Breastfeeding is related to a lower risk of infections and possibly diabetes and overweight in later life, while the situation for allergies is less clear [1], which suggests that breast-milk-specific components may contribute to such benefits. Among them are the nondigestible human milk oligosaccharides (HMOs), the third largest solid breast milk component. HMOs are elongations of the milk sugar lactose by galactose, N-acetylglucosamine, fucose, and sialic acid, which results in structures similar to those on the mucosa. Most HMOs are not present in farmed-animal milks and are different from generic prebiotics such as galacto- and plant-derived fructo-oligosaccharides. Maternal fucosyltransferases FUT2 and FUT3, encoded by the Secretor and Lewis genes, respectively, followed by lactation stage, have the most striking impact on the HMO composition [2]. The presence or absence of functional FUT2 and FUT3 not only affects the abundance of individual fucosyl-HMOs, but also the total HMO concentration in breast milk. The maternal nutritional and health status might influence HMO composition in the breast milk; however, today there are only circumstantial data to this end. Clinical observational studies in breastfed infant-mother dyads associate specific HMOs with infant gut microbiota, morbidity, infectious diarrhea, and allergies. Although observational studies do not establish causality, together with experimental data they suggest possible biological roles for HMOs. In particular, it is believed that they affect the (i) establishment of the early-life microbiota dominated by bifidobacteria, (ii) resistance to pathogens, and (iii) intestinal mucosal barrier and immunity, thereby contributing to immune protection (Fig. 1a) [3].

Clinical intervention trials with infant formula supplemented with 1 HMO (2′fucosyllactose, 2′FL) or 2 HMOs (2′FL with lacto-N-neotetraose) demonstrated that they allow for age-appropriate growth and are well tolerated [4, 5]. A priori defined secondary outcomes suggested that
Fig. 1. Illustration of the different biological functions of HMO (a) and risk for infection-related illnesses and medication use in infants fed a formula supplemented with 2 HMOs (redrawn from Puccio et al. [5]). Illnesses and medication use were reported by parents and verified by a study physician (b). URT, upper respiratory tract; LRT, lower respiratory tract. Odds ratios with 95% confidence intervals are shown based on percent of infants with at least 1 event at 1 year of age (Fisher's exact test: * p < 0.05, ** p < 0.001) [6].
feeding an infant formula with 2 HMOs relates to fewer reported lower respiratory tract illnesses and reduced requirement for related medication (antibiotics and antipyretics) during the first year of life [5]. In parallel, the early-life microbiota composition and community structure in infants fed the 2-HMO formula shifted towards that of breastfed infants. Formula containing 2 HMOs shifted the global microbiota profile towards that of breastfed infants, characterized by a *Bifidobacterium* dominance and lower abundance of *Escherichia*, for example. Interestingly, infants with a microbiota community structure typical for control-formula-fed infants had a 2 times higher risk to use antibiotics during the first year of life than those with a microbiota community typical for breastfed infants.

Together, clinical observational studies corroborated by preclinical experimental data and clinical intervention trials support a role for specific HMOs in immune protection leading to the reduced use of antibiotics. Further clinical studies, well-designed observational and especially placebo-controlled interventions, are warranted to further substantiate and grow our understanding of the HMO biology and significance for infant nutrition.

**References**