INFANT FEEDING MODE AND ITS ASSOCIATION WITH THE USE OF HEALTHCARE SERVICES IN THE FIRST YEAR OF LIFE

by © Sharmeen Jalal Chowdhury

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Abstract

This research had two goals. First, a systematic review was conducted to examine the relationship between mode of infant feeding and risk of hospitalization due to respiratory tract infections in healthy full-term infants. Second, a cross-sectional study was conducted in the Eastern Region of Newfoundland and Labrador to evaluate differences in healthcare use by feeding mode in infants in the first year of life. Chapter one includes an introduction and chapter four provides a summary and discussion of the findings. Chapters two and three include versions of the systematic review manuscript and the cross-sectional study manuscript, respectively. The systematic review demonstrated breastfeeding reduced the risk of hospitalization due to a respiratory tract infection in the first year of life and the cross-sectional study revealed that exclusively formula-fed infants had significantly more emergency department and hospital visits compared to exclusively breastfed infants or mixed-fed infants in their first year of life.

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List of abbreviations

RTI	Respiratory tract infection
PubMed	Search engine for Published Medical Literature
CINAHL	Cumulative Index of Nursing and Allied Health Literature
EMBASE	Excerpta Medica database
BF	Breastfeeding
WHO	World Health Organization
PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analysis
CI	Confidence interval
MeSH	Medical subject heading
USPSTF	US Preventive Services Task Force
UK	United Kingdom
OR	Odds ratio
HR	Hazard ratio
EBF	Exclusive Breast Feeding
PROBIT	Promotion of Breastfeeding Intervention Trial
IFS	Infant Feeding Survey
NL	Newfoundland and Labrador
FiNaL	Feeding infants in Newfoundland and Labrador
EFF	Exclusively formula fed
AOM	Acute otitis media
NEC	Necrotising enterocolitis
OECD	Organization for Economic Co-operation and Development
GDP	Gross domestic product

BFRWG Breastfeeding Research Working Group

NMS Non-Medical Supplementation

UNICEF United Nations Children's Fund

ORS Oral Rehydration Solutions

GI Gastrointestinal

UTI Urinary tract infection

HREA Human Research Ethics Authority

SPSS Statistical Package for the Social Science

ENT Ear, nose, throat

NICU Neonatal intensive care unit

PICU Pediatric intensive care unit

List of publications

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Chapter 1 Introduction and Overview

1.1 *Introduction*

The health benefits of breastfeeding are well-documented. The World Health Organization (WHO) recommends exclusive breastfeeding to six months with continued breastfeeding up to 2 years of life. [1] Breastfeeding reduces the rates of infant mortality and morbidity and substantially decreases the risk of chronic childhood illnesses. [1, 2] Numerous studies conducted in different jurisdictions demonstrate that breastfed infants have lower rates of common infections that result in cost savings due to a decreased use of healthcare services as compared to formula-fed infants. [1-13] However, some studies have reported equivocal results on the protective effects of breastfeeding specifically in developed countries. [14-17] Authors of those studies suggest that the decreased infection rates reported among breastfed children found were due to the confounding demographic, socioeconomic and environmental factors rather than breast milk itself. [14-17].

In this chapter, the background, rationale and the purpose of the research are explained.

1.2 Background

1.2.1 *Health benefits of breastfeeding*

A significant body of evidence exists demonstrating the health benefits of breastfeeding for infants and children. [1-13, 18-23] Numerous studies also report the long-term protective effects of breastfeeding against chronic Non-Communicable Diseases (NCDs) such as diabetes, hypertension, dyslipidemia, coronary heart diseases, cancer and obesity. [24-32] Evidence suggests that the pathological processes of NCDs in adulthood begin in early life [24] and several biological mechanisms, behavioral patterns, and physiological influences can explain the protective role of breastfeeding from those diseases. [24-33] The findings of several studies show that breast milk

provides protection against obesity, [24, 25, 26] mainly because it has less protein and fat content than that of breast-milk substitutes. [24] High fat and protein contents are known to increase the Insulin Growth Factor-type 1 (IGF-1) secretion, leading to the stimulation of the adipocytes and subsequent weight gain. [25] On the contrary, leptin, found in breast milk, affects the growth factors and decreases the synthesis of adipocytes. [26] Breastfeeding also influences the intake of total calories and protein as well as insulin secretion. [25] Studies have revealed that the effects of breastfeeding in preventing NCDs are independent of physical activity and dietary habits in later life. [25, 26] The existing evidence suggests that breastfeeding during infancy can prevent the development of type 2 diabetes (T2DM) in the later part of life, [24, 27] because it has a significant protective role in the development of insulin resistance and subsequent hyperinsulinemia by increasing the long-chain polyunsaturated fatty acid contents in skeletal muscle membrane. [28] In addition, fasting blood glucose levels have been shown to be inversely proportionate to the long-chain polyunsaturated fatty acid contents in skeletal muscle membrane. [28] Several studies have proven that artificial formulas are associated with an increased release of insulin in infants and consequently, modify the physiological release of glucagon and insulin from the pancreas that leads to the development of insulin resistance. [28]

Breast milk also contains less sodium and more long-chain unsaturated fatty acids than infant formulas [29], which has been suggested to affect both systolic and diastolic blood pressures in later life. [24, 27] In several studies, breastfed infants have been found to have higher blood cholesterol levels in infancy and lower in adulthood compared to formula-fed infants. [30, 31] This is partly because of the higher cholesterol contents of breastmilk compared to artificial formulas. [30] Also, the high intake of cholesterol by breastfed infants has long-term inhibitory effects on cholesterol endogenesis, mediated through hydroxymethyl glutaryl coenzyme A in the liver, a restrictive enzyme in cholesterol biosynthesis pathway, resulting in decreased synthesis. [30]

Consequently, breastfeeding demonstrates a protective effect against coronary heart diseases (CHD) by lowering the concentrations of low-density lipoprotein (LDL), total cholesterol and blood pressure. [24,27,29]

1.2.2 *Infant feeding and risk of infection*

Infectious diseases are one of the leading causes of infant morbidity and mortality. [1, 2, 3, 28] Numerous studies conducted in different populations have shown protective effects of breastfeeding, especially of exclusive breastfeeding, [1-13, 32-38] against common childhood infections including respiratory tract infections (RTIs), [1-13, 32, 33, 34, 36, 37] gastrointestinal infections (GI infections) [1-13,32, 35-38] and acute otitis media (AOM) [2, 3, 12, 13, 33, 38, 39]. However, there is a paucity of information regarding the intensity of the effects of breastfeeding on cause-specific mortalities and morbidities. [35, 36] Some studies have suggested there is a graded beneficial effect of breastfeeding for three months or more on reducing the risks of common childhood infections. [8, 12, 13] Other studies report statistically significant advantages of exclusive breastfeeding only, [4, 8, 13, 35, 38, 39] though, the evidence is less conclusive regarding the effect of non-exclusive breastfeeding. Some studies indicate a higher risk of mortality due to diarrhea and RTIs among formula-fed infants, but the results have not always been statistically significant. [38, 39] In one meta-analysis that included data from six developing countries, the authors reported that breastfeeding provided a higher degree of protection against mortality due to diarrhea than that of RTIs in infants 6 months or younger, [3] however, the authors found no difference in the rates of infection among older infants between 6 and 11 months of age. [3]

One significant limitation of previously published studies includes the lack of consistency in the use of a definition of breastfeeding, making it difficult to measure in a valid and reliable way the exposure (e.g., breastfeeding). Few studies adhere to the definition proposed by the WHO which

defines breastfeeding as: exclusive (i.e., no water, drink or other food, except breast milk and prescribed medicine are given to infants); predominant (i.e. infants are breastfed predominantly but water, ritual fluids or water-based drinks, oral rehydration solutions (ORS), vitamins, minerals and medicine are also given) and; partial (i.e., infants receive other liquids and solids in addition to breastmilk) breastfeeding. [9-13, 37, 38]. Also, several studies have not provided a specific definition or information on the duration of breastfeeding, making it difficult to interpret the study results. [14-17] These limitations can result in misclassification of the exposure and the inability to examine a dose-response relationship between breastfeeding and risk of infection. Another limitation of some studies is the lack of adjustment for known confounding factors (e.g., age, level of education, type of delivery) in the statistical analysis. [14-17] It has also been argued that the protective effects of breastfeeding seen in developing countries may be overestimated and not generalizable to developed countries. Many of these countries do not have public health measures such as proper sanitation and immunization and their maternal and child health care may not be at an optimum level, potentially contributing to higher rates of infant mortality. [3]

1.2.3 *Economic benefits of breastfeeding*

Several studies have assessed the association between infant feeding mode and healthcare use and costs (i.e., hospitalizations, emergency and physician visits). Evidence shows that breastfeeding provides economic benefits due to a lower risk of hospitalization in the first 6 months of life for respiratory, gastrointestinal, and other types of infections. [4-7] In the United States (US), it has been projected that an increase in exclusive breastfeeding rates from the current rate of 12% to 90% at 6 months, the WHO recommendation, would save an estimated $13 billion US dollars per year. [5] An Australian study, estimated that between $60-120 million dollars annually could be saved by preventing hospitalizations of infants due to common childhood infections if breastfeeding rates

increased to the recommended level at six months. [4] In the United Kingdom, a study reported that an increase in breastfeeding rates to 65% at 4 months could save up to £26.8 million annually by lowering the treatment costs of GI infections, RTIs, AOM, and necrotizing enterocolitis (NEC) of infants. [6] In Mexico, the cost of inadequate breastfeeding has been estimated to be between $745.6 and $2,416 million per year due to the increased likelihood of infectious diseases among infants (e.g., RTIs, GI infections, AOM, NEC). [7]

1.2.4 *Breastfeeding in Canada and Newfoundland and Labrador*

In Canada, although the average breastfeeding initiation rate is 90.3% and one of the highest among the developed countries, [44] there is significant variation across the provinces and territories. According to the Canadian Community Health Survey (CCHS, 2012), the province of Newfoundland and Labrador (NL) has the lowest breastfeeding initiation rate in Canada (i.e., 69.6%) whereas British Columbia and the Yukon have the highest initiation rates (i.e., 97.2% and 99.2%, respectively), [45, 46] Although the breastfeeding initiation rate has improved in NL over recent years, many women discontinue breastfeeding earlier than intended, with only 17% or one in five, continuing to exclusively breastfeed for 6 months. [46, 47] The reasons for NL's low breastfeeding rate are complex, and many regions of the province have an deep-rooted tradition of formula-feeding, as demonstrated in previously published research conducted in the province. [17-22]

1.2.5 *Breastfeeding in the Eastern Regional Health Authority in Newfoundland and Labrador*

The Eastern Health Authority of NL is the largest health authority in the province, and more than half (about 61%) of the population of the province live in this region. [46] The breastfeeding initiation rate (72%) in this region is higher than the provincial average (69.6%), but significantly

lower than the national average (90.3%). [44, 46] Hospital records show that less than half (e.g., 45%) of infants born in this health region are exclusively breastfed from birth to hospital discharge, and of those who initiate breastfeeding only 13.8% of those are still exclusively breastfeeding at 6 months. [45, 47]

Research in other jurisdictions has shown that improving breastfeeding rates enhances healthcare outcomes across all social groups and produces savings in healthcare costs. Few studies on the effects of breastfeeding on infants use of healthcare services have been conducted in NL or in any other region of Canada. [17-22] Although two of these studies reported a strong protective effect of breastfeeding against severe infections in infants that required hospital admission, these study samples included Aboriginal communities and therefore may not generalizable to other provincial populations. [17, 18]

1.3 Health care service utilization

Health services utilization is the result of the integration of multi-directional, dynamic and interrelated factors. [40] Several models have emerged in different jurisdictions world-wide to identify those factors and their impacts to develop a framework for measuring the utilization of health care services by general populations, as well as specific groups, such as those with low-income, children, elderly, women, homeless and those who are HIV-positive. [40, 41] Most of those models mention that health services use only takes place if an individual is predisposed to receive medical care, is in the enabling conditions that allow him/her to obtain health services and if he/she perceives a need for those services. [40, 41] In the current research, the frequency of doctor (family physicians and specialists) and hospital visits, emergency department visits, medication use and investigations carried out due to illnesses are used as valid measures of health

care utilization. Several studies that have been conducted on the utilization of health care in different developed jurisdictions have used these measures to examine the health care use. [3-6]

1.3.1 *Canadian Health Care Services*

The countries of the Organization for Economic Co-operation and Development (OECD) have comparable systems of accounting for money spent on different sectors including health care services. The World Bank report shows that the 35 OECD countries have devoted an average of 12.4% of their Gross Domestic Product (GDP) on healthcare services, whereas Canada's spending has been 10.4% of its GDP. [42] New patient management technologies, drug therapies and increasing consumer demand are the primary drivers of the expenditure in healthcare in this country. [43] in 2016, Canada spent $228.1 billion on the provision of health care services. [43]

1.3.2 *Newfoundland and Labrador Healthcare Services*

Health care expenditure in NL is $7,256 per capita, the highest in the country, with the exception of the territories. [43] Nearly two-thirds (about 70%) of healthcare spending is contributed by the public sector (provincial and territorial government 65% and other sources 5%) and the remaining (30%) is supplied by the private sector (out of pocket 14.6%, private health insurance 12.2%, and others 3.3%). Hospital services (29.5%), drug supply (16%) and physician services (15.3%) are the three largest categories of healthcare spending. [43] Per capita health care spending for infants living in NL has been an estimated at $10,800 (2014), almost three times the average per capita health care spend ($3915) per person by the government. [43]

1.4 Rationale for current research

The WHO strongly recommends that all infants be exclusively breastfed (i.e., infants receive no water or other liquids or solids except breast milk) until 6 months of age, and that breastfeeding be continued along with the introduction of complementary foods for up to the second year of their life and beyond. [1] Evidence shows that the death rates of children under 5 years of age are higher due to RTIs and GI infections than other childhood diseases, especially in developing countries. Although infant mortality has been reduced substantially in the last several decades, progress is less than satisfactory for infant morbidity. [1,2] The WHO and UNICEF have jointly developed "A Global Strategy for Infant Feeding", based on the available evidence of nutritional requirements in the first year of life and the crucial role of appropriate feeding practices to achieve optimal health outcomes. [1] It is reported in the strategic positional paper that nearly 50% of the burden of GI infections and RTIs in childhood are attributed to malnutrition, which is mostly due to inadequate breastfeeding during the first twelve months of life. [1] Evidence also demonstrates that only about 24% of infants are exclusively breastfed for 6 months throughout the world, exposing them to early and inadequate formula feeding that leads to malnourishment and illness. [1]

1.5 Problem statement

Canada spends about $228.1 billion or 10.4% of its GDP on health care services. [43] Per capita health care expenditure in the province of NL is $7,256, the highest in the country. [43] In 2014, per capita healthcare spending on infants by the NL government was estimated to be $10,800, almost three times higher than the average per capita healthcare spend ($3915) per person by the government. [43] Due to higher than average healthcare use and expenditures in NL, the provincial government, health authorities, and hospital administrators have an interest in understanding the

drivers of healthcare utilization in order to invest in interventions to reduce this use and unsustainable expenditures. Infants in the first year of life are vulnerable to infections, and this age-group uses healthcare services substantially more than other age-groups with the exception of seniors (65 years and older).

