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THE ECONOMIC BURDEN OF BOTTLE-FEEDING

by

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Thesis submitted to
the Faculty of Graduate and Postdoctoral Studies
in partial fulfilment of the requirements for the
MSc degree in Epidemiology

University of Ottawa

April, 2002

ABSTRACT

Bottle-feeding has been associated with excess childhood disease. The costs of managing this burden have not yet been quantified in Canada. This thesis estimated the direct costs of three childhood diseases (diarrhea, otitis media and lower respiratory infection) attributable to bottle-feeding among Ontario infants under the age of one year in 1994. A systematic review identified relative risks among bottle-fed children. The prevalence of bottle-feeding was determined from the National Longitudinal Survey of Children and Youth, 1994/1995. Impact fractions were calculated for each of the three diseases and applied to the costs of physician visits and hospitalizations which were provided by the Institute for Clinical Evaluative Sciences. The net direct costs of bottle-feeding were estimated as the sum of attributable costs minus cost savings. The cost of health care attributable to bottle-feeding was estimated to be $2.2 million. A sensitivity analysis revealed that bottle-feeding could have yielded cost savings of $88,900 or cost just under $4.0 million. This estimate was conservative as the costs of drugs were not included.

ACKNOWLEDGEMENTS

Bob Spasoff provided excellent thesis supervision and I am very thankful for his dedication, patience and support. His depth of knowledge and experience was critical to the research process and the opportunity to work with him was one of the most positive aspects of this thesis. Doug Coyle provided exceptional advice and guidance on health economics. Doug Manuel graciously facilitated my access to ICES data which was essential for this research. The support and contribution of my husband, Trevor Banks, allowed me to complete this project. My children, Ross and Chloe provided continual inspiration for my commitment to breastfeeding research. Family and friends must also be thanked for providing encouragement, extra child care, and at times, a quiet place to work.

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INTRODUCTION

The Canadian Pediatric Society (CPS) identifies breastfeeding as the optimum method of feeding for babies and recommends exclusive breastfeeding of infants for the first six months of life [1]. To derive maximum benefits of breastfeeding, prolonged breastfeeding for the first year of life and well into the second year is also encouraged. A 1995 Quebec study [2] into infant feeding practices found that the recommendations of the CPS are generally not followed. Among 288 children, 61.1% (176) were breastfed at birth but only 20 children were exclusively breastfed at six months of age.

The benefits of breastfeeding are many and researchers continue to learn more about breast milk and why it is the perfect food for babies. Besides providing complete nutrition for infants, breast milk provides immunologic benefits, has been demonstrated to be protective against illness, and changes in vitamin and mineral content as baby grows thus meeting a baby's changing nutritional needs.

Although the protective effect of breast milk is most striking in developing nations, studies conducted in affluent nations comparing morbidity in breast and formula fed babies have found similar protective effects. A number of epidemiologic studies [3] with varying study designs have estimated the risk of developing disease among breastfed and formula fed babies in the developed world. The most compelling evidence of a protective effect is for diarrhea (gastrointestinal disease), otitis media and respiratory infection.

Given the benefits of breastfeeding, and the increased morbidity associated with formula feeding, what does it cost society when babies are not breastfed? A number of studies conducted in the United States [4 5 6 7] have found the costs of care for breastfed

babies to be less than that of formula fed babies. To date, the burden of disease associated with artificial feeding has not been quantified in a Canadian context, nor have the health care costs associated with the management of formula fed infants been estimated. Quantifying reductions in spending for infants' medical visits and hospitalizations and reduction is important: if breastfeeding is shown to save money, health care stakeholders can build a case for: protecting and promoting breastfeeding as stipulated in the World Health Organization's (WHO) *International Code of Marketing of Breastmilk Substitutes* [8]; supporting breastfeeding promotion; and increasing the availability of lactation consultants for post-partum mothers.

This thesis will first estimate the burden of illness for three childhood diseases (diarrhea, otitis media and respiratory disease) associated with bottle feeding in Ontario infants under twelve months of age. The direct costs (for physician visits and hospitalizations) attributable to bottle feeding will then be estimated. Indirect costs of formula feeding will be discussed but not estimated.

1.0 BACKGROUND

1.1 The Adverse Effects Of Bottle-Feeding

In her 1999 textbook, Riordan [9] refers to breast milk as "white blood": a substance similar to unstructured living tissue (such as blood) capable of transporting nutrients, affecting biochemical systems, enhancing immunity and destroying pathogens. Breast milk substitutes often are thought to be comparable to breast milk but a good understanding of breast milk, its components, and its contribution to infant health indicates that this is not the case.

1.1.1 The Theoretical Superiority of Breast milk

Breast milk is species specific, that is, it has adapted throughout human existence to meet the nutritional and anti-infective requirements of the human infant to ensure survival, optimal growth and development [9]. Human milk comprises nutrient proteins, lipids, vitamins, minerals, anti-infective properties, hormones, enzymes and growth factors. Besides providing the proper quantity and precise mixture of essential nutrients, breast milk ensures the bioavailability of these nutrients. As such, breast milk contains transfer factors for iron, zinc, folic acid, and vitamin B_{12}, and the fats contained in human milk come partially predigested by the enzymes also present in breast milk [9 10].

The intake of breast milk is self-regulated by babies, the composition of which changes as a baby grows and as nutritional needs change. Researchers continue to discover that it is the baby's characteristics that help to determine breast milk composition, and that human milk is variable over time, within a feed, and over a day. Breast milk differs between babies (with premature babies receiving more 'specialized' milk) and from

one woman to another. The uniqueness of this substance between babies and its variability over time makes it a difficult substance for pharmaceutical companies to replicate.

One of the greatest advantages of breast milk is its ability to actively inhibit and destroy many bacteria, viruses, fungi and parasites that babies confront. Breast milk contains a number of immune cells (specifically phagocytes and lymphocytes), antibodies and other immunoglobulins that work to protect the infant [9] [10]. Breastfeeding also confers long-term protection by stimulating an active immune response. Polio virus or rubella immunization of the mother (for example) provides active immunity to the infant, because the virus will likely appear in her milk and thus immunize the infant. Bottle-fed infants are denied these benefits, and vaccination may be less effective as formula does not enhance the immune response to vaccination as breast milk does.

1.1.2 The Benefits of Breastfeeding

Breastfeeding has been shown to prevent several childhood diseases. The three childhood diseases for which the protective effect of breastfeeding is most compelling are:

- diarrhea: breastfeeding minimizes diarrhea and gastrointestinal infections by providing anti-infective factors and by reducing exposure to other foods or water that may contain pathogens [9];
- otitis media: protective effect attributed to immunologic factors present in breast milk, feeding position [9]; and,
- respiratory illness: breast milk contains anti-infective properties and antibodies [9].

Research has demonstrated that the advantages of breastfeeding extend well beyond infancy as artificial feeding has been implicated in childhood diseases such as

tonsilitis, celiac disease, lymphoma, diabetes, juvenile rheumatoid arthritis, neurological abnormalities, and atopic disease [9]. Research has also found that adults afflicted with inflammatory bowel disease, Crohn's Disease, and multiple sclerosis were more likely to have been bottle-fed as infants [9].

The benefits of breastfeeding extend beyond morbidity. Emerging research has shown that the intellectual development of breastfed children is slightly but significantly better than that of bottle fed children [11]; a finding that has been linked to the absence of long-chain polyunsaturated fatty acids (such as docosahexaenoic acid, or DHA) from infant formulas. These fatty acids have been found to be essential nutrients for developing nervous tissue, and are found in large quantities in breast milk.

There are also psychological benefits that breastfeeding provides to mothers and babies: breastfeeding promotes strong attachment between mother and child. The concept of attachment parenting is becoming more relevant, particularly as scientists understand more about maternal infant bonding and how this contributes to brain development among children under the age of six [10].

Breastfeeding has been implicated in maternal health as a protective factor against heart disease, osteoporosis, premenopausal breast cancer, ovarian cancer and endometrial cancer [4]. Unrestricted breastfeeding also has a contraceptive effect that is beneficial to mothers in developing nations. Increased spacing between births (and maximizing time at the breast) has implications for a child's increased chance of survival.

1.1.3 The Theoretical Risks of Bottle-Feeding

Bottle-feeding can increase the risk of ill health by many pathways, many of which are inherent in the consumption of any commercially prepared and mass-marketed food product. When evaluating the risks of bottle-feeding, it is not only the ingredients of formula that must be considered, but also the potential for contamination, production errors, or other user-dependent mistakes.

1.1.3.1 The Composition of Infant Formula

Formula ingredients are based on the composition of breast milk which alters over time to meet the changing needs of a developing infant. Well-intentioned formula manufacturers try to mimic breast milk but the science of bottle feeding changes as more is learned about breast milk. Minchin [12] points out that "...what goes into formula is what is believed to be essential and safe at the time of creating the standard...". Infant formula is not a complete food because ingredients are added only when they are discovered to be important and already present in breast milk. Babies consuming formula prior to the discovery of a new breast milk component or to a change in formula composition receive a food that is deficient.

Infant formula lacks the immunological and other health promoting factors present in human milk; the components of which can at times be foreign or mixed in nonphysiological proportions. For example, breast milk contains very little iron, but it is well absorbed due the transfer factor present in the milk that makes it unavailable to gut bacteria. Infant formula contains over 20 times the amount of iron found in breast milk, of which large amounts are consumed by the gut bacteria [13]. This has the potential to

compromise resistance to infection as well as the absorption of trace minerals such as zinc and copper. This example coupled with the fact that infants consuming low-iron formulas risk iron deficiency anemia demonstrates the delicate balance some nutrients require.

In another example, infant formula contains large amounts of protein. But the protein formula is not easily digested by infants, so excessive amounts must be added to ensure that the infant receives the required amount [13]. These high levels force the break down and excretion of the excess leading to additional stress for the immature liver and kidneys. In contrast, breast milk contains lower amounts of protein which are supplemented with readily absorbed nitrogenous compounds for nutrition.

Another nutrient requiring balance is vitamin D: at high levels, vitamin D can be toxic. Holick et al. [14] tested infant formula samples and found vitamin D at levels of 200% to 419% of the amount stated on the label.

Excess aside, the history of infant formula production has involved a series of deficiencies and omissions of ingredients in infant formula. The following list as summarized by Minchin [12] documents some of the past deficiencies in infant formula:

- a zinc-deficient formula caused retardation and skin lesions in infants,
- a vitamin B_6 deficiency in formula led to seizures in infants,
- marginal folic acid levels and absence of vitamin C led to megaloblastic anemia,
- biotin-deficient animals died of a SIDS-like syndrome, so biotin was added to all formulas,
- cystine is now added because of the infant's inability to synthesize it, (adults have the capability of making this amino acid from other dietary components)

- taurine, essential for myelination of the central nervous system, was almost completely absent from formulas until 1984,
- improperly heated soy formula and/or lack of iodine caused incidents of goiter,
- vitamin K deficiency led to prolonged prothrombin time in infants,
- soy formulas deficient in carnitine place certain infants at risk for fatty infiltration of the liver, specifically those with cystic fibrosis,
- soy oil has been added to a US formula to provide a source of alpha-linoleic acid. Babies are able only partially to convert this to DHA.

1.1.3.2 Contaminants in Infant Formula

The two biggest contaminants identified in infant formula are heavy metals (particularly lead and aluminum) and bacteria. Lead soldered cans (once used to store infant formula) have been phased out of use, an action which has contributed to a drop in the levels of lead in infant formula [12 13]. Bottle fed infants continue to be exposed to lead through the water used to reconstitute formula. Most formula labels advise boiling water, an action which concentrates any lead in the water, thus exposing infants to lead with each feeding [12 13]. Aluminum levels in formula can be up to 60 times higher than in breast milk, and can disturb calcium and phosphorus metabolism in babies [13].

In addition to contamination by heavy metals, the potential for bacterial contamination arises when raw or improperly pasteurized milk introduces bacteria to the drying process used to manufacture powdered formula. Bacterial contamination of infant formulas has lead to at least one outbreak of *Salmonella ealing* in the United Kingdom in 1985 (causing one infant death, and hospitalizing 15% of affected infants) [15], and has been

the cause of at least five infant formula recalls over the past two decades. In several instances, random lots of laboratory-tested infant formula have been found to contain bacterial and elemental contaminants that, while a risk to infant health, do not rise to the level of threat considered appropriate for a widespread recall by the Food and Drug Administration (FDA) in the United States.

1.1.3.3 Errors in Formula Production

Confidence in infant formula rests on the adherence of everyone involved in a complex production and manufacturing process to the highest possible standards of practice. Minchin [12] cites the case of a formula manufacturer employee who sprayed cans of infant formula with pesticides (in 1980), but the most disastrous formula manufacturing error was that which exposed at least 20,000 to 50,000 infants to chloride deficient formula in 1978 and 1979. At least 120 infants were identified as having been affected by this error but it is suspected that any child whose only source of nutrition was this formula would have been damaged. Affected infants consuming this formula suffered from a loss of appetite, failure to gain weight, muscular weakness, lethargy, vomiting and severe hypochloremic, hypokalemic metabolic alkalosis [16]. In addition, almost all affected babies experienced slowed growth in length, weight and head circumference [17]. Years later, affected children continue to feel the long-term effects of this manufacturing error and suffer from consistently delayed speech, slow gross motor development, increased convulsion rates, rotting teeth, kidney defects, mild retardation and cerebral palsy [18 19].

