Effect of environmental exposure on infant gut microbiota composition and diversity in the Canadian Healthy Infant Longitudinal Development (CHILD) national birth cohort

by

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Abstract

Background: The development of infant gut microbiota plays a crucial role in immune system development, and infant gut microbiota dysbiosis has been linked to asthma and allergic disease. Studies have shown that Bacteroidetes phylum was less abundant in the guts of allergic children. Although extensive research has been conducted to investigate the effects of delivery mode and infant feeding on gut mircobiota, not much is known about the influence of hospital microbial environment and exposure to household cleaning products on infant gut microbiota composition and diversity.

Objective: To assess the impact of exposure to hospital microbial environment and household cleaning products, on the infant gut microbiota composition and diversity.

Methods: Fecal samples from a subset of 787 children from the Edmonton, Winnipeg and Vancouver sites of the Canadian Healthy Infant Longitudinal Development (CHILD) birth cohort were included in the study. Infant hospital length-of-stay after birth was obtained from birth chart reviews and parent report at 3 months postpartum. Personal use of household cleaning products namely: disinfectant (multi-surface cleaner), detergent and other chemicals (spray air-freshener) were obtained from mothers at 3 months post-delivery. Infant gut microbiota at 3-4 months was characterized by Illumina 16S rRNA sequencing. Microbial relative abundance, Shannon diversity and Chao1 species richness were determined.

Results: Newborn exposure to the hospital environment for more than one day was associated with higher fecal abundance, at infant age 3-4 months, of microbes belonging to the *Lachnospiraceae* family (p=0.041). In addition, *Pseudomonadaceae* (p=0.04) and genus *Pseudomonas* (p=0.027) were more abundant in the gut of infants with extended hospital stays after birth, in both vaginally and caesarean-delivered infants. High indoor disinfectant exposure was associated with low fecal abundance of Actinobacteria (p=0.0002) at the phylum level and of *Bifidobacteriaceae* (p=0.0003) at the family level. Moreover, total microbial diversity was reduced at the order level (p= 0.028) in infants in the high exposure group.

Conclusion: The findings provide evidence of gut microbiota dysbiosis associated with exposure to hospital microbial environment and household cleaning products. The impact of these compositional changes on the development of gut immunity and atopic disease later in life requires further study.

Preface

This thesis is an original work by Mon Tun. The thesis has been written in a paper format thesis according to the guidelines of the Faculty of Graduate Studies and Research at the University of Alberta.

This thesis consists of a literature review (Chapter 1). It is followed by two studies (Chapter 2 and 3) designed to address each of the specific objectives.

Chapter 1 consists of a literature review on hospital acquired infections, household cleaning products, human gut microbiota. In section 1.1 and 1.2, hospital acquired infections, mode of transmission of nosocomial pathogens in hospital environment, household cleaning products are summarized. In section 1.3, human gut microbiota and factors influencing the establishment of infant gut microbita in early life are reviewed. In section 1.4, epidemiological studies of the relationships between household cleaning products and asthma and allergic diseases are reviewed.

In Chapter 2, results of the first research questions are presented. In this chapter, the associations of exposure to hospital microbial environment in early life and changes in infant gut microbiota composition at 3-4 months were examined in the CHILD (Canadian Healthy Infant Longitudinal Development) longitudinal birth cohort. A version of this chapter is in preparation for submission to Pediatric Journal as “Impact of early life hospitalization on infant gut microbiota composition at 3-4 months”.

In Chapter 3, results of the second study are presented. In this chapter, the impact of exposure to household cleaning products on infant gut microbiota composition and diversity at 3-4 months were investigated in the CHILD longitudinal birth cohort. A version of Chapter 3 is in preparation for submission to Environmental Science Pollution Journal as "Impact of postnatal exposure to household cleaning products on infant gut microbiota composition at 3-4 months". I was responsible for the data analysis and wrote the first draft of the manuscript.

In the final chapter, Chapter 4, general discussion and conclusions are presented. This chapter highlights the main findings from the two studies, clinical significance of those findings, strength and limitations of the studies and implications for future research.

Dedication

This thesis is dedicated to my parents and my husband.

For their endless love, support and encouragement.

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The successful accomplishment of this project should in particular owe to the consistent and enormous supervision and support from Dr. Anita Kozyrskyj, for her guidance and support, and editing, amending and supporting the project. Your excellent scientific guidance, advice, patience and support motivated me to successfully complete my research project and this thesis.

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Lastly, I would like to thank my parents for their continuous support.

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CHAPTER 1

Literature Review

1.1 Hospital Acquired Infections (HAIs)

Global pattern of HAIs is on the rise and is affecting the healthcare systems worldwide, and it is the fourth leading cause of death in Canada (World Health Organization, 2011). In Canada, about 8% of children and 10% of adults acquired HAIs during hospitalization (Gravel et al., 2007). More than 50% of HAIs are caused by antibiotic resistant organisms (AROs) (Jones, 2001) , such as: methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), *Pseudomonas*, *Acinetobacter* and *Clostridium* (Patient Safety Network, 2015). MRSA, VRE and extended-spectrum beta-lactamase (ESBL) producing organisms are the three most common antibiotic-resistant bacteria causing HAIs in Canada (Public Health Agency of Canada & National Noscomial Infections Surveillance System, 2002; Valiquette et al., 2014). Moreover, MRSA infection rates have increased 10 fold since 1995 (Public Health Agency of Canada, 2013). Furthermore, incidence of HAIs caused by multidrug resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii* is a rising concern (Gaynes et al., 2005). Another major HAI is *Clostridium difficile* infection (Public Health Agency of Canada, 2013) . AROs incurred an annual additional cost of $40 to $52 million to Canadian patients (Birnbaum 2003; (Public Health Agency of Canada, 2013).

HAIs can easily spread from patient to patient through the hands of healthcare workers during treatment or personal care or by touching contaminated shared surfaces, such as bathrooms, toilets or equipment. Several studies have demonstrated that contamination of healthcare workers' hands (Petit et al., 1999; Hayden et al., 2008; Stiefel et al., 2011; Curie et al.), clothing (Tomas et al., 2015), disposable gloves (Moore et al., 2013; Hayden et al., 2008; Hughes et al., 2013), and gowns (Graham et al., 2008; Tomas et al., 2015; Rock et al., 2014) contributed to cross-transmission and dissemination of nosocomial pathogens to persons at risk. A study by Kramer (2006) showed that MRSA and *C. difficile* are able to adapt and survive long enough in the healthcare environment to cause infection (Kramer et al., 2006). Weinstein (1991) reported that the hands of healthcare workers and contamination from environment contributed 40 – 45% of nosocomial pathogens source in Intensive Care Unit (ICU) (Weinstein, 1991).

Hand sanitizer dispensers can become contaminated with pathogens that cause HAIs with the greatest colonization on the lever, and thus are potential fomites (Simon et al., 2012). It is known that frequent hand washing often damages the skin of health care workers and can lead to colonization by pathogenic bacteria. A study by Kolly (2006) showed that the levels of bacteria shed from the hands of healthcare workers were associated with their skin health condition; for example, dry skin sheds more bacteria, and it may increase the infection transfer risk for healthcare workers' with poor skin condition in acute care settings (Kolly et al., 2006). In addition, healthcare workers introduced skin commensals and pathogenic bacteria into glove

boxes indicating that unused, non-sterile gloves can transmit potential pathogens in hospitals (Hughes et al., 2013).

In Canada, the average length of hospital stay after vaginal delivery is about 2 days but post caesarean delivery is 4 days (Public Health Agency of Canada, 2008). An extended hospital stay increases infant exposure to the hospital microbial environment and elevates the risk for gut colonization with opportunistic microorganisms.

1. 2 Household cleaning products

Over the past decade, with the increase in attention to cleanliness of the home, the utilization of disinfectants, cleaning agents and cleaning sprays has increased (Bello, Quinn, Perry, & Milton, 2010). Disinfectants kill microorganisms and are used as part of the strategies to prevent transmission of infections. Detergents remove grease, dirt, dust, debris and fats. In Canada, the average Canadian family uses 20-40 litres of cleaning products each year (Bio-Vert, 2015). There is a growing concern of exposure to household cleaning products generated toxic chemicals. A survey conducted in Europe demonstrated that all-purpose cleaners, bathroom cleaners, glass and window cleaners, and kitchen cleaners were the most commonly used household products (Dimitroulopoulou et al., 2015).

Many household cleaning products contain dangerous potent chemicals that remain on the surfaces after cleaning or leave toxic residues on people and household surfaces, and contribute to environmental pollution (Wolkoff et al., 1998).

Furthermore, many of those chemical compounds have not been adequately tested for safety in real world applications, while some are known pollutants, irritants, and carcinogens EWG Skin Deep Database, 2009; Sarantis, Malkan, & Archer, 2009; Perry, 2009), and contribute to poor indoor air quality. In addition, synthetic chemicals from household cleaning products can cause disruption to endocrine system (Colburn, Dumanoski, & Myers, 1999; Krimsky, 2000), i.e. the chemicals mimic natural estrogen and can activate or block estrogen receptors in the cells (McLachlan & Arnold, 1996).

Common household products that include VOCs include air fresheners, insect sprays, cleaners and polishes (Heavner, Morgan, & Ogden, 1995; Maroni, Seifert, & Lindvall, 1995a). Higher indoor VOC levels were associated with air freshener and aerosol use (Farrow, Taylor, Northstone, & Golding, 2003), and humans may be exposed to those VOCs via inhalation route. Despite evidence of potential harm in products designed for personal and home hygiene, many people are not aware of the extent to which some of the chemicals in the products they use to clean themselves or their homes are dangerous (Ouimette, 2011). Altman (2008) demonstrated that women were not aware of the association between exposure to daily household cleaning products and presence of industrial chemicals in their blood stream (Altman et al., 2008).

According to Health Canada, Canadians spend an average of 90% of their time indoors and indoor air at home is 2 to 5 times more polluted than outdoor air (Health Canada, 2015). Moreover, energy conservation measures for buildings have led to reduced air exchange rates and promotion of indoor moisture build-up

(Bornehag et al., 2005; Weschler, 2009a). Numerous studies have identified the association between exposure to chemical substances in cleaning products and adverse health effects; i.e. asthma, atopic sensitization (Dumas et al., 2012; Mäkelä, Kauppi, Suuronen, Tuppurainen, & Hannu, 2011; Vizcaya et al., 2011a; J. P. Zock et al., 2007; J. Zock Author et al., 2009). In addition, the utilization and incorporation of disinfectants, bactericides and antiseptics in common household products (Levy, 2001a; Rosenberg, 2000a) may increase selective pressure on bacteria to develop resistant to those agents, as well as cross-resistant to antibiotics.

1.3 Human gut microbiota

The human gut microbiota is a complex and dynamic ecosystem, and it is estimated to harbor approximately 100 trillion of bacterial cells and more than a 100 times the number of genes of the human genome (Ley, Peterson, & Gordon, 2006; Qin et al., 2010). Over the past decades, with the advanced of molecular biotechnology techniques, our knowledge on the role of gut microbiota and its development has increased, as well as, its relationship with human health is being increasingly recognized (van Best, Hornef, Savelkoul, & Penders, 2015).The normal adult human gut microbiota comprises of two major phyla, namely Bacteroidetes and Firmicutes, and followed by the phyla Proteobacteria, Actinobacteria,and Verrucomicrobia. The newborn infant gastrointestinal tract is mainly dominated by facultative anaerobes, *Enterobacteriaceae*, that create an anaerobic environment to

promote the colonization of strict anaerobic bacteria *Bifidobacterium, Clostridium,* and *Bacteroides* (Johnson & Versalovic, 2012).

Human gut microbiota is important for host health, especially as the early establishment of gut microbiota in a newborn infant is thought to be important for the development of the immune system (Penders et al., 2006a). Although an individual's genetic predisposition likely plays a role in this establishment (Dicksved et al., 2008a; Johansson, Sjögren, Persson, Nilsson, & Sverremark-Ekström, 2011; Zoetendal, Akkermans, Akkermans-van Vliet, de Visser, & de Vos, 2001a), it is highly influenced by environmental factors. Infant gut bacterial colonization is influenced by an array of factors: mode of delivery (caesarean or vaginal), gestational age, diet (breast milk vs. formula), sanitation, antibiotic treatment, and indoor environment (pets, siblings) (Adlerberth, Ingegerd,1959, Author, Wold, Agnes E,1955, Author, Göteborgs universitet, Sahlgrenska akademin, Institutionen för biomedicin, avdelningen för infektionssjukdomar, Publisher, & University of Gothenburg, Sahlgrenska Academy, Institute of Biomedicine, Department of,Infectious Medicine, 2009; Azad et al., 2013; Marques et al., 2010).

1.3.1 Prenatal influences on gut microbiota development

It is widely accepted that the intrauterine environment and newborn infant are sterile until delivery; however, some studies showed the presence of bacteria DNA in human placenta, umbilical cord blood, amniotic fluid and meconium (Aagaard et al., 2014; DiGiulio, 2012; Funkhouser & Bordenstein, 2013; Jiménez et al., 2008) using

culture-independent methods, suggesting the translocation of the mother's gut bacteria via the bloodstream (Jiménez et al., 2008).Yet, research with culture-based methods is needed to determine the origin of detected bacterial DNA sequences.

1.3.2 Extrinsic influences on bacterial colonization in infant gut

The intestine of the newborn infant is initially colonized by facultative anaerobes such as *E. coli* and other members belonging to *Enterobacteriaceae* family (Dave, Higgins, Middha, & Rioux, 2012; Johnson & Versalovic, 2012) that generated an anaerobic environment favoring the development of obligate anaerobes, bifidobacteria and *Bacteroides* (Koenig et al., 2011; Tilg & Kaser, 2011). A study done by Palmer (2007) revealed that there is important inter-individual variability in infant gut bacteria colonization pattern. By 1 year of age, infant intestinal microbiota is similar to the one of an adult; however, typical adult microbiota profile is established around 3 years of age, with higher abundance of Bacteroidetes and Firmicutes and lower abundance of Proteobacteria and gram-negative bacteria. In addition, the influence of the mother on the child's microbiota is evident during the first year after birth (Matamoros, Gras-Leguen, Le Vacon, Potel, & Cochetiere, 2013)

Mode of delivery has strong influence on infant gut bacterial colonization. Vaginally-delivered infants are colonized by maternal vaginal and fecal bacteria, namely: *Lactobacillus* and *Bifidobacterium* (Dominguez-Bello, Costello, Contreras, Magris, Hidalgo, Fierer, Knight, & Gordon, 2010). The gut of infants born by caesarean-section (CS) is colonized by organisms from maternal skin (e.g.,

staphylococci), rather than by the usual gut microbes (Dominguez-Bello et al., 2010). Furthermore, Azad (2013) observed that *Bacteroides* were depleted and *Escherichia-Shigella* were siginificantly lower in CS delivered infants (Azad et al., 2013). Moreover, a study conducted in Sweden by Jakobsson and colleagues found that there was delayed colonization and reduced Th-1 response in infants delivered by CS (Jakobsson et al., 2014).

Another strong factor influencing the infant gut microbial development is the early infant diet. There was overrepresentation of *Bifidobacterium* and underreprestatnion of *Bacteroides sp.* and *Clostridium sp.* in breast-fed infants compared to formula-fed infats (Harmsen et al., 2000; Stark, Lee, & Parsonage, 1982; Yoshioka, Iseki, & Fujita, 1983). In addition, few studies pointed out that breast-fed infants had lower species richness and diversity (Azad et al., 2013; Bäckhed et al., 2015; Bezirtzoglou, Tsiotsias, & Welling, 2011; Fallani et al., 2010; Penders et al., 2006a). Breast milk contains oligosaccharides that selectively stimulate the growth of bifidobacteria and lactobacilli (T. R. Abrahamsson & Sherman, 2014; Zivkovic, German, Lebrilla, Mills, & Klaenhammer, 2011).

Antibiotics exposure in the early life does have short and long-term implications on microbial diversity and health consequences. *Bifidobacterium* and *Bacteroides* were reduced (Barrett et al., 2013), and Proteobacteria were increased (Fouhy et al., 2012) in the infants exposed to antibiotics at birth. Besides, exposure to broad-spectrum antibiotics was associated with reduction in gut micriobita diversity (Jernberg, Löfmark, Edlund, & Jansson, 2007).

1.3.3 Hospital microbial environment and infant gut microbiota

Infants born by CS are also exposed initially to bacteria originating from hospital environment and health care workers. CS delivered babies stay longer in hospital than vaginally-delivered infants. In the US, about 60% of newborns stay more than 1 day in the hospital after delivery (Maternity care [microform] : Appropriate follow-up services critical with short hospital stays : Report to the honorable ron wyden, U.S. senate / united states general accounting office1996). In Canada, the average length of hospital stay after vaginal delivery is about 2 days, but for post caesarean delivery it is 4 days (Public Health Agency of Canada, 2008). Moreover, a higher percentage of CS delivered infants was treated with antibiotics compared to those who were delivered vaginally. Selective pressure exerted by antibiotics plays a crucial role in emergence and development of AROs (Donskey, 2004).

The intestinal tract provides an important reservoir of antibiotic-resistant gram-negative bacilli, including *Enterobacteriaceae* species, *Pseudomonas aeruginosa*, and *Acinetobacter* species (Shcimpff et al., 1972; Tancrede et al., 1985; Wingard et al., 1986; Pena et al., 1998; Olson et al., 1984; Lucet et al., 1999; Weiner et al., 1999; Corbella et al., 1996; Donseky et al., 2004). The gastrointestinal tract of newborn can be easily colonized by extended-spectrum β-lactamase bacteria (ESBL) (Bizzarro & Gallagher, 2007), and the colonization rate is directly proportional to the duration of hospital stay (Gloria et al., 2015; Boo et al., 2005; Kothari et al., 2013;

Nordberg et al., 2013). Furthermore, findings from the KOALA cohort showed that each additional day of hospitalization after birth increased the likelihood of *C. difficile* colonization in the gut of 1-month old infants by 1.13 (95% CI: 1.01 - 1.25) (Penders et al., 2006a). An extended hospital stay increases infant exposure to the hospital microbial environment and elevates the risk for gut colonization with opportunistic microorganisms. Since factors associated with hospitalization such as infant infections and their antibiotic treatment, are frequently associated with alterations to microbiota composition (Tamara et al., 2013), it is challenging to determine the influence of hospital microbial environment on infant microbiota composition and diversity.

1.4 Household cleaning products and atopic diseases (allergy, asthma)

Involvement in domestic tasks and home cleaning is a sex-related behaviour. Women are usually the chief persons responsible for cleaning their homes. Findings from Bernstein (2009) showed that in asthmatic women, symptoms were worsened after completing house cleaning tasks independent of chemical severity exposure index and cleaning duration (Bernstein, Brandt, Rezvani, Abbott, & Levin, 2009). Furthermore, preliminary findings from Henderson (2008) and Sherriff (2005) suggested that foetal exposure to household cleaning products was associated with persistent wheezing and diminished lung function in early childhood which was independent of exposure to other indoor air pollutants and potential confounding

factors (Henderson, Sherriff, Farrow, & Ayres, 2008; Sherriff, Farrow, Golding, & Henderson, 2005).

Homes with more disinfectants and detergents exposure are thought to increase Th2 based disease, such as asthma and other atopic diseases, by creating cleaner environment with reduced exposure to environmental antigens. In contrast, Casas (2013) proved that the passive exposure to cleaning products may increase airway inflammation in children and may have an adverse effect on lung function which is consistent with the hypothesis of an inflammatory role of cleaning agents (Casas et al., 2013). Disinfectants and detergents may contain many other irritant or sensitizing agents that may have impact on allergy or respiratory reactions. To our knowledge, there are no published studies assessing the impact of maternal prenatal exposure to those household cleaners on the gut microbiota of infants.

1.5 Summary

Limiting early life infection impedes natural immune system development and leads to allergic disease outcomes (Strachan et al., 1989). This pathway may be a function of the effect of delivery method, antibiotic use and local sanitation practices on the infant gut microbiota (Adlerberth et al., 2007; Abrahamsson et al., 2007). The potential for infants contracting microbial pathogens is the highest within a hospital environment where high rates of antibiotic resistant *S. aureus* and gram-negative microorganisms have been reported amongst health care workers with damaged hands (Rocha et al., 2009). Yet, the influence of early life exposure to hospital environment and household cleaning products on infant gut microbiota composition is unknown.

Hence, this study aimed to find out the effects of exposure to hospital environment and household cleaning products on infants gut microbiota composition and diversity.

1.6 Hypothesis and Objectives

This thesis aimed to test two hypothesis that the gut of infants who were exposed to microbial enviroment in early life is colonized by opporutnictic pathogens, and exposure to household cleaning products postpartum may control microbiota composition and diversity of the infants. The primary objective of this study was to investigate the effect of environmental exposure on infanct gut microbiota composition and diversity in the Canadian Healthy Infant Longitudinal Development (CHILD) national birth cohort. The specific objectives of this study were

(i) to examine the impact of early life exposure to hospital microbial environment on infant gut microbiota composition and diversity at 3-4 months of age

(ii) to examine the impact of postnatal exposure to household cleaning products on infant gut microbiota composition and diversity at 3-4 months of age

1.7 Sample size calculation

Penders (2006) estimated that *C. difficile* prevalence was higher in infants who stayed in hospital for 2-3 days (40%) compared to the infants with no hospital admission history (20%).

From the manual calculation stated below and in consideration of 15% dropped out rate, 91 participants were enrolled in my study.

Sample size calculation for the comparison of two proportions with 80% power

$N = (Z_{\alpha/2}+Z_{\beta})^2 * (p_1(1-p_1)+p_2(1-p_2)) / (p_1-p_2)^2$; $Z_{\beta} = 0.84$ (80% Power); $Z_{\alpha/2} = 1.96$

$N= (2.80)^2 * (0.4 (1-0.4) + 0.2 (1 – 0.2)) / (0.4 – 0.2)^2$

N= 71

p_1 and p_2 are the expected sample proportions of the two groups

$Z_{\alpha/2}$ is the critical value of the Normal distribution at α/2 (e.g. for a confidence level of 95%, α is 0.05 and the critical value is 1.96)

Z_{β} is the critical value of the Normal distribution at β (e.g. for a power of 80%, β is 0.2 and the critical value is 0.84).

1.8 Overview of study design

The CHILD is a longitudinal, population-representative birth cohort study of 3624 pregnant mothers recruited from four provinces of Canada: British Columbia (Vancouver, urban), Alberta (Edmonton, urban), Manitoba (Winnipeg, urban; Mordern and Winker, rural), and Ontario (Toronto, urban) between 2008 and 2012 (Moraes et al., 2014). Approximately 85% of pregnant mothers were enrolled during their second trimester at health care locations with the following inclusion criteria: a live birth at 36 weeks gestation or greater and with birth weight of 2,500 g or more. The enrolled women were followed throughout pregnancy; and their children were followed from birth to the age of 5 years.

Birth hospitalization with duration of stay >1 day in hospital and infants with hospital admission in first 3 months were categorised into the group with exposure to hospital environment in early life. A list of 31 household chemical products was classified into four groups according to their mechanism of actions, namely: disinfectant, detergent, other cleaning products and eco products, based on purpose of cleaning process (see Chapter 3, Index). The frequency of various cleaning products use was provided and classified into 5 categories: 0 for not use at all, 1 for less than a month, 2 for monthly, 3 for weekly, and 4 for daily usage. The scores for each chemical exposure were summed separately for each group to produce a total score for each respondent. The total scores from each group were divided into two groups, higher and lower exposure groups in order to make comparisons of effect sizes during analyses. In addition, in order to explore the combination effect of disinfectant and

other cleaning/ chemical products, four groups of combined disinfectant and other cleaning/ chemical products were created, namely: group 1 (low disinfectant & low other cleaning products), group 2 (low disinfectant & high other cleaning products), group 3 (high disinfectant & low other cleaning products), and group 4 (high disinfectant and high other cleaning products).

1.9 Different ways of profiling infant gut microbiota

Cutlure-based analyses used differential media to select for specific bacteria based on their metabolic requirements and they are time consuming. With the culture-based techniques, scientists are able to isolate only 10% - 25% of the mcirobiota. Most of the microorganisms in the gut are anaerobic and more than 80% of bactearia are uncultivable under standard laboratory conditions (Lagier et al., 2012; 2015). Molecular-based techniques involve using 16S ribosomal RNA (rRNA) gene as a marker of genetic diversity. 16S rRNA genes are relatively small size, higly consevered in prokaryotes, with enough similarity to identify members belonging to the same larger phylogenetic group; however, they are not specific primers for some variable regions (Peterson et al., 2012). With the development of biomedical technology, bacterial gene sequencing has rapidly evoloved to Sanger sequencing (full-length 16S rRNA sequencing), pyrosequencing and illumina sequencing. Illimina sequencing method has 98% accuracy with the lowest error rate and produces the greates output with the lowest reagent cost. (**Table 1.1)** shows the accuracy,

advantages and disadvantanges of the currently available sequencing techniquies (Quail et al., 2012; Liu et al., 2012; Jandhyala et al., 2015).

1.10 Summary of analysis

Statsistical analyses were performed using SPSS software (version 22; IBM SPSS Statistics, IBM Corporation). Chi-squared test was performed in the first step to explore the data and to assess the potential confouding variables according to exposure groups. Infants with a hospital admission with the first 3 months of life were categorized as exposed to the hospital environment (hospital length of stay > 1 day yes/no) and grouped by length of stay (1 day or less, 2-3 days, 4 days or more). The scores for each chemical exposure (disinfectant, detergent, other cleaning/ chemical products and eco products) were summed separately for each group to produce a total score for each respondent. The total scores from each group were divided into two groups, higher and lower quartile in order to make comparisons of effect sizes during analyses. Micriobiota measures were classified in two groups (below vs. above median), and quartiles which were categorised as highest (top quartile) or lowest (bottom quartile) to create dichotomous outcome variables.

The analysis was focused on dominant taxa to minimise multiple comparisons. Gut microbiota median richness, diversity and relative abundance of dominant taxa were compared by Kruskal-Wallis (for more than 2 groups) and Mann-Whitney U-test according to exposure parameters. Crude p-values were adjusted for multiple comparisons by false discovery rate (FDR) using Statistical Analysis Systems (SAS) Software (version 9.4.; SAS Institute, Inc.).

Regression analysis was used to determine the relationships between the measured between exposure parameters and gut microbiota outcome.Univariate analysis and backward stepwise multiple logistic regression were used to identify potential confounding variables. The variables with a crude p-value of <0.25 after the univariate analysis were included in the mutlivariate analyses. Associations between each expsoure variables (exposure to hospital microbial envirionment, length of stay in the hospital, postnatal exposure to four groups of household cleaning products) and infant gut mircobiota composition and diversity was determined using logistic regression analysis. Interaction terms between houshold cleaning products were also tested in the models; however, none of them was statistically significant in the models.

1.11 References

Aagaard, K., Ma, J., Antony, K. M., Ganu, R., Petrosino, J., & Versalovic, J. (2014). *The placenta harbors a unique microbiome* Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=edswsc&AN=000336668800002&site=eds-live&scope=site

Abrahamsson, T. R., & Sherman, P. M. (2014). Multifaceted effects of human milk oligosaccharides. *The Journal of Infectious Diseases, 209*(3), 323-324. doi:10.1093/infdis/jit559

Adlerberth, Ingegerd,1959, Author, Wold, Agnes E,1955, Author, Göteborgs universitet, Sahlgrenska akademin, Institutionen för biomedicin, avdelningen för infektionssjukdomar, Publisher, & University of Gothenburg, Sahlgrenska Academy, Institute of Biomedicine, Department of,Infectious Medicine. (2009). Establishment of the gut microbiota in western infants. *Acta Paediatrica (Oslo, Norway : 1992),* 229. doi:10.1111/j.1651-2227.2008.01060.x

Adlerberth, I., Strachan, D. P., Matricardi, P. M., Ahrné, S., Orfei, L., Åberg, N. Wold, A. E. (2007). Mechanisms of asthma and allergic inflammation: Gut microbiota and development of atopic eczema in 3 European birth cohorts. *The Journal of Allergy and Clinical Immunology, 120*, 343-350. doi:10.1016/j.jaci.2007.05.018

Altman, R. G., Morello-Frosch, R., Brody, J. G., Rudel, R., Brown, P., & Averick, M. (2008). *Pollution comes home and gets personal: Women's experience of household chemical exposure* American Sociological Association. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=edsjsr&AN=edsjsr.27638769&site=eds-live&scope=site

Azad, M. B., Konya, T., Maughan, H., Guttman, D. S., Field, C. J., Chari, R. S., Kozyrskyj, A. L. (2013). Gut microbiota of healthy Canadian infants: Profiles by mode of delivery and infant diet at 4 months. *CMAJ: Canadian Medical Association Journal, 185*(5), 385-394 10p. doi:10.1503/cmaj.121189

Bäckhed, F., Roswall, J., Peng, Y., Feng, Q., Jia, H., Kovatcheva-Datchary, P., Wang, J. (2015). Resource: Dynamics and stabilization of the human gut microbiome during the first year of life. *Cell Host & Microbe, 17*, 690-703. doi:10.1016/j.chom.2015.04.004

Barrett, E., Kerr, C., Murphy, K., O'Sullivan, O., Ryan, C. A., Dempsey, E. M., Stanton, C. (2013). *The individual-specific and diverse nature of the preterm infant microbiota* Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=edswsc&AN=000330515000010&site=eds-live&scope=site

Bello, A., Quinn, M. M., Perry, M. J., & Milton, D. K. (2010). Quantitative assessment of airborne exposures generated during common cleaning tasks: A pilot study. *Environmental Health: A Global Access Science Source, 9*, 76-85. doi:10.1186/1476-069X-9-76

Bernstein, J. A., Brandt, D., Rezvani, M., Abbott, C., & Levin, L. (2009). Evaluation of cleaning activities on respiratory symptoms in asthmatic female homemakers. *Annals of Allergy, Asthma & Immunology: Official Publication of the American College of Allergy, Asthma, & Immunology, 102*(1), 41-46. doi:10.1016/S1081-1206(10)60106-8

Bezirtzoglou, E., Tsiotsias, A., & Welling, G. W. (2011). Molecular biology & genetics: Microbiota profile in feces of breast and formula-fed newborns by using fluorescence in situ hybridization (FISH). *Anaerobe, 17*, 478-482. doi:10.1016/j.anaerobe.2011.03.009

Bio-Vert. (2015). Studies, facts and statistics on cleaning and the environment. Retrieved from http://www.bio-vert.com/en/documentation.php

Birnbaum, D. (2003). Antimicrobial resistance: A deadly burden no country can afford to ignore. *Canada Communicable Disease Report = Releve´ Des Maladies Transmissibles Au Canada, 29*(18), 157-164. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=cmedm&AN=14524197&site=eds-live&scope=site

Bizzarro, M. J., & Gallagher, P. G. (2007). Antibiotic-resistant organisms in the neonatal intensive care unit. *Seminars in Perinatology, 31*(1), 26-32 7p. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=rzh&AN=105990536&site=eds-live&scope=site

Boo, N., Ng, S., & Lim, V. K. E. (2005). A case-control study of risk factors associated with rectal colonization of extended-spectrum beta-lactamase producing klebsiella sp. in newborn infants. *Journal of Hospital Infection, 61*, 68-74. doi:10.1016/j.jhin.2005.01.025

Bornehag, C., Author, Sundell, J., A., Hagerhed-Engman, L., Sigsggard, T., A., Janson, S., A., Aberg, N., A., & Karlstads universitet, Fakulteten för samhälls- och livsvetenskaper, Avdelningen för hälsa,och milj. (2005). Dampness at home and its association with airway, nose and skin symptoms among 10 851 preschool children in Sweden: A cross sectional study. *Indoor Air 2005 15 (Suppl 10) 48-55,* Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=edsswe&AN=edsswe.oai.DiVA.org.kau.18004&site=eds-live&scope=site

Canadian Institute for Health Information. (2006). Giving birth in Canada the costs. Retrieved from https://secure-cihi-ca.login.ezproxy.library.ualberta.ca/free_products/Costs_Report_06_Eng.pdf

Canadian Union of Public Employee. (2014). Healthcare associated infections: A backgrounder. Retrieved from http://cupe.ca/sites/cupe/files/healthcare-associated-infections-cupe-backgrounder.pdf

Casas, L., Zock, J. P., Carsin, A. E., Fernandez-Somoano, A., Esplugues, A., Santa-Marina, L., Sunyer, J. (2013). The use of household cleaning products during pregnancy and lower respiratory tract infections and wheezing during early life. *International Journal of Public Health, 58*(5), 757-764 8p. doi:10.1007/s00038-012-0417-2

Colborn, T., Dumanoski, D., & Myers, J. P. (1997). *Our stolen future : Are we threatening our fertility, intelligence, and survival? : A scientific detective story : With a new epilogue by the authors* New York : Penguin Group, c1997. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=cat03710a&AN=alb.2209089&site=eds-live&scope=site

Corbella, X., Pujol, M., Ayats, J., Sendra, M., Ardanuy, C., Domínguez, M. A., Gudiol, F. (1996). *Relevance of digestive tract colonization in the epidemiology of nosocomial infections due to multiresistant acinetobacter baumannii* University of Chicago Press. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=edsjsr&AN=edsjsr.4459610&site=eds-live&scope=site

Dave, M., Higgins, P. D., Middha, S., & Rioux, K. P. (2012). The human gut microbiome: Current knowledge, challenges, and future directions. *Translational Research: The Journal of Laboratory & Clinical Medicine, 160*(4), 246-257 12p. doi:10.1016/j.trsl.2012.05.003

DiGiulio, D. B. (2012). Diversity of microbes in amniotic fluid. *Seminars in Fetal and Neonatal Medicine, 17*, 2-11. doi:10.1016/j.siny.2011.10.001

Dimitroulopoulou, C., Lucica, E., Johnson, A., Ashmore, M. R., Sakellaris, I., Stranger, M., & Goelen, E. (2015). EPHECT I: European household survey on domestic use of consumer products and development of worst-case scenarios for daily use. *Science of the Total Environment, 536*, 880-889. doi:10.1016/j.scitotenv.2015.05.036

Dominguez-Bello, M., Costello, E. K., Contreras, M., Magris, M., Hidalgo, G., Fierer, N., Gordon, J. I. (2010). *Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns* National Academy of Sciences. doi:10.1073/pnas.1002601107

Donskey, C. J. (2004). *The role of the intestinal tract as a reservoir and source for transmission of nosocomial pathogens* University of Chicago Press. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=edsjsr&AN=edsjsr.4536578&site=eds-live&scope=site

Dumas, O., Donnay, C., Heederik, D. J. J., Héry, M., Choudat, D., Kauffmann, F., & Le Moual, N. (2012). *Occupational exposure to cleaning products and asthma in hospital workers* BMJ Publishing Group. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=edsjsr&AN=edsjsr.23567842&site=eds-live&scope=site

Eiref, S. D., Leitman, I. M., & Riley, W. (2012). Hand sanitizer dispensers and associated hospital-acquired infections: Friend or fomite? *Surgical Infections, 13*(3), 137-140 4p. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=rzh&AN=108126555&site=eds-live&scope=site

Envrionmental Working Group. (2009b). Pollution in people: Cord blood contaminants in Minority Newborns. washington, DC. Retrieved from http://www.ewg.org/files/2009-Minority-Cord-Blood-Report.pdf

Fadeyi, M. O., Weschler, C. J., & Tham, K. W. (2009). *The impact of recirculation, ventilation and filters on secondary organic aerosols generated by indoor chemistry* Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=edswsc&AN=000267964300012&site=eds-live&scope=site

Fallani, M., Young, D., Scott, J., Norin, E., Amarri, S., Adam, R., Doré, J. (2010). Intestinal microbiota of 6-week-old infants across Europe: Geographic influence beyond delivery mode, breast-feeding, and antibiotics. *Journal of Pediatric Gastroenterology and Nutrition, 51*(1), 77-84. doi:10.1097/MPG.0b013e3181d1b11e

Farrow, A., Taylor, H., Northstone, K., & Golding, J. (2003). Symptoms of mothers and infants related to total volatile organic compounds in household products. *Archives of Environmental Health, 58*(10), 633-641. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=eih&AN=15002729&site=eds-live&scope=site

Fouhy, F., Guinane, C. M., Hussey, S., Wall, R., Ryan, C. A., Dempsey, E. M., Cotter, P. D. (2012). *High-throughput sequencing reveals the incomplete, short-term recovery of infant gut microbiota following parenteral antibiotic treatment with ampicillin and gentamicin* Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=edswsc&AN=000310055800049&site=eds-live&scope=site

Funkhouser, L. J., & Bordenstein, S. R. (2013). *Mom knows best: The universality of maternal microbial transmission* Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.log

in.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=edswsc&AN=000323771900011&site=eds-live&scope=site

Gaynes, R., & Edwards, J. R. (2005). Overview of nosocomial infections caused by gram-negative bacilli. *Clinical Infectious Diseases, 41*(6), 848-854. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=a9h&AN=17989235&site=eds-live&scope=site

Gravel, D., Taylor, G., Ofner, M., Johnston, L., Loeb, M., Roth, V. R., Matlow, A. (2007). Point prevalence survey for healthcare-associated infections within canadian adult acute-care hospitals. *Journal of Hospital Infection, 66*, 243-248. doi:10.1016/j.jhin.2007.04.008

Gravel, D., Matlow, A., Ofner-Agostini, M., Loeb, M., Johnston, L., Bryce, E., Taylor, G. (2007). A point prevalence survey of health care-associated infections in pediatric populations in major canadian acute care hospitals. *American Journal of Infection Control, 35*(3), 157-162. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=cmedm&AN=17433938&site=eds-live&scope=site

Harmsen, H. J. M., Wildeboer-Veloo, A., Raangs, G. C., Wagendorp, A. A., Klijn, N., Bindels, J. G., & Welling, G. W. (2000). Analysis of intestinal flora

development in breast-fed and formula-fed infants by using molecular identification and detection methods. *Journal of Pediatric Gastroenterology and Nutrition,* (1) Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=edsagr&AN=edsagr.US201302945115&site=eds-live&scope=site

Hayden, M. K., Blom, D. W., Lyle, E. A., Moore, C. G., & Weinstein, R. A. (2008). *Risk of hand or glove contamination after contact with patients colonized with vancomycin-resistant enterococcus or the colonized patients' environment* University of Chicago Press. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=edsjsr&AN=edsjsr.30144916&site=eds-live&scope=site

Health Canada. (2015). Indoor air quality. Retrieved from http://www.hc-sc.gc.ca.login.ezproxy.library.ualberta.ca/ewh-semt/air/in/index-eng.php

HEAVNER, D. L., MORGAN, W. T., & OGDEN, M. W. (1995). *Determination of volatile organic-compounds and ets apportionment in 49 homes* Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=edswsc&AN=A1995QB47500001&site=eds-live&scope=site

Henderson, J., Sherriff, A., Farrow, A., & Ayres, J. G. (2008). *Household chemicals, persistent wheezing and lung function: Effect modification by atopy?* Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=edswsc&AN=000253876000011&site=eds-live&scope=site

Hertz-Picciotto, I., Cassady, D., Lee, K., Bennett, D. H., Ritz, B., & Vogt, R. (2010). Study of use of products and exposure-related behaviors (SUPERB): Study design, methods, and demographic characteristics of cohorts. *Environmental Health: A Global Access Science Source, 9*, 54-54. doi:10.1186/1476-069X-9-54

Huerta-García, G. C., Miranda-Novales, G., Díaz-Ramos, R., Vázquez-Rosales, G., & Solórzano-Santos, F. (2015). Intestinal colonization by extended-spectrum beta-lactamase-producing enterobacteriaceae in infants. *Revista De Investigacio´n Cli´nica; Organo Del Hospital De Enfermedades De La Nutricio´n, 67*(5), 313-317. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=cmedm&AN=26696335&site=eds-live&scope=site

Hughes, K. A., Cornwall, J., Theis, J., & Brooks, H. J. L. (2013). Bacterial contamination of unused, disposable non-sterile gloves on a hospital orthopaedic ward. *Australasian Medical Journal, 6*(6), 331-338. doi:10.4066/AMJ.2013.1675

Ichinohe, T., Pang, I. K., & Iwasaki, A. (2010). Influenza virus activates inflammasomes via its intracellular M2 ion channel. *Nature Immunology, 11*(5), 404-410. doi:10.1038/ni.1861

Infections in hospital - reduce the risk. (2015). Retrieved from https://www.betterhealth.vic.gov.au/health/conditionsandtreatments/infections-in-hospital-reduce-the-risk?viewAsPdf=true

Isolation of pathogenic bacteria from hospital staff apparel in nigeria (2006). Medical Association of Malawi, 2006-05-08. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=edsoai&AN=edsoai.738389483&site=eds-live&scope=site; http://www.ajol.info/index.php/mmj/article/view/10896/14484; http://www.ajol.info/index.php/mmj/article/view/10896

Jakobsson, H. E., Abrahamsson, T. R., Jenmalm, M. C., Harris, K., Quince, C., Jernberg, C., Andersson, A. F. (2014). Decreased gut microbiota diversity, delayed bacteroidetes colonisation and reduced Th1 responses in infants delivered by caesarean section. *Gut, 63*(4), 559-566. doi:10.1136/gutjnl-2012-303249

Jandhyala, S. M., Talukdar, R., Subramanyam, C., Vuyyuru, H., Sasikala, M., & Nageshwar Reddy, D. (2015). Role of the normal gut microbiota. *World Journal of Gastroenterology, 21*(29), 8787-8803. doi:10.3748/wjg.v21.i29.8787

Jernberg, C., Löfmark, S., Edlund, C., & Jansson, J. K. (2007). Long-term ecological impacts of antibiotic administration on the human intestinal microbiota. *ISME Journal: Multidisciplinary Journal of Microbial Ecology, 1*(1), 56-66. doi:10.1038/ismej.2007.3

Jiménez, E., Marín, M. L., Martín, R., Odriozola, J. M., Olivares, M., Xaus, J., Rodríguez, J. M. (2008). Is meconium from healthy newborns actually sterile? *Research in Microbiology, 159*, 187-193. doi:10.1016/j.resmic.2007.12.007

Johansson, M. A., Sjögren, Y. M., Persson, J., Nilsson, C., & Sverremark-Ekström, E. (2011). Early colonization with a group of lactobacilli decreases the risk for allergy at five years of age despite allergic heredity. *Plos One, 6*(8), 1-8. doi:10.1371/journal.pone.0023031

Johnson, C. L., & Versalovic, J. (2012). *The human microbiome and its potential importance to pediatrics* Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=edswsc&AN=000304709600043&site=eds-live&scope=site

Jones, R. N. (2001). Resistance patterns among nosocomial pathogens: Trends over the past few years. *Chest, 119*(2), 397S-404S. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=cmedm&AN=11171776&site=eds-live&scope=site

Kampmann, C., Author, Uppsala universitet, Medicinska och farmaceutiska vetenskapsområdet, Medicinska fakulteten, Institutionen för medicinska vetenskaper, Klinisk mikrobiologi,och infektionsmedicin, & Uppsala universitet, Medicinska och farmaceutiska vetenskapsområdet, Medicinska och farmaceutiska vetenskapsområdet, centrumbildningar mm, Centrum för,klinisk forskning. (2016). Composition of human faecal microbiota in resistance to campylobacter infection. *Clinical Microbiology and Infection,* Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=edsswe&AN=edsswe.oai.DiVA.org.uu.276830&site=eds-live&scope=site

Koenig, J. E., Spor, A., Scalfone, N., Fricker, A. D., Stombaugh, J., Knight, R., . . . Klaenhammer, T. R. (2011). *Succession of microbial consortia in the developing infant gut microbiome* National Academy of Sciences. doi:10.1073/pnas.1000081107

Kolly, C. A., Arbogast, J. W., & Macinga, D. R. (2006). Poster abstract: Bacterial shedding and desquamation from the hands of healthcare workers correlates with skin condition. *AJIC: American Journal of Infection Control, 34*, E85-E86. doi:10.1016/j.ajic.2006.05.156

Kothari, C., Gaind, R., Chandreshwor Singh, L., Sinha, A., Kumari, V., Arya, S., Deb, M. (2013). Community acquisition of ß-lactamase producing enterobacteriaceae in neonatal gut. *BMC Microbiology, 13*(1), 1-6. doi:10.1186/1471-2180-13-136

Kramer, A., Schwebke, I., & Kampf, G. (2006). How long do nosocomial pathogens persist on inanimate surfaces? A systematic review. *BMC Infectious Diseases, 6*(1), 130-8. doi:10.1186/1471-2334-6-130

Krimsky, S. (2000). *Hormonal chaos : The scientific and social origins of the environmental endocrine hypothesis* Baltimore, MD : Johns Hopkins University Press, c2000. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=cat03710a&AN=alb.2399588&site=eds-live&scope=site

Lagier, J., Hugon, P., Khelaifia, S., Fournier, P., La Scola, B., & Raoult, D. (2015). The rebirth of culture in microbiology through the example of culturomics to study human gut microbiota. *Clinical Microbiology Reviews, 28*(1), 237-264. doi:10.1128/CMR.00014-14

Levy, S. B. (2001). Antibacterial household products: Cause for concern. *Emerging Infectious Diseases, 7*(3), 512. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=eih&AN=5009956&site=eds-live&scope=site

Ley, R. E., Peterson, D. A., & Gordon, J. I. (2006). Review: Ecological and evolutionary forces shaping microbial diversity in the human intestine. *Cell, 124*, 837-848. doi:10.1016/j.cell.2006.02.017

Liu, L., Li, Y., Li, S., Hu, N., He, Y., Pong, R., Law, M. (2012). Comparison of next-generation sequencing systems. *Journal of Biomedicine & Biotechnology, 2012*, 1-11 11p. doi:2012/251364

Lucet, J., Decre, D., Fichelle, A., Joly-Guillou, M., Pernet, M., Deblangy, C., Regnier, B. (1999). Control of a prolonged outbreak of extended-spectrum beta-lactamase-producing enterobacteriaceae in a university hospital. *Clinical Infectious Diseases, 29*(6), 1411. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=eih&AN=5144140&site=eds-live&scope=site

Mäkelä, R., Kauppi, P., Suuronen, K., Tuppurainen, M., & Hannu, T. (2011). Occupational asthma in professional cleaning work: A clinical study. *Occupational Medicine, 61*(2), 121-126. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=eih&AN=58769111&site=eds-live&scope=site

Maroni, M., Seifert, B., & Lindvall, T. (1995). *Indoor air quality : A comprehensive reference book* Amsterdam ; New York : Elsevier Science, 1995. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=cat03710a&AN=alb.1739664&site=eds-live&scope=site

Marques, T. M., Wall, R., Ross, R. P., Fitzgerald, G. F., Ryan, C. A., & Stanton, C. (2010). Programming infant gut microbiota: Influence of dietary and environmental factors. *Current Opinion in Biotechnology, 21*, 149-156. doi:10.1016/j.copbio.2010.03.020

Matamoros, S., Gras-Leguen, C., Le Vacon, F., Potel, G., & Cochetiere, d. L. (2013). Review: Development of intestinal microbiota in infants and its impact on health. *Trends in Microbiology, 21*, 167-173. doi:10.1016/j.tim.2012.12.001

Maternity care [microform] : Appropriate follow-up services critical with short hospital stays : Report to the honorable ron wyden, U.S. senate / united states general accounting office (1996). Washington, D.C. : The Office ; Gaithersburg, MD] (P.O. Box 6015, Gaithersburg 20884-6015) : The Office distributor, 1996]. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=edsgpr&AN=gpr000473135&site=eds-live&scope=site; http://catalog.gpo.gov.login.ezproxy.library.ualberta.ca/fdlpdir/locate.jsp?ItemNumber=0546-D&SYS=000473135; http://purl.access.gpo.gov.login.ezproxy.library.ualberta.ca/GPO/LPS12181

Moore, G., Dunnill, C. W., & Wilson, A. P. (2013). The effect of glove material upon the transfer of methicillin-resistant staphylococcus aureus to and from a gloved hand. *AJIC: American Journal of Infection Control,* (1), 19. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.log

in.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=edsgao&AN=edsgcl.314026697&site=eds-live&scope=site

Nordberg, V., Quizhpe Peralta, A., Galindo, T., Turlej-Rogacka, A., Iversen, A., Giske, C. G., & Navér, L. (2013). High proportion of intestinal colonization with successful epidemic clones of ESBL-producing enterobacteriaceae in a neonatal intensive care unit in ecuador. *Plos One, 8*(10), 1-7. doi:10.1371/journal.pone.0076597

