

Breast Milk, Formula Milk, Cow Milk, Soy Milk and Malaria

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ABSTRACT

Mother's milk is known for centuries to be beneficial for infants and to prevent many diseases, including malaria. What are the constituents of breast milk responsible for this efficacy? Do formula milk, cow milk or soy milk has same properties?

Keywords: Mother's milk, Formula milk, Infants, Diseases, Cow milk, Soy milk

A FEW HISTORICAL DATA

It all begins in 1952 with the work of the Liverpool School of Tropical Medicine [1,2].

They found that in rats inoculated with *Plasmodium berghei* and living on a diet of milk there was a strong suppression of the growth of the parasites. This was valid for whole cow's milk, reconstituted dried milk from different origins and human milk. Most rats on normal laboratory diet died in a few days. The authors suggested that the milk might contain an inhibitory substance and that herein lies the explanation of the common observation that severe malaria is not often seen in very young infants. In these first experiments only blood-transmitted malaria had been studied.

The London School of Tropical Medicine followed-up on this early work and confirmed that a milk diet had a suppressive action on *Plasmodium cynomogi* in monkeys. But after a return to normal diet a severe recrudescence took place [3].

In a more recent study, 137 infants exclusively breast fed and 358 control infants from the Democratic Republic of the Congo were assessed for fever and malaria infections by polymerase chain reaction, at 6 months of age. Breast feeding was significantly associated with a reduced risk of clinical malaria [4].

The World Health Organization now recommends exclusive breastfeeding for the first 6 months of life.

NOMADS AND TROPICAL DISEASES

Fulani are a widely spread African ethnic group characterized by lower susceptibility to *Plasmodium falciparum* and clinical malaria morbidity. They are characterized by a higher rate of lactase persistence. This trait is common in Europe and certain African people with

traditions of raising cattle. Lactase non-persistence in other African tribes is often called lactase intolerance. The potential immunoprotective properties of dietary cow milk as a reason for the malaria resistance of Fulani warrant further investigation. [5]

Milk-drinking African nomads show an unusual freedom from infection with *Entamoeba histolytica* compared with similar nomads taking a mixed diet. The authors related this to a low content in iron in cow's milk. A personal communication from Dr. Patrick Ogwang informs that in Uganda malaria is highest in East and North Uganda where the staple food is cereals with high iron content, in western Uganda where milk and low iron foods are eaten most malaria is low. In the past however, people in East and North also kept cows (zebu) and took milk regularly and malaria was not as rampant.

One of the first mistakes of Western medicine in Africa was the iron supplementation to the Somali nomads in 1968. Blood analysis of these nomads had shown that according to European standards they were suffering from anemia [6].

The incidence of infections was studied in 137 iron deficient Somali nomads, 67 of whom were treated with placebo and 71 with iron. Seven episodes of infection occurred in the placebo group and 36 in the group treated with iron; these 36

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episodes included activation of pre-existing malaria, brucellosis and tuberculosis. This difference suggested that host defence against these infections was better during iron deficiency than during iron repletion.

In an outbreak of *Plasmodium falciparum* malaria following re-feeding after famine cerebral malaria was restricted to children eating grain. Those given grain were more likely to experience cerebral malaria. Nomad children consuming a predominantly milk diet were free of this complication despite an equivalent incidence of uncomplicated malaria. Freedom of nomads from cerebral complications may be due to inhibition by the milk diet of rapid division of the parasite combined with delayed recovery after famine of T cell function [7].

Some early results

Formula-fed babies contract gastroenteritis more than breast-fed babies, which is of concern to mothers who cannot breastfeed or, as with HIV-infected mothers, are discouraged from breastfeeding. The ability of endogenous breast milk xanthine oxidase to generate the antimicrobial radical nitric oxide has been measured and its influence on the growth of *Escherichia coli* and *Salmonella enteritides* examined. Breast milk, but not formula feed, generated nitric oxide. Xanthine oxidase activity substantially inhibited the growth of both bacteria. An important natural antibiotic system is missing in formula feeds; the addition of xanthine oxidase may improve formula for use when breastfeeding is not a safe option [8].