This manufacturing error led to the United States Infant Formula Act of 1980 which mandated the nutrient requirements for formula and sought to bring standards to

the infant formula industry. In the United States, there is the general impression that the FDA closely and carefully monitors infant formula but the FDA actually sets forth only minimal standards regarding the production and sale of infant formula.

In Canada, the only regulation of infant formula rests with the Food and Drug Act [20], which oversees the nutrient content and labelling aspects of infant formula. There are specifications included in the Act that cover the microbial and physical quality of the ingredients, quality control and testing procedures, details of the manufacturing process, testing around expiration dates, and evidence of nutritional adequacy. At best, the provisions in the Act [20] are minimal requirements for infant formula: the onus is on the manufacturer to provide information on the degree to which specifications are followed. No independent system, inspection, or random analysis of infant formula is done. Infant formula manufacturers complete their own testing [21], and the system is at best, self-regulating.

1.1.3.4 Other Adverse Effects

Bottle-feeding had the potential to harm infants in other ways:

- unattended infants with propped bottles experience increased risk of aspiration and reduced contact with caregivers,
- micro-waved formula can cause burns in the mouths and throats of babies,
- improperly prepared formula can cause serious health problems such as under or over nutrition,
- baby bottle caries: this destructive dental condition occurs when a baby is put to sleep with a bottle containing formula, milk, juices or other fluids high in

carbohydrates, which pool in the mouth during sleep causing severe decay in the front teeth,

- the quality of the water with which many formulas must be reconstituted,
- levels of nitrosamines (chemicals implicated in the development of cancer) in bottle nipples,
- interaction of infant formula with the container in which it is stored, such as the case with lead in soldered cans (discussed above).

1.1.3.5 Infant Formula Recalls

Many of the risks of infant formula can be summarized by the long list of recalls. Between 1982 and 2000, there were 27 recalls of infant formula in the United States due to health and safety problems. Eight of these recalls were classified by the FDA as "Class I" or potentially life threatening. Infant formulas have been recalled for a variety of reasons including deficiency of nutrients, bacteria contamination, physical appearance that makes the product unfit for consumption, and glass particles found in the product. The most recent infant formula recall (by the Canadian Food Inspection Agency in 2000), involved concentrated cans of formula that experienced a slight fluctuation in temperature during the final stage of canning that may have affected the sterility of the product.

Infant formula recalls for health and safety reasons that occur in the United States are almost always duplicated in Canada as well, particularly as the two jurisdictions share common distributors of formula [22]. The only instance in which formula recalls may not be recalled in Canada are when products are recalled for lack of adherence to US nutritional content or labelling reasons.

1.2 Evidence On The Economic Burden Of Bottle Feeding

Heinig [23] has classified the few publications that examine the direct cost savings associated with breastfeeding into two study approaches: hypothetical (for example, synthetic studies) and observational (for example, empirical studies). 'Hypothetical' studies identify differences in outcomes (usually illness rates) based on infant feeding practices. The costs of these outcomes are estimated and a cost savings is calculated by multiplying the cost by the estimated difference in the number of cases [23]. The advantages of the hypothetical approach are: low cost, results that are easy to interpret, and results that can be used to target outcomes and populations for intervention programs and observational studies. The disadvantage of the hypothetical approach is the many assumptions that are made in the course of such research, which are apt to be challenged by peers and policy-makers.

'Observational' studies involve the direct observation of a population in which infant feeding groups and outcomes may be linked (for example, patients in a managed care organization or a hospital pediatrics clinic). Data on outcomes are collected for a defined period of time and comparisons are made of actual costs incurred within each feeding group over the study period [23]. Although these studies are often expensive and time-consuming to conduct, the advantage of the observational approach is that study results are based on actual data. While results from observational studies may be easily generalized to similar organizations and settings, generalization to other types of organizations or to the population at large is questionable.

Examples of Heinig's [23] hypothetical model include a commentary by Riordan [4], and economic analyses conducted by Drane [24] and Ball & Wright [5]. In 1997, Riordan estimated the costs (in United States dollars) incurred among infants who had not been breastfed. Using disease incidence rates and cost of treatment estimates from the literature, Riordan calculated a potential annual cost of over $1 billion for diarrhea, respiratory syncytial virus, insulin-dependent diabetes mellitus and otitis media that could be saved by breastfeeding. The three childhood diseases included in the cost estimate that are most relevant to this thesis include:

- diarrheal diseases: $291.3 million ($133.3 million in ambulatory costs and $158 million in hospitalizations)
- respiratory syncytial virus (RSV): $225 million in hospitalization costs
- otitis media: $660 million in treatment costs.

These cost savings were thought to be conservative given that the direct cost of pharmaceuticals as well as indirect costs (such as 'lost work' time) were not factored into the estimate. The biggest limitation of Riordan's cost estimates is that they lack scientific rigour. The calculations on which her estimates were based were crude, and there was no discussion of the validity of estimates taken from the literature. Although it is assumed that Riordan's estimates apply to 1997, the price year to which her estimates apply was not explicitly stated and the exact population to which these estimates apply to was not made clear.

In another example of a hypothetical model, Drane [24] in 1997 conducted an economic analysis that estimated the cost savings to the Australian health care system (for

hospitalizations) if the nationwide prevalence of exclusive breastfeeding at three months was increased from 60 to 80%. Although Drane studied a variety of outcomes (including necrotising enterocolitis, gastrointestinal illness and eczema) , the most relevant to this thesis is gastrointestinal illness. Using incidence rates for breast and bottle fed infants derived from a study conducted by Howie et al. [25], Drane calculated the attributable risk per cent among infants exposed to formula to be 82%. Applying this impact measure to the formula fed infants in the Australian population of babies (approximately 240,000), Drane derived the number of cases among the formula fed population, the number of cases among the formula fed group that were attributable to formula feeding, and the number of cases among the breastfed population. Using diagnostic related group (DRG) cost data, Drane calculated the cost for each of these groups and modelled the cost savings associated with increasing the proportion of exclusive breast feeders.

The cost per hospitalization for gastrointestinal illness was estimated to be $1,219. Drane estimated that by increasing the nation-wide prevalence of exclusive breastfeeding from 60% to 80%, the hospitalization costs would drop from $11,585,376 per year to $7,840,608 per year. This represents a potential cost savings of $3,744,768 per year. While substantial, these cost savings are underestimated as they only focus on hospitalization data, and do not model potential savings such as reductions in general practitioner visits or maternal absenteeism.

The main shortcoming of the analysis is that Drane did not adequately define the study setting. The price year for which cost estimates are applicable was not stated, and it was unclear what year the cohort of 240,000 infants (on which the study was based) were

born. More details about the review process needed to be included, particularly how studies were selected and deemed to be high quality, and how incidence rates were extracted from studies. Information on the specific model used to calculate gastrointestinal illness costs was also needed as cost estimates for this outcome were based on a model used for a different outcome.

In a hypothetical study that determined the excess cost of health care services in formula fed infants for the first year of life, Ball and Wright [5] observed the frequency of health service utilization for three illnesses: lower respiratory tract illnesses, otitis media, and gastrointestinal illness. Subjects for this study were drawn from two cohorts. Disease incidence and utilization for lower respiratory tract illness and otitis media were gathered by chart review from the children enrolled in the Tucson Children's Respiratory Study [26] (n=944), while incidence and utilization associated with gastrointestinal illness were taken (by chart review) from the study conducted by Howie et al. [25] (n=644).

Costs of care were estimated using the experience of infants enrolled in the Thomas-Davis Medical Centre, an HMO clinic located in Tucson, Arizona. Direct costs for 1995 pediatric services were provided by this HMO. Health care utilization for a range of services for each illness was calculated by feeding status, and the utilization by never-breastfed children compared with that of children breastfed for greater than or equal to 3 months. After adjusting for confounding factors (maternal education level and maternal smoking), there were 2033 excess office visits, 212 excess days of hospitalization, and 609 excess prescriptions per 1,000 never breastfed infants compared with infants exclusively breastfed for at least 3 months. These additional health care

services cost the health system between $331.00 and $475.00 (US Dollars) per never breastfed infant during the first year of life. The main advantage of this study is that its estimates of health care utilization have been adjusted for confounding factors that could affect utilization of health care. It is unlikely that differences between mothers who breastfed and those who did not affected the results of this study as confounding factors for each of the two populations were controlled for in the analysis.

The extent to which the disease incidence rates from the two cohorts of infants (the Tucson cohort and the Scottish cohort) can be compared is not clear. Although the methods on which the two studies are based are very similar, some differences exist between the two, particularly with respect to how data on disease incidence were collected. The Tucson Children's Respiratory Study ascertained incidence of lower respiratory illness at the acute visit(s) to a physician, and the incidence of otitis media through chart review. In the study conducted by Howie et al. [25], a nurse visited the home on a regular basis to identify episodes of illness, which were then confirmed through a medical record review. It may not be appropriate to apply disease incidence rates from two different studies to the same utilization data if fundamental differences between the studies accounted for difference in the incidence rates.

Two examples of studies fitting Heinig's [23] observational approach include those completed by Hoey and Ware [6], and Montgomery and Splett [7]. In 1997, Hoey and Ware studied 269 randomly selected infants born to mothers in an HMO group (Raleigh, North Carolina) between September 1992 and August 1993, to assess the cost-effectiveness of breastfeeding versus bottle feeding for the first year of life. Breastfed infants were defined

as those receiving breast milk for at least the first six months of life, while bottle fed infants were those receiving formula from birth. Utilization and costs for medical care including office visits, drug prescriptions, and hospitalizations were retrospectively abstracted (via chart review) and analyzed.

Although the average numbers of office visits (including well and sick visits) and prescriptions were similar between the two groups, breastfed infants had fewer inpatient hospital admissions than their bottle fed counterparts (0.13 versus 0.20 discharges per 1,000 babies respectively). There was an average cost savings of approximately $60 per breastfed baby for office visits, and hospitalization costs were about $150 lower per breastfed baby, leading to an average cost savings of just over $200 per breastfed infant for the first year of life. Applying these results onto the entire HMO cohort of infants (n=2,140), Hoey and Ware projected cost savings of up to $140,000 if the rate of breastfeeding at six months in their HMO cohort was increased from 17% to 50%.

The main advantage of this study is that estimates of resource use and cost data were based on actual data, but results must be considered in light of study limitations. Close to half of the original cohort were not considered in the analysis as 10% did not meet the eligibility criteria, and just over one third (35%) of babies switched feeding in the first six months. Out of the original sample, 41 infants were breastfeeding at six months, and 107 were bottle fed, which made for small numbers in the relevant groups. As such, the cost savings attributed to hospitalizations were based on only 10 hospitalizations: 2 among the breastfed infants, and 8 among the bottle fed infants.

Another limitation of the study was the lack of adjustment for demographic factors, as study groups were not comparable in this respect. Differences between the groups may have affected utilization of health care resources, and the observed cost savings.

To determine if breastfeeding is associated with a reduction in Medicaid expenditures among a low-income population served by the Special Supplemental Nutrition Program for Women, Infants and Children (WIC) in Colorado, Montgomery and Splett [7] retrospectively identified and tracked cohorts of exclusively breastfed (n=406) and formula fed (n=470) infants for their first six months of life. Cohorts were compared with respect to WIC costs and Medicaid expenditures. Resource utilization was measured using data for the period August 1993 to December 1993 and costs were measured using 1993/1994 dollars. Medicaid expenditures were compared between the breastfeeding and formula feeding cohorts by t-tests and analysis of covariance. Regression techniques were used to adjust Medicaid expenditures for each feeding cohort as the two cohorts differed with respect to age of mother, ethnicity, employment and smoking status.

The mean, unadjusted total Medicaid expenditures for infants in the breastfeeding cohort were approximately $102 (US Dollars) less than for infants in the formula feeding cohort, but the difference was not statistically significant ($484.80 ± $964.14 versus $586.67 ± $1,222.36). Mean pharmacy payments, a subcategory of total Medicaid expenditures, were significantly lower for the breast-fed cohort than for the formula fed cohort ($16.83 and $37.56 respectively, $p<0.05$).

It is doubtful that this study can be generalized to the general population of Ontario infants. This study is beneficial in demonstrating medicaid cost savings among breastfed infants in a low-income population but it is questionable whether these results could be replicated to the same magnitude in a general population.

1.3 Methodologic Issues of Studies

Comparing the Morbidity of Breast and Bottle Fed Babies

Published studies that have examined and compared the morbidity and overall health of breastfed babies to that of bottle-fed babies date as far back as the 1930's. Since that time, numerous studies of this kind have been published. Besides establishing breastfeeding as a mode of feeding that is superior to bottle feeding, the decades of research that have compared the two feeding modes have identified a number of methodologic limitations associated with such research.