It has been demonstrated that breastfeeding reduces the risk of common childhood infections and healthcare utilization however study results are not consistent. Therefore, research on this topic can provide vital information to decision-makers and policymakers that will help inform resource allocation and clinical decision-making.

1.6 Purpose of research and research objectives

1.6.1 *Purpose of research*

The purpose of this research is two-fold. First to examine through a systematic review, the quality of evidence on the mode of infant feeding and the risk hospitalization due to RTIs in the first year of life in healthy full term infants in developed countries and second to examine the relationship between infant feeding mode and the use of healthcare services in full term healthy infants in their first year of life in one health region in the province of Newfoundland and Labrador.

1.6.2 *Specific Research Objectives*

The specific research objectives that guide this thesis are as follows:

1. To identify, summarize and appraise in a systematic review the published literature on the mode of infant feeding and the risk of hospitalization due to RTIs in full-term healthy infants in developed countries.

2. a. To investigate the relationship between mode of infant feeding (e.g., exclusive breastfeeding, mixed feeding, exclusive formula feeding) and healthcare utilization during the first year of life, in healthy full term infants living in the Eastern Health Region of Newfoundland and Labrador. For example:Are there differences by mode of infant feeding in the use of 1) physician services (e.g., visits to a family practitioner, specialist, radiological assessments) 2) hospital services (e.g., ER visits, hospital admissions, the length of stay, NICU/PICU) 3) medications and 4) radiological tests?

   2b. To determine whether infant feeding mode (i.e., exclusive breastfeeding, mixed feeding, exclusive formula feeding) is significantly associated with increased health services use in an infant's first year of life, after adjustment for known confounders (e.g. socioeconomic status, mother's education) using a multivariate model.

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Chapter 2

Infant Feeding Mode and Hospitalization due to Respiratory Tract Infection during Infancy: A Systematic Review

Chowdhury S MD[1], Aslanova R MD, MSc[3], Midodzi W Ph.D.[1], Newhook L MD, FRCPC, MSc [1,3], Twells LK* Ph.D. [1,2]

1. Faculty of Medicine, Memorial University, Health Sciences Centre, 300 Prince Philip Drive, St. John's, NL, A1B 3V6, Canada

2. School of Pharmacy, Memorial University, Health Sciences Centre, 300 Prince Philip Drive, St. John's, NL, A1B 3V6, Canada

3. Eastern Health, Health Sciences Centre, 300 Prince Philip Drive, St. John's, NL, A1B 3V6, Canada

Sharmeen Chowhurry, MD, MSc(c)

Memorial University, St. John’s, NL, Canada, A1B 3V6

sjc421@mun.ca

Rana Aslanova, MD, MSc

Eastern Health, St. John's, NL, Canada, A1B 3V6

rana.aslanova@med.mun.ca

William K. Midodzi, PhD, Assistant Professor

Faculty of Medicine, Memorial University, St. John’s, NL, Canada, A1B 3V6

william.midodzi@med.mun.ca

Leigh Anne Newhook, MD, FRCPC, Associate Professor of Pediatrics

Memorial University, St. John’s, NL, Canada, A1B3V6

lnewhook@mun.ca

Laurie K Twells, PhD, Associate Professor

School of Pharmacy and Faculty of Medicine, Memorial University

St. John's, NL, Canada

ltwells@mun.ca

Short Title: Infant-feeding mode, RTIs and Hospitalization

***Corresponding author contact information:**

L. K. Twells, PhD.

Associate Professor, School of Pharmacy and Faculty of Medicine, Memorial University,

300 Prince Philip Drive, St. John's, Newfoundland and Labrador, Canada A1B 3V6.

Telephone: 709.864 6655

Fax: 709.777 7044

Email: ltwells@mun.ca

Contributors: LT, LN and WM conceived the study concept and methodology. SC conducted the systematic review. SC and RA assessed the full-text relevant articles and independently assessed studies for eligibility and inclusion. SC and RA evaluated the methodological quality of the eligible articles. SC wrote the initial draft with input from all authors. LT, LN and WM were involved in critical revisions of the systematic review. All authors reviewed and approved the final manuscript. (A version of this manuscript has been submitted for peer review to the Archives of Disease in Childhood, June 2017.)

2.1 Abstract

Background: Respiratory tract infections (RTIs) are very common and a leading cause of hospitalizations in infants. There is conflicting evidence regarding whether breastfeeding is protective against RTIs in infants in developed countries. The intent of this systematic review is to assess the quality of evidence on the mode of infant feeding and the risk of hospitalization because of RTIs in full-term infants in developed countries.

Methods: PubMed, CINAHL, EMBASE, the Cochrane Library, Google Scholar and reference lists were searched. Keywords included: 'infant feeding modes' or 'breastfeeding' or 'partial breastfeeding' or 'formula feeding' or 'bottle feeding' and 'respiratory tract infections' or 'RTIs' or 'respiratory infections' and 'hospitalization' or 'child hospital admission' or 'infant hospital admission'. Studies were included if they 1) were conducted in a developed country 2) described infant feeding modes as breastfed, exclusively breastfed, partially breastfed, not breastfed or formula-fed/ bottle-fed 3) included a minimum exposure of 3 months of breastfeeding or 6 months of total breastfeeding compared with no breastfeeding 4) presented effect estimates (odds ratio [OR] or Hazard Ratio [HR] with 95% CI and 5) reported RTIs as physician diagnosed, parent reported or recorded in a hospital database. Two reviewers independently assessed each study.

Results: Six articles (one randomized control trial, four prospective cohort studies and one cross sectional study) met the predefined inclusion criteria and were selected for the systematic review. Four of six articles reported a protective effect of breastfeeding against hospitalization due to an RTI in the first year of life and this relationship persisted after adjustment, but was dependent on breastfeeding definition and duration.

Conclusion: Of six studies reviewed, four demonstrated breastfeeding reduced the risk of hospitalization due to an RTI in the first year of life. There were a limited number of high-quality studies published on infant feeding mode, RTIs and risk of hospitalization in an infant's first year of life. More research is needed that adheres to published definitions of breastfeeding exposure.

Keywords: Breastfeeding, Formula feeding, Hospitalization, Respiratory Tract Infections

2.2 Background

Respiratory tract infections (RTIs) are very common in infants and in children aged 5 years or younger. RTIs contribute to a significant proportion of health care visits, are a primary cause of hospitalization and increase the risk of mortality. [1,2] RTIs divided into upper and lower RTIs and are most often caused by viral infections (>90%). In developing countries, an increasing body of evidence demonstrates the positive impact breastfeeding has on lowering the risk of infant morbidity and mortality from infectious diseases, both respiratory and gastrointestinal in the first two years of life. [1,3,4,5,6,7,8,9] Breastfeeding may also protect against some non-communicable diseases (e.g., diabetes and necrotizing enterocolitis). [10,11,12,13] Several studies and reviews do show a protective effect of breastfeeding on reducing infant hospitalization in general, however the effect often becomes less significant after adjustment for confounders (e.g., maternal education, parental smoking).[8,12,13,14,15,16] A key methodological challenge when comparing study results is adherence to the World Health Organization (WHO) recommended definition of breastfeeding, especially exclusive breastfeeding (EBF): as no other food or drink (water included), except breast milk (and prescribed medicine) as the food required for optimal nutrition during the first 6 months of an infant's life. [17]

Evidence from existing literature, including a meta-analysis supports a reduction in the prevalence of RTIs with breastfeeding, [8,16] however, there is no recent systematic review, investigating the effect of infant feeding mode on hospitalization due specifically to RTIs in developed countries. Hospitalization has been selected as an important outcome as it is a measure of the severity of illness. The main objective of this systematic review is to identify and summarize the literature on the relationship between mode of infant feeding and the risk of hospitalization for RTIs in the first year of life in developed countries.

2.3 Methods

This study was conducted using the guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA; www.prisma-statement.org). [18]

2.3.1 *Eligibility Criteria*

This systematic review included all studies from developed countries that reported on hospitalization of infants due to RTIs. Studies were chosen if they described infant feeding modes as breastfed or exclusively breastfed or partially breastfed, not breastfed or formula-fed. Studies were included if they had a minimum exposure of 3 months of breastfeeding or 6 months of total or any breastfeeding compared with no breastfeeding. Only studies that reported effect estimates (e.g., Odds Ratio (OR) or Hazard Ratio (HR)) and their 95% confidence intervals (CIs) were included. Exclusion criteria were: systematic reviews (including meta-analyses), commentaries, research protocols and case–control studies. As we were interested in healthy full term infants, studies were excluded if they included infants that had any pre-existing illnesses, were either low birth weight or premature (i.e., <2500 grams, <37 weeks) or were in intensive case.

2.3.2 *Search strategy*

The final search was conducted for articles in PubMed (from 1960), CINAHL (from 1982), Cochrane Collection (from 1975), Embase (from 1966) and Google Scholar (from 1960) and included those published up to and including June 2, 2016. The search terms comprised the medical subject heading (MeSH) terms and free text words for ‘infant feeding modes’ or ‘breast feeding’ or ‘partial breast-feeding’ or ‘formula-feeding’ or ‘bottle feeding’ and ‘respiratory tract infections’ or ‘RTIs’ or ‘respiratory infections’ and ‘hospitalization’ or ‘child hospital admission’ or ‘infant hospital admission’. The limiting terms of ‘human’, the target age group (0–12 months) and ‘English Language’ and ‘Full text available’ were chosen. Targeted reference screening and citation tracking of relevant articles were conducted to determine other related publications not

identified by the initial search. The search process is presented in Figure 2.1: PRISMA Flow Diagram of Selection Process and Included Studies.

2.3.3 *Study selection and assessment of bias in studies*

For secondary screening, studies were selected based on the relevance of the title and abstract. Two reviewers assessed the full text for relevant articles and for eligibility (SC, RA). The reviewers assessed eligible studies for methodological quality independently. Assessment was conducted using the US Preventive Services Task Force (USPSTF) Quality Rating Criteria [19] for randomized controlled trials and cohort studies. As studies on breastfeeding and illnesses may be subject to limitations regarding the misclassification of exposure and outcome and issues of confounding, the reviewers used four methodological standards to evaluate the internal and external validity of the selected studies and to correct for these known limitations. These criteria were: a complete definition of breastfeeding, avoidance of detection bias, a precise definition of RTI, and adjustment for potential confounding variables. [20] Mode of infant feeding is often not clearly defined in research studies and adherence to the WHO definition, in particular EBF, varies. Detection bias is usually inherent in hospitalization studies, especially when comparing different countries, as hospitals will have different criteria for admitting patients. The definition of an RTI can also be inconsistent or incomplete (e.g., include only upper or lower). Known confounders for hospitalization (socio-demographics, maternal education, parental smoking, other siblings) are not always adjusted for in analysis and the choice of confounder may vary from study to study. Individual articles were scored by two reviewers after assessing possible biases. There were no cases of major discrepancy between the two reviewers (100% agreement). Only studies rated as 'good' or 'fair' by the USPSTF criteria were included. **(Table 2.1 Assessment of Bias of Included Articles)**

Table 2.1 Assessment of Bias of Articles

Articles **First author and date of publication**	**Consideration of the confounders during selection**	**Maintenance of comparable groups (at least 80% F/U)**	**Equal, reliable and valid measurement**	**Clear definition of intervention**	**Important outcome considered**	**Adjustment of confounders in analysis**	**Overall assessment**
Kramer et al,[21] 2001	Good	Good	Good	Fair	Good	Good	Good
Paricio-Talyero et al,[22] 2005	Good	Good	Good	Good	Good	Good	Good
Oddy et al,[23] 2003	Good	Good	Good	Fair	Good	Good	Good
Howie et al,[24] 1990	Good	Good	Good	Fair	Fair	Good	Fair
Tarrant M et al,[25] 2010	Good	Good	Good	Fair	Good	Good	Good
Payne et al.[26] 2016	Good	Good	Good	Good	Good	Good	Good

2.3.4 *Data extraction and analysis*

Data from the articles to be included were extracted using a standard predefined data abstraction sheet that included: author's name, year of publication, country where study took place, study population, sample size, type of study, exposure to breastfeeding, reason for hospitalization, potential confounders included in analysis and crude and adjusted results between mode of infant feeding and hospitalization (if provided). The primary outcome was infant hospitalization for RTIs. Exposure data was the mode of infant feeding (i.e., breastfed or formula-fed/bottle fed). In addition to exposure and outcome measures, data were collected on the confounders included in the study (e.g., socioeconomic status, maternal age, education, employment, pre-existing illness, smoking, gestational age and childcare attendance).