Work done on the shores of Lake Victoria suggested that milk might be deficient in certain nutrients required by the parasite, but that these are present in any normal diet. For the first three months in life children are exclusively breast-fed and they stay malaria free. At the third or fourth month mothers usually start giving them a variety of foods in addition to the breast milk and these extras might supply the nutrients required by the parasite.

In 1983 a five month study was undertaken in Brazil to test the effect of a total milk diet on the susceptibility of mice to various doses of the rodent malaria *P. berghei*. The development of humoral immunity was followed by quantitation of the specific serum immunoglobulins (IgG and IgM). High levels of IgG antibodies persisted for 150 days, IgM antibodies were only observed during the two first weeks of infection. The results indicated that a milk diet administered to mice as the only source of food protected them against fatal malaria infection regardless of the number of parasites inoculated. The acquired immunity was still present in the mice at 150 days post inoculation. [9,10].

But these very promising treatments were ignored by BigPharma and subsidized research. Obviously dairy milk or dried milk is not an interesting cash cow in the fight against malaria.

The detrimental role of para-aminobenzoic acid (PABA)

In the light of resistance to most, if not all, of the pharmaceutical molecules (chloroquine, amodiaquine, lumefantrine, chloroquine, sulfadoxine-pyrimethmine) some research groups have tried to better understand all these fifty years old findings. And the proposed detrimental role of PABA (p-aminobenzoic acid) seems to be confirmed. PABA is a precursor of folic acid.

A large scale clinical trial was run on 25 000 infants in Pemba, Zanzibar. The iron and folic acid-containing groups of the trial had to be stopped on the recommendation of the data and safety monitoring board. It resulted in an increased risk of severe illness and death [11-15].

The National Institute for Medical Research finds that milk contains very little p-aminobenzoic acid (PABA), not more than 0.004 ppm [16].

This substance is much more plentiful in some of the constituents of a good laboratory diet, where the vegetal components contain up to 60 ppm of PABA. In vitro *Plasmodium* requires PABA for satisfactory growth. Experiments were undertaken to study this possibility. Rats were maintained on different diets: normal diet, milk, milk with 1000 ppm of PABA. Only the rats on the milk diet stayed free of *Plasmodium berghei* on day 12. *Plasmodium* requires exogenous dietary PABA for survival [17].

Plasmodium generates its own PABA in its apicomplexan organelle, but not in quantities sufficient to guarantee survival and multiplication of trophozoites and schizonts in the infected erythrocyte. And as the human body does not generate its own PABA or folates, but takes them essentially from green vegetables, the parasite has to rely on this supply. If the diet is exclusively on milk it has no chance to survive.

PABA is an intermediate in the synthesis of folate. And the folate supplements sold in our nutrition might be harmful to African new-borns infected by malaria [18].

Iron, zinc, potassium, selenium

Iron is essential for the survival and multiplication of the *Plasmodium* parasite. In humans iron deficiency appears to protect against severe malaria while iron supplementation increases risks of infection and disease.

Anemia may even protect against malaria as it was found at the University of North Carolina. Researchers studied the red blood cells of 135 anemic children aged 6-24 months in a malaria-endemic region of The Gambia and confirmed that anemia offers greater natural protection against blood-stage malaria infection than sickle-cell trait [19].

It would thus be advisable to keep the iron concentrations rather on the low side. This can be achieved by drinking milk. Lactoferrin, a glycoprotein found in milk, has the

ability to bind Fe ions with high affinity and to regulate iron distribution within the body [20].

Zinc is an essential element with strong bactericidal properties and very efficient against diarrhea and other diseases. UNICEF estimates that a formula-fed child living in unhygienic conditions is between 6 and 25 times more likely to die of diarrhea and four times more likely to die of pneumonia than a breastfed child. Zinc stimulates the immune system and increases CD4. Most medical plants like *Artemisia* are rich in zinc [21].

This might be one of the reasons why human milk is rich in zinc. The zinc content of milk varies with species, lower in cow milk, and stage of lactation, much higher in colostrum. This is probably contributing to the immunity of new-borns against malaria. Variations in zinc absorption from different milks and formulas employed in infant feeding are of serious concern [22].

There is considerable evidence to suggest that the bioavailability of zinc from human milk is especially favorable. It has been confirmed with radioactive zinc studies in adults in whom absorption with mature human milk averaged 57% compared with 32% for cow's milk. Hence, zinc plasma concentrations of infants fed with cow's milk-based infant formula was significantly lower. Zinc absorption from soy-based infant formulas is especially poor. The poor absorption of zinc from soy formulas has been found to be attributable to the phytate present in these formulas.