Two epidemiologic research designs dominate the literature: cohort studies (prospective and retrospective) and case-control studies. Most prospective studies identified a cohort of infants, and followed them forward in time observing feeding patterns and disease incidence for a set time period (such as the first two years of life). The few retrospective cohort studies conducted resurrect an infant's feeding and disease history from medical records and/or questionnaires administered to parents. Finally, the case-control studies identified cases in hospital, and selected controls from the general population of infants. In the absence of a randomized controlled trial that assigns babies to breastfeeding and bottle feeding groups (which is unethical and impossible since the decision to breastfeed or bottle feed is extremely personal) the study designs summarized

above have provided the best available evidence on the effect of breastfeeding on infant illness and overall health. Unfortunately, these studies have been subject to a number of methodologic limitations and biases that have the potential to yield spurious results. These methodologic issues are summarized here.

In 1979, Sauls [27] from Ross Laboratories documented some of the difficulties associated with comparing the morbidity of breast and bottle fed babies. Sauls pointed out that differences between mothers who choose to breastfeed and those who choose to bottle feed, apart from the method of feeding they choose, may invalidate the comparisons of their infants. Sauls identified some of the societal/cultural variables, family variables, individual variables, and events during pregnancy, labour delivery and peurperium that influence the decision to breast or bottle feed one's baby. Current literature demonstrates that women who choose to breastfeed their infants tend to be older, highly educated, employed, married and non-smokers [28].

Over and above the decision to breastfeed, Sauls claimed that almost any deviation from normal maternal or infant health increases the likelihood of an infant being bottle fed, which has the potential to load the bottle fed group with potentially less healthy infants with higher risks than breastfed infants. Similarly, breastfed infants who remain healthy tend to continue to breastfeed while those becoming ill for reasons unrelated to milk source tend to be switched to bottle feeding. Today, the maternal and infant health issues that would demand a switch from breastfeeding to bottle feeding are extremely rare, and increasingly, continued breastfeeding is recommended in circumstances of ill health [21].

Sauls cautioned that future studies in this area should give consideration to the introduction of solid foods. When such foods are added to the diet, Sauls argues that it is difficult to ascribe any effect to the milk source itself, thus limiting study periods to the first six weeks of life or less (since some infants begin solid foods as early as six weeks).

Methodologic commentaries following Sauls have not only built on his ideas, but have also suggested more issues, and ways to correct for methodologic inadequacies in study design. In a 1984 review of the literature, Kovar et al. [3] identified the limitations among the studies that they reviewed:

- Failure to control for confounding variables related to both the choice of the method of feeding and the outcome measure (as discussed by Sauls)
- Non-blind assessment
- Failure to determine whether an infant's health condition determined the feeding method or the feeding method preceded the health condition
- Small samples with the potential for unspecified biases
- Lack of precision in specifying the categories of feeding and health outcomes.

Because of these methodologic limitations, Kovar et al. called for cautious interpretations of study results, and argued that future prospective studies aimed at detecting the effects of breastfeeding on the health of infants in the general population of developed countries would have to be large to remedy severe problems of confounding and the apparent modest health benefits attributable specifically to breastfeeding.

Bauchner et al. [29] in 1986, assessed the extent to which studies of the association between breastfeeding and infection met four methodological standards relating to

scientific validity and generalizability of the studies. The four methodologic standards as developed by Bauchner et al. are: avoidance of detection bias, adjustment for confounders, a good definition of breastfeeding and a good definition of the outcome event. Each of these methodologic standards is briefly discussed here.

1. Detection Bias

Detection bias occurs when the outcome event is detected more completely in one group than in the other. As discussed by Bauchner et al. [29], detection bias may occur in cohort studies if mothers of breastfed babies utilize health care differently than do mothers of bottle fed babies. Frequent and regular surveillance of each subject for the occurrence of an illness is recommended in order to maximize the equivalence of detection of the outcomes of interest in all subjects.

In case-control studies, detection bias can also occur, and as such, it is critical that breastfed and bottle fed babies have an equal likelihood of being identified as a case. This is particularly true in hospital based case-control studies that identify cases as babies who are hospitalized for a particular infection. As discussed above, breastfed and bottle fed babies with the same degree of illness may not be equally likely to be admitted, thus elevating the proportion of hospitalized infants who are bottle-fed. To avoid detection bias in the case-control study design, Bauchner et al. recommend stratifying the cases according to 'seriousness of disease'. In theory, regardless of the mode of feeding or other confounding variables, infants who are seriously ill will almost always come to the attention of a physician and be hospitalized. Breastfeeding will thus appear to have a smaller apparent effect among those infants who are severely ill, while it might have a

large impact among those who have milder illnesses.

2. Adjustment for Confounders

Bauchner et al. [29] also identify the need for epidemiologic studies to control for confounding. In order to attribute differences in the rates of infection between the two groups to the mode of feeding, other factors related to bottle feeding that might affect the risk of infection either must be distributed equally among members of the two groups, or must be adjusted for in the statistical analyses. Such confounders include (but are not limited to) socioeconomic status, family size, maternal smoking, maternal level of education, and use of day care.

3. Good Breastfeeding Definition

Two other methodologic standards by which Bauchner et al. [29] rated studies were good definitions of breastfeeding and good definitions of the outcome event. Having good definitions offers some protection against misclassification. A good definition of breastfeeding is one that will take into account duration and exclusivity of breastfeeding. Infant feeding is typically organized into three groups: exclusively breastfed, partially breastfed, and not breastfed. Comparing babies who are exclusively breastfed to those who are exclusively bottle fed is not often possible, as we know that a good proportion of babies are weaned from the breast at a very young age, or receive formula supplementation early in life, limiting the sample size of exclusively breastfed babies for comparison.

Epidemiologic studies must therefore acknowledge the exclusivity of breastfeeding else misclassification of babies is bound to occur. Nondifferential misclassification, where

breastfed babies have been classified as bottle fed and vice versa (equally in the two groups), will bias the outcome measure (usually the relative risk) towards the null value, leading to the conclusion that breastfeeding does not have an effect and that morbidity rates are similar between breast and bottle fed babies. Nondifferential misclassification is of particular relevance when exclusivity of breastfeeding is the issue. In many of the studies reviewed for this thesis, a baby who has received any breastmilk is classified as a breastfed baby. Without stating how long the baby was breastfed or collecting information on supplemental bottles, a baby who is breastfed only at night, and given bottles for the rest of the day may be put into the same group as babies who have been exclusively breastfed for at least six months. Although scientists continue to debate about how much breastmilk is needed to confer protection from infection, a recent study by Scariati et al. [30] found a dose-response relationship between the amount of breast milk an infant receives and the risk of infection: the more breast milk a baby receives in the first six months of life, the less likely that she will develop diarrhea or ear infection.

4. Good Outcome Definition

In addition to a good feeding definition, Bauchner et al. [29] also recommend that the outcome event in a study be clearly defined to ensure that study results are generalizable. A good outcome definition, as for breastfeeding will also offer protection against the misclassification of babies. Related to a good outcome definition, Kovar et al. [3] suggested that assessment of illness (outcome) blind to breastfeeding status could prevent further bias from entering into study methodology.

In evaluating 20 studies (14 cohort studies and six case-control studies) published between January 1970 and August 1984 according to the four methodologic standards above, Bauchner et al. found that only six of the studies met three or four of these standards. Four of these six studies found that breastfeeding was not protective against infections, and two found that breastfeeding was protective against infections. The investigators concluded that the studies that met the methodological standards suggest that breastfeeding has at most a minimal protective effect in industrialized nations, but this conclusion seems ironic given that the investigators did not clearly state which infectious diseases they were investigating (lack of a good outcome definition). One can infer from reading the reference list that such infections as otitis media, respiratory illness, allergy, salmonella, and gastrointestinal illness were included in the analysis.

In 1991, Cunningham et al. [31] reviewed the state of knowledge in a commentary on breastfeeding and health in the 1980's. As with previous methodologic papers, Cunningham et al. underscored the need for good breastfeeding definitions and for the control of confounding factors as well as the need to assign the illness in question to the feeding method used just before the onset of illness (as alluded to by Kovar et al. [3]). Much of the research devoted to morbidity comparisons between breast and bottle fed babies has attempted to correct for some of the methodologic shortcomings identified by the investigators above. The result has been some well-conducted methodologically rigourous studies, which add to the mounting evidence that breastfeeding does protect babies from illness.

1.4 Research Questions

To estimate the economic burden of illness for three childhood diseases (diarrhea, otitis media and respiratory disease) among Ontario infants under twelve months of age, this thesis will answer the following research questions:

1. What is the infant morbidity associated with bottle feeding compared to breastfeeding for the following illnesses: diarrhea, otitis media and respiratory illness?
2. What proportion of the above illnesses can be attributed to bottle feeding? (calculation of the population attributable fraction)
3. What are the direct costs (hospitalizations and physician visits) associated with illness attributable to bottle feeding?
4. How would the estimates of the direct cost of illness change if estimates of disease morbidity among bottle versus breast fed were varied? (sensitivity analysis).

The population chosen for this thesis was Ontario infants under the age of one. This age group was chosen because the benefits of breastfeeding are most pronounced in this age group and are easier to quantify than among older age groups.

1.5 Format of Thesis

Because this thesis is a "hypothetical study" (as described by Heinig [23]) and does not follow a particular epidemiologic study design (for example a cohort or case-control study) the sequence of sections in this thesis does not follow a conventional order. In some cases it has been necessary to report results prior to completing the entire methods section.

In this thesis, the term "relative risk" has been used generically to refer to cumulative incidence ratios, incidence density ratios, and odds ratios.

2.0 SYSTEMATIC REVIEW OF THE LITERATURE

2.1 Methods

A systematic review of the literature was conducted to identify and assess morbidity studies that compare the rate of illness among breast and artificially fed babies. The effect estimates (relative risks) from these studies were used to calculate the population attributable fraction (PAF). This section summarizes the methods undertaken for the systematic review.

2.1.1 Systematic Reviews

A systematic review, as defined by the Cochrane Handbook [32] is: "a review of a clearly formulated question that uses systematic and explicit methods to identify, select and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review". In summarizing the results of multiple primary investigations, systematic reviews seek to limit bias and random error by using strategies such as a comprehensive search of relevant studies, the use of explicit, reproducible criteria in the selection of articles for review, the appraisal of primary research designs and study characteristics, and data synthesis (where applicable).

Cook et al. [33] further make the distinction between qualitative and quantitative systematic reviews. When the results of primary studies are summarized but not statistically combined, the review is a qualitative systematic review. In contrast, statistical methods used to analyze and summarize the results of included studies are typically known as meta-analysis, or quantitative systematic reviews.

2.1.1.1 Meta-Analysis of Observational Studies

Meta-analysis has traditionally been used to combine the results of randomized controlled trials in those instances where individual studies are small and unable to yield valid conclusions on their own [34]. Meta-analysis was considered for this thesis but was not pursued given the controversy associated with meta-analysis of observational studies [35-37].

Experts [35-37] at least agree that the methodology for meta-analysis of observational research is in its infancy, and is often done uncritically. Greenland [38] suggests that meta-analysis of epidemiologic research is most useful when the goal is to identify and estimate differences among study-specific effects (that is, test hypotheses about sources of differences and magnitude of biases between studies) instead of estimating overall summary effects. Shapiro [35] argues that meta-analysis of non-experimental studies serves to reinforce systematic bias and unidentified/uncontrolled confounding to produce spurious statistical stability. Despite these concerns, meta-analysis of epidemiologic research proceeds while experts continue to debate whether or not it should be applied.

Much of the research conducted on breastfeeding and disease morbidity is not amenable to meta-analysis, given that the exposure to breastmilk/formula changes over time and is variably defined across studies. Definitions for outcomes also vary (some studies provide very specific definitions) and there are variable amounts of adjustment for confounders in each of the individual studies. For these reasons, it was decided that a qualitative systematic review would be pursued to identify relative risks for use in the calculation of the PAF.

2.1.2 Features of a Qualitative Systematic Review

Cook et al. [33] identify four features of a qualitative systematic review: a focussed question; the use of comprehensive sources and an explicit search strategy; the use of uniformly applied, criterion-based selection; and rigorous critical appraisal. It is these features that distinguish systematic reviews from narrative reviews, which are often broad in scope, and may be susceptible to the use of biased sources, search strategies and selection processes. The four features of a qualitative systematic review as it applies to this thesis are described below.

1. Focused Question

Systematic reviews are generated to answer specific, often narrow, clinical questions in depth. Such questions can be formulated explicitly according to four variables: a specific population and setting, the condition of interest, an exposure to a test or treatment, and one or more specific outcomes. The focussed question addressed in this systematic review is: what is the difference in morbidity rates between breast and bottle fed (exposure) infants age 12 months or younger (population) for the following specific outcomes: diarrhea, otitis media and/or respiratory disease?

2. Comprehensive Sources and Explicit Search Strategy

As a starting point in the identification of primary research, The Cochrane Database of Systematic Reviews was searched, with attention to the following Groups: Acute Respiratory Infections; Ear Nose and Throat Disorders; Infectious Diseases; and, Neonatal and Pregnancy and Childbirth. The Database of Abstracts of Reviews of Effectiveness Studies (DARE) was also searched. A pre-existing systematic review of the

effects of breast and bottle feeding on infant morbidity was not found in either source.

