Summary

Background: Respiratory and gastrointestinal infections are common during childhood, especially in young infants < 2 years of age. Although these common infections are rarely fatal in high-income countries as Denmark, they are a source of significant morbidity burden to the children and their families, and lead to a substantial economic burden on society. Children attending daycare have an increased risk of infections, mainly due to an increased exposure to pathogens through social interaction between children, and due to a not yet fully developed immune system. Strategies to prevent infections in daycare settings are of great importance in a country like Denmark, where 90% of children are cared for outside the home in daycare facilities by the age of 2 years. Probiotics, defined as “live microorganisms that when administered in adequate amounts, confer a health benefit on the host” have been suggested in prevention of respiratory and gastrointestinal infections in children.

Objective: The main objective of this PhD thesis was to examine the effect of probiotics in reducing absence from daycare due to respiratory and gastrointestinal infections in Danish infants during their first months in a daycare setting, and to explore potential factors modifying the risk of infections. Further, the current evidence on the use of probiotics in prevention of respiratory infections in children attending daycare was systematically reviewed.

Methods: Paper I reports on a randomized, placebo-controlled trial investigating the effect of probiotics on absence from daycare due to respiratory and gastrointestinal infections in Danish infants (The ProbiComp study). A total of 290 infants were randomly allocated to receive placebo or a combination of Bifidobacterium animalis subsp. lactis BB-12 and Lactobacillus rhamnosus GG in a dose of 10⁹ colony-forming units per day of each for a 6-month intervention period. Absence from daycare, symptoms of illness, and doctor’s visits were registered by the parents using daily and weekly web-based questionnaires. Information on household characteristics, i.e. household size, number and age of siblings, family history of allergy, pets, and parental education was obtained in background interviews with the parents.

Paper II consists of a systematic review and meta-analysis, which were performed according to the guidelines in the Cochrane Handbook for Systematic Reviews of Interventions. The review included randomized placebo-controlled studies examining the effect of probiotics on respiratory
infections in children attending daycare, and meta-analyses were performed on subgroups for separate probiotic strains or combination of strains used in the studies.

In **Paper III**, longitudinal data from the ProbiComp study was used to explore potential risk factors of respiratory infections, diarrhea and absence from daycare during the first months after enrolment to daycare, including factors related to the household, child characteristics, and the type of daycare.

**Results:** In **Paper I**, we found no difference in number of days absent from daycare between the probiotic and placebo group. Moreover, there were no group differences in any of the secondary outcomes including number of children with doctor diagnosed upper or lower respiratory infections, number of doctor’s visits, number of antibiotic treatments, occurrence and duration of diarrhea, days with symptoms of common cold, days with fever, days with vomiting, and parental absence from work due infant illness.

In **Paper II**, 15 randomized controlled trials were included, with a total of 5,121 children aged 3 months to 7 years. However, due to a very high diversity in reported outcomes and in probiotic strains used in the studies, the number of studies available for strain-specific analysis was limited. Based on data from three studies, children receiving *Lactobacillus rhamnosus* GG showed a significant reduction in duration of respiratory symptoms, whereas no significant differences were observed for other analyzed outcomes. Based on data from two studies, *Bifidobacterium animalis* subsp. *lactis* BB-12 had no beneficial effect on duration of respiratory symptoms and daycare absence. Meta-analysis on other strains or combination of strains was not possible due to limited data and differences in ways of reporting the outcome.

**Paper III** included 269 infants, observed for a mean of 5.6 months following enrolment to daycare. The risk of acquiring at least one URTI was higher in infants with previous respiratory infections, and was inversely associated with birthweight, infant age at enrolment to daycare. Moreover, the risk was lower in infants in family daycare compared to infants in age-integrated facilities and in infants from households with pets. No significant risk factors of lower respiratory infections and diarrhea were identified.

**Discussion and conclusion:** The findings from the ProbiComp study do not support the use of a combination of *Bifidobacterium animalis* subsp. *lactis* BB-12 and *Lactobacillus rhamnosus* GG for prevention of absence from daycare due to respiratory and gastrointestinal infections in Danish infants during the first months in daycare. The systematic review and meta-analysis suggested that
Lactobacillus rhamnosus GG may be beneficial in reducing duration of respiratory symptoms in children attending daycare, whereas the potential effects of other probiotic strains were not possible to assess due to limited available data. A number of previously published studies have suggested that probiotics may play a role in prevention of respiratory and gastrointestinal infections in children. However, the findings from this PhD thesis underline that the evidence is still not clear on which particular strains to recommend, the optimal dose, and the timing. There is, therefore, still a need for more studies in this area. In order to plan and target preventive strategies to those at highest risk, it is important to identify potential factors modifying the risk of infections, and results from the ProbiComp study suggested that infection risk in infants starting daycare is modified by both environmental factors and factors related to the child and household, which is in line with previous findings.