Potassium concentrations in mother's milk are 2 times higher at postpartum in colostrum than one month later in mature milk. It is likely that potassium plays a key role. The potassium concentration in the plasma of neonates is much higher than in the plasma of the mothers: 5.9 mmol/l versus 3.8 mmol/l [23,24].

The content of selenium in colostrum is significantly higher (28.6 ng/ml) than that in mature milk (15.1 ng/ml) [25].

Fats, taurine, linoleic acid, oxidants

Mother's milk is rich in fats: 4.4 % versus 3.3% in bovine milk. A fatty diet kills the sporozoites in the hepatocytes by mediating oxidative stress [26].

And rich in linoleic acid, a strong antimalarial. Linoleic may also act as a growth promotor in the neonate. Concentration was quantified in human milk and infant formula. Concentration of the biologically important conjugated linoleic acid in human milk ranged from 2.23 to 5.43 mg/g; that of formula from undetectable to 2.04 mg/g fat [27,28].

Arachidonic acid and docosahexaenoic acid, n-3 and n-6 long chain polyunsaturated fatty acids, are well present in mother's milk but are absent from many infant formulas. During neonatal life, there is a rapid accretion of arachidonic

and docosahexaenoic acid in infant brain. Cognitive development of breast-fed infants is generally better [29-32].

Arachidonic acid also has strong antimalarial properties via PGE production. Already in 2000 it had been demonstrated in a study on Gabonese children with and without malaria that prostaglandins are important pro-inflammatory mediators of the host-immune response to infection [33].

The concentration of arachidonic acid is on the average 0.5% by wt in breast milk. The IUPAC Lipid Handbook confirms that human milk contains arachidonic acid, but cow's milk does not [34-37].

Arachidonic acid is much higher in breast milk than in formula milk or bovine milk [38,39].

Immunoglobulins

Mother's milk is rich in taurine: 358 mg/kg. Cow's milk only contains 50 mg/kg, formula milk 30. Taurine has a strong effect on immunity. Replacement 50% of the sulfated amino acid methionine from plant origin by taurine from mammal origin doubles IgA in broilers and increases IgM by 50% [40-42].

Neonates and young infants up to 6 months are relatively protected against symptomatic malaria. The prevailing paradigm was that maternal antimalarial antibodies transferred to the fetus in the last trimester of pregnancy protect the infant from early infections. However direct evidence and research results do not support this paradigm [43].

The mystery of the invasion of hepatocytes through Kupffer cells may eventually find an answer in this context. Kupffer cells are specialized macrophages and protect the liver against microbes, contaminants and other aggressions. Why these phagocytes are used as entry gate by sporozoites indeed is difficult to understand [44].

Some studies have shown that IgA antibodies preferentially attach to hepatocytes, blocking the entry for sporozoites. Their number on the surface of Kupffer cells is much lower, 10% versus 63% on hepatocytes. If so, it is logical to expect that taurine has prophylactic antimalarial properties [45].

Breast milk is a remarkably "altruistic" secretion, that is, its contents are directed at protecting the infant with minimal benefit to the mother. The concentration of antibodies, mainly IgA, is 10-100 folds higher than in serum. In colostrum it is as high as 90 g/L.

Mother's milk is rich in hydrogen peroxide in the first postpartum week. Hydrogen peroxide like other ROS kills parasites [46].

Estimation of nitrate and nitrite concentrations of milk sources may provide another insight. In colostrum (1-3 days postpartum) nitrite concentrations are much higher than in mature milk (0.08 mg/100 mL versus 0.001) [47].

According to the authors this change is partly due to the changing intestinal microflora in the baby and the changing metabolic demands as the baby grows. The beneficial effects of NO in adult stomachs on gastroprotective and immunomodulatory functions are known. Arginine plays a key role in the metabolism of nitrates. Therefore, it is reasonable to surmise that nitrite must be supplied to the newborn by colostrum. A recent thesis from Sweden confirms and documents well all these positive elements. Dietary nitrates have potent anti-inflammatory effects, without impairing the ability to clear an infection. They are able to restore the gastric and colonic mucus layer in case of colitis [48].