Primary studies were then identified by a computerized search of the following databases: Medline (1966 to 1999), Cumulative Index to Nursing and Allied Health (CINAHL, 1982 to 1999) and Health Star (1975 to 1999). The time frames used to search CINAHL and Health Star were the years available for these databases. The search strategy used to identify potential studies is presented in Appendix A. A meta-analysis [39] which found breastfeeding to protect against otitis media (Relative Risk: 0.87, 95% Confidence Interval: 0.79-0.95) was found via the computerized search. This study was not appropriate for use in this thesis as the point estimates based on combined studies did not consider study details such as confounding and definitions of breastfeeding. Also, half of the studies used in calculation of the point estimate were conducted among children older than 12 months. In addition to this computerized search, the references of identified studies were consulted to identify further studies.

3. Criterion-based selection, uniformly applied

Studies identified through the search of computerized databases were evaluated using the following inclusion and exclusion criteria:

Inclusion criteria:

- studies comparing the morbidity (rates of disease) between breast and bottle fed babies for three illnesses: diarrhea/gastrointestinal illness, otitis media, and respiratory illness, as these were the outcomes for which narrative reviews (Kovar et al.) demonstrated the most compelling evidence of a protective effect of breastfeeding;

- studies conducted between 1966 and 1999, as these were the years available for the computerized databases at the time of the literature search;
- studies published in English, which could be read and understood by the investigator;
- studies which contained empirical data for the derivation of effect measures (relative risks); and,
- studies conducted in industrialized (developed) nations, which were thought to be the most generalizable to the population of Ontario infants.

Exclusion criteria:

- studies with inadequate sample size [a], which could limit the ability to detect a difference in incidence rates between breast and bottle fed babies;
- studies that did not attempt to control or adjust for confounders, which could lead to spurious relative risk estimates;
- studies conducted on certain subpopulations of individuals (for example: First Nations or Black populations), which could limit generalizability to the general population of Ontario infants; and,
- studies for which there were empirical data, but insufficient information to calculate or derive relative risk estimates.

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[a] Kovar et al.[3] suggest that the severe problem of confounding in observational studies of breastfeeding and the modest health benefits attributable specifically to breastfeeding mean that prospective studies to detect the effects of breastfeeding on the health of infants in the general population of developed countries have to be large. Alho et al., for example, estimated that a sample size of 1900 infants would be large enough to detect a 2% between the sample population rate and the true population rate at a 95% confidence level assuming a 60% population incidence rate of acute otitis media during the first two years of life. Although sample size is unrelated to confounding factors, it does allow for the statistical adjustment of known confounders.

4. Rigorous critical appraisal

A common practice in systematic review methods is to evaluate studies according to some kind of quality rating scale. Quality appraisal is considered to be an essential component of systematic reviews as a way of assessing the rigour of studies. Such appraisals give rise to a quality score which is usually based on some subjective assignment of points based on features of the studies [38]. Although quality rating scales exist for randomized controlled trials, no such scale has been published for use with observational studies.

The use of quality rating scales for the appraisal of observational studies has met with resistance. Greenland [38] suggests that quality scoring submerges important information by combining disparate study features into a single score, and introduces a subjective element [35 38] into the study at the very time when reviewers should be as systematic as possible. The Meta-analysis of Observational Studies in Epidemiology (MOOSE) Group [40] echoes these thoughts, stating that quality scales constructed to evaluate observational studies may lack demonstrated validity, that is, that quality score results may not be associated with quality. Rather than taking aggregate quality scores, MOOSE recommends focusing on key components of study design.

In those instances where quality rating scales are to be used, Petitti [34] recommends that they be tailored to the topic, and be reliable and valid. MOOSE [40] also recommends reporting on quality scoring if it has been completed, and that subgroup or sensitivity analysis be used rather than using the aggregate quality scores as weights in analysis.

Inclusion and exclusion criteria ensured that identified studies were relevant to the population of Ontario infants, but a tool was needed to evaluate the quality of these studies. Those studies not excluded were reviewed according to the Newcastle-Ottawa Quality Assessment Scale (NOS).

The NOS was developed by investigators from the University of Newcastle, Australia and the University of Ottawa, Canada to assess the quality of nonrandomized studies [41]. The NOS judges studies on three broad perspectives: the selection of the study groups, the comparability of groups, and the ascertainment of the exposure or outcome of interest. The NOS works on a 'star system' whereby high quality methodologic elements achieve a star. Since its development, the NOS has been used in the assessment of: the association of coronary heart disease with hormone replacement therapy in postmenopausal women [41]; the association of connective tissue disease with silicone breast implants [41]; and more recently in a systematic review of studies comparing bilateral and single internal mammary arteries [42]. The NOS for cohort studies appears in Appendix B, with the case-control scale appearing in Appendix C.

2.1.3 The Adapted Newcastle-Ottawa Scale (ANOS)

The scale in its original form required some modification in order reflect the subject matter studied in this thesis. Specifically, the scale was adapted on two levels: first, to reflect research on acute disease and second, to account for the four methodologic limitations specific to breastfeeding research as documented by Bauchner et al. [29]. These limitations have been discussed in section 1.3 and include: avoidance of detection bias, adjustment for confounders, a definition of breastfeeding that incorporates both duration

and exclusivity, and clearly defined outcome events.

2.1.3.1 ANOS: Cohort Studies

Table One summarizes both the original NOS and the adaptations made in the formation of the ANOS for cohort studies. The best score cohort studies could obtain using the ANOS was eight stars.

TABLE ONE: COMPARISON OF THE NOS TO THE ANOS COHORT STUDIES	
ORIGINAL NOS	**ADAPTED NOS**
SELECTION	
1) Representativeness of the exposed cohort a) truly representative of the average (describe) in the community ★ b) somewhat representative of the average in the community ★ c) selected group of users eg nurses, volunteers d) no description of the derivation of the cohort	*Excluded from Adapted NOS* Representativeness is not essential for a study to be internally valid; is more important to choose a cohort that will yield the most accurate estimate of effect.
2) Selection of the non exposed cohort a) drawn from the same community as the exposed cohort★ b) drawn from a different source c) no description of the derivation of the non exposed cohort	*Excluded from Adapted NOS* Cohorts were not selected on the basis of exposed/non-exposed groups. In all studies a cohort of children was selected (mostly from birth) and then followed forward in time to assess changes in exposure and morbidity. All studies would have fallen under a), so this criterion was not discriminating.

TABLE ONE: COMPARISON OF THE NOS TO THE ANOS COHORT STUDIES	
ORIGINAL NOS	**ADAPTED NOS**
3) Ascertainment of exposure a) secure record (eg surgical records)★ b) structured interview ★ c) written self report d) no description	*Modified in Adapted NOS* Ascertainment of feeding status a) structured interview ★ b) medical records c) written self report (self-administered questionnaire) d) no description Secure records (such as surgical records) are not available for the outcomes under study. This choice was deleted. The structured interview was retained as the best manner to collect information about the duration and exclusivity of breastfeeding.
4) Demonstration that outcome of interest was not present at start of study a) yes ★ b) no	*Excluded from Adapted NOS* All cohorts were chosen from birth, or very early in life. In both instances, one could be certain that the outcome was not present at the beginning of the study. All studies would have fallen under a), so this criterion was not discriminating.
	New category added to Adapted NOS Definition of breastfeeding a) definition takes into account both duration and exclusivity ★ b) definition based on duration only c) definition not provided This category was added to reflect the need for studies to protect against the misclassification of babies by feeding status. Breast-fed babies classified as bottle fed and vice-versa will bias outcome measure (relative risk) to the null value, with an eventual conclusion that breastfeeding does not have an effect on infant morbidity.
COMPARABILITY	
1) Comparability of cohorts on the basis of the design or analysis a) study controls for (select the most important factor) ★ b) study controls for any additional factor ★ (This criterion could be modified to indicate specific control for a second important factor.)	*Incorporated into Adapted NOS* The most important factor chosen for adjustment was socioeconomic status. Studies received a star for the adjustment for one of the following: income, education, social class, or occupation. Additional important factors included: maternal age, maternal smoking, use of daycare and size of family (ie: number of siblings). A study that adjusted for at least one of these other factors received a star (for a potential of 2 stars).

TABLE ONE: COMPARISON OF THE NOS TO THE ANOS COHORT STUDIES	
ORIGINAL NOS	**ADAPTED NOS**
OUTCOME	
1) Assessment of outcome a) independent blind assessment ★ b) record linkage ★ c) self report d) no description	*Modified in Adapted NOS* Assessment of outcome/Avoidance of detection bias a) active surveillance at least once per month via structured interview (ie: interview by telephone), diary or self-completed questionnaire ★ b) assessment based on visits for infectious illness (ie: counts of sick visits) Blind assessment was excluded to reflect the fact that breastfeeding is usually assessed at the same point in time as infant illness is measured, and is expected to change over time. The concept of frequent and regular surveillance was incorporated into this category to protect against detection bias. Surveillance of each subject for the occurrence of an infectious illness is recommended in order to maximize the equivalence of detection of the outcomes of interest in all subjects.
2) Was follow-up long enough for outcomes to occur a) yes (select adequate follow up period for outcome of interest) ★ b) no	*Incorporated into Adapted NOS* A time period of 6 months was deemed long enough for infants to be affected by the outcomes under study.
3) Adequacy of follow up of cohorts a) complete follow up - all subjects accounted for ★ b) subjects lost to follow up unlikely to introduce bias - small number lost - > *x* % (select an adequate %) follow up, or description provided of those lost)★ c) follow up rate < *x* % (select an adequate %) and no description of those lost d) no statement	*Modified in Adapted NOS* Adequacy of follow up of cohorts a) subjects lost to follow up unlikely to introduce bias and small number lost - <20% ★ b) person-time analysis with reasonable proportion of subjects followed to ≥6 months★ c) no statement Category b in the original NOS was collapsed with category a. Studies which had a complete follow-up are captured by the less than 20% cut-off.

TABLE ONE: COMPARISON OF THE NOS TO THE ANOS COHORT STUDIES	
ORIGINAL NOS	**ADAPTED NOS**
	New category added to Adapted NOS Definition of outcome a) diagnosis defined according to specific predetermined criteria ★ b) diagnostic criteria not provided This category was added to reflect the need for studies to protect against the misclassification of outcome, which could bias the resulting effect estimate (relative risk).

2.1.3.2 ANOS: Case-Control Studies

Table Two summarizes both the original NOS and the adaptations made in the formation of the ANOS for case-control studies. The best score case-control studies could obtain using the ANOS was 10 stars.

TABLE TWO: COMPARISON OF THE NOS TO THE ANOS CASE-CONTROL STUDIES	
ORIGINAL NOS	**ADAPTED NOS**
SELECTION	
1) Is the case definition adequate? a) yes, with independent validation★ b) yes, eg record linkage or based on self reports c) no description	*Modified in Adapted NOS:* Is the case definition adequate?/Definition of outcome a) yes, with clear diagnostic criteria ★ b) yes, based on record linkage or self reports c) no description Independent validation (ie: through medical records) may be difficult. The most important aspect of the case definition for this kind of research is having clear, pre-defined diagnostic criteria that will prevent misclassification of cases.

TABLE TWO: COMPARISON OF THE NOS TO THE ANOS CASE-CONTROL STUDIES	
ORIGINAL NOS	**ADAPTED NOS**
2) Representativeness of the cases a) consecutive or obviously representative series of cases ★ b) potential for selection biases or not stated	*Modified in Adapted NOS:* Representativeness of the cases/Avoidance of selection bias a) consecutive or obviously representative series of cases (cases of disease equally likely to be enrolled in study independent of feeding group) ★ b) potential for selection biases or not stated Feeding status has the potential to influence an infant's likelihood of getting into a case-control study, particularly in hospital-based case-control studies where breastfed babies are not as likely to be admitted. This category was thus modified the need to protect against selection bias.
3) Selection of Controls a) community controls ★ b) hospital controls c) no description	*Modified in Adapted NOS:* Selection of Controls a) selection of controls fulfills the study base principle (Wacholder et al. [43]) that cases and controls are representative of the same base experience ★ b) selection of controls does not fulfill the study base principle
4) Definition of Controls a) no history of disease (endpoint)★ b) no description of source	*Modified in Adapted NOS* a) control does not currently have disease ★ b) no description of source This criterion required modification to reflect the acute nature of the three illnesses, and the chance for recurrence in children under 12 months of age. It was thought that excluding all children who had sustained previous bouts of illness was unrealistic, and would leave a very small pool of children from which to choose controls. Similarly, choosing controls who had disease histories identical to the case child (ie: if the case child was suffering from its third otitis media infection at the time of study, a suitable control infant would be a well child with a prior history of two otitis media infections) was also unrealistic. It was thus decided that controls who did not currently have the disease would be acceptable.