2.4 Results

The primary literature search was done by one reviewer. The initial search of the literature resulted in 4670 articles (PubMed (508), CINAHL (58), Cochrane Collection (9), Embase (460) and Google Scholar (3635) of which 979 were duplicates and 1986 reported an inappropriate outcome measure. A further 1705 were screened by titles and abstract with 1487 excluded due to ineligibility (e.g., inappropriate age, data sources not reported). 192 were excluded as they took place in developing countries. A full-text review was conducted of 26 articles: 20 were excluded due to: < 12 months of follow-up, missing data on hospitalization and > 80% loss to follow-up. Six articles met the inclusion criteria and were selected with full agreement between two reviewers (SC, RA). **(Figure 2.1 PRISMA Flow Diagram of Selection Process and Included Studies)**

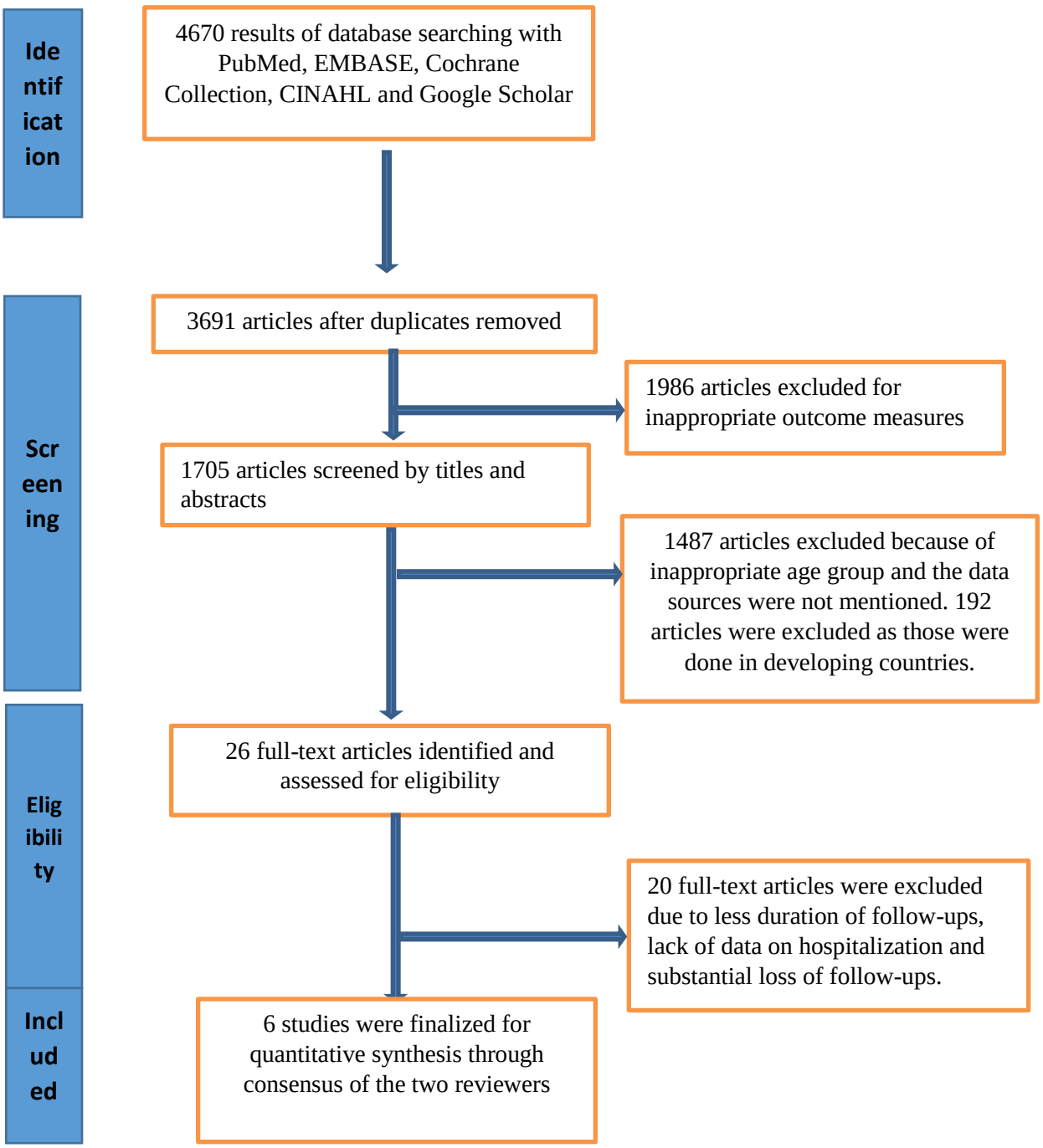

Figure 2.1 Final PRISMA Flow Diagram showing the procedure for identifying the literature that were reviewed.

2.4.1 *Study descriptions*

Six studies published between 1990 to 2016 were included in the systematic review: one randomized controlled trial (RCT), four prospective cohort studies and one cross-sectional survey. [21,22,23,24,25,26] The studies took place in Belarus, Hong Kong, Australia, Scotland, Spain and the United Kingdom (UK). The study from Belarus was selected because it resembles developed western countries in terms of its health service and sanitary conditions, the supply of uncontaminated water and public health measures. [21] All six articles reported effect estimates as ORs or HRs with 95%CI's. The RCT included follow up to 12 months. [21] Of the four cohort studies, two had 12 month follow up [22,23], one had 24 month follow up [24], and one up to 8 years of follow up. [25] The cross-sectional study had follow up of 8 to 10 months. [26] Of the six studies, five studies were given an overall assessment of good quality [21,22,23,25,26] while one was given fair. [24] (**Table 2.2 Study Findings**)

Table 2.2 Study findings

Study and Design	Source of Data	Duration, Outcome measured (months)	Breastfed and formula-fed number	Feeding measures and source of information	Outcome measure and source of information	Confounders considered	Children hospitalized: reason, breastfed or formula-fed
Kramer et al.,[21] 2001 Randomized Controlled Trial	Promotion of Breastfeeding Intervention Trial (PROBIT) Belarus	1996–1997, 12 months	7895 pairs control, 8547 pairs with intervention	Ever/Never Breastfed Medical records at post-natal discharge and well-child visits	Hospital admission due to RTI Hospital and clinic records	Maternal age, education, atopic family history, maternal smoking in pregnancy, gender, birth weight, delivery type, parity	[3]RTI, IG[1] 17.9%, CG[2] 20.5%. aOR[4] 0.85; 95% CI 0.57, 1.27
Paricio-Talyero et al.,[22] 2006 Prospective cohort	Nutritional Well Child Programme Spain	1996–1999, 12 months	1385 infants BF, 1163 FF	Initiation/ Duration/excusivity Maternal report at 3,4 and 6 months	Infection Hospital discharge record	Gender, birth weight, siblings, prematurity, maternal age, education and employment, smoking, parity, economic level and hospital type	[3]RTIs, aOR[4] 1.43, 95% CI 1.27, 1.59. P<.0001
Oddy et al., [23] 2003 Prospective cohort	The Western Australian Pregnancy Cohort Study Australia	1989–1992, 12 months	2456 infants BF, 2196 FF	Initiation/ Duration/full/partial breastfeeders Maternal questionnaire at 12 months, diary cards for parents	Upper and Lower respiratory tract infection Maternal report	Gender, older siblings, gestational age , maternal age, maternal education and smoking in pregnancy,childcare or play group attendance, family income, history of atopy	Upper [3]RTI 1.1%, 2.6% Lower [3]RTI, 2.8%, 5.1% aOR[4] 2.65, 95% CI 1.30, 5.41. P=0.007
Howie et al., [24] 1990 Prospective cohort	A representative sample of infants in Dundee, recruited in maternity ward Scotland	1983–1986, 24 months	674 pairs 267 bottle-fed from beginning, 407 BF	Early weaners /Partial/ Full breastfeeders Home visit at 2wks, 1,2,3,6 9,12,15,18,21and24 months	Hospital admission for gastrointestinal, respiratory and other infections, Home visits, hospital records	Maternal age, parity, social class, marital state, height, smoking, education, previous illness, pregnancy complications , duration of labour, infant's birth weight,	[3]RTI, OR[4] 0.44, 95% CI 0.149, 1.31.

						gender, parity delivery type, Apgar score, immunization	
Tarrant M et al., [25] 2010 Prospective cohort	Birth Registry Hong Kong	1997-2005, 8 years	8327 mother-infant pairs Never BF 4439, partial BF 2851, BF only 491	Initiation/ Duration/ Exclusivity Maternal questionnaire postnatal, 3,9 and 18 months	Public hospital admissions for RTIs, gastrointestinal infections, and all infectious diseases. Maternal report	Household smoking, parental education, employment, type of housing, mode of delivery, gestational age, maternal age and parity. Infant gender, birth weight, birth order, and type of hospital for delivery	[3]RTI, HR[5] 0.64, 95% CI 0.42, 0.97.
Payne et al., [26] 2016 Cross-sectional survey	The Infant Feeding Survey UK	September 2010-August 2016	9813 infants included Never BF 1874, at least once BF 7939, 6m BF 3379	Initiation, duration, exclusivity Maternal questionnaire at 6weeks, 4-6months and 8-10months	Infection Maternal Report	Mother's age, education, smoking, socioeconomic condition, ethnicity, gestational age, birth weight, siblings, mode of delivery, childcare setting.	[3]RTI, for BF ≥6m OR[4] 0.47, 95%CI 0.3,0.73. for BF 3-6m OR[4] 0.59, 95%CI 0.36, 1.0

[1]IG-Intervention Group, [2]CG-Control Group, [3]RTI-respiratory tract infection, [4]OR-Odds Ratio, [5]HR-Hazard Ratio.

In the study by Kramer et al. conducted a cluster RCT was conducted in Belarus under the Promotion of Breastfeeding Intervention Trial (PROBIT). [21] The authors enrolled 17,046 mother-infant pairs who were randomized to either a control or an intervention group within a Baby Friendly Initiative (BFI) breastfeeding promotion program (i.e., the intervention. Infants were followed for one year and data was collected on healthcare use and infant feeding from well-child visits at 1,2,3,6,9 and 12 months. The authors adhered to the WHO definition of breastfeeding. [18,21] The proportion of *EBF* in the intervention and control groups at 3 and 6 months were 43.3% and 6.4%($p<.001$) and 7.9% vs. 0.6% ($p=.01$).The proportion of infants predominantly breastfed in the intervention and control groups at 3 and 6 months were 51.9% vs 28.3% ($p<.05$) and 10.6% vs 1.6%($p=.003$), respectively. The proportion of *any BF* in the intervention and control groups were 72.7% vs 60%, 49.8% vs 36.1%, 36.1% vs 24.4% and 19.7% vs 11.4% at three, six, nine and twelve months, respectively ($p<.05$).The relevant outcome measure for the current study included one or more episodes of an RTI leading to a hospitalization, although this was not the primary outcome for the PROBIT study.

In the prospective cohort study conducted by Talayero et al. 1385 infants of Marina Alta of Alicante, Spain, were followed from birth to 12 months between 1996 and 1999. The authors collected data on infant feeding mode and hospital and primary care center admissions at the six-month well-infant visit as part of the National Child Health Program. The authors adhered to the WHO definition of breastfeeding [18,22] and reported that of the 1385 children in the cohort, 84.5% initially received EBF (which the authors describe as full breastfeeding). *EBF* decreased to 68.4% after 1 month, 60% after 2 months, 51.7% after 3 months, 41.1% after 4 months, 32.4% after 5 months, and 14.6% after 6 months. The mean duration of EBF was 2.79 months. The outcome measure abstracted for the current study was hospitalization due to an infection that included RTIs.

Oddy et al. conducted a prospective birth cohort study in Perth, Australia where 2602 infants were enrolled through antenatal clinics in tertiary hospitals between 1989 and 1992. The authors categorized breastfeeding as *predominant* and *partial* as per the WHO definition, but did not use the WHO definition for *EBF*, [18,23] and reported that of the 2602 infants, 26.9%, 48.4%, 61.4% and 77.8% discontinued predominant breastfeeding at the second, fourth, sixth and eighth months, respectively. Mothers discontinued partial breastfeeding by 21.2%, 37.7%, 48.0% and 58.2% at 2, 4, 6 and 8 months, respectively. The relevant outcome measure abstracted was hospital admissions for RTIs.

In the prospective cohort study conducted by Howie et al. in Dundee, UK, the authors followed 674 pairs of mothers and babies for 24 months. Data on infant feeding mode were collected from hospital records and health visitors' reports monthly for up to six months, and then once every third month until two years of age by health visitors. The authors did not adhere to the WHO definition of infant feeding. [18,24] In this study, mother-baby pairs were divided into four groups based on feeding method: full breast feeders (i.e., exclusively breastfed for thirteen weeks or more); partial breastfeeders (i.e., supplements introduced before thirteen weeks); early weaners (i.e., breastfeeding discontinued before thirteen weeks) and bottle feeders (i.e., bottle-fed from birth). At 13 weeks, of the 674 mother-child pairs, 14.4% were full breast feeders, 19.3% partial, 26.7% early weaners and 39.6% bottle feeders. This study primarily set out to examine the relationship between infant feeding and gastrointestinal infection, however for the purposes of this study, the relevant outcome measure abstracted from the study was hospitalization due to an RTI.

In the study by Tarrant et al. 8327 mother-infant pairs were recruited into a prospective population-based birth cohort study in Hong Kong. The authors collected data on infant feeding and healthcare use at birth and at subsequent well-child visits at 3, 6,9 and 18 months. Breastfeeding data were collected from mothers at the first postnatal visit and then at subsequent visits. The WHO definition

of breastfeeding was not adhered to. [18,25] The authors reported that out of the 8327 mother-infant pairs, 93% reported breastfeeding status. Of those 43% of mothers initiated breastfeeding and 57% of infants were never breastfed. In the first three months, approximately 6.4% of infants had breastmilk only (i.e., no other liquids or solids) and this reduced to 3% after six months. One-third (36.6%) were partially breastfed (i.e., breastmilk and formula). The relevant outcome measure was hospitalization due to RTI.

Payne et. al. analyzed data from the UK Infant Feeding Survey (IFS). The IFS is administered in three stages to mothers when infants are approximately six weeks old (first stage), four to six months (second stage) and eight to ten months of age (third stage). In this cross-sectional study, of the 30,760 infants selected from registered births between August and October 2010, 9813 infants met the inclusion criteria for analysis, after excluding those who did not complete all three surveys. The response rates for the survey were 51%, 80% and 86% in the first, second and third stages, respectively. The authors adhered to the WHO definitions for EBF [18] and reported that 28% and 5% of infants were EBF at 6 weeks and 6 months, respectively. 19% of infants were never breastfed, 11% were breastfed for less than 7 days and 34% received some breastfeeding for at least 6 months. The relevant outcome measure abstracted was hospitalization due to an RTI. [26]

2.4.2 *Exposure measurement: Infant feeding mode*

In all six studies, maternal reports were the main source of infant feeding information. Feeding was measured at different time points across the studies: at postnatal discharge and during well-child visits, [21] at 3,4 and 6 months, [22] at 12 months and from diary cards for parents visit,[23] at second week then 1,2,3,6 9,12,15,18,21 and 24 months' post-delivery, [24] at postnatal visit, 3, 9 and 18th month visit, [25] and at 6 weeks, 6 months and 8 months. [26] The definition of

breastfeeding used in the studies varied. Three of the six studies adhered to the WHO definition of EBF, [21,22,26] while one study adhered to the WHO definition of predominant and partial [23]. In the remaining two studies, one used the term full breastfeeding (i.e., no introduction of any supplements before 13 weeks); partial breastfeeding (i.e., those who breastfed for 13 weeks but introduced supplements); and early weaners (i.e., those who started breastfeeding but discontinued before 13 weeks), [24] while in the last study EBF and partial breastfeeding were not clearly defined: EBF was defined as "only breastmilk" and partial breastfeeding included "breastmilk plus formula".[25]

2.4.3 *Outcome measurement*

In all six studies, hospitalization due to an RTI was the relevant outcome. Two studies reported hospitalization for any infection, including RTIs [22,26] one for RTIs, gastrointestinal infections and atopic eczema, [21] one for RTIs (upper and lower), [23] and two for RTIs, gastrointestinal infections and other infections. [24,25] The sources of hospital data were maternal interview and review of hospital records [22,23,24,25,26] and hospital and clinic records. [21]