Olson, B., Weinstein, R. A., Nathan, C., Chamberlin, W., & Kabins, S. A. (1984). Epidemiology of endemic pseudomonas aeruginosa: Why infection control efforts have failed. *Journal of Infectious Diseases, 150*(6), 808. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=edb&AN=79846872&site=eds-live&scope=site

Ouimette, M. Y. (2011). *Cleaning house: Considerations of ecological health and sustainability in the selection of household cleaning products* Boston College, 2011. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=edsoai&AN=edsoai.844619314&site=eds-live&scope=site; http://hdl.handle.net.login.ezproxy.library.ualberta.ca/2345/3054

Palmer, C., Bik, E. M., DiGiulio, D. B., Reiman, D. A., & Brown, P. O. (2007). Development of the human infant intestinal microbiota. *PLoS Biology,* (7), 1556. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=edsgao&AN=edsgcl.166988647&site=eds-live&scope=site

Patient Safety Network. (2015). Health care-associated infections. Retrieved from https://psnet-ahrq-gov.login.ezproxy.library.ualberta.ca/primers/primer/7/health-care-associated-infections

Pena, C., Pujol, M., Ardanuy, C., Ricart, A., Pallares, R., Linares, J., Gudiol, F. (1998). *Epidemiology and successful control of a large outbreak due to klebsiella pneumoniae producing extended-spectrum beta-lactamases* Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=edswsc&AN=000071301100008&site=eds-live&scope=site

Penders, J., Thijs, C., Vink, C., Stelma, F. F., Snijders, B., Kummeling, I., Stobberingh, E. E. (2006). Factors influencing the composition of the intestinal microbiota in early infancy. *Pediatrics,* (2), 511. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=edsgao&AN=edsgcl.156549563&site=eds-live&scope=site

Peterson, D. A., Frank, D. N., Pace, N. R., & Gordon, J. I. (2008). Review: Metagenomic approaches for defining the pathogenesis of inflammatory bowel diseases. *Cell Host & Microbe, 3*, 417-427. doi:10.1016/j.chom.2008.05.001

Pittet, D., Dharan, S., Touveneau, S., Sauvan, V., & Perneger, T. V. (1999). Bacterial contamination of the hands of hospital staff during routine patient care. *Archives of Internal Medicine, 159*(8), 821-887 8p. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=rzh&AN=107030068&site=eds-live&scope=site

Public Health Agency of Canada. (2008). Canadian perinatal health report. Retrieved from http://www.violapolomeno.com/cphr-rspc08-eng.pdf

Public Health Agency of Canada. (2013). Report on the state of public health in canada. Retrieved from http://www.phac-aspc.gc.ca.login.ezproxy.library.ualberta.ca/cphorsphc-respcacsp/2013/assets/pdf/2013-eng.pdf

Public Health Agency of Canada (PHAC). (2010). Essential resources for effective infection prevention and control programs: A matter of patient safety: A discussion Paper2010. Retrieved from http://www.phac-aspc.gc.ca.login.ezproxy.library.ualberta.ca/nois-sinp/guide/ps-sp/pdf/ps-sp-eng.pdf

Public Health Agency of Canada (PHAC). (2010). Essential resources for effective infection prevention and control programs: A matter of patient safety: A discussion Paper2010. Retrieved from http://www.phac-aspc.gc.ca.login.ezproxy.library.ualberta.ca/nois-sinp/guide/ps-sp/index-eng.php

Public Health Agency of Canada (PHAC). (2014). **Fact sheet - *clostridium difficile* *(C. difficile)***. Retrieved from http://www.phac-aspc.gc.ca.login.ezproxy.library.ualberta.ca/id-mi/cdiff-eng.php

Qin, J., Li, R., Raes, J., Arumugam, M., Burgdorf, K. S., Manichanh, C., Xie, Y. (2010). A human gut microbial gene catalogue established by metagenomic sequencing. *Nature, 464*(7285), 59-65. doi:10.1038/nature08821

Quail, M. A., Smith, M., Coupland, P., Otto, T. D., Harris, S. R., Connor, T. R., Gu, Y. (2012). A tale of three next generation sequencing platforms: Comparison of ion torrent, pacific biosciences and illumina MiSeq sequencers. *BMC Genomics, 13*(1), 341-153. doi:10.1186/1471-2164-13-341

Rocha, L. A., Ferreira de Almeida, E. B., & Gontijo Filho, P. P. (2009). Changes in hands microbiota associated with skin damage because of hand hygiene procedures on the health care workers. *American Journal of Infection Control, 37*(2), 155-159. doi:10.1016/j.ajic.2008.04.251

Rock, C., Thom, K. A., Masnick, M., Johnson, J. K., Harris, A. D., & Morgan, D. J. (2014). *Frequency of klebsiella pneumoniae carbapenemase (KPC)–Producing*

and non-KPC-producing klebsiella species contamination of healthcare workers and the environment University of Chicago Press. doi:10.1086/675598

Rosenberg, S. (2000). Consumer and market use of antibacterials at home. *The Pediatric Infectious Disease Journal, 19*(10), S114-S116. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=cmedm&AN=11052400&site=eds-live&scope=site

Schimpff, S. C., Young, V. M., Greene, W. H., Vermeulen, G. D., Moody, M. R., & Wiernik, P. H. (1972). Origin of infection in acute nonlymphocytic leukemia. significance of hospital acquisition of potential pathogens. *Annals of Internal Medicine, 77*(5), 707-714. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=cmedm&AN=4628214&site=eds-live&scope=site

Schubert, A. M., Sinani, H., & Schloss, P. D. (2015). Antibiotic-induced alterations of the murine gut microbiota and subsequent effects on colonization resistance against clostridium difficile. *Mbio, 6*(4), e00974-e00974. doi:10.1128/mBio.00974-15

Sherriff, A., Farrow, A., Golding, J., & Henderson, J. (2005). *Frequent use of chemical household products is associated with persistent wheezing in pre-school age children* Retrieved from

http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=edswsc&AN=000225960100012&site=eds-live&scope=site

Snyder, G. M., Thom, K. A., Furuno, J. P., Perencevich, E. N., Roghmann, M., Strauss, S. M., . . . Harris, A. D. (2008). *Detection of methicillin-resistant staphylococcus aureus and vancomycin-resistant enterococci on the gowns and gloves of healthcare workers* The University of Chicago Press. doi:10.1086/588701

Stark, P. L., Lee, A., & Parsonage, B. D. (1982). Colonization of the large bowel by clostridium difficile in healthy infants: Quantitative study. *Infection and Immunity, 35*(3), 895-899. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=cmedm&AN=7068220&site=eds-live&scope=site

Stiefel, U., Cadnum, J. L., Eckstein, B. C., Guerrero, D. M., Tima, M. A., & Donskey, C. J. (2011). *Contamination of hands with methicillin-resistant staphylococcus aureus after contact with environmental surfaces and after contact with the skin of colonized patients* University of Chicago Press. doi:10.1086/657944

Strachan, D. P. (1989). *Hay fever, hygiene, and household size* British Medical Association. Retrieved from

http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=edsjsr&AN=edsjsr.29706049&site=eds-live&scope=site

Tamara, P., Giada de, P., Jorge R., M., Marta, O., Ascensión, M., María Dolores, A., Esther, N. (2013). Influence of early environmental factors on lymphocyte subsets and gut microbiota in infants at risk of celiac disease: The PROFICEL study / influencia de factores ambientales tempranos sobre las subpoblaciones de linfocitos y la microbiota intestinal de niños con riesgo de desarrollar enfermedad celíaca: El estudio PROFICEL. *Nutrición Hospitalaria,* (2), 464. doi:10.3305/nh.2013.28.2.6310

Tancrède, C. H., & Andremont, A. O. (1985). *Bacterial translocation and gram-negative bacteremia in patients with hematological malignancies* University of Chicago Press. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=edsjsr&AN=edsjsr.30104644&site=eds-live&scope=site

Tilg, H., & Kaser, A. (2011). Gut microbiome, obesity, and metabolic dysfunction. *Journal of Clinical Investigation,* (6), 2126. doi:10.1172/JCI58109

Tomas, M. E., Cadnum, J. L., Mana, T. S. C., Jencson, A. L., Koganti, S., Alhmidi, H., . . . Donskey, C. J. (2016). Utility of a novel reflective marker visualized by flash photography for assessment of personnel contamination during removal of

personal protective equipment. *Infection Control and Hospital Epidemiology,* , 1-3. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=cmedm&AN=26976219&site=eds-live&scope=site

United States Environmental Protection Agency and US Department of Health and Human Services 1. (1991). Building air quality: A guide for building owners and facility managers. Retrieved from http://www.cdc.gov.login.ezproxy.library.ualberta.ca/niosh/pdfs/iaq.pdf

Valiquette, L., Chakra, C. N. A., & Laupland, K. B. (2014). Financial impact of health care-associated infections: When money talks. *The Canadian Journal of Infectious Diseases & Medical Microbiology = Journal Canadien Des Maladies Infectieuses Et De La Microbiologie Me´dicale / AMMI Canada, 25*(2), 71-74. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=cmedm&AN=24855473&site=eds-live&scope=site

van Best, N., Hornef, M. W., Savelkoul, P. H. M., & Penders, J. (2015). On the origin of species: Factors shaping the establishment of infant's gut microbiota. *Birth Defects Research Part C: Embryo Today: Reviews,* (4), 240. doi:10.1002/bdrc.21113

Vizcaya, D., Mirabelli, M. C., Antó, J., Orriols, R., Burgos, F., Arjona, L., & Zock, J. (2011). *A workforce-based study of occupational exposures and asthma symptoms in cleaning workers* BMJ Publishing Group. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=edsjsr&AN=edsjsr.41408468&site=eds-live&scope=site

Vonier, P. M., Crain, D. A., McLachlan, J. A., Guillette, , Louis J., & Arnold, S. F. (1996). *Interaction of environmental chemicals with the estrogen and progesterone receptors from the oviduct of the american alligator* National Institute of Environmental Health Sciences. National Institutes of Health. Department of Health, Education and Welfare. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=edsjsr&AN=edsjsr.10.2307.3432968&site=eds-live&scope=site

Weinstein, R. A. (1991). Epidemiology and control of nosocomial infections in adult intensive care units. *The American Journal of Medicine, 91*(3), 179S-184S. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=cmedm&AN=1928162&site=eds-live&scope=site

Wiener, J., Quinn, J. P., Bradford, P. A., Goering, R. V., Nathan, C., Bush, K., & Weinstein, R. A. (1999). Multiple antibiotic-resistant klebsiella and escherichia

coli in nursing homes. *Jama, 281*(6), 517-523. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=cmedm&AN=10022107&site=eds-live&scope=site

Wingard, J. R., Dick, J., Charache, P., & Saral, R. (1986). Antibiotic-resistant bacteria in surveillance stool cultures of patients with prolonged neutropenia. *Antimicrobial Agents and Chemotherapy, 30*(3), 435-439. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=cmedm&AN=3640591&site=eds-live&scope=site

Wolkoff, P., Schneider, T., Kildesø, J., Degerth, R., Jaroszewski, M., & Schunk, H. (1998). Risk in cleaning: Chemical and physical exposure. *The Science of the Total Environment, 215*(1-2), 135-156. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=cmedm&AN=9599458&site=eds-live&scope=site

World Health Organization. (2011). *Report on the burden of endemic health care-associated infection worldwide.*. Retrieved from http://apps.who.int.login.ezproxy.library.ualberta.ca/iris/bitstream/10665/80135/1/9789241501507_eng.pdf

Yoshioka, H., Iseki, K., & Fujita, K. (1983). Development and differences of intestinal flora in the neonatal period in breast-fed and bottle-fed infants. *Pediatrics, 72*(3), 317. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=a9h&AN=4752117&site=eds-live&scope=site

Zivkovic, A. M., German, J. B., Lebrilla, C. B., Mills, D. A., & Klaenhammer, T. R. (2011). *Human milk glycobiome and its impact on the infant gastrointestinal microbiota* National Academy of Sciences. doi:10.1073/pnas.1000083107

Zock, J. P., Plana, E., Jarvis, D., Antó, J. M., Kromhout, H., Kennedy, S. M., Kogevinas, M. (2007). The use of household cleaning sprays and adult asthma: An international longitudinal study. *American Journal of Respiratory & Critical Care Medicine, 176*(8), 735-741 7p. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=rzh&AN=105833261&site=eds-live&scope=site

Zock, J., Author, Plana, E., Author, Antó, J. M., Author, Benke, G., Author, Blanc, P. D., Author, Carosso, A., Author, . . . Uppsala universitet, Medicinska och farmaceutiska vetenskapsområdet, Medicinska fakulteten, Institutionen för medicinska vetenskaper, Arbets-,och milj. (2009). Domestic use of hypochlorite bleach, atopic sensitization, and respiratory symptoms in adults. *Journal of Allergy and Clinical Immunology,* 731. Retrieved from

http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=edsswe&AN=edsswe.oai.DiVA.org.uu.122950&site=eds-live&scope=site

Zoetendal, E. G., Akkermans, A. D. L., Akkermans-van Vliet, W. M., de Visser, ,J.Arjan G., & de Vos, W. M. (2001). The host genotype affects the bacterial community in the human gastronintestinal tract. *Microbial Ecology in Health & Disease, 13*(3), 129-134. doi:10.1080/089106001750462669

Table 1.1 Advantages and disadvantages of few of the currently available sequencing techniques

Techniques used in next generation sequencing	Accuracy	Advantages	Disadvantages
454 Pyrosequencing	99.9%	Less amount of sample, long read lengths, large number of samples can be easily read	Homopolymer errors, Expensive
Short gun Sequencing	98%	Short reads in short time	Assembly process is computationally expensive
Illumina Sequencing (Sequencing by synthesis)	98%	Accurate, quicker, reliable and cheap	Expensive
Pacific Bio Sequencing (single molecule real-time sequencing)	99.9%	Fast and provides long read lenght	Expensive equipment
Ion Torrent Sequencing (Ion semiconductor)	98%	Fast and less expensive	Multiple monomer errors
SOLiD (Sequencing by Ligation) Sequencing	99.9%	Less expensive when compared to other methods	Slow and difficult to sequence palindromers

CHAPTER 2

Impact of early life hospitalization on infant gut microbiota composition at 3 – 4 months

2.1 Introduction

Hospital acquired infections (HAIs) are an ongoing problem. In Canada, an estimate of 220,000 persons becomes infected, and 8,000 persons die from HAIs (Zoutman et al., 2003). The isolation of pathogenic bacteria from the hands and clothing of hospital staff in several jurisdictions suggests that patients, as well as hospital staff, are in close proximity to antibiotic-resistant strains of bacteria namely: methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), *Pseudomonas*, *Acinetobacter* and *Clostridium* (Infections in hospital - reduce the risk.2015; Orji Mu & Mabata TI, 2006; Patient Safety Network, 2015). Those pathogens can persist on inanimate surfaces for weeks or even months (Kramer, Schwebke, & Kampf, 2006). Two of the most common causes of HAIs in Canada are MRSA and *Clostridium difficile* infection (Public Health Agency of Canada, 2008).

The human gut harbors trillions of bacterial species which interact with the host immune system to maintain tissue homeostasis. Microbial colonization of the infant gut is a complex process and known to play a major role in immunological and metabolic pathways (Rodríguez et al., 2015). The colonization process promotes short and long-term health benefits and many early life factors can modify it. Although an individual's genetic predisposition likely plays a role in the gut microbiota

establishment (Zoetendal et al., 2001; Dicksved et al., 2008; Johansson et al., 2011), perinatal factors, such as mode of delivery, diet, antibiotic use and maternal stress influence the microbial colonization. In addition, the influence of the mother's intimate contacts during birth, nursing and early feeding on the child's microbiota is evident during the first year after birth (Matamoro et al., 2013).

Differences in the postnatal microbial composition may explain the higher incidence of immune mediated diseases, such as allergy in children exposed to hospital microbial environment in early life (van Nimwegen et al., 2011). Infants born by CS are also exposed initially to bacteria originating from the mother's skin (Dominguez-Bello et al., 2010), the hospital environment and health care workers. Exposure to contaminated healthcare environment is associated with gut colonization of opportunistic microorganisms (Bhalla, Aron, & Donskey, 2007; McFarland, Mulligan, Kwok, & Stamm, 1989). Furthermore, infants born through CS often stay in hospital longer and receive antibiotics more frequently than do infants born vaginally. Approximately 60% of newborns continue to be hospitalized for longer than 1 day following birth in US hospitals (Maternity care [microform] : Appropriate follow-up services critical with short hospital stays : Report to the honorable ron wyden, U.S. senate / united states general accounting office1996). Findings from the KOALA cohort showed that home birth (46%) compared with hospital birth (54%) was associated with a decreased the risk of atopic disease which were mediated by *C.difficile* colonization (van Nimwegen et al., 2011). *Pseudomonas aeruginosa* intestinal carriage increases from ~3% in normal people to ~20% in hospitalized patients (Stoodley & Thom, 1970). The intestinal carriage of *P. aeruginosa* is likely a

consequence of the opportunistic nature of this species. Intestinal micriobiota plays a secondary to a breach in host defenses (Levison 1973). In addition, Penders (2006) pointed out that each additional day of hospitalization after birth increased the likelihood of *C. difficile* colonization in the gut of 1-month old infants by 1.13 (95%CI: 1.01 - 1.25) (Penders et al., 2006b). Genus *Clostridium* and *Enterococcus*, resistant to cefazolin and ampicillin, were elevated 3 months after emergency CS (Azad et al., 2015).

The influence of early life exposure to hospital environment on infant gut microbiota composition is unknown. The HAIs exposure has a real potential for gut colonization with opportunistic microorganisms, and subsequent alteration of the gut microbiota composition and hence the immune system development.

Therefore, the aim of this study is to assess if gut microbiota is affected by exposure to hospital environment in early life. To be specific, we were focused to reveal whether MRSA, VRE, *Pseudomonas*, *Acinetobacter* and *Clostridium* were more abundant in the gut of prolonged hospitalized infants.

2.2 Materials and Methods

2.2.1 Study design

This study population consisted of 787 infants whose mothers were enrolled from the Edmonton, Winnipeg and Vancouver sites of the Canadian Healthy Infant Longitudinal Development (CHILD) population based birth cohort. Table 2.1 shows the demographic characteristics of the study population. Mode of delivery, breastfeeding status, household pets, siblings, smoking status, and maternal intra-

partum antibiotic exposure, infant's antibiotic exposure, and infant hospitalization history including birth hospitalization were obtained from standardized questionnaire at birth and at 3 months post-partum. Fecal samples were collected from the infants at 3-4 months of age. Duration of hospital stay was documented from hospital records. Birth hospitalization with length of stay > 1 day in hospital and infants with hospital admission in first 3 months were categorized into the group with exposure to hospital environment in early life.

The covariates with the capacity to affect either exposure variable or outcome variable or both were included in the study, such as mode of delivery, readmission to hospital in first 3 months, breastfeeding status, intra-partum antibiotic prophylaxis and infant antibiotic therapy. Those covariates were obtained either from birth chart reviews or maternal report at 3 months postpartum or both.

2.2.2 Sample collection, DNA extraction and PCR amplification

During a scheduled home visit at 3-4 months, homecare nurse collected fecal samples from the infants. Fecal samples were refrigerated during transportation and stored at -80°C until analysis. Total DNA was isolated with QIAamp DNA stool Mini Kit, and the hypervariable V4 region of the 16S rRNA gene was amplified using universal bacterial primers.

2.2.3 Sequencing and taxonomy assignment

Pooled PCR products were sequenced using the MiSeq Illumina Sequencing at the University of Toronto Centre for the Analysis of Genome Evolution & Function (CAGEF). Sequences were de-barcoded and quality filtered by removing reads having more than 10 sites with a Phred quality score less than 20 using QIIME pipeline (version 1.8.0). Closed-picking algorithm in QIIME was performed with sequences that pass quality control in order to cluster them into OTUs at 97 % identity cut-off. Microbiota diversity within samples (α diversity) was calculated using two standard metrics: the Chao1 estimator of OTU richness (which estimates the number of different OTUs present) and the Shannon diversity index (which evaluates both the number of OTUs and the evenness of their distribution). Those metrics were calculated at OTU and family levels.

2.2.4 Statistical analysis

All analyses were performed in SPPS version 22.0 (SPSS, Inc., Chicago, IL, USA). Chi-square test was used to assess the distribution of potential confounders according to early life exposure to hospital environment status. The analysis was focused on dominant taxa to minimize multiple comparisons. The nosocomial pathogens that have significant public health threats were tested for changes at the genus level. The gut microbial profile of infants hospitalized for more than 1 day after birth was compared to the profile of infants without hospitalization. Median richness,

diversity and relative abundance of dominant taxa were compared by non-parametric Mann-Whitney U-test and Kruskal-Wallis test. Crude p-values were adjusted for multiple comparisons by positive False Discovery Rate (FDR) correction in SAS. A p-value of <0.05 was defined as statistically significant, and 95% confidence intervals (CIs) were calculated. Univariate analysis and backward stepwise multiple logistic regression were used to identify variables independently associated with the outcome variables. Variables with a p-value of <0.25 in univariate analyses were included in multivariable analyses. The following variables were included in the multivariable models as potential confounders: mode of delivery, breastfeeding status and direct antibiotic exposure as well as maternal intra-partum antibiotic exposure.

Micriobiota measures were classified in two groups (below vs. above median), and quartiles which were categorized as highest (top quartile) or lowest (bottom quartile) to create dichotomous outcome variables. We selected highest quartile for *Pseudomondaceae*, *Lachnospiraceae*, *Ruminococcaceae*, genus *Pseudomonas*, genus *Acinetobacter*, Chao1 richness and Shannon diversity, and lowest quartile of genus *Clostridium* for the outcome varaible of interest at 3-4 months. An association between hospitalization for more than 1 day and infant gut microbiota diversity and composition was determined using logistic regression analysis. Logistic regression was also run to determine associations between length of hospital stay and gut microbiota composition at 3-4 months of age. Additionally, Pearson correalation analysis was conducted to examine the relationships between duration of hospital stay and Bacteroidetes at the phylum level and *Bacteroidaceae* at the family level.

Due to a large amount of zero (i.e. zero percentage) observed in gut microbiota relative abundance, zero-inflated negative binomial regressions (ZINB) were conducted for the most abundant gut microbiota at phyla level. Tests were performed unadjusted and adjusted for mode of delivery, breast feeding status, antibiotic exposure and hospital readmission in first 3 months. Analyses for ZINB were conducted using STATA SE 12.0.

2.3 Results

2.3.1 Study population

Of the787 infants in this general population, 557 (71%) infants were hospitalized for more than 1 day after birth. The characteristics of the mother-infant pairs were described in (**Table 2.1)**. There were significant differences between the two groups with respect to gender (p = 0.036), mode of delivery (p= 0.001), intra-partum antibiotic exposure (IAP) (p=0.001), breast-feeding status at 3 months (p= 0.041), gestational age (p=0.001) and presence of siblings (p=0.006). No significant differences were detected in the direct antibiotic exposure (p= 0.511), presence of household pets (p=0.828) and prenatal smoke exposure (p=0.880) according to hospitalization status. Among the hospitalized infants, 362 (65%) were vaginally delivered. Two hundred and four (26%) of the infants were delivered via CS and 195 (96%) of them were admitted to hospital. Half of the infants in the exposure group were exclusively breastfed.

The duration of hospital stay was classified into three groups: group 0 (0-1 day), group 1 (2-3 days), and group 2 (≥ 4 days), and their characteristics are

described in (**Table 2.2)**. Significant differences were found between the three groups in terms of mode of delivery (p=0.001), breast-feeding status at 3 months (p=0.025), presence of siblings at home (p=0.020) and gestational age (p=0.001). More than half of the study population stayed between 2-3 days in hospital. Of those 107 (14%) infants with hospital stay for four or more days, 67 (64%) of them were born by CS and 11 (10.3%) were pre-term babies. Infants were exclusively or partially breast-fed, 89% in group 0, 83% in group 1 and 77% in group 2, respectively.

2.3.2 Fecal microbiota composition, diversity and richness

i) Effect of hospitalization

Results revealed significant effect of hospitalization in early life on the infant gut microbiota composition (**Table 2.3**). At the phylum level, Firmicutes were significantly over-represented among infants with a hospital stay for more than one day (median relative abundance 24% vs. 19%, p= 0.022) at 3–4 months. Among dominant microbial families, *Lachnospiraceae* and *Pseudomondaceae* were more abundant in hospitalized infants (3.7% vs. 2.1%, p = 0.041; 0.00023% vs. 0.00012%, p=0.004). The same trend of differences was also observed in a comparison restricted to infants who were vaginally-delivered, and unexposed to indirect antibiotics. Effect modification by mode of delivery was observed at a lower taxonomic level (**Figure 2.1)**. *Pseudomondaceae*, *Lachnospriaceace* and genus *Pseudomonas* were significantly more abundant in vaginally-delivered infants than infants who were born by CS.

In addition, *Ruminococcaceae* was more abundant in infants who were vaginally-delivered, exclusively breastfed and had no indirect antibiotic exposure (median relative abundance (0.16% vs. 0.02%, p = 0.037). Microbiota richness at OTU level tended to be increased in infants with exposure to hospital environment in early life (median Chao1 richness estimator: 360.84 vs. 336.08. *p*= 0.011). Conversely, gut microbiota diversity was lower in hospitalized infants which was not statistically significant (median Shannon diversity index: 3.13 vs. 3.17, *p*= 0.894) at 3-4 months of age.

We conducted multivariate logistic regression to further explore the association of early life exposure to hospital environment and gut microbiota composition and diversity (**Table 2.5 and 2.6**). Early life hospitalization increased the risk of a high relative abundance of *Pseudomondaceae* (OR 1.72, 1.21 – 2.44, p=0.002) and *Lachnospiraceae* (OR 1.44, 1.02 – 2.04, p= 0.039) in the infant gut microbiota at 3-4 months (**Table 2.5**). At the genus level, early life exposure to hospital environment increased the risk of high relative abundance of *Pseudomonas* (OR 1.73, 1.21 – 2.48, p= 0.002). These associations were independent of breastfeeding, caesarean delivery, readmission and antibiotic exposure (both directly and indirectly). Moreover, hospitalized infants have 15% higher risk of colonization with *Acinetobacter* (OR 1.49, 1.06 – 2.10, p =0.023) in exclusively breastfed, no history of readmission and antibiotics free infants. Early life hospitalization was associated with low abundance of *Clostridium* (OR 0.87. 0.62 – 1.22, p= 0.618). There was 1.7 times increase in Chao1 richness in infants with hospitalization history

(OR 1.68, 1.12 – 2.53, p = 0.013; **Table 2.7**) compared to those with no history of hospitalization.

ii) Effect of length of hospital stay

At the phylum level, Bacteroidetes were under-represented among infants with a hospital stay of more than 1 day (**Table 2.3**). Moreover, the relative abundance of Bacteriodetes was inversely proportional to the duration of hospital stay (**Table 2.4**). Although not statistically significant, the decreased in abundance of Bacteroidetes was more pronounced in CS dlivered infants with extended hospital stay compared to vaginally-delivered babies (**data not shown**). In elective CS delivered infants, there was a significant correlation between duration of hospital stay and Bacteroidetes at the phylum level (r= -0.263, n= 83, p=0.016, two tails). Similar significant correlation result was observed for *Bacteroidaceae* (r= -0.253, n=83, p=0.021, two tails) at the family level. Longer hospital stay was associated with reduced abundance of Bacteroidetes and *Bacteroidaceae*.

Infants who stayed ≥ 4 days in hospital had significantly the highest abundance of *Pseudomondaceae* (p= 0.003) (**Table 2.4**). A similar trend was observed when the study was restricted to infants who were vaginally-delivered and had no antibiotic exposure (both directly and indirectly). In addition, *Ruminococcaceae* (p = 0.015) and *Lachnospiriceae* (p = 0.041) were most abundant in group 1 (2-3 day) in a stratified analysis by direct antibiotic exposures status. The

highest richness (p=0.002) was detected in group 1, although the highest diversity (p= 0.180) was observed in group 0 which was not statistically significant.

Infants who stayed longer in hospital were more likely to have high relative abundance of *Pseudomonas*, 1.8 times (OR 1.72, 1.20 – 2.47, p= 0.003) in group 1 (2– 3 days stay) compare to group 0 (0-1 day stay) and 2.4 times (OR 2.43, 1.39 – 4.23, p=0.002) in group 2 (≥ 4 days stay) when compared to group 0 (**Table 2.8**) independent of breastfeeding, caesarean delivery, readmission and antibiotic exposure (both directly and indirectly). In addition, prolonged hospitalization for 4 or more days increased the risk of high relative abundance of *Acinetobacter* (OR 1.68, 1.12 – 2.84, p =0.045) in exclusively breastfed, antibiotic free infants with no history of readmission (**Table 2.8**). Infants with the duration of stay of 2-3 days were associated with 1.8 times more likely to have a high Chao1 richness (OR 1.79, 1.19 – 2.68, p =0.005) (**Table 2.10**).

iii) Stratified analysis by mode of delivery

We conducted a stratified analysis according to mode of delivery for the duration of hospital stay. In the vaginally-delivered group, we observed that the abundance of genus *Pseudomonas* (p=0.008) was directly proportional to the duration of hospital stay, whereas *Pseudomondaceae* (0.000065% in group 1 vs. 0% in group 0 & 2, p=0.003) (**Figure 2.2**) and *Lachnospiraceae* (4.62% in group 1 vs. 2.04% in group 0 & 2.93% in group 2, p= 0.003) (**Figure 2.3**) were more abundant in group 1 (2-3 day). Higher bacterial richness was detected in vaginally-delivered babies with

2-3 days stay in the hospital. In CS delivered infants, we did not find any significant findings for the overall abundance; however, relative abudance of genus *Prevotella*, *Faecalibacterium* and the bacterial diversity were inversely proportional to the duration of hospital stay which were statistically significant (p = 0.032, p= 0.020 and p= 0.031) (**Figure 2.4**). In contrast, *Lactobacillales* at order level was directly proportional to the duration of hospital stay (p = 0.013) (**Figure 2.4**). Furthermore, *Lactobacillales* were more abundant in infants with history of exposure to hospital microbial environment for more than 1 day (**Figure 2.5**).

Likewise, we built multivariable logistic regression for the stratified analysis according to birth mode. In vaginally-delivered group, infants with 2-3 days hospital stay had 16% and 19% higher risk of having more abundance of *Lachnospiraceae* (OR 1.62, 1.13 – 2.34, p= 0.009) and *Pseudomondaceae* (OR 1.93, 1.33 – 2.81, p=0.001) compared to group 0 infants. Moreover, similar trend was observed for genus *Pseudomonas* in the same infants group, with 18% higher risk of gut being colonized with the bacteria (OR 1.83, 1.25 – 2.69, p=0.002) compared to the infants who had short duration of stay in the hospital (data not shown).

CS delivered infants received higher percentage of parenteral antibiotics (a combination of ampicillin and gentamicin) after birth compared to vaginally-delivered infants (5.4% vs. 1.2%) (data not shown). Percentage of infants treated with parenteral antibiotic was associated with the duration of stay in the hospital (**Figure 2.6)**. Additionally, in CS delivered group, infants with ≥ 4 days stay in hospital had higher abundance of *Pseudomondaceae* compared to group 1 (0.000326% in group 2 vs. 0% in group 1, p=0.044).

iv) Zero-inflated negative binomial (ZINB) regression

The likelihood ratios for all the gut microbiota at phyla level in ZINB models were not significant (data not shown).

2.4 Discussion

In this study cohort of 787 Canadian infants, extended hospitalization after birth was associated with enrichment of Firmicutes, *Pseudomondaceae* and *Lachnospriaceae*, and increased richness of gut microbiota at 3-4 months. We found that this early life hospitalization doubled the odds of gut intestinal carriage of *Pseudomonas* (OR 1.73, 1.21 - 2.48). A study published almost 50 years ago by Stoodley et al (Stoodley & Thom, 1970) showed that *P. aeruginosa* intestinal carriage increases from 3% in the community to 20% in hospitalized adult patients. Despite the difference in study populations (infants vs. adults), the intestinal carriage of *P. aeruginosa* is likely a consequence of the opportunistic nature of this species. Indigenous microbiota protect against colonization with potentially pathogenic microorganisms. The disruption of indigenous flora by antimicrobial exposure may increase the risk of colonization by *Pseudomondacease* or *C. difficile* (Munyaka, Eissa, Bernstein, Khafipour, & Ghia, 2015). Colonization resistance can be reduced by disruption of the normal flora from antibiotic use and promote pathologic colonization with *Pseudomonas aeruginosa* (Marshall et al., 1993; I. Adlerberth & Wold, 2009).

In our findings, the *Pseudomondaceae* family was more abundant in the gut of hospitalized infants who were vaginally-delivered and had no exposure to antibiotics

(both directly and indirectly). Vogel & Knothe (1985) reported that *P. aeruginosa* was more substantially detected in the stool of hospitalized adults received two or three concurrent, or courses of antibiotics versus those not treated with antibiotics. The conflicting findings with our study could be due to type and duration of antibiotics use that did not disrupt the anaerobic mircobiota. For instance, cefazolin and penicillin G use for intrapartum prophylaxis has low biliary excretion and less disruption of gut flora (Brogard et al., 1975; Karachalios & Charalabopoulos, 2002). In contrast, ampicillin given to infants for sepsis prophylaxis is excreted mainly via bile and resulted in high concentration in the gut (Acred, Brown, Turner, & Wilson, 1962) and may result in disruption of gut flora. Murdoch et al (1990) demonstrated that there was no colonization by those bacteria in haematological malignancies patients, and broad spectrum therapy with ceftazidime and gentamicin had less effect on gut microbiota with the exception of overgrowth of enterococci.

Nonetheless, our findings of higher abundance of *Pseudomondaceae* family in caesarean-section delivered infants who also received higher percentage of parenteral antibiotics, was consistent with Vogel & Knothe (1985) findings. *P. aeruginosa* belongs to *Pseudomondanceae* family, and is a nosocomial pathogen. *P. aerugnionsa*, one of the top pathogens in Canada (Adam et al., 2013), is naturally less susceptible to antimicrobials. Moreover, Adam et al (2013) pointed out that there is an increasing trend of gentamicin resistance rates of *P. aeruginosa* in children in Canadian hospitals.

Findings from Lowbury et al (1970) and Kominos et al (1972) showed that hands of nursing personnel are the principle mode of transmission in hospital. Döring

et al (1991) reported that 0% to 43% increase in hand cultures of hospital staff during their duty. The study, too, pointed out the route of transmission from hospital sinks to staff's hands during hand washing similar to Döring et al (1996) findings. In our study, the high abundance of *Pseudomonas* in hospitalized infants could be due to cross-transmission from healthcare personnel.

Ozkurt et al (2005) showed that longer stay in hospital was associated with acquisition of imepenem resistant *P. aerugninosa* (Ozkurt, Ertek, Erol, Altoparlak, & Akcay, 2005). Our results revealed similar findings that the duration of hospital stay was directly proportional to the abundance of *P.aeruginosa*; however, we did not test for antibiotic resistance. Ohara et al (2003) showed the opposite findings that duration of hospital stay is not a risk factor for acquisition of this bacterial species *P. aeruginosa.*

Lachnospiraceae and *Ruminococcae* are the most abundant Firmicutes families in gut environments, accounting for roughly 50 % and 30% phylotypes, respectively. Our findings showed that *Lachnospiraceae* was more abundant in hospitalized infants, which are similar to the results from (Perez-Cobas et al., 2013). Early flourishes of *Lachnospiraceae* may be linked with obesity (Cho et al., 2012) due to their short chain fatty acid (SCFA) production (Duncan et al., 2002).

Previous studies have shown a reduced abundance of Bacteroidetes in CS delivered infants, including elective CS (Jakobsson et al., 2013; Azad et al., 2013). A lowered abundance of Bacteroides at the genus level in the gut of infants has been associated with the development of atopic dermatitis (Abrahamsson et al.,

2012). In our present study, the relative proportions of Bacteroidetes at the phylum level and Bacteroidaceae at the family level were lowest among infants born by elective CS with the longest hospital stay. These findings suggest new evidence that gutmicrobial composition following CS may additionally be affected by duration of hospital stay.

We could not find evidence that early life hospitalization had an impact on the relative abundance of *C. difficle*, *Enterococcus* and *Staphylococcus aureus.* Penders et al (2006) found that each additional day of hospitalization after birth increased the likelihood of gut colonization with *C. difficile* by 1.13 (95% CI: 1.01 – 1.25) at 1 month which was inconsistent with our findings. Differences between the microbiota profiling methods and types of antibiotics may explain the discrepancy with literature findings.

Although not statistically significant, genus *Enterococcus* was more abundant after CS delivery which is consistent with Azad et al (2015) study on infant gut microbiota (data not shown). However, we found an opposite trend with Azad infant microbiota study that genus *Clostridium* was less abundant after caesarean delivery. Employment of quantitative polymerase chain reaction (qPCR), different sequencing methods and taxonomay classification in Azad's study may explain the contrary findings. *C. difficile* infection is strongly associated with previous antibiotic use. In our study population, about 7% of babies received antibiotics during the first three months and approximate 40% of mothers received intra-partum antibiotic prophylaxis. The majority of the mothers who received intra-partum antibiotics prophylaxis were given either penicillin G or cefazolin which have less implication

on *C. difficile* colitis. Furthermore, duration of antibiotics exposure plays a vital role in *C. difficile* infection.

Acinetobacter colonized primarily in the hospital environment and has no known predilection for age, gender and race. *Acinetobacter baumannii* has emerged as an important nosocomial pathogen for hospitalized neonates with several outbreaks reported (Chang et al., 2007; Robenshtok et al., 2006). The resistance of *Acinetobacteer* spp. to antimicrobials and its persistence in NICUs is a threat to neonates (Touati et al., 2009; Villegas & Hartstein, 2003). Interestingly, we observed that infants with prolonged hospital stay for four or more days had 17% (OR 1.68, 95% CI 1.12 – 2.84) higher chance of gut colonization with genus *Acinetobacter* compared to infants who stayed in hospital for 0-1 day. Roy et al (2010) found *Acinetobacter baumannii* in the gut of 11% of the babies, and 61% and 21% of those isolates were multidrug-resistant and carbapenam-resistant. We did not test for antimicrobial resistant in our study. In addition, prolonged hospital stay and antimicrobial therapy, which has little or no activity against *Acinetobacter*, are the major risk factors for *Acinetobacter* colonization (Allen & Green, 1987; Cisneros & Rodríguez-Baño, 2002; Falagas & Karveli, 2007; Montefour et al., 2008). Study by Buxton (1978) demonstrated that one third of the hospital personnel had transient hand colonization with multiple strains of *Acinetobacter* spp. (Buxton, Anderson, Werdegar, & Atlas, 1978), and inadequate hand hygiene remains a significant factor in the transmission of this pathogen (Fierobe et al., 2001).

2.5 Conclusion

This study highlights the association between exposure to the hospital microbial environment after birth and changes to infant gut microbial composition within the first 3 months of life. The role of these changes in relation to the development of gut immunity and atopic disease later in life requires further study. The nosocomial pathogens can survive on the surfaces for months and, hence, can be a continuous source of transmission if no regular preventive surface disinfection is performed. The costs associated with HAIs are significant and there is a need for multidisciplinary collaboration in identifying interrelation of host factors and empowering staff compliance with standard precaution requirements (i.e. hand hygiene and personal protective equipment (PPE) use). Furthermore, the findings from this study can be implied to inform delivery decision-making in favor of vaginal deliveries, to inform policy to reduce length of hospital stay, to reinforce HAI prevetion protocols and to target use of specific probiotics to treat and prevent diseases.

2.6 References

Abrahamsson, T., Author, Jakobsson, H. E., A., Andersson, A. F., A., Björksten, B., Author, Engstrand, L., A., Jenmalm, M., Author, . . . Linköpings universitet, Institutionen för klinisk och,experimentell medicin. (2014). Low gut microbiota diversity in early infancy precedes asthma at school age. *Clinical and Experimental Allergy,* , 842. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edsswe&AN=edsswe.oai.DiVA.org.liu.109137&site=eds-live&scope=site

ACRED, P., BROWN, D. M., TURNER, D. H., & WILSON, M. J. (1962). Pharmacology and chemotherapy of ampicillin--a new broad-spectrum penicillin. *British Journal of Pharmacology and Chemotherapy, 18*, 356-369. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=13859205&site=eds-live&scope=site

Adam, H. J., Baxter, M. R., Davidson, R. J., Rubinstein, E., Fanella, S., Karlowsky, J. A., Zhanel, G. G. (2013). Comparison of pathogens and their antimicrobial resistance patterns in paediatric, adult and elderly patients in canadian hospitals. *The Journal of Antimicrobial Chemotherapy, 68 Suppl 1*, i31-i37. doi:10.1093/jac/dkt024

Adlerberth, I., & Wold, A. E. (2009). Establishment of the gut microbiota in western infants. *Acta Paediatrica, 98*(2), 229-238 10p. doi:10.1111/j.1651-2227.2008.01060.x

Allen, K. D., & Green, H. T. (1987). Hospital outbreak of multi-resistant acinetobacter anitratus: An airborne mode of spread? *The Journal of Hospital Infection, 9*(2), 110-119. Retrieved fromhttp://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=2883217&site=eds-live&scope=site

Azad, M. B., Konya, T., Persaud, R. R., Guttman, D. S., Chari, R. S., Field, C. J., Kozyrskyj, A. L. (2015). Impact of maternal intrapartum antibiotics, method of birth and breastfeeding on gut microbiota during the first year of life: A prospective cohort study. *BJOG: An International Journal of Obstetrics and Gynaecology,* doi:10.1111/1471-0528.13601

Bhalla, A., Aron, D. C., & Donskey, C. J. (2007). Staphylococcus aureus intestinal colonization is associated with increased frequency of S. aureus on skin of hospitalized patients. *BMC Infectious Diseases, 7*(1), 1-7. doi:10.1186/1471-2334-7-105

BLACK, J., CALESNICK, B., WILLIAMS, D., & WEINSTEIN, M. J. (1963). Pharmacology of gentamicin, a new broad-spectrum antibiotic. *Antimicrobial Agents and Chemotherapy, 161*, 138-147. Retrieved

fromhttp://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=14274880&site=eds-live&scope=site

Brogard, J. M., Dorner, M., Pinget, M., Adloff, M., & Lavillaureix, J. (1975). *The biliary excretion of cefazolin* University of Chicago Press. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edsjsr&AN=edsjsr.30061742&site=eds-live&scope=site

Brown, E. M., Sadarangani, M., & Finlay, B. B. (2013). The role of the immune system in governing host-microbe interactions in the intestine. *Nature Immunology,* (7), 660. Retrieved fromhttp://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edsgao&AN=edsgcl.336175871&site=eds-live&scope=site

Buxton, A. E., Anderson, R. L., Werdegar, D., & Atlas, E. (1978). Nosocomial respiratory tract infection and colonization with acinetobacter calcoaceticus. epidemiologic characteristics. *The American Journal of Medicine, 65*(3), 507-513. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=362918&site=eds-live&scope=site

Cavalcante, R. D., Canet, P., & Fortaleza, C. (2014). *Risk factors for the acquisition of imipenem-resistant acinetobacter baumannii in a burn unit: An appraisal of the effect of colonization pressure* Retrieved fromhttp://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edswsc&AN=000340185700009&site=eds-live&scope=site

Chang, P. Y., Hsueh, P. R., Wu, P. S., Chan, P. C., Yang, T. T., Lu, C. Y., . . . Huang, L. M. (2007). Multidrug-resistant acinetobacter baumannii isolates in pediatric patients of a university hospital in taiwan. *Journal of Microbiology, Immunology, and Infection = Wei Mian Yu Gan Ran Za Zhi, 40*(5), 406-410. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=17932600&site=eds-live&scope=site

Cho, I., Yamanishi, S., Cox, L., Methé, B.,A., Zavadil, J., Li, K., Blaser, M. J. (2012). Antibiotics in early life alter the murine colonic microbiome and adiposity. *Nature, 488*(7413), 621-626. doi:10.1038/nature11400

Cisneros, J. M., & Rodríguez-Baño, J. (2002). Nosocomial bacteremia due to acinetobacter baumannii: Epidemiology, clinical features and treatment. *Clinical Microbiology & Infection, 8*(11), 687-693. doi:10.1046/j.1469-0691.2002.00487.x

Dominguez-Bello, M., Costello, E. K., Contreras, M., Magris, M., Hidalgo, G., Fierer, N., & Knight, R. (2010). Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. *Proceedings of the National Academy of Sciences of the United States,* (26), 11971. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edsgao&AN=edsgcl.231313568&site=eds-live&scope=site

Donskey, C. J. (2004). *The role of the intestinal tract as a reservoir and source for transmission of nosocomial pathogens* University of Chicago Press. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edsjsr&AN=edsjsr.4536578&site=eds-live&scope=site

Döring, G., Jansen, S., Noll, H., Grupp, H., Frank, F., Botzenhart, K., Wahn, U. (1996). Distribution and transmission of pseudomonas aeruginosa and burkholderia cepacia in a hospital ward. *Pediatric Pulmonology, 21*(2), 90-100. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=8882212&site=eds-live&scope=site

Döring, G., Ulrich, M., Müller, W., Bitzer, J., Schmidt-Koenig, L., Münst, L., Botzenhart, K. (1991). Generation of pseudomonas aeruginosa aerosols during

handwashing from contaminated sink drains, transmission to hands of hospital personnel, and its prevention by use of a new heating device. *Zentralblatt Für Hygiene Und Umweltmedizin = International Journal of Hygiene and Environmental Medicine, 191*(5-6), 494-505. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=1909134&site=eds-live&scope=site

Duncan, s. H., Barcenilla, A., Stewart, C. S., Pryde, S. E., & Flint, H. J. (2002). Acetate utilization and butyryl coenzyme A (CoA): Acetate-CoA transferase in butyrate-producing bacteria from the human large intestine.*Applied and Environmental Microbiology,* (10), 5186. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edsgao&AN=edsgcl.97187405&site=eds-live&scope=site

Falagas, M. E., & Karveli, E. A. (2007). The changing global epidemiology of acinetobacter baumannii infections: A development with major public health implications. *Clinical Microbiology and Infection: The Official Publication of the European Society of Clinical Microbiology and Infectious Diseases, 13*(2), 117-119. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=17328722&site=eds-live&scope=site

Fierobe, L., Lucet, J., Decré, D., Muller-Serieys, C., Deleuze, A., Joly-Guillou, M., Desmonts, J. (2001). *An outbreak of imipenem-resistant acinetobacter baumannii in critically ill surgical patients* SLACK Incorporated. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edsjsr&AN=edsjsr.30141444&site=eds-live&scope=site

Hentges, D. J., Stein, A. J., Casey, S. W., & Que, J. U. (1985). Protective role of intestinal flora against infection with pseudomonas aeruginosa in mice: Influence of antibiotics on colonization resistance. *Infection and Immunity, 47*(1), 118-122. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=2856912&site=eds-live&scope=site

Infections in hospital - reduce the risk. (2015). Retrieved from https://www.betterhealth.vic.gov.au/health/conditionsandtreatments/infections-in-hospital-reduce-the-risk?viewAsPdf=true

Isolation of pathogenic bacteria from hospital staff apparel in nigeria (2006). Medical Association of Malawi, 2006-05-08. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edsoai&AN=edsoai.738389483&site=eds-live&scope=site; http://www.ajol.info/index.php/mmj/article/view/10896/14484; http://www.ajol.info/index.php/mmj/article/view/10896

Isolation of pathogenic bacteria from hospital staff apparel in nigeria (2006). Medical Association of Malawi, 2006-05-08. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edsoai&AN=edsoai.738389483&site=eds-live&scope=site; http://www.ajol.info/index.php/mmj/article/view/10896/14484; http://www.ajol.info/index.php/mmj/article/view/10896

Jakobsson, H. E., Rodríguez-Piñeiro, A.,M., Schütte, A., Ermund, A., Boysen, P., Bemark, M., Johansson, M. E. V. (2015). The composition of the gut microbiota shapes the colon mucus barrier. *EMBO Reports, 16*(2), 164-177. doi:10.15252/embr.201439263