TABLE TWO: COMPARISON OF THE NOS TO THE ANOS CASE-CONTROL STUDIES	
ORIGINAL NOS	**ADAPTED NOS**
COMPARABILITY	
1) Comparability of cases and controls on the basis of the design or analysis a) study controls for (Select the most important factor.) ★ b) study controls for any additional factor ★ (This criteria could be modified to indicate specific control for a second important factor.)	*Incorporated into Adapted NOS* The most important factor chosen for adjustment was socioeconomic status where the study received a star for the adjustment for one of the following: income, education, social class, or occupation. Additional important factors included: maternal age, maternal smoking, use of daycare and size of family (ie: number of siblings). A study that adjusted for at least one of these other factors received a star (for a potential of 2 stars).
EXPOSURE	
1) Ascertainment of exposure a) secure record (eg surgical records) ★ b) structured interview where blind to case/control status ★ c) interview not blinded to case/control status d) written self report or medical record only e) no description	*Modified in Adapted NOS:* Ascertainment of feeding status a) structured interview ★ b) medical records c) written self report (self-administered questionnaire) d) no description Secure records (such as surgical records) are not available for the outcomes under study. This category was deleted. The structured interview was retained as the best manner to collect information about the duration and exclusivity of breastfeeding.
2) Same method of ascertainment of exposure for cases and controls a) yes ★ b) no	*Incorporated in Adapted NOS* Same method of ascertainment of feeding status for cases and controls a) yes ★ b) no
3) Non-Response rate a) same rate for both groups ★ b) non respondents described c) rate different and no designation	*Modified in Adapted NOS:* Non-Response rate a) subjects lost unlikely to introduce bias- <20% in both groups and description provided of those lost ★ b) no statement Differential non-response rates are not necessarily a problem; having the same rate of response is both groups does not necessarily indicate an ideal study circumstance. This category was modified to reflect the need for reasonable proportions of follow-up in each of the groups.

2.1.4 The Critical Appraisal Process

The cohort and case-control studies that met the inclusion criteria and were not excluded were evaluated for quality using the ANOS by two raters, namely, the principal author of this thesis and one of the thesis advisors (RAS). After scoring, indices of agreement for the ANOS were calculated for overall test scores and for individual items.

Differing interpretations of the ANOS led to further clarification of several items and another revision of the scale. The revised scales in their final forms appear in Appendices D (Cohort Studies) and E (Case-control Studies). Raters revised ratings and then calculated indices of agreement for overall scores and for individual items.

Association between ANOS scores was assessed using Pearson's correlation coefficient:

$$r = \frac{cov_{xy}}{s_x s_y}$$

Where: cov_{xy} = covariance of the raters' (x and y) scores
s_x = the standard deviation of rater one's scores (x)
s_y = the standard deviation of rater two's scores (y)

The square of the correlation coefficient (r^2) can be interpreted as the proportion of variability in y that can be explained by knowing x and vice-versa.

For individual items within the ANOS, Cohen's Kappa was used as an index of agreement. In a 2x2 contingency table, kappa measures the agreement (in the concordant cells) while correcting for chance agreement [44]:

$$K = \frac{\text{observed agreement - chance agreement}}{1 - \text{chance agreement}}$$

Upon calculation of Cohen's Kappa for the 7 individual items, guidelines as cited by Feinstein [45] were used to evaluate the strength of agreement between raters:

Value of Kappa	Strength of Agreement
<0	Poor
0 - 0.20	Slight
0.21 - 0.40	Fair
0.41 - 0.60	Moderate
0.61 - 0.80	Substantial
0.81 - 1.00	Almost Perfect

The two raters compared test scores post-evaluation, resolved discrepancies, and assigned a final score to each of the studies. It is this final ANOS score and evaluation of key components of the ANOS upon which selection of the studies for the main analysis and those used as part of the sensitivity analysis were made.

2.1.5 Selection of Relative Risks

The selection of relative risks for use in the economic analysis was based on the critical appraisal process. Aggregate quality scores were first considered, and the PAF was calculated for any study achieving at least a 'passing grade' (five stars out of eight stars for cohort studies).

As recommended by MOOSE [40], key study components assessed by the ANOS were identified. These components were regular surveillance of subjects at least once per month and the control of confounding factors. These factors were chosen based on the standards for breastfeeding research put forth by Bauchner et al. [29]. Failure of studies to provide adequate surveillance of babies has the potential to introduce detection bias into the study, a phenomenon that has the potential to sway the relative risk in favour of breastfeeding babies. Likewise, the failure to control for confounding factors such as

socioeconomic status and (at least one of) maternal age, maternal smoking, use of daycare or size of family (ie number of siblings) can also cause a misleading relative risk. Each of these factors alone could account for morbidity differences between breast and bottle fed babies. Since no study could control for all of these confounding factors (over and above socioeconomic status), control for one of the additional factors was deemed sufficient.

Definition of breastfeeding was also identified as a key study component as inadequate classification of babies could lead to nondifferential misclassification, causing the relative risk to move toward the null value. Although important, this factor was not used in the process of selecting studies for the main analysis. The population data (NLSCY) used in the calculation of the PAF did not contain information on formula supplementation or the exclusivity of breastfeeding. It was decided not to select studies based on this factor as the resultant PAF could not incorporate exclusivity of breastfeeding in its calculation.

PAFs calculated from relative risks from studies which received a star for regular surveillance of subjects and two stars for control of confounding factors were selected for the economic analysis.

2.2 Results

2.2.1 Identified Studies

A total of 239 primary studies were identified by the computerized search of Medline, CINAHL and Health Star. Of these studies, 42 met the inclusion criteria. Just under half (103) of the identified studies did not meet the inclusion criteria because they were conducted in developing nations. The remainder (92) did not meet the inclusion

criteria because they studied a disease or outcome not relevant to this thesis, did not examine breastfeeding, or were conducted among children greater than one year of age. A further 5 studies were found through a review of the references of the 42 included studies. This process (together with the computerized literature search) yielded a total of 47 studies. Of these 47 studies, 38 were cohort studies and nine were case-control studies. All 47 studies were reviewed and evaluated according to the exclusion criteria.

2.2.2 Excluded Studies

Twenty-four [46-69] of the 38 cohort studies met the exclusion criteria and were not used. The most common reason for exclusion was absent or inadequate adjustment for confounding variables (nine studies [46-54]). Inadequate sample size was the cause for exclusion of eight cohort studies [55-62]. The remaining studies were excluded because relative risks could not be derived from the data presented (five studies [63-67]), or because the study was conducted in a subpopulation of infants that could not be generalized to the greater population of Ontario infants (2 studies [68-69]) such as studies with a high proportion of Black infants.

Among those studies meeting the inclusion criteria, but not the exclusion criteria, two additional studies were excluded. One study (Wilson et al. [70]) was excluded because it was a seven-year follow-up to one of the previously identified cohort studies (Howie et al. [25]), for which the earlier study was most relevant to morbidity rates among infants in their first year of life. A second cohort study was excluded because it modelled changes to the risk of otitis media after the discontinuation of breastfeeding (Sassen et al. [71]). Thus, a total of 26 cohort studies were excluded: 24 that met the exclusion criteria, and 2

others that were not appropriate for use in the analysis. This left a total of 12 cohort studies [25,30,72-81] that were used in the analysis. A list of the excluded cohort studies, and their reason for exclusion, appears in Appendix F. The cohort studies used in the analysis are summarized in Appendix G.

Of the nine case-control studies that met the inclusion criteria, eight were excluded [82-89]. The reasons for exclusion of these studies included: lack of or inadequate adjustment for confounders (4 studies [82-85]), insufficient sample size (2 studies [86-87]) and lack of empirical data for children in the first year of life (2 studies [88-89]). A list of excluded case-control studies, and their reason for exclusion, appears in Appendix H.

2.2.3 Critical Appraisal/Quality Rating: Cohort Studies

The 12 cohort studies that met the inclusion criteria and were not excluded were evaluated for quality by two raters using the ANOS. Individual study scores by rater appear in Appendix I.

Two ANOS items caused discrepancies between the raters: assessment of outcome/avoidance of detection bias (surveillance) and adequacy of follow-up of cohorts. The discrepancy between raters for assessment of outcome/avoidance of detection bias (point 2 under 'Outcome') was the requirement that subjects be monitored at least once per month via structured interview. One rater awarded stars for surveillance regardless of how it was completed, while the other rater awarded stars to those studies that completed surveillance under specifications of the ANOS (that is, surveillance by structured interview). It was decided that the critical point of this item was surveillance once per month, and that the method by which this occurred was less important. A structured

interview is the ideal but surveillance by other methods such as a diary or self-completed questionnaire was considered acceptable. The ANOS was modified to reflect this change, and the raters' scores were modified such that any form of surveillance, regardless of method, received the star.

The second discrepancy between raters was the criterion that assessed adequacy of follow-up (point 4 under "Outcome"). In the ANOS, this item was problematic as one rater awarded stars based on proportion of subjects followed-up (<20% of subjects lost to follow-up) while the other rater scored studies according to whether they fulfilled this cut-off, and provided a description of those lost. Describing lost subjects allows comparison to remaining study subjects to determine if any differences between these two groups might affect the study outcome. For the purpose of this thesis, it was decided that having an adequate follow-up was satisfactory. The ANOS was further modified to reflect this change, and the raters' scores were modified such that any study with less than 20% of subjects lost was awarded the star.

Measures of concordance between the two raters were calculated on scores as they appeared after completing the ANOS modifications summarized above. Out of 12 cohort studies, one rater awarded a total of 67 stars, with scores ranging from 3 to 8 stars. The other rater awarded a total of 66.5 stars[b], with scores ranging from 4 to 8 stars. The two

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[b] The ANOS does not theoretically allow for half stars to be awarded. Rubin et al. evaluated four outcomes (diarrhea, otitis media, lower respiratory disease, and upper respiratory disease) in which definitions fulfilling the ANOS criterion "Definition of Outcome" were satisfactory for only two of the four outcomes (diarrhea and upper respiratory disease). This study could be scored separately for each of the four outcomes giving rise to four final scores (to reflect the differing fulfilment of the above items), but for the purposes of evaluating the concordance of overall study scores between raters, a half star was awarded for this item, giving rise to an overall score of 6.5 stars for the study.

raters were discordant on seven out of 12 final ANOS scores. Correlation between the overall test scores between the two raters as assessed by Pearson's correlation coefficient (r) was 0.838. Squaring the correlation coefficient demonstrated that 70% of the variation in one rater's scores was explained by the other rater's scores.

Table Three summarizes the agreement and strength of agreement [45] between raters for the seven individual ANOS criteria as measured by Cohen's Kappa.

TABLE THREE: MEASURES AND STRENGTH OF ASSOCIATION FOR INDIVIDUAL ANOS CRITERIA		
ANOS Criterion	**Kappa**	**Strength of Agreement**
Definition of Breastfeeding	0.824	Almost perfect
Ascertainment of Exposure	0.333	Fair
Comparability	0.25	Fair
Definition of Outcome	0.833 - 1.000[c]	Almost perfect
Surveillance	1	Perfect
Length of Follow-Up	1	Perfect
Adequacy of Follow-up	1	Perfect

In all but two of the items, the strength of agreement between raters was almost perfect. For the ascertainment of exposure item, the raters were discordant on three studies, making the strength of agreement fair. The strength of agreement for comparability was also fair, with discordance between raters on three studies.

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[c] To measure the concordance of raters for the "Definition of Outcome" criterion, each of the four outcomes studied by Rubin et al. were assessed separately. One rater awarded a star for all four outcomes. The other rater awarded a star for two of the outcomes (diarrhea and upper respiratory disease). Cohen's Kappa was calculated for each of the four outcomes, thus reflecting the range in the Kappa statistic as summarized in the above table.

After quality appraisal and assessment of concordance, the two raters compared test scores post-evaluation, resolved discrepancies, and assigned a final score to each of the studies. The final score for each of the 12 studies by outcome is summarized in Table Four.

TABLE FOUR: QUALITY ASSESSMENT SCORES FOR COHORT STUDIES AS EVALUATED BY THE ADAPTED NEWCASTLE-OTTAWA SCALE (ANOS)			
Adapted NOS Score	**Gastrointestinal Disease (Diarrhea)**	**Otitis Media**	**Respiratory Disease**
8 Stars	Howie 1990 [25]	Howie 1990 [25]	Cushing 1999 [74] Howie 1990 [25]
7 Stars		Duffy 1997 [75]	
6 Stars	Rubin 1990 [80]		Rubin - URI 1990 [80]
5 Stars	Fergusson 1981 [77] Scariati 1997 [30]	Alho 1990 [72] Duncan 1993 [76] Rubin 1990 [80] Scariati 1997 [30] Teele 1989 [81]	Alho 1990 [72] Fergusson 1981 [77] Rubin - LRI 1990 [80]
4 Stars	Beaudry 1995 [73] Raisler 1999 [79]	Kero 1987 [78] Raisler 1999 [79]	Beaudry 1985 [73] Raisler 1999 [79]

2.2.4 Critical Appraisal/Quality Rating: Case-Control Studies

Only one case-control study was eligible for appraisal by the ANOS. This study was conducted by Leventhal et al. [90] and examined illness among infants who were less than 90 days of age. As evaluated by the ANOS for case-control studies, the final scores awarded by the two raters were discordant by one star (for the item assessing definition of

breastfeeding - under Exposure). Since the groups of exclusive and partial breast feeders could not be derived in the study as published, the two raters agreed to withhold a star under this criterion, giving rise to a final score of eight stars. Measures of concordance for overall scores and for individual criteria could not be calculated for one study.

It is doubtful that the odds ratios for illness as estimated for the first 90 days of life will hold for the first year of life. This study was therefore excluded from any quantitative analysis (calculation of the PAF) in this thesis. All calculations of the PAF were made based on cohort studies.