The study by Kramer et al. reported no significant differences in the risk of hospitalization due to RTIs between the intervention and control groups after adjustment for the following confounders: birth weight, number of other children in household, and maternal smoking during pregnancy (intervention 17.9%; control 20.5%; aOR 0.85, 95%CI 0.57-1.27). [21]

The study by Talayero et al**.** reported that of the 5.6% (n=78) hospitalization episodes that occurred during the first year of life, 49% (n=38) were due to RTIs. Most hospitalizations (45%) occurred during the first 3 months of life. Of these hospitalized infants, 35% were never breastfed, 49% received EBF for less than 4 months and 17% were EBF for at least 4 months. The authors reported in adjusted analysis, that for every month without EBF, the risk of hospitalization for infection was 1.43 times greater in the first year of life (95%CI 1.27-1.59, p< .0001). The authors report that full

breastfeeding showed a statistically significant protection against RTI's, when considered separately from other infections (data was not shown). After estimating the attributable risk, for each additional month of full breastfeeding (i.e., Full or EBF), 30% of hospital admissions would have been prevented due to infection. [22]

Oddy et al**.** reported that the proportion of infants hospitalized for upper and lower RTIs were 1.5% and 5.2%, respectively. In crude analysis, less than two months of predominant breastfeeding versus more than 2 months was significantly associated with a hospital admission due to upper RTIs (OR 2.47 95% CI 1.25 to 4.89, p= 0.009) but in adjusted analysis that controlled for gender, presence of older siblings, maternal age and education, gestational age and smoking during pregnancy, the result became non-significant (aOR 1.85, 95%CI 0.79 to 4.34, p= 0.158). Partial or any breastfeeding for less than six months was not significantly associated with an increased risk of hospitalization due to an upper RTI in crude (OR 1.65 95%CI 0.83 to 3.33, p=0.156) or in adjusted analysis (aOR 2.05, 95%CI 0.88 to 4.76, p= 0.097), but partial or any breastfeeding for less than six months was significantly associated with hospital admission due to lower RTIs in both crude (OR 2.16 95%CI 1.33 to 3.52, p= 0.002) and adjusted analysis (aOR 2.39, 95%CI 1.30 to 4.42, p=0.005). Less than six months of predominant breastfeeding was significantly associated with risk of hospital admission due to lower RTIs in both crude (OR 1.86 95%CI 1.02 to 3.40, p= 0.042) and adjusted analysis (aOR 2.65 95%CI 1.30 to 5.41, p=0.007). When a composite variable of all respiratory morbidity was analyzed that included hospital, doctor and clinic visits or hospital admissions, breastfeeding was shown to be protective ($p<0.01$). [23]

In the study by Howie et al., 4.9% of infants were hospitalized due to an RTI in the first year of life. Of 674 mother-infant pairs 39.6% were bottle feeders, 26.7% were early weaners, 19.3% were partial breastfeeders and 14.4% were full breastfeeders. The authors adjusted (social class, maternal age, parental smoking) for rates of RTIs in bottle-feeders were significantly greater (37.0%) than

full (25.6%) and partial breastfeeders (24.2%),($p<0.05$) at ages 0-13 weeks. Full and partial breastfed babies had significantly lower rates of RTIs ($p<0.05$) than bottle-fed infants due to RTIs at 40-52 weeks. After controlling for covariates (social class, maternal age, parental smoking, duration of breastfeeding), breastfed babies (1->52 weeks vs never) did not have a lower risk of hospitalization due to RTIs at age one (aOR 0.44, 95% CI .149-1.31, $p>0.05$). [24]

In the study by Tarrant et al. the authors reported that 5.9% of infants were hospitalized due to any infection, and of these over half (53%) were admitted for an RTI in the first 3 months. In this study, breastfeeding (i.e., no formula) for three months or more had a protective effect against hospitalization due to an RTI in the first six months of life (HR 0.64, 95% CI 0.42– 0.97). The study authors also reported that partial breastfeeding (i.e., breastfeeding and formula) for three months reduced the risk of hospitalization due to RTIs (HR 0.79 95%CI 0.64-0.97), however there was no similar association seen after 6 months. [25]

The study by Payne et al. found that 7% of infants had a hospitalization due to an infection and of these 61.7% were admitted due to an RTI. Breastfeeding (any breastfeeding) compared to never breastfeeding for six months or more, reduced the risk of hospitalization due to RTIs in adjusted analysis (aOR: 0.47 95%CI: 0.3–0.73, $p=0.001$). Results were adjusted for birth order, special care after delivery, age mother left full time education, gestational age and infant age. Sub-group analysis showed this protective effect was significant for those who EBF for more than six weeks (OR 0.38, 95%CI: 0.02-0.63, $p<0.001$), but not for those who EBF for less than 6 weeks (OR 0.59, 95%CI:0.35–1.01, $p=0.053$). Any breastfeeding for 3–6 months was significantly associated with a lower rate of hospitalization for an RTI compared to never breastfeeding (OR0.59, 95%CI: 0.36–1.0, $p=0.048$), although this effect was not significant in the sub-group analysis when comparing those who were EBF for more compared to less than 6 weeks. The authors conclude that the protective effect of breastfeeding against infections (including RTIs) and hospitalization is more

pronounced when breastfeeding occurs for 3 months or more, or exclusively for 6 weeks or more. [26]

2.5 Discussion

Of the six studies included in the systematic review, four reported a protective effect of breastfeeding on the risk of hospitalization due to an RTI, after adjustment for confounders. [22,23,25,26] while two did not [21, 24]. In three of the four positive studies, there were graded beneficial effects between breastfeeding and the risk of hospitalization due to RTIs and these effects were of a greater magnitude in those infants who were EBF. [22,23,26] Two of the four positive studies adhered to the WHO definition of EBF [22,26] while one study adhered to the WHO definition of predominant and partial [23].

Talayero et al. reported in adjusted analysis, that for every month without EBF, the risk of hospitalization for infection was 1.43 times greater in the first year of life and that full breastfeeding (EBF) protected against RTI's, when considered separately from other infections. [22] Oddy et al. reported that partial/any breastfeeding and predominant breastfeeding for less than six months protected against hospital admission due to lower RTIs in adjusted analysis. [23] Tarrant et al. reported that breastfeeding (no formula) and partial breastfeeding (mixed feeding) for three months or more protected against hospitalization due to an RTI in the first six months of life, however this relationship was not seen after 6 months. [25] Payne et al. reported in adjusted analysis, that any breastfeeding compared to never breastfeeding for six months or more, reduced the risk of hospitalization due to RTIs, but the protection was limited to those infants who had been EBF for more than six weeks. Any breastfeeding versus never breastfeeding for 3–6 months was also associated with a lower rate of hospitalization for RTIs. Based on these results, the authors suggest that the protective effect of breastfeeding against infection (including RTIs), and therefore

hospitalization is more pronounced when breastfeeding occurs for 3 months or more and is exclusive for the first six weeks of life. [26] Two studies did not show breastfeeding as protective against the risk of hospitalization due to RTIs [21,24]. In the cluster randomized trial, the largest study of the group conducted by Kramer in Belarus, the objective of the study was to assess the impact of breastfeeding promotion on breastfeeding initiation and duration and respiratory infection (among other illnesses). Mothers intending to breastfeed were randomized to the intervention or control group. Various outcomes were examined in this trial, including hospitalization due to RTIs, for which there was found to be no difference between groups. [21] The study could demonstrate the significant impact a health promotion program had on breastfeeding rates for example; the rates of *EBF* were significantly higher in the intervention compared to the control group at 3 and 6 months, 43.3% vs 6.4% and 7.9% vs. 0.6%, respectively. In relation to assessing the protective effect of breastfeeding on RTIs and subsequent hospitalization, it should be noted that in this study the rates of breastfeeding initiation and breastfeeding to 3 and 6 months or more were very high in both groups; the proportion of *any breastfeeding* in the intervention and control group were 72.7% vs 60% and 49.8% vs 36.1%, at three and six months, respectively. In the study by Howie, the focus of which was hospitalization due to infant illness, gastrointestinal not RTI, the authors report that breastfeeding is protective for respiratory illnesses during the first 3 and last 3 months in the first year of life, but that breastfeeding for more than 13 weeks does not protect against hospitalization due to RTIs when compared to bottle-fed infants. [24]

The protective mechanisms of breastfeeding, especially EBF against RTIs in infants might be due to the presence of immunoglobulins in breastmilk and the avoidance of contamination from alternative feeding. [8] This mechanism supports some of evidence that longer duration of breastfeeding provides an extended period of immunological protection against RTIs.

In a recent systematic review by Williams et al. (2013) published on infant feeding and hospitalization in developed countries, the authors concluded there was no protective relationship between infant feeding mode and hospitalization due to illnesses in developed countries. [27] The current review focused on the outcome of hospitalization, due to an RTI only (no other illness), whereas the outcome of interest in the Williams review was "whether infants were hospitalized during their infancy" for *any* illness. The authors of that review did not find breastfeeding to be protective of hospitalization due to RTIs.

The limitations of this systematic review include: inconsistent use of standard definitions of breastfeeding (e.g., EBF, full, partial, predominant), and variability in describing duration of breastfeeding (e.g., 0-13 weeks, > 2 months, > 4 months, 3-6 months). Although four of six studies did adhere to the WHO definition of breastfeeding, capturing feeding data particularly on the WHO definition of EBF is challenging, as it requires more resources to regular monitoring of EBF and its strict adherence by mothers. There was little information on alternative feeding or the introduction of solids, information that may be important to include in future studies when examining illness in infants in the first year of life. As this review included studies conducted in several countries, Belarus, Hong Kong, UK, Australia and Spain, and with varying hospital admission rates as reported in this review, it is likely, as suggested by Bauchner et al. that detection bias exists. [20] Future studies could collect data on infant feeding mode at the time of hospital admission, albeit a snap-shot in time, in addition to more detailed data would help provide a more complete picture of infant feeding overtime. Infant hospitalization data did not include length of stay, diagnostic or severity of illness measures, although hospitalization itself is a measure of severity. Studies adjusted for a range of potentially confounding variables (e.g., low birth weight, other siblings, maternal age, maternal smoking, parental education), but were not consistent in their inclusion, making interpretation of the exposure outcome relationship difficult. There may also be residual

confounding, especially in the five observational studies. Finally, there was inconsistency in how study results were reported making fair and valid comparisons difficult. The strengths of this study include; a comprehensive and systematic search on multiple databases with a priori inclusion and exclusion criteria strictly followed during study selection, assessment of inclusion and adjustment for confounders in each study. Exposure data were collected from maternal reports or hospital records. Previous studies have shown maternal reports on breastfeeding to be reliable. [28,29] Parents recall on infant hospitalization has been shown to be valid. [30,31] Finally, the studies included in this review, collected data from the parents at frequent and regular time intervals reducing the impact of recall bias.

2.6 Conclusion

There were a limited number of high-quality studies published that examined the relationship between breastfeeding, RTIs and the risk of hospitalization in the first year of an infant's life in developed countries. As experimental evidence is limited in this area of study, there is a real need for observational cohort studies to be more rigorous in their methodologies, specifically when defining breastfeeding and recording duration. New and better methods must be developed to more accurately capture breastfeeding as an exposure. In this systematic review, four of six studies demonstrated that: breastfeeding, was protective for hospitalization due to an RTI and; that breastfeeding for three months or more reduced the risk of hospitalization due to an RTI and the protective effect was greater in those infants who were EBF.

*** High income countries according to the list provided by the World Bank (as of July2015).**

Source: http://data.worldbank.org/about/country-and-lending-groups

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Chapter 3 Research Paper #2

Feeding Mode and Its Impact on Health Service Utilization in Infants in First Year of Life: A Cross-sectional study in the Eastern Health Region of Newfoundland and Labrador

Chowdhury S MD[1], Midodzi WK Ph.D[1], Newhook LA MD, FRCPC, MSc [1,3,6], Gill N MSc[4], Halfyard B MSc[5], Newhook JT Ph.D[6], Twells LK Ph.D. [1,2],

1. Faculty of Medicine, Memorial University, Health Sciences Centre, 300 Prince Philip Drive, St. John's, NL, A1B 3V6, Canada

2. School of Pharmacy, Memorial University, Health Sciences Centre, 300 Prince Philip Drive, St. John's, NL, A1B 3V6, Canada

3. Eastern Health, Health Sciences Centre, 300 Prince Philip Drive, St. John's, NL, A1B 3V6, Canada

4. Perinatal Program NL, Janeway Children's Health and Rehabilitation Centre, St. John's, NL, Canada

5. Health Analytics and Evaluation Services, Newfoundland and Labrador Centre for Health Information, St. John's, NL, Canada

6. Janeway Pediatric Research Unit, Faculty of Medicine, Memorial University, St. John's, NL, Canada

Short Title: Infant-feeding mode and Health Care Utilization.

Corresponding author contact information:

L. K. Twells, Ph.D.

Associate Professor, School of Pharmacy and Faculty of Medicine, Memorial University,

300 Prince Philip Drive, St. John's, Newfoundland and Labrador, Canada A1B 3V6.

Telephone: 709.777.8920

Fax: 709.777.7044

Email: ltwells@mun.ca

Contributors: LT and LN conceived the study concept and methodology. For this study, data were provided to SC for secondary analysis by LT and LN. SC was responsible for data entry, data cleaning and data analysis. WM provided data analysis support. NG and BH provided support for data collection and analysis of healthcare use data. All authors were involved in the interpretation of study findings. SC wrote the initial draft with input from all authors. All authors provided critical revisions of the paper. All authors reviewed and approved the final manuscript. (A version of this manuscript has been submitted for peer review to the Journal of Paediatrics and Child Health, 2018.)

3.1 Abstract

Background

This study was conducted to evaluate if differences in infant-feeding mode impact early health services utilization (HSU).

Methods

The Feeding infant in Newfoundland and Labrador (FiNaL) Study was designed to evaluate infant feeding practices in Newfoundland and Labrador (NL), Canada. Information regarding demographics, maternal attributes, attitudes and other psychosocial attributes were collected during the 3rd trimester, while information on IFM was collected in the prenatal period (intent) and during the postnatal periods at three months and between 6 and 12 months. Consenting mothers were contacted at 12 months' post-delivery to examine the use of health care services by the infant in the first year of life. HSU outcomes included: family doctor and emergency department visits, hospital admissions, medication use and radiological investigations. IFM was categorized by: exclusively breastfeeding (EBF), mixed feeding (MF) and exclusively formula feeding (EFF). Descriptive statistics were conducted to compare maternal characteristics and HSU outcomes associated with IFM. Multiple logistic regression was performed to assess the effect of IFM on HSU with adjustment for potential confounders. Adjusted odds ratios (aOR) and 95% confidence intervals (95% CI) were calculated.