Johansson, M. A., Sjögren, Y. M., Persson, J., Nilsson, C., & Sverremark-Ekström, E. (2011). Early colonization with a group of lactobacilli decreases the risk for allergy at five years of age despite allergic heredity. *Plos One,6*(8), 1-8. doi:10.1371/journal.pone.0023031

Kamada, N., Seo, S., Chen, G. Y., & Nunez, G. (2013). Role of the gut microbiota in immunity and inflammatory disease. *Nature Reviews Immunology,* (5), 321. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edsgao&AN=edsgcl.330005056&site=eds-live&scope=site

Karachalios, G., & Charalabopoulos, K. (2002). *Biliary excretion of antimicrobial drugs* Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edswsc&AN=000182370700003&site=eds-live&scope=site

Karachalios, G., & Charalabopoulos, K. (2002). Biliary excretion of antimicrobial drugs. *Chemotherapy, 48*(6), 280-297. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=12673103&site=eds-live&scope=site

Kominos, S. D., Copeland, C. E., & Grosiak, B. (1972). Mode of transmission of pseudomonas aeruginosa in a burn unit and an intensive care unit in a general hospital. *Applied Microbiology, 23*(2), 309-312. Retrieved fromhttp://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=4622827&site=eds-live&scope=site

Kramer, A., Schwebke, I., & Kampf, G. (2006). How long do nosocomial pathogens persist on inanimate surfaces? A systematic review. *BMC Infectious Diseases, 6*(1), 130-8. doi:10.1186/1471-2334-6-130

Kuhn, K. A., & Stappenbeck, T. S. (2013). Review: Peripheral education of the immune system by the colonic microbiota. *Seminars in Immunology, 25*(-), 364-369. doi:10.1016/j.smim.2013.10.002

Levison, M. E. (1973). Effect of colon flora and short-chain fatty acids on growth in vitro of pseudomonas aeruginsoa and enterobacteriaceae. *Infection and Immunity, 8*(1), 30-35. Retrieved fromhttp://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=4198102&site=eds-live&scope=site

Lowbury, E. J., Thom, B. T., Lilly, H. A., Babb, J. R., & Whittall, K. (1970). Sources of infection with pseudomonas aeruginosa in patients with tracheostomy. *Journal of Medical Microbiology, 3*(1), 39-56. Retrieved fromhttp://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=4988647&site=eds-live&scope=site

Marshall, J. C., Christou, N. V., & Meakins, J. L. (1993). The gastrointestinal tract. the "undrained abscess" of multiple organ failure. *Annals of Surgery, 218*(2), 111-119. Retrieved fromhttp://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=8342990&site=eds-live&scope=site

Matamoros, S., Gras-Leguen, C., Le Vacon, F., Potel, G., & Cochetiere, d. L. (2013). Review: Development of intestinal microbiota in infants and its impact on health. *Trends in Microbiology, 21*, 167-173. doi:10.1016/j.tim.2012.12.001

Maternity care [microform] : Appropriate follow-up services critical with short hospital stays : Report to the honorable ron wyden, U.S. senate / united states general accounting office (1996). Washington, D.C. : The Office ; Gaithersburg, MD] (P.O. Box 6015, Gaithersburg 20884-6015) : The Office distributor, 1996]. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edsgpr&AN=gpr000473135&site=eds-live&scope=site; http://catalog.gpo.gov/fdlpdir/locate.jsp?ItemNumber=0546-D&SYS=000473135; http://purl.access.gpo.gov/GPO/LPS12181

McFarland, L. V., Mulligan, M. E., Kwok, R. Y. Y., & Stamm, W. E. (1989). Nosocomial acquisition of clostridium difficile infection. *The New England Journal of Medicine,* (4), 204. Retrieved fromhttp://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edsgao&AN=edsgcl.7021538&site=eds-live&scope=site

Montefour, K., Frieden, J., Hurst, S., Helmich, C., Headley, D., Martin, M., & Boyle, D. A. (2008). Acinetobacter baumannii: An emerging multidrug-resistant pathogen in critical care. *Critical Care Nurse,* (1), 15. Retrieved fromhttp://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.co

m/login.aspx?direct=true&db=edsgao&AN=edsgcl.175458395&site=eds-live&scope=site

Moraes, T. J., Lefebvre, D. L., Chooniedass, R., Becker, A. B., Brook, J. R., Denburg, J., . . . Befus, A. D. (2015). *The canadian healthy infant longitudinal development birth cohort study: Biological samples and biobanking*Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edswsc&AN=000346916700011&site=eds-live&scope=site

Munyaka, P. M., Eissa, N., Bernstein, C. N., Khafipour, E., & Ghia, J. (2015). Antepartum antibiotic treatment increases offspring susceptibility to experimental colitis: A role of the gut microbiota. *Plos One, 10*(11), 1-22. doi:10.1371/journal.pone.0142536

MURDOCH, D. A., GIBBS, S., PRICE, C., EASMON, S., FRANKLIN, J., LISTER, T. A., & TABAQCHALI, S. (1990). *Effect of ceftazidime and gentamicin on the oropharyngeal and fecal flora of patients with hematological malignancies* Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edswsc&AN=A1990DY59500014&site=eds-live&scope=site

OHARA, T., & ITOH, K. (2003). Significance of pseudomonas aeruginosa colonization of the gastrointestinal tract. *Internal Medicine, 42*(11), 1072-1076. doi:10.2169/internalmedicine.42.1072

Örebro universitet, H., Originator, Uppsala universitet, Medicinska och farmaceutiska vetenskapsområdet, Medicinska fakulteten, Institutionen för onkologi, radiologi och,klinisk immunologi, Dicksved, J., Author, Halfvarson, J., Author, Rosenquist, M., Author, Järnerot, G., Author, Jansson, J. K., Author. (2008). Molecular analysis of the gut microbiota of identical twins with crohns disease. *The ISME Journal,* 716. Retrieved fromhttp://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edsswe&AN=edsswe.oai.DiVA.org.oru.3529&site=eds-live&scope=site

Ozkurt, Z., Ertek, M., Erol, S., Altoparlak, U., & Akcay, M. N. (2005). The risk factors for acquisition of imipenem-resistant pseudomonas aeruginosa in the burn unit. *Burns, 31*, 870-873. doi:10.1016/j.burns.2005.04.015

Patient Safety Network. (2015). Health care-associated infections. Retrieved from https://psnet.ahrq.gov/primers/primer/7/health-care-associated-infections

Penders, J., Thijs, C., Vink, C., Stelma, F. F., Snijders, B., Kummeling, I., Stobberingh, E. E. (2006). Factors influencing the composition of the intestinal microbiota in early infancy. *Pediatrics,* (2), 511. Retrieved fromhttp://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.co

m/login.aspx?direct=true&db=edsgao&AN=edsgcl.156549563&site=eds-live&scope=site

Perez-Cobas, A., Gosalbes, M. J., Friedrichs, A., Knecht, H., Artacho, A., Eismann, K., Moya, A. (2013). *Gut microbiota disturbance during antibiotic therapy: A multi-omic approach* Retrieved fromhttp://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edswsc&AN=000325557200012&site=eds-live&scope=site

Public Health Agency of Canada. (2008). Canadian perinatal health report. Retrieved from http://www.violapolomeno.com/cphr-rspc08-eng.pdf

Public Health Agency of Canada (PHAC). (2010). Essential resources for effective infection prevention and control programs: A matter of patient safety: A discussion Paper2010. Retrieved from http://www.phac-aspc.gc.ca/nois-sinp/guide/ps-sp/index-eng.php

Public Health Agency of Canada (PHAC). (2013). **Healthcare-associated Infections—Due diligence**. Retrieved from http://www.phac-aspc.gc.ca/cphorsphc-respcacsp/2013/infections-eng.php

Public Health Agency of Canada (PHAC). (2013). Report on the state of public health in canada. Retrieved from http://www.phac-aspc.gc.ca/cphorsphc-respcacsp/2013/assets/pdf/2013-eng.pdf

Public Health Agency of Canada (PHAC). (2014). **Fact sheet - *clostridium difficile* *(C. difficile)***. Retrieved from http://www.phac-aspc.gc.ca/id-mi/cdiff-eng.php

Robenshtok, E., Paul, M., Leibovici, L., Fraser, A., Pitlik, S., Ostfeld, I., Weinberger, M. (2006). The significance of acinetobacter baumannii bacteraemia compared with klebsiella pneumoniae bacteraemia: Risk factors and outcomes. *Journal of Hospital Infection, 64*, 282-287. doi:10.1016/j.jhin.2006.06.025

Rodríguez, J. M., Murphy, K., Stanton, C., Ross, R. P., Kober, O. I., Juge, N., Collado, M. C. (2015). The composition of the gut microbiota throughout life, with an emphasis on early life. *Microbial Ecology in Health and Disease, 26*, 26050-26050. doi:10.3402/mehd.v26.26050

Roy, S., Viswanathan, R., Singh, A., Das, P., & Basu, S. (2010). Gut colonization by multidrug-resistant and carbapenem-resistant acinetobacter baumannii in neonates. *European Journal of Clinical Microbiology & Infectious Diseases,* (12) Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edsagr&AN=edsagr.US201301917867&site=eds-live&scope=site

Simon, G. L., & Gorbach, S. L. (1986). The human intestinal microflora. *Digestive Diseases and Sciences, 31*(9), 147. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.co

m/login.aspx?direct=true&db=edo&AN=ejs16997550&site=eds-live&scope=site

Stoodley, B. J., & Thom, B. T. (1970). Observations on the intestinal carriage of pseudomonas aeruginosa. *Journal of Medical Microbiology, 3*(3), 367-375. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=4990646&site=eds-live&scope=site

Strober, W. (2013). Impact of the gut microbiome on mucosal inflammation. *Trends in Immunology,* (9), 423. doi:10.1016/j.it.2013.07.001

Touati, A., Achour, W., Cherif, A., Hmida, H. B., Afif, F. B., Jabnoun, S., Hassen, A. B. (2009). Outbreak of acinetobacter baumannii in a neonatal intensive care unit: Antimicrobial susceptibility and genotyping analysis.*Annals of Epidemiology, 19*(6), 372-378 7p. doi:10.1016/j.annepidem.2009.03.010

van Nimwegen, F. A., Penders, J., Stobberingh, E. E., Postma, D. S., Koppelman, G. H., Kerkhof, M., Thijs, C. (2011). Asthma and lower airway disease: Mode and place of delivery, gastrointestinal microbiota, and their influence on asthma and atopy. *The Journal of Allergy and Clinical Immunology, 128*, 948-955.e3. doi:10.1016/j.jaci.2011.07.027

Villegas, M. V., & Hartstein, A. I. (2003). *Acinetobacter outbreaks, 1977-2000* SLACK Incorporated. Retrieved

from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edsjsr&AN=edsjsr.30141601&site=eds-live&scope=site

Vogel, F., & Knothe, H. (1985). Changes in aerobic faecal bacterial flora of severely ill patients during antibiotic treatment. *Klinische Wochenschrift, 63*(22), 1174. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edb&AN=72316345&site=eds-live&scope=site

Yeoh, N., Burton, J. P., Suppiah, P., Reid, G., & Stebbings, S. (2013). The role of the microbiome in rheumatic diseases. *Current Rheumatology Reports,* (3), 1. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edsgao&AN=edsgcl.322872153&site=eds-live&scope=site

Zoetendal, E. G., Akkermans, A. D. L., Akkermans-van Vliet, W. M., de Visser, ‚J.Arjan G., & de Vos, W. M. (2001). The host genotype affects the bacterial community in the human gastronintestinal tract. *Microbial Ecology in Health & Disease, 13*(3), 129-134. doi:10.1080/089106001750462669

Zoutman, D. E., Ford, B. D., Bryce, E., Gourdeau, M., Hébert, G., Henderson, E., & Paton, S. (2003). Major articles: The state of infection surveillance and control

in canadian acute care hospitals. *AJIC: American Journal of Infection Control, 31*, 266-273. doi:10.1067/mic.2003.88

Table 2.1 Population characteristics of hospitalized and non-hospitalized infants

	No Hospital admission by 3 months N (%), 230 (29.2%)	Hospital admission by 3 months N (%), 557 (70.8%)	*p*
Sex (N= 787)			
Male	112(48.7%)	317 (56.9%)	0.036
Female	118 (51.3%)	240 (43.1%)	
Birth Mode (N = 777)			
Casesarean-elective	2 (0.9%)	81 (14.5%)	0.001
Casesarean-emergency	7 (3.2%)	114 (20.5%)	
Vaginal	211 (95.9%)	362 (65%)	
IAP (N= 778)			
No	166 (75.1%)	214 (38.4%)	0.0001
Yes	55 (24.9%)	343 (61.6%)	
Antibiotic Exposure by 3 months (N = 781)			
No	214 (93.9%)	511 (92.4%)	0.511
Yes	14 (6.1%)	42 (7.6%)	
Diet (N = 785)			
Exclusively breastfed	136 (59.4%)	279 (50.2%)	0.041
Partially breastfed	66 (28.8%)	177 (31.8%)	
Not breastfed	27 (11.8%)	100 (18%)	
Older Siblings (N= 780)			
No	97 (43.5%)	303 (54.4%)	0.006
Yes	126 (56.5%)	254 (45.6%)	
Furry Pets (N= 785)			
No	61 (26.6%)	155 (27.9%)	0.828
Yes	168 (73.4%)	401 (72.1%)	
Smoke (N= 785)			
No	197 (86 %)	476 (85.6%)	0.880
Yes	32 (14 %)	80 (14.4%)	
Term Delivery (N= 775)			
No	4 (1.8%)	27 (4.8%)	0.001
Yes	214 (94.7%)	530 (95.2%)	
Readmission (N = 783)			
No	229 (99.6%)	519 (93.2%)	0.001
Yes	1 (0.4%)	38 (6.8%)	

Table 2.2 Population characteristics by duration of hospital stay

	Group 0 (0 - 1 Day) N (%) 238 (30.2%)	**Group 1 (2 - 3 Days) N (%) 442 (56.2%)**	**Group 2 (≥ 4 Days) N (%) 107 (13.6%)**	***p***
Sex (N= 787)				
Male	117 (49.2%)	250 (56.6%)	62 (57.9%)	0.135
Female	121 (50.8%)	192 (43.4%)	45 (42.1%)	
Birth Mode (N= 777)				
Casesarean-elective	2 (3.1%)	59 (13.3%)	22 (20.6%)	0.001
Casesarean-emergency	7 (3.1%)	69 (15.6%)	45 (42.1%)	
Vaginal	219 (96.1%)	314 (71.0%)	40 (37.4%)	
IAP (N= 780)				
No	102 (44.2%)	235 (53.2%)	63 (58.9%)	0.020
Yes	129 (55.8%)	207 (46.8%)	44 (41.1%)	
Antibiotic Exposure by 3 months (N = 781)				
No	223 (94.5%)	406 (92.7%)	96 (89.7%)	0.280
Yes	13 (5.5%)	32 (7.3%)	11 (10.3%)	
Diet (N= 785)				
Exclusively breastfed	141 (59.5%)	227 (51.5%)	47 (43.9%)	0.025
Partially breastfed	69 (29.1%)	139 (31.5%)	35 (32.7%)	
Not breastfed	27 (11.4%)	75 (17%)	25 (23.4%)	
Older Siblings (N= 780)				
No	102 (44.2%)	235 (53.2%)	63 (58.9%)	0.020
Yes	129 (55.8%)	207 (46.8%)	44 (41.1%)	
Furry Pets (N= 780)				
No	65 (27.4%)	127 (28.8%)	24 (22.4%)	0.416
Yes	172 (72.6%)	314 (71.2%)	83 (77.6%)	
Smoke (N= 785)				
No	204 (86.1%)	383 (86.8%)	86 (80.4%)	0.225
Yes	33 (13.9%)	58 (13.2%)	21 (19.6%)	
Term Delivery (N= 775)				
No	4 (1.7%)	16 (3.6%)	11 (10.3%)	0.001
Yes	222 (93.3%)	426 (96.4%)	96 (89.7%)	

Table 2.3 Relative abundance of dominant phyla and *families* in fecal microbiota of infants at 3-4 months of age (according to Hospitalization status) N=787

	Microbiota at 3 - 4 months (N=787)			
Dominant Taxa	**No Hospitalization in 3 Months (N= 230, 29.2%) Median (IQR)**	**Hospitalized in 3 months (N= 557, 70.8%) Median (IQR)**	**P-value**	**FDR *P***
Actinobacteria	4.68 (0.99 - 15.34)	5.73 (1.47 - 14.68)	0.352	0.352
Bifidobacteriaceae	3.98 (0.63 - 14.77)	5.06 (1.13 - 14.06)	0.407	0.407
Bacteroidetes	20.71 (0.08 - 63.03)	10.32 (0.07 - 56.79)	0.317	0.317
Bacteroidaceae	14.50 (0.07 - 54.53)	8.14 (0.05 - 50.98)	0.471	0.471
Firmicutes	19.54 (7.68 - 40.32)	24.09 (10.67 - 46.57)	**0.022**	0.055*
Enterococcaceae	0.02 (0.00 - 0.07)	0.03 (0.00 - 0.10)	0.196	0.196
Staphylococcaceae	0.00 (0.00 - 0.01)	0.00 (0.00 - 0.01)	0.813	0.813
Clostridiaceae	0.41 (0.06 - 3.24)	0.42 (0.05 - 2.36)	0.783	0.783
Lachnospiraceae	2.10 (0.04 - 8.63)	3.70 (0.10 - 10.56)	**0.041**	0.055*
Ruminococcaceae	0.12 (0.00 - 1.79)	0.14 (0.01 - 1.83)	0.334	0.334
Veillonellaceae	5.14 (0.93 - 14.13)	4.49 (0.85 - 16.10)	0.812	0.812
Proteobacteria	20.37 (9.56 - 42.33)	20.40 (9.10 - 40.62)	0.586	0.586
Pseudomonadaceae	0.00012 (0.00 -0.000425)	0.00023 (0.00 - 0.000631)	**0.004**	**0.013**
Moraxellaceae	0.00 (0.00 - 0.000537)	0.00 (0.00 - 0.000654)	0.070*	0.070*
Enterobacteriaceae	16.51 (6.74 - 42.28)	18.21 (6.24 - 39.12)	0.679	0.679
g_Entercococcus	0.00 (0.00 - 0.02)	0.00 (0.00 - 0.02)	0.200	0.200
g_staphylococcus	0.00 (0.00 - 0.01)	0.00 (0.00 - 0.01)	0.813	0.813
g_Clostridium	0.03 (0.00 - 0.60)	0.02 (0.00 - 0.46)	0.465	0.465
g_Pseudomonas	0.00010(0.00 - 0.000336)	0.00024 (0.00 - 0.000522)	**0.005**	**0.013**
g_Acinetobacter	0.00 (0.00 - 0.000529)	0.00 (0.00 - 0.000652)	0.084	0.084
Chao 1-Overall	336.08 (285.16 - 397.36)	360.84 (294.05 - 423.02)	**0.011**	-
Shannon-Overall	3.17 (2.61 - 3.62)	3.13 (2.65 - 3.54)	0.894	-

IQR= Interquartile range, FDR = False Discovery Rate.Comparison by non parametric Mann-Whitney U-test. *P* values <0.1 are indicated with '*'. P values <0.05 are indicated in boldface type.

Table 2.4 Relative abundance of dominant phyla and *families* in fecal microbiota of infants at 3-4 months of age (according to Duration of Hospital Stay) N=787

	Microbiota at 3-4 months (N=787)				
Dominant Taxa	**Admission (0 - 1 Day) (N= 238, 30.2%) Median (IQR)**	**Admission (2 - 3 Days) (N= 442, 56.2%) Median (IQR)**	**Admission (≥ 4 Days) (N= 107, 13.6%) Median (IQR)**	**P-value**	**FDR *P***
Actinobacteria	4.90 (1.02 - 15.34)	5.72 (1.54 - 14.42)	4.83 (0.53 - 15.83)	0.587	0.798
Bifidobacteriaceae	4.42 (0.70 - 14.77)	5.02 (1.28 - 13.62)	4.09 (0.17 - 15.66)	0.742	0.798
Bacteroidetes	21.17 (0.09 - 61.42)	15.05 (0.07 - 58.06)	1.50 (0.06 - 54.44)	0.423	0.653
Pervotellaceae	0.00 (0.00 - 0.01)	0.00 (0.00 - 0.01)	0.00 (0.00 - 0.01)	0.431	0.653
Firmicutes	19.17 (7.32 - 40.32)	24.51 (10.81 - 45.95)	23.75 (10.53 - 47.90)	0.058*	0.233
Enterococcaceae	0.02 (0.00 - 0.07)	0.03 (0.00 - 0.11)	0.02 (0.00 - 0.09)	0.217	0.603
Staphylococcaceae	0.001317 (0.00 - 0.0128)	0.001617 (0.00013 - 0.0075)	0.00213 (0.00 - 0.007539)	0.900	0.900
Clostridiaceae	0.39 (0.04 - 3.01)	0.45 (0.05 - 2.30)	0.38 (0.04 - 2.56)	0.953	0.953
Lachnospiraceae	2.04 (0.04 - 8.63)	3.77 (0.19 - 10.56)	3.13 (0.02 - 10.72)	0.061*	0.233
Ruminococcaceae	0.11 (0.00 - 1.66)	0.19 (0.01 - 1.89)	0.05 (0.00 - 1.31)	0.070*	0.233
Veillonellaceae	5.07 (0.88 - 14.28)	4.49 (0.78 - 16.56)	4.25 (1.00 - 13.78)	0.958	0.958
Proteobacteria	20.84 (9.81 - 43.10)	20.62 (9.11 - 40.74)	18.50 (8.22 - 40.00)	0.665	0.798
Pseudomonadaceae	0.00 (0.00 - 0.00425)	0.00 (0.00 - 0.000585)	0.000199(0.00 - 0.000747)	**0.003**	**0.025**
Moraxellaceae	0.00 (0.00 - 0.000537)	0.00 (0.00 - 0.000685)	0.00 (0.00 - 0.000541)	0.306	0.637
Enterobacteriaceae	17.58 (6.79 - 42.40)	18.43 (6.25 - 39.24)	17.23 (6.03 - 36.10)	0.703	0.798
g_Entercococcus	0.02 (0.00 - 0.07)	0.03 (0.00 - 0.10)	0.02 (0.00 - 0.08)	0.302	0.637
g_staphylococcus	0.001317 (0.00 - 0.01275)	0.001617 (0.00013 - 0.0075)	0.00213 (0.00 - 0.007539)	0.900	0.900
g_Clostridium	0.03 (0.00 - 0.59)	0.03 (0.00 - 0.41)	0.01 (0.00 - 0.65)	0.856	0.856
g_Pseudomonas	0.00 (0.00 - 0.000299)	0.00 (0.00 - 0.000514)	0.000168 (0.00 - 0.000654)	**0.003**	**0.025**
g_Acinetobacter	0.00 (0.00 - 0.000537)	0.00 (0.00 - 0.000684)	0.00 (0.00 - 0.000541)	0.344	0.637
Chao 1-Overall	335.76 (283.81 - 397.10)	367.61 (297.59 - 427.54)	354.82 (274.12 - 400.29)	**0.002**	-
Shannon-Overall	3.17 (2.63 - 3.62)	3.15 (2.66 - 3.55)	3.04 (2.37 - 3.48)	0.180	-

IQR= Interquartile range, FDR = False Discovery Rate.Comparison by non parametric Mann-Whitney U-test. *P* values <0.1 are indicated with '*'. P values <0.05 are indicated in boldface type.

Table 2.5 Crude and adjusted likelihood ratio of abundance of key gut microbiota measures at 3-4 months according to hospitalization status

	Microbiota at 3 months						
	OR (95% CI)						
Ref = No hospital admission	***Pseudomondaceae* (below vs. above median)**	***Lachnospiraceae* (below vs. above median)**	***Ruminococcaceae* (below vs. above median)**	***Enterobacteriaceae* (below vs. above median)**	***g_Acinetobacter* (below vs. above median)**	**g_ *Pseudomonas* (below vs. above median)**	**g_ *Clostridium* (below vs. above median)**
Crude OR for Hospitalization in 3 months	**1.7(1.24- 2.34)***	1.33(0.98-1.81)	1.02(0.75-1.39)	1.10(0.81-1.50)	1.37(0.10 -1.88)	**1.71(1.24 2.38)***	0.84(0.62-1.15)
Adjusted for caesarean delivery	**1.74(1.24 -2.44)***	**1.48(1.06 -2.06)***	1.05(0.75-1.46)	1.11(0.80-1.55)	1.20(0.86 -1.68)	**1.71(1.24-2.38)***	0.83(0.60 -1.15)
Adjusted for exclusively breastfeeding at 3 months	**1.62(1.18 -2.24)***	1.29(0.94 -1.77)	1.01(0.74-1.38)	1.11(0.81-1.51)	1.37(0.10 -1.89)	**1.65(1.19-2.29)***	0.86(0.63-1.17)
Adjusted for direct antibiotic exposure	**1.71(1.24 -2.36)***	1.33(0.97 -1.81)	1.02(0.75-1.40)	1.10(0.81-1.50)	**1.38(1.00 -1.90)***	**1.74(1.25-2.41)***	0.83(0.61-1.13)
Adjusted for indirect antibiotic exposure (IAP)	**1.78(1.27- 2.51)***	1.35(0.97 -1.88)	1.04(0.75-1.45)	1.09(0.79-1.52)	1.40(0.10 -1.95)	**1.81(1.28 1.57)***	0.85(0.61- 1.19)
Adjusted for readmission in 3 months	**1.70(1.24 -2.34)***	**1.38(1.01 -1.89)***	1.05(0.77-1.43)	1.09(0.80-1.48)	1.36(0.96 - 1.91)	**1.72(1.24 2.39)***	0.88(0.65 -1.20)
Adjusted for caesarean delivery, exclusively breastfeed, direct and indirect antibiotic exposure, readmission	**1.72(1.21-2.44)***	**1.44(1.02 -2.04)***	1.04(0.74-1.47)	1.12 (0.80-1.58)	**1.49(1.06- 2.10) ***	**1.73(1.21-2.48)***	0.87 (0.62-1.22)

* are statistically significant (p <0.05). OR = odds ratio, CI = Confidence Interval, IAP = Intra-partum Antibiotic Phylaxis

Table 2.6 Crude and adjusted likelihood ratio of abundance of key gut microbiota measures at 3-4 months (Highest or Lowest quartile vs. the rest)

	Microbiota at 3 months						
	OR (95% CI)						
Ref = No hospital admission	**High *Pseudomondaceae* (highest quartile vs. others)**	**High *Lachnospiraceae* (highest quartile vs. others)**	**High *Ruminococcaceae* (highest quartile vs. others)**	**High *Enterobacteriaceae* (highest quartile vs. others)**	**High *g_Acinetobacter* (highest quartile vs. others)**	**High *g_Pseudomonas* (highest quartile vs. others)**	**Low *g_ Clostridium* (lowest quartile vs. others)**
Crude OR for Hospitalization in 3 months	**1.54(1.05- 2.25)***	1.34(0.93-1.94)	1.03(0.72 -1.47)	0.82(0.58-1.17)	1.25(0.87 - 1.80)	**1.54(1.05 - 2.25)***	0.94 (0.65 - 1.34)
Adjusted for caesarean delivery	1.47(0.99- 2.20)	1.46(0.99 - 2.15)	1.01(0.69 - 1.48)	0.87(0.60 - 1.26)	1.14(0.77 - 1.69)	1.42(0.95 - 2.12)	0.89 (0.61 - 1.30)
Adjusted for exclusively breastfeeding at 3 months	**1.50(1.02 -2.19)***	1.28(0.88 - 1.85)	1.05(0.73 - 1.50)	0.87(0.61 - 1.24)	0.93(0.65 - 1.34)	**1.50(1.03 - 2.20)***	0.93 (0.65 - 1.34)
Adjusted for direct antibiotic exposure	**1.52(1.04 -2.23)***	1.32(0.91 - 1.91)	1.06(0.74 - 1.53)	0.82(0.58 - 1.17)	0.92(0.64 - 1.32)	**1.53(1.04 - 2.23)***	0.92 (0.64 - 1.32)
Adjusted for indirect antibiotic exposure (IAP)	**1.68(1.13 -2.51)***	1.33(0.90 - 1.96)	1.01(0.69 - 1.47)	0.91(0.63 - 1.33)	1.21(0.82 - 1.78)	**1.47(0.98 - 2.19)***	1.00 (0.68 - 1.47)
Adjusted for readmission in 3 months	**1.51(1.03 -2.20)***	1.39(0.96 - 2.01)	1.03(0.72 - 1.48)	0.80(0.56 -1.14)	1.32(0.91 - 1.90)	**1.52(1.04 - 2.22)***	1.03 (0.72 - 1.47)
Adjusted for caesarean delivery, exclusively breastfeed, direct and indirect antibiotic exposure, readmission	1.48 (0.93 - 2.12)	1.42(0.95 - 2.13)	1.00(0.67 - 1.48)	0.94(0.64 - 1.40)	1.26(0.84 - 1.89)	1.34(0.88 - 2.03)	0.99 (0.66 - 1.47)

* are statistically significant (p <0.05). OR = odds ratio, CI = Confidence Interval, IAP = Intrapartum Antibiotic Phylaxis

Table 2.7 Crude and adjusted likelihood ratio of richness and diversity measures of gut microbiota at 3-4 months (according to hospitalization status)

Ref = No hospital admission	Chao1 Richness (below vs. above median)	Shannon Diversity (below vs. above median)	Chao1 Richness (highest quartile vs. others)	Shannon Diversity (highest quartile vs. others)
Crude OR for Hospitalization in 3 months	1.27 (0.94 - 1.74)	0.93 (0.68 - 1.26)	1.55 (1.06 - 2.27)**	0.89 (0.62 - 1.26)
Adjusted for caesarean delivery	1.29 (0.93 - 1.79)	0.93 (0.67 - 1.29)	1.61 (1.08 - 2.39)**	0.88 (0.61 - 1.28)
Adjusted for exclusively breastfeeding at 3 months	1.26 (0.92 - 1.72)	0.89 (0.66 - 1.22)	1.51 (1.03 - 2.21)**	0.86 (0.60 - 1.22)
Adjusted for direct antibiotic exposure	1.29 (0.94 - 1.76)	0.91 (0.67 - 1.24)	1.55 (1.06 - 2.26)**	0.88 (0.62 - 1.25)
Adjusted for indirect antibiotic exposure (IAP)	1.33 (0.96 - 1.86)	0.90 (0.64 - 1.25)	1.61 (1.08 - 2.40)**	0.85 (0.58 - 1.24)
Adjsted for readmission in 3 months	1.34 (0.98 - 1.83)	0.94 (0.69 - 1.28)	1.64 (1.12 - 2.40)**	0.92 (0.64 - 1.30)
Adjusted for caesarean delivery, exclusively breastfeed, direct and indirect antibiotic exposure, readmission	1.35 (0.96 - 1.91)	0.89 (0.63 - 1.25)	1.68 (1.12 - 2.53)**	0.85 (0.57 - 1.25)

** are statistically significant ($p < 0.05$). OR = odds ratio, CI = Confidence Interval, IAP = Intrapartum Antibiotic Phylaxis

Table 2.8 Crude and adjusted likelihood ratio of abundance of key gut microbiota measures at 3-4 months according to duration of stay in the hospital (below vs. above median)

		Microbiota at 3 months			
		OR (95% CI)			
Ref Group 0 = 0- 1 Day Group 1 = 2-3 Days Group 2 = ≥ 4 Days		***Pseudomondaceae*** **(below vs. above median)**	***Lachnospiraceae*** **(below vs. above median)**	***Ruminococcaceae*** **(below vs. above median)**	***Enterobacteriaceae*** **(below vs. above median)**
Crude OR for Hospitalization in 3 months	Group 1	**1.68(1.21-2.32)***	**1.41(1.03-1.94)***	1.11(0.81-1.53)	1.05(0.76-1.43)
	Group 2	**2.13(1.34-3.39)***	1.22(0.77-1.93)	0.74(0.47-1.17)	0.96(0.61-1.52)
Adjusted for caesarean delivery	Group 1	**1.74(1.23-2.45)***	**1.52(1.09-2.13)***	1.07(0.77-1.49)	1.06(0.76-1.48)
	Group 2	**2.29(1.37-3.82)***	1.51 (0.91-2.50)	0.75(0.45-1.25)	0.98(0.59-1.62)
Adjusted for exclusively breastfeeding at 3 months	Group 1	**1.61(1.16-2.24)***	1.36 (0.99-1.87)	1.11(0.80-1.52)	1.05(0.76-1.44)
	Group 2	**2.01(1.26-3.21)***	1.15 (0.72-1.83)	0.71(0.45-1.14)	0.96(0.60-1.52)
Adjusted for direct antibiotic exposure	Group 1	**1.70(1.23-2.36)***	**1.41(1.02-1.94)***	1.12(0.81-1.53)	1.04(0.76-1.43)
	Group 2	**2.15(1.35-3.42)***	1.20 (0.76-1.90)	0.74(0.46-1.17)	0.96(0.61-1.51)
Adjusted for indirect antibiotic exposure (IAP)	Group 1	**1.77(1.25-2.50)***	1.41 (1.01-1.97)	1.08(0.77-1.51)	1.05(0.75-1.46)
	Group 2	**2.31(1.41-3.80)***	1.24 (0.76-2.03)	0.74(0.45-1.20)	0.95(0.58 -1.55)
Adjusted for readmission in 3 months	Group 1	**1.68(1.21-2.32)***	**1.43(1.04-1.96)***	1.11(0.81-1.52)	1.05(0.76-1.43)
	Group 2	**2.16(1.33-3.51)***	1.31 (0.81 -2.11)	0.70(0.43-1.14)	0.9 (0.60-1.56)
Adjusted for caesarean delivery, exclusively breastfeed, direct and indirect antibiotic exposure, readmission	Group 1	**1.74(1.22-2.48)***	1.47(1.04 -2.08)	1.05(0.74 -1.47)	1.06(0.76 -1.50)
	Group 2	**2.26(1.30-3.93)***	1.54(0.89 - 2.66)	0.69(0.40 - 1.20)	0.99(0.58-1.70)

** are statistically significant (p <0.05). OR = odds ratio, CI = Confidence Interval, IAP = Intrapartum Antibiotic Phylaxis

Table 2.8 (continued) Crude and adjusted likelihood ratio of abundance of key gut microbiota measures at 3-4 months according to duration of stay in the hospital (below vs. above median)

		Microbiota at 3 months		
		OR (95% CI)		
Ref Group 0 = 0- 1 Day Group 1 = 2-3 Days Group 2 = ≥ 4 Days		***g_Acinetobacter*** **(below vs. above median)**	***g_Pseudomonas*** **(below vs. above median)**	***g_Clostridium*** **(below vs. above median)**
Crude OR for Hospitalization in 3 months	Group 1	1.25 (0.91- 1.73)	**1.66(1.19-2.31)***	0.95(0.70-1.31)
	Group 2	1.47(0.93 - 2.33)	**2.26(1.41-3.61)***	0.67(0.42-1.06)
Adjusted for caesarean delivery	Group 1	1.13(0.81 - 1.59)	**1.68(1.19-2.39)***	0.92 (0.66- 1.28)
	Group 2	1.16(0.70 - 1.93)	**2.36(1.41-3.95)***	0.63 (0.38 -1.05)
Adjusted for exclusively breastfeeding at 3 months	Group 1	1.33(0.94 - 1.88)	**1.60(1.14-2.24)***	0.97 (0.70- 1.33)
	Group 2	1.87(1.12 - 3.11)	**2.14(1.34-3.44)***	0.67 (0.42 -1.07)
Adjusted for direct antibiotic exposure	Group 1	1.26(0.91 - 1.75)	**1.68(1.20-2.35)***	0.93 (0.68-1.28)
	Group 2	1.47(0.93 - 2.33)	**2.28(1.42-3.64)***	0.64 (0.40 -1.02)
Adjusted for indirect antibiotic exposure (IAP)	Group 1	1.21(0.86-1.70)	**1.76(1.24-2.50)***	0.96 (0.69 -1.34)
	Group 2	1.37(0.84-2.25)	**2.49(1.51-4.12)***	0.68 (0.41 -1.11)
Adjusted for readmission in 3 months	Group 1	1.27(0.92 - 1.76)	**1.66(1.19-2.32)***	0.97 (0.71 -1.33)
	Group 2	1.71(1.05 - 2.77)	**2.33(1.43-3.80)***	0.75 (0.46 -1.22)
Adjusted for caesarean delivery, exclusively breastfeed, direct and indirect antibiotic exposure, readmission	Group 1	1.28(0.90-1.80)	**1.72(1.20-2.47)***	0.93 (0.66 -1.32)
	Group 2	1.68(1.12-2.84)	**2.43(1.39-4.24)***	0.71(0.41-1.23)

** are statistically significant (p <0.05). OR = odds ratio, CI = Confidence Interval, IAP = Intrapartum Antibiotic Phylaxis

Table 2.9 Crude and adjusted likelihood ratio of abundance of key gut microbiota measures at 3-4 months according to duration of stay in the hospital (highest or lowest quartile vs. the rest)

		Microbiota at 3 months			
		OR (95% CI)			
		Pseudomondaceae **(highest quartile vs. others)**	***Lachnospiraceae*** **(highest quartile vs. others)**	***Ruminococcaceae*** **(highest quartile vs. others)**	***Enterobacteriaceae*** **(lowest quartile vs. others)**
Crude OR for Hospitalization in 3 months	Group 1	**1.51(1.02-2.22)***	1.35(0.9-1.97)	1.12 (0.78- 1.61)	0.80 (0.56 -1.14)
	Group 2	**2.18 (1.30-3.64)***	1.40 (0.82 -2.37)	0.80 (0.46- 1.40)	0.74 (0.43 -1.26)
Adjusted for caesarean delivery	Group 1	**1.51(1.00 -2.26)***	1.43 (0.96-2.11)	1.06 (0.72- 1.54)	0.84 (0.58 -1.23)
	Group 2	**2.16(1.22 -3.82)***	1.65 (0.93 -2.95)	0.76 (0.41- 1.39)	0.82 (0.45 -1.47)
Adjusted for exclusively breastfeeding at 3 months	Group 1	1.48(0.99-2.18)	1.29 (0.88 -1.88)	1.14 (0.79- 1.64)	0.83 (0.56 -1.20)
	Group 2	**2.09(1.24 -3.51)***	1.30 (0.76 -2.21)	0.81 (0.46- 1.43)	0.79 (0.46 -1.36)
Adjusted for direct antibiotic exposure	Group 1	**1.50(1.01-2.21)***	1.33 (0.91-1.94)	1.15 (0.80- 1.67)	0.79 (0.55 -1.13)
	Group 2	**2.16(1.29- 3.62)***	1.35 (0.79-2.29)	0.82 (0.47- 1.44)	0.74 (0.44 -1.27)
Adjusted for indirect antibiotic exposure (IAP)	Group 1	**1.66(1.10- 2.50)***	1.41 (0.95 -2.09)	1.06 (0.72- 1.55)	0.89 (0.61 -1.30)
	Group 2	**2.58(1.50- 4.43)***	1.51 (0.86-2.67)	0.76 (0.42- 1.36)	0.87 (0.49 -1.54)
Adjusted for readmission in 3 months	Group 1	**1.51 (1.02 - 2.22)***	1.36 (0.93 - 1.98)	1.10 (0.77 - 1.59)	0.79 (0.55 - 1.13)
	Group 2	**2.16 (1.26 - 3.70)***	1.46 (0.84 - 2.53)	0.72 (0.40 - 1.30)	0.71 (0.41 - 1.25)
Adjusted for caesarean delivery, exclusively breastfeed, direct and indirect antibiotic exposure, readmission	Group 1	**1.47 (1.03 - 2.23)***	1.38 (0.92 - 2.07)	1.04 (0.70 - 1.53)	0.91 (0.62 - 1.35)
	Group 2	**2.03 (1.10 - 3.76)***	1.68 (0.89 - 3.15)	0.65 (0.34 – 1.25)	0.91 (0.48 – 1.72)

*are statistically significant ($p < 0.05$). OR = odds ratio, CI = Confidence Interval, IAP = Intrapartum Antibiotic Phylaxis

Table 2.9(continued) Crude and adjusted likelihood ratio of abundance of key gut microbiota measures at 3-4 months according to duration of stay in the hospital (highest or lowest quartile vs. the rest)

		Microbiota at 3 months		
		OR (95% CI)		
		g_Acinetobacter **(highest quartile vs. others)**	***g_Pseudomonas*** **(highest quartile vs. others)**	***g_Clostridium*** **(lowest quartile vs. others)**
Crude OR for Hospitalization in 3 months	Group 1	1.32(0.91-1.91)	**1.53 (1.0 - 2.25)***	1.03(0.72 - 1.48)
	Group 2	0.96 (0.55- 1.66)	**2.09 (1.24 - 3.50)***	0.99 (0.59 -1.69)
Adjusted for caesarean delivery	Group 1	1.19 (0.81- 1.76)	**1.53 (1.04- 2.25)***	0.97 (0.66 - 1.42)
	Group 2	0.77 (0.42- 1.41)	**2.09 (1.24- 3.50)***	0.90 (0.50 - 1.61)
Adjusted for exclusively breastfeeding at 3 months	Group 1	1.34 (0.92- 1.94)	**1.50 (1.02- 2.21)***	1.02 (0.71 - 1.48)
	Group 2	1.00 (0.58- 1.75)	**2.02 (1.20- 3.40)***	0.99 (0.58 - 1.68)
Adjusted for direct antibiotic exposure	Group 1	1.31 (0.91- 1.90)	**1.52 (1.03- 2.24)***	1.01 (0.70 - 1.46)
	Group 2	0.93 (0.54- 1.62)	**2.08 (1.24- 3.49)***	0.97 (0.57 - 1.64)
Adjusted for indirect antibiotic exposure (IAP)	Group 1	1.26 (0.85- 1.87)	**1.50 (1.01- 2.26)***	1.08 (0.73 - 1.59)
	Group 2	0.89 (0.50- 1.61)	**2.02 (1.16- 3.52)***	1.09 (0.62 - 1.92)
Adjusted for readmission in 3 months	Group 1	1.34 (0.93 - 1.94)	**1.53 (1.04 - 2.25)***	1.06 (0.74 - 1.53)
	Group 2	1.14 (0.64 - 2.01)	**2.12 (1.24 - 3.64)***	1.28 (0.72 - 2.25)
Adjusted for caesarean delivery, exclusively breastfeed, direct and indirect antibiotic exposure, readmission	Group 1	1.27 (0.85 - 1.90)	1.41 (0.93 - 2.15)	1.04 (0.70 - 1.55)
	Group 2	0.94 (0.49 - 1.81)	**1.80 (1.03 - 3.33)***	1.22 (0.64 - 2.30)

*are statistically significant ($p < 0.05$). OR = odds ratio, CI = Confidence Interval, IAP = Intrapartum Antibiotic Phylaxis

Table 2.10 Crude and adjusted likelihood ratio of richness and diversity measures of gut microbiota at 3-4 months (according to length of stay in the hospital)

		OR (95% CI)			
Ref Group 0 = 0-1 Day Group 1 = 2-3 Days Group 2 = ≥ 4 Days		**Chao1 Richness (below vs. above median)**	**Shannon Diversity (below vs. above median)**	**Chao1 Richness (highest quartile vs. others)**	**Shannon Diversity (highest quartile vs. others)**
Crude OR for Hospitalization in 3 months	Group 1	1.41 (1.03 - 1.94)**	0.95 (0.69 - 1.30)	1.77 (1.20 - 2.60)*	0.89 (0.62 - 1.27)
	Group 2	1.22 (0.77 - 1.93)	0.67 (0.42 - 1.06)	1.11 (0.63 - 1.96)	0.74 (0.43 - 1.28)
Adjusted for caesarean delivery	Group 1	1.38 (0.99 - 1.92)	0.92 (0.66 - 1.29)	1.74 (1.17 - 2.60)*	0.87 (0.60 - 1.27)
	Group 2	1.22 (0.74 - 2.03)	0.64 (0.38 - 1.06)	1.16 (0.63 - 2.14)	0.72 (0.40 - 1.31)
Adjusted for exclusively breastfeeding at 3 months	Group 1	1.40 (1.02 - 1.92)*	0.92 (0.67 - 1.26)	1.72 (1.17 - 2.53)*	0.86 (0.60 - 1.24)
	Group 2	1.19 (0.75 - 1.89)	0.63 (0.39 - 0.99)	1.05 (0.59 - 1.86)	0.70 (0.41 - 1.21)
Adjusted for direct antibiotic exposure	Group 1	1.43 (1.04 - 1.97)*	0.93 (0.68 - 1.28)	1.77 (1.20 - 2.60)*	0.88 (0.61 - 1.26)
	Group 2	1.23 (0.78 - 1.94)	0.65 (0.41 - 1.03)	1.12 (0.63 - 1.99)	0.71 (0.41 - 1.23)
Adjusted for indirect antibiotic exposure (IAP)	Group 1	1.43 (1.02 - 2.00)*	0.90 (0.65 - 1.26)	1.76 (1.18 - 2.63)*	0.85 (0.58 - 1.24)
	Group 2	1.28 (0.78 - 2.08)	0.61 (0.38 - 1.00)	1.14 (0.62 - 2.08)	0.69 (0.39 - 1.22)
Adjsted for readmission in 3 months	Group 1	1.42 (1.04 - 1.95)*	0.95 (0.69 - 1.30)	1.78 (1.21 - 2.62)*	0.90 (0.63 - 1.29)
	Group 2	1.28 (0.79 - 2.06)	0.68 (0.42 - 1.10)	1.19 (0.66 - 2.16)	0.82 (0.47 - 1.45)
Adjusted for caesarean delivery, exclusively breastfeed, direct and indirect antibiotic exposure, readmission	Group 1	1.44 (1.02 - 2.03)*	0.86 (0.61 - 1.22)	1.79 (1.19 - 2.68)*	0.82 (0.56 - 1.21)
	Group 2	1.33 (0.77 - 2.29)	0.58 (0.34 - 1.00)	1.31 (0.68 - 2.53)	0.70 (0.37 - 1.34)

** are statistically significant ($p < 0.05$). OR = odds ratio, CI = Confidence Interval, IAP = Intrapartum Antibiotic Prophylaxi

Figure 2.1Median relative abundance of bacterial taxa in infant gut microbiota at 3-4 months by mode of delivery by 3 months of age