In breastfed infants “good bacteria” of the gut are important in determining the “direction” of maturation of immunity. Together with other maternal and infant factors, the breastfed infant's mucosal and systemic immune responses

are influenced by a different micro eco milieu of the gut compared to the formula fed infant. An environment that does not encourage the hatching of *Trichuris trichuria* eggs due to the absence of the required ‘pro hatching’ bacteria. *Escherichia coli* in the gut in the breastfed, is deemed another indirect anti-parasitic potential that lies within breast milk [49].

Several protector mechanisms have been proposed for Lactobacillus against gastroenteritis. The most likely mechanism is its role as immunomodulator. Higher bottle feeding with milk poorer than breast milk in Lactobacillus increases the risk of diarrhea. In a trial probiotics Lactobacillus and Bifidobacterium shortened duration of diarrhea to 34.1 h versus 58 h with placebo and reduced the number of stools (7.3 vs. 15.9 with placebo) [50-53].

Immunoglobulins are much higher in breast milk than in formula or cow milk (**Figure 1**).

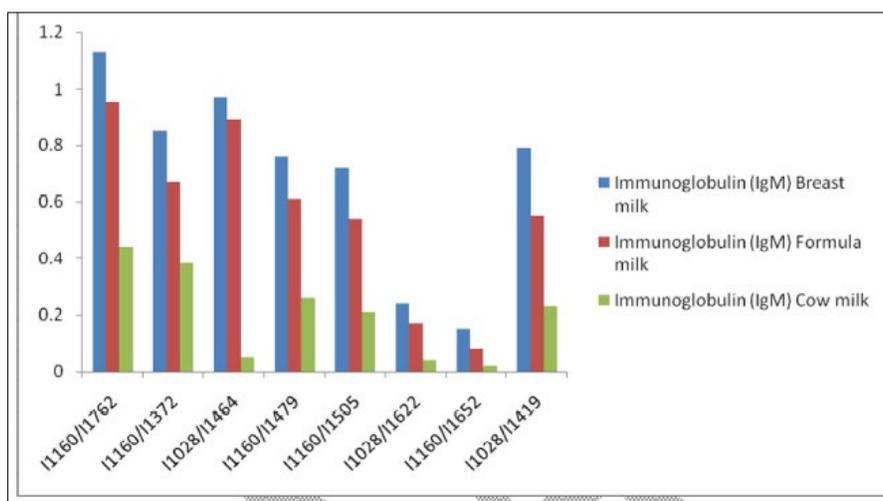


Figure 1. Bar graph showing immunoglobulin amount in different milks.

Lactoferrin, the best vaccine against malaria

Breast milk also contains lactoferrin, 5-13 g/L in colostrum and 2-4 g/L in milk. The concentration of lactoferrin in milk varies widely from one species to another. It is highest in human milk (2 g/L, 25x MI, moderate in murine milk (0.28 mg/L, 3.5x M) and very low in ruminant milk (-0.01 mg/L in bovine milk, 0.12×10^{-6} M). There is an international trend toward the addition of lactoferrin to infant formula [54,55].

The bactericidal and bacteriostatic properties of lactoferrin are well known Lactoferrin indeed binds strongly to iron, and almost irreversibly. This complex in a dose dependent manner enhances ROS production. A variety of free radical ions inhibits a variety of tumors, intracellular parasites and microbes.

A lower expression of the multidrug resistant gene (MDR1) is noticed. This can be a helpful in decreasing the resistance mechanisms of pathogens.

In parallel there is a 4-fold increase in phagocytic capacity of macrophages. Mouse peritoneal macrophages or human blood monocytes co-cultured with intracellular forms of *Trypanosoma cruzi* in the presence of human lactoferrin took up greater numbers of organisms than in the absence of lactoferrin [56,57].

The binding of lactoferrin to iron is 250 times higher than for the parent molecule transferrin and down to a much lower pH. Iron is one on the most important promoters of Plasmodium development [58].

Lactoferrin is to a large extent destroyed at temperatures $>60^{\circ}\text{C}$. Breast milk is thus by far preferable to sterilized cow milk or powdered milk [59].