Results

The sample included 242 mother-infant pairs that consented to take part in the study and agreed to

provide self-reported information on HSU for their infants in the first year of life. The sociodemographic characteristics of mothers included: 94% older than 26 years, 95% had post-secondary education, and 4.5% were single mothers. Concerning IFM, 55% were EBF, 28% were MF, and 17% were EFF at the age of one month. EFF infants had a significantly increased number of visits to: the emergency department (aOR= 2.31; 95% CI= 1.03-5.20) and hospital admissions (aOR= 4.35; 95% CI= 1.32-14.1) after adjustment for maternal age, level of education, marital status and dwelling area. Other HSU outcomes such as family doctor visits, specialists visits, medication use, and radiologic testing in the first year showed a higher prevalence associated with EFF.

Conclusion

Exclusively formula-fed infants had significantly more hospital admissions and emergency department visits in their first year of life compared to exclusively breastfed infants.

Keywords

Infant, Breastfeeding, Healthcare Services Use.

3.2 Introduction

Evidence demonstrates that breastfeeding has the most significant impact on child survival,[1,2] preventing over 800,000 deaths (13 percent of all deaths) of children under five in the developing world primarily through prevention of infectious diseases.[2,3,4,5] Even in industrialized nations, non-breastfed children are at a significant risk of dying [6,7] and six months of exclusive breastfeeding can decrease the risk of childhood illnesses such as gastrointestinal (GI) infections,[6-13] respiratory infections (RTIs), [6-9,10-13] acute otitis media (AOM),[6,10,11,12,13] childhood asthma, necrotising enterocolitis (NEC), obesity, type 1 and 2 diabetes, cancer and sudden infant death syndrome (SIDS). [7,9, 13]

Several studies have examined the health care costs of not breastfeeding including the number and duration of hospitalizations, emergency department and physician office visits. [14,15,16,17] Breastfeeding has been associated with economic benefits due to a lower risk of hospitalization in the first six months of life with a clear dose-response relationship.[8,12] A United States economic analysis study showed that if 90% of exclusively breastfed for 6 months were achieved instead of the 12% existing rates, up to 13 billion US dollars would be saved per year.[15] An Australian study estimated hospital system costs of about $1-2 million annually for the treatment of common childhood infections due to not breastfeeding, and that the Australian healthcare system could save between 60-120 million dollars if breastfeeding rates increased.[14] In the United Kingdom, a study evaluated that approximately £26.8 million could be gained annually by avoiding the costs of treating GI infections, RTIs, AOM, and NEC if EBF rates increased to 65% at four months and 100% of babies had been breastfed at discharge from the hospital.[16]

In 2014, members of the Organization for Economic Co-operation and Development (OECD) that have comparable systems of accounting, spent on average 12.4% of their Gross Domestic Product (GDP) on healthcare services.[18] During that period, Canada was among the top countries regarding percentage of GDP spending on health (10.4%), which was less than that of the United States (17.1%), Germany (11.3%), France (11.5%) but slightly more than that of the United Kingdom (9.1%), Australia (9.4%) and Japan (10.2%). [18] In most of those countries, the trend of rising proportion of GDP spent on healthcare has been growing steadily since the 1980's. The primary drivers of increased expenditure on healthcare costs include new patient management technologies, drug therapies and increasing consumer demand or utilization. [18] In 2016, the public health expenditure in Canada was $228 billion. Except the Territories, NL reported the highest per capita healthcare expenditure of $7,256. About 71% of that spending came from the public sector (provincial and territorial government 66%;other sources 6%), and 29% came from private sources (out of pocket 14%; private insurance 14%; others 3%). [19] The largest share of those health dollars (more than 60%) was spent on the hospital services (29.5%), drug supply (16%) and physician services (15.3%). Per-person health care spending is the highest for seniors and infants in this region of Canada. On average, in 2014, the NL provincial government spent approximately $10,800 per infant in their first year of life for medical services. This amount was nearly three times that of the average health care spend ($3915) per person by the provincial government. [19]

The province of NL has the lowest breastfeeding initiation rates (69.6%) and six-month exclusive breastfeeding duration rates in Canada. [20,22] Although the BF initiation rates have improved in NL, many women stop breastfeeding before 6 months. Rates of EBF are below national and global recommendations, with only 17% of NL women exclusively breastfeeding for 6 months. [20, 22, 23] Reasons why provincial breastfeeding rates are so low are multifactorial, and many regions of NL

have an entrenched formula feeding culture that is intergenerational, as demonstrated in previous research. [24, 25] Lower socioeconomic status is associated with infants being fed breastmilk substitutes. Low BF rates in this population increase the disproportionate burden of illness on families who are already socioeconomically disadvantaged. [24-29] Statistics shows that mothers who are young, unpartnered and have less formal education were less likely to initiate breastfeeding and discontinue BF early. The most common reasons reported by the mothers for stopping breastfeeding before six months were their perception of having insufficient breastmilk (44%), difficulty in feeding technique (18%) and medical conditions of the mother or child (9%). [20,21,22]

Eastern Health is the largest regional health authority in the province of NL. In 2014, about 61% of the population of NL (319,000/526,977) were living in the Eastern Health region. [21] According to the 2011-2012 Canadian Community Health Survey, breastfeeding initiation in the Eastern Heath region was significantly higher (at 72%) than the provincial rate of 69.6%. [20,22,23] There were 3,061 live births in Eastern Health facilities in 2014. Approximately, 45.1% (1,300 of 2,883) of mothers were exclusively breastfeeding from birth to discharge and 75.2% (2,169 of 2,883) of mothers provided at least some breastmilk to their babies between birth and discharge. Exclusive breastfeeding rates decreased to 13.8% by six months postnatal in this health region. [21,22,23] Few studies on the effects of breastfeeding on infants and mothers have been conducted in NL or other regions of Canada. [24-29] Two studies concluded that breastfeeding was strongly protective against severe infection requiring hospital admission; however, both studies were small and focused on Indigenous populations [24,25], and neither study conducted a cost analysis related to hospitalizations and HSU.

This study of HSU in infancy was conducted in the Eastern Health Region of NL, Canada. We aimed to study whether infant feeding mode was associated with HSU by infants in their first year of life.

3.3 Methods

3.3.1 *Study Design, Population and Setting*

The FiNaL Study

The Breastfeeding Research Working Group (BF RWG) group initiated the *Feeding infants in Newfoundland and Labrador* (FiNaL) Study to evaluate maternal attitudes and infant feeding practices in Newfoundland and Labrador (NL), Canada through the administration of a questionnaire at three time periods (phase 1,2,3). In this prospective province-wide birth cohort study, pregnant women in their third trimester of pregnancy (phase 1) were recruited. Follow-up surveys were administered at when the infant was 1-3 months old (phase 2) and 6-12 months old (phase 3). A detailed questionnaire was administered at each phase. Information regarding feeding mode and psychosocial factors such as maternal age, education, socioeconomic factors and social supports were collected. Of the mothers who filled in all three surveys, a sub-sample were consented and enrolled in the HSU study. The study was approved by the NL Provincial Health Research Ethics Authority (HREA), # 2013.292 and is included in Appendix A.

3.3.2 *Data Collection*

Inclusion criteria: The FiNaL Study recruited expectant mothers who were 18 years or older, were English-speaking individuals (in their third trimester of pregnancy) and living in NL. Recruitment was carried out at pre-natal classes, in the offices of family physicians, nurse practitioners, obstetricians and public health nurses and through social media and posters. Participants were also

recruited through telephone or e-mail contact with a member of the research team in response to social media and posters placed in community settings. The questionnaires were completed in paper form (returned in postage-paid envelopes), by telephone or on-line by using Survey-monkey.

Exclusion criteria: Pre-term infants and those with major congenital disorders or inability to feed orally (*n*=59) were excluded. Also, mothers with serious health issues preventing breastfeeding (n=4), twin or multiple pregnancies (n=12, representing 24 infants), infants placed in social services from the birthing parents (*n*=2) and infants deceased at birth or just after birth (*n*=2) were excluded.

The FiNaL Study enrolled 1,283 expectant mothers in their third trimester living in the province of NL. Of them 66% (*n*=844) intended to exclusively breastfeed to 6 months. From those participants, 51% (*n*=658) participated in the first postnatal survey (1-3 months postnatal, phase 2) and 44% (*n*=561) completed the second postnatal survey (6-12 months, phase 3).

3.3.3 *The Health Services Utilization (HSU) Study*

During the postnatal phases of the FiNaL study, information on HSU by the infants was collected. Mothers residing in the Eastern Health region of NL who have already taken part in the FiNaL Study, phase 3 were invited to participate in this study and were re-consented. Of the 561 mothers who completed the questionnaire in phase 3 of the FiNaL Study, a total of 362 (65.4%) were eligible to take part in the study. Reasons for in-eligibility (*n*= 199) included preterm infants, having congenital disorder leading to inability or difficulty for oral feeding (*n*=59), multiple births (*n*=12, a total of 24 infants), deceased at or just after birth (*n*=2), refused by parents (*n*=2) and parents unable to breastfed due to illness (*n*=4). Other participants were excluded due to the duplication of names, study withdrawal and having a residence outside the Eastern Health region. Of them, 242 (67%) of mothers consented to take part in the HSU study and returned the questionairre.

3.3.4 *HSU study variables and outcomes*

Data on HSU were collected from a self-reported questionnaire and included questions on episodes of infectious diseases including diagnosis of ear infection, RTIs, GI infections, and UTIs. RTI's included episodes of influenza, croup, whooping cough, pneumonia and bronchiolitis. GI infections included gastroenteritis/stomach flu. Information regarding physicians and hospital visits, medication use, and medical investigations related to those infections were collected. The FiNaL Study provided demographic information on family structure, mothers' health, ethnicity, maternal age, educational and socioeconomic status. The frequency of infections was calculated by the total number of episodes reported by the parent.

Participant recruiting process is illustrated in **Figure 3.1 Flowchart of participant recruitment process.**

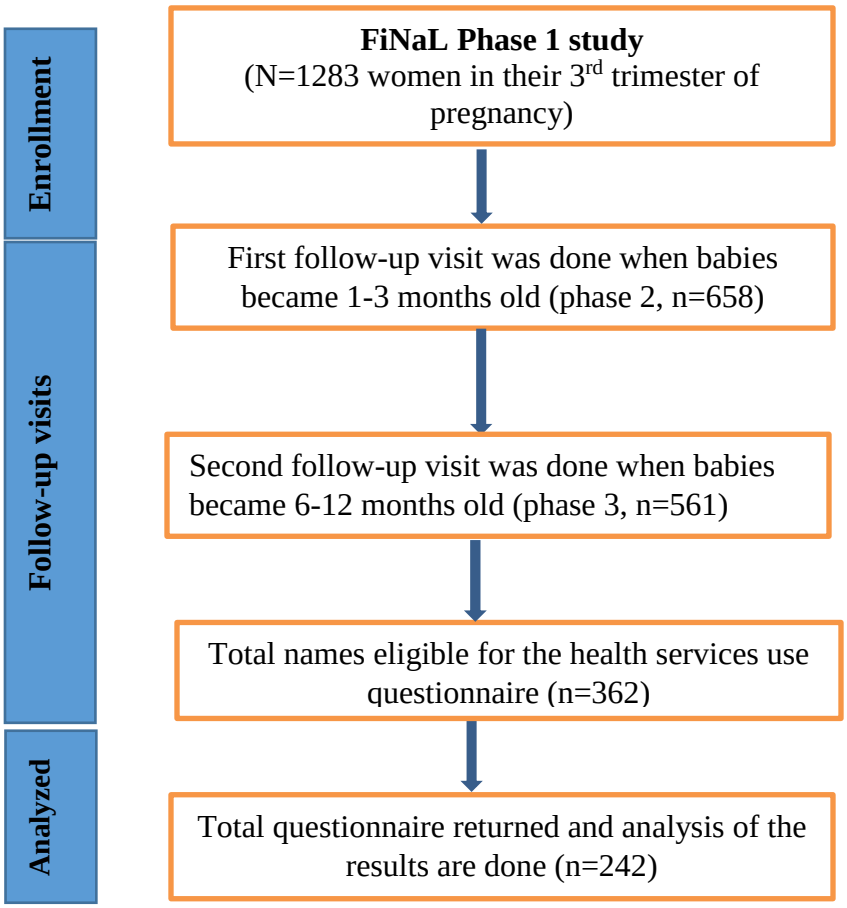

Figure 3.1: Flowchart of participant recruitment process

3.3.5 *Definitions of study exposures*

The FiNaL Study collected data on breastfeeding duration rates at both postnatal phases of the study. Infant feeding modes (IFM) were defined following the WHO/UNICEF criteria. 'Exclusive breastfeeding (EBF)' was used when infant received only breastmilk (including breastmilk that has been expressed or from a wet nurse) and nothing else, except for oral rehydration solution (ORS), medicines and vitamins and minerals when needed. [1] 'Mixed feeding' (MF) was classified as an infant receiving breastmilk and other food or liquid including water, non-human milk, and formula. 'Exclusive formula feeding' (EFF) was classified as the IFM where infants were fed only on a breast-milk substitute. [1]

3.3.6 *Statistical Analysis*

Descriptive statistics, either sample size (n's) and percentages for categorical variables and means (with standard deviation) for continuous variables were presented to compare baseline maternal characteristics and HSU outcomes associated with IFM. We used generalized linear models to evaluate the effects of infant feeding modes on the frequency of any infection while adjusting for potential confounding factors. As the number of physicians and hospital visits per patient were measured as whole numbers or counts and were considered to be discrete measures, the HSU were presented as percentages due to its non-normal distribution. Logistic regression was used to assess health care services utilization. The significance of the model was assessed using the χ-squared likelihood ratio statistic. Multiple logistic regression analysis was subsequently performed using RTIs, GI infections, ear infection, UTI and hospital admissions as binary (yes/no) response

variables. Potential confounding factors assessed were maternal age (years), education, marital status and dwelling area (urban/rural). The significance level was set at 5% (α=0.05) for confounding factors. Main exposure variables were EBF, MF, or EFF and adjusted odds ratio (aOR) and 95% confidence interval (CI) were calculated. EFF was chosen as the reference category in the final logistic regression model. The statistical package SPSS V.23 was used.

3.3.7 *Ethics Considerations*

The study received ethical approval from the Provincial Human Research Ethics Authority (HREA) # 09.81.

3.4 Results

Of the 362 eligible mothers in the HSU study, 242 (67%) mothers returned the HSU questionnaire with complete information. Infant feeding mode from the returned questionnaire showed that 134 (55%) were exclusively breastfed (EBF), 68 (28%) mixed fed (MF) and 40 (17%) infants were exclusively formula fed (EFF) for at least one month.