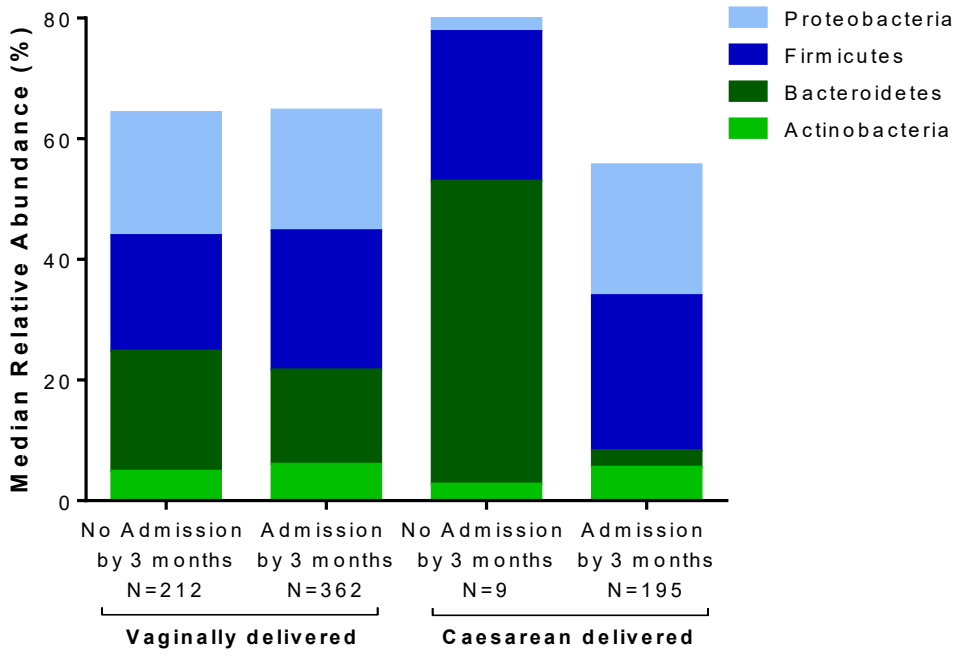


Figure 2.1 Vaginal Delivery

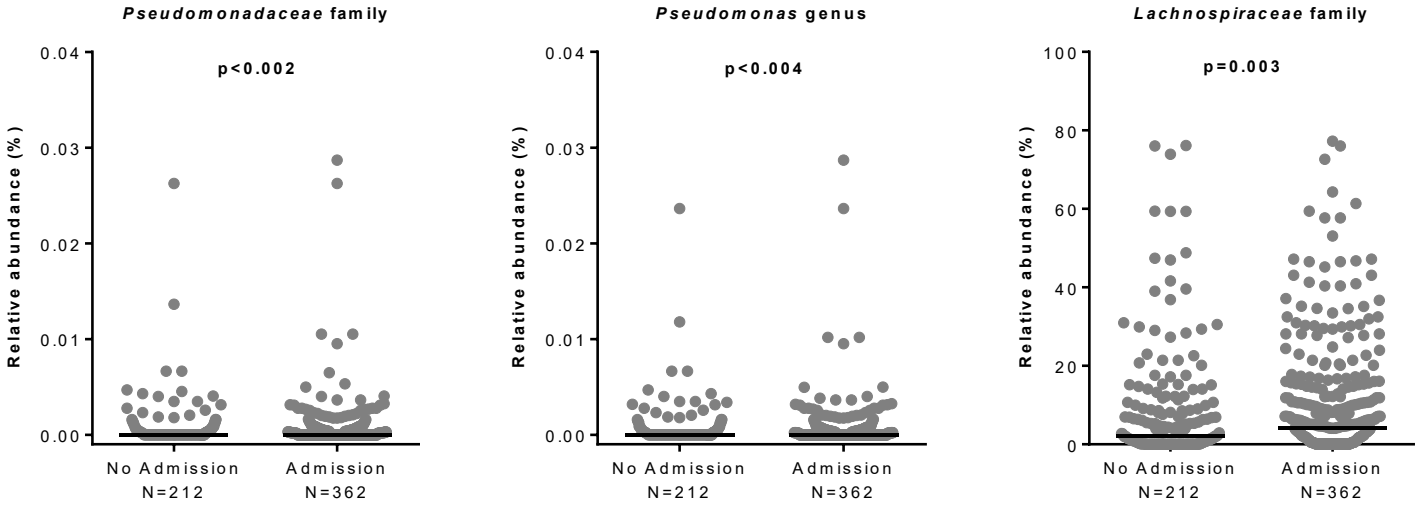


Figure 2.1 Caesarean Delivery

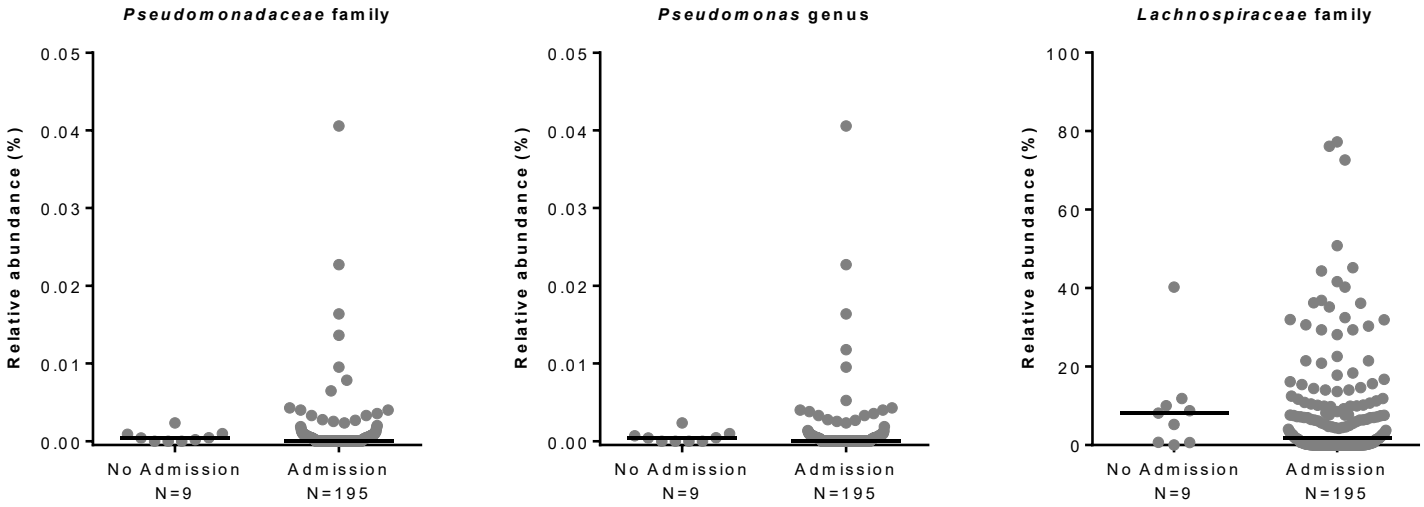


Figure 2.2 Median Relative abundance of *Pseudomondaceae* and genus *Pseudomonas* in fecal microbiota by duration of hospital stay at 3-4 months. Dots indicate medians. Comparison by Kruskal-Wallis test

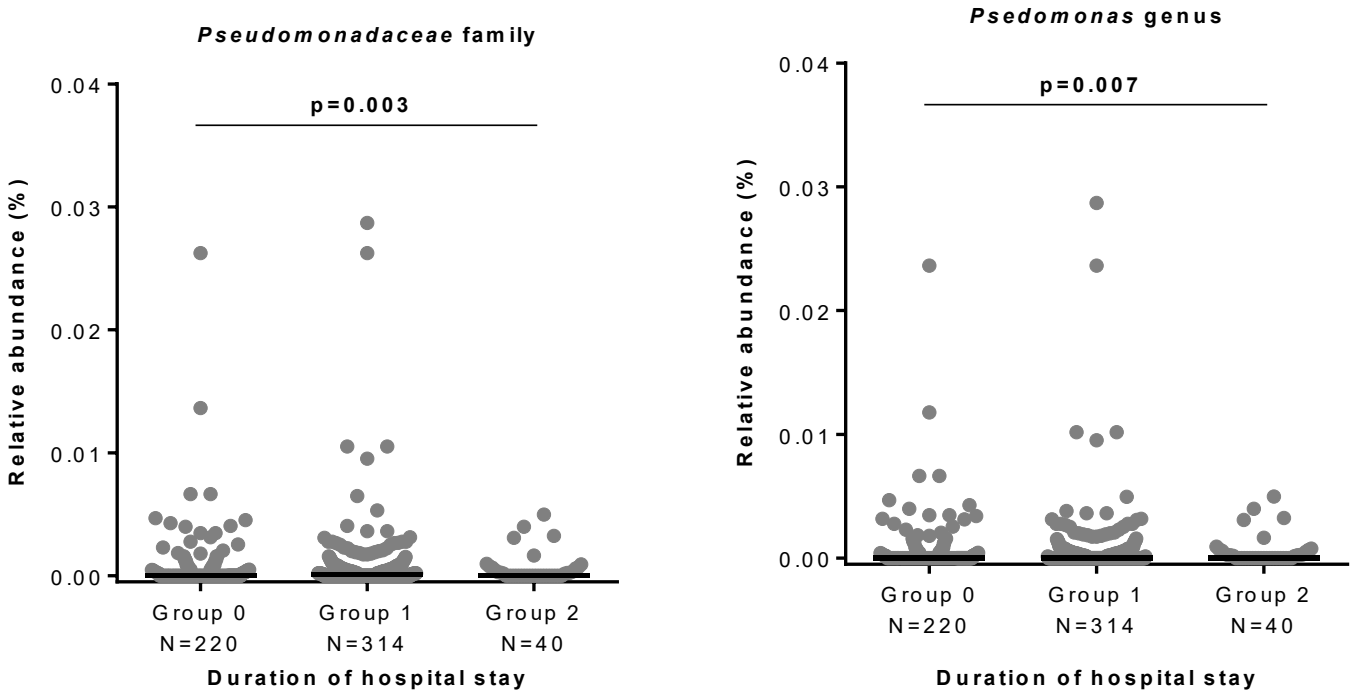


Figure 2.3 Median Relative abundance of *Lachnospiraceae* in fecal microbiota by duration of hospital stay at 3-4 months. Dots indicate medians. Comparison by Kruskal-Wallis test

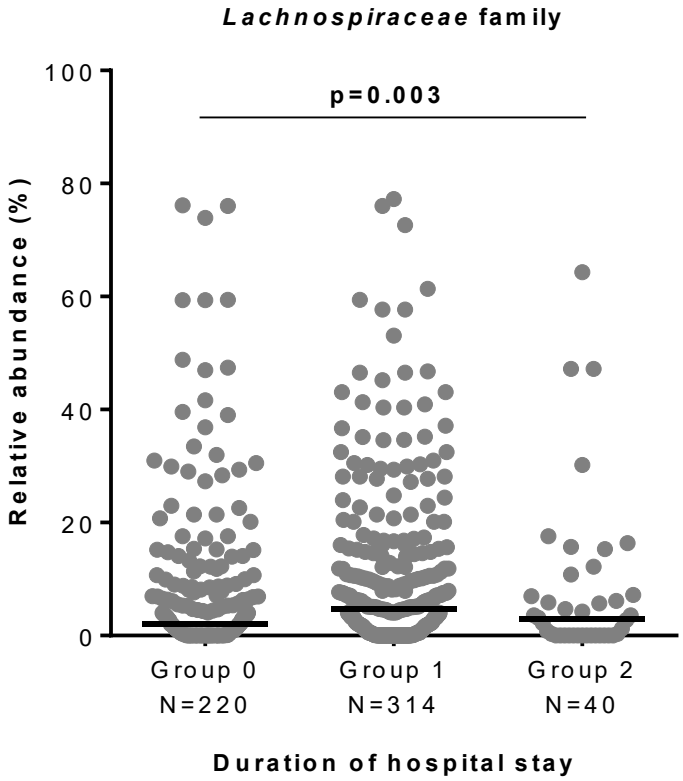


Figure 2.4 Median Relative abundance of *Lactobacillales, Fecalibacterium* and *Prevotella* in fecal microbiota by duration of hospital stay at 3-4 months (Caesarean delivered infants)

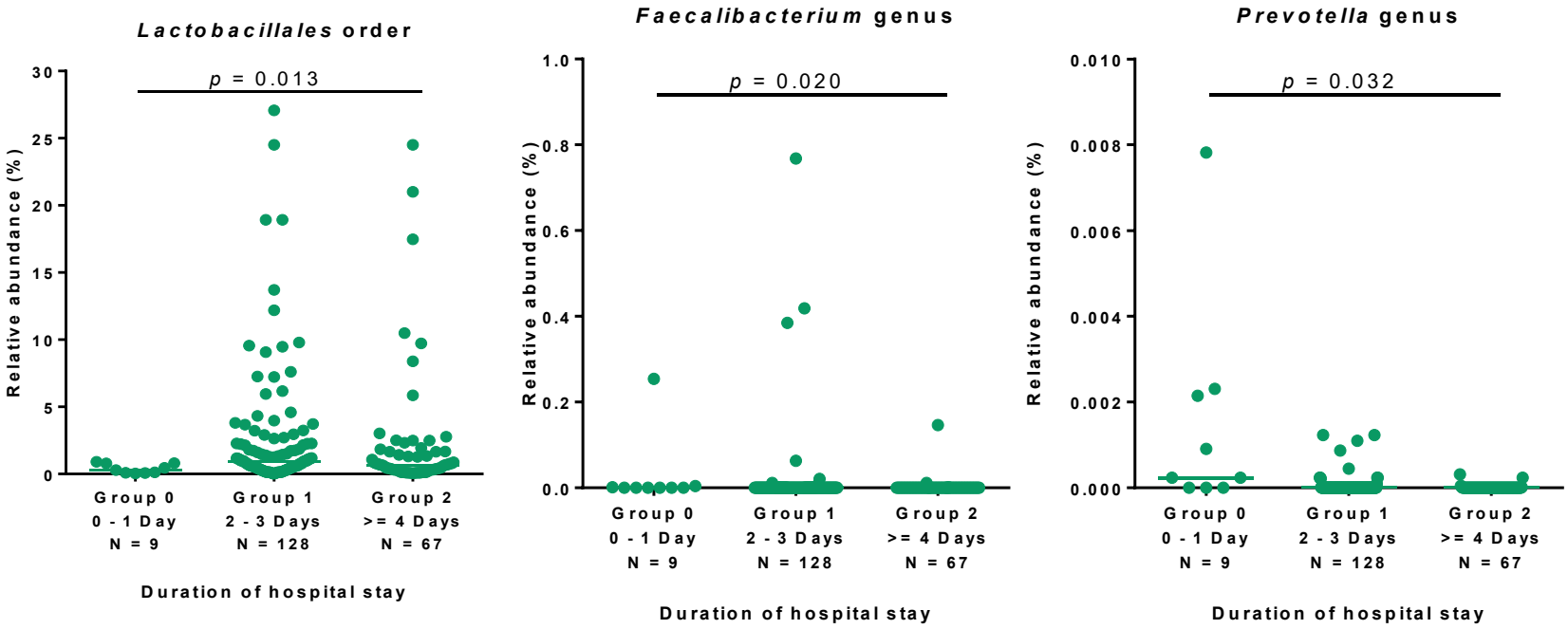


Figure 2.5 Median Relative abundance of *Lactobacillales and Ruminococcaceae* in fecal microbiota by hospitalization status at 3-4 months (Caesarean delivered infants)

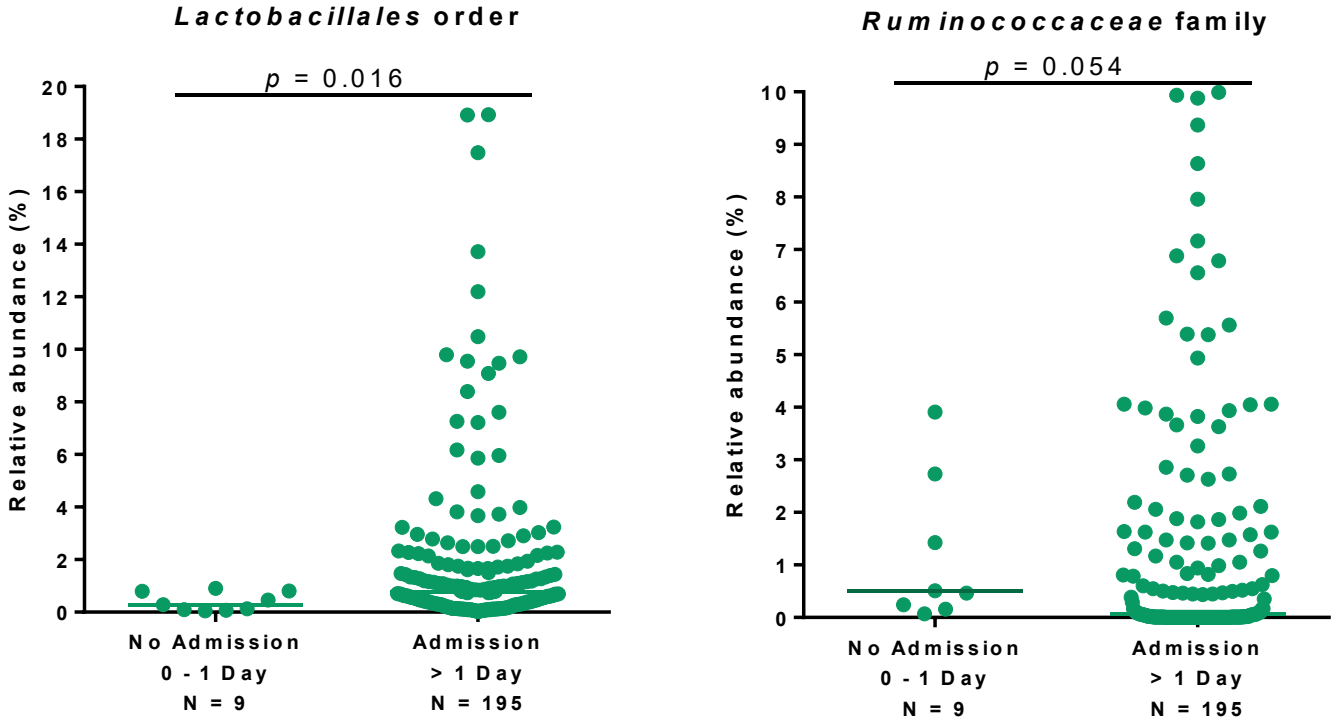


Figure 2.6 Median Relative abundance of *Pseudomondaceae, Prevotellaceae, Fecalibacterium* in fecal microbiota by duration of hospital stay at 3-4 months.

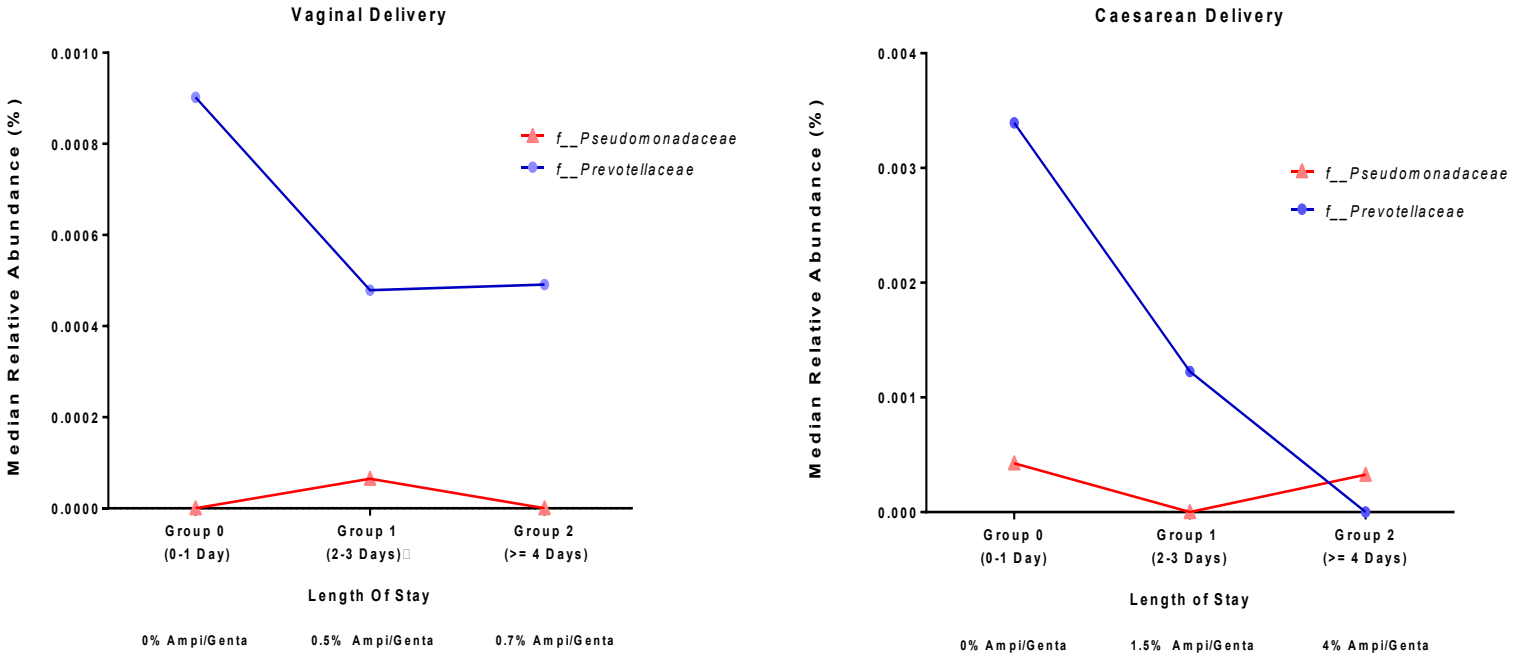
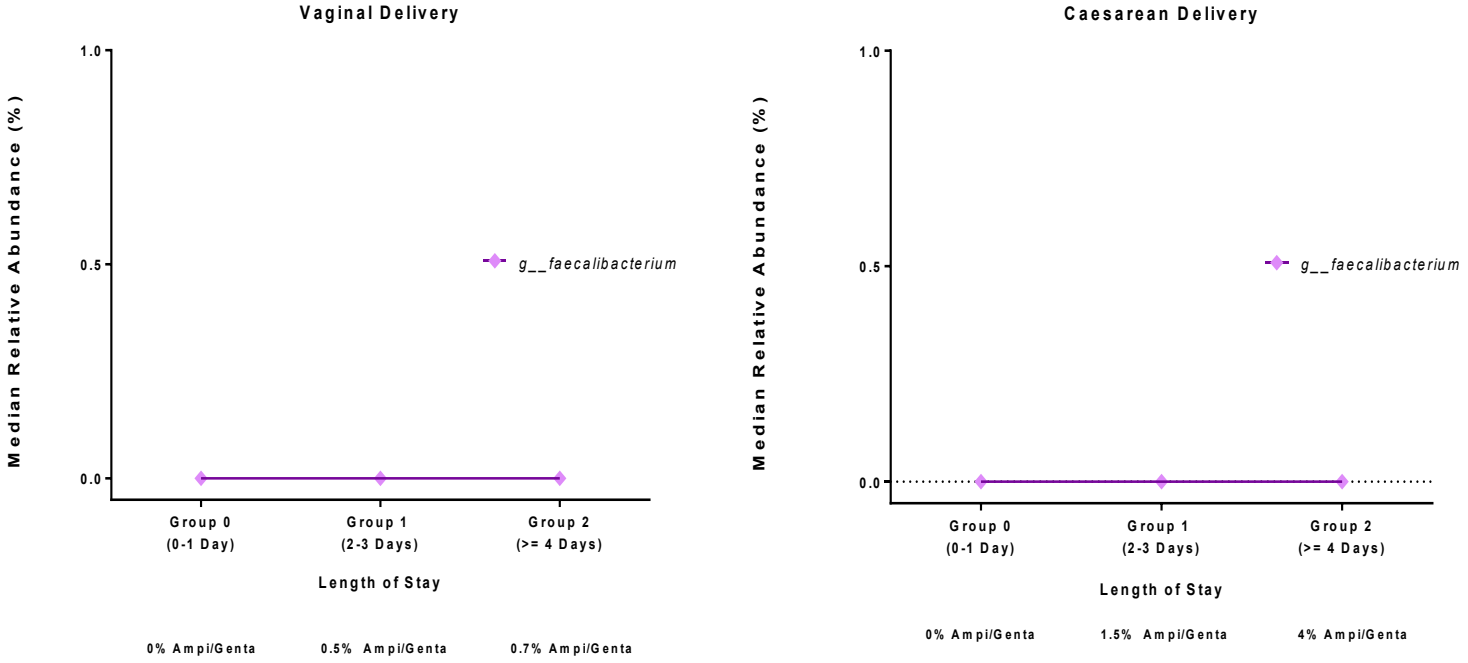


Figure 2.6 Median Relative abundance of *Pseudomondaceae, Prevotellaceae, Fecalibacterium* in fecal microbiota by duration of hospital stay at 3-4 months.



CHAPTER 3

Impact of postnatal exposure to household cleaning products on infant gut microbiota composition at 3-4 months

3.1 Introduction

Emphasis on cleanliness of the home has been increased in the last decade which has led to the increased use of disinfectants and cleaning agents, and cleaning sprays (Bello et al., 2010). Cleaning products contribute to the total burden of exposure to chemicals in the general population and this is an emerging public health issue. Cleaning agents are grouped into different product categories according to their technical functions and purpose of use. Disinfectants are used to kill microorganisms and prevent transmission of infections. Detergents remove grease, dirt, dust, debris and fats. There is mounting evidence explaining the role of cleaning products on increased asthma prevalence in most developed countries (Jaakkola & Jaakkola, 2006; J. Zock, Vizcaya, & Le Moual, 2010). Deleterious effects of occupational exposure to cleaning products have been reported for asthma (Vizcaya et al., 2013; J. Zock et al., 2010), and asthma severity, particularly in cleaners (Vizcaya et al., 2011b; J. Zock et al., 2010) and healthcare professionals (Mirabelli et al., 2007).

Both disinfectants and detergents have been subject to intense technological development, and as a result new chemicals have been introduced in the indoor environment in the industrialized countries. Those chemicals remain on the surfaces after cleaning (Wolkoff et al., 1998). Humans may expose to those surface chemicals via the inhalation route. To be specific, VOCs emissions from cleaning products are the primary concern. VOCs are irritants and indoor sources include cleaning products, solvents, polishes, room fresheners, and polishes (Maroni, Seifert, & Lindvall, 1995b). Infants spend 80% (Holt, Macaubas, Stumbles, & Sly, 1999), and both adults and children spend more than 90% of their time indoors (Bornehag et al., 2005). Moreover, energy conservation measures for buildings have led to reduced air exchange rates and promotion of indoor moisture build-up (Bornehag et al., 2005; Weschler, 2009a). Furthermore, antimicrobial agents are increasingly being incorporated into a wide variety of products for use in the home (Levy, 2001b; Rosenberg, 2000b), and scientists are concerned with the addition of those agents into the household cleaning products because it may result in bacteria cross-resistant to antibiotics.

The establishment of gut microbiota in a newborn infant is thought to be important for the development of the immune system, and hence for the host health (Penders et al., 2007). Although an individual's genetic predisposition likely plays a role in this process (Dicksved et al., 2008b; Zoetendal, Akkermans, Akkermans-van Vliet, de Visser, & de Vos, 2001b), it is highly influenced by environmental factors (Heavey & Rowland, 1999). Increased richness and diversity of infant intestinal microbiota has been associated with vaginal delivery, emergency CS

(Azad et al., 2013) and pet ownership (Azad et al., 2013), while breastfeeding has been associated with lower richness and diversity, but greater proliferation of beneficial microbes (Azad & Kozyrskyj, 2012). Lower diversity of gut microbiota has been associated with allergic diseases (T. R. Abrahamsson et al., 2012; Bisgaard et al., 2011).

Homes with more exposure to disinfectants and detergents are thought to increase T-helper cell type 2 based diseases, such as asthma and atopic disorders, by creating cleaner environment with reduced exposure to environmental antigens. In contrast, Casas et al (2013) proved that the passive exposure to cleaning products may increase airway inflammation in children and may have an adverse effect on lung function that is consistent with the hypothesis of an inflammatory role of cleaning agents. Disinfectants and detergents may contain many other irritant or sensitizing agents, VOCs that may have an impact on allergy or respiratory reactions. To our knowledge, there are no published studies assessing the impact of exposure to those household cleaners on the gut microbiota of infants. Hence, the purpose of this study is to evaluate the effect of early life exposure to household cleaning products, in particular disinfectant, detergent, eco products and other cleaning products, on the infant gut microbiota composition and diversity.

3.2 Methods

3.2.1 Study Design

The present study includes 787 children data from the Canadian Healthy Infant Longitudinal Development (CHILD) population based birth cohorts of the Edmonton, Winnipeg and Vancouver sites. Women were enrolled during the first trimester of their pregnancy at public hospitals with the following criteria: a live birth at 36 weeks gestation or greater and with birth weight of 2,500 g or more. The enrolled women were followed throughout pregnancy; and their children were followed from birth to the age of 5 years. Written informed consent was obtained from all participants and the study was approved by the Ethics Committee of the University of Alberta, the University of Manitoba Human Research Ethics Board and the University of British Columbia/Children's and Women's Health Centre of British Columbia Research Ethics Board.

3.2.2 Exposures

At 3 months post-partum, mothers were asked to complete questionnaires on aspects of their health, environment, socioeconomic status, lifestyle and personal use of cleaning products. They were asked "Which of the following products (a list of 31 chemical based products) do you personally use?" Available responses were daily, weekly, monthly, less than monthly and not used at all. From the list of 31 products, they were categorized into four groups according to their mechanism of actions, namely: disinfectant, detergent, other cleaning products and eco products, and based on purpose of cleaning process (see **Index**). The frequency of various cleaning

products use was provided and classified into 5 categories: 0 for not use at all, 1 for less than a month, 2 for monthly, 3 for weekly, and 4 for daily usage. The scores for each chemical exposure were summed separately for each group to produce a total score for each respondent. The total scores from each group were divided into two groups, higher and lower exposure group in order to make comparisons of effect sizes during analyses. In addition, in order to explore the combination effect of disinfectant and other cleaning/ chemical products, four groups of combined disinfectant and other cleaning/ chemical products were created, namely: group 1 (low disinfectant & low other cleaning products), group 2 (low disinfectant & high other cleaning products), group 3 (high disinfectant & low other cleaning products), and group 4 (high disinfectant and high other cleaning products). Maternal history of allergy and asthma were also reported in the questionnaire. Questions related to environmental exposures such as indoor smoking (parents and visitors), number of siblings, pets, maternal history of asthma and allergy were also included.

3.2.3 Fecal microbiota analysis

Fecal samples were collected at 3-4 months of age. Samples were refrigerated during transportation to the lab and then stored at –80°C in sterile containers until analysis. QIAamp DNA stool Mini Kit was used to isolate total DNA, and the hypervariable V4 region of the 16S rRNA gene was amplified using universal bacterial primers. Fecal microbiota was profiled by MiSeq Illumina high-throughput sequencing of the hyper-variable V4 region of the 16S rRNA

gene at the University of Toronto Centre for the Analysis of Genome Evolution & Function (CAGEF). Sequences were de-barcoded and quality filtered by removing reads having more than 10 sites with a Phred quality score less than 20 using QIIME pipeline (version 1.8.0). Forward and reverse reads were assembled using PandaSeq for a final length of 144 bp (unassembled sequences discarded), demultiplexed and filtered against the GREENGENES reference database (v12.10) to remove all sequences with < 97% similarity. Remaining sequences were clustered with Usearch61 at 97% sequence similarity against the GREENGENES database (closed-picking algorithm), and taxonomic assignment was achieved using the RDP classifier constrained by GREENGENES. OTUs with overall relative abundance below 0.0001 were excluded from subsequent analyses. OTUs relative abundance and α-diversity metrics (Shannon and Simpson diversity indices, Chao1 species richness index) were generated in QIIME to profile infant gut microbiota in individual fecal samples.

3.2.4 Statistical analysis

Statsistical analyses were performed using SPSS software (version 22; IBM SPSS Statistics, IBM Corporation). We perfomred chi-squared test in the first step to explore the data and to assess the distribution of potential confounding variables according to four categories of cleaning products (**Table 3.1 – 3.4**). Significance was set at $p < 0.05$. We focused the analysis on dominant taxa to minimize the multiple comparisons. We employed Mann-Whitney U-test to compare the median relative abudance of dominant bacterial taxa, as well as microbial richness and diversity. Multiple comparisons were corrected by converting crude p-values to False

Discovery Rate (FDR) values (q-values) in Statistical Analysis Systems (SAS) Software (version 9.4.; SAS Institute, Inc.). Univarite analysis and backward stepwise multiple logistic regression were used to identify the variables independently associated with the outcome variables. All the variables with a crude p-value of <0.25 after the univariate analysis were included in the mutlivariate analyses. The gut mircobiota measures were categorized into two groups (below vs. above median), and quartiles (highest or lowest quartile vs. the rest quartiles) to create dichotomous outcome variables.

Association between each household cleaning product (disinfectant, detergent, other cleaning/chemical products, and eco produts) exposure and infant gut mircobiota composition and diversity was determined using logistic regression analysis. All anlayses were adjusted for mode of delivery, breast feeding status, and antibiotic exposure (both directly and indirectly). Because of the associations previously observed between exposure to hospital microbial environment after birth and changes in infant gut microbiota composition at 3 months, analyses were also adjusted for hospital admission for more than 1 day after birth and readmission in first 3 months. In aiddtion, varaibles which were detected as significant from chi-squared test, were included in the model. Interaction terms between houshold cleaning products were also tested in the models; however, none of them were statistically significant in the models.

3.3 Results

3.3.1 Study population

Demographic characteristic of the mother-infant pairs are described in (**Table 3.1 – 3.4**) according to the four categories of different cleaning products. About 53% (n=414) of the studied participants were high disinfectant users, 52% (n=407) were high detergent users, 48% (n=376) were high eco products users, and 48% (n=378) were high other cleaning product users. Among the group of disinfectant, the most commonly used product was multi-surface cleaner, whereas in the group of detergent and other chemical products, hand washing detergent and spray air freshener were the most common respectively (**Table 3.5 – 3.7).** The frequency of household disinfectant usage was significantly correlated with detergent usage (r= 0.33, p=0.0001) and other chemical products (r=0.31, p=0.0001). There was weak correlation between using of disinfectant and eco products; however, it was not statistically significant (r=0.021, p= 0.548).

Significant differences were observed between the two levels of exposure in household disinfectant (Low vs. High) status in terms of mode of delivery (p=0.003), hospitalized for more than 1 day after birth (p=0.041), breast feeding status (p=0.005), and smoke exposure status. Likewise, mode of delivery (p=0.020), breast feeding status (p=0.041) and presence of pets at home (p=0.0001) were significant between the two exposure levels in other cleaning products. Similarly, mode of delivery (p=0.021) and presence of furry pets (p=0.017) were statistically significant among the two groups of household detergents. In addition, breast feeding status (p

=0.044), hospitalized for more than 1 day after birth (p=0.007) and presence of maternal allergy status (p=0.024) were statistically significant among the two groups of eco products.

3.3.2 Fecal microbiota composition, diversity and richness

Composition of the infant gut microbiota at the phylum level by household cleaning products exposure is shown in (**Figure 3.1– 3.4).** Significant effects of exposure to different household cleaning products on the relative abundance of several bacterial taxa were observed (**Table 3.8 – 3.19).**

i) *Effect of Exposure to Household Disinfectant Products*

At 3-4 months of age, infants exposed to high disinfectant products had reduced abundance of Actinobacteria phylum (4.2% vs. 6.8%. p = 0.0002), *Bifidobacteriaceae* (family 3.5% vs.6%, p= 0.0003), and increased abundance of *Peptostreptococcaceae* family (0.00086 vs. 0.00041, p= 0.013) and *Verrucomicrobiaceae* family (0.027 vs. 0.0019, p =0.027) *(***Table 3.8).** The same trend of differences was observed when the analysis was stratified by vaginal delivery, exclusively breastfed and no exposure to antibiotic (directly and indirectly) (data not shown). Exposure to high disinfectant was associated with reduced diversity at order level (1.43 vs. 1. 48%, p=.028). No difference in gut microbiota richness was detected among the two exposure groups (**Table 3.10).**

To further investigate the association between exposure to household disinfectants and gut microbiota, we performed multivariable logistic regression analyses. Exposure to high level of household disinfectant products during infancy period was associated with 34% reduction in Actinobacteria (OR 0.66, 0.50 – 0.90, p=0.006), 33% reduction in *Bifidobcateriaceae* (OR 0.67, 0.50 – 0.90, p=0.007), 42% reduction in *Actinomycetaceae* (OR 0.58, 0.43 – 0.78, p=0.0001) and 33% reduction in genus *Bifidobacterium* (OR 0.67, 0.50 – 0.90, p=0.007). In contrast, infants exposed to high household disinfectant had 14% higher risk of colonization with *Peptostreptococcaceae* (OR 1.44, 1.08- 1.93, p=0.013) and *Verrucomicrobiaceae* (OR 1.36, 1.03 – 1.85, p= 0.0001). These associations were independent of caesarean delivery, breast feeding, antibiotic exposure (both directly and indirectly), early life hospitalization, readmission, and indoor smoke exposure (**Table 3.20).**

ii) *Effect of Exposure to Household Detergent Products*

In infants with exposure to high levels of household detergents, genus *Ruminococcus* and *Pseudomonas* were found to be more abundant, (p= 0.014 & p=0.032) (**Table 3.12).** However, gut bacterial richness and diversity did not differ between the two levels of detergent exposure (**Table 3.13).**

We observed that infants exposed to high household detergents had a high relative abundance of genus *Ruminococcus* (OR 1.41, 1.06 – 1.88, p=0.020) and genus *Dorea* (OR 1.46, 1.05 – 2.05, p=0.026) after adjusting for caesarean delivery, breastfeeding, antibiotic exposure (both direct and indirect), early life hospitalization, readmission, and pets at home (**Table 3.21)**.

iii) *Effect of Exposure to Household Other Chemicals Products*

Pseudomonadaceae (p=0.025) and *Verrucomicrobiaceae* (p=0.009) were overrepresented in the infants who were exposed to high level of other cleaning/ chemical products (**Table. 3.14).** Nonetheless, no difference in richness and diversity was observed between the two exposure groups (**Table. 3.15).**

After adjusting for the potential confounding variables, i.e. caesarean delivery, breastfeeding, antibiotic exposure (both direct and indirect), early life hospitalization, readmission, and pets at home, infants exposed to high level of other chemical products had a 1.4 times increased risk of having high relative abundance of Verrucomicrobia (OR 1.38, 1.03 – 1.84, p=0.022), *Pesudomondaceae* (OR 1.37, 1.02 – 1.84, p=0.034), genus *Akkermansia* (OR 1.38, 1.03 – 1.84, p= 0.030) and genus *Pseudomonas* (OR 1.41, 1.05 – 1.90, p=0.023) when compared to low exposure group (**Table 3.22).** Moreover, we found that bacterial richness was 1.4 times higher (OR 1.44, 1.03 – 2.01, p=0.033) and diversity were 1.5 times higher (OR 1.53, 1.09 – 2.13, p =0.014) in the infants with exposure to high levels of other chemical products during the infancy period.

iv) *Effect of Exposure to Household Eco Products*

Gut mircorbiota composition at 3-4 months differed by the eco products exposure status. We observed greater abundance of *Alcaligenaceae* (0.0006% vs. 0.00043%, p=0.027) and

Desulfovibrionaceae (0.00039% vs. 0.00021%, p=0.022) in the infants exposed to high level of eco products in the home environment **(Table 3.17).** In addition, proportions of genera *Sutterella* and *Bilophila* were elevated in high eco product exposure group, (0.0006% vs. 0.0004%, p=0.023) and (0.00035% vs. 0.00014%, p=0.007) respectively. In contrast, proportions of genus *unclassified Clostridiaceae* and *unclassified Ruminococcaceae* were reduced in high eco product exposure group, (0.083% vs. 0.153%, p= 0.013) and (0.00061% vs. 0.00131%, p=0.037) respectively **(Table 3.18).**

In the multivariable logistic regression analysis, we found that there were 14% greater abundance of *Desulfovibrionaceae* (OR 1.43, 1.07 – 1.92, p = 0.015) and genus *Collinsella* (OR 1.46, 1.09 - 1.95, p=0.011) in the infants exposed to high levels of eco products compared to low exposure group. In addition, genus *Bilophilia* was 1.6 times higher (OR 1.59, 1.19 – 2.13, p= 0.022) and genus *Sutterella* was 1.5 times higher (OR 1.51, 1.08 – 2.12, p = 0.017) in the high exposure group. However, exposure to high levels of eco products was associated with low abundance of *unclassified Clostridiaceae* (OR 0.71, 0.53 – 0.96, p=0.023) **(Table 3.23).**

v) *Combined Effect of Exposure to Household Disinfectant and Other Cleaning Products*

The family *Pesudomondaceae* was more abundant in group 2 (low disinfectant and high other chemical) and group 4 (high disinfectant and high other chemical) when compared to group

1 (low disinfectant and low other chemical), (p = 0.028 and p= 0.044) **(Figure 3.5).** Similarly, genus *Pseudomonas* was observed more abundant in group 2 and group 4 compared to group 1 (p = 0.012 and p= 0.045), respectively **(Figure 3.6).**

Additionally, genus *Pseudomonas* was 18% more abundant in group 2 (OR 1.82, 1.14 – 1.89, p =0.012) compared to group 1 after adjusting for mode of delivery, breastfeeding status, direct and indirect antibiotic exposure, hospitalization and readmission in the first 3 months and indoor smoke exposure status **(Table 3.24).**

3.4 Discussion

Household cleaning products contain dangerous chemicals and the active ingredients vary from alcohols, peroxides and halides to antimicrobial chemicals, such as triclosan and quaternary ammonium compounds (QAC) (Bondi, 2011). Triclosan, incorporated into soaps, laundry detergent other consumer products, has antimicrobial activity at 0.2% - 2% concentration which is often bacteriostatic (Boyce & Pittet, 2002). QAC is mainly bacteriostatic and Chlorhexidine is less active against Gram-positive bacteria.

We observed differential representation of gut microbiota in the infants exposed to different types of household cleaning products. The main findings from the current study were reduced abundance of Actinobacteria, *Bifidobacteriaceae*, and diversity of the gut microbiota at

3-4 months in the infants exposed to high levels of disinfectant. Moreover, there were overrepresentation of *Peptostreptococcaceae* and *Verrucomicrobiaceae* in the high disinfectant exposure group.

Low gut microbiota diversity during the first month of life was associated with asthma in children at 7 years of age (T. Abrahamsson Author et al., 2014). According to Bjorksten et al (2000 & 2001), the non-allergic children had a greater prevalence of *Lactobaciillus* and *Bifidobacterium spp*. compared to allergic children, which was further supported by the group of Sjogren (2009). Furthermore, several studies demonstrated that exposure to spray cleaners, chlorine bleach sprays, disinfectants, air fresheners, drain cleaners, oven cleaners, furniture polish, carpet cleaners and floor waxing was associated with development of asthma (Medina-Ramon et al., 2006; Nielsen & Bach, 1999; Obadia, Liss, Lou, Purdham, & Tarlo, 2009; Quirce & Barranco, 2010; J. Zock et al., 2001; J. Zock et al., 2010). In addition, there is mounting evidence explaining the role of exposure to cleaning products in increasing asthma prevalence in most developed countries (J. Zock et al., 2010)). One possible mechanism for this finding is that homes with more chemical exposure were cleaner and the risk of developing T-helper cell type 2 based diseases was higher.

Peptostreptococcus species are commensal organisms in the mouth, skin, gastrointestinal, vaginal and urinary tract of human beings. Azad (2013) reported that *Peptostreptococcaceae* were more abundant in infants with pets in their houses; however, they were significantly reduced among infants with older siblings. In our study, overrepresentation of

Peptostreptococcaceae in high disinfectant exposure group was independent of pets and siblings at home. *Peptostreptococcus* are gram positive slow-growing bacteria with increasing resistance to antimicrobial drugs (Laura M. Koeth et al., 2004; Reig & Baquero, 1994; Sally A. Roberts, 2006). Antibiotics target bacterial cell wall; however, it is equivocal for disinfectants action on bacterial cell wall. Researchers have found that when disinfectants are used in low levels, they actually make bacteria stronger and resistant to antibiotic treatment. Studies have demonstrated the effectiveness of in vitro activity of various antibacterial products; however, there is still a need to evaluate the effectiveness of those products in real-life household setting (Larson & Duarte, 2001).

Similar to high level of household disinfectant exposure, infants with exposure to high household detergent had higher abundance of *Rumniococcus* and *Dorea*. In addition, we observed an increased abundance of *Clostridium* and lesser abundance of *Bacteroides* and *Bifidobacterium* although they were not statistically significant. Goshal and colleagues pointed out that gut microbial dysbiosis is involved in Irritable Bowel Syndrome (IBS) pathogenesis via facilitating the adhesion of pathogens to the bowel wall (Ghoshal et al., 2012). *Ruminococcus*, *Dorea*, *Clorstridium* were overrepresented and *Bacteriodes* and *Bifidobacterium* were underrepresented in pediatric IBS patients (Ghoshal et al., 2012; Rajilić–Stojanović et al., 2011; Saulnier et al., 2011).

The genera *Sutterella* and *Bilophila* were observed at higher proportion in the infants with exposure to high eco products group. Both of them are Gram-negative, anaerobic bacteria

that belong to the family *Alcaligenaceae* and *Desulfovibrionaceae*, respectively. *Sutterella* was found to be increased in children with autism with gastrointestinal symptoms, e.g. constipation and diarrhoea (Wang et al., 2013).

The present study also identified a greater abundance of *Pesudomondaceae* and *Pseudomonas* in the infants exposed to high level of other chemical products. To be specific, *Pesudomondaceae* and *Pseudomonas* were more abundant in group 2 (low disinfectant and high other chemical) and group 4 (high disinfectant and high other chemical) when compared to group 1 (low disinfectant and low other chemical), ($p = 0.028$ and $p= 0.045$) **Figure 3.5. – 3.6.** *Pseudomonas* is Gram-negative opportunistic pathogen. Gram-negative bacteria are more intrinsically resistant to antibiotics than Gram-positive bacteria. *Pseudomonas* has the ability to adapt to different environments by producing different types of extracellular polysaccharides and encapsulating themselves with those matrix materials (Franklin, Nivens, Weadge, & Howell, 2011). Besides, *Pseudomonas aeruginosa* enhances production of antimicrobial chemicals in response to N-acetylglucosamine (GlcNAc) and peptidoglycans (Korgaonkar & Whiteley, 2011). A study by Korgaonkar (2011) showed that *P. aerugninosa* virulence is enhanced when exposed to peptidoglycan fragments shed from Gram-positive bacteria. Moreover, the study done by Rusell et al (2011) showed that effector proteins of *Pseudomonas*, Tse1 and Tse 3, secreted from type VI secretion system (T6SS) degrades the peptidoglyan of other bacteria and conferring a growth advantage of *P. aeruginosa.* According to Mashburn (2005) *in-vivo* culture with *Staphylococcus aureus*, *P. aerugninosa* lyses *S. aureus* and utilized iron released from lysed *S. aureus* for growth in low iron environment (Mashburn, Jett, Akins, & Whiteley, 2005). In

addition, efflux pumps in *P. aerugninosa* promote export of disinfectants, detergents, organic solvents and dyes (Poole, 2001).

We observed high *Pseudomonas* in group 2 (low disinfectant and high other cleaning products) and group 4 (high disinfectant and high other cleaning products). One possible mechanism is high levels of disinfectant eliminated Gram-positive bacteria which had led to the emergence of resistant *Pseudomonas*, and other cleaning products (air freshener) had no additional effect to further increase *Pseudomonas*. Nevertheless, low level of disinfectant had some effect on killing of Gram-positive bacteria which resulted in release of peptidoglycan which was utilized as a substrate by *Pseudonmonas*. The presence of air freshener droplets may enhance utilization of peptidoglyan by *Pseudomonas* or affecting other bacteria. Furthermore, *Pseudomonas* possessed efflux pumps which help them to be selected out by antibacterial agents (Poole, 2001). Additionally, triclosan, antimicrobial chemical, is a substrate for multidrug efflux pumps in *Pseudomonas aeruginosa* (Chuanchuen et al., 2001).

Disinfectants' effects were relatively short life and most cleaned sites and surfaces became substantially contaminated after 90 min to 3 h (Scott, Bloomfield, & Barlow, 1984). Potential mechanisms could be due to re-growth of residual survivors not destroyed by cleaning process or reposition from the air. Moreover, daily or weekly use of disinfectants is unlikely to reduce the risk of exposure to pathogens (Josephson, Rubino, & Pepper, 1997; Scott et al., 1984). The ineffectiveness of non-specific routine cleaning activities in reducing infection exposure is

further supported by a recent study of inner city population (Larson & Duarte, 2001). Felix (2010) suggested the requirement of specific protocol for appropriate use of disinfectants to increase microbial reductions (Medrano-Félix et al., 2011). Concerns have been raised about the potential for long term use of household antibacterial cleaning products to increase resistance to antiseptics or cross-resistance with antibiotics (Hooton & Levy, 2001; Levy, 2000).

VOCs are irritants (Maroni et al., 1995b) and levels of VOCs can be 5-10 times higher indoors than outdoors (SAMET, 1990), and may persist from several months to years (Weschler, 2009b). Moreover, Bello (2010) reported that VOCs from short-term cleaning tasks can remain in the air and there is potential exposure to anyone entering the air. A study done by Farrow (2003) pointed out the association between air-fresheners in the home and increased incidence of diarrhoea and earaches in infants, and headaches and depression in the mothers.

The use of antibacterial cleaning products may change the environmental microbiota and there is no study showing the benefits of using those products in a healthy household. Any potential benefit of using antibacterial products for home hygiene must be weighed against the theoretical risk for antiseptic or antibiotic resistance.