Very low density lipoproteins (VLDL), similarly to malaria sporozoites are removed from the blood circulation by the liver within minutes after injection by Anopheles mosquitoes. The sporozoite's surface is covered by the

circumsporozoite protein (CS). Lactoferrin, a protein with antibacterial properties found in breast milk is also rapidly cleared from the circulation by hepatocytes in case of

malaria infection. CS, lactoferrin and remnant VLDLs compete *in vitro* and *in vivo* for binding sites on liver cells [60] (Figure 2).

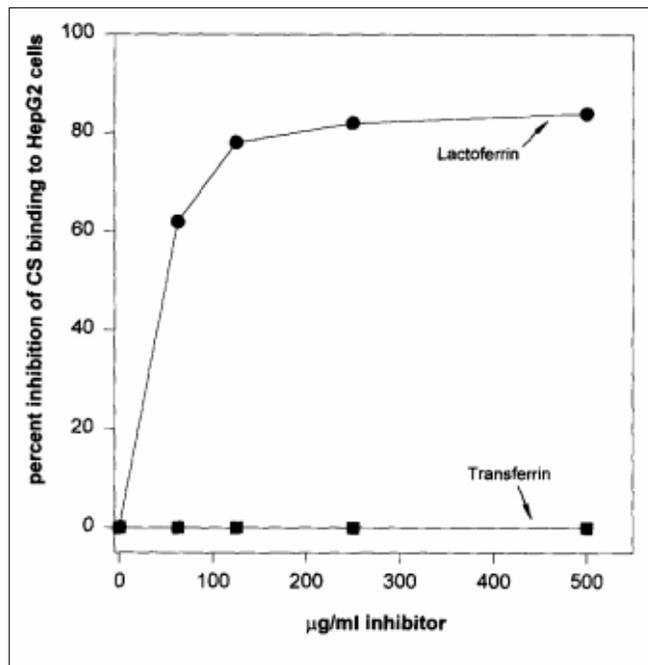


Figure 2. Graph showing percent inhibition.

Other authors also found that lactoferrin inhibits sporozoite invasion liver cells in a concentration-dependent fashion. Up to 80%, this is much higher than the 32% of the GSK-Bill Gates vaccine.

Studies have shown that lactoferrin is the special constituent that allows iron-catalyzed toxic O_2 species to efficiently work their damage. Adding 10^{-8} M pure lactoferrin has a significant impact on hemolysis. Lactoferrin seems particularly suited to focus its products directly onto membranes of target cells. Lactoferrin is highly cationic, which suggests that it might be readily absorbable to negatively charged cellular membranes of erythrocytes.

Plasmodium falciparum extensively remodels its host red blood cell. The zeta potential is an electrochemical property of cell surfaces that is determined by the net electrical charge of molecules exposed at the surface of cell membranes. The RBC membrane is negatively charged and is surrounded by a fixed layer of cations. Using an electrophoretic mobility assay, it was found that the main zeta potential was significantly lower in RBCs infected with *Plasmodium falciparum* [61,62].

Lactoferrin can also be found in honey, generated by the metabolism of bees. Bee sting contains the highest concentration of lactoferrin. It is secreted by the serous cells of the major and minor salivary glands. It has an iron-chelating property which deprives microorganisms of this essential element. In addition, lactoferrin has demonstrated

potent antiviral, antifungal and antiparasitic activity, towards a broad spectrum of species. Lactoferrin exhibits *in vitro* anti-inflammatory activities and several domains are present within its polypeptide chain that demonstrates antimicrobial effects [63].

Mycobacterium tuberculosis and most bacteria, except *Borrelia* (Lyme), must import iron from its host for survival, and its siderophore-dependent iron acquisition pathways are well established. Lactoferrin extracts excess iron from host proteins.

So maybe the message of Melinda Gates in the Wall Street Journal of May 20, 2016 has a lot of merit "Many newborn deaths can be prevented by simple, inexpensive measures, such as, teaching women to breast-feed, which immediately gives a baby nutrients and hydration, and guards against infection, one of the biggest killers of newborns. Each year 2.9 million infants die in their first 28 days of life."

But a press release of April 28, 2017 shows that the Gates Foundation supports research into milk to find new drug molecules which enhance the absorption and efficacy of existing drugs. The interest of Bill Gates in milk is only to find new molecules for the BigPharma business.

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