2.2.5 Relative Risks Selected for Analysis

Table Five summarizes the relative risks from the studies that achieved five or more stars on the ANOS. The first column of Table Five lists the studies selected for further analysis, while the second column lists relative risks reported in those studies.

TABLE FIVE: RESCALE OF STUDY RESULTS (RELATIVE RISKS) USED IN THE CALCULATION OF THE POPULATION ATTRIBUTABLE FRACTION

Study/ Year/ ANOS Score	Results as presented in Study	Rescaling Methods	Rescaled Relative Risks
GASTROINTESTINAL DISEASE (DIARRHEA)			
Fergusson et al. [7] 1981 5 stars	RR's not presented: adjusted rates of gastrointestinal illness were provided	Adjusted rates of disease were used to calculate relative risks. The reference group were babies breastfed greater than 3 months. Data on gastrointestinal disease were for the first 4 months of life.	Breast >3 mos: 1.00 Breast 2-3 mos: 1.17 Breast 1-2 mos: 1.36 Breast <1 month: 1.58 Formula: 1.82

TABLE FIVE: RESCALE OF STUDY RESULTS (RELATIVE RISKS) USED IN THE CALCULATION OF THE POPULATION ATTRIBUTABLE FRACTION			
Study/ Year/ ANOS Score	**Results as presented in Study**	**Rescaling Methods**	**Rescaled Relative Risks**
Howie et al. [25] 1990 8 stars	RR's not presented: cumulative incidence presented for each quarter of the first year of life	1. The study defined breast feeders as full (exclusively breastfed) and partial. These two groups were collapsed into a breastfeeding group by taking the weighted average of the two groups' cumulative incidence. 2. Quarter- specific cumulative incidence ratios (CIRs) were calculated for the three groups. 3. The CIR for the first year of life was derived by taking the average of the quarter-specific CIRs. 4. Dr. Howie was contacted via email in an attempt to obtain cumulative incidences for the entire first year of life for the three diseases under study. There was no reply.	Breast feeders: 1.00 Early Weaners: 1.93 Bottle feeders: 2.13
Rubin et al. [80] 1990 6 stars	Breast: 1.00 Formula: 1.07 Person-time methods (incidence density) used in the calculation of the RRs.	No rescale necessary *Breastfed group* were children exclusively breastfed, and children who received more breast milk than formula. *Formula fed group* were children who received equal amounts of breast milk and formula, children who received less breast than formula, and children who were exclusively formula fed.	
Scariati et al. [30] 5 stars	Full breast: 1.00 Breast>Formula: 0.9 Breast=Formula: 1.1 Breast<Formula: 1.3 Full formula: 1.8	No rescale necessary	

TABLE FIVE: RESCALE OF STUDY RESULTS (RELATIVE RISKS) USED IN THE CALCULATION OF THE POPULATION ATTRIBUTABLE FRACTION			
Study/ Year/ ANOS Score	**Results as presented in Study**	**Rescaling Methods**	**Rescaled Relative Risks**
OTITIS MEDIA			
Alho et al. [72] 1990 5 stars	Acute Otitis Media: Breast >12 mos: 1.00 Breast 7-11mos: 1.07 Breast 3-6 mos: 1.14 Breast <3 mos: 1.6	No rescale necessary	
Duffy et al. [75] 1997 7 stars	Full breast: 1.00 Partial breast: 3.06 No breast:4.57	No rescale necessary	
Duncan et al. [76] 1993 5 stars	No breast/ breast <4 mos: 1.00 Breast ≥4 mos + formula <4 mos:0.8 Breast≥4 mos + formula 4-6mos:0.72 Breast ≥ 6 mos 0.61	The average of 'Breast ≥4 mos + formula <4 mos' and 'Breast≥4 mos + formula 4-6mos:0.72' was taken to collapse these two groups Reciprocal of the 'Breast ≥ 6 mos' estimate (ie: 1/0.61) was used to make breastfeeding the reference group. The remaining levels were also divided by the 'Breast ≥6 mos' estimate, reflecting the creation of the new reference group.	No breast/ breast <4 mos: 1.64 Breast ≥4 mos: 1.29 Breast ≥ 6 mos 1.00
Howie et al. [25] 1990 8 stars	RR's not presented: cumulative incidence presented for each quarter of the first year of life	See notes under Howie et al., table heading: Gastrointestinal Disease	Breast feeders: 1.00 Early Weaners: 0.83 Bottle feeders: 0.97
Rubin et al. [80] 1990 5 stars	Breast: 1.00 Formula: 1.28	No rescale necessary See notes under Rubin et al., table heading: Gastrointestinal Disease	
Scariati et al. [30] 1997 5 stars	Full breast: 1.00 Breast>Formula: 1.2 Breast=Formula: 1.4 Breast<Formula: 1.6 Full formula: 1.7	No rescale necessary	

TABLE FIVE: RESCALE OF STUDY RESULTS (RELATIVE RISKS) USED IN THE CALCULATION OF THE POPULATION ATTRIBUTABLE FRACTION			
Study/ Year/ ANOS Score	**Results as presented in Study**	**Rescaling Methods**	**Rescaled Relative Risks**
Teele et al. [81] 1989 5 stars	<1 episode of OM in first year of life Ever breast: 0.64 Never breast: 1.00 <3 episodes of OM in first year of life Ever breast: 0.51 Never breast: 1.00	Reciprocal of the 'Ever breast' estimate (ie: 1/0.64) was used to make breastfeeding the reference group.	≥1 episode of OM in first year of life Ever breast: 1.00 Never breast: 1.56 ≥3 episodes of OM in first year of life Ever breast: 1.00 Never breast: 1.96
RESPIRATORY DISEASE			
Alho et al. [72] 1990 5 stars	Wheezy Bronchitis: Breast >12 mos: 1.00 Breast 7-11mos: 1.15 Breast 3-6 mos: 1.15 Breast <3 mos: 1.5	No rescale necessary	
Cushing et al. [74] 1998 8 stars	Upper Respiratory: Full breast: 1.10 Partial breast: 1.11 No breast: 1.00 Lower Respiratory: Full breast: 0.79 Partial breast: 0.95 No breast: 1.00	Reciprocal of the 'Full breast' estimate (ie: 1/1.10) was used to make breastfeeding the reference group. The remaining levels were also divided by the 'Full breast' estimate, reflecting the creation of the new reference group.	Upper Respiratory: Full breast: 1.00 Partial breast: 1.00 No breast: 0.91 Lower Respiratory: Full breast: 1.00 Partial breast: 1.20 No breast: 1.26
Fergusson et al. [77] 1981 5 stars	RR's not presented: adjusted rates of respiratory illness were provided for each feeding group for the first year of life	Adjusted rates of disease were used to calculate relative risks. The reference group were babies breastfed greater than 8 months.	Breast >8 mos: 1.00 Breast 4-7 mos: 1.05 Breast <4 mos: 1.10 Formula: 1.15
Howie et al. [25] 1990 8 stars	RR's not presented: cumulative incidence presented for each quarter of the first year of life	See notes under Howie et al., table heading: Gastrointestinal Disease	Breast feeders: 1.00 Early Weaners: 1.18 Bottle feeders: 1.21

TABLE FIVE: RESCALE OF STUDY RESULTS (RELATIVE RISKS) USED IN THE CALCULATION OF THE POPULATION ATTRIBUTABLE FRACTION			
Study/ Year/ ANOS Score	**Results as presented in Study**	**Rescaling Methods**	**Rescaled Relative Risks**
Rubin et al. [80] 1990 6 stars-URI 5 stars-LRI	Upper Respiratory: Breast: 1.00 Formula: 0.984 Lower Respiratory: Breast feeders: 1.00 Formula feeders: 1.00	No rescale necessary See notes under Rubin et al., table heading: Gastrointestinal Disease	

When selected for the most salient methodologic standards (surveillance of subjects and control of confounding factors), four studies were retained for the economic analysis. These studies were those completed by Cushing et al. [74], Howie et al. [25], Rubin et al. [80], and Scariati et al. [30].

3.0 IMPACT FRACTIONS

Impact fractions measure the proportional reduction in disease incidence resulting from a particular change - either a decrease in the prevalence of a hazardous risk factor or an increase in the prevalence of protective risk factor [91]. Two variants of impact fractions that were used in this thesis were: the population attributable fraction (PAF) and the population prevented fraction (PPF).

3.1 Methods

Calculation of the PAF/PPF requires information about the relative risk of disease associated with a given risk factor (RR) and the prevalence of the risk factor in a population (p).

3.1.1 Manipulation Of Relative Risks

Manipulation of individual study results (the relative risk) was required to derive estimates that could be used in the PAF calculation. In many cases, the main adjustment that needed to be made was to rescale relative risks such that breastfeeding was the reference group (relative risk of breastfeeding set to one). The third column of Table Five (page 49) documents how the relative risks were manipulated.

3.1.2 Prevalence Data

3.1.2.1 The National Longitudinal Survey of Children and Youth

An estimate of the prevalence of breast and bottle feeding among the target population was needed to calculate the PAF. The National Longitudinal Survey of Children and Youth 1994/1995 was used to estimate the prevalence of various feeding practices among Ontario infants under the age of one.

The National Longitudinal Survey of Children and Youth (NLSCY) was initiated by Statistics Canada in 1994 to develop a national database on the characteristics and life experiences of children and youth in Canada as they grow from infancy to adulthood [92]. The target population of the NLSCY consisted of Canadian children aged newborn to 11 years of age.

Sampling for the NLSCY reflects a modified version of the Statistics Canada Labour Force Survey (LFS) sampling design, which is a multi-stage stratified sample of dwellings [92]. Provinces were initially divided into three strata: major urban centres, urban towns and rural areas. Within the major urban centres, clusters containing approximately 150 to 250 dwellings were constituted and stratified by geography and/or socioeconomic characteristics. Remaining towns and rural areas in each province were stratified with geographical areas by socioeconomic characteristics. In most strata, six clusters were selected.

A requirement of the NLSCY was to select households with children aged newborn to 11 years of age. This was a challenge, as only 26% of Canadian households contain at least one child in this age range. Sampled households were derived from three possible components labelled Main, Integrated and Territories [92]. The Main component included households with children that were currently or had recently been in the LFS (12,900 households). The Integrated component included those households selected for the purposes of the National Population Health Survey (2,700 households) in which the randomly selected individual for longitudinal follow-up was age 0 to 11. The Territories component included 2,300 children (as opposed to households) and was an integrated

sample used for both the NLSCY and the National Population Health Survey. The Territories component was not part of the public use data release of the NLSCY, which was used for this thesis.

This initial cycle of the NLSCY resulted in a responding sample of 13,439 households, in which 22,831 children were selected to participate, with an overall household response rate of 86.3% (15,578 households selected to participate, 13,439 responded) [92]. The response rate in Ontario was 82.5% (4,268 selected, 3,519 responded) [92]. The reasons for non-response included the inability of the interviewer to make contact, refusal to take part in the survey, special circumstances such as illness or death, and extreme weather conditions. Responding and non-responding households differed on the following factors:

- non-responding households were more often in census metropolitan areas (CMAs) and therefore urban;
- parent(s) in non-responding households were more often over the age of 40; and,
- parent(s) in non-responding households more often had a low level of education (0-8 years).

In each NLSCY household, one child 0 to 11 years of age was selected at random and a question was asked about who in the household was the Person Most Knowledgeable (PMK) about the child. For 91.3% of the responding children, the PMK was the mother (89.9% biological and 1.4% step, adoptive or foster mother) [92]. For questions relating to breastfeeding, the responses were restricted to those of the biological mother.

The NLSCY questions relating to breastfeeding [92] were asked of the PMK for the population less than 2 years of age. The first question asked was: "Is the baby currently being breastfed?". If the answer was "yes" the questions skipped to another section of the survey, and the PMK was not asked any further questions about breastfeeding. If the response was "no", the respondent was asked if the baby was ever breastfed, even if only for a short time. If the answer was "yes", the respondent was asked for the duration of breastfeeding.

In addition to questions on initiation and the duration of breastfeeding, PMKs who were not breastfeeding at the time of the survey were also asked questions on the reason(s) for initiating breastfeeding, the reason(s) for discontinuing breastfeeding, and who aided them in making decisions to initiate or discontinue breastfeeding. There were no questions on the exclusivity of breastfeeding. Survey questions and possible responses are presented in Appendix J.

For calculation of the PAF, estimates for Ontario from the NLSCY were used to derive estimates of breast and bottle feeding. While the NLSCY did not ask about bottle feeding per se, it was assumed that the proportion of infants who were bottle fed could be derived by subtracting the proportion of infants being breastfed from the total population of infants.

Information on the duration of breastfeeding was not available for infants who were breastfeeding at the time of the survey (although this would equal age). Because the month and year of birth of the infant was suppressed on the public release micro-data file, it was impossible to derive the duration of breastfeeding for children who were

breastfeeding at the time of the survey. To achieve accurate estimates of the prevalence of bottle feeding for use in the calculation of the PAF, information on the duration of breastfeeding among the cohort of infants age 12 to 23 months at the time of the survey was used. It was reasoned that only a small proportion of infants in this cohort would be breastfeeding at the time of the survey, and among those still breastfeeding, one could definitively categorize these infants as having breastfed for twelve months or longer.