3.5 Strengths and Limitations

The study was conducted in a large population-based longitudinal cohort study following up the mothers since pregnancy and the children up to 3-5 years of age, and the study finding can be generalised to the population. High-throughput genetic sequencing method was employed in our study.

We did not monitor the personal exposure to cleaning agents by products and the exposure status of cleaning products were entirely dependent on the self-reported questionnaire. Likewise, our study did not have the ability to differentiate which cleaning products have VOCs and which do not. Therefore, we could not perform the separate analysis for VOCs vs. Non-VOCs.

3.6 Conclusion

There is no study done on the impact of exposure to household cleaning products on the overall community structure of the infant gut microbiota. To the best of our knowledge, this is the first study looking at the association between the household cleaning products on infants' gut microbiota composition and diversity, suggesting the important role of the indoor environment shaping the incipient gut microbiota. However, the mechanism through which household cleaning products affecting the gut microbiota composition and diversity is not well understood.

Studies are required to further assess the relationships between exposure to indoor household cleaning products and composition and diversity of infant gut bacteria, and their associations with development of chronic or metabolic disease development in the older children. In particular, there is a need to identify specific agent(s) responsible for gut microbiota dysbiosis and pathophysiological mechanism of this association.

3.7 References

Abrahamsson, T. R., Jakobsson, H. E., Andersson, A. F., Bjorksten, B., Engstrand, L., & Jenmalm, M. C. (2012). *Low diversity of the gut microbiota in infants with atopic eczema* Retrieved fromhttp://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edswsc&AN=000299951700021&site=eds-live&scope=site

Abrahamsson, T., Author, Jakobsson, H. E., A., Andersson, A. F., A., Björksten, B., Author, Engstrand, L., A., Jenmalm, M., Author, . . . Linköpings universitet, Institutionen för klinisk och,experimentell medicin. (2014). Low gut microbiota diversity in early infancy precedes asthma at school age. *Clinical and Experimental Allergy,* , 842. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edsswe&AN=edsswe.oai.DiVA.org.liu.109137&site=eds-live&scope=site

Azad, M. B., Konya, T., Maughan, H., Guttman, D. S., Field, C. J., Chari, R. S., . . . Kozyrskyj, A. L. (2013). Gut microbiota of healthy canadian infants: Profiles by mode of delivery and infant diet at 4 months. *CMAJ: Canadian Medical Association Journal, 185*(5), 385-394 10p. doi:10.1503/cmaj.121189

Azad, M. B., Konya, T., Maughan, H., Guttman, D. S., Field, C. J., Sears, M. R., . . . Kozyrskyj, A. L. (2013). Infant gut microbiota and the hygiene hypothesis of allergic disease: Impact

of household pets and siblings on microbiota composition and diversity. *Allergy, Asthma & Clinical Immunology, 9*(1), 1-9. doi:10.1186/1710-1492-9-15

Azad, M. B., & Kozyrskyj, A. L. (2012). Perinatal programming of asthma: The role of gut microbiota. *Clinical & Developmental Immunology,* , 932072-932072 1p. doi:2012/932072

Bello, A., Quinn, M. M., Perry, M. J., & Milton, D. K. (2010). *Quantitative assessment of airborne exposures generated during common cleaning tasks: A pilot study* Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edswsc&AN=000285311100001&site=eds-live&scope=site

Bisgaard, H., Li, N., Bonnelykke, K., Chawes, B., Skov, T., Paludan-Muller, G., . . . Krogfelt, K. A. (2011). *Reduced diversity of the intestinal microbiota during infancy is associated with increased risk of allergic disease at school age* Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edswsc&AN=000294283400025&site=eds-live&scope=site

Bjorksten. (2000). *The intestinal microflora in allergic estonian and swedish 2-year-old children (vol 29, pg 342, 1999)* Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edswsc&AN=000088167800020&site=eds-live&scope=site

Björkstén, B., Sepp, E., Julge, K., Voor, T., & Mikelsaar, M. (2001). Asthma, rhinitis, other respiratory diseases: Allergy development and the intestinal microflora during the first year of life. *The Journal of Allergy and Clinical Immunology, 108*, 516-520. doi:10.1067/mai.2001.118130

Bondi, C. A. M. (2011). Applying the precautionary principle to consumer household cleaning product development. *Journal of Cleaner Production, 19*, 429-437. doi:10.1016/j.jclepro.2010.07.008

Bornehag, C. G., A., Hagerhed-Engman, L., Sigsgaard, T., A., Janson, S., Author, Aberg, N., A., DBH-study group, t., Author, & Karlstads universitet, Fakulteten för samhälls- och livsvetenskaper, Avdelningen för hälsa,och milj. (2005). Dampness at home and its association with airway, nose and skin symptoms among 10 851 preschool children in sweden:: A cross sectional study. *Indoor Air,* Retrieved fromhttp://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edsswe&AN=edsswe.oai.DiVA.org.kau.18003&site=eds-live&scope=site

Boyce, J. M., & Pittet, D. (2002). Guideline for hand hygiene in health-care settings: Recommendations of the healthcare infection control practices advisory committee and the HICPAC/SHEA/APIC/IDSA hand hygiene task force. *MMWR: Morbidity & Mortality Weekly Report, 51*(42), 1-1 45p. Retrieved

from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=rzh&AN=106806132&site=eds-live&scope=site

Casas, L., Zock, J., Torrent, M., García-Esteban, R., Gracia-Lavedan, E., Hyvärinen, A., & Sunyer, J. (2013). Use of household cleaning products, exhaled nitric oxide and lung function in children. *The European Respiratory Journal, 42*(5), 1415-1418. doi:10.1183/09031936.00066313

Chuanchuen, R., Beinlich, K., Hoang, T. T., Becher, A., Karkhoff-Schweizer, R., & Schweizer, H. P. (2001). *Cross-resistance between triclosan and antibiotics in pseudomonas aeruginosa is mediated by multidrug efflux pumps: Exposure of a susceptible mutant strain to triclosan selects nfxB mutants overexpressing MexCD-OprJ* Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edswsc&AN=000166539600008&site=eds-live&scope=site

Dicksved, J., Halfvarson, J., Rosenquist, M., Järnerot, G., Tysk, C., Apajalahti, J., . . . Jansson, J. K. (2008). Molecular analysis of the gut microbiota of identical twins with crohn's disease. *ISME Journal: Multidisciplinary Journal of Microbial Ecology, 2*(7), 716-727. doi:10.1038/ismej.2008.37

Farrow, A., Taylor, H., Northstone, K., & Golding, J. (2003). Symptoms of mothers and infants related to total volatile organic compounds in household products. *Archives of Environmental Health, 58*(10), 633-641. Retrieved

from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=eih&AN=15002729&site=eds-live&scope=site

Franklin, M. J., Nivens, D. E., Weadge, J. T., & Howell, P. L. (2011). *Biosynthesis of the pseudomonas aeruginosa extracellular polysaccharides, alginate, pel, and psl* Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edswsc&AN=000208863500176&site=eds-live&scope=site

Ghoshal, U. C., Shukla, R., Ghoshal, U., Gwee, K., Ng, S. C., & Quigley, E. M. M. (2012). The gut microbiota and irritable bowel syndrome: Friend or foe? *International Journal of Inflammation, 2012*, 151085-151085. doi:10.1155/2012/151085

Heavey, P. M., & Rowland, I. R. (1999). The gut microflora of the developing infant: Microbiology and metabolism. *Microbial Ecology in Health & Disease, 11*(2), 75-83. doi:10.1080/089106099435808

Holt, P. G., Macaubas, C., Stumbles, P. A., & Sly, P. D. (1999). The role of allergy in the development of asthma. *Nature, 402*(6760), 12. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=a9h&AN=8755465&site=eds-live&scope=site

Hooton, T. M., & Levy, S. B. (2001). Antimicrobial resistance: A plan of action for community practice. *American Family Physician, 63*(6), 1087-1098. Retrieved

from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=11277546&site=eds-live&scope=site

Jaakkola, J. J. K., & Jaakkola, M. S. (2006). Professional cleaning and asthma. *Current Opinion in Allergy and Clinical Immunology, 6*(2), 85-90. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=16520670&site=eds-live&scope=site

Johansson, M. A., Sjögren, Y. M., Persson, J., Nilsson, C., & Sverremark-Ekström, E. (2011). Early colonization with a group of lactobacilli decreases the risk for allergy at five years of age despite allergic heredity. *Plos One,6*(8), 1. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edb&AN=74398433&site=eds-live&scope=site

Josephson, K. L., Rubino, J. R., & Pepper, I. L. (1997). Characterization and quantification of bacterial pathogens and indicator organisms in household kitchens with and without the use of a disinfectant cleaner. *Journal of Applied Microbiology,* (6) Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edsagr&AN=edsagr.US201302881053&site=eds-live&scope=site

Korgaonkar, A. K., & Whiteley, M. (2011). Pseudomonas aeruginosa enhances production of an antimicrobial in response to N-acetylglucosamine and peptidoglycan. *Journal of Bacteriology,* (3-4), 909. Retrieved

fromhttp://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edsgao&AN=edsgcl.249309920&site=eds-live&scope=site

Larson, E., & Duarte, C. G. (2001). Home hygiene practices and infectious disease symptoms among household members. *Public Health Nursing, 18*(2), 116-127 12p. Retrieved fromhttp://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=rzh&AN=107027036&site=eds-live&scope=site

Laura M. Koeth, Caryn E. Good, Peter C. Appelbaum, Ellie, J. C. G., Arne C. Rodloff, Marina Claros, & Luc J. Dubreuil. (2004). Surveillance of susceptibility patterns in 1297 european and US anaerobic and capnophilic isolates to co-amoxiclav and five other antimicrobial agents. *Journal of Antimicrobial Chemotherapy (JAC), 53*(6), 1039-1044. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=eih&AN=19810477&site=eds-live&scope=site

Levy, S. B. (2000). Antibiotic and antiseptic resistance: Impact on public health. *The Pediatric Infectious Disease Journal, 19*(10), S120-S122. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=11052402&site=eds-live&scope=site

Levy, S. B. (2001). Antibacterial household products: Cause for concern. *Emerging Infectious Diseases, 7*(3), 512. Retrieved

from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=eih&AN=5009956&site=eds-live&scope=site

Maroni, M., Seifert, B., & Lindvall, T. (1995). *Indoor air quality : A comprehensive reference book* Amsterdam ; New York : Elsevier Science, 1995. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=cat03710a&AN=alb.1739664&site=eds-live&scope=site

Mashburn, L. M., Jett, A. M., Akins, D. R., & Whiteley, M. (2005). Staphylococcus aureus serves as an iron source for pseudomonas aeruginosa during in vivo coculture. *Journal of Bacteriology,* (1-2), 554. Retrieved fromhttp://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edsgao&AN=edsgcl.129169920&site=eds-live&scope=site

Medina-Ramon, M., Zock, J. P., Kogevinas, M., Sunyer, J., Basagana, X., Schwartz, J., . . . Anto, J. M. (2006). *Short-term respiratory effects of cleaning exposures in female domestic cleaners* Retrieved fromhttp://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edswsc&AN=000237934500018&site=eds-live&scope=site

Medrano-Félix, A., Martínez, C., Castro-del Campo, N., León-Félix, J., Peraza-Garay, F., Gerba, C. P., & Chaidez, C. (2011). Impact of prescribed cleaning and disinfectant use on

microbial contamination in the home. *Journal of Applied Microbiology, 110*(2), 463-471. doi:10.1111/j.1365-2672.2010.04901.x

Mirabelli, M. C., Zock, J. P., Plana, E., Antó, J. M., Benke, G., Blanc, P. D., . . . Kogevinas, M. (2007). Occupational risk factors for asthma among nurses and related healthcare professionals in an international study.*Occupational & Environmental Medicine, 64*(7), 474-479 6p. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=rzh&AN=106011029&site=eds-live&scope=site

Nielsen, J., & Bach, E. (1999). *Work-related eye symptoms and respiratory symptoms in female cleaners* Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edswsc&AN=000081391000004&site=eds-live&scope=site

Obadia, M., Liss, G. M., Lou, W., Purdham, J., & Tarlo, S. M. (2009). *Relationships between asthma and work exposures among non-domestic cleaners in ontario* Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edswsc&AN=000269475100006&site=eds-live&scope=site

Penders, J., Thijs, C., van, d. B., Kummeling, I., Snijders, B., Stelma, F., . . . Stobberingh, E. E. (2007). Gut microbiota composition and development of atopic manifestations in infancy: The KOALA birth cohort study. *Gut,* (5), 661. Retrieved

from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edsgao&AN=edsgcl.164474810&site=eds-live&scope=site

Poole, K. (2001). Multidrug efflux pumps and antimicrobial resistance in pseudomonas aeruginosa and related organisms. *Journal of Molecular Microbiology and Biotechnology, 3*(2), 255-264. Retrieved fromhttp://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=11321581&site=eds-live&scope=site

Quirce, S., & Barranco, P. (2010). *Cleaning agents and asthma* Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edswsc&AN=000286704300001&site=eds-live&scope=site

Rajilić–Stojanović, M., Biagi, E., Heilig, H. G. H. J., Kajander, K., Kekkonen, R. A., Tims, S., & de Vos, W. M. (2011). Original research: Global and deep molecular analysis of microbiota signatures in fecal samples from patients with irritable bowel syndrome. *Gastroenterology, 141*, 1792-1801. doi:10.1053/j.gastro.2011.07.043

Reig, M., & Baquero, F. (1994). Antibacterial activity of clavulanate and tazobactam on peptostreptococcus spp. *The Journal of Antimicrobial Chemotherapy, 33*(2), 358-359. Retrieved fromhttp://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=8182024&site=eds-live&scope=site

Rosenberg, S. (2000). Consumer and market use of antibacterials at home. *The Pediatric Infectious Disease Journal, 19*(10), S114-S116. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=11052400&site=eds-live&scope=site

Russell, A. B., Hood, R. D., Bui, N. K., LeRoux, M., Vollmer, W., & Mougous, J. D. (2011). Type VI secretion delivers bacteriolytic effectors to target cells. *Nature, 475*(7356), 343. doi:10.1038/nature10244

Sally A. Roberts. (2006). Antimicrobial susceptibility of anaerobic bacteria in new zealand: 1999–2003. *Journal of Antimicrobial Chemotherapy (JAC), 57*(5), 992-998. Retrieved fromhttp://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=eih&AN=20508094&site=eds-live&scope=site

SAMET, J. (1990). *Environmental controls and lung-disease - report of the ats workshop on environmental controls and lung-disease, santa-fe, new-mexico, march 24-26, 1988* Retrieved fromhttp://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edswsc&AN=A1990EB31300031&site=eds-live&scope=site

Saulnier, D. M., Riehle, K., Mistretta, T., Diaz, M., Mandal, D., Raza, S., . . . Versalovic, J. (2011). Original research: Gastrointestinal microbiome signatures of pediatric patients with

irritable bowel syndrome. *Gastroenterology,141*, 1782-1791. doi:10.1053/j.gastro.2011.06.072

Scott, E., Bloomfield, S. F., & Barlow, C. G. (1984). *Evaluation of disinfectants in the domestic environment under 'in use' conditions* Cambridge University Press. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edsjsr&AN=edsjsr.3862688&site=eds-live&scope=site

Sjögren, Y. M., Author, Jenmalm, M., Author, Böttcher, M., Author, Björkstén, B., Author, Sverremark-Ekström, E., Author, Linköpings universitet, Institutionen för klinisk och,experimentell medicin, & Linköpings universitet, H., Originator. (2009). Altered early infant gut microbiota in children developing allergy up to 5 years of age. *Clinical and Experimental Allergy,* , 518. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edsswe&AN=edsswe.oai.DiVA.org.liu.17517&site=eds-live&scope=site

Vizcaya, D., Mirabelli, M. C., Antó, J., Orriols, R., Burgos, F., Arjona, L., & Zock, J. (2011). *A workforce-based study of occupational exposures and asthma symptoms in cleaning workers* BMJ Publishing Group. Retrieved fromhttp://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edsjsr&AN=edsjsr.41408468&site=eds-live&scope=site

Vizcaya, D., Mirabelli, M. C., Orriols, R., Antó, J. M., Barreiro, E., Burgos, F., . . . Zock, J. (2013). Functional and biological characteristics of asthma in cleaning workers. *Respiratory Medicine, 107*, 673-683. doi:10.1016/j.rmed.2013.01.011

Wang, L., Christophersen, C. T., Sorich, M. J., Gerber, J. P., Angley, M. T., & Conlon, M. A. (2013). Increased abundance of sutterella spp. and ruminococcus torques in feces of children with autism spectrum disorder. *Molecular Autism, 4*(1), 1-7. doi:10.1186/2040-2392-4-42

Weschler, C. J. (2009). Changes in indoor pollutants since the 1950s. *Atmospheric Environment, 43*(-), 153-169. doi:10.1016/j.atmosenv.2008.09.044

Weschler, C. J., & Nazaroff, W. W. (2008). Semivolatile organic compounds in indoor environments. *Atmospheric Environment, 42*, 9018-9040. doi:10.1016/j.atmosenv.2008.09.052

Wolkoff, P., Schneider, T., Kildesø, J., Degerth, R., Jaroszewski, M., & Schunk, H. (1998). Risk in cleaning: Chemical and physical exposure. *The Science of the Total Environment, 215*(1-2), 135-156. Retrieved fromhttp://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=9599458&site=eds-live&scope=site

Zock, J., Kogevinas, M., Sunyer, J., Almar, E., Muniozguren, N., Payo, F., . . . Antó, J. M. (2001). *Asthma risk, cleaning activities and use of specific cleaning products among spanish indoor cleaners* Finnish Institute of Occupational Health; National Institute of Occupational Health (Denmark); National Institute of Occupational Health (Norway); National Institute for Working Life. Retrieved fromhttp://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edsjsr&AN=edsjsr.40967118&site=eds-live&scope=site

Zock, J., Vizcaya, D., & Le Moual, N. (2010). Update on asthma and cleaners. *Current Opinion in Allergy and Clinical Immunology, 10*(2), 114-120. doi:10.1097/ACI.0b013e32833733fe

Zoetendal, E. G., Akkermans, A. D. L., Akkermans-van Vliet, W. M., de Visser, ‚J.Arjan G., & de Vos, W. M. (2001). The host genotype affects the bacterial community in the human gastronintestinal tract. *Microbial Ecology in Health & Disease, 13*(3), 129-134. doi:10.1080/089106001750462669

Table 3.1 Distribution of disinfectant exposure status at 3-4 months according to study covariates

	LOW DisINFECTANT Exposure N (%)	HIGH DisINFECTANT Exposure N (%)	P-value
Sex (N= 787)			
Male	197 (45.9%)	232 (54.1%)	0.365
Female	176 (49.2%)	182 (50.8%)	
Birth Mode (N= 777)			
Casesarean-elective	32 (38.6%)	51 (61.4%)	**0.003**
Casesarean-emergency	44 (36.4%)	77 (63.6%)	
Vaginal	292 (51%)	281 (49%)	
IAP (N= 778)			
No	200 (54.2%)	180 (44%)	**0.015**
Yes	169 (45.8%)	229 (56%)	
Hospital Admission (N= 787)			
No	122 (53%)	108 (47%)	**0.041**
Yes	251 (45.1%)	306 (54.9%)	
Readmission (N= 787)			
No	352 (47.1%)	396 (52.9%)	0.408
Yes	21 (53.8%)	18 (46.2%)	
Antibiotic Exposure by 3 months (N = 781)			
No	341 (47%)	384 (53%)	0.865
Yes	27 (48.2%)	29 (51.8%)	
Diet (N = 785)			
Exclusively breastfed	212 (51.1%)	203 (48.9%)	**0.005**
Partially breastfed	115 (47.3%)	128 (52.7%)	
Not breastfed	44 (34.6%)	83 (65.4%)	
Older Siblings (N= 780)			
No	195 (48.8%)	205 (51.2%)	0.367
Yes	173 (45.5%)	207 (54.5%)	
Furry Pets (N= 785)			
No	111 (51.4%)	105 (48.6%)	0.154
Yes	260 (45.7%)	309 (54.3%)	
Smoke (N= 785)			
No	330 (49.0%)	343 (51%)	0.015
Yes	41 (36.6%)	71 (63.4%)	
Term Delivery (N= 775)			
No	13 (41.9%)	18 (58.1%)	0.528
Yes	355 (47.7%)	389 (52.3%)	
Maternal Asthma (N= 784)			
No	294 (48.4%)	313 (51.6%)	0.248
Yes	77 (43.5%)	100 (56.5%)	

	LOW DisINFECTANT Exposure N (%)	HIGH DisINFECTANT Exposure N (%)	P-value
Maternal Preg Asthma (N= 786)			
No	344 (48%)	373 (52%)	0.240
Yes	28 (41.2%)	40 (58.8%)	
Maternal Allergy (N= 771)			
No	129 (46.4%)	149 (53.6%)	0.656
Yes	237 (48.1%)	256 (51.9%)	

P values <0.05 are indicated in boldface type.

Table 3.2 Distribution of detergent exposure status at 3-4 months according to study covariates

	LOW Detergent Exposure N (%)	HIGH Detergent Exposure N (%)	P-value
Sex (N = 787)			
Male	199 (46.4%)	230 (53.6%)	0.244
Female	181 (50.6%)	177 (49.4%)	
Birth Mode (N = 777)			
Casesarean-elective	29 (34.9%)	54 (65.1%)	**0.021**
Casesarean-emergency	56 (46.3%)	65 (53.7%)	
Vaginal	292 (51%)	281 (49%)	
IAP (N= 778)			
No	190 (50.4%)	190 (47.4%)	0.226
Yes	187 (49.6%)	211 (52.6%)	
Hospital Admission (N= 787)			
No	121 (52.6%)	109 (47.4%)	0.119
Yes	259 (46.5%)	298 (53.5%)	
Readmission (N= 787)			
No	358 (47.9%)	390 (52.1%)	0.298
Yes	22 (56.4%)	17 (43.6%)	
Antibiotic Exposure by 3 months (N = 781)			
No	345 (47.6%)	380 (52.4%)	0.388
Yes	30 (53.6%)	26 (46.4%)	
Diet (N = 785)			
Exclusively breastfed	216 (52%)	199 (48%)	0.069
Partially breastfed	106 (43.6%)	137 (56.4%)	
Not breastfed	56 (44.1%)	71 (55.9%)	
Older Siblings (N= 780)			
No	201 (50.2%)	199 (49.8%)	0.272
Yes	176 (46.3%)	204 (53.7%)	
Furry Pets (N= 785)			
No	119 (55.1%)	97 (44.9%)	**0.017**
Yes	259 (45.5%)	310 (54.5%)	
Smoke (N= 785)			
No	330 (49%)	343 (51%)	0.226
Yes	48 (42.9%)	407 (51.8%)	
Term Delivery (N= 775)			
No	15 (48.4%)	16 (51.6%)	0.988
Yes	361 (48.5%)	383 (51.5%)	
Maternal Asthma (N= 784)			
No	297 (48.9%)	310 (51.1%)	0.458
Yes	81 (45.8%)	96 (54.2%)	

	LOW Detergent Exposure N (%)	HIGH Detergent Exposure N (%)	P-value
Maternal Preg Asthma (N= 786)			
No	347 (48.4%)	370 (51.6%)	0.749
Yes	32 (46.4%)	37 (53.6%)	
Maternal Allergy (N= 771)			
No	133 (47.8%)	145 (52.2%)	0.994
Yes	236 (47.9%)	257 (52.1%)	

P values <0.05 are indicated in boldface type.

Table 3.3.Distribution of other cleaning products exposure status at 3-4 months according to study covariates

	LOW Other chemical products Exposure N (%)	HIGH Other chemical products Exposure N (%)	P-value
Sex (N = 787)			
Male	225 (52.4%)	204 (47.6%)	0.769
Female	184 (51.4%)	174 (48.6%)	
Birth Mode (N = 777)			
Casesarean-elective	43 (51.8%)	40 (48.2%)	**0.020**
Casesarean-emergency	49 (40.5%)	72 (59.5%)	
Vaginal	312 (54.5%)	261 (45.5%)	
IAP (N= 778)			
No	212 (52.5%)	168 (44.9%)	**0.035**
Yes	192 (47.5%)	206 (55.1%)	
Hospital Admission (N= 787)			
No	126 (54.8%)	104 (45.2%)	0.310
Yes	283 (50.8%)	274 (49.2%)	
Readmission (N= 787)			
No	388 (51.9%)	360 (48.1%)	0.810
Yes	21 (53.8%)	18 (46.2%)	
Antibiotic Exposure by 3 month (N=781)			
No	373 (51.4%)	352 (48.6%)	0.759
Yes	30 (53.6%)	26 (46.4%)	
Diet (N = 785)			
Exclusively breastfed	226 (54.5%)	189 (45.5%)	**0.041**
Partially breastfed	128 (52.7%)	115 (47.3%)	
Not breastfed	53 (41.7%)	74 (58.3%)	
Older Siblings (N= 780)			
No	203 (50.8%)	197 (49.2%)	0.455
Yes	203 (53.4%)	177 (46.6%)	
Furry Pets (N= 785)			
No	135 (62.5%)	81 (37.5%)	**0.0001**
Yes	272 (47.8%)	297 (52.2%)	
Smoke (N= 785)			
No	358 (53.2%)	315 (46.8%)	0.064
Yes	49 (43.8%)	63 (56.2%)	
Term Delivery (N= 775)			
No	15 (48.4%)	16 (51.6%)	0.670
Yes	389 (52.3%)	355 (47.7%)	
Maternal Asthma (N= 784)			
No	321 (52.9%)	286 (47.1%)	0.314
Yes	86 (48.6%)	91 (51.4%)	

	LOW Other chemical products Exposure N (%)	HIGH Other chemical products Exposure N (%)	P-value
Maternal Preg Asthma (N= 786)			
No	374 (52.2%)	343 (47.8%)	0.647
Yes	34 (49.3%)	35 (50.7%)	
Maternal Allergy (N= 771)			
No	155 (55.8%)	123 (44.2%)	0.106
Yes	245 (49.7%)	248 (50.3%)	

P values <0.05 are indicated in boldface type.

Table 3.4 Distribution of eco products exposure status at 3-4 months according to study covariates

	LOW Eco products Exposure N (%)	HIGH Eco products Exposure N (%)	P-value
Sex (N = 787)			
Male	231 (53.8%)	198 (46.2%)	0.319
Female	180 (50.3%)	178 (49.7%)	
Birth Mode (N = 777)			
Casesarean-elective	46 (55.4%)	37 (44.6%)	0.310
Casesarean-emergency	70 (57.9%)	51 (42..1%)	
Vaginal	291 (50.8%)	282 (49.2%)	
IAP (N= 778)			
No	187 (45.9%)	193 (52%)	0.456
Yes	220 (54.1%)	178 (48%)	
Hospital Admission (N= 787)			
No	103 (44.8%)	127 (55.2%)	**0.007**
Yes	308 (55.3%)	249 (44.7%)	
Readmission (N= 787)			
No	396 (52.9%)	352 (47.1%)	0.078
Yes	15 (38.5%)	24 (61.5%)	
Antibiotic Exposure by 3 month (N=781)			
No	378 (52.1%)	347 (47.9%)	0.571
Yes	27 (48.2%)	29 (51.8%)	
Diet (N = 785)			
Exclusively breastfed	200 (48.2%)	215 (51.8%)	**0.044**
Partially breastfed	133 (54.7%)	110 (45.3%)	
Not breastfed	76 (59.8%)	51 (40.2%)	
Older Siblings (N= 780)			
No	211 (52.8%)	189 (47.2%)	0.800
Yes	197 (51.8%)	183 (48.2%)	
Furry Pets (N= 785)			
No	121 (56%)	95 (44%)	0.176
Yes	288 (50.6%)	281 (49.4%)	
Smoke (N= 785)			
No	347 (51.6%)	326 (48.4%)	0.456
Yes	62 (55.4%)	50 (44.6%)	
Term Delivery (N= 775)			
No	16 (51.6%)	15 (48.4%)	0.941
Yes	389 (52.3%)	355 (47.7%)	
Maternal Asthma (N= 784)			
No	317 (52.2%)	290 (47.8%)	0.954
Yes	92 (52%)	85 (48%)	

	LOW Eco products Exposure N (%)	HIGH Eco products Exposure N (%)	P-value
Maternal Preg Asthma (N= 786)			
No	373 (52%)	344 (48%)	0.786
Yes	37 (53.6%)	32 (46.4%)	
Maternal Allergy (N= 771)			
No	160 (57.6%)	118 (42.4%)	**0.024**
Yes	242 (49.1%)	251 (50.9%)	

P values <0.05 are indicated in boldface type.

Table 3.5 List of Disinfectant products (frequencies in the descending order)

No.	Disinfectant
1	Multisurface cleaner
2	Toilet Bowl Cleaner
3	Purell type cleaner
4	Floor cleaner
5	Bleach
6	Disinfectant in home in general
7	Disinfectant in Bedroom
8	Bathroom tile cleaner

Table 3.6 List of Detergent products (frequencies in the descending order)

No.	Detergent
1	Handwashing Detergent
2	Dishwasher Detergent
3	Uncented Laundry Detergent
4	Scented Lanundry Detergent
5	Glass Cleaner
6	Fabric Softener
7	Oven Cleaner
8	Chemical Hand Cleaner (e.g. Grease)

Table 3.7 List of Other Cleaning products (frequencies in the descending order)

No.	Other Chemicals/ Cleaning products
1	Spray air freshner
2	Scented candle
3	Solvents (Nail polish)
4	Liquid /Solid Air freshner
5	Unscented Candle
6	Plug in deodorizer/ air freshener
7	Dusting polish / spray
8	Furniture polish
9	Drain cleaner
10	Incense
11	Floor polish
12	Insecticide
13	Silver/ Brass polish

Table 3.8 Median relative abundance of dominant bacterial taxa at the phylum and family level in infant gut microbiota at 3-4 months, according to post-natal disinfectant exposure in home

Bacterial Taxa	LOW DISINFECTANT (n= 373. 47.4%) Median (IQR)	HIGH DISINFECTANT (n=414, 52.6%) Median (IQR)	*P*	*FDR P*
Actinobacteria	6.79 (1.93 - 19.70)	4.18 (1.02 - 12.55)	**0.0002**	**0.006**
Bifidobacteriaceae	6.024 (1.484 - 17.982)	3.511 (0.554 - 11.489)	**0.0003**	**0.006**
Actinomycetaceae	0.029174 (0.005504 - 0.115411)	0.019022 (0.003583 - 0.076785)	**0.036**	0.206
Micrococcaceae	0.01127 (0.002328 - 0.059851)	0.007037 (0.001655 - 0.040081)	**0.046**	0.219
Coriobacteriaceae	0.055 (0.008 - 0.222)	0.036 (0.007 - 0.135)	0.074	0.302
Bacteroidetes	13.361 (0.078 - 57.826)	15.614 (0.073 - 58.449)	0.895	0.895
Bacteroidaceae	9.01 (0.065 - 51.507)	9.207 (0.047 - 52.834)	0.832	0.832
Pervotellaceae	0.0005 (0 - 0.0054)	0.0005 (0 - 0.0077)	0.434	0.620
Porphyromonadaceae	0.0038 (0.0014 - 0.168)	0.0038 (0.0015 - 0.1873)	0.985	0.985
Firmicutes	22.531 (9.722 - 41.679)	23.868 (10.384 - 46.62)	0.227	0.580
Staphylococcaceae	0.0015 (0 - 0.0124)	0.0014 (0 - 0.0073)	0.254	0.580
Gemellaceae	0.0049 (0.0013 - 0.0266)	0.0045 (0.0008 - 0.0179)	0.102	0.364
Enterococcaceae	0.0266 (0.0034 - 0.0941)	0.0208 (0.0029 - 0.0933)	0.637	0.696
Lactobacillaceae	0.0006 (0 - 0.025)	0.0009 (0 - 0.0288)	0.549	0.678
Streptococcaceae	0.593 (0.202 - 1.852)	0.504 (0.186 - 1.678)	0.292	0.580
uncl_Clostridiales	0.0003 (0 - 0.0024)	0.0005 (0 - 0.0034)	0.161	0.483
Clostridiaceae	0.437 (0.0453 - 2.4718)	0.412 (0.0462 - 2.4768)	0.718	0.718
Lachnospiraceae	2.775 (0.071 - 10.093)	3.58 (0.061 - 9.988)	0.724	0.724
Peptostreptococcaceae	0.000405 (0 - 0.013324)	0.000866 (0 - 0.014011)	**0.013**	0.172
Ruminococcaceae	0.139168 (0.004763 - 1.902803)	0.109487 (0.004511 - 1.654363)	0.665	0.704
Veillonellaceae	4.0009 (0.775 - 15.064)	5.1703 (0.899 - 16.03)	0.265	0.580
*Tissierellaceae_*	0.0011 (0 - 0.005)	0.0013 (0 - 0.006)	0.569	0.678
Erysipelotrichaceae	0.0298 (0.001 - 0.335)	0.0399 (0.001 - 0.464)	0.355	0.580
Proteobacteria	20.356 (9.775 - 41.362)	20.845 (8.197 - 41.547)	0.844	0.844
Alcaligenaceae	0.000574 (0 - 0.002837)	0.000504 (0 - 0.001938)	0.350	0.580
Desulfovibrionaceae	0.000212 (0 - 0.001304)	0.000361 (0 - 0.001447)	0.151	0.483
Pasteurellaceae	0.031617 (0.002317 - 0.293668)	0.031169 (0.003565 - 0.290556)	0.545	0.678
Pseudomonadaceae	0 (0 - 0.000511)	0 (0 - 0.000585)	0.327	0.580
Moraxellaceae	0 (0 - 0.000662)	0 (0 - 0.000602)	0.863	0.863
Enterobacteriaceae	16.9715 (6.625 - 39.8711)	18.2023 (6.5018 - 39.5291)	0.948	0.948
Verroucomicrobia	0.001931 (0.000267 - 0.00729)	0.002732 (0.00057 - 0.00831)	**0.027**	0.172
Verrucomicrobiaceae	0.001931 (0.000267 - 0.00729)	0.002732 (0.00057 - 0.00831)	**0.027**	0.172

Results are presented as median and inter quartile range in brackets. Comparisons were performed by Mann-Whitney U-test. Positive false discovery rate was used to adjust *P* values for multiple testing, and *FDR P* values <0.1 are indicated with '*****'. P values <0.05 are indicated in boldface type.
Dominant bacterial taxa with overall median relative abundance > 0 and family *Pseudomondaceae* were included in the analysis.

Table 3.9 Median relative abundance of dominant bacterial taxa at the genus level in infant gut microbiota at 3-4 months, according to post-natal disinfectant exposure in home

Bacterial Taxa	LOW DISINFECTANT (n= 373. 47.4%) Median (IQR)	HIGH DISINFECTANT (n=414, 52.6%) Median (IQR)	*P*	*FDR P*
g__Actinomyces	0.027326 (0.00504 - 0.107113)	0.016302 (0.003002 - 0.069338)	**0.027**	0.172
g__Rothia	0.01127 (0.002328 - 0.059851)	0.007037 (0.001655 - 0.040081)	**0.046**	0.219
g__Bifidobacterium	6.0244 (1.4844 - 17.9829)	3.5111 (0.5548 - 11.4892)	**0.0001**	0.0001*
g__Atopobium	0.002534 (0 - 0.020108)	0.002425 (0 - 0.014433)	0.627	0.696
g__Collinsella	0.000383 (0 - 0.002849)	0.000399 (0 - 0.001461)	0.593	0.692
g__Eggerthella	0.005356 (0 - 0.047908)	0.007661 (0 - 0.047251)	0.301	0.580
g__Bacteroides	9.0102 (0.0655 - 51.5071)	9.2075 (0.0478 - 52.8345)	0.832	0.832
g__Parabacteroides	0.0036 (0.0013 - 0.1374)	0.0035 (0.0013 - 0.1147)	0.751	0.751
g__Prevotella	0.000598 (0 - 0.005437)	0.000578 (0 - 0.007747)	0.434	0.620
g_staphylococcus	0.00154 (0 - 0.012413)	0.001488 (0 - 0.00739)	0.254	0.580
g__uncl_Gemellaceae	0.004963 (0.001323 - 0.026688)	0.004527 (0.000817 - 0.017995)	0.102	0.364
g__uncl_Lactobacillales_Other_Ot	0.001337 (0 - 0.020668)	0.000979 (0 - 0.010018)	0.069	0.302
g_Enterococcus	0.024168 (0.00281 - 0.089114)	0.018615 (0.002316 - 0.09217)	0.844	0.844
g__Streptococcus	0.583901 (0.199985 - 1.852634)	0.504986 (0.186967 - 1.678346)	0.308	0.580
g__uncl_Clostridiales	0.000394 (0 - 0.002424)	0.000541 (0 - 0.003404)	0.161	0.483
g__uncl_Clostridiaceae	0.113351 (0.010813 - 0.685347)	0.10838 (0.009524 - 0.828087)	0.781	0.781
g_Clostridium	0.025191 (0.003 - 0.774474)	0.024249 (0.003083 - 0.376397)	0.392	0.590
g__uncl_Lachnospiraceae_Other	0.00334 (0 - 0.022008)	0.003557 (0 - 0.026347)	0.623	0.696
g__uncl_Lachnospiraceae	0.132212 (0.007912 - 2.965284)	0.26016 (0.007763 - 3.610068)	0.348	0.580
g__Blautia	0.001735 (0.000155 - 0.076638)	0.001879 (0.000261 - 0.098778)	0.461	0.641
g__Dorea	0.000581 (0 - 0.004917)	0.000634 (0 - 0.00402)	0.863	0.863
g__Epulopiscium	0.001288 (0 - 0.006886)	0.001165 (0 - 0.007273)	0.567	0.678
*g___Ruminococcus_*	0.035635 (0.003232 - 2.039799)	0.02291 (0.003795 - 1.709763)	0.784	0.784
g__uncl_Peptostreptococcaceae	0 (0 - 0.011241)	0.000436 (0 - 0.009873)	**0.021**	0.172
g__uncl_Ruminococcaceae	0.000908 (0 - 0.006955)	0.001066 (0 - 0.005983)	0.862	0.862
g__Oscillospira	0.00849 (0.001099 - 0.872093)	0.004214 (0.000836 - 0.896609)	0.471	0.641
g__Ruminococcus	0.000984 (0 - 0.082007)	0.000845 (0 - 0.06427)	0.771	0.771
g__Dialister	0.00018 (0 - 0.003011)	0.000213 (0 - 0.002308)	0.952	0.952
g__Megasphaera	0.000856 (0 - 0.00441)	0.000935 (0 - 0.004592)	0.645	0.696
g__Veillonella	2.581349 (0.427626- 14.07946)	3.408462 (0.505453-15.323204)	0.375	0.590
g__uncl_Erysipelotrichaceae	0.003174 (0.000312 - 0.176731)	0.003767 (0.000561 - 0.216005)	0.193	0.525
*g___Eubacterium_*	0.000381 (0 - 0.0267)	0.000286 (0 - 0.01835)	0.747	0.747
g__Sutterella	0.000574 (0 - 0.002837)	0.000504 (0 - 0.001899)	0.388	0.590
g__Bilophila	0.000142 (0 - 0.001149)	0.000279 (0 - 0.001345)	0.169	0.483
g__uncl_Enterobacteriaceae_Other	0.010054 (0.003973 - 0.026973)	0.010745 (0.003849 - 0.033906)	0.334	0.580
g__uncl_Enterobacteriaceae	16.5402 (6.3976 - 39.4745)	17.6505 (5.9268 - 39.2256)	0.810	0.810
g__Citrobacter	0.023032 (0.00148 - 0.170071)	0.023239 (0.002459 - 0.212235)	0.317	0.580

Bacterial Taxa	LOW DISINFECTANT (n= 373. 47.4%) Median (IQR)	HIGH DISINFECTANT (n=414, 52.6%) Median (IQR)	*P*	*FDR P*
g__Trabulsiella	0.004915 (0.00171 - 0.015351)	0.00478 (0.001564 - 0.015707)	0.960	0.960
g__Haemophilus	0.030661 (0.002174 - 0.292435)	0.030593 (0.003026 - 0.290322)	0.549	0.678
g_Akkermansia	0.001931 (0.000267 - 0.00729)	0.002732 (0.00057 - 0.00831)	**0.027**	0.172
g_Pseudomonas	0 (0 - 0.000448)	0 (0 - 0.000517)	0.339	0.580

Results are presented as median and inter quartile range in brackets. Comparisons were performed by Mann-Whitney U-test. Positive false discovery rate was used to adjust *P* values for multiple testing, and *FDR P* values <0.1 are indicated with '*'. P values <0.05 are indicated in boldface type.
40 genera with overall median relative abundance > 0 and genus Pseudomonas were included in the analysis.

Table 3.10 Infant fecal microbiota richness and diversity according to household disinfectant exposure at 3-4 months

Infants	LOW DISINFECTANT (n= 373. 47.4%) Median (IQR)	HIGH DISINFECTANT (n=414, 52.6%) Median (IQR)	*P-value*
All Infants			
Chao 1-Overall	348.136 (287.192 - 406.037)	358.473 (293.75 - 423.108)	0.129
Shannon-Overall	3.149 (2.667 - 3.547)	3.12 (2.582 - 3.576)	0.574
Chao 1-Order Level	15 (14 - 17)	15 (14 - 17)	0.233
Shannon- Order Level	1.479 (1.2 - 1.825)	1.435 (1.11 - 1.764)	**0.028**
Chao 1-Family Level	27 (24 - 30)	27 (25 - 31)	0.129
Shannon- Family Level	1.847 (1.409 - 2.223)	1.784 (1.381 - 2.146)	0.128
Chao 1- Genus Level L6	44 (38 - 51)	44 (40 - 52)	0.162
Shannon- Genus Level L6	1.985 (1.498 - 2.366)	1.943 (1.473 - 2.355)	0.316

Results are presented as median and inter quartile range in brackets. Comparisons were performed by Mann-Whitney U-test.
P values <0.05 are indicated in boldface type.

Table 3.11 Median relative abundance of dominant bacterial taxa at the phylum and family level in infant gut microbiota at 3-4 months, according to post-natal detergent exposure in home

Bacterial Taxa	LOW DETERGENT (n= 380, 48.3%) Median (IQR)	HIGH DETERGENT (n= 407, 51.7%) Median (IQR)	*P*	*FDR P*
Actinobacteria	5.69 (1.46 - 14.48)	5.41 (1.16 - 15.24)	0.408	0.736
Bifidobacteriaceae	4.79975 (0.97415 - 13.76216)	4.47759 (0.72086 - 14.77357)	0.638	0.827
Actinomycetaceae	0.02695 (0.00519 - 0.10417)	0.02223 (0.00365 - 0.09213)	0.203	0.528
Micrococcaceae	0.00822 (0.00182 - 0.04738)	0.01085 (0.00179 - 0.0543)	0.664	0.827
Coriobacteriaceae	0.04013 (0.00781 - 0.17429)	0.04605 (0.00873 - 0.17933)	0.792	0.855
Bacteroidetes	17.79799 (0.09169 - 56.67172)	7.75137 (0.06526 - 61.30117)	0.453	0.736
Bacteroidaceae	14.31572 (0.06923 - 52.54402)	2.76335 (0.04229 - 52.04023)	0.193	0.528
Pervotellaceae	0.00065 (0 - 0.00686)	0.00053 (0 - 0.00644)	0.946	0.946
Porphyromonadaceae	0.00355 (0.0014 - 0.18476)	0.00413 (0.00152 - 0.10434)	0.505	0.763
Firmicutes	22.49901 (8.88094 - 42.73998)	23.91416 (10.54746 - 46.55552)	0.252	0.630
Staphylococcaceae	0.00163 (0.00013 - 0.01213)	0.00141 (0 - 0.00633)	0.058	0.528
Gemellaceae	0.00486 (0.00091 - 0.02435)	0.00479 (0.0012 - 0.02106)	0.744	0.834
Enterococcaceae	0.02183 (0.00328 - 0.09194)	0.02434 (0.0033 - 0.09545)	0.816	0.855
Lactobacillaceae	0.00077 (0 - 0.02274)	0.00091 (0 - 0.03236)	0.464	0.736
Streptococcaceae	0.51181 (0.19708 - 1.57107)	0.59706 (0.20044 - 2.04053)	0.322	0.698
uncl_Clostridiales	0.00033 (0 - 0.00285)	0.00063 (0 - 0.00335)	0.062	0.528
Clostridiaceae	0.35743 (0.03098 - 2.19621)	0.49402 (0.0632 - 2.77169)	0.160	0.528
Lachnospiraceae	2.88903 (0.06747 - 10.04896)	3.52125 (0.0632 - 10.0008)	0.607	0.827
Peptostreptococcaceae	0.00042 (0 - 0.0131)	0.00067 (0 - 0.01509)	0.147	0.528
Ruminococcaceae	0.10462 (0.00324 - 1.53581)	0.14006 (0.00603 - 1.98637)	0.091	0.528
Veillonellaceae	3.87639 (0.62266 - 14.35992)	5.21714 (1.0049 - 16.56306)	0.082	0.528
*Tissierellaceae_*	0.00118 (0 - 0.00552)	0.00124 (0 - 0.00691)	0.687	0.827
Erysipelotrichaceae	0.03704 (0.00129 - 0.36837)	0.03512 (0.00152 - 0.40759)	0.905	0.905
Proteobacteria	20.56201 (9.97301 - 42.26709)	20.44141 (8.1267 - 40.73512)	0.357	0.725
Alcaligenaceae	0.00058 (0 - 0.00302)	0.00049 (0 - 0.00184)	0.178	0.528
Desulfovibrionaceae	0.00028 (0 - 0.0017)	0.00027 (0 - 0.0013)	0.924	0.924
Pasteurellaceae	0.0313 (0.00272 - 0.29344)	0.0316 (0.0027 - 0.28351)	0.969	0.969
Pseudomonadaceae	0 (0 - 0.00049)	0 (0 - 0.00063)	**0.045**	0.528
Moraxellaceae	0 (0 - 0.00061)	0 (0 - 0.00059)	0.877	0.877
Enterobacteriaceae	18.0872 (7.18817 - 40.83123)	17.69436 (5.7903 - 38.99763)	0.440	0.736
Verroucomicrobia	0.0023 (0.00043 - 0.00797)	0.00216 (0.00034 - 0.00759)	0.999	0.999
Verrucomicrobiaceae	0.0023 (0.00043 - 0.00797)	0.00216 (0.00034 - 0.00759)	0.999	0.999

Results are presented as median and inter quartile range in brackets. Comparisons were performed by Mann-Whitney U-test. Positive false discovery rate was used to adjust *P* values for multiple testing, and *FDR P* values <0.1 are indicated with '*****'. P values <0.05 are indicated in boldface type.
Dominant bacterial taxa with overall median relative abundance > 0 and family *Pseudomondaceae* were included in the analysis.