3.4.1 *Demographics*

Most of the maternal respondents in this study were 26 years of age or older (94%), most had post-secondary education (95%) and earned more than $30,000 annually (total household income) (97%). Most of the participants were non-smokers (97%), primiparous (60%), residents of an urban area (69%) and were partnered (96%). Almost all participants (98%) had a regular family doctor. Almost all infants were immunized (95%). (**Table 3.1**). Results show that mothers who were older than 26 years (p=0.034), had any type of post-secondary education (p=0.001), and were married (p=0.002) tended to breastfeed their infants exclusively for at least one month.

This was a sub-sample of the larger province-wide FiNaL Study. There were no significant differences between the participants of the FiNaL study and the HSU study (**See Appendix C**),

except regarding residence (more than 52% of the FiNaL Study participants were from rural areas whereas, only 31% participants of the current study reported living in rural areas). This was expected as the current study was limited to the Eastern region of NL, while the FiNaL Study was a province-wide study with representation from other areas of the province. The demographic information of the responders and the non-responders of the HSU questionnaire was also analyzed. Mothers who were partnered, completed post-secondary education with a household income of more than $30,000/year and experienced a vaginal delivery were more likely to complete the HSU questionnaire ($p \leq 0.05$). There were no differences in age, parity, residence or smoking status between the responders and non-responders (data not shown).

Table 3.1: Baseline characteristics of mothers and infants by infant feeding mode.

Factors	Overall n (%)	EBF n (%)	Mixed Feeding n (%)	EFF n (%)	*p*Values
Group sample, N	242	134 (55.4)	68 (28.1)	40 (16.5)	
Maternal/household factors					
Younger age (18-25 yrs.)	15 (6.2)	7 (5.2)	2 (2.9)	6 (15.0)	*0.034*
Caesarian delivery	60 (24.8)	34 (25.4)	18 (26.5)	8 (20.0)	*0.734*
Current Smokers	8 (3.3)	2 (1.5)	3 (4.4)	3 (7.5)	*0.147*
Multiparous	96 (39.7)	56 (41.8)	22 (32.4)	18 (45.0)	*0.325*
Post-Secondary education	230 (95.0)	133 (99.3)	63 (92.6)	34 (85.0)	*0.001*
Total household income (>30,000 Can$)	235 (97.1)	132 (98.5)	66 (97.1)	37 (92.5)	*0.138*
Single mothers	11 (4.5)	3(2.2)	2 (2.9)	6 (15.0)	*0.002*
Rural dwellers	75(31.0)	43(32.1)	18(26.5)	14 (35.0)	*0.599*
Child factors					
Has regular family doctor	237 (97.9)	132 (98.5)	67 (98.5)	38 (95.0)	*0.361*
Immunization before 12 months	230 (95.0)	124 (92.5)	67 (98.5)	39(97.5)	*0.132*
History of influenza vaccination	91 (37.6)	48 (35.8)	23 (33.8)	20 (50.0)	*0.2*

n= grouped sample size
n=number of events
%= percentage of events by group total by total (N)
SD=Standard deviation
EBF=Exclusively breastfed
EFF=Exclusively formula fed

3.4.2 *Common Infections During Infancy*

Half the infants (*n*=121) were reported to have had at least one type of infection in their first year of life; 31% had an ear infection, 17% a yeast infection, 16% an RTI, 7% a GI infection, and 4% a UTI. The top five reasons for healthcare services use were ear infection (31%), yeast infection (17%), croup (11%), jaundice (11%) and GI infections (6%). EBF and MF infants had a significantly lower risk of a UTI (3.0% and 1.5% respectively) compared to the EFF infants (4%) in the first year of life ($p \leq 0.05$) (data not shown in the tables). No other associations between feeding mode and infections were observed. The effect of EBF on the risk of infection did not change in the adjusted analyses (data not shown).

3.4.3 *Health Services Use*

Most survey participants (84%) visited their family doctor (*n*=203) with their infant in the first year of life, irrespective of feeding mode. Of them, more than 81% of the EBF infants (*n*=109) had visits to a family doctor compared to 90% of those who were EFF (*n*=36) and 85% of those infants (*n*=58) who were MF.

More than 49% of survey participants (*n*=119) reported consultations with specialists for their infants. EBF and MF infants had a lower number of specialist visits (49% and 46% respectively) compared to that of the EFF infants (58%).

Nearly 43% of infants (*n*=103) had visits with health professionals other than doctors (e.g., dietitian, public health nurse, lactation consultant) and more than one-third (33%) underwent

radiological tests (e.g., x-ray, ultrasonogram). Half (50%) of the mothers (*n*=122) reported that their infants visited the emergency department (ED); EFF infants had more ED visits (63%) than their EBF and MF peers (44% and 56% respectively). EBF infants had significantly less hospital visits (5%) than that of MF (9%) and EFF (20%) infants (p=0.014)**.**

Nearly 60% of infants (*n*=145) were prescribed medications by the health professionals, of them 64% had antibiotics. Results show that EBF infants were prescribed significantly fewer antibiotics than their MF and EFF peers (53% vs 73% and 79%; (p=0.017)). (**Table 3.2**).

Table 3.2: Health service utilization by infant feeding modes

Outcome variables	**Overall n (%)**	**EBF n (%)**	**Mixed Feeding n (%)**	**EFF n (%)**	***p*Values**
Total sample, N	**242**	**134 (55.4)**	**68 (28.1)**	**40 (16.5)**	
Family doctor visit	203 (83.9)	109(81.3)	58 (85.3)	36 (90.0)	*0.397*
Any specialist consultation	119 (49.2)	65 (48.5)	31 (45.6)	23 (57.5)	*0.476*
Surgical specialist	54 (45.4)	31 (47.7)	15 (48.4)	8 (34.8)	*0.523*
Medical subspecialist	88 (74.0)	45 (69.2)	22 (71.0)	21 (91.3)	*0.106*
Paediatrician	64 (53.8)	35 (53.8)	14 (45.2)	15 (65.2)	*0.344*
ENT specialist	20 (16.8)	10 (15.4)	7 (22.6)	3 (13.0)	*0.587*
Allergist	12 (10.1)	5 (7.7)	4 (12.9)	3 (13.0)	*0.636*
Ophthalmologist	9 (7.6)	5 (7.7)	2 (6.5)	2 (8.7)	*0.952*
Other specialist	56 (47.1)	32 (49.2)	12 (38.7)	12 (52.2)	*0.540*
Consultation with other health professionals	103(42.6)	53 (39.6)	35 (51.5)	15 (37.5)	*0.210*
Dietician	7 (6.8)	3 (5.7)	2 (5.7)	2 (13.3)	*0.553*
Public health nurse	44 (42.7)	22 (41.5)	13 (37.1)	9 (60.0)	*0.316*
Lactation consultant	66 (64.1)	35 (66.0)	24 (68.6)	7 (46.7)	*0.306*
Others	28 (27.2)	11 (20.8)	12 (34.3)	5 (33.3)	*0.319*
Radiological tests	80 (33.1)	40 (29.9)	22 (32.4)	18 (45.0)	*0.200*
X-ray	46 (56.8)	23 (56.1)	12 (54.5)	11 (61.1)	*0.909*
Ultrasound	35 (43.8)	18 (45.0)	11 (50.0)	6 (33.3)	*0.558*
	122 (50.4)	59 (44.0)	38 (55.9)	25 (62.5)	*0.069*

Emergency department visit

Hospital use	21 (8.7)	7 (5.2)	6 (8.8)	8 (20.0)	*0.014*
Overnight hospital stay	16 (76.2)	5 (71.4)	5 (83.3)	6 (75.0)	*0.877*
NICU admission	7 (33.3)	4 (57.1)	3 (50.0)	0 (00.0)	***0.120***
PICU admission	1 (4.8)	0 (00.0)	0 (00.0)	1 (12.5)	*0.426*
Any prescribed medication	145 (60.0)	75 (56.0)	41 (60.3)	29 (72.5)	*0.173*
Antibiotics	93 (64.1)	40 (53.3)	30 (73.2)	23 (79.3)	***0.017***
Anti-fungal	32 (22.1)	22 (29.3)	7 (17.1)	3 (10.3)	*0.074*
Puffers	25 (17.2)	10 (13.3)	9 (22.0)	6 (20.7)	*0.431*
Anti-reflux medication	16 (11.0)	8 (10.7)	2 (4.9)	6 (20.7)	*0.114*
Other medication	44 (30.3)	27 (36.0)	7 (17.1)	10 (34.5)	*0.091*
Vitamins	192 (91.9)	122 (91.0)	58 (85.3)	12 (30.0)	*0.000*

Note. Infants had more than one type of visit, so individual numbers do not add up to the total number

Trend analysis:

The majority of all infants had visits to family doctors (57%), specialists (68%), emergency department (88%) and hospital (91%), however EBF infants were less likely than EFF and MF infants to report HSU in the first year of life. The majority of all infants were prescribed 1-2 medications (59%) in the first year of life, and there was a linear trend towards more prescriptions for medicines in the EFF and MF infants when compared to their EBF peers.

Upon evaluating the data, the results of the questionnaire revealed that there was a significant trend of more frequent use of health care services especially regarding family doctor visits and specialist visits, by the EFF and MF infants compared to that of EBF infants (**Table: 3.3).**

Table: 3.3: Trend analysis of frequency of visits for healthcare services by infant feeding mode

Outcome variables	**Number of visit**	**Overall**	**EBF**	**Mixed Feeding**	**EFF**	***p*Values***
		N=242	**134**	**68**	**40**	
Family doctor visit visit	***Total***	**203**	**109**	**58**	**36**	*0.044 (0.037)*
	1-2 visit	116 (57.1)	71 (65.1)	27 (46.6)	18 (50.0)	
	3 or more	87 (42.9)	38 (34.9)	31 (53.4)	18 (50.0)	
Any specialist visit	***Total***	**119**	**65**	**31**	**23**	*0.037 (0.559)*
	1-2 visit	81(68.1)	52 (80.0)	16 (51.6)	13 (56.5)	
	3 or more	36 (30.3)	13 (20.0)	13 (42.0)	10 (43.5)	
Paediatrician	***Total***	**63**	**35**	**14**	**14**	*0.039 (0.035)*
	1-2 visit	44 (69.8)	29 (82.9)	7 (50.0)	8 (57.1)	
	3 or more	19 (30.2)	6 (17.1)	7 (50.0)	6 (42.9)	
ENT specialist	***Total***	**18**	**10**	**6**	**2**	*0.335 (0.153)*
	1-2 visit	14 (77.8)	9 (90.0)	4 (66.7)	1 (50.0)	
	3 or more	4 (22.2)	1 (10.0)	2 (33.3)	1 (50.0)	
Allergist	***Total***	**12**	**5**	**4**	**3**	*0.466 (0.297)*
	1-2 visit	11 (91.7)	4 (80.0)	4 (100.0)	3 (100.0)	
	3 or more	1 (8.3)	1 (20.0)	0	0	
Ophthalmologist	***Total***	**9**	**5**	**2**	**2**	
	1-2 visit	9 (100)	5 (100.0)	2 (100.0)	2 (100.0)	
Other specialist	***Total***	**57**	**34**	**12**	**11**	*0.105 (0.073)*
	1-2 visit	43 (75.4)	29 (85.3)	7 (58.3)	7 (63.6)	
	3 or more	14 (24.6)	5 (14.7)	5 (41.7)	4 (36.4)	
ED visit	***Total***	**122**	**59**	**38**	**25**	*0.130*

						(0.069)
	1-2 visit	107 (87.7)	54 (91.5)	34 (89.5)	19 (76.0)	
	3 or more	15 (12.3)	5 (8.5)	4 (10.5)	6 (24.0)	
Hospital visit	***Total***	**21**	**7**	**6**	**8**	*0.501*
						(0.346)
	1-2 visit	19 (90.5)	6 (85.7)	5 (83.3)	8 (100.0)	
	3 or more	2 (9.5)	1 (14.3)	1 (16.7)	0	
Any medication prescribed	***Total***	**145**	**75**	**41**	**29**	*0.097*
						(0.042)
	1-2 med	86 (59.3)	44 (58.7)	23 (56.1)	19 (65.5)	
	3 or more	17 (11.7)	10 (13.3)	4 (9.8)	3 (10.3)	
Antibiotics	***Total***	**67**	**31**	**19**	**17**	*0.406*
						(0.393)
	1-2 med	54 (80.6)	23 (74.2)	17 (89.5)	14 (82.4)	
	3 or more	13 (19.4)	8 (25.8)	2 (10.5)	3 (17.6)	
Antifungal	***Total***	**22**	**15**	**5**	**2**	*0.168*
						(0.364)
	1-2 med	21 (95.5)	15 (100.0)	4 (80.0)	2 (100.0)	
	3 or more	1 (4.5)	0	1 (20.0)	0	
Puffer	***Total***	**16**	**8**	**5**	**3**	*0.386*
						(0.551)
	1-2 med	14 (87.5)	7 (87.5)	5 (100.0)	2 (66.7)	
	3 or more	2 (12.5)	1 (12.5)	0	1 (33.3)	
Other medications	***Total***	**29**	**20**	**4**	**5**	*0.536*
						(0.523)
	1-2 med	25 (86.2)	17 (85.0)	3 (75.0)	5 (100.0)	
	3 or more	4 (13.8)	3 (15.0)	1 (25.0)	0	

*pValues in parenthesis are presented for linear trend.

3.4.4 *Multivariate Modelling*

After adjusting for maternal age, level of education, marital status and residence, EFF infants compared to infants who were EBF, had more ED visits (aOR 2.31, 95% CI [1.03-5.20]) and significantly more hospital visits, (aOR 4.35, 95% CI [1.35-14.1]). There were no significant differences between MF infants and infants who were EBF (**Table 3.4**).

Table 3.4: Multivariate analysis of health care service utilization

Study Outcomes	Model	EBF (reference)	Feeding *OR (95% CI)*	EFF *OR (95% CI)*
Any doctor visit	*Unadjusted*	1.00	0.90 (0.39-2.07)	2.95 (0.65-13.29)
	Adjusted[a]	1.00	0.90 (0.40-2.07)	4.66 (0.60-36.28)
Family doctor visit	*Unadjusted*	1.00	1.33 (0.59-2.97)	2.06 (0.67-6.33)
	Adjusted[a]	1.00	1.33 (0.60-2.96)	6.88 (0.90-52.88)
Specialist visit	*Unadjusted*	1.00	0.89 (0.50-1.60)	1.44 (0.70-2.93)
	Adjusted[a]	1.00	0.89 (0.50-1.60)	1.29 (0.59-2.82)
ED visit	*Unadjusted*	1.00	1.61 (0.90-2.90)	**2.12 (1.03-4.38)***
	Adjusted[a]	1.00	1.61(0.90-2.90)	**2.31(1.03-5.20)***
Hospital use	*Unadjusted*	1.00	1.76(0.57-5.45)	**4.54(1.53-13.4)***
	Adjusted[a]	1.00	1.76 (0.57-5.45)	**4.35(1.35-14.1)***
Radiological Test[b]	*Unadjusted*	1.00	1.12 (0.60-2.11)	1.92 (0.93-3.97)
	Adjusted[a]	1.00	1.12 (0.60-2.11)	1.48 (0.66-3.34)
Medication use[c]	*Unadjusted*	1.00	1.20 (0.66-2.16)	2.07 (0.96-4.49)
	Adjusted[a]	1.00	1.20 (0.66-2.16)	2.26 (0.94-5.42)

Note. OR= odds ratio; CI= confidence interval

*Significant data at 95% CI

[a]Adjusted OR (aOR) for maternal age, level of education, marital status and residence

[b]Radiological tests include X-ray and ultrasonogram

[c]Medications: antibiotics, antifungals, puffers, vitamins and other medications

3.5 Discussion

In this study, a sample of 242 mother-infant pairs were enrolled in order to examine HSU in the first year of life in the Eastern Health Region of NL. Their inclusion was based on participation in phase 2 of the FiNaL Study.