To derive meaningful population estimates from the survey, the weighting variable provided on the NLSCY micro-data file was applied to the analysis, adjusting the estimates for clusters (a sampling fraction related to population growth in a cluster), non-response, and rural-urban factors as well as defining the number of persons in the population that the respondent represents.

Design effect, which measures the degree of sampling complexity, is a ratio of the true variance (recognizing the sample design) of the sample proportion to the variance of the sample proportion from a simple random sample of the same size [92]. Clustered survey designs usually have a higher variance than a simple random sample (and thus a design effect greater than one), while a good stratified design has a lower variance than a simple random sample (and a design effect less than one). In the case of a complex, stratified, multistage clustered design like the LFS (on which the NPHS and the NLSCY is based), the efficiency of stratification is compromised by clustering, and the end result is a design effect usually higher than one [93]. Design effects are used in the construction of coefficient of variation tables which provide a guideline of the degree of accuracy of the population estimates. In addition to using the coefficient of variation tables (provided as part of

NLSCY documentation) in the calculation of 95% confidence intervals, these tables also provided information on when to use caution in the interpretation of the findings and when not to use population estimates.

3.1.2.2 Alignment of NLSCY Prevalence Estimates with Relative Risks

The shortcoming associated with the NLSCY data for prevalence of breastfeeding was that estimates were available for the duration of breastfeeding, but not for exclusivity of breastfeeding. This feature of the data was problematic when aligning prevalence estimates with published studies, as most presented their results according to duration and exclusivity of breastfeeding (as required by the ANOS).

Another challenge was that some studies measured breastfeeding for the entire first year of life, while others only measured breastfeeding for the first six months of life or other time periods. The NLSCY presents breastfeeding prevalence data for the entire first year of life, and information on the age of the child at the time of the survey is suppressed on the micro-data file.

The specific assumptions made in the procedure of aligning study results with NLSCY prevalence estimates are summarized below:

1. Studies categorizing feeding groups according to the WHO [94] classification of breastfeeding (Raisler et al. [79], Rubin et al. [80], Scariati et al. [30]):

The WHO [94] classification of breastfeeding groups infants into 5 categories depending on the exclusivity of breastfeeding. These groups are: infants fully breastfed ("full breast"), infants receiving more breast milk than formula ("breast>formula"), infants receiving equal amounts of breast milk and formula ("breast=formula"), infants receiving

less breast milk than formula ("breast<formula"), and infants fully formula fed ("full formula"). Infants can be categorized into any of these groups at any point in time (thus reflecting changes in exposure over time) and studies that collected breastfeeding data in this manner did so on a monthly basis.

To align the NLSCY estimates with these feeding groups, breastfeeding duration was considered for the entire first year of life. The duration of time (in months) that an infant was breastfed was compared to the first 12 months of life. For example, an infant who had been breastfed for 8 months out of 12 months likely received more breast milk than formula (comparable to the "breast>formula" group) as she was breastfed for most of the first year of life.

It was assumed that infants who were still breastfeeding at the time of NLSCY data collection, or had been breastfed for longer than 10 months could be categorized into the "full breast" group. Infants who had been breastfed for 7-9 months out of the first 12 months of life (NLSCY) likely received more breast milk that formula when considering the entire first year of life and were categorized into the "breast>formula" group. In constructing the "breast=formula" group, it was assumed that infants who had breastfed for 3-6 months (NLSCY) likely received equal amounts of breast milk and formula, as infants who had been breastfed for 6 months had been for half of the year. Infants in the "breast<formula"group were those who had breastfed for one to 12 weeks and certainly received less breast milk than formula for the first year of life. It was assumed that NLSCY infants who had never been breastfed or had been breastfed for less than one week could be categorized into the "full formula" group. Although infants breastfed for

less than one week did receive some breast milk, it was argued that this group of infants likely had heavy formula supplementation in the first week of life, as infants who have been breastfed for less than one week are usually those who experience early breastfeeding problems and thus cease breastfeeding very early [21].

2. Studies categorizing infants according to full breastfeeding, partial breastfeeding, and no breastfeeding (Cushing et al. [74], Duffy et al. [75], Duncan et al. [76])

Alignment of the NLSCY prevalence estimates with these feeding groups was based on the classification described in point number one, above. The full breastfeeding and no breastfeeding groups were considered identical to the full and no breastfeeding groups as in point one. The remaining groups ("breast>formula", "breast=formula" and "breast<formula") were used to construct the partial breastfeeding group, as these infants were those infants who likely received some mixture of breast milk and formula.

3. Studies categorizing infants according to duration only (Alho et al. [72], Fergusson et al. [77], Howie et al. [25])

Although Howie et al. [25] collected data exclusivity of breastfeeding, relative risks calculated from study data collapsed full and partial breast feeders together, thus leaving a final categorization of infants according to duration. This information on duration could be easily aligned with NLSCY data, and no assumptions needed to be made.

4. Studies dichotomizing infants according to a dichotomous exposure to breast milk: ever breast, never breast (Teele et al. [81])

The never breastfed group was identical to that described in point number one, above. The remaining durations were used to construct the "ever breast" group.

3.1.3 Calculation of Impact Fractions

3.1.3.1 Calculation of Population Attributable Fractions

The population attributable fraction (PAF) estimates the proportion of an outcome that can be attributed to a certain hazardous risk factor (assuming a causal relationship demonstrated by biologic plausibility, consistency of findings, dose-response relationship, magnitude of association and correct temporal sequence), and thus the proportion that can potentially be prevented by modifying the risk factor [95].

The PAF was calculated for each of the three outcomes (diarrhea, otitis media and respiratory infection) according to the following formula:

$$\frac{\sum_{i=1}^{k} \mathbf{p}_i(\mathbf{RR}_i - 1)}{\sum_{i=1}^{k} \mathbf{p}_i(\mathbf{RR}_i - 1) + 1}$$

where p is the probability of an infant being breast/bottle-fed (depending on the level of exposure, *i*), and the RR is the relative risk associated with being breast/bottle-fed.

3.1.3.2 Calculation of Population Prevented Fractions

In the event that bottle feeding was found to be a protective exposure (demonstrated by a relative risk of less than one), a population prevented fraction (PPF) was calculated. Prevented fractions measure the proportion of disease that has already been prevented by the exposure (in this case, bottle feeding) [95]. The PPF thus estimates the amount of disease that has already been prevented in the population under study. The PPF was calculated using the following formula:

$$\mathbf{PPF} = 1 - \sum_{i=1}^{k} \mathbf{p}_i(\mathbf{RR}_i)$$

where p is the proportion of the population that is breast/bottle-fed (depending on the level of exposure, *i*), and the RR is the relative risk associated with being breast/bottle-fed.

3.2 Results

3.2.1 Rescaled Relative Risks

Column four of Table Five (page 49) lists the relative risks that were rescaled for use in the calculation of PAF/PPF.

3.2.2 Prevalence of Bottle-feeding

3.2.2.1 NLSCY Estimates

At the time of the survey, there were an estimated 29,225 Ontario children aged 12-23 months who had been bottle fed from birth (never breastfed). Approximately 6,634 were currently breastfeeding at the time of the survey, while 106,161 had been breastfed at some time during their lives, but had been weaned by the time of the survey. Table Six summarizes prevalence of breastfeeding practices among Ontario infants aged 12-23 months at the time of the survey. Estimates of breastfeeding prevalence were excluded for infants under the age of 12 months since a substantial proportion (36%) of these children were breastfeeding at the time of the survey, and information on their duration of breastfeeding could not be derived.

TABLE SIX: PREVALENCE OF BREASTFEEDING FOR CHILDREN AGE 12-23 MONTHS, ONTARIO, 1994

Duration of Breastfeeding	Population	Proportion of all Children aged 12-23 months (n=146 546)	Proportion of Children aged 12-23 months*, excluding those with missing data, 95% CI (n=141 699)
Never Breastfed	29 225	19.9%	20.6% (15.8-25.4)
Less than one week	4 550[M]	3.1%	3.2% (1.19-5.2)
1 to 12 weeks	28 395	19.4%	20.0% (15.4-24.6)
3 to 6 months	40 468	27.6%	28.6% (23.2-34.0)
7 to 12 months	26 346	18.0%	18.6% (13.9-23.3)
More than 12 months *	12 715[M]	8.7%	9.0% (5.5-12.5)
Don't Know	322[U]	0.2%	
Not Stated	4 525[M]	3.1%	
Total	146 546	100%	100%

* Includes 6,634 children breastfeeding at the time of the survey

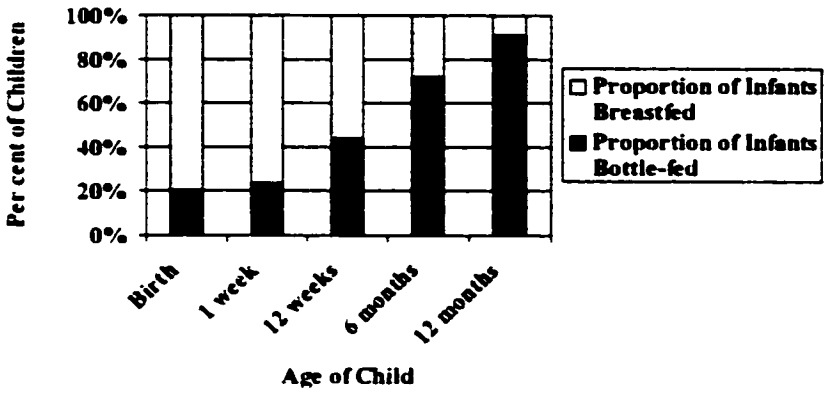
U These estimates do not meet Statistics Canada's quality standards. Conclusions based on these data will be unreliable, and most likely invalid.

M Interpret with caution. Estimates may reflect high sampling variability.

Data Source: National Longitudinal Survey Of Children And Youth, Statistics Canada, 1994

Figure One summarizes information about the prevalence of bottle feeding among this cohort of 12 to 23 month old children. Although the NLSCY did not query about bottle feeding specifically, it was assumed that this prevalence could be derived from the data provided about breastfeeding.

Figure One: Prevalence of Bottle Feeding Practices for Ontario Children Age 12-23 months



The prevalence of bottle-feeding increased with increasing age, with 72.4% of infants exclusively bottle-feeding by age six months. By the age of 12 months, fully 91% of children were bottle-feeding.

3.2.2.2 Realigned Prevalence Estimates

Table Seven summarizes the alignment of NLSCY prevalence estimates with the relative risks from the literature. The fourth column of Table Seven presents the feeding groups on which study relative risks were based, and the fifth column shows how the NLSCY feeding duration categories were collapsed to align with the study feeding groups.

TABLE SEVEN: ALIGNMENT OF STUDY RESULTS WITH NLSCY DURATION CATEGORIES				
Study/ Studies	**Outcome**	**Feeding Duration**	**Feeding Groups Defined in Study/Studies**	**Corresponding NLSCY Feeding Duration Categories**
Cushing et al. [74] 1998	Respiratory Disease	first six months of life	**Full breast**	**Full breast** current breastfeeders breast >12 mos breast 10-12 mos
			Partial breast	**Partial breast** breast 7-9 mos breast 3-6 mos
Duffy et al. [75] 1997	Otitis media	first six months of life		breast 9-12 weeks breast 5-8 weeks breast 1-4 weeks
			No breast	**No breast** breast <1 week never
Howie et al. [25] 1990	Gastrointestinal Disease Otitis Media Respiratory Disease	first 13 weeks of life	**Breastfeeders** (≥ 13 weeks of breastfeeding)	**Breastfeeders** current breastfeeders breast >12 mos breast 10-12 mos breast 7-9 mos breast 3-6 mos
			Early Weaners (<13 weeks of breastfeeding)	**Early weaners** breast 9-12 weeks breast 5-8 weeks breast 1-4 weeks breast <1 week
			Bottle feeders (at birth)	**Bottle feeders** never

TABLE SEVEN: ALIGNMENT OF STUDY RESULTS WITH NLSCY DURATION CATEGORIES				
Study/ Studies	**Outcome**	**Feeding Duration**	**Feeding Groups Defined in Study/Studies**	**Corresponding NLSCY Feeding Duration Categories**
Raisler et al. [79] 1999	Gastrointestinal Disease	first six months of life	**Full breast** **Breast>formula** **Breast=formula** **Breast<formula**	**Full breast** current breastfeeders breast >12 mos breast 10-12 mos **Breast>formula** breast 7-9 mos **Breast=formula** breast 3-6 mos **Breast<formula**
Scariati et al. [30] 1997	Gastrointestinal Disease	first six months of life		breast 9-12 weeks breast 5-8 weeks breast 1-4 weeks **Full formula** breast <1 week never
Rubin et al. [80] 1990	Gastrointestinal Disease Otitis Media Respiratory Disease	first 12 months of life	**Breast** full breastfeeders breast>formula **Formula** breast=formula breast<formula formula	**Breast** current breastfeeders breast >12 mos breast 10-12 mos breast 7-9 mos **Formula** breast 3-6 mos breast 9-12 weeks breast 5-8 weeks breast 1-4 weeks breast <1 week never