Table 3.12 Median relative abundance of dominant bacterial taxa at the genus level in infant gut microbiota at 3-4 months, according to post-natal detergent exposure in home

Bacterial Taxa	LOW DETERGENT (n= 380, 48.3%) Median (IQR)	HIGH DETERGENT (n= 407, 51.7%) Median (IQR)	*P*	*FDR P*
g__Actinomyces	0.02346 (0.00478 - 0.09613)	0.01777 (0.0031 - 0.08398)	0.294	0.688
g__Rothia	0.00822 (0.00182 - 0.04738)	0.01085 (0.00179 - 0.0543)	0.664	0.827
g__Bifidobacterium	4.79975 (0.97415 - 13.62081)	4.47759 (0.72086 - 14.77357)	0.631	0.827
g__Atopobium	0.00189 (0 - 0.01551)	0.00325 (0 - 0.01858)	0.300	0.688
g__Collinsella	0.00031 (0 - 0.00198)	0.00045 (0 - 0.00212)	0.124	0.528
g__Eggerthella	0.00544 (0 - 0.04098)	0.00735 (0 - 0.04978)	0.452	0.736
g__Bacteroides	14.31572 (0.06923 - 52.54402)	2.76335 (0.04229 - 52.04023)	0.193	0.528
g__Parabacteroides	0.0034 (0.00131 - 0.16856)	0.00365 (0.00137 - 0.09382)	0.811	0.855
g__Prevotella	0.00065 (0 - 0.00686)	0.00053 (0 - 0.00644)	0.946	0.946
g_staphylococcus	0.00163 (0.00013 - 0.01213)	0.00141 (0 - 0.00633)	0.058	0.528
g__uncl_Gemellaceae	0.00486 (0.00091 - 0.02435)	0.00479 (0.0012 - 0.02106)	0.744	0.834
g__uncl_Lactobacillales_Other_Ot	0.00133 (0 - 0.01747)	0.00099 (0 - 0.0117)	0.350	0.725
g_Enterococcus	0.01984 (0.00236 - 0.08918)	0.02294 (0.00264 - 0.09197)	0.682	0.827
g__Streptococcus	0.50498 (0.19305 - 1.56778)	0.59706 (0.20044 - 2.04053)	0.307	0.688
g__uncl_Clostridiales	0.00033 (0 - 0.00285)	0.00063 (0 - 0.00335)	0.062	0.528
g__uncl_Clostridiaceae	0.09316 (0.00792 - 0.65068)	0.1533 (0.01224 - 0.88514)	0.110	0.528
g_Clostridium	0.01963 (0.00306 - 0.58007)	0.02889 (0.00307 - 0.50441)	0.704	0.832
g__uncl_Lachnospiraceae_Other	0.00299 (0 - 0.02376)	0.00399 (0 - 0.02383)	0.373	0.735
g__uncl_Lachnospiraceae	0.12146 (0.0078 - 2.93875)	0.30985 (0.00799 - 3.5309)	0.182	0.528
g__Blautia	0.00174 (0.00013 - 0.08662)	0.00176 (0.00031 - 0.10047)	0.492	0.761
g__Dorea	0.00054 (0 - 0.00272)	0.00068 (0 - 0.01006)	0.138	0.528
g__Epulopiscium	0.00126 (0 - 0.00928)	0.00113 (0 - 0.00626)	0.153	0.528
*g___Ruminococcus_*	0.000576 (0 - 0.071418)	0.001628 (0 - 0.078426)	0.655	0.827
g__uncl_Peptostreptococcaceae	0.00019 (0 - 0.01064)	0.00042 (0 - 0.01105)	0.090	0.528
g__uncl_Ruminococcaceae	0.00081 (0 - 0.00518)	0.00116 (0 - 0.0079)	0.148	0.528
g__Oscillospira	0.00381 (0.00089 - 0.71997)	0.00654 (0.00106 - 1.08068)	0.143	0.528
g__Ruminococcus	0.00057 (0 - 0.07141)	0.00162 (0 - 0.07842)	**0.014**	0.528
g__Dialister	0.00025 (0 - 0.00284)	0.00016 (0 - 0.0024)	0.641	0.827
g__Megasphaera	0.00089 (0 - 0.00462)	0.00086 (0 - 0.00428)	0.814	0.855
g__Veillonella	2.54888 (0.37771 - 13.47697)	3.67711 (0.59731 - 15.5883)	0.119	0.528
g__uncl_Erysipelotrichaceae	0.00402 (0.00041 - 0.1993)	0.00252 (0.00043 - 0.19337)	0.609	0.827
*g___Eubacterium_*	0.00027 (0 - 0.01936)	0.00036 (0 - 0.02681)	0.427	0.736
g__Sutterella	0.00057 (0 - 0.00302)	0.00049 (0 - 0.00184)	0.203	0.528
g__Bilophila	0.00021 (0 - 0.00167)	0.00023 (0 - 0.00121)	0.977	0.977
g__uncl_Enterobacteriaceae_Other	0.01053 (0.00396 - 0.0292)	0.01071 (0.00394 - 0.02996)	0.720	0.834

Bacterial Taxa	LOW DETERGENT (n= 380, 48.3%) Median (IQR)	HIGH DETERGENT (n= 407, 51.7%) Median (IQR)	*P*	*FDR P*
g__uncl_Enterobacteriaceae	17.4141 (7.05895 - 39.89882)	17.47526 (5.54604 - 37.80679)	0.390	0.736
g__Citrobacter	0.0211 (0.00155 - 0.18654)	0.02513 (0.00238 - 0.1962)	0.586	0.827
g__Trabulsiella	0.0052 (0.00156 - 0.01459)	0.00462 (0.00165 - 0.01629)	0.955	0.955
g__Haemophilus	0.03059 (0.0026 - 0.2924)	0.03065 (0.00262 - 0.28351)	0.934	0.934
g_Akkermansia	0.0023 (0.00043 - 0.00797)	0.00216 (0.00034 - 0.00759)	0.999	0.999
g_lactobacillus	0.00077 (0 - 0.02274)	0.00091 (0 - 0.03236)	0.464	0.736
g_Acinetobacter	0 (0 - 0.00061)	0 (0 - 0.00059)	0.990	0.990
g_Pseudonmonas	0 (0 - 0.00042)	0 (0 - 0.00056)	**0.032**	0.528

Results are presented as median and inter quartile range in brackets. Comparisons were performed by Mann-Whitney U-test. Positive false discovery rate was used to adjust *P* values for multiple testing, and *FDR P* values <0.1 are indicated with '*'. P values <0.05 are indicated in boldface type.
40 genera with overall median relative abundance > 0 and genus Pseudomonas were included in the analysis.

Table 3.13 Infant fecal microbiota richness and diversity according to household detergent exposure at 3-4 months

Infants	LOW DETERGENT (n= 380, 48.3%) Median (IQR)	HIGH DETERGENT (n= 407, 51.7%) Median (IQR)	*P-value*
All Infants			
Chao 1-Overall	358.403 (288.416 - 413.376)	353.222 (292.375 - 411.263)	0.945
Shannon-Overall	3.136 (2.619 - 3.55)	3.141 (2.65 - 3.576)	0.592
Chao 1-Order Level	15 (14 - 17)	15 (14 - 17)	0.433
Shannon- Order Level	1.457 (1.179 - 1.801)	1.46 (1.12 - 1.773)	0.245
Chao 1-Family Level	27 (24 - 30)	27 (25 - 31)	0.289
Shannon- Family Level	1.803 (1.41 - 2.18)	1.82 (1.381 - 2.208)	0.830
Chao 1- Genus Level L6	44 (38 - 51)	44 (39 - 52)	0.132
Shannon- Genus Level L6	1.949 (1.483 - 2.338)	1.948 (1.495 - 2.375)	0.954

Results are presented as median and inter quartile range in brackets. Comparisons were performed by Mann-Whitney U-test.
P values <0.05 are indicated in boldface type.

Table 3.14 Median relative abundance of dominant bacterial taxa at the phylum and family level in infant gut microbiota at 3-4 months, according to post-natal other cleaning/ chemical products exposure in home

Bacterial Taxa	LOW OTHER CHEMICALS (n= 409, 52%) Median (IQR)	HIGH OTHER CHEMICALS (n= 378, 48%) Median (IQR)	*P*	*FDR P*
Actinobacteria	5.382 (1.243 - 14.552)	5.536 (1.44 - 15.257)	0.670	0.670
Bifidobacteriaceae	4.577 (0.9 - 13.532)	4.946 (0.958 - 14.786)	0.695	0.695
Actinomycetaceae	0.026 (0.005 - 0.102)	0.021 (0.003 - 0.094)	0.259	0.321
Micrococcaceae	0.01 (0.002 - 0.049)	0.008 (0.001 - 0.047)	0.241	0.316
Coriobacteriaceae	0.041 (0.008 - 0.184)	0.043 (0.007 - 0.166)	0.709	0.709
Bacteroidetes	13.86 (0.078 - 57.977)	13.86 (0.078 - 57.977)	0.758	0.758
Bacteroidaceae	9.01 (0.058 - 52.847)	9.443 (0.045 - 51.227)	0.526	0.526
Pervotellaceae	0.00065 (0 - 0.00686)	0.00053 (0 - 0.00648)	0.731	0.731
Porphyromonadaceae	0.00364 (0.00144 - 0.13174)	0.00402 (0.00152 - 0.21645)	0.420	0.420
Firmicutes	22.702 (10.087 - 43.095)	23.452 (10.03 - 46.734)	0.582	0.582
Staphylococcaceae	0.00163 (0 - 0.01044)	0.0014 (0 - 0.00756)	0.290	0.334
Gemellaceae	0.00512 (0.00129 - 0.02157)	0.00417 (0.00088 - 0.02324)	0.418	0.418
Enterococcaceae	0.02545 (0.00337 - 0.10423)	0.02163 (0.00324 - 0.0857)	0.553	0.553
Lactobacillaceae	0.00094 (0 - 0.02829)	0.00062 (0 - 0.02742)	0.861	0.861
Streptococcaceae	0.538 (0.199 - 1.679)	0.562 (0.194 - 1.956)	0.893	0.893
uncl_Clostridiales	0.0004 (0 - 0.00222)	0.00055 (0 - 0.0035)	0.150	0.289
Clostridiaceae	0.466 (0.04 - 2.625)	0.403 (0.048 - 2.357)	0.846	0.846
Lachnospiraceae	2.708 (0.06 - 9.277)	3.779 (0.081 - 10.854)	0.143	0.289
Peptostreptococcaceae	0.00068 (0 - 0.01586)	0.0005 (0 - 0.01237)	0.695	0.695
Ruminococcaceae	0.094 (0.003 - 1.411)	0.175 (0.005 - 1.88)	0.085	0.246
Veillonellaceae	4.277 (0.765 - 15.733)	5.17 (0.925 - 15.771)	0.549	0.549
*Tissierellaceae_*	0.00119 (0 - 0.00653)	0.00125 (0 - 0.00633)	0.580	0.580
Erysipelotrichaceae	0.02859 (0.00137 - 0.32219)	0.0487 (0.00148 - 0.49449)	0.210	0.308
Proteobacteria	21.248 (9.321 - 43.786)	19.409 (9.105 - 39.361)	0.192	0.308
Alcaligenaceae	0.00061 (0 - 0.00228)	0.00043 (0 - 0.00233)	0.197	0.308
Desulfovibrionaceae	0.00022 (0 - 0.00134)	0.00038 (0 - 0.00142)	0.057	0.220
Pasteurellaceae	0.03161 (0.0029 - 0.29102)	0.03073 (0.00252 - 0.29124)	0.763	0.763
Pseudomonadaceae	0 (0 - 0.0005)	0 (0 - 0.00064)	**0.025**	0.149
Moraxellaceae	0 (0 - 0.00061)	0 (0 - 0.0006)	0.519	0.519
Enterobacteriaceae	19.05 (6.728 - 43.137)	16.544 (6.168 - 35.312)	0.180	0.308
Verroucomicrobia	0.0019 (0.00029 - 0.00602)	0.00283 (0.00057 - 0.01106)	**0.009**	0.078*
Verrucomicrobiaceae	0.0019 (0.00029 - 0.00602)	0.00283 (0.00057 - 0.01106)	**0.009**	0.078*

Results are presented as median and inter quartile range in brackets. Comparisons were performed by Mann-Whitney U-test. Positive false discovery rate was used to adjust *P* values for multiple testing, and *FDR P* values <0.1 are indicated with '*'. P values <0.05 are indicated in boldface type.
Dominant bacterial taxa with overall median relative abundance > 0 and family *Pseudomondaceae* were included in the analysis.

Table 3.15 Median relative abundance of dominant bacterial taxa at the genus level in infant gut microbiota at 3-4 months, according to post-natal other cleaning/ chemical products exposure in home

Bacterial Taxa	LOW OTHER CHEMICALS (n= 409, 52%) Median (IQR)	HIGH OTHER CHEMICALS (n= 378, 48%) Median (IQR)	*P*	*FDR P*
g__Actinomyces	0.02345 (0.00456 - 0.08864)	0.01814 (0.00302 - 0.0841)	0.445	0.445
g__Rothia	0.01004 (0.00231 - 0.04959)	0.00807 (0.00166 - 0.04729)	0.241	0.316
g__Bifidobacterium	4.577 (0.835 - 13.442)	4.946 (0.958 - 14.786)	0.709	0.709
g__Atopobium	0.00226 (0 - 0.01635)	0.00269 (0 - 0.01826)	0.947	0.947
g__Collinsella	0.00031 (0 - 0.00222)	0.00044 (0 - 0.00186)	0.246	0.316
g__Eggerthella	0.00533 (0 - 0.04128)	0.00844 (0 - 0.05196)	0.076	0.243
g__Bacteroides	9.01 (0.058 - 52.847)	9.443 (0.045 - 51.227)	0.526	0.526
g__Parabacteroides	0.00344 (0.00133 - 0.09764)	0.0036 (0.00133 - 0.16704)	0.789	0.789
g__Prevotella	0.00065 (0 - 0.00686)	0.000`53 (0 - 0.00648)	0.731	0.731
g_staphylococcus	0.00163 (0 - 0.01044)	0.0014 (0 - 0.00756)	0.290	0.334
g__uncl_Gemellaceae	0.00512 (0.00129 - 0.02157)	0.00417 (0.00088 - 0.02324)	0.418	0.418
g__uncl_Lactobacillales_Other_Ot	0.00133 (0 - 0.01653)	0.00092 (0 - 0.01333)	0.515	0.515
g_Enterococcus	0.023 (0.002 - 0.103)	0.019 (0.002 - 0.08)	0.661	0.661
g__Streptococcus	0.535 (0.198 - 1.679)	0.562 (0.192 - 1.956)	0.865	0.865
g__uncl_Clostridiales	0.0004 (0 - 0.00222)	0.00055 (0 - 0.0035)	0.150	0.289
g__uncl_Clostridiaceae	0.117 (0.011 - 0.896)	0.105 (0.008 - 0.663)	0.466	0.466
g_Clostridium	0.02 (0.002 - 0.541)	0.029 (0.003 - 0.528)	0.475	0.475
g__uncl_Lachnospiraceae_Other	0.00238 (0 - 0.02157)	0.00483 (0 - 0.02717)	0.113	0.280
g__uncl_Lachnospiraceae	0.12325 (0.00753 - 2.9657)	0.36263 (0.00824 - 3.80668)	0.103	0.275
g__Blautia	0.00156 (0 - 0.08599)	0.00229 (0.00033 - 0.10268)	0.144	0.289
g__Dorea	0.00051 (0 - 0.00225)	0.00079 (0 - 0.01463)	**0.008**	0.078*
g__Epulopiscium	0.0012 (0 - 0.00749)	0.00127 (0 - 0.00695)	0.922	0.922
*g___Ruminococcus_*	0.01924 (0.00352 - 1.75737)	0.03578 (0.0034 - 2.03979)	0.371	0.379
g__uncl_Peptostreptococcaceae	0.0003 (0 - 0.01232)	0.00033 (0 - 0.0092)	0.733	0.733
g__uncl_Ruminococcaceae	0.000688 (0.00 - 0.005054)	0.001328 (0.00 - 0.01112)	**0.043**	0.187
g__Oscillospira	0.00384 (0.00093 - 0.73282)	0.00634 (0.00106 - 1.07364)	0.300	0.334
g__Ruminococcus	0.00101 (0 - 0.07178)	0.00082 (0 - 0.07913)	0.686	0.686
g__Dialister	0.00027 (0 - 0.00318)	0 (0 - 0.00226)	0.308	0.334
g__Megasphaera	0.00079 (0 - 0.00432)	0.00107 (0 - 0.0047)	0.319	0.336
g__Veillonella	2.916 (0.471 - 14.907)	3.194 (0.479 - 14.045)	0.882	0.882
g__uncl_Erysipelotrichaceae	0.00328 (0.00035 - 0.14675)	0.00331 (0.00053 - 0.22554)	0.399	0.399
*g___Eubacterium_*	0.00021 (0 - 0.01308)	0.0004 (0 - 0.03784)	**0.030**	0.149
g__Sutterella	0.0006 (0 - 0.00227)	0.00043 (0 - 0.00233)	0.213	0.308

Bacterial Taxa	LOW OTHER CHEMICALS (n= 409, 52%) Median (IQR)	HIGH OTHER CHEMICALS (n= 378, 48%) Median (IQR)	*P*	*FDR P*
g__Bilophila	0.00014 (0 - 0.00122)	0.00027 (0 - 0.00133)	0.077	0.243
g__uncl_Enterobacteriaceae_Other	0.0107 (0.0037 - 0.03)	0.0105 (0.004 - 0.0275)	0.988	0.988
g__uncl_Enterobacteriaceae	18.632 (6.563 - 42.3)	16.464 (5.792 - 35.017)	0.166	0.303
g__Citrobacter	0.02303 (0.0019 - 0.18607)	0.02323 (0.00222 - 0.19854)	0.828	0.828
g__Trabulsiella	0.00491 (0.00179 - 0.01556)	0.00477 (0.00156 - 0.01561)	0.598	0.598
g__Haemophilus	0.03065 (0.0028 - 0.29055)	0.03059 (0.00231 - 0.29097)	0.725	0.725
g_Akkermansia	0.0019 (0.00029 - 0.00602)	0.00283 (0.00057 - 0.01106)	**0.009**	0.078*
g_lactobacillus	0.00094 (0 - 0.02829)	0.00062 (0 - 0.02742)	0.861	0.861
g_Acinetobacter	0 (0 - 0.0006)	0 (0 - 0.0006)	0.439	0.439
g_Pesudoomonas	0 (0 - 0.00044)	0 (0 - 0.00054)	**0.027**	0.149

Results are presented as median and inter quartile range in brackets. Comparisons were performed by Mann-Whitney U-test. Positive false discovery rate was used to adjust *P* values for multiple testing, and *FDR P* values <0.1 are indicated with '*'. P values <0.05 are indicated in boldface type.
40 genera with overall median relative abundance > 0 and genus Pseudomonas were included in the analysis.

Table 3.16 Infant fecal microbiota richness and diversity according to household cleaning/ chemical products exposure

Infants	LOW OTHERS CHEMICAL (n= 409, 52%) Median (IQR)	HIGH OTHERS CHEMICAL (n= 378, 48%) Median (IQR)	*P-value*
All Infants			
Chao 1-Overall	348.136 (289 - 404.829)	360.022 (289.989 - 424.266)	0.171
Shannon-Overall	3.114 (2.655 - 3.481)	3.178 (2.592 - 3.643)	0.119
Chao 1-Order Level	15 (14 - 17)	15 (14 - 17)	0.263
Shannon- Order Level	1.442 (1.129 - 1.771)	1.476 (1.141 - 1.802)	0.400
Chao 1-Family Level	27 (24 - 30)	27 (24 - 31)	0.383
Shannon- Family Level	1.788 (1.407 - 2.149)	1.843 (1.377 - 2.253)	0.087
Chao 1- Genus Level L6	44 (39 - 51)	44 (39 - 52)	0.363
Shannon- Genus Level L6	1.934 (1.519 - 2.289)	1.991 (1.451 - 2.436)	0.087

Results are presented as median and inter quartile range in brackets. Comparisons were performed by Mann-Whitney U-test.
P values <0.05 are indicated in boldface type.

Table 3.17 Median relative abundance of dominant bacterial taxa at the phylum and family level in infant gut microbiota at 3-4 months, according to post-natal eco products exposure in home

Bacterial Taxa	LOW ECO Products (n= 411, 52.2%) Median (IQR)	HIGH ECO Products (n= 376, 47.8%) Median (IQR)	*P*	*FDR P*
Actinobacteria	5.397 (1.086 - 14.219)	5.49 (1.529 - 16.175)	0.256	0.256
Bifidobacteriaceae	4.484 (0.628 - 13.281)	4.907 (1.245 - 14.829)	0.276	0.276
Actinomycetaceae	0.023 (0.005 - 0.092)	0.025 (0.004 - 0.114)	0.492	0.492
Micrococcaceae	0.00756 (0.00176 - 0.04911)	0.01126 (0.00192 - 0.04875)	0.293	0.293
Coriobacteriaceae	0.04065 (0.00873 - 0.1586)	0.04763 (0.00783 - 0.18592)	0.509	0.509
Bacteroidetes	9.825 (0.076 - 55.189)	16.221 (0.076 - 61.176)	0.633	0.633
Bacteroidaceae	7.751 (0.051 - 49.283)	10.318 (0.057 - 54.487)	0.644	0.644
Pervotellaceae	0.00059 (0 - 0.00603)	0.00058 (0 - 0.0069)	0.841	0.841
Porphyromonadaceae	0.00401 (0.00154 - 0.16704)	0.00363 (0.00145 - 0.20036)	0.696	0.696
Firmicutes	24.79 (10.533 - 46.734)	20.527 (9.132 - 40.875)	0.089	0.127
Staphylococcaceae	0.0014 (0 - 0.00669)	0.00164 (0 - 0.01183)	0.252	0.252
Gemellaceae	0.00438 (0.00098 - 0.01713)	0.00492 (0.00125 - 0.02975)	0.149	0.149
Enterococcaceae	0.02434 (0.00345 - 0.10076)	0.02181 (0.00305 - 0.09172)	0.656	0.656
Lactobacillaceae	0.00085 (0 - 0.01972)	0.00089 (0 - 0.03639)	0.512	0.512
Streptococcaceae	0.535 (0.187 - 1.661)	0.562 (0.202 - 1.945)	0.470	0.470
uncl_Clostridiales	0.00053 (0 - 0.00335)	0.0004 (0 - 0.00283)	0.323	0.323
Clostridiaceae	0.474 (0.056 - 2.981)	0.392 (0.037 - 2.171)	0.143	0.143
Lachnospiraceae	3.214 (0.075 - 10.122)	3.196 (0.06 - 9.996)	0.696	0.696
Peptostreptococcaceae	0.00085 (0 - 0.01334)	0.00044 (0 - 0.01382)	0.217	0.217
Ruminococcaceae	0.13713 (0.00541 - 1.9252)	0.12993 (0.00389 - 1.58304)	0.282	0.282
Veillonellaceae	5.172 (0.855 - 16.559)	4.18 (0.844 - 14.846)	0.460	0.460
*Tissierellaceae_*	0.00119 (0 - 0.0058)	0.00122 (0 - 0.00656)	0.725	0.725
Erysipelotrichaceae	0.0411 (0.0016 - 0.4491)	0.0299 (0.0012 - 0.3532)	0.197	0.197
Proteobacteria	20.396 (9.077 - 40.735)	20.562 (9.306 - 41.887)	0.552	0.552
Alcaligenaceae	0.00043 (0 - 0.00166)	0.0006 (0 - 0.00485)	**0.027**	0.078*
Desulfovibrionaceae	0.00021 (0 - 0.00115)	0.00039 (0 - 0.00229)	**0.022**	0.078*
Pasteurellaceae	0.03043 (0.00248 - 0.28696)	0.03273 (0.00307 - 0.29731)	0.314	0.314
Pseudomonadaceae	0 (0 - 0.00055)	0 (0 - 0.00052)	0.117	0.127
Moraxellaceae	0 (0 - 0.00061)	0 (0 - 0.00059)	0.621	0.621
Enterobacteriaceae	18.31 (6.851 - 38.691)	17.5 (5.743 - 40.646)	0.849	0.849
Verroucomicrobia	0.00254 (0.00041 - 0.00887)	0.00201 (0.0004 - 0.00659)	0.264	0.264
Verrucomicrobiaceae	0.00254 (0.00041 - 0.00887)	0.00201 (0.0004 - 0.00659)	0.264	0.264

Results are presented as median and inter quartile range in brackets. Comparisons were performed by Mann-Whitney U-test. Positive false discovery rate was used to adjust *P* values for multiple testing, and *FDR P* values <0.1 are indicated with '*****'. P values <0.05 are indicated in boldface type.
Dominant bacterial taxa with overall median relative abundance > 0 and family *Pseudomondaceae* were included in the analysis.

Table 3.18 Median relative abundance of dominant bacterial taxa at the genus level in infant gut microbiota at 3-4 months, according to post-natal eco products exposure in home

Bacterial Taxa	LOW ECO Products (n= 411, 52.2%) Median (IQR)	HIGH ECO Products (n= 376, 47.8%) Median (IQR)	*P*	*FDR P*
g__Actinomyces	0.02038 (0.00442 - 0.08447)	0.02147 (0.00338 - 0.09213)	0.618	0.618
g__Rothia	0.00756 (0.00176 - 0.04911)	0.01126 (0.00192 - 0.04875)	0.294	0.294
g__Bifidobacterium	4.484 (0.62 - 13.281)	4.907 (1.242 - 14.829)	0.272	0.272
g__Atopobium	0.00226 (0 - 0.019)	0.00258 (0 - 0.01458)	0.547	0.547
g__Collinsella	0.0003 (0 - 0.00196)	0.00051 (0 - 0.00226)	0.166	0.166
g__Eggerthella	0.00713 (0 - 0.0489)	0.00542 (0 - 0.04269)	0.344	0.344
g__Bacteroides	7.751 (0.051 - 49.283)	10.318 (0.057 - 54.487)	0.644	0.644
g__Parabacteroides	0.00365 (0.00133 - 0.10163)	0.0033 (0.00131 - 0.18079)	0.687	0.687
g__Prevotella	0.00059 (0 - 0.00603)	0.00058 (0 - 0.0069)	0.841	0.841
g_staphylococcus	0.0014 (0 - 0.00669)	0.00164 (0 - 0.01183)	0.252	0.252
g__uncl_Gemellaceae	0.00438 (0.00098 - 0.01713)	0.00492 (0.00125 - 0.02975)	0.149	0.149
g__uncl_Lactobacillales_Other_Ot	0.00127 (0 - 0.01511)	0.00111 (0 - 0.01413)	0.882	0.882
g_Enterococcus	0.0216 (0.0026 - 0.0927)	0.0198 (0.0025 - 0.0873)	0.793	0.793
g__Streptococcus	0.535 (0.187 - 1.661)	0.562 (0.2 - 1.945)	0.450	0.450
g__uncl_Clostridiales	0.00053 (0 - 0.00335)	0.0004 (0 - 0.00283)	0.323	0.323
g__uncl_Clostridiaceae	0.153 (0.014 - 0.952)	0.083 (0.006 - 0.62)	**0.013**	0.078*
g_Clostridium	0.028 (0.003 - 0.625)	0.022 (0.002 - 0.507)	0.431	0.431
g__uncl_Lachnospiraceae_Other	0.00309 (0 - 0.02383)	0.00391 (0 - 0.02327)	0.995	0.995
g__uncl_Lachnospiraceae	0.13693 (0.00803 -3.45319)	0.23268 (0.00753 - 3.06863)	0.569	0.569
g__Blautia	0.00162 (0.00022 - 0.07968)	0.00211 (0.00013 - 0.0999)	0.693	0.693
g__Dorea	0.00067 (0 - 0.00553)	0.00054 (0 - 0.00408)	0.172	0.172
g__Epulopiscium	0.00132 (0 - 0.00815)	0.00109 (0 - 0.00675)	0.616	0.616
*g___Ruminococcus_*	0.0207 (0.0034 - 1.9584)	0.0335 (0.0033 - 1.7131)	0.799	0.799
g__uncl_Peptostreptococcaceae	0.00039 (0 - 0.01099)	0.0002 (0 - 0.01003)	0.177	0.177
g__uncl_Ruminococcaceae	0.00131 (0 - 0.00701)	0.00061 (0 - 0.00616)	**0.037**	0.089*
g__Oscillospira	0.0064 (0.00122 - 0.90777)	0.00439 (0.00078 - 0.78632)	0.123	0.127
g__Ruminococcus	0.00115 (0 - 0.08088)	0.00078 (0 - 0.06772)	0.276	0.276
g__Dialister	0.00024 (0 - 0.00264)	0 (0 - 0.00291)	0.576	0.576
g__Megasphaera	0.00097 (0 - 0.00453)	0.00084 (0 - 0.00445)	0.466	0.466
g__Veillonella	3.787 (0.522 - 15.475)	2.829 (0.407 - 13.189)	0.171	0.171
g__uncl_Erysipelotrichaceae	0.00285 (0.00049 - 0.22544)	0.00371 (0.00026 - 0.16571)	0.328	0.328
*g___Eubacterium_*	0.00032 (0 - 0.02681)	0.00028 (0 - 0.01961)	0.595	0.595
g__Sutterella	0.00043 (0 - 0.0016)	0.0006 (0 - 0.00474)	**0.023**	0.078*
g__Bilophila	0.00014 (0 - 0.00109)	0.00035 (0 - 0.00205)	**0.007**	0.078*

Bacterial Taxa	LOW ECO Products (n= 411, 52.2%) Median (IQR)	HIGH ECO Products (n= 376, 47.8%) Median (IQR)	*P*	*FDR P*
g__uncl_Enterobacteriaceae_Other	0.01117 (0.00413 - 0.03009)	0.01001 (0.0038 - 0.02777)	0.314	0.314
g__uncl_Enterobacteriaceae	18.114 (6.738 - 37.707)	16.636 (5.282 - 39.746)	0.855	0.855
g__Citrobacter	0.026 (0.002 - 0.203)	0.019 (0.001 - 0.184)	0.220	0.220
g__Trabulsiella	0.00491 (0.00178 - 0.01472)	0.00473 (0.00141 - 0.01739)	0.684	0.684
g__Haemophilus	0.03014 (0.00236 - 0.28696)	0.03116 (0.00293 - 0.29731)	0.415	0.415
g_Akkermansia	0.00254 (0.00041 - 0.00887)	0.00201 (0.0004 - 0.00659)	0.264	0.264
g_lactobacillus	0.00085 (0 - 0.01972)	0.00089 (0 - 0.03639)	0.512	0.512
g_Acinetobacter	0 (0 - 0.00061)	0 (0 - 0.00059)	0.615	0.615
g_Pseudomonas	0 (0 - 0.00049)	0 (0 - 0.00048)	0.203	0.203

Results are presented as median and inter quartile range in brackets. Comparisons were performed by Mann-Whitney U-test. Positive false discovery rate was used to adjust *P* values for multiple testing, and *FDR P* values <0.1 are indicated with '*'. P values <0.05 are indicated in boldface type.
40 genera with overall median relative abundance > 0 and genus Pseudomonas were included in the analysis.

Table 3.19 Infant fecal microbiota richness and diversity according to household eco products exposure at 3-4 months

Infants	LOW ECO products (n= 411, 52.2%) Median (IQR)	HIGH ECO products (n= 376, 47.8%) Median (IQR)	*P-value*
All Infants			
Chao 1-Overall	366 (294 - 411.14285)	348.599 (286.623 - 413.545)	0.228
Shannon-Overall	3.141 (2.663 - 3.53)	3.132 (2.627 - 3.585)	0.873
Chao 1-Order Level	15 (14 - 17)	15 (14 - 17)	0.469
Shannon- Order Level	1.455 (1.131 - 1.778)	1.47 (1.14 - 1.788)	0.568
Chao 1-Family Level	27 (24 - 31)	27 (24 - 30)	0.307
Shannon- Family Level	1.83 (1.436 - 2.186)	1.795 (1.369 - 2.205)	0.850
Chao 1- Genus Level L6	45 (39 - 52)	44 (38 - 50)	**0.044**
Shannon- Genus Level L6	1.969 (1.545 - 2.344)	1.931 (1.47 - 2.364)	0.792

Results are presented as median and inter quartile range in brackets. Comparisons were performed by Mann-Whitney U-test.
P values <0.05 are indicated in boldface type.

Table 3.20 Crude and adjusted likelihood ratio of abundance of key gut microbiota measures at 3-4 months according to household disinfectant exposure status

Microbiota Measure							
	Microbiota at 3- 4 months`						
	OR (95% CI)						
Ref Group = LOW DISINFECTANT	**Actinobacteria (below vs. above median)**	***Bifidobacteriacea (below vs. above median)***	***Actinomycetaceae (below vs. above median)***	***Peptostreptococcaceae (below vs. above median)***	***Verrucomicrobiaceae (below vs. above median)***	***g__Bifidobacterium (below vs. above median)***	***g__Actinomyces (below vs. above median)***
Crude OR for HIGH DISINFECTANT	0.65 (0.49 - 0.86)	0.65 (0.49 - 0.86)	0.63 (0.48 - 0.84)	1.39 (1.05 - 1.85)	1.39 (1.05 - 1.85)	0.65 (0.49 - 0.86)	0.66 (0.50 - 0.88)
Adjusted for Caesarean delivery	0.67 (0.50 - 0.89)	0.67 (0.50 - 0.89)	0.61 (0.46 - 0.81)	1.42 (1.06 - 1.88)	1.42 (1.06 - 1.88)	0.67 (0.50 - 0.89)	0.63 (0.47 - 0.84)
Adjusted for **Diet**	0.65 (0.49 - 0.87)	0.66 (0.50 - 0.87)	0.61 (0.46 - 0.81)	1.39 (1.05 - 1.84)	1.39 (1.05 - 1.84)	0.66 (0.50 - 0.87)	0.64 (0.49 - 0.86)
Adjusted for Antibiotic	0.67 (0.50 - 0.87)	0.66 (0.50 - 0.87)	0.64 (0.48 - 0.85)	1.40 (1.06 - 1.86)	1.40 (1.06 - 1.86)	0.66 (0.50 - 0.87)	0.67 (0.50 - 0.88)
Adjusted for IAP	0.66 (0.50 - 0.88)	0.66 (0.50 - 0.88)	0.61 (0.46 - 0.81)	1.41 (1.06 - 1.88)	1.39 (1.04 - 1.72)	0.66 (0.50 - 0.88)	0.63 (0.48 - 0.84)
Adjusted for Readmission	0.64 (0.49 - 0.86)	0.65 (0.49 - 0.86)	0.64 (0.48 - 0.84)	1.39 (1.05 - 1.84)	1.39 (1.05 - 1.84)	0.65 (0.49 - 0.86)	0.66 (0.50 - 0.88)
Adjusted for Hospital Admission	0.63 (0.48 - 0.84)	0.64 (0.48 - 0.85)	0.63 (0.47 - 0.83)	1.41 (1.07 - 1.87)	1.41 (1.07 - 1.87)	0.64 (0.48 - 0.85)	0.66 (0.50 - 0.87)
Adjusted for **SMOKE**	0.63 (0.48 - 0.84)	0.64 (0.48 - 0.84)	0.62 (0.47 - 0.82)	1.42 (1.07 - 1.89)	1.42 (1.07 - 1.89)	0.64 (0.48 - 0.84)	0.65 (0.49 - 0.86)
Adjusted for Caesarean, Diet, IAP, Readmission, Hospital Admisison, Antibiotic, **SMOKE**	0.66 (0.50 - 0.89)	0.67 (0.50 - 0.90)	0.58 (0.43 - 0.78)	1.44 (1.08 - 1.93)	1.36 (1.03 - 1.68)	0.67 (0.50 - 0.90)	0.60 (0.45 - 0.80)

*highlighted in yellow are statistically significant (p <0.05), OR = odds ratio, CI = Confidence Interval, IAP = Intrapartum Antibiotic Phylaxis

Table 3.21 Crude and adjusted likelihood ratio of abundance of key gut microbiota measures at 3-4 months according to household detergent exposure status

Microbiota Measure		
	Microbiota at 3-4 months OR (95% CI)	
Ref Group = LOW DETERGENT	***g__Ruminococcus* (below vs. Above median)**	***g_Dorea* (highest quartile vs. Others)**
Crude OR for HIGH DETERGENT	1.34 (1.01 - 1.77)	1.45 (1.05 - 2.02)
Adjusted for Caesarean delivery	1.38 (1.04 - 1.83)	1.48 (1.07 - 2.06)
Adjusted for Diet	1.34 (1.01 - 1.77)	1.45 (1.04 - 2.01)
Adjusted for Antibiotic	1.35 (1.02 - 1.79)	1.48 (1.07 - 2.06)
Adjusted for IAP	1.35 (1.02 - 1.79)	1.47 (1.06 - 2.03)
Adjusted for Readmission	1.34 (1.02 - 1.78)	1.45 (1.05 - 2.01)
Adjusted for Hospital Admission	1.33 (1.01 - 1.76)	1.43 (1.03 - 1.99)
Adjusted for PETS	1.34 (1.01 - 1.78)	1.42 (1.02 - 1.97)
Adjusted for Caesarean, Diet, Antibiotic, IAP, Readmission, Hospital Admission, Pets	1.41 (1.06 - 1.88)	1.46 (1.05 - 2.05)

*highlighted in yellow are statistically significant ($p < 0.05$), OR = odds ratio, CI = Confidence Interval, IAP = Intrapartum Antibiotic Prophylaxis

Table 3.22 Crude and adjusted likelihood ratio of abundance of key gut microbiota measures at 3-4 months according to household other cleaning/ chemical products exposure status

Microbiota Measure							
	Microbiota at 3-4 months OR (95% CI)						
Ref Group = LOW OTHER CLEANING PRODUCTS	**Verrucomicrobia (below vs. Above median)**	***Pesudomondaceae (below vs. Above median)***	***g_Dorea (below vs. Above median)***	***g_Akkermansia (below vs. Above median)***	***g_Pseudomonas (below vs. Above median)***	**Chao1 Richness (Highest quartile vs. Others)**	**Shannon Diversity (Highest quartile vs. Others)**
Crude OR for HIGH OTHER CLEANING PRODUCTS	1.38 (1.04 - 1.83)	1.37 (1.04 - 1.82)	1.35 (1.02 - 1.79)	1.42 (1.06 - 1.89)	1.40 (1.05 - 1.86)	1.46 (1.06 - 2.02)	1.59 (1.14 - 2.20)
Adjusted for Caesarean delivery	1.38 (1.04 - 1.83)	1.40 (1.05 - 1.86)	1.32 (0.99 - 1.76)	1.42 (1.06 - 1.90)	1.43 (1.07 - 1.91)	1.48 (1.07 - 2.05)	1.61 (1.16 - 2.23)
Adjusted for **Diet**	1.39 (1.05 - 1.84)	1.35 (1.02 - 1.79)	1.34 (1.02 - 1.78)	1.41 (1.06 - 1.89)	1.37 (1.03 - 1.83)	1.45 (1.04 - 2.00)	1.56 (1.13 - 2.16)
Adjusted for Antibiotic	1.37 (1.03 - 1.81)	1.37 (1.03 - 1.82)	1.37 (1.03 - 1.81)	1.37 (1.03 - 1.81)	1.39 (1.05 - 1.86)	1.45 (1.05 - 2.01)	1.56 (1.13 - 2.17)
Adjusted for IAP	1.39 (1.05 - 1.84)	1.39 (1.05 - 1.85)	1.31 (1.01 - 1.74)	1.39 (1.05 - 1.84)	1.44 (1.08 - 1.92)	1.47 (1.06 - 2.03)	1.59 (1.14 - 2.20)
Adjusted for Readmission	1.38 (1.04 - 1.83)	1.38 (1.04 - 1.82)	1.34 (1.01 - 1.77)	1.38 (1.04 - 1.83)	1.40 (1.05 - 1.86)	1.46 (1.05 - 2.02)	1.58 (1.14 - 2.19)
Adjusted for Hospital Admission	1.38 (1.04 - 1.82)	1.36 (1.02 - 1.80)	1.35 (1.02 - 1.79)	1.38 (1.04 - 1.82)	1.38 (1.03 - 1.84)	1.44 (1.04 - 2.00)	1.59 (1.15 - 2.21)
Adjusted for **Pets**	1.37 (1.03 - 1.82)	1.37 (1.03 - 1.83)	1.33 (1.00 - 1.77)	1.37 (1.03 - 1.82)	1.39 (1.04 - 1.86)	1.44 (1.03 - 1.99)	1.54 (1.11 - 2.15)
Adjusted for Caesarean, Diet, Antibiotic, IAP, Readmission, **Hospital Admission, Pets**	1.38 (1.03 - 1.84)	1.37 (1.02 - 1.84)	1.30 (0.97 - 1.73)	1.38 (1.03 - 1.84)	1.41 (1.05 - 1.90)	1.44 (1.03 - 2.01)	1.53 (1.09 - 2.13)

*highlighted in yellow are statistically significant ($p < 0.05$), OR = odds ratio, CI = Confidence Interval, IAP = Intrapartum Antibiotic Prophylaxis

Table 3.23 Crude and adjusted likelihood ratio of abundance of key gut microbiota measures at 3-4 months according to household eco products exposure status

Microbiota Measure					
	Microbiota at 3-4 months				
	OR (95% CI)				
Ref Group 0 = LOW ECO PRODUCTS	***Desulfovibrionaceae (below vs. above median)***	***g_Collinsella (below vs. above median)***	***g_Bilophilia (below vs. above median)***	***g_uncl_Clostridiaceae (below vs. above median)***	***g__Sutterella_HR (Highest quartile vs. Others)***
Crude OR for HIGH ECO PRODUCTS	1.35 (1.02 - 1.79)	1.44 (1.09 - 1.90)	1.48 (1.12 - 1.96)	0.72 (0.54 - 0.95)	1.50 (1.08 - 2.07)
Adjusted for Caesarean delivery	1.38 (1.04 - 1.83)	1.45 (1.09 - 1.92)	1.52 (1.14 - 2.01)	0.74 (0.56 - 0.98)	1.46 (1.05 - 2.03)
Adjusted for Diet	1.37 (1.03 - 1..82)	1.43 (1.08 - 1.89)	1.51 (1.14 - 2.00)	0.72 (0.55 - 0.96)	1.50 (1.08 - 2.08)
Adjusted for Antibiotic	1.32 (0.99 - 1.75)	1.45 (1.09 - 1.92)	1.45 (1.09 - 1.92)	0.71 (0.54 - 0.95)	1.49 (1.08 - 2.06)
Adjusted for IAP	1.39 (1.05 - 1.85)	1.44 (1.09 - 1.91)	1.52 (1.14 - 2.02)	0.77 (0.55 - 1.06)	1.49 (1.07 - 2.06)
Adjusted for Readmission	1.34 (1.01 - 1.78)	1.46 (1.10 - 1.93)	1.47 (1.11 - 1.95)	0.71 (0.54 - 0.94)	1.52 (1.10 - 2.10)
Adjusted for Hospital Admission	1.36 (1.03 - 1.81)	1.42 (1.07 - 1.89)	1.50 (1.13 - 1.99)	0.71 (0.54 - 0.95)	1.48 (1.07 - 2.05)
Adjusted for **Maternal Allergy**	1.41 (1.06 - 1.87)	1.45 (1.09 - 1.93)	1.55 (1.17 - 2.06)	0.72 (0.54 - 0.95)	1.54 (1.11 - 2.14)
Adjusted for Caesarean, Diet, Antibiotic,IAP, Readmission, **Hospital Admission, Maternal Allergy**	1.43 (1.07 - 1.92)	1.46 (1.09 - 1.95)	1.59 (1.19 - 2.13)	0.77 (0.55 - 0.96)	1.51 (1.08 - 2.12)

*highlighted in yellow are statistically significant (p <0.05), OR = odds ratio, CI = Confidence Interval, IAP = Intrapartum Antibiotic Prophylaxis

Table 3.24 Crude and adjusted likelihood ratio of abundance of *Pseudomondaceae* and *Pseudomonas* at 3-4 months according to combined exposure effect of household disinfectant and other cleaning/ chemical products

Microbiota Measure			
	Microbiota at 3-4 months OR (95% CI)		
Ref Group= Group 1		***f_pesudomondaceae (below vs. Above median)***	***g_Pseudomonas (below vs. Above median)***
Crude OR for DISINFECTANT & Other Cleaning products	Group 2	1.59 (1.03 - 2.47)	1.77 (1.13 - 2.75)
	Group 3	1.19 (0.80 - 1.79)	1.28 (0.85 - 1.93)
	Group 4	1.43 (0.99 - 2.01)	1.44 (1.01 - 2.06)
Adjusted for Caesarean delivery	Group 2	1.64 (1.06 -2.56)	1.89 (1.21 - 2.96)
	Group 3	1.25 (0.83 - 1.88)	1.34 (0.89 - 2.04)
	Group 4	1.47 (1.03 - 2.10)	1.49 (1.04 - 2.14)
Adjusted for **Diet** at 3 months	Group 2	1.52 (0.98 - 2.36)	1.69 (1.08 - 2.64)
	Group 3	1.12 (0.75 - 1.69)	1.21 (0.80 - 1.84)
	Group 4	1.37 (0.96 - 1.94)	1.39 (0.97 - 2.00)
Adjusted for Antibiotic at 3 months	Group 2	1.59 (1.03 - 2.48)	1.77 (1.14 - 2.77)
	Group 3	1.21 (0.80 - 1.81)	1.30 (0.86 - 1.97)
	Group 4	1.42 (0.99 - 2.02)	1.45 (1.01 - 2.07)
Adjusted for IAP at 3 months	Group 2	1.62 (1.04 – 2.52)	1.86 (1.19 – 2.91)
	Group 3	1.26 (0.84 – 1.89)	1.35 (0.89 – 2.05)
	Group 4	1.48 (1.04 – 2.11)	1.51 (1.05 - 2.18)
Adjusted for Readmission at 3 months	Group 2	1.60 (1.03 - 2.48)	1.77 (1.13 - 2.75)
	Group 3	1.20 (0.80 - 1.80)	1.28 (0.85 - 1.94)
	Group 4	1.42 (1.00 - 2.02)	1.44 (1.01 - 2.06)
Adjusted for Hospital Admission at 3 months	Group 2	1.64 (1.05 - 2.55)	1.82 (1.16 - 2.84)
	Group 3	1.18 (0.79 - 1.78)	1.27 (0.84 - 1.93)
	Group 4	1.37 (0.96 - 1.95)	1.39 (0.97 - 1.99)
Adjusted for **SMOKE**	Group 2	1.56 (1.00 - 2.42)	1.74 (1.11 - 2.71)
	Group 3	1.16 (0.77 - 1.75)	1.26 (0.83 - 1.90)
	Group 4	1.38 (0.97 - 1.97)	1.41 (0.99 - 2.03)
Adjusted for Caesarean, Diet, Readmission, Hospitalization , Antibiotic, **SMOKE**	Group 2	1.55 (0.98 - 2.46)	1.82 (1.14 - 1.89)
	Group 3	1.09 (0.71 0 1.66)	1.22 (0.79 - 1.88)
	Group 4	1.39 (0.96 - 2.01)	1.42 (0.97 - 2.07)

*highlighted in yellow are statistically significant (p <0.05), OR = odds ratio, CI = Confidence Interval, IAP = Intrapartum Antibiotic Prophylaxis, SMOKE= indoor smoke exposure, Group 1 = low disinfectant and low other cleaning products, Group 2 = low disinfectant and high other cleaning products, Group 3 =

high disinfectant and low other cleaning products, Group 4 = high disinfectant and high other cleaning products.

Figure 3.1 Gut microbiota compositions at 3-4 months according to household disinfectant exposure status.

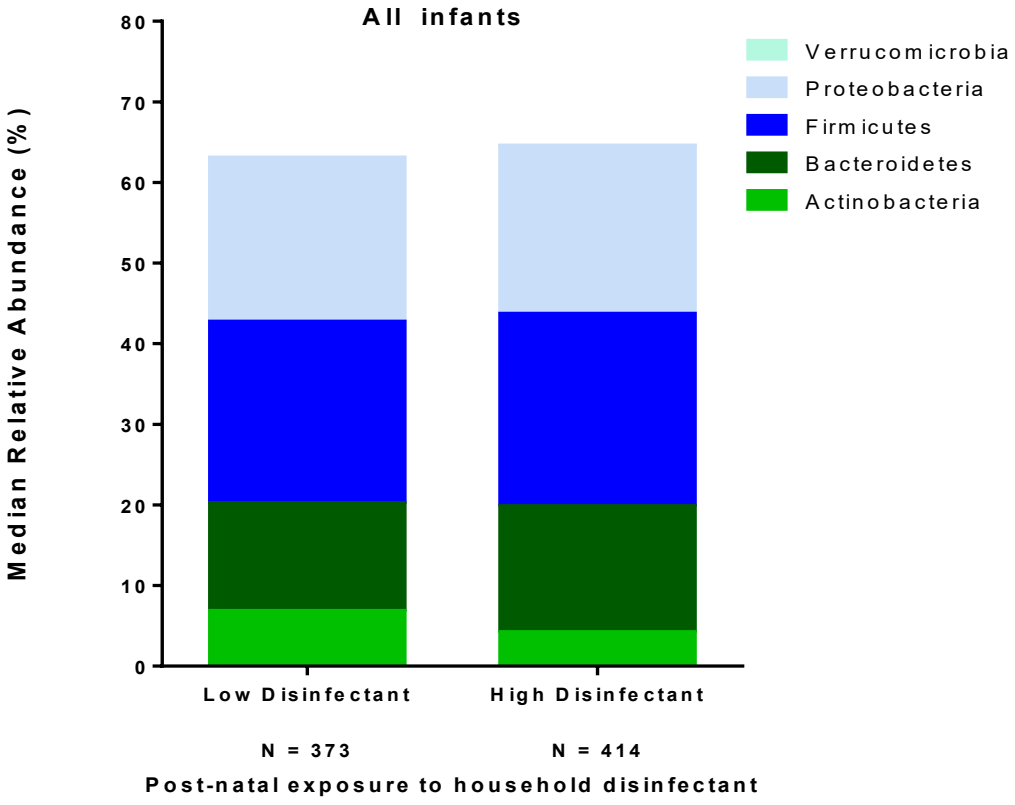


Figure 3.2 Gut microbiota composition at 3-4 months according to household detergent exposure status.