The main findings of this cross-sectional study were that exclusive breastfeeding even for the first month of life decreased the use of health services (e.g., emergency department use and hospital visits) compared to those infants who were exclusively formula fed or mixed fed. This finding continued after adjustment of maternal age, education, marital status and residence. In this study, we examined the association between infant feeding mode and the frequency (expressed as the number of infectious episodes) and the severity of health care services use (e.g., episodes of family doctor visits, hospitalization, emergency visits, radiological investigations and use of medications) for common infections in infants throughout the first year of life. Due to the low breastfeeding rates in this population we were only able to compare HSU and infant feeding modes with EBF for up to only one month of age.

According to the WHO, pneumonia or other acute respiratory tract infections and gastroenteritis or diarrhea are two of the most significant causes of death in children under five years. Since 1990, infant mortality has decreased substantially from these infections, but the same progress has not been observed regarding morbidity. [1,30] A Global Strategy developed by the WHO and United Nations Children's Fund (UNICEF) for infant feeding suggested the lack of breastfeeding, in particular exclusive breastfeeding during the first twelve months of life, was an important risk

factor for infant and childhood mortality and morbidity. The WHO also reported that nearly 50% of the burden of diarrheal disease and RTIs in childhood were attributable to malnutrition and more than 75% of the cause of that malnutrition was inappropriate feeding practices in the first year of life. [1,30] The WHO report also stated that only 35% or one in three infants worldwide were exclusively breastfed for four months or less. The WHO recommends that every infant should be exclusively breastfed at least for the first six months of life. After that, children should receive nutritious and safe complementary foods to meet their evolving nutritional requirements, but breastfeeding should be continued for up to two years of age and beyond. [1]

Several studies revealed that in children who have experienced early exposure to the use of formula, the risk of physician and hospital visits increase for infections such as RTIs and GI infections. [3,6,8,10,11,12,13] Evidence has shown that exclusive breastfeeding, followed by partial or predominant breastfeeding during first six months or more of life was associated with a decreased risk of common childhood infections. [3,6,8,10,11,12,13] Our study findings are in line with the results of those studies. The protective effects of breastfeeding could be explained by the presence of several factors in the breast milk. Its epidermal growth factor induces the maturation of the intestinal epithelium, oligosaccharides, and immunoglobin A prevent attachment of infectious agents, and lactoferrin disrupts the bacterial outer membrane. [31,32]

In the second study of this thesis, the relationships between infant feeding mode and health care services use was examined using multiple linear regression. Although this was a small pilot study, significant differences were observed in ED and hospital visits. Further evidence is needed from larger cohort studies, in order to further understand this relationship and to determine the impact on health care outcomes and costs.

Two of the previous studies showed that breastfeeding had no protective effects on infants who were breastfeeding for less than four months. The authors also mentioned that infants who were

breastfed for more than four months had lower hospitalization rates for infectious diseases (HR 2.45, 95% CI 1.28–4.66) than their peers who were breastfed for four months or less. Also, the infants who were breastfed for at least six months had lower risks of otitis media (OR 1.95, 95% CI 1.06 –3.59) and pneumonia (OR 4.27, 95% CI 1.27–14.35) compared with the infants who were breastfed for four months or less. [6,33] As the data was analyzed for just one month the effect of breastfeeding for longer duration could not be assessed in this study.

Information about the diagnosis of infants' diseases and the regarding health care services uses were provided by the mothers in response to the questionnaires. This self-reported method is widely accepted in the epidemiologic studies, and it reliably reflects the actual occurrences. [34] Although the assessment of breastfeeding of infants through the questionnaire is a valid method, misclassification might have occurred. Of all postnatal eligible participants of the FiNaL Study, surveys with all necessary information were returned by 65% of mothers. Compared with respondents who were included in the analyses, those who were excluded because of the missing data were younger, less educated, smokers, rural residents and had low-income. Evidence showed that those characteristics of mothers were associated with a shorter period of exclusive breastfeeding in Canada. [20] This might have led to an underestimation of the disease incidence and frequency of health care usage.

Previous research in Canada on this topic has demonstrated the protective effects of breastfeeding in infants. Results showed substantial benefits against childhood diseases [24,25] and that breastfeeding promotion programs could be a critical intervention. Our study results are similar to previously published studies.

Assessing the health as well as the economic costs (due to the use of medical services) of low breastfeeding rates is a significant task. Estimation of health services use, and related cost is necessary for developing cost-effective interventions to improve the breastfeeding rates. This

information could help policymakers regarding the development of educational policies and development of breastfeeding support programs.

The present study provides, for the first time (to our knowledge), estimates of health care services utilization by a sample of full-term healthy infants living in Canada. The analysis of HSU by infant feeding mode has not been published. Further research is needed to determine the cost of services utilized in the first year of life and how this relates to infant feeding mode as this information provides empirical data around the impact of not breastfeeding. For instance, Brazil could be an excellent example of showing success in increasing breastfeeding rates. [35] They achieved significantly improved breastfeeding rates by using a combination of strategies that include education campaigns, training programs at the federal and local levels and laws and regulations around the use of breastmilk substitutes. [35] An integrated provincial breastfeeding program should have the key components that include training programs, communications for health promotion at a population level, political will and legislation, advocacy, evaluation research and appropriate funding.

There are several limitations of our study. Due to challenges with collecting exposure data on feeding mode duration, our exclusive breastfeeding rate was considered valid and reliable for the first month only. Therefore, it was quite surprising to find a significant difference between ED and hospital visits between EBF and EFF infants after controlling for confounders. However, this was a pilot study, and we intend to do future studies to understand this relationship better. This was a cross-sectional study, and as a result the temporal relationship between exposure and outcome cannot be established. The data on exposure and outcome were self-reported and could result in misclassification of either. As a pilot study, our results are based on a relatively small sample size, however the socio-demographic characteristics of the HSU study respondents were similar with

those of the participants of the FiNaL Study, a province wide study on over 1000 expectant mothers. Futher analysis of the results showed no difference between the non-responding eligible mothers and the participants of this study. The likelihood of selection bias is minimal. The FiNaL study had a selection bias of higher education and household income mothers and the participants of this study are representative of those mothers in the province of NL. The data presented in this second study provides critical evidence on health care services use by infants in their first year of life by infant feeding mode suggesting that infants who are EFF are more likely to use ED and hospital services.

3.6 Conclusion

Exclusively formula-fed and mixed-fed infants had higher use of health care services such as the ED and hospital visits, in the Eastern Health Regions of NL, Canada during their first year of life compared to infants EBF for at least 1 month. The study results also showed infants who were EBF had lower use of other health services such as family doctor, specialist visits, prescriptions, and radiologic testing compared to EFF and MF infants, although not statistically significant.

NL has the lowest breastfeeding initiation and duration rates in Canada and the reasons for this are complex and related to socioeconomic, cultural, clinical, and healthcare challenges. To increase breastfeeding rates, a coordinated, multifaceted and multi-level approach is required. There are very few studies published using Canadian data on this topic and research on health care services use according to infant feeding mode has never been conducted in NL. This study will provide regionally-relevant data that can inform the trend of health care services use by infants and will help to inform the development of policies and programs. By developing targeted interventions to improve breastfeeding rates in our province, we can ultimately enhance infant

health and improve the cost-effectiveness of the health care system by implementing appropriate preventative measures.

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Conflict of interest

None of the authors declared any conflict of interest.

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Chapter 4 Discussion

This program of research was designed to investigate associations between mode of infant feeding and 1) hospitalization due to RTI's and 2) health services use in an infant's first year of life. The final chapter of this thesis provides a summary discussion of the findings, the strengths and limitations of the studies and the clinical implications of the findings, identification of future research, and conclusions of this study.

The first section includes a summary of the findings. The second section provides a description and discussion of the strengths and limitations of the studies. The third section outlines the clinical implications and knowledge translation. The fourth section describes potential areas for future research in this area. The final section includes a summary of the conclusions of this research.

4.1 Summary

Respiratory tract infection (RTI) is a leading cause of mortality and hospitalizations in infants. [1,2,3] Studies have demonstrated the protective effects of breastfeeding against some chronic non-communicable diseases [4,5,6,7], as well as some common childhood infections including RTIs. [8-23] Most evidence showing the protective effects of breastfeeding against common childhood infections has evolved from studies conducted in developing countries [1,2,14-17]; thus, there is a debate whether those benefits apply to infants in developed countries. Therefore, a systematic review (research paper #1) had been conducted to assess the existing evidence on mode of infant feeding and the risk of hospitalization due to RTIs for full-term infants in developed countries. Studies included in the review paper reported an unadjusted association

between breastfeeding and a decreased risk of hospitalization due to RTIs. When potential confounding variables had been included in analyses, the adjusted effects of breastfeeding become statistically non-significant except in two studies. [18,23] Further analyses revealed that protective effects were of more significant magnitudes in those infants who were exclusively breastfed or breastfed for a particular period [18,19,23].

Infectious disease is one of the leading reasons for healthcare services use by infants in developed countries. [24-27] NL has the lowest exclusive breastfeeding rate of 17% at six months [28,29] and the highest per capita healthcare expenditure ($7,256) among the provinces of Canada. [29,30] Eastern Health is the largest integrated regional health authority in NL that provides healthcare to more than 60% of the population of the province. [28] According to the Canadian Community Health Survey, the breastfeeding initiation rate in the Eastern Health region is 72% that is higher than the provincial rate (69.6%) but lower than the national rate of 90.3%. [28,31,32] Hospital records report that about 45% of infants in this health region have been exclusively breastfed from birth to discharge from the hospital, but by the time they are six months old this percentage reduces to 14%. [30,31,32]

Based on the results of the systematic review (research paper #1), we conducted a cross-sectional study to evaluate whether there are any differences in health services by infants when comparing feeding mode in the Eastern Health region of NL. In total, 242 mother/infants pairs were included in the cross-sectional study (research paper #2), and the results show that half of these infants have used healthcare services at least for one type of infection in their first year of life. Further analysis shows that EFF infants need significantly more ED visits and hospital stays than that of EBF infants or MF infants. That trend remains significant after adjusting for confounding factors.

4.2 Current study findings

For the review paper (research paper #1), relevant literature had been extensively searched, and six articles [18-23] are selected with the full agreement of the two reviewers. Four of those studies were prospective cohorts, [18-20,22] one was cross-sectional survey [23] and the other one was a randomized trial [21]. All the included studies had been conducted in developed countries, with good health service delivery systems, sanitary conditions, and public health measures. The six studies included in the review consistently reported the protective effects of breastfeeding against infant hospitalization due to RTIs before adjusting for confounders. Considering the possible confounding variables (such as, maternal age, parity, socioeconomic status, employment, education, smoking, pregnancy complications, duration of labor, previous systemic illness, infant's birth weight, gender, delivery type, Apgar score and delivery center) in analyses, the adjusted effects of breastfeeding became statistically significant only in two studies [18,22] On further analysis, three of the studies [18,19,23] had shown greater magnitudes of protective effects in exclusively breastfed infants compared to their peers [18,19,23] and one study reported the graded benefits of breastfeeding for 3 months or more [22].

The cross-sectional study (research paper #2) was conducted to assess the use of health services by healthy full-term infants within the first year of life due to infections in the Eastern Health Region of NL. The population sample for the study was a subsample of the previously collected province-wide sample from the Feeding Infants in Newfoundland and Labrador (FiNaL) study that completed phase 3 of the survey. Information on the intents of mothers regarding infant feeding and psychosocial factors such as maternal age, education, socioeconomic factors, social supports had been collected from phase 1, during the prenatal period of the FiNaL study whereas

information regarding the feeding practices during their first year of life had been accumulated from the phase 2 and 3. On the other hand, health service utilization data was gathered from the survey questionnaire of this study. The data of 242 mother-infant pairs, who were living in the Eastern Health Region of NL had been collected and analyzed. Multiple logistic regression is performed to assess health service use by infants comparing the different modes of feeding after adjusting potential confounders.

Survey results showed that out of 242 infants, 55% were EBF (n=134), 28% were MF (n=68) and 17% infants were EFF (n=40) at the end of the first month of life. The demographic characteristics of the participants demonstrated that 6% mothers were younger than 26 years, 95% of them had post-secondary education, 5% were single-mothers, and almost 98% of them had family doctors. Results also revealed that participants who are older than 26 years (p=0.034), have a post-secondary education (p=0.001) and were partnered p=(0.002) practiced breastfeeding to their infants. This survey was done on a sub-sample of the province-wide FiNaL study, but there was no difference between the participants regarding the demographics, except their residence. As this survey was limited to the Eastern Health region of NL, almost two-thirds of the participants were living in an urban area compared to the residence of less than 50% mothers in the FiNaL study.

Almost half of the infants (n=121) had used health care services for at least one type of infection in their first year of life; ear infection (31%), yeast infection (17%), croup (11%), jaundice (11%) and GI infections (6%) were the top reasons. Results showed that EBF and MF infants had significantly ($p \leq 0.05$) lower risks of UTI compared to that of the EFF infants in their first year, no other associations between feeding mode and infections were observed. The effect of

breastfeeding on the risk of infection did not change in the adjusted analysis comparing to that of unadjusted analysis.

Most of the survey participants (84%) visited their family physicians (81% of the EBF, 85% of EFF and 90% of mixed fed infants) and almost half of them had specialist consultations/appointments. Further analysis showed that EFF infants had a higher number of specialist visit (58%) compared to that of EBF and MF infants (49% and 46% respectively). More than 50% of infants (*n*=122) visited the emergency department, and nearly 9% infants (n=21) had to stay at the hospital. EBF infants had significantly less hospital stays (p=0.014) than their EFF and MF peers (5% versus 20% and 9% respectively). Nearly 64% infants were prescribed antibiotics and results showed that EBF infants (53%) had significantly lower (p=0.017) prescription of antibiotics than EFF (79%) and MF (73%) infants.

