 15% WPC34%, 85% corn, and no soy would result in 40% of the protein coming from milk protein, a PDCAAS value of 0.73 and a PE% of 13.3. For comparison CSB has a PDCAAS value of 0.65 and a PE% of 17.2, and WSB has a PDCAAS value of 0.64 and PE% of 21.0, according to U.S. specifications (8).

**Flavor and satiating effect.** Both flavor and the satiating effect of a blend are likely to influence energy intake, which is crucial in feeding vulnerable groups. Adding milk powder to the blends influences flavor. Adding only 2–5% of SMP to a blend gives it a milky and also creamy flavor, even though there is no fat in SMP. The flavor of whey is more neutral, but with no negative effects on the flavor of the blends. Both SMP and WPC34% have ~50% (wt:wt) lactose, and the use of these products adds a sweet taste. Flavor is important for acceptability of the product for the vulnerable groups, and especially in malnourished young children, the intake is likely to increase if the flavor is sweet. If the addition of milk powder results in a considerable increase in protein intake, a high protein intake could also directly result in a blunting of the appetite (16).

Adding a milk protein powder to a blend is likely to affect satiety. WPRO are categorized as fast proteins and caseins as slow proteins, according to the pace at which AA emerge in the circulation after ingestion (142). Whey appears to provide a more satiating effect than casein does (143) after a meal, but there are no data available on the effect on energy intake over a longer time. Whey is absorbed rapidly from the intestine, and this might potentially lead to better overall nitrogen balance and postprandial protein utilization (144).

**Energy density, fat content, and quality.** Because individuals in vulnerable population groups may need a high energy intake for recovery, it is fundamental that the products have a high energy density. This has been considered in the formulation of FBF, which aims at having an energy density of 1 kcal/g (4.2 kJ/g), which is usually regarded as being sufficient, but in reality the energy density is often lower. FBF may be provided with oil, but the dosage is critical because a too-high oil content will decrease the nutrient density. However, increasing the energy density further by adding more oil in the blends should be considered. In CSB and WSB, the fat energy percentage is ~14, which is low compared with recommendations for feeding infants and young children. Reviews focused on low-income countries have suggested that there is a risk of a negative effect on growth if the fat energy percentage of the whole diet is below 22 to 25 (145,146). It is likely that a main reason for the very positive effects of RUTF is the very high energy density of the product, 5 times as high as a CSB-based porridge.

Another important aspect to consider when formulating an improved blend is the fat quality, especially the amount of polyunsaturated fatty acids and the (n-3):(n-6) fatty acid ratio, as it might have effects on growth, cognitive development, immune function, and oxidative stress. Soybean oil has a favorable fatty acid profile, so if soy is eliminated from blends where soybeans that are not defatted are used, it should be considered to add soybean oil or other oils with a high (n-3) fatty acid content, such as canola oil.

**Lactose.** Lactose maldigestion and intolerance are common in many populations (48). However, it seems that milk consumption allows adequate growth of children, even when they are malnourished and have diarrhea (147). The content of lactose in both SMP and WPC34% is ~50 g/100 g. Thus, assuming an energy content of 400 kcal/100 g (1.68 MJ/100 g) dry FBF, the lactose content of such a blend will be 100 g/L if the blend contains 20% SMP or WPC34%, which is equivalent to a lactose content ~10% of both weight and energy content. Adding 15% SMP or WPC34% will likewise result in a lactose content in the blend of 7.5%. We find it unlikely that such a low lactose content is a problem, even in individuals with lactase deficieny. The lactose content will add sweetness to the taste, which is likely to be positive.

Studies in pigs have suggested that lactose could also have a positive effect on growth because of its high digestibility, enhanced calcium absorption, and beneficial luminal effects (126).

**Minerals and vitamins.** FBF is fortified with a mineral-vitamin mix. Different mineral-vitamin mixes are used. If WPC34% or SMP is added to FBF, the content of calcium, phosphorus, and zinc especially will increase, especially if SMP is used because it contains almost twice the amount as WPC34%. If phosphorus is not added to the mineral mix, the extra phosphorus is important because a considerable part of the phosphorus in the blends is bound by phytate and thus not available. There are several studies showing a close inverse relation between plasma phosphate in the malnourished and death (148). If it is decided to add whey or SMP to the FBF, the composition of the mineral mixes should be evaluated to decide if there is a need for adjustments. With vegetable sources in FBF, most of the phosphorus can be in the form of phytic acid, inositol hexaphosphate, which is the
storage form of phosphorus for the plant. Thus, approximate analysis of the FBF for total phosphorus is not sufficient. Because dairy products contain bioavailable phosphorus, adding SMP or WPC to FBF will be favorable if it is not included in the mineral-vitamin mix.