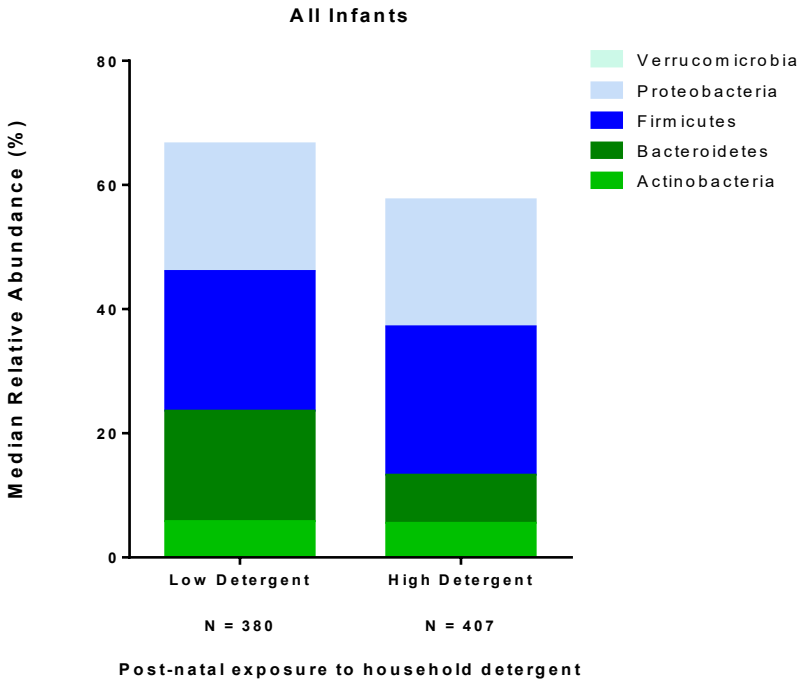


Figure 3.3 Gut microbiota composition at 3-4 months according to household other cleaning/ chemical products exposure status.

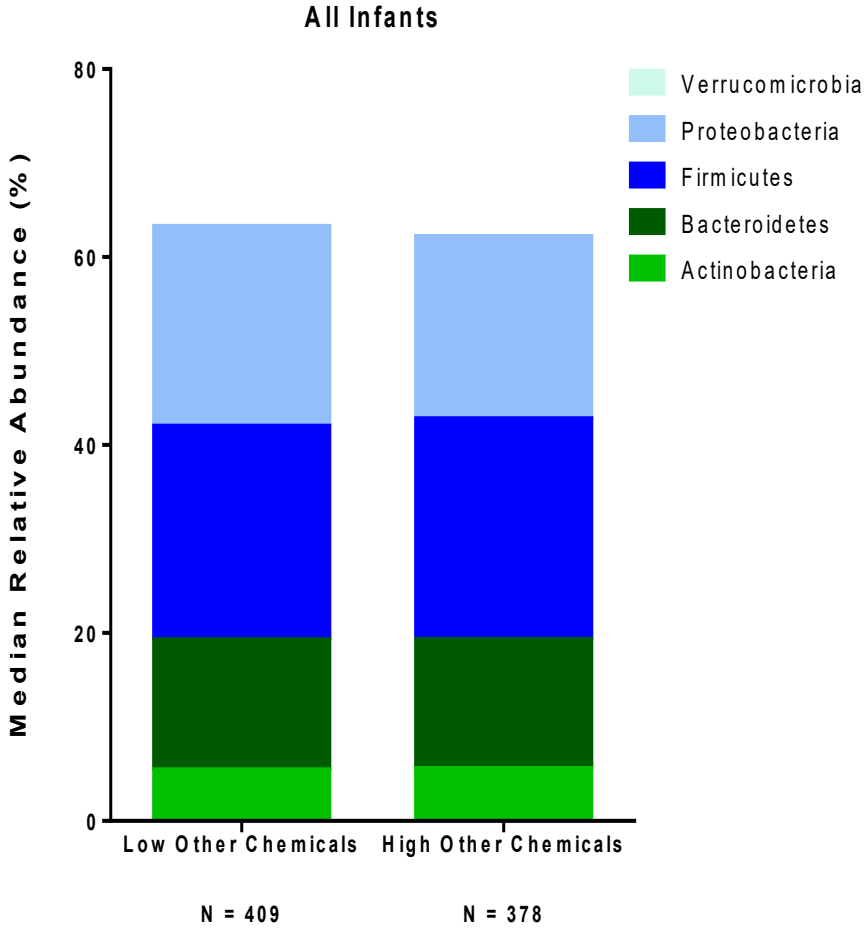


Figure 3.4 Gut microbiota composition at 3-4 months according to household eco products exposure status.

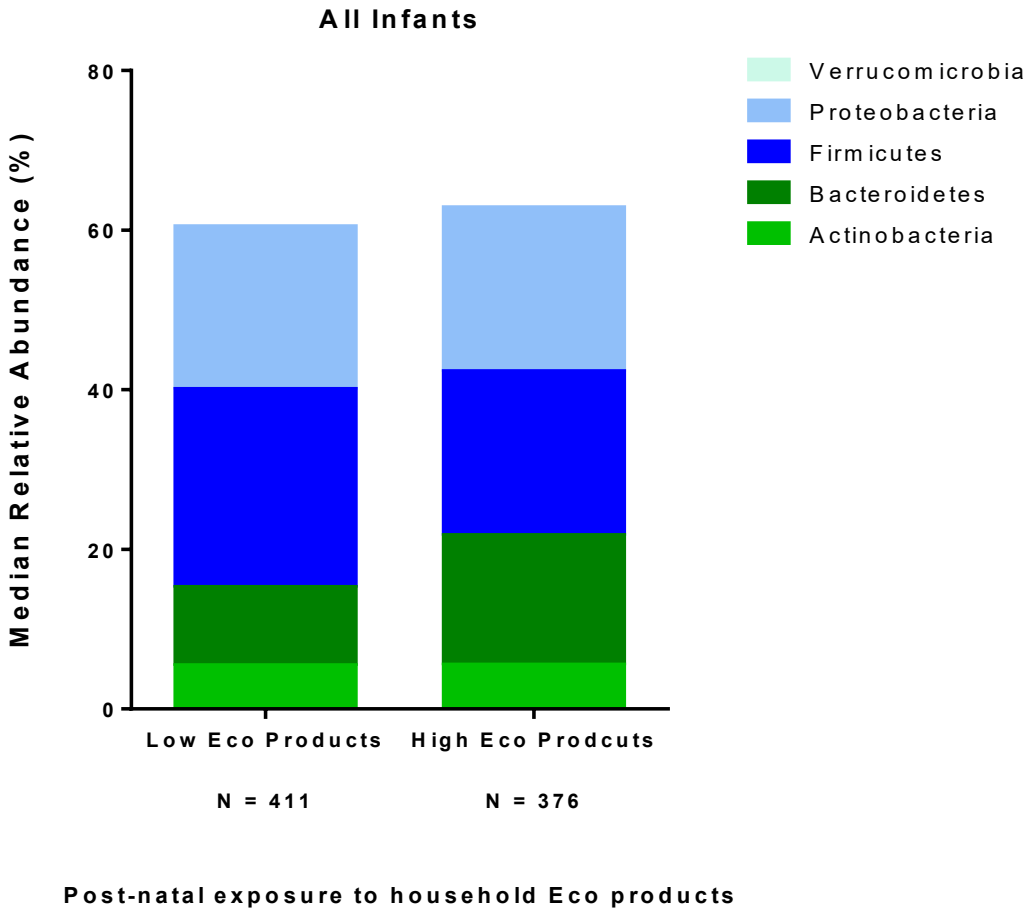


Figure 3.5 Relative abundance of family *Pseudomondaceae* in 4 groups of disinfectant and other cleaning products.

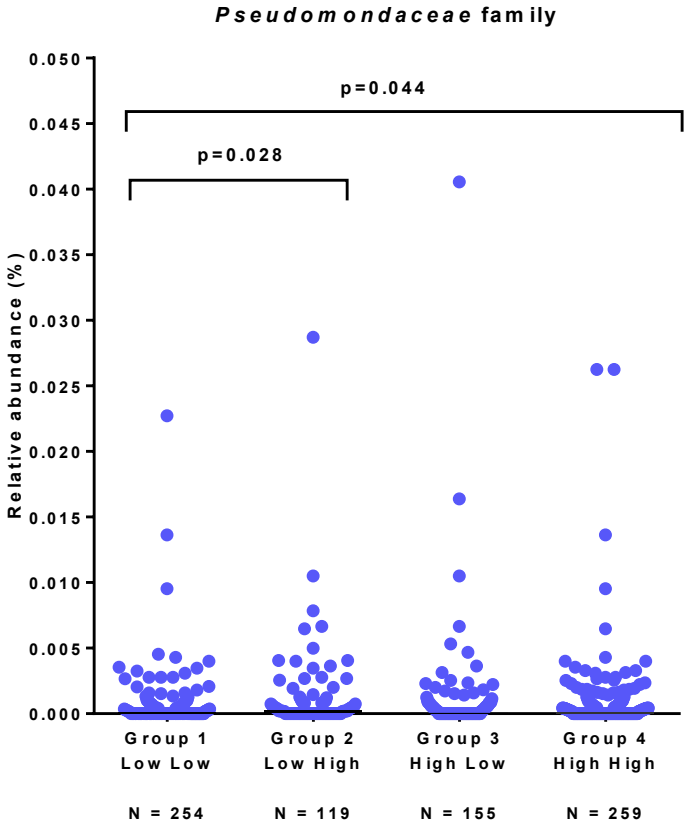
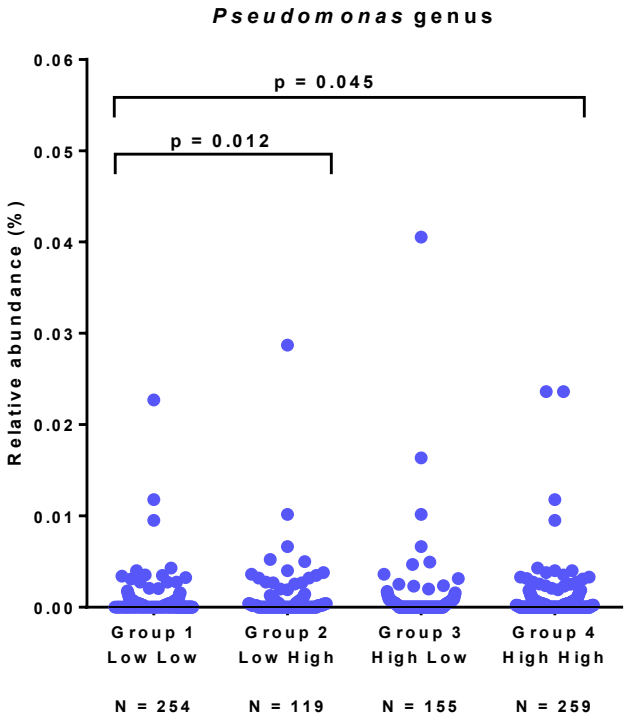


Figure 3.6 Relative abundance of genus *Pseudomonas* in 4 groups of disinfectant and other cleaning products.



Index

Which of the following products have been USED in your home since your baby was born?

(Day=daily, Wk=weekly, Mth=monthly, <Mth=less than monthly, No=not used)

50.1 Liquid or solid air freshener: Day Wk Mth <Mth No

50.2 Spray air freshener: Day Wk Mth <Mth No

50.3 Plug-in deodorizer/air freshener: Day Wk Mth <Mth No

50.4 Floor Cleaner: Day Wk Mth <Mth No

50.5 Furniture polish: Day Wk Mth <Mth No

50.6 Floor polish: Day Wk Mth <Mth No

50.7 Dusting polish or spray: Day Wk Mth <Mth No

50.8 Drain cleaner: Day Wk Mth <Mth No

50.9 Hand dishwashing detergent: Day Wk Mth <Mth No

50.10 Dishwasher detergent: Day Wk Mth <Mth No

50.11 Bleach: Day Wk Mth <Mth No

50.12 Multi-surface cleaner: Day Wk Mth <Mth No

50.13 Silver or brass polish: Day Wk Mth <Mth No

50.14 Disinfectant in bedrooms: Day Wk Mth <Mth No

50.15 Disinfectant in home in general: Day Wk Mth <Mth No

50.16 Unscented candle: Day Wk Mth <Mth No

50.17 Scented candle: Day Wk Mth <Mth No

50.18 Incense: Day Wk Mth <Mth No

50.19 Eco & organic cleaning product: Day Wk Mth <Mth No

50.20 Glass cleaner: Day Wk Mth <Mth No

50.21 Chemical hand cleaner (e.g., for grease): Day Wk Mth <Mth No

50.22 Purell-type hand cleaner: Day Wk Mth <Mth No

50.23 Unscented laundry detergent: Day Wk Mth <Mth No

50.24 Scented laundry detergent: Day Wk Mth <Mth No

50.25 Fabric softener: Day Wk Mth <Mth No

50.26 Toilet bowl cleaner: Day Wk Mth <Mth No

50.27 Oven cleaner: Day Wk Mth <Mth No

50.28 Bathroom tile cleaner: Day Wk Mth <Mth No

50.29 Solvents (e.g. nail polish/paint remover): Day Wk Mth <Mth No

50.30 Insecticide: Day Wk Mth <Mth No

50.31 Other products not listed above: Day Wk Mth <Mth No

50.31a If Other products, specify type

CHAPTER 4

General Discussion and Conclusion

4.1 Summary of the Results

In this thesis, using data from the CHILD longitudinal birth cohort, the impact of early life exposure to hospital microbial environment and household cleaning products on infant gut microbiota composition and diversity were investigated.

In Chapter 2, early life exposure to hospital microbial environment in early life had significant effect on the infant gut microbiota composition and diversity at 3-4 months of age. In infants with a hospital stay for more than 1 day, there were overrepresentation of Firimicutes phylum (p= 0.022), and *Lachnospiraceae* and *Pseudomonadaceae* family (p=0.041 and p=0.004 respectively). Furthermore, microbiota richness at OTU level was higher in hospitalized infants. More importantly, *Pseudomonadaceae* (p=0.004) and *Pseudomonas* (p=0.005) were more abundant in the gut of infants with extended hospital stays after birth both in vaginally and caesarean delivered infants. Additionally, multivariate logistic regression analyses revealed that prolonged hospitalization for 4 or more days was associated with 1.87 times more likely to have a higher abundance of *Acinetobacter* (p=0.017) in exclusively breastfed, antibiotics free infants with no history of readmission.

In Chapter 3, more than half of the CHILD cohort households used disinfectants at least once a month, mostly multi-surface cleaner. In the group of detergent, the most commonly used

product was hand washing detergent, whereas in the group of other chemical products, spray air freshener was the most common. At 3-4 months of age, high indoor disinfectant exposure was associated with low fecal abundance of Actinobacteria (p=0.0002) at the phylum level and of *Bifidobacteriaceae* (p=0.021) at the family level. Moreover, exposure to high disinfectant was associated with reduced diversity at order level (p=0.028). Infants exposed to high levels of household detergent was associated with higher abundance of genera *Ruminococcus* and *Pseudomonas* (p = 0.014 and p = 0.032), whereas in infants who were exposed to high levels of other cleaning/chemical products, *Pseudomondaceae* (p=0.025) and *Verrucomicrobiaceae* (p=0.009) were overrepresented. In addition, infants exposed to high level of eco products in the home environment had greater abundance of *Alcaligenaceae* (p=0.027) and *Desulfovibrionaceae* (p=0.022).

In summary, exposure to hospital microbial environment after birth was significantly associated with changes in the infant gut microbial composition, including greater colonization with hospital-acquired pathogens within the first 3 months of life. Exposure to household disinfectant was associated with reduction of beneficial gut microbiota *Bifidobacteriaceae* in the CHILD cohort at 3-4 months of age.

4.2 Strength of the Study

This study has several strengths. First, we employed high-throughput Illumina sequencing of 16S rRNA gene for profiling the infant gut microbiota. 16S rRNA gene is a universal gene for use in bacterial phylogeny and taxonomy, and by far the most common housekeeping genetic marker employed (Janda JM and Abbott SL, 16S rRNA Gene Sequencing for Bacterial Identification in the Diagnostic Laboratory: Pluses, Perils, and Pitfalls. J Clin Microbiol.2007 Sep; 45(9): 2761–2764). It is conserved in sequence and function throughout various taxa, yet the hyper-variable regions (eg. V4) of this genetic marker provide good taxonomic resolution and have sufficient variability between species to be distinguished. Another advange of the use of 16S rRNA gene is its length (1500 bp), which is large enough for informatics purposes, as well as availability of sequence data in databases. Furthermore, Illumina sequencing technology is widely used in taxonomic studies of the microbiome, for instance the Human MIcrobiome Project (Human Microbiome Project Consortium, 2012a. A framework for human microbiome research. Nature 486, 215–221). Illumina sequencing uses sequencing by synthesis following 317 amplification of the input DNA (gene) (Di Bella JM, Bao Y, Gloor GB, Burton JP, Reid G. 2013.High throughput sequencing methods and analysis for microbiome research. J Microbial Methods, 93:401-444; Jason et al., 2015).

Second, the participants in this thesis were selected from three sites (Edmonton, Winnipeg and Vancouver) of the CHILD longitudinal cohort study across Canada and considered to be representative of Canadian general population. In contrast to a series of cross-

sectional studies, prospective longitudinal cohort study design collected the information from the same people over time which allows us to measure the changes in the outcome variable over the time. Furthermore, it allows us to associate the changes in one variable to changes in another variable. Moreover, there is less recall bias and more data accuracy which allows us to formulate temporal relationships as well as to hypothesize casual relationships. Besides, data on mode of delivery, hospital admission, and duration of hospital stay and intra-partum antibiotics prophylaxis antibiotics exposure status in first 3 months were retrieved from birth chart reviews or maternal report at 3 month post-partum or both. What is more, most of the questionnaire on household cleaning products usage have been used in Seattle Healthy Homes study, and there was an internal validity test that research assistant looked for the products that the mother reported in questionnaire during home visit. Additionally, the large sample size permitted us to conduct a stratified analysis to investigate the effect of exposure to hospital environment independent of delivery mode.

Third, we employed multivariate logistic regression models to screen the data for confounders, covariates and explored whether the observed associations were attributable to gut microbiota dysbiosis in early life. The unadjusted crude odds ratio was obtained for each covariate. The final models for research question one (early life exposure to hospital microbial environment) were adjusted for delivery mode, infant diet (breastfeeding status), direct and indirect antibiotic exposure and hospital readmission in first 3 months. The final models for research question two (household cleaning products exposure) were controlled for hospital admission covariate in addition to the variables adjusted for research question one. The rationale

for adjusting these covariates was that they have an impact on gut microbiota composition and diversity. In addition, varaibles which were detected as significant from chi-squared test (pets, smoke, maternal allergy history) were included in the respective models of household cleaning products. Despite adjusting for those covariates in logistic regression models, the associations between hospital microbial environment exposure and gut microbiota dysbiosis, and household cleaning products exposure and gut microbita changes, remained.

Lastly, infant hospitalization history (exposure estimate) and gut microbiota (outcome estimate) were objectively measured which provides less measurement error and more validity of the study.

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4.3 Limitations of the Study

On the contrary, this study has a number of limitations. Firstly, exposure variables (household cleaning products usages) and some important confounding variables, e.g. smoking exposure, breastfeeding status and infant antibiotic exposure were measured by self-administered questionnaire. This limits our ability to use objective measurement for those variables of interest. The study on impact of household cleaning products exposure is cross-sectional, questionnaire-based approach, and recall bias and measurement bias may be a problem. Further studies are needed to objectively assess the postnatal exposure to household cleaning products. Besides, the information on specific products used is needed. In addition, we were not able to differentiate

which cleaning products generate VOCs and which forbids us from performing separate analysis for VOCs vs. Non-VOCs.

Secondly, one potential source of bias in our study is selection bias. In other words, the the recruited study participants were predominantly from urban area. Although 80% of Canadian population lives in urban (Statistics Canada 2011), it may limit the generalizability of our results to the whole Canadian population.

Thirdly, about 60% of infants exposed to hospital environment were exposed to intra-partum antibiotics (IAPs) which may have affected their gut microbiota composition (Azad et al., 2015) as well as their sensitivity to the antibiotics. However, stratified analysis by IAP exposure status as well as the adjustment for IAPs exposure was conducted in the multivariable logistic regression models.

Fourthly, the study on impact of hospital microbial environment exposure was a temporal design; however, it was a cross-sectional design for household cleaning products study. It is unlikely that infant gut microbiota composition altered cleaning products usage. Nonetheless, reverse causation is not impossible. Intact gut microbiota was required for the expression of proinflammatory chemokines which are necessary for influenza clearance (Ichinohe et al., 2010). Gut microbiota dysbiosis (alteration in microbiota composition) can promote intestinal infection (Schubert et al., 2015; Kampmann et al., 2016) and respiratory virus infections such as influenza (Ichinohe et al., 2011) which may have led to the use of household cleaning products.

Finally, the high throughput sequencing is desirable for identifying complete and unbiased sample; however, the technology lacks to identify differences among individual species (Jost et al., 2012) and qPCR was not employed either for speicies identification.

4.4 Clinical relevance

Infant gut microbiota establishment in early life is crucial for the maturation of the immune system and is profoundly influenced by early life exposures. Increased richness and diversity of infant gut microbiota has been associated with vaginal delivery (Azad et al., 2013) and pet ownership (Azad et al., 2013), while breastfeeding has been associated with lower richness and diversity, but greater proliferation of beneficial microbes (Azad et al., 2012). However, there was little evidence showing the effect of exposure to hospital microbial environment, as well as the effect of household cleaning products on infant gut microbiota composition and diversity.

Significant associations between hospital microbial environment exposure and changes in infant gut microbiota composition provide evidence of infant gut colonization with hospital-acquired pathogens within the first 3 months of life. The impact of these compositional changes may affect the development of gut immunity and with possible consequences of allergic disease later in life.

The relationship between household cleaning products exposure and infant gut microbiota dysbiosis reported in this thesis is the first study showing the important role of the indoor environment shaping the nascent gut microbiota. The novel findings in this study will add one more piece of evidence to the adverse effects of household cleaning products on human health. Moreover, the findings from this study can be applied to inform delivery decision-making in favour of vaginal deliveries unless there are maternal or fetal indications for CS, to inform policy to safely minimize length of hospital stay, to reinforce HAI prevention protocols, to target use of specific probiotics to treat and prevent atopic or allergic diseases, and to raise awareness on harmful effects of commercial household cleaning products.

4.5 Implications for future research

The findings reported in this thesis showed the significant effects of exposure to HAIs and household cleaning products on infant gut microbiota dysbiosis; yet, much need to be learnt about the link between gut microbiota dysbiosis and health outcomes (chronic metabolic disease, and atopic or allergic disease). Additionally, studies are required to further assess the mechanism through which HAIs or household cleaning products affecting the gut microbiota dysbiosis, and this information would be very beneficial in clinical practice.

4.6 Conclusions

In this thesis, the associations between exposure to hospital microbial environment and infant gut micorbiota dysbiosis were reported. It was also suggested that there was greater colonization with hospital-acquired pathogens in the gut of infants with extended hospital stay. Moreover, the beneficial gut bacteria were depleted in the infants who were exposed to high level of household disinfectant. Findings from this thesis will provide a population-based evidence of exposure to nosocomial pathogens and household cleaning products, and their impact on infant gut microbiota composition and diversity.

BIBLIOGRAPHY

References for Chapter 1

Aagaard, K., Ma, J., Antony, K. M., Ganu, R., Petrosino, J., & Versalovic, J. (2014). *The placenta harbors a unique microbiome* Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=edswsc&AN=000336668800002&site=eds-live&scope=site

Abrahamsson, T. R., & Sherman, P. M. (2014). Multifaceted effects of human milk oligosaccharides. *The Journal of Infectious Diseases, 209*(3), 323-324. doi:10.1093/infdis/jit559

Adlerberth, Ingegerd,1959, Author, Wold, Agnes E,1955, Author, Göteborgs universitet, Sahlgrenska akademin, Institutionen för biomedicin, avdelningen för infektionssjukdomar, Publisher, & University of Gothenburg, Sahlgrenska Academy, Institute of Biomedicine, Department of,Infectious Medicine. (2009). Establishment of the gut microbiota in western infants. *Acta Paediatrica (Oslo, Norway : 1992),* 229. doi:10.1111/j.1651-2227.2008.01060.x

Adlerberth, I., Strachan, D. P., Matricardi, P. M., Ahrné, S., Orfei, L., Åberg, N. Wold, A. E. (2007). Mechanisms of asthma and allergic inflammation: Gut microbiota and development

of atopic eczema in 3 European birth cohorts. *The Journal of Allergy and Clinical Immunology, 120*, 343-350. doi:10.1016/j.jaci.2007.05.018

Altman, R. G., Morello-Frosch, R., Brody, J. G., Rudel, R., Brown, P., & Averick, M. (2008). *Pollution comes home and gets personal: Women's experience of household chemical exposure* American Sociological Association. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=edsjsr&AN=edsjsr.27638769&site=eds-live&scope=site

Azad, M. B., Konya, T., Maughan, H., Guttman, D. S., Field, C. J., Chari, R. S., Kozyrskyj, A. L. (2013). Gut microbiota of healthy Canadian infants: Profiles by mode of delivery and infant diet at 4 months. *CMAJ: Canadian Medical Association Journal, 185*(5), 385-394 10p. doi:10.1503/cmaj.121189

Bäckhed, F., Roswall, J., Peng, Y., Feng, Q., Jia, H., Kovatcheva-Datchary, P., Wang, J. (2015). Resource: Dynamics and stabilization of the human gut microbiome during the first year of life. *Cell Host & Microbe, 17*, 690-703. doi:10.1016/j.chom.2015.04.004

Barrett, E., Kerr, C., Murphy, K., O'Sullivan, O., Ryan, C. A., Dempsey, E. M., Stanton, C. (2013). *The individual-specific and diverse nature of the preterm infant microbiota* Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.

library.ualberta.ca/login.aspx?direct=true&db=edswsc&AN=000330515000010&site=eds-live&scope=site

Bello, A., Quinn, M. M., Perry, M. J., & Milton, D. K. (2010). Quantitative assessment of airborne exposures generated during common cleaning tasks: A pilot study. *Environmental Health: A Global Access Science Source, 9*, 76-85. doi:10.1186/1476-069X-9-76

Bernstein, J. A., Brandt, D., Rezvani, M., Abbott, C., & Levin, L. (2009). Evaluation of cleaning activities on respiratory symptoms in asthmatic female homemakers. *Annals of Allergy, Asthma & Immunology: Official Publication of the American College of Allergy, Asthma, & Immunology, 102*(1), 41-46. doi:10.1016/S1081-1206(10)60106-8

Bezirtzoglou, E., Tsiotsias, A., & Welling, G. W. (2011). Molecular biology & genetics: Microbiota profile in feces of breast and formula-fed newborns by using fluorescence in situ hybridization (FISH). *Anaerobe, 17*, 478-482. doi:10.1016/j.anaerobe.2011.03.009

Bio-Vert. (2015). Studies, facts and statistics on cleaning and the environment. Retrieved from http://www.bio-vert.com/en/documentation.php

Birnbaum, D. (2003). Antimicrobial resistance: A deadly burden no country can afford to ignore. *Canada Communicable Disease Report = Releve´ Des Maladies Transmissibles Au Canada, 29*(18), 157-164. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.

library.ualberta.ca/login.aspx?direct=true&db=cmedm&AN=14524197&site=eds-live&scope=site

Bizzarro, M. J., & Gallagher, P. G. (2007). Antibiotic-resistant organisms in the neonatal intensive care unit. *Seminars in Perinatology, 31*(1), 26-32 7p. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=rzh&AN=105990536&site=eds-live&scope=site

Boo, N., Ng, S., & Lim, V. K. E. (2005). A case-control study of risk factors associated with rectal colonization of extended-spectrum beta-lactamase producing klebsiella sp. in newborn infants. *Journal of Hospital Infection, 61*, 68-74. doi:10.1016/j.jhin.2005.01.025

Bornehag, C., Author, Sundell, J., A., Hagerhed-Engman, L., Sigsggard, T., A., Janson, S., A., Aberg, N., A., & Karlstads universitet, Fakulteten för samhälls- och livsvetenskaper, Avdelningen för hälsa,och milj. (2005). Dampness at home and its association with airway, nose and skin symptoms among 10 851 preschool children in Sweden: A cross sectional study. *Indoor Air 2005 15 (Suppl 10) 48-55,* Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=edsswe&AN=edsswe.oai.DiVA.org.kau.18004&site=eds-live&scope=site

Canadian Institute for Health Information. (2006). Giving birth in Canada the costs. Retrieved from https://secure-cihi-ca.login.ezproxy.library.ualberta.ca/free_products/Costs_Report_06_Eng.pdf

Canadian Union of Public Employee. (2014). Healthcare associated infections: A backgrounder. Retrieved from http://cupe.ca/sites/cupe/files/healthcare-associated-infections-cupe-backgrounder.pdf

Casas, L., Zock, J. P., Carsin, A. E., Fernandez-Somoano, A., Esplugues, A., Santa-Marina, L., Sunyer, J. (2013). The use of household cleaning products during pregnancy and lower respiratory tract infections and wheezing during early life. *International Journal of Public Health, 58*(5), 757-764 8p. doi:10.1007/s00038-012-0417-2

Colborn, T., Dumanoski, D., & Myers, J. P. (1997). *Our stolen future : Are we threatening our fertility, intelligence, and survival? : A scientific detective story : With a new epilogue by the authors* New York : Penguin Group, c1997. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=cat03710a&AN=alb.2209089&site=eds-live&scope=site

Corbella, X., Pujol, M., Ayats, J., Sendra, M., Ardanuy, C., Domínguez, M. A., Gudiol, F. (1996). *Relevance of digestive tract colonization in the epidemiology of nosocomial infections due to multiresistant acinetobacter baumannii* University of Chicago Press.

Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=edsjsr&AN=edsjsr.4459610&site=eds-live&scope=site

Dave, M., Higgins, P. D., Middha, S., & Rioux, K. P. (2012). The human gut microbiome: Current knowledge, challenges, and future directions. *Translational Research: The Journal of Laboratory & Clinical Medicine, 160*(4), 246-257 12p. doi:10.1016/j.trsl.2012.05.003

DiGiulio, D. B. (2012). Diversity of microbes in amniotic fluid. *Seminars in Fetal and Neonatal Medicine, 17*, 2-11. doi:10.1016/j.siny.2011.10.001

Dimitroulopoulou, C., Lucica, E., Johnson, A., Ashmore, M. R., Sakellaris, I., Stranger, M., & Goelen, E. (2015). EPHECT I: European household survey on domestic use of consumer products and development of worst-case scenarios for daily use. *Science of the Total Environment, 536*, 880-889. doi:10.1016/j.scitotenv.2015.05.036

Dominguez-Bello, M., Costello, E. K., Contreras, M., Magris, M., Hidalgo, G., Fierer, N., Gordon, J. I. (2010). *Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns* National Academy of Sciences. doi:10.1073/pnas.1002601107

Donskey, C. J. (2004). *The role of the intestinal tract as a reservoir and source for transmission of nosocomial pathogens* University of Chicago Press. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=edsjsr&AN=edsjsr.4536578&site=eds-live&scope=site

Dumas, O., Donnay, C., Heederik, D. J. J., Héry, M., Choudat, D., Kauffmann, F., & Le Moual, N. (2012). *Occupational exposure to cleaning products and asthma in hospital workers* BMJ Publishing Group. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=edsjsr&AN=edsjsr.23567842&site=eds-live&scope=site

Eiref, S. D., Leitman, I. M., & Riley, W. (2012). Hand sanitizer dispensers and associated hospital-acquired infections: Friend or fomite? *Surgical Infections, 13*(3), 137-140 4p. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=rzh&AN=108126555&site=eds-live&scope=site

Envrionmental Working Group. (2009b). Pollution in people: Cord blood contaminants in Minority Newborns. washington, DC. Retrieved from http://www.ewg.org/files/2009-Minority-Cord-Blood-Report.pdf

Fadeyi, M. O., Weschler, C. J., & Tham, K. W. (2009). *The impact of recirculation, ventilation and filters on secondary organic aerosols generated by indoor chemistry* Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=edswsc&AN=000267964300012&site=eds-live&scope=site

Fallani, M., Young, D., Scott, J., Norin, E., Amarri, S., Adam, R., Doré, J. (2010). Intestinal microbiota of 6-week-old infants across Europe: Geographic influence beyond delivery mode, breast-feeding, and antibiotics. *Journal of Pediatric Gastroenterology and Nutrition, 51*(1), 77-84. doi:10.1097/MPG.0b013e3181d1b11e

Farrow, A., Taylor, H., Northstone, K., & Golding, J. (2003). Symptoms of mothers and infants related to total volatile organic compounds in household products. *Archives of Environmental Health, 58*(10), 633-641. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=eih&AN=15002729&site=eds-live&scope=site

Fouhy, F., Guinane, C. M., Hussey, S., Wall, R., Ryan, C. A., Dempsey, E. M., Cotter, P. D. (2012). *High-throughput sequencing reveals the incomplete, short-term recovery of infant gut microbiota following parenteral antibiotic treatment with ampicillin and gentamicin* Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=edswsc&AN=000310055800049&site=eds-live&scope=site

Funkhouser, L. J., & Bordenstein, S. R. (2013). *Mom knows best: The universality of maternal microbial transmission* Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=edswsc&AN=000323771900011&site=eds-live&scope=site

Gaynes, R., & Edwards, J. R. (2005). Overview of nosocomial infections caused by gram-negative bacilli. *Clinical Infectious Diseases, 41*(6), 848-854. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=a9h&AN=17989235&site=eds-live&scope=site

Gravel, D., Taylor, G., Ofner, M., Johnston, L., Loeb, M., Roth, V. R., Matlow, A. (2007). Point prevalence survey for healthcare-associated infections within canadian adult acute-care hospitals. *Journal of Hospital Infection, 66*, 243-248. doi:10.1016/j.jhin.2007.04.008

Gravel, D., Matlow, A., Ofner-Agostini, M., Loeb, M., Johnston, L., Bryce, E., Taylor, G. (2007). A point prevalence survey of health care-associated infections in pediatric populations in major canadian acute care hospitals. *American Journal of Infection Control, 35*(3), 157-162. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=cmedm&AN=17433938&site=eds-live&scope=site

Harmsen, H. J. M., Wildeboer-Veloo, A., Raangs, G. C., Wagendorp, A. A., Klijn, N., Bindels, J. G., & Welling, G. W. (2000). Analysis of intestinal flora development in breast-fed and formula-fed infants by using molecular identification and detection methods. *Journal of Pediatric Gastroenterology and Nutrition,* (1) Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=edsagr&AN=edsagr.US201302945115&site=eds-live&scope=site

Hayden, M. K., Blom, D. W., Lyle, E. A., Moore, C. G., & Weinstein, R. A. (2008). *Risk of hand or glove contamination after contact with patients colonized with vancomycin-resistant*

enterococcus or the colonized patients' environment University of Chicago Press. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=edsjsr&AN=edsjsr.30144916&site=eds-live&scope=site

Health Canada. (2015). Indoor air quality. Retrieved from http://www.hc-sc.gc.ca.login.ezproxy.library.ualberta.ca/ewh-semt/air/in/index-eng.php

HEAVNER, D. L., MORGAN, W. T., & OGDEN, M. W. (1995). *Determination of volatile organic-compounds and ets apportionment in 49 homes* Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=edswsc&AN=A1995QB47500001&site=eds-live&scope=site

Henderson, J., Sherriff, A., Farrow, A., & Ayres, J. G. (2008). *Household chemicals, persistent wheezing and lung function: Effect modification by atopy?* Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=edswsc&AN=000253876000011&site=eds-live&scope=site

Hertz-Picciotto, I., Cassady, D., Lee, K., Bennett, D. H., Ritz, B., & Vogt, R. (2010). Study of use of products and exposure-related behaviors (SUPERB): Study design, methods, and

demographic characteristics of cohorts. *Environmental Health: A Global Access Science Source, 9*, 54-54. doi:10.1186/1476-069X-9-54

Huerta-García, G. C., Miranda-Novales, G., Díaz-Ramos, R., Vázquez-Rosales, G., & Solórzano-Santos, F. (2015). Intestinal colonization by extended-spectrum beta-lactamase-producing enterobacteriaceae in infants. *Revista De Investigacio´n Cli´nica; Organo Del Hospital De Enfermedades De La Nutricio´n, 67*(5), 313-317. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=cmedm&AN=26696335&site=eds-live&scope=site

Hughes, K. A., Cornwall, J., Theis, J., & Brooks, H. J. L. (2013). Bacterial contamination of unused, disposable non-sterile gloves on a hospital orthopaedic ward. *Australasian Medical Journal, 6*(6), 331-338. doi:10.4066/AMJ.2013.1675

Ichinohe, T., Pang, I. K., & Iwasaki, A. (2010). Influenza virus activates inflammasomes via its intracellular M2 ion channel. *Nature Immunology, 11*(5), 404-410. doi:10.1038/ni.1861

Infections in hospital - reduce the risk. (2015). Retrieved from https://www.betterhealth.vic.gov.au/health/conditionsandtreatments/infections-in-hospital-reduce-the-risk?viewAsPdf=true

Isolation of pathogenic bacteria from hospital staff apparel in nigeria (2006). Medical Association of Malawi, 2006-05-08. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=edsoai&AN=edsoai.738389483&site=eds-live&scope=site; http://www.ajol.info/index.php/mmj/article/view/10896/14484; http://www.ajol.info/index.php/mmj/article/view/10896

Jakobsson, H. E., Abrahamsson, T. R., Jenmalm, M. C., Harris, K., Quince, C., Jernberg, C., Andersson, A. F. (2014). Decreased gut microbiota diversity, delayed bacteroidetes colonisation and reduced Th1 responses in infants delivered by caesarean section. *Gut, 63*(4), 559-566. doi:10.1136/gutjnl-2012-303249

Jandhyala, S. M., Talukdar, R., Subramanyam, C., Vuyyuru, H., Sasikala, M., & Nageshwar Reddy, D. (2015). Role of the normal gut microbiota. *World Journal of Gastroenterology, 21*(29), 8787-8803. doi:10.3748/wjg.v21.i29.8787

Jernberg, C., Löfmark, S., Edlund, C., & Jansson, J. K. (2007). Long-term ecological impacts of antibiotic administration on the human intestinal microbiota. *ISME Journal: Multidisciplinary Journal of Microbial Ecology, 1*(1), 56-66. doi:10.1038/ismej.2007.3

Jiménez, E., Marín, M. L., Martín, R., Odriozola, J. M., Olivares, M., Xaus, J., Rodríguez, J. M. (2008). Is meconium from healthy newborns actually sterile? *Research in Microbiology, 159*, 187-193. doi:10.1016/j.resmic.2007.12.007

Johansson, M. A., Sjögren, Y. M., Persson, J., Nilsson, C., & Sverremark-Ekström, E. (2011). Early colonization with a group of lactobacilli decreases the risk for allergy at five years of age despite allergic heredity. *Plos One, 6*(8), 1-8. doi:10.1371/journal.pone.0023031

Johnson, C. L., & Versalovic, J. (2012). *The human microbiome and its potential importance to pediatrics* Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=edswsc&AN=000304709600043&site=eds-live&scope=site

Jones, R. N. (2001). Resistance patterns among nosocomial pathogens: Trends over the past few years. *Chest, 119*(2), 397S-404S. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=cmedm&AN=11171776&site=eds-live&scope=site

Kampmann, C., Author, Uppsala universitet, Medicinska och farmaceutiska vetenskapsområdet, Medicinska fakulteten, Institutionen för medicinska vetenskaper, Klinisk mikrobiologi,och infektionsmedicin, & Uppsala universitet, Medicinska och farmaceutiska vetenskapsområdet, Medicinska och farmaceutiska vetenskapsområdet, centrumbildningar mm, Centrum för,klinisk forskning. (2016). Composition of human faecal microbiota in resistance to campylobacter infection. *Clinical Microbiology and Infection,* Retrieved from

http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=edsswe&AN=edsswe.oai.DiVA.org.uu.276830&site=eds-live&scope=site

Koenig, J. E., Spor, A., Scalfone, N., Fricker, A. D., Stombaugh, J., Knight, R., . . . Klaenhammer, T. R. (2011). *Succession of microbial consortia in the developing infant gut microbiome* National Academy of Sciences. doi:10.1073/pnas.1000081107

Kolly, C. A., Arbogast, J. W., & Macinga, D. R. (2006). Poster abstract: Bacterial shedding and desquamation from the hands of healthcare workers correlates with skin condition. *AJIC: American Journal of Infection Control, 34*, E85-E86. doi:10.1016/j.ajic.2006.05.156

Kothari, C., Gaind, R., Chandreshwor Singh, L., Sinha, A., Kumari, V., Arya, S., Deb, M. (2013). Community acquisition of ß-lactamase producing enterobacteriaceae in neonatal gut. *BMC Microbiology, 13*(1), 1-6. doi:10.1186/1471-2180-13-136

Kramer, A., Schwebke, I., & Kampf, G. (2006). How long do nosocomial pathogens persist on inanimate surfaces? A systematic review. *BMC Infectious Diseases, 6*(1), 130-8. doi:10.1186/1471-2334-6-130

Krimsky, S. (2000). *Hormonal chaos : The scientific and social origins of the environmental endocrine hypothesis* Baltimore, MD : Johns Hopkins University Press, c2000. Retrieved from

http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=cat03710a&AN=alb.2399588&site=eds-live&scope=site

Lagier, J., Hugon, P., Khelaifia, S., Fournier, P., La Scola, B., & Raoult, D. (2015). The rebirth of culture in microbiology through the example of culturomics to study human gut microbiota. *Clinical Microbiology Reviews, 28*(1), 237-264. doi:10.1128/CMR.00014-14

Levy, S. B. (2001). Antibacterial household products: Cause for concern. *Emerging Infectious Diseases, 7*(3), 512. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=eih&AN=5009956&site=eds-live&scope=site

Ley, R. E., Peterson, D. A., & Gordon, J. I. (2006). Review: Ecological and evolutionary forces shaping microbial diversity in the human intestine. *Cell, 124*, 837-848. doi:10.1016/j.cell.2006.02.017

Liu, L., Li, Y., Li, S., Hu, N., He, Y., Pong, R., Law, M. (2012). Comparison of next-generation sequencing systems. *Journal of Biomedicine & Biotechnology, 2012*, 1-11 11p. doi:2012/251364

Lucet, J., Decre, D., Fichelle, A., Joly-Guillou, M., Pernet, M., Deblangy, C., Regnier, B. (1999). Control of a prolonged outbreak of extended-spectrum beta-lactamase-producing enterobacteriaceae in a university hospital. *Clinical Infectious Diseases, 29*(6), 1411. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=eih&AN=5144140&site=eds-live&scope=site

Mäkelä, R., Kauppi, P., Suuronen, K., Tuppurainen, M., & Hannu, T. (2011). Occupational asthma in professional cleaning work: A clinical study. *Occupational Medicine, 61*(2), 121-126. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=eih&AN=58769111&site=eds-live&scope=site

Maroni, M., Seifert, B., & Lindvall, T. (1995). *Indoor air quality : A comprehensive reference book* Amsterdam ; New York : Elsevier Science, 1995. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=cat03710a&AN=alb.1739664&site=eds-live&scope=site

Marques, T. M., Wall, R., Ross, R. P., Fitzgerald, G. F., Ryan, C. A., & Stanton, C. (2010). Programming infant gut microbiota: Influence of dietary and environmental factors. *Current Opinion in Biotechnology, 21*, 149-156. doi:10.1016/j.copbio.2010.03.020

Matamoros, S., Gras-Leguen, C., Le Vacon, F., Potel, G., & Cochetiere, d. L. (2013). Review: Development of intestinal microbiota in infants and its impact on health. *Trends in Microbiology, 21*, 167-173. doi:10.1016/j.tim.2012.12.001

Maternity care [microform] : Appropriate follow-up services critical with short hospital stays : Report to the honorable ron wyden, U.S. senate / united states general accounting office (1996). Washington, D.C. : The Office ; Gaithersburg, MD] (P.O. Box 6015, Gaithersburg 20884-6015) : The Office distributor, 1996]. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=edsgpr&AN=gpr000473135&site=eds-live&scope=site; http://catalog.gpo.gov.login.ezproxy.library.ualberta.ca/fdlpdir/locate.jsp?ItemNumber=0546-D&SYS=000473135; http://purl.access.gpo.gov.login.ezproxy.library.ualberta.ca/GPO/LPS12181

Moore, G., Dunnill, C. W., & Wilson, A. P. (2013). The effect of glove material upon the transfer of methicillin-resistant staphylococcus aureus to and from a gloved hand. *AJIC: American Journal of Infection Control,* (1), 19. Retrieved from

http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=edsgao&AN=edsgcl.314026697&site=eds-live&scope=site

Nordberg, V., Quizhpe Peralta, A., Galindo, T., Turlej-Rogacka, A., Iversen, A., Giske, C. G., & Navér, L. (2013). High proportion of intestinal colonization with successful epidemic clones of ESBL-producing enterobacteriaceae in a neonatal intensive care unit in ecuador. *Plos One, 8*(10), 1-7. doi:10.1371/journal.pone.0076597

Olson, B., Weinstein, R. A., Nathan, C., Chamberlin, W., & Kabins, S. A. (1984). Epidemiology of endemic pseudomonas aeruginosa: Why infection control efforts have failed. *Journal of Infectious Diseases, 150*(6), 808. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=edb&AN=79846872&site=eds-live&scope=site

Ouimette, M. Y. (2011). *Cleaning house: Considerations of ecological health and sustainability in the selection of household cleaning products* Boston College, 2011. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=edsoai&AN=edsoai.844619314&site=eds-live&scope=site; http://hdl.handle.net.login.ezproxy.library.ualberta.ca/2345/3054

Palmer, C., Bik, E. M., DiGiulio, D. B., Reiman, D. A., & Brown, P. O. (2007). Development of the human infant intestinal microbiota. *PLoS Biology,* (7), 1556. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=edsgao&AN=edsgcl.166988647&site=eds-live&scope=site

Patient Safety Network. (2015). Health care-associated infections. Retrieved from https://psnet-ahrq-gov.login.ezproxy.library.ualberta.ca/primers/primer/7/health-care-associated-infections

Pena, C., Pujol, M., Ardanuy, C., Ricart, A., Pallares, R., Linares, J., Gudiol, F. (1998). *Epidemiology and successful control of a large outbreak due to klebsiella pneumoniae producing extended-spectrum beta-lactamases* Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=edswsc&AN=000071301100008&site=eds-live&scope=site

Penders, J., Thijs, C., Vink, C., Stelma, F. F., Snijders, B., Kummeling, I., Stobberingh, E. E. (2006). Factors influencing the composition of the intestinal microbiota in early infancy. *Pediatrics,* (2), 511. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.

library.ualberta.ca/login.aspx?direct=true&db=edsgao&AN=edsgcl.156549563&site=eds-live&scope=site

Peterson, D. A., Frank, D. N., Pace, N. R., & Gordon, J. I. (2008). Review: Metagenomic approaches for defining the pathogenesis of inflammatory bowel diseases. *Cell Host & Microbe, 3*, 417-427. doi:10.1016/j.chom.2008.05.001

Pittet, D., Dharan, S., Touveneau, S., Sauvan, V., & Perneger, T. V. (1999). Bacterial contamination of the hands of hospital staff during routine patient care. *Archives of Internal Medicine, 159*(8), 821-887 8p. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=rzh&AN=107030068&site=eds-live&scope=site

Public Health Agency of Canada. (2008). Canadian perinatal health report. Retrieved from http://www.violapolomeno.com/cphr-rspc08-eng.pdf

Public Health Agency of Canada. (2013). Report on the state of public health in canada. Retrieved from http://www.phac-aspc.gc.ca.login.ezproxy.library.ualberta.ca/cphorsphc-respcacsp/2013/assets/pdf/2013-eng.pdf

Public Health Agency of Canada (PHAC). (2010). Essential resources for effective infection prevention and control programs: A matter of patient safety: A discussion Paper2010.