Trend analysis revealed that increased use of health care services was associated with the EFF infants compared to the EBF infants. However, in the multivariate analysis, only ED visits (aOR 2.31, 95% CI [1.03-5.20]) and hospital uses, (aOR 4.35, 95% CI [1.35-14.1]) remained significant after adjusting for maternal age, level of education, marital status, and residence.

4.3 Strengths and Limitations of the Studies

The systematic review (research paper #1) included in this thesis has several strengths and limitations. The most significant limitation of the study is inconsistency regarding the definition of infant feeding modes across the studies with various measures of exclusivity and duration applied. Although most articles have cited the WHO definition for different types of infant feeding methods, the authors have not followed the criteria strictly while defining those in their

studies. There has been no discussion or reporting on the types of alternative foods or complementary feeding or when they were initiated in the studies.

There is a possibility of detection bias, as hospitals in the various countries and regions have different thresholds for the admission of children. On the other hand, this may contribute to the heterogeneity of the study population. Sometimes, the information contained in those studies has been confusing to interpret as all the authors have not followed the same method of reporting of breastfeeding rates at the time of hospitalization. Moreover, the data on hospitalization does not include the length of stay or the degree of severity of illness, although hospital admission itself is regarded as a measure of severity.

The potential confounding variables mentioned in both univariable and multivariable modelling in the studies are siblings, [18-23] maternal age, [19-23] low socioeconomic condition, [18,19,20,22,23] low birth weight, [18-22] maternal smoking, [18-23] male gender, [18,19,20,22] parental education, [18-23] caesarean delivery. [18-22] Though the confounding variables included in those studies have been proven by the literature to be valid factors influencing the exposure and outcome of the studies, there are some other physiological, psychological and environmental factors related to mothers and infants that may have impacted both feeding mode and infant illness.

The main strength of the review study (research paper #1) is that a comprehensive search on multiple databases has been conducted following a predefined inclusion and exclusion criteria. Moreover, the studies have been assessed and graded by the reviewers following the US Preventive Services Task Force (USPSTF) Quality Rating Criteria for randomized controlled trials and cohort studies. [33] From the search findings of the previous studies, the potential confounding factors have been identified and adjusted in the statistical analysis.

There are several limitations of the cross-sectional study (research paper #2) as well. The term 'exclusively breastfed' has been used for the survey, but due to challenges around measurement it is limited to the infant's first month does not fulfill the criteria for the WHO recommended a definition of exclusive breastfeeding [3]. As it is a cross-sectional study, the temporal relationship between exposure and outcomes cannot be established from the results. However, most of the evidence on breastfeeding and morbidity in infants is based on observational studies, because it is neither ethical nor feasible to assign healthy, full-term infants randomly to be breastfed or formula fed. Analysis of the data shows that all the demographic characteristics of the respondents of this study are similar to those of the participants of the FiNaL study except residence. On the other hand, the participating mothers in the FiNaL study have a higher socioeconomic and educational status compared to that of the provincial level, [38] so, this study results may not be generalized to the whole population of the province.

In our study, the relationships between infant feeding modes and health care services use have been assessed by multiple linear regression, but the results should be interpreted cautiously, because of the small sample size. Further research is required through large cohort studies to estimate the magnitude of these significant effects better and to determine their importance in health care. As in the study, data regarding infant feeding modes have been collected for just one month, the effect of breastfeeding for longer duration could not be assessed. There is a likely underestimation of the protective effects of breastfeeding on infants' HSU. Because some of the studies included in the systematic review demonstrate that the protective effects of breastfeeding against infectious diseases including RTIs are proportionate to the duration of breastfeeding. [18,22,23]

Only 65% of all postnatal eligible participants of the FiNaL Study have fully completed the surveys. Mothers who were excluded because of missing data were younger, less educated, more likely to be smokers and had lower income as compared to those who fully completed the survey. Evidence shows that these are characteristics associated with mothers with a shorter period of exclusive breastfeeding in Canada, [30] leading to a further underestimation of HSU.

Also, information about the diagnosis of infants' illnesses' and the usage of health care services in both studies was provided by mothers in response to questionnaires, so there is a chance of self-report bias. Previous studies show that self-reported method of data collection reliably reflects actual occurrences [36,37] and as short-term recalls (< 1 year) were applicable to this study, there was less chance of recall bias.

The main strength of this study is that it has provided, for the first time (to our knowledge), the estimates of HSU by infants in NL. The results of this study have concurred with other studies conducted in other OECD countries, showing that that breastfeeding is associated with reduced risk of HSU.

4.4 Clinical Implications

The systematic review (research paper #1) provides the evidence that breastfeeding, especially exclusive breastfeeding has protective effects for infants against RTIs, including in developed countries with proper public health measures, sanitation and extensive immunization.

National and provincial recommendations for breastfeeding must be accompanied by policies that enable an environment for mothers to breastfeed in public places, allow for extended maternity leave, workplace policies for mothers returning to work, and legislation that regulates

the marketing and distribution of infant formula. NL has the lowest breastfeeding initiation and exclusive breastfeeding rates in Canada, resulting from a complex mix of socioeconomic, cultural, clinical, and healthcare challenges. Changing this health care problem requires a coordinated, multifaceted approach if breastfeeding initiation and duration rates are to be significantly improved. Few published studies have used Canadian data on this topic. [38-44] Moreover, research on HSU by infants has never been conducted in NL. Though this is a small study, it provides regionally relevant data to demonstrate the trend of HSU by infants. This data can be used to develop future studies by researchers, and it will help policymakers to find home-grown solutions to this critical public health care issue. By developing targeted interventions to improve breastfeeding rates in NL, infant health can be improved significantly, and the health care delivery system can become cost-effective.

4.5 Future Research

Although breastfeeding has been proven to have many beneficial effects on infant health, it is not clear if it is causally associated with decreased hospitalizations due to RTIs. The systematic review (research paper #1) highlights the paucity of high-quality studies comparing infant feeding mode and infant hospitalization due to RTIs. While the best study design for establishing causality, randomized controlled trials (RCTs), are not practical in this context, more high-quality prospective cohort studies regarding infant feeding mode and healthcare utilization are necessary with well-defined exposure (by using validated definitions such as the WHO definitions of infant feeding) and outcomes.

Without the feasibility to use RCTs, adjustment for confounding variables is necessary for the statistical analysis of the data. Therefore future studies should precisely record all known confounders affecting the potentiality for hospitalization. Researchers are advised to follow a universally accepted and validated the definition of infant feeding modes and infections to avoid misclassifications of exposure variables and outcomes variables. It is also important to record the duration of breastfeeding, the timing of introduction of complimentary liquids and foods and the frequency of infections and the length of hospital stay.

As in other regions of Canada, there are few studies in NL comparing infant feeding mode and health care utilization. This cross-sectional study (research paper #2) is the first study in NL (to our knowledge) that estimates the HSU by infant feeding mode. Further research is needed to determine the actual costs of those services and the interventions needed to increase breastfeeding rates substantially.

4.6 Conclusion

Our systematic review (research paper #1) provides evidence that there is a lack of high-quality research examining the relationship between breastfeeding and hospitalization of infants due to RTIs during the first year of life in developed countries. We need well-conducted cohort studies that will reduce the misclassification of exposure status and will include a better measurable outcome of the health care utilization.

The cross-sectional study (research paper #2) has demonstrated that EFF and MF infants have higher use of health care services than EBF infants due to common childhood infections in the Eastern Health regions of NL, Canada during their first year of life. This study will provide

valuable data to initiate further cohort studies to inform researchers regarding this topic. Decision makers can also use these results to take coordinated actions to improve breastfeeding rates in our province and improve infant health that would potentially result in significant savings to the healthcare delivery system.

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Appendix A

NEWFOUNDLAND AND LABRADOR
HREB
HEALTH RESEARCH ETHICS BOARD

Ethics Office
Suite 200, Eastern Trust Building
95 Bonaventure Avenue
St. John's, NL
A1B 2X5

This replaces correspondence dated March 26, 2015

March 31, 2015
Ms Sharmeen Chowdhury
Patient Research Centre
Health Science Centre

Dear Ms Chowdhury.

Reference #15.058

Re: Infant Feeding and its Impact on Health Care Services Use in Infants for First Year of Life in the Eastern Health Region of Newfoundland and Labrador

Your application received an expedited review by a Sub-Committee of the Health Research Ethics Board and **full approval** was granted effective **March 26, 2015.**

This approval will lapse on March 26, 2016. **It is your responsibility to ensure that the Ethics Renewal form is forwarded to the HREB office prior to the renewal date; you may not receive a reminder, therefore the ultimate responsibility is with you as the Principle Investigator.** *The information provided in this form must be* ***current to the time of submission*** *and submitted to the HREB* ***not less than 30 nor more than 45 days*** *of the anniversary of your approval date.* The Ethics Renewal form can be downloaded from the HREB website http://www.hrea.ca.

This is to confirm that the following documents have been reviewed and approved or acknowledged (as indicated):
• Application, approved
• Prenatal Questionnaire, approved
• Data Abstract Form, approved
The Health Research Ethics Board advises THAT IF YOU DO NOT return the completed Ethics Renewal form prior to date of renewal:
- *Your ethics approval will lapse*
- *You will be required to stop research activity immediately*
- *You may not be permitted to restart the study until you reapply for and receive approval to undertake the study again*

Lapse in ethics approval may result in interruption or termination of funding

"This is your ethics approval. Organizational approval may also be required. It is your responsibility to seek the necessary organizational approval from the Regional Health Authority or other organization as appropriate. You can refer to the HREA website for further guidance on organizational approvals."

You are also solely responsible for providing a copy of this letter, along with your application form, to the Office of Research Services should your research depend on funding administered through that office.

Modifications of the protocol/consent are not permitted without prior approval from the Health Research Ethics Board. Implementing changes in the protocol/consent without HREB approval may result in the approval of your research study being revoked, necessitating cessation of all related research activity. Request for modification to the protocol/consent must be outlined on an amendment form (available on the HREB website) and submitted to the HREB for review. This research ethics board (the HREB) has reviewed and approved the research protocol and documentation as noted above for the study which is to be conducted by you as the qualified investigator named above at the specified site. This approval and the views of this Research Ethics Board have been documented in writing. In addition, please be advised that the Health Research Ethics Board currently operates according to *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans*; *ICH Guidance E6: Good Clinical Practice* and applicable laws and regulations. The membership of this research ethics board is constituted in compliance with the membership requirements for research ethics boards as defined by *Health Canada Food and Drug Regulations Division 5; Part C*

Notwithstanding the approval of the HREB, the primary responsibility for the ethical conduct of the investigation remains with you.

We wish you every success with your study.

Sincerely,

Dr Fern Brunger, PhD (Chair Non-Clinical Trials)
Ms. Patricia Grainger, (Vice-Chair Non-Clinical Trials)
Health Research Ethics Board

Cc: Dr Laurie Twells

email: info@hrea.ca Phone: 777-6974 FAX: 777-8776

Appendix B

Health Services Utilization variables to be included on questionnaire/telephone interview for mothers	
	Questions to be asked
Health Services	Do you have a regular medical doctor? Yes No
Overnight patient	Up to and including your child's first birthday has he/she been a patient overnight in a hospital? Yes No If yes, how many independent admissions? What is the name of the hospital(s)?
Number of nights as a patient	If yes, for the first visit how many nights was your infant in hospital as a patient? 2nd visit …
NICU admission	Up to and including your child's first birthday has your infant been a patient in hospital in the neonatal intensive care unit? If yes, how many times?
Number of nights in NICU	For the 1st visit, how many nights? 2nd visit…
PICU admission	Up to and including your child's first birthday has your infant been a patient in hospital in the pediatric intensive care unit? If yes, how many times?
Number of nights in PICU	For the 1st visit, how many nights? 2nd visit…

Family doctor	How many times have you taken your infant to see a family doctor up to and including your child's first birthday for problems other than normal child checkups or immunizations?
Other medical doctor	How many consultations with other medical doctors (specialist, pediatrician, ENT surgeon, allergist, etc.) has your child had up to and including your child's first birthday?
Radiology use	Up to and including your child's first birthday has your child needed any x-rays or ultrasounds or other radiologic testing? Yes No If yes, list
Any health professional	Have you had a consultation with any other health professional (dietician, public health nurse, lactation consultant etc) up to and including your child's first birthday except for normal child checkups or immunizations? Yes No

ER visits	Have you taken your infant to the emergency room up to and including your child's first birthday? Yes No How many times? _____ Reasons for ER visits_____
Immunizations	Is your child fully immunized? Yes No 2 months, 4 months, 6 months, 12 months

	Has your child been diagnosed with any of the following conditions? Ear infection Asthma Reactive Airways Disease Bronchiolitis Pneumonia Meningitis Gastroenteritis/stomach flu Rotavirus Blood infection Influenza Croup Whooping cough Gastroesophageal reflux Yeast infection Anemia or iron deficiency anemia Jaundice Thyroid Kidney or bladder disease Urinary tract infections Brain abnormality Heart disease Bowel/liver disease Bone disease Blood disease Genetic condition (name) Allergies (list) Developmental disorder (name) ☐ Other _____

Medications	**Has your child been prescribed any medications up to their 1st birthday?** Yes No If yes, list type/names and how often? **TYPE** **Number of times** Antibiotics Antifungal Puffers Other
	Thank you for taking the time to participate in this study! We are studying health care usage for infants in the first year of life. If you are agreeable, please provide your child's MCP number which will be used to collect information from your child's hospital chart. This will be kept strictly confidential and only used for this research purpose. Identifying information will not be collected. Child's MCP _____

Appendix C

Table: Comparison of demographics between participants of FiNaL study and HSU study

Variables	FiNaL Prenatal (N = 1283) n (%)	HSU study (N = 242) n (%)
Marital status		
Married/Common law	1111 (86.6%)	230 (95.0%)
Single	160 (12.5%)	11 (4.5%)
Level of education		
Higher secondary or less	221 (17.2%)	11 (4.5%)
Post - secondary	1062 (82.8%)	231 (95.0%)
Total household income		
< 30,000	153 (11.9%)	6 (2.5%)
> 30,000	1130 (88.1%)	235 (97.1%)
Parity		
Multiparous	599 (46.7%)	96 (39.7)
Primiparous	666 (51.9%)	144 (59.5)
Smoking status		
Currently non-smoking	1172 (91.3%)	234 (96.7%)
Currently smoking	106 (8.35)	8 (3.3%)
Type of delivery		
Vaginal	482 (73.0%)	173 (71.5%)
Caesarean	176 (26.7%)	60 (24.8%)
Age (years)		
18-25	258 (20.1%)	15 (6.2%)
>= 26	1025 (79.9%)	226 (93.4%)
Dwelling area		
Urban	430 (33.5%)	158 (65.3%)
Rural	675 (52.6%)	75 (31.0%)