1. Introduction

Respiratory and gastrointestinal infections are common during childhood, and are substantial contributors to pediatric morbidity\(^1\). 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 additionally lead to a substantial economic burden on society in terms of parental absence from work to take care of the sick child, and increased medical costs\(^2,3\). Young children < 3 years of age are also the group with most antibiotic prescriptions\(^4,5\). Preventive strategies are therefore warranted. Daycare centers are one of the major settings which pose an increased risk of infections, and it has been estimated that the risk is up to 3 times higher compared to children cared for at home\(^6\). Children attending daycare have an increased risk, mainly due to an increased exposure to pathogens through social interaction between children, and due to a not yet fully developed immune system in infants\(^7\). The risk is highest in the youngest infants aged 0-2 years\(^6,8,9\), and particularly within the first months after enrolment to daycare\(^8\). In Denmark, 90% of children are cared for outside the home in daycare facilities by the age of 2 years\(^10\), and the average number of days absent from daycare due to illness is estimated to 12 days a year\(^11\).

Probiotics, defined as "live microorganisms that when administered in adequate amounts, confer a health benefit on the host"\(^12,13\), have been suggested in prevention and treatment of various health outcomes, and recent systematic reviews and meta-analyses have suggested an effect of probiotics in prevention of respiratory and gastrointestinal infections in children, including children in daycare settings\(^14-17\). However, clinical studies are performed in different settings, with a variety of probiotic strains or combination of strains, and with children in different age groups. It is emphasized in several reviews that a proven probiotic effect in one setting may not be readily transferred to another setting, and that more randomized controlled trials are needed to establish which probiotic strains should be used, the optimal dose, and the appropriate age\(^17-20\).
1.1 Objectives

The main objective of this PhD thesis was to examine the effect of probiotics on absence from daycare due to respiratory and gastrointestinal infections in Danish infants during their first months in a daycare setting.

Specific objectives were:

- To examine the effect of a combination of two probiotic strains *Lactobacillus rhamnosus* GG and *Bifidobacterium animalis* subsp. *lactis* BB-12 on absence from daycare due to respiratory and gastrointestinal infections in healthy infants starting daycare (**Paper I**)
- To systematically review the evidence on the effect of probiotics in prevention of respiratory infections in children attending daycare (**Paper II**)
- To explore potential risk factors of infections in Danish infants during their first months in a daycare setting (**Paper III**)