The absorption of the minerals calcium, iron, and zinc is competitive. Therefore, it should be kept in mind that a high calcium content might decrease the absorption of iron and zinc. This may affect the iron and zinc status in individuals whose sole or main diet for a period consists of FBF.

The mineral-vitamin mix used for blended foods includes B-12, which is of special interest in low-income countries where the intake of animal foods is often low or nil (149). The level of fortification is ~1.2 µg/100 g (Table 1). Furthermore, milk powder is a good source of B-12. If 15% SMP is added to a FBF, this will increase the B-12 content with ~0.6 µg/100 g.

Technical aspects. There are technical issues to consider when formulating new blends with milk protein. Most of these are not considered in this article. Whey contains many different specific proteins that may have specific beneficial effects. When producing the blends, processing should be performed in a manner to minimize protein denaturation. If FBF is made into porridge that should boil, e.g., for 10 min to overcome water contamination issues, some denaturation might occur, thereby reducing potential beneficial health effects of specific proteins.

There are both advantages and disadvantages of adding milk protein (as either SMP or WPC) to FBF and advantages and disadvantages of adding WPC in comparison to SMP (Table 7).

From our study, it is clear that the scientific evidence for beneficial effects of adding milk protein to FBF is not very strong. The strongest evidence comes from the studies of RUTF with a high proportion of protein being milk protein, which show a high weight gain and successful recovery. However, most of these studies focus on young children with severe malnutrition, and the RUTF typically contains a high milk protein content and energy density, and they often cover a large proportion of the energy intake. Other important evidence comes from studies of young pigs.

Because the addition of milk protein to FBF increases the price considerably, there is a need to document the beneficial effects before implementing these blends in programs to vulnerable groups. It is beyond the scope of this article to suggest detailed trial designs, but we will highlight some areas that need further studies.

**TABLE 7 Effects of adding WPC or SMP to FBF**

<table>
<thead>
<tr>
<th>Adding WPC or SMP to FBF</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advantages</td>
<td>Improves the protein quality, measured as PDCAAS.</td>
<td>Increases the price considerably, which is an important limiting factor in all relief feeding.</td>
</tr>
<tr>
<td></td>
<td>With improved protein quality it is possible to reduce the total amount of protein in the blend, which could have potential metabolic advantages.</td>
<td>Adds lactose to the product, which could potentially have negative effects, but which is not likely to be important in the amounts suggested.</td>
</tr>
<tr>
<td></td>
<td>Allows for a reduced content of soy and cereal and thereby a reduction of potential antinutritional effects.</td>
<td>With improved protein quality, it is possible to reduce the total amount of protein in the blend, which could have potential metabolic advantages.</td>
</tr>
<tr>
<td></td>
<td>Likely to improve weight gain, linear growth, and recovery from malnutrition, but studies are needed to confirm this.</td>
<td>With improved protein quality, it is possible to reduce the total amount of protein in the blend, which could have potential metabolic advantages.</td>
</tr>
<tr>
<td></td>
<td>Improves flavor; SMP more so than WPC.</td>
<td></td>
</tr>
</tbody>
</table>

**Using whey (WPC34%) compared with SMP**

| Advantages | Has been 25–33% less expensive up to early 2007. | Might in the future be more expensive than SMP. |
| | Has a slightly better protein quality measured as PDCAAS, but not likely to be important. | Might not be as widely available as SMP. |
| | Potential beneficial effects on the immune system and muscle synthesis have been suggested, but convincing evidence is lacking. Relevant to perform studies to examine this further. | Does not improve flavor to the same degree as SMP. |
| | We have not been able to identify studies suggesting that casein-dominated milk powders such as SMP have advantages over whey. | | |

**Recommendations on research**

There is a need to perform strict controlled intervention studies comparing FBF with and without milk protein. These studies should be performed in vulnerable groups where it is likely that adding milk protein would result in important health benefits that would justify a considerably more expensive product. Such groups could be moderately malnourished infants and young children and PLWHA.

Animal studies should also be considered. Pigs are a useful model for humans, especially regarding the gastrointestinal function. Piglets during the weaning period, when the gastrointestinal tract is vulnerable and mortality is high, present an especially relevant model for the weaning period in human populations where malnutrition and persistent diarrhea are common.

Flavor, satiating effect, fat content, and energy density are likely to affect energy intake, which is crucial in feeding of vulnerable and malnourished groups. It will be possible to examine this in short-term crossover studies in relevant vulnerable groups fed different blends with and without whey or SMP ad libitum. The outcome in such studies would be the energy intake from the blends.

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