Retrieved from http://www.phac-aspc.gc.ca.login.ezproxy.library.ualberta.ca/nois-sinp/guide/ps-sp/pdf/ps-sp-eng.pdf

Public Health Agency of Canada (PHAC). (2010). Essential resources for effective infection prevention and control programs: A matter of patient safety: A discussion Paper2010. Retrieved from http://www.phac-aspc.gc.ca.login.ezproxy.library.ualberta.ca/nois-sinp/guide/ps-sp/index-eng.php

Public Health Agency of Canada (PHAC). (2014). **Fact sheet - *clostridium difficile (C. difficile*)**. Retrieved from http://www.phac-aspc.gc.ca.login.ezproxy.library.ualberta.ca/id-mi/cdiff-eng.php

Qin, J., Li, R., Raes, J., Arumugam, M., Burgdorf, K. S., Manichanh, C., Xie, Y. (2010). A human gut microbial gene catalogue established by metagenomic sequencing. *Nature, 464*(7285), 59-65. doi:10.1038/nature08821

Quail, M. A., Smith, M., Coupland, P., Otto, T. D., Harris, S. R., Connor, T. R., Gu, Y. (2012). A tale of three next generation sequencing platforms: Comparison of ion torrent, pacific biosciences and illumina MiSeq sequencers. *BMC Genomics, 13*(1), 341-153. doi:10.1186/1471-2164-13-341

Rocha, L. A., Ferreira de Almeida, E. B., & Gontijo Filho, P. P. (2009). Changes in hands microbiota associated with skin damage because of hand hygiene procedures on the health

care workers. *American Journal of Infection Control, 37*(2), 155-159. doi:10.1016/j.ajic.2008.04.251

Rock, C., Thom, K. A., Masnick, M., Johnson, J. K., Harris, A. D., & Morgan, D. J. (2014). *Frequency of klebsiella pneumoniae carbapenemase (KPC)–Producing and non-KPC-producing klebsiella species contamination of healthcare workers and the environment* University of Chicago Press. doi:10.1086/675598

Rosenberg, S. (2000). Consumer and market use of antibacterials at home. *The Pediatric Infectious Disease Journal, 19*(10), S114-S116. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=cmedm&AN=11052400&site=eds-live&scope=site

Schimpff, S. C., Young, V. M., Greene, W. H., Vermeulen, G. D., Moody, M. R., & Wiernik, P. H. (1972). Origin of infection in acute nonlymphocytic leukemia. significance of hospital acquisition of potential pathogens. *Annals of Internal Medicine, 77*(5), 707-714. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=cmedm&AN=4628214&site=eds-live&scope=site

Schubert, A. M., Sinani, H., & Schloss, P. D. (2015). Antibiotic-induced alterations of the murine gut microbiota and subsequent effects on colonization resistance against clostridium difficile. *Mbio, 6*(4), e00974-e00974. doi:10.1128/mBio.00974-15

Sherriff, A., Farrow, A., Golding, J., & Henderson, J. (2005). *Frequent use of chemical household products is associated with persistent wheezing in pre-school age children* Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=edswsc&AN=000225960100012&site=eds-live&scope=site

Snyder, G. M., Thom, K. A., Furuno, J. P., Perencevich, E. N., Roghmann, M., Strauss, S. M., . . . Harris, A. D. (2008). *Detection of methicillin-resistant staphylococcus aureus and vancomycin-resistant enterococci on the gowns and gloves of healthcare workers* The University of Chicago Press. doi:10.1086/588701

Stark, P. L., Lee, A., & Parsonage, B. D. (1982). Colonization of the large bowel by clostridium difficile in healthy infants: Quantitative study. *Infection and Immunity, 35*(3), 895-899. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=cmedm&AN=7068220&site=eds-live&scope=site

Stiefel, U., Cadnum, J. L., Eckstein, B. C., Guerrero, D. M., Tima, M. A., & Donskey, C. J. (2011). *Contamination of hands with methicillin-resistant staphylococcus aureus after contact with environmental surfaces and after contact with the skin of colonized patients* University of Chicago Press. doi:10.1086/657944

Strachan, D. P. (1989). *Hay fever, hygiene, and household size* British Medical Association. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=edsjsr&AN=edsjsr.29706049&site=eds-live&scope=site

Tamara, P., Giada de, P., Jorge R., M., Marta, O., Ascensión, M., María Dolores, A., Esther, N. (2013). Influence of early environmental factors on lymphocyte subsets and gut microbiota in infants at risk of celiac disease: The PROFICEL study / influencia de factores ambientales tempranos sobre las subpoblaciones de linfocitos y la microbiota intestinal de niños con riesgo de desarrollar enfermedad celíaca: El estudio PROFICEL. *Nutrición Hospitalaria,* (2), 464. doi:10.3305/nh.2013.28.2.6310

Tancrède, C. H., & Andremont, A. O. (1985). *Bacterial translocation and gram-negative bacteremia in patients with hematological malignancies* University of Chicago Press. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.

library.ualberta.ca/login.aspx?direct=true&db=edsjsr&AN=edsjsr.30104644&site=eds-live&scope=site

Tilg, H., & Kaser, A. (2011). Gut microbiome, obesity, and metabolic dysfunction. *Journal of Clinical Investigation,* (6), 2126. doi:10.1172/JCI58109

Tomas, M. E., Cadnum, J. L., Mana, T. S. C., Jencson, A. L., Koganti, S., Alhmidi, H., . . . Donskey, C. J. (2016). Utility of a novel reflective marker visualized by flash photography for assessment of personnel contamination during removal of personal protective equipment. *Infection Control and Hospital Epidemiology,* , 1-3. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=cmedm&AN=26976219&site=eds-live&scope=site

United States Environmental Protection Agency and US Department of Health and Human Services 1. (1991). Building air quality: A guide for building owners and facility managers. Retrieved from http://www.cdc.gov.login.ezproxy.library.ualberta.ca/niosh/pdfs/iaq.pdf

Valiquette, L., Chakra, C. N. A., & Laupland, K. B. (2014). Financial impact of health care-associated infections: When money talks. *The Canadian Journal of Infectious Diseases & Medical Microbiology = Journal Canadien Des Maladies Infectieuses Et De La Microbiologie Me´dicale / AMMI Canada, 25*(2), 71-74. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.

library.ualberta.ca/login.aspx?direct=true&db=cmedm&AN=24855473&site=eds-live&scope=site

van Best, N., Hornef, M. W., Savelkoul, P. H. M., & Penders, J. (2015). On the origin of species: Factors shaping the establishment of infant's gut microbiota. *Birth Defects Research Part C: Embryo Today: Reviews,* (4), 240. doi:10.1002/bdrc.21113

Vizcaya, D., Mirabelli, M. C., Antó, J., Orriols, R., Burgos, F., Arjona, L., & Zock, J. (2011). *A workforce-based study of occupational exposures and asthma symptoms in cleaning workers* BMJ Publishing Group. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=edsjsr&AN=edsjsr.41408468&site=eds-live&scope=site

Vonier, P. M., Crain, D. A., McLachlan, J. A., Guillette, , Louis J., & Arnold, S. F. (1996). *Interaction of environmental chemicals with the estrogen and progesterone receptors from the oviduct of the american alligator* National Institute of Environmental Health Sciences. National Institutes of Health. Department of Health, Education and Welfare. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=edsjsr&AN=edsjsr.10.2307.3432968&site=eds-live&scope=site

Weinstein, R. A. (1991). Epidemiology and control of nosocomial infections in adult intensive care units. *The American Journal of Medicine, 91*(3), 179S-184S. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=cmedm&AN=1928162&site=eds-live&scope=site

Wiener, J., Quinn, J. P., Bradford, P. A., Goering, R. V., Nathan, C., Bush, K., & Weinstein, R. A. (1999). Multiple antibiotic-resistant klebsiella and escherichia coli in nursing homes. *Jama, 281*(6), 517-523. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=cmedm&AN=10022107&site=eds-live&scope=site

Wingard, J. R., Dick, J., Charache, P., & Saral, R. (1986). Antibiotic-resistant bacteria in surveillance stool cultures of patients with prolonged neutropenia. *Antimicrobial Agents and Chemotherapy, 30*(3), 435-439. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=cmedm&AN=3640591&site=eds-live&scope=site

Wolkoff, P., Schneider, T., Kildesø, J., Degerth, R., Jaroszewski, M., & Schunk, H. (1998). Risk in cleaning: Chemical and physical exposure. *The Science of the Total Environment, 215*(1-

2), 135-156. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=cmedm&AN=9599458&site=eds-live&scope=site

World Health Organization. (2011). *Report on the burden of endemic health care-associated infection worldwide.*. Retrieved from http://apps.who.int.login.ezproxy.library.ualberta.ca/iris/bitstream/10665/80135/1/9789241501507_eng.pdf

Yoshioka, H., Iseki, K., & Fujita, K. (1983). Development and differences of intestinal flora in the neonatal period in breast-fed and bottle-fed infants. *Pediatrics, 72*(3), 317. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=a9h&AN=4752117&site=eds-live&scope=site

Zivkovic, A. M., German, J. B., Lebrilla, C. B., Mills, D. A., & Klaenhammer, T. R. (2011). *Human milk glycobiome and its impact on the infant gastrointestinal microbiota* National Academy of Sciences. doi:10.1073/pnas.1000083107

Zock, J. P., Plana, E., Jarvis, D., Antó, J. M., Kromhout, H., Kennedy, S. M., Kogevinas, M. (2007). The use of household cleaning sprays and adult asthma: An international

longitudinal study. *American Journal of Respiratory & Critical Care Medicine, 176*(8), 735-741 7p. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=rzh&AN=105833261&site=eds-live&scope=site

Zock, J., Author, Plana, E., Author, Antó, J. M., Author, Benke, G., Author, Blanc, P. D., Author, Carosso, A., Author, . . . Uppsala universitet, Medicinska och farmaceutiska vetenskapsområdet, Medicinska fakulteten, Institutionen för medicinska vetenskaper, Arbets-,och milj. (2009). Domestic use of hypochlorite bleach, atopic sensitization, and respiratory symptoms in adults. *Journal of Allergy and Clinical Immunology,* 731. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com.login.ezproxy.library.ualberta.ca/login.aspx?direct=true&db=edsswe&AN=edsswe.oai.DiVA.org.uu.122950&site=eds-live&scope=site

Zoetendal, E. G., Akkermans, A. D. L., Akkermans-van Vliet, W. M., de Visser, ‚J.Arjan G., & de Vos, W. M. (2001). The host genotype affects the bacterial community in the human gastronintestinal tract. *Microbial Ecology in Health & Disease, 13*(3), 129-134. doi:10.1080/089106001750462669

References for Chapter 2

Abrahamsson, T., Author, Jakobsson, H. E., A., Andersson, A. F., A., Björksten, B., Author, Engstrand, L., A., Jenmalm, M., Author, . . . Linköpings universitet, Institutionen för klinisk och,experimentell medicin. (2014). Low gut microbiota diversity in early infancy precedes asthma at school age. *Clinical and Experimental Allergy,* , 842. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edsswe&AN=edsswe.oai.DiVA.org.liu.109137&site=eds-live&scope=site

ACRED, P., BROWN, D. M., TURNER, D. H., & WILSON, M. J. (1962). Pharmacology and chemotherapy of ampicillin--a new broad-spectrum penicillin. *British Journal of Pharmacology and Chemotherapy, 18*, 356-369. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=13859205&site=eds-live&scope=site

Adam, H. J., Baxter, M. R., Davidson, R. J., Rubinstein, E., Fanella, S., Karlowsky, J. A., Zhanel, G. G. (2013). Comparison of pathogens and their antimicrobial resistance patterns in paediatric, adult and elderly patients in canadian hospitals. *The Journal of Antimicrobial Chemotherapy, 68 Suppl 1*, i31-i37. doi:10.1093/jac/dkt024

Adlerberth, I., & Wold, A. E. (2009). Establishment of the gut microbiota in western infants. *Acta Paediatrica, 98*(2), 229-238 10p. doi:10.1111/j.1651-2227.2008.01060.x

Allen, K. D., & Green, H. T. (1987). Hospital outbreak of multi-resistant acinetobacter anitratus: An airborne mode of spread? *The Journal of Hospital Infection, 9*(2), 110-119. Retrieved fromhttp://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=2883217&site=eds-live&scope=site

Azad, M. B., Konya, T., Persaud, R. R., Guttman, D. S., Chari, R. S., Field, C. J., Kozyrskyj, A. L. (2015). Impact of maternal intrapartum antibiotics, method of birth and breastfeeding on gut microbiota during the first year of life: A prospective cohort study. *BJOG: An International Journal of Obstetrics and Gynaecology,* doi:10.1111/1471-0528.13601

Bhalla, A., Aron, D. C., & Donskey, C. J. (2007). Staphylococcus aureus intestinal colonization is associated with increased frequency of S. aureus on skin of hospitalized patients. *BMC Infectious Diseases, 7*(1), 1-7. doi:10.1186/1471-2334-7-105

BLACK, J., CALESNICK, B., WILLIAMS, D., & WEINSTEIN, M. J. (1963). Pharmacology of gentamicin, a new broad-spectrum antibiotic. *Antimicrobial Agents and Chemotherapy, 161*, 138-147. Retrieved fromhttp://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=14274880&site=eds-live&scope=site

Brogard, J. M., Dorner, M., Pinget, M., Adloff, M., & Lavillaureix, J. (1975). *The biliary excretion of cefazolin* University of Chicago Press. Retrieved

from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edsjsr&AN=edsjsr.30061742&site=eds-live&scope=site

Brown, E. M., Sadarangani, M., & Finlay, B. B. (2013). The role of the immune system in governing host-microbe interactions in the intestine. *Nature Immunology,* (7), 660. Retrieved fromhttp://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edsgao&AN=edsgcl.336175871&site=eds-live&scope=site

Buxton, A. E., Anderson, R. L., Werdegar, D., & Atlas, E. (1978). Nosocomial respiratory tract infection and colonization with acinetobacter calcoaceticus. epidemiologic characteristics. *The American Journal of Medicine, 65*(3), 507-513. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=362918&site=eds-live&scope=site

Cavalcante, R. D., Canet, P., & Fortaleza, C. (2014). *Risk factors for the acquisition of imipenem-resistant acinetobacter baumannii in a burn unit: An appraisal of the effect of colonization pressure* Retrieved fromhttp://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edswsc&AN=000340185700009&site=eds-live&scope=site

Chang, P. Y., Hsueh, P. R., Wu, P. S., Chan, P. C., Yang, T. T., Lu, C. Y., . . . Huang, L. M. (2007). Multidrug-resistant acinetobacter baumannii isolates in pediatric patients of a

university hospital in taiwan. *Journal of Microbiology, Immunology, and Infection = Wei Mian Yu Gan Ran Za Zhi, 40*(5), 406-410. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=17932600&site=eds-live&scope=site

Cho, I., Yamanishi, S., Cox, L., Methé, B.,A., Zavadil, J., Li, K., Blaser, M. J. (2012). Antibiotics in early life alter the murine colonic microbiome and adiposity. *Nature, 488*(7413), 621-626. doi:10.1038/nature11400

Cisneros, J. M., & Rodríguez-Baño, J. (2002). Nosocomial bacteremia due to acinetobacter baumannii: Epidemiology, clinical features and treatment. *Clinical Microbiology & Infection, 8*(11), 687-693. doi:10.1046/j.1469-0691.2002.00487.x

Dominguez-Bello, M., Costello, E. K., Contreras, M., Magris, M., Hidalgo, G., Fierer, N., & Knight, R. (2010). Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. *Proceedings of the National Academy of Sciences of the United States,* (26), 11971. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edsgao&AN=edsgcl.231313568&site=eds-live&scope=site

Donskey, C. J. (2004). *The role of the intestinal tract as a reservoir and source for transmission of nosocomial pathogens* University of Chicago Press. Retrieved

from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edsjsr&AN=edsjsr.4536578&site=eds-live&scope=site

Döring, G., Jansen, S., Noll, H., Grupp, H., Frank, F., Botzenhart, K., Wahn, U. (1996). Distribution and transmission of pseudomonas aeruginosa and burkholderia cepacia in a hospital ward. *Pediatric Pulmonology, 21*(2), 90-100. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=8882212&site=eds-live&scope=site

Döring, G., Ulrich, M., Müller, W., Bitzer, J., Schmidt-Koenig, L., Münst, L., Botzenhart, K. (1991). Generation of pseudomonas aeruginosa aerosols during handwashing from contaminated sink drains, transmission to hands of hospital personnel, and its prevention by use of a new heating device. *Zentralblatt Für Hygiene Und Umweltmedizin = International Journal of Hygiene and Environmental Medicine, 191*(5-6), 494-505. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=1909134&site=eds-live&scope=site

Duncan, s. H., Barcenilla, A., Stewart, C. S., Pryde, S. E., & Flint, H. J. (2002). Acetate utilization and butyryl coenzyme A (CoA): Acetate-CoA transferase in butyrate-producing bacteria from the human large intestine.*Applied and Environmental Microbiology,* (10), 5186. Retrieved

from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edsgao&AN=edsgcl.97187405&site=eds-live&scope=site

Falagas, M. E., & Karveli, E. A. (2007). The changing global epidemiology of acinetobacter baumannii infections: A development with major public health implications. *Clinical Microbiology and Infection: The Official Publication of the European Society of Clinical Microbiology and Infectious Diseases, 13*(2), 117-119. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=17328722&site=eds-live&scope=site

Fierobe, L., Lucet, J., Decré, D., Muller-Serieys, C., Deleuze, A., Joly-Guillou, M., Desmonts, J. (2001). *An outbreak of imipenem-resistant acinetobacter baumannii in critically ill surgical patients* SLACK Incorporated. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edsjsr&AN=edsjsr.30141444&site=eds-live&scope=site

Hentges, D. J., Stein, A. J., Casey, S. W., & Que, J. U. (1985). Protective role of intestinal flora against infection with pseudomonas aeruginosa in mice: Influence of antibiotics on colonization resistance. *Infection and Immunity, 47*(1), 118-122. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=2856912&site=eds-live&scope=site

Infections in hospital - reduce the risk. (2015). Retrieved from https://www.betterhealth.vic.gov.au/health/conditionsandtreatments/infections-in-hospital-reduce-the-risk?viewAsPdf=true

Isolation of pathogenic bacteria from hospital staff apparel in nigeria (2006). Medical Association of Malawi, 2006-05-08. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edsoai&AN=edsoai.738389483&site=eds-live&scope=site; http://www.ajol.info/index.php/mmj/article/view/10896/14484;http://www.ajol.info/index.php/mmj/article/view/10896

Isolation of pathogenic bacteria from hospital staff apparel in nigeria (2006). Medical Association of Malawi, 2006-05-08. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edsoai&AN=edsoai.738389483&site=eds-live&scope=site; http://www.ajol.info/index.php/mmj/article/view/10896/14484;http://www.ajol.info/index.php/mmj/article/view/10896

Jakobsson, H. E., Rodríguez-Piñeiro, A.,M., Schütte, A., Ermund, A., Boysen, P., Bemark, M., Johansson, M. E. V. (2015). The composition of the gut microbiota shapes the colon mucus barrier. *EMBO Reports, 16*(2), 164-177. doi:10.15252/embr.201439263

Johansson, M. A., Sjögren, Y. M., Persson, J., Nilsson, C., & Sverremark-Ekström, E. (2011). Early colonization with a group of lactobacilli decreases the risk for allergy at five years of age despite allergic heredity. *Plos One,6*(8), 1-8. doi:10.1371/journal.pone.0023031

Kamada, N., Seo, S., Chen, G. Y., & Nunez, G. (2013). Role of the gut microbiota in immunity and inflammatory disease. *Nature Reviews Immunology,* (5), 321. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edsgao&AN=edsgcl.330005056&site=eds-live&scope=site

Karachalios, G., & Charalabopoulos, K. (2002). *Biliary excretion of antimicrobial drugs* Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edswsc&AN=000182370700003&site=eds-live&scope=site

Karachalios, G., & Charalabopoulos, K. (2002). Biliary excretion of antimicrobial drugs. *Chemotherapy, 48*(6), 280-297. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=12673103&site=eds-live&scope=site

Kominos, S. D., Copeland, C. E., & Grosiak, B. (1972). Mode of transmission of pseudomonas aeruginosa in a burn unit and an intensive care unit in a general hospital. *Applied Microbiology, 23*(2), 309-312. Retrieved

fromhttp://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=4622827&site=eds-live&scope=site

Kramer, A., Schwebke, I., & Kampf, G. (2006). How long do nosocomial pathogens persist on inanimate surfaces? A systematic review. *BMC Infectious Diseases, 6*(1), 130-8. doi:10.1186/1471-2334-6-130

Kuhn, K. A., & Stappenbeck, T. S. (2013). Review: Peripheral education of the immune system by the colonic microbiota. *Seminars in Immunology, 25*(-), 364-369. doi:10.1016/j.smim.2013.10.002

Levison, M. E. (1973). Effect of colon flora and short-chain fatty acids on growth in vitro of pseudomonas aeruginsoa and enterobacteriaceae. *Infection and Immunity, 8*(1), 30-35. Retrieved fromhttp://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=4198102&site=eds-live&scope=site

Lowbury, E. J., Thom, B. T., Lilly, H. A., Babb, J. R., & Whittall, K. (1970). Sources of infection with pseudomonas aeruginosa in patients with tracheostomy. *Journal of Medical Microbiology, 3*(1), 39-56. Retrieved fromhttp://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=4988647&site=eds-live&scope=site

Marshall, J. C., Christou, N. V., & Meakins, J. L. (1993). The gastrointestinal tract. the "undrained abscess" of multiple organ failure. *Annals of Surgery, 218*(2), 111-119. Retrieved fromhttp://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=8342990&site=eds-live&scope=site

Matamoros, S., Gras-Leguen, C., Le Vacon, F., Potel, G., & Cochetiere, d. L. (2013). Review: Development of intestinal microbiota in infants and its impact on health. *Trends in Microbiology, 21*, 167-173. doi:10.1016/j.tim.2012.12.001

Maternity care [microform] : Appropriate follow-up services critical with short hospital stays : Report to the honorable ron wyden, U.S. senate / united states general accounting office (1996). Washington, D.C. : The Office ; Gaithersburg, MD] (P.O. Box 6015, Gaithersburg 20884-6015) : The Office distributor, 1996]. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edsgpr&AN=gpr000473135&site=eds-live&scope=site; http://catalog.gpo.gov/fdlpdir/locate.jsp?ItemNumber=0546-D&SYS=000473135; http://purl.access.gpo.gov/GPO/LPS12181

McFarland, L. V., Mulligan, M. E., Kwok, R. Y. Y., & Stamm, W. E. (1989). Nosocomial acquisition of clostridium difficile infection. *The New England Journal of Medicine,* (4), 204. Retrieved

fromhttp://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edsgao&AN=edsgcl.7021538&site=eds-live&scope=site

Montefour, K., Frieden, J., Hurst, S., Helmich, C., Headley, D., Martin, M., & Boyle, D. A. (2008). Acinetobacter baumannii: An emerging multidrug-resistant pathogen in critical care. *Critical Care Nurse,* (1), 15. Retrieved fromhttp://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edsgao&AN=edsgcl.175458395&site=eds-live&scope=site

Moraes, T. J., Lefebvre, D. L., Chooniedass, R., Becker, A. B., Brook, J. R., Denburg, J., . . . Befus, A. D. (2015). *The canadian healthy infant longitudinal development birth cohort study: Biological samples and biobanking*Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edswsc&AN=000346916700011&site=eds-live&scope=site

Munyaka, P. M., Eissa, N., Bernstein, C. N., Khafipour, E., & Ghia, J. (2015). Antepartum antibiotic treatment increases offspring susceptibility to experimental colitis: A role of the gut microbiota. *Plos One, 10*(11), 1-22. doi:10.1371/journal.pone.0142536

MURDOCH, D. A., GIBBS, S., PRICE, C., EASMON, S., FRANKLIN, J., LISTER, T. A., & TABAQCHALI, S. (1990). *Effect of ceftazidime and gentamicin on the oropharyngeal and fecal flora of patients with hematological malignancies* Retrieved

from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edswsc&AN=A1990DY59500014&site=eds-live&scope=site

OHARA, T., & ITOH, K. (2003). Significance of pseudomonas aeruginosa colonization of the gastrointestinal tract. *Internal Medicine, 42*(11), 1072-1076. doi:10.2169/internalmedicine.42.1072

Örebro universitet, H., Originator, Uppsala universitet, Medicinska och farmaceutiska vetenskapsområdet, Medicinska fakulteten, Institutionen för onkologi, radiologi och,klinisk immunologi, Dicksved, J., Author, Halfvarson, J., Author, Rosenquist, M., Author, Järnerot, G., Author, Jansson, J. K., Author. (2008). Molecular analysis of the gut microbiota of identical twins with crohns disease. *The ISME Journal,* 716. Retrieved fromhttp://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edsswe&AN=edsswe.oai.DiVA.org.oru.3529&site=eds-live&scope=site

Ozkurt, Z., Ertek, M., Erol, S., Altoparlak, U., & Akcay, M. N. (2005). The risk factors for acquisition of imipenem-resistant pseudomonas aeruginosa in the burn unit. *Burns, 31*, 870-873. doi:10.1016/j.burns.2005.04.015

Patient Safety Network. (2015). Health care-associated infections. Retrieved from https://psnet.ahrq.gov/primers/primer/7/health-care-associated-infections

Penders, J., Thijs, C., Vink, C., Stelma, F. F., Snijders, B., Kummeling, I., Stobberingh, E. E. (2006). Factors influencing the composition of the intestinal microbiota in early infancy. *Pediatrics,* (2), 511. Retrieved fromhttp://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edsgao&AN=edsgcl.156549563&site=eds-live&scope=site

Perez-Cobas, A., Gosalbes, M. J., Friedrichs, A., Knecht, H., Artacho, A., Eismann, K., Moya, A. (2013). *Gut microbiota disturbance during antibiotic therapy: A multi-omic approach* Retrieved fromhttp://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edswsc&AN=000325557200012&site=eds-live&scope=site

Public Health Agency of Canada. (2008). Canadian perinatal health report. Retrieved from http://www.violapolomeno.com/cphr-rspc08-eng.pdf

Public Health Agency of Canada (PHAC). (2010). Essential resources for effective infection prevention and control programs: A matter of patient safety: A discussion Paper2010. Retrieved from http://www.phac-aspc.gc.ca/nois-sinp/guide/ps-sp/index-eng.php

Public Health Agency of Canada (PHAC). (2013). **Healthcare-associated Infections—Due diligence**. Retrieved from http://www.phac-aspc.gc.ca/cphorsphc-respcacsp/2013/infections-eng.php

Public Health Agency of Canada (PHAC). (2013). Report on the state of public health in canada. Retrieved from http://www.phac-aspc.gc.ca/cphorsphc-respcacsp/2013/assets/pdf/2013-eng.pdf

Public Health Agency of Canada (PHAC). (2014). **Fact sheet - *clostridium difficile (C. difficile*)**. Retrieved from http://www.phac-aspc.gc.ca/id-mi/cdiff-eng.php

Robenshtok, E., Paul, M., Leibovici, L., Fraser, A., Pitlik, S., Ostfeld, I., Weinberger, M. (2006). The significance of acinetobacter baumannii bacteraemia compared with klebsiella pneumoniae bacteraemia: Risk factors and outcomes. *Journal of Hospital Infection, 64*, 282-287. doi:10.1016/j.jhin.2006.06.025

Rodríguez, J. M., Murphy, K., Stanton, C., Ross, R. P., Kober, O. I., Juge, N., Collado, M. C. (2015). The composition of the gut microbiota throughout life, with an emphasis on early life. *Microbial Ecology in Health and Disease, 26*, 26050-26050. doi:10.3402/mehd.v26.26050

Roy, S., Viswanathan, R., Singh, A., Das, P., & Basu, S. (2010). Gut colonization by multidrug-resistant and carbapenem-resistant acinetobacter baumannii in neonates. *European Journal of Clinical Microbiology & Infectious Diseases,* (12) Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edsagr&AN=edsagr.US201301917867&site=eds-live&scope=site

Simon, G. L., & Gorbach, S. L. (1986). The human intestinal microflora. *Digestive Diseases and Sciences, 31*(9), 147. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edo&AN=ejs16997550&site=eds-live&scope=site

Stoodley, B. J., & Thom, B. T. (1970). Observations on the intestinal carriage of pseudomonas aeruginosa. *Journal of Medical Microbiology, 3*(3), 367-375. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=4990646&site=eds-live&scope=site

Strober, W. (2013). Impact of the gut microbiome on mucosal inflammation. *Trends in Immunology,* (9), 423. doi:10.1016/j.it.2013.07.001

Touati, A., Achour, W., Cherif, A., Hmida, H. B., Afif, F. B., Jabnoun, S., Hassen, A. B. (2009). Outbreak of acinetobacter baumannii in a neonatal intensive care unit: Antimicrobial susceptibility and genotyping analysis.*Annals of Epidemiology, 19*(6), 372-378 7p. doi:10.1016/j.annepidem.2009.03.010

van Nimwegen, F. A., Penders, J., Stobberingh, E. E., Postma, D. S., Koppelman, G. H., Kerkhof, M., Thijs, C. (2011). Asthma and lower airway disease: Mode and place of delivery, gastrointestinal microbiota, and their influence on asthma and atopy. *The Journal of Allergy and Clinical Immunology, 128*, 948-955.e3. doi:10.1016/j.jaci.2011.07.027

Villegas, M. V., & Hartstein, A. I. (2003). *Acinetobacter outbreaks, 1977-2000* SLACK Incorporated. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edsjsr&AN=edsjsr.30141601&site=eds-live&scope=site

Vogel, F., & Knothe, H. (1985). Changes in aerobic faecal bacterial flora of severely ill patients during antibiotic treatment. *Klinische Wochenschrift, 63*(22), 1174. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edb&AN=72316345&site=eds-live&scope=site

Yeoh, N., Burton, J. P., Suppiah, P., Reid, G., & Stebbings, S. (2013). The role of the microbiome in rheumatic diseases. *Current Rheumatology Reports,* (3), 1. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edsgao&AN=edsgcl.322872153&site=eds-live&scope=site

Zoetendal, E. G., Akkermans, A. D. L., Akkermans-van Vliet, W. M., de Visser, ‚J.Arjan G., & de Vos, W. M. (2001). The host genotype affects the bacterial community in the human gastronintestinal tract. *Microbial Ecology in Health & Disease, 13*(3), 129-134. doi:10.1080/089106001750462669

Zoutman, D. E., Ford, B. D., Bryce, E., Gourdeau, M., Hébert, G., Henderson, E., & Paton, S. (2003). Major articles: The state of infection surveillance and control in canadian acute care

hospitals. *AJIC: American Journal of Infection Control, 31*, 266-273.

doi:10.1067/mic.2003.88

References for Chapter 3

Abrahamsson, T. R., Jakobsson, H. E., Andersson, A. F., Bjorksten, B., Engstrand, L., & Jenmalm, M. C. (2012). *Low diversity of the gut microbiota in infants with atopic eczema* Retrieved fromhttp://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edswsc&AN=000299951700021&site=eds-live&scope=site

Abrahamsson, T., Author, Jakobsson, H. E., A., Andersson, A. F., A., Björksten, B., Author, Engstrand, L., A., Jenmalm, M., Author, . . . Linköpings universitet, Institutionen för klinisk och,experimentell medicin. (2014). Low gut microbiota diversity in early infancy precedes asthma at school age. *Clinical and Experimental Allergy,* , 842. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edsswe&AN=edsswe.oai.DiVA.org.liu.109137&site=eds-live&scope=site

Azad, M. B., Konya, T., Maughan, H., Guttman, D. S., Field, C. J., Chari, R. S., . . . Kozyrskyj, A. L. (2013). Gut microbiota of healthy canadian infants: Profiles by mode of delivery and infant diet at 4 months. *CMAJ: Canadian Medical Association Journal, 185*(5), 385-394 10p. doi:10.1503/cmaj.121189

Azad, M. B., Konya, T., Maughan, H., Guttman, D. S., Field, C. J., Sears, M. R., . . . Kozyrskyj, A. L. (2013). Infant gut microbiota and the hygiene hypothesis of allergic disease: Impact

of household pets and siblings on microbiota composition and diversity. *Allergy, Asthma & Clinical Immunology, 9*(1), 1-9. doi:10.1186/1710-1492-9-15

Azad, M. B., & Kozyrskyj, A. L. (2012). Perinatal programming of asthma: The role of gut microbiota. *Clinical & Developmental Immunology,* , 932072-932072 1p. doi:2012/932072

Bello, A., Quinn, M. M., Perry, M. J., & Milton, D. K. (2010). *Quantitative assessment of airborne exposures generated during common cleaning tasks: A pilot study* Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edswsc&AN=000285311100001&site=eds-live&scope=site

Bisgaard, H., Li, N., Bonnelykke, K., Chawes, B., Skov, T., Paludan-Muller, G., . . . Krogfelt, K. A. (2011). *Reduced diversity of the intestinal microbiota during infancy is associated with increased risk of allergic disease at school age* Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edswsc&AN=000294283400025&site=eds-live&scope=site

Bjorksten. (2000). *The intestinal microflora in allergic estonian and swedish 2-year-old children (vol 29, pg 342, 1999)* Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edswsc&AN=000088167800020&site=eds-live&scope=site

Björkstén, B., Sepp, E., Julge, K., Voor, T., & Mikelsaar, M. (2001). Asthma, rhinitis, other respiratory diseases: Allergy development and the intestinal microflora during the first year of life. *The Journal of Allergy and Clinical Immunology, 108*, 516-520. doi:10.1067/mai.2001.118130

Bondi, C. A. M. (2011). Applying the precautionary principle to consumer household cleaning product development. *Journal of Cleaner Production, 19*, 429-437. doi:10.1016/j.jclepro.2010.07.008

Bornehag, C. G., A., Hagerhed-Engman, L., Sigsgaard, T., A., Janson, S., Author, Aberg, N., A., DBH-study group, t., Author, & Karlstads universitet, Fakulteten för samhälls- och livsvetenskaper, Avdelningen för hälsa,och milj. (2005). Dampness at home and its association with airway, nose and skin symptoms among 10 851 preschool children in sweden:: A cross sectional study. *Indoor Air,* Retrieved fromhttp://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edsswe&AN=edsswe.oai.DiVA.org.kau.18003&site=eds-live&scope=site

Boyce, J. M., & Pittet, D. (2002). Guideline for hand hygiene in health-care settings: Recommendations of the healthcare infection control practices advisory committee and the HICPAC/SHEA/APIC/IDSA hand hygiene task force. *MMWR: Morbidity & Mortality Weekly Report, 51*(42), 1-1 45p. Retrieved

from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=rzh&AN=106806132&site=eds-live&scope=site

Casas, L., Zock, J., Torrent, M., García-Esteban, R., Gracia-Lavedan, E., Hyvärinen, A., & Sunyer, J. (2013). Use of household cleaning products, exhaled nitric oxide and lung function in children. *The European Respiratory Journal, 42*(5), 1415-1418. doi:10.1183/09031936.00066313

Chuanchuen, R., Beinlich, K., Hoang, T. T., Becher, A., Karkhoff-Schweizer, R., & Schweizer, H. P. (2001). *Cross-resistance between triclosan and antibiotics in pseudomonas aeruginosa is mediated by multidrug efflux pumps: Exposure of a susceptible mutant strain to triclosan selects nfxB mutants overexpressing MexCD-OprJ* Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edswsc&AN=000166539600008&site=eds-live&scope=site

Dicksved, J., Halfvarson, J., Rosenquist, M., Järnerot, G., Tysk, C., Apajalahti, J., . . . Jansson, J. K. (2008). Molecular analysis of the gut microbiota of identical twins with crohn's disease. *ISME Journal: Multidisciplinary Journal of Microbial Ecology, 2*(7), 716-727. doi:10.1038/ismej.2008.37

Farrow, A., Taylor, H., Northstone, K., & Golding, J. (2003). Symptoms of mothers and infants related to total volatile organic compounds in household products. *Archives of Environmental Health, 58*(10), 633-641. Retrieved

from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=eih&AN=15002729&site=eds-live&scope=site

Franklin, M. J., Nivens, D. E., Weadge, J. T., & Howell, P. L. (2011). *Biosynthesis of the pseudomonas aeruginosa extracellular polysaccharides, alginate, pel, and psl* Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edswsc&AN=000208863500176&site=eds-live&scope=site

Ghoshal, U. C., Shukla, R., Ghoshal, U., Gwee, K., Ng, S. C., & Quigley, E. M. M. (2012). The gut microbiota and irritable bowel syndrome: Friend or foe? *International Journal of Inflammation, 2012*, 151085-151085. doi:10.1155/2012/151085

Heavey, P. M., & Rowland, I. R. (1999). The gut microflora of the developing infant: Microbiology and metabolism. *Microbial Ecology in Health & Disease, 11*(2), 75-83. doi:10.1080/089106099435808

Holt, P. G., Macaubas, C., Stumbles, P. A., & Sly, P. D. (1999). The role of allergy in the development of asthma. *Nature, 402*(6760), 12. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=a9h&AN=8755465&site=eds-live&scope=site

Hooton, T. M., & Levy, S. B. (2001). Antimicrobial resistance: A plan of action for community practice. *American Family Physician, 63*(6), 1087-1098. Retrieved

from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=11277546&site=eds-live&scope=site

Jaakkola, J. J. K., & Jaakkola, M. S. (2006). Professional cleaning and asthma. *Current Opinion in Allergy and Clinical Immunology, 6*(2), 85-90. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=16520670&site=eds-live&scope=site

Johansson, M. A., Sjögren, Y. M., Persson, J., Nilsson, C., & Sverremark-Ekström, E. (2011). Early colonization with a group of lactobacilli decreases the risk for allergy at five years of age despite allergic heredity. *Plos One,6*(8), 1. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edb&AN=74398433&site=eds-live&scope=site

Josephson, K. L., Rubino, J. R., & Pepper, I. L. (1997). Characterization and quantification of bacterial pathogens and indicator organisms in household kitchens with and without the use of a disinfectant cleaner. *Journal of Applied Microbiology,* (6) Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edsagr&AN=edsagr.US201302881053&site=eds-live&scope=site

Korgaonkar, A. K., & Whiteley, M. (2011). Pseudomonas aeruginosa enhances production of an antimicrobial in response to N-acetylglucosamine and peptidoglycan. *Journal of Bacteriology,* (3-4), 909. Retrieved

fromhttp://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edsgao&AN=edsgcl.249309920&site=eds-live&scope=site

Larson, E., & Duarte, C. G. (2001). Home hygiene practices and infectious disease symptoms among household members. *Public Health Nursing, 18*(2), 116-127 12p. Retrieved fromhttp://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=rzh&AN=107027036&site=eds-live&scope=site

Laura M. Koeth, Caryn E. Good, Peter C. Appelbaum, Ellie, J. C. G., Arne C. Rodloff, Marina Claros, & Luc J. Dubreuil. (2004). Surveillance of susceptibility patterns in 1297 european and US anaerobic and capnophilic isolates to co-amoxiclav and five other antimicrobial agents. *Journal of Antimicrobial Chemotherapy (JAC), 53*(6), 1039-1044. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=eih&AN=19810477&site=eds-live&scope=site

Levy, S. B. (2000). Antibiotic and antiseptic resistance: Impact on public health. *The Pediatric Infectious Disease Journal, 19*(10), S120-S122. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=11052402&site=eds-live&scope=site

Levy, S. B. (2001). Antibacterial household products: Cause for concern. *Emerging Infectious Diseases, 7*(3), 512. Retrieved

from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=eih&AN=5009956&site=eds-live&scope=site

Maroni, M., Seifert, B., & Lindvall, T. (1995). *Indoor air quality : A comprehensive reference book* Amsterdam ; New York : Elsevier Science, 1995. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=cat03710a&AN=alb.1739664&site=eds-live&scope=site

Mashburn, L. M., Jett, A. M., Akins, D. R., & Whiteley, M. (2005). Staphylococcus aureus serves as an iron source for pseudomonas aeruginosa during in vivo coculture. *Journal of Bacteriology,* (1-2), 554. Retrieved fromhttp://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edsgao&AN=edsgcl.129169920&site=eds-live&scope=site

Medina-Ramon, M., Zock, J. P., Kogevinas, M., Sunyer, J., Basagana, X., Schwartz, J., . . . Anto, J. M. (2006). *Short-term respiratory effects of cleaning exposures in female domestic cleaners* Retrieved fromhttp://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edswsc&AN=000237934500018&site=eds-live&scope=site

Medrano-Félix, A., Martínez, C., Castro-del Campo, N., León-Félix, J., Peraza-Garay, F., Gerba, C. P., & Chaidez, C. (2011). Impact of prescribed cleaning and disinfectant use on

microbial contamination in the home. *Journal of Applied Microbiology, 110*(2), 463-471. doi:10.1111/j.1365-2672.2010.04901.x

Mirabelli, M. C., Zock, J. P., Plana, E., Antó, J. M., Benke, G., Blanc, P. D., . . . Kogevinas, M. (2007). Occupational risk factors for asthma among nurses and related healthcare professionals in an international study.*Occupational & Environmental Medicine, 64*(7), 474-479 6p. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=rzh&AN=106011029&site=eds-live&scope=site

Nielsen, J., & Bach, E. (1999). *Work-related eye symptoms and respiratory symptoms in female cleaners* Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edswsc&AN=000081391000004&site=eds-live&scope=site

Obadia, M., Liss, G. M., Lou, W., Purdham, J., & Tarlo, S. M. (2009). *Relationships between asthma and work exposures among non-domestic cleaners in ontario* Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edswsc&AN=000269475100006&site=eds-live&scope=site

Penders, J., Thijs, C., van, d. B., Kummeling, I., Snijders, B., Stelma, F., . . . Stobberingh, E. E. (2007). Gut microbiota composition and development of atopic manifestations in infancy: The KOALA birth cohort study. *Gut,* (5), 661. Retrieved

from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edsgao&AN=edsgcl.164474810&site=eds-live&scope=site

Poole, K. (2001). Multidrug efflux pumps and antimicrobial resistance in pseudomonas aeruginosa and related organisms. *Journal of Molecular Microbiology and Biotechnology, 3*(2), 255-264. Retrieved fromhttp://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=11321581&site=eds-live&scope=site

Quirce, S., & Barranco, P. (2010). *Cleaning agents and asthma* Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edswsc&AN=000286704300001&site=eds-live&scope=site

Rajilić–Stojanović, M., Biagi, E., Heilig, H. G. H. J., Kajander, K., Kekkonen, R. A., Tims, S., & de Vos, W. M. (2011). Original research: Global and deep molecular analysis of microbiota signatures in fecal samples from patients with irritable bowel syndrome. *Gastroenterology, 141*, 1792-1801. doi:10.1053/j.gastro.2011.07.043

Reig, M., & Baquero, F. (1994). Antibacterial activity of clavulanate and tazobactam on peptostreptococcus spp. *The Journal of Antimicrobial Chemotherapy, 33*(2), 358-359. Retrieved fromhttp://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=8182024&site=eds-live&scope=site

Rosenberg, S. (2000). Consumer and market use of antibacterials at home. *The Pediatric Infectious Disease Journal, 19*(10), S114-S116. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=11052400&site=eds-live&scope=site

Russell, A. B., Hood, R. D., Bui, N. K., LeRoux, M., Vollmer, W., & Mougous, J. D. (2011). Type VI secretion delivers bacteriolytic effectors to target cells. *Nature, 475*(7356), 343. doi:10.1038/nature10244

Sally A. Roberts. (2006). Antimicrobial susceptibility of anaerobic bacteria in new zealand: 1999–2003. *Journal of Antimicrobial Chemotherapy (JAC), 57*(5), 992-998. Retrieved fromhttp://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=eih&AN=20508094&site=eds-live&scope=site

SAMET, J. (1990). *Environmental controls and lung-disease - report of the ats workshop on environmental controls and lung-disease, santa-fe, new-mexico, march 24-26, 1988* Retrieved fromhttp://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edswsc&AN=A1990EB31300031&site=eds-live&scope=site

Saulnier, D. M., Riehle, K., Mistretta, T., Diaz, M., Mandal, D., Raza, S., . . . Versalovic, J. (2011). Original research: Gastrointestinal microbiome signatures of pediatric patients with

irritable bowel syndrome. *Gastroenterology,141*, 1782-1791. doi:10.1053/j.gastro.2011.06.072

Scott, E., Bloomfield, S. F., & Barlow, C. G. (1984). *Evaluation of disinfectants in the domestic environment under 'in use' conditions* Cambridge University Press. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edsjsr&AN=edsjsr.3862688&site=eds-live&scope=site

Sjögren, Y. M., Author, Jenmalm, M., Author, Böttcher, M., Author, Björkstén, B., Author, Sverremark-Ekström, E., Author, Linköpings universitet, Institutionen för klinisk och,experimentell medicin, & Linköpings universitet, H., Originator. (2009). Altered early infant gut microbiota in children developing allergy up to 5 years of age. *Clinical and Experimental Allergy,* , 518. Retrieved from http://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edsswe&AN=edsswe.oai.DiVA.org.liu.17517&site=eds-live&scope=site

Vizcaya, D., Mirabelli, M. C., Antó, J., Orriols, R., Burgos, F., Arjona, L., & Zock, J. (2011). *A workforce-based study of occupational exposures and asthma symptoms in cleaning workers* BMJ Publishing Group. Retrieved fromhttp://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edsjsr&AN=edsjsr.41408468&site=eds-live&scope=site

Vizcaya, D., Mirabelli, M. C., Orriols, R., Antó, J. M., Barreiro, E., Burgos, F., . . . Zock, J. (2013). Functional and biological characteristics of asthma in cleaning workers. *Respiratory Medicine, 107*, 673-683. doi:10.1016/j.rmed.2013.01.011

Wang, L., Christophersen, C. T., Sorich, M. J., Gerber, J. P., Angley, M. T., & Conlon, M. A. (2013). Increased abundance of sutterella spp. and ruminococcus torques in feces of children with autism spectrum disorder. *Molecular Autism, 4*(1), 1-7. doi:10.1186/2040-2392-4-42

Weschler, C. J. (2009). Changes in indoor pollutants since the 1950s. *Atmospheric Environment, 43*(-), 153-169. doi:10.1016/j.atmosenv.2008.09.044

Weschler, C. J., & Nazaroff, W. W. (2008). Semivolatile organic compounds in indoor environments. *Atmospheric Environment, 42*, 9018-9040. doi:10.1016/j.atmosenv.2008.09.052

Wolkoff, P., Schneider, T., Kildesø, J., Degerth, R., Jaroszewski, M., & Schunk, H. (1998). Risk in cleaning: Chemical and physical exposure. *The Science of the Total Environment, 215*(1-2), 135-156. Retrieved fromhttp://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=9599458&site=eds-live&scope=site

Zock, J., Kogevinas, M., Sunyer, J., Almar, E., Muniozguren, N., Payo, F., . . . Antó, J. M. (2001). *Asthma risk, cleaning activities and use of specific cleaning products among spanish indoor cleaners* Finnish Institute of Occupational Health; National Institute of Occupational Health (Denmark); National Institute of Occupational Health (Norway); National Institute for Working Life. Retrieved fromhttp://login.ezproxy.library.ualberta.ca/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edsjsr&AN=edsjsr.40967118&site=eds-live&scope=site

Zock, J., Vizcaya, D., & Le Moual, N. (2010). Update on asthma and cleaners. *Current Opinion in Allergy and Clinical Immunology, 10*(2), 114-120. doi:10.1097/ACI.0b013e32833733fe

Zoetendal, E. G., Akkermans, A. D. L., Akkermans-van Vliet, W. M., de Visser, ‚J.Arjan G., & de Vos, W. M. (2001). The host genotype affects the bacterial community in the human gastronintestinal tract. *Microbial Ecology in Health & Disease, 13*(3), 129-134. doi:10.1080/089106001750462669