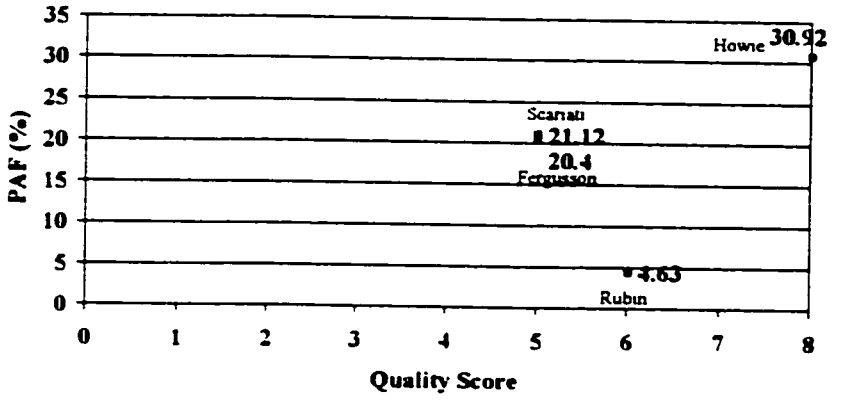
TABLE SEVEN: ALIGNMENT OF STUDY RESULTS WITH NLSCY DURATION CATEGORIES				
Study/ Studies	**Outcome**	**Feeding Duration**	**Feeding Groups Defined in Study/Studies**	**Corresponding NLSCY Feeding Duration Categories**
Teele et al. [81] 1989	Otitis Media	first 12 months of life	**Ever breast**	**Ever breast** current breastfeeders breast >12 mos breast 10-12 mos breast 7-9 mos breast 3-6 mos breast 9-12 weeks breast 5-8 weeks breast 1-4 weeks
			Never breast	**Never breast** breast <1 week never

3.2.3 Impact Fractions for Bottle Feeding

3.2.3.1 Gastrointestinal Disease (Diarrhea)

Figure Two demonstrates the PAFs for each study by the ANOS aggregate quality score. Bottle feeding was associated with diarrhea is all studies as the relative risks were greater than one. The PAFs for gastrointestinal illness ranged from a low of 4.63% for the study conducted by Rubin et al. [80] to a high of 30.92% for the study conducted by Howie et al. [25]. Interestingly, Howie and Rubin were the two highest quality studies with eight and six stars respectively. Two other moderately scoring studies (Fergusson [77] and Scariati [30]) fell between the two PAF values at approximately 20%.

Figure Two: Population Attributable Fraction by ANOS Quality Score for Gastrointestinal Disease



When the two most important quality components (surveillance and control of confounding factors) were considered apart from the aggregate quality scores (Figure Three), Howie [25], Rubin [80] and Scariati [30] were retained for the economic analysis. Methodologic details for each of these studies are briefly discussed in Appendix K. Scariati [30], with a PAF of 21.12% emerged as the median point estimate upon which excess costs of formula feeding were calculated. The results attained by Scariai et al.[30] meant that just over one fifth of diarrhea cases among Ontario infants age 12 months or younger could be attributed to formula feeding. Table Eight summarizes the results of the calculation of the PAF for these three studies.

Figure Three: Population Attributable Fractions for Studies Scoring Full Stars on ANOS Criteria of Surveillance and Control of Confounders Gastrointestinal Disease

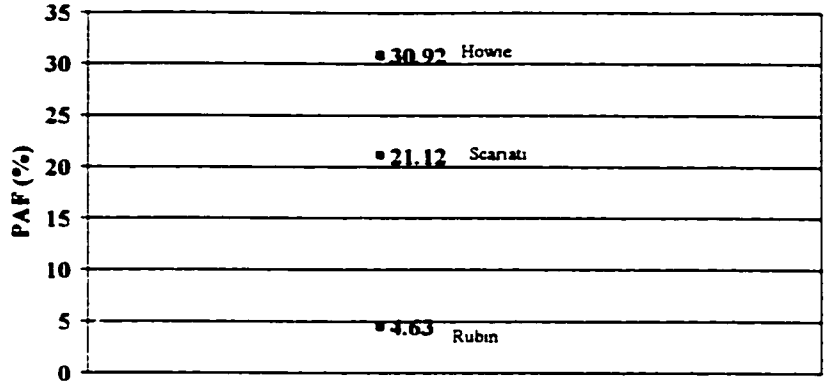


TABLE EIGHT: POPULATION ATTRIBUTABLE FRACTION GASTROINTESTINAL DISEASE (DIARRHEA)

Study	ANOS Score	Feeding Category	Effect (RR)*	Prevalence** of Breastfeeding	PAF
Howie et al. [25] 1990	8	Breast feeders	1.00	56.1%	30.92%
		Early weaners	1.93	23.2%	
		Bottle feeders	2.13	20.6%	
Scariati et al. [30] 1997	5	Full breast	1.00	17.3%	21.12%
		Breast>formula	0.9	10.2%	
		Breast=formula	1.1	28.6%	
		Breast<formula	1.3	20.0%	
		Full formula	1.8	23.8%	
Rubin et al. [80] 1990	6	Breast	1.00	27.6%	4.63%
		Formula	1.067	72.4%	

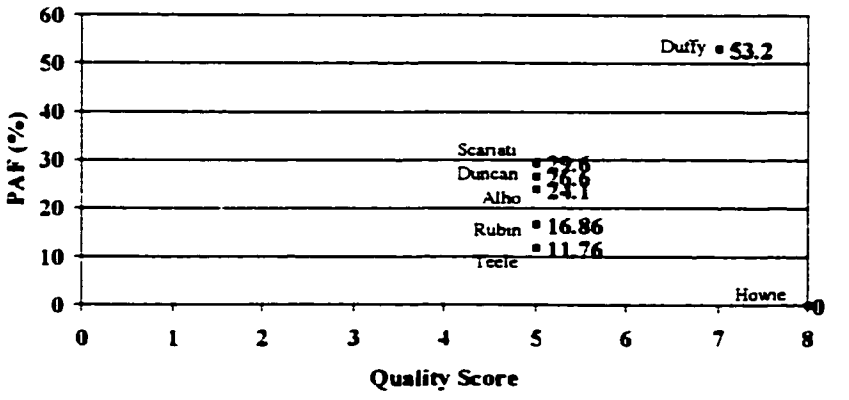
* Relative Risk, taken from study

** Taken from the 1994 National Longitudinal Survey of Children and Youth, Statistics Canada

3.2.3.2 Otitis Media

Population attributable fractions for otitis media for each of the studies by quality score appear in Figure Four. In all but one study, formula feeding was associated with an increased risk of otitis media (relative risks greater than one). The exception was the relative risks estimated from the study by Howie et al. [25] where early weaners (infants weaned from breast milk before 13 weeks of age) and Bottle-feeders (infants bottle fed from birth) had relative risks of less than one (0.83 and 0.97 respectively). Since a PAF could not be calculated with relative risks less than one (it appears on Figure Four as 0), the PPF was calculated to be 4.66%, meaning that approximately five per cent of otitis media in this population of infants had been prevented by bottle feeding. Where PAFs could be calculated, the range was from 0% (representing the study by Howie et al. [25]) to 53.2% (calculated using the relative risks from Duffy et al. [75]).

Figure Four: Population Attributable Fraction by ANOS Quality Score for Otitis Media



When studies were judged based for full marks for surveillance and control of confounding, Scariati [30], Rubin [80] and Howie [25] were retained (Figure Five) for the economic analysis. Individual study details are summarized in Appendix L. The PAF calculated using relative risks from the study by Rubin et al. emerged as the median study with a score of 16.86%. Table Nine summarizes the results of the calculation of the PAF/PPF for these three studies.

Figure Five: Population Attributable Fractions for Studies Scoring Full Stars on ANOS Criteria of Surveillance and Control of Confounders
Otitis Media

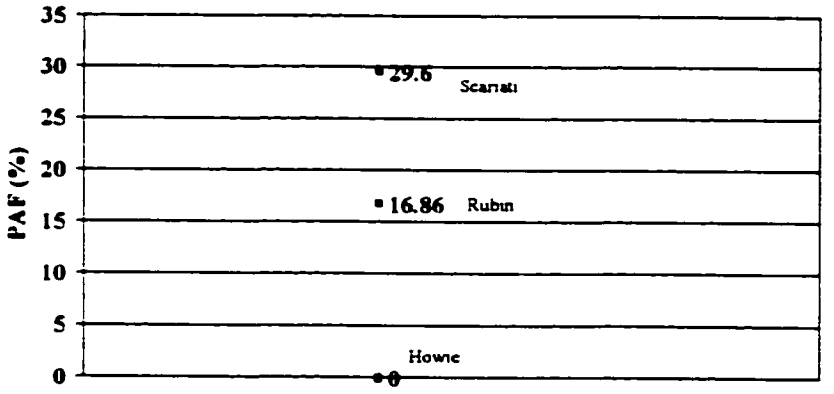


TABLE NINE: POPULATION ATTRIBUTABLE FRACTION, OTITIS MEDIA					
Study	**ANOS Score**	**Feeding Category**	**Effect (RR)***	**Prevalence** of Breastfeeding**	**PAF/PPF**
Scariati et al. [30] 1997	5	Full breast Breast>formula Breast=formula Breast<formula Full formula	1.00 1.2 1.4 1.6 1.7	17.3% 10.2% 28.6% 20.0% 23.8%	PAF=29.60%
Rubin et al. [80] 1990	6	Breast Formula	1.00 1.28	27.6% 72.4%	PAF=16.86%
Howie et al. [25] 1990	8	Breast feeders Early weaners Bottle feeders	1.00 0.83 0.97	56.1% 23.2% 20.6%	PPF=4.66%
* Relative Risk, taken from study ** Taken from the 1994 National Longitudinal Survey of Children and Youth, Statistics Canada					

3.2.3.3 Respiratory Disease

Figure Six shows the PAF for each of the individual studies by their overall quality score. The challenge to interpreting these results was that relative risks from some studies included both upper and lower respiratory disease together, while others assessed upper and lower respiratory disease separately. The most consistent results were for upper respiratory illness where no effect was observed, and the relative risks were slightly above or below 1.00. Both Rubin [80] and Cushing [74] did not find an effect of bottle feeding on the incidence of upper respiratory disease. These two studies were of high quality, achieving an ANOS score of six and eight respectively. Bottle-feeding had an adverse but inconsistent effect on lower respiratory disease. Although most relative risks were greater than one, the exception was Rubin et al. [80], where the risk of lower respiratory disease

among breast and bottle fed babies was equal. The PAFs calculated based on individual studies ranged from 0% for Rubin [80] to 22.56% for Alho et al. [72] Among those studies that examined upper and lower respiratory disease concurrently, the results were intermediate as expected, with the study by Fergusson [77] leading to a PAF of 6.34%, and the study by Howie et al. [25] giving rise to a PAF of 7.75%. As study results consistently gave rise to a PAF of zero for upper respiratory disease, this outcome was excluded from any further analysis.

Figure Six: Population Attributable Fraction by ANOS Quality Score for Respiratory Disease

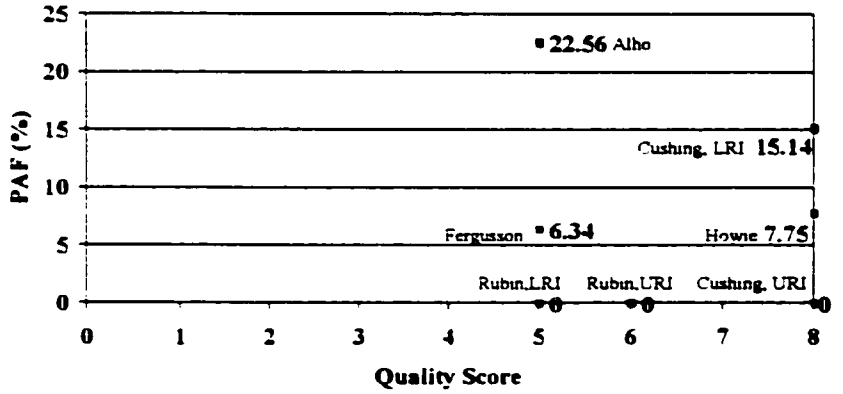


Figure Seven shows the distribution of PAFs among studies that scored full marks on regular surveillance and control of confounding factors in the ANOS. Economic analysis thus focused on lower respiratory illness. Studies retained for the economic analysis included Cushing [74], Rubin [80] and Howie [25]. The details for each of these studies appear in Appendix M. The range in PAFs were from 0% as generated from Rubin et al. [80] to 15.14% from Cushing et al. [74] The PAF based on the study by Howie et al. [25] emerged as the median estimate, and it was this PAF upon which the main economic analysis was based.

Although the estimate by Howie et al. [25] is for both upper and lower respiratory disease, it was applied to lower respiratory disease cost estimates. The resulting PAF is likely conservative. If a PAF for upper respiratory disease is zero (and relative risks for upper respiratory disease are close to one), combining upper respiratory disease with lower respiratory disease will dilute the protective effect of breastfeeding. Table Ten summarizes the results of the calculation of the PAF for these three studies.

Figure Seven: Population Attributable Fractions for Studies Scoring Full Stars on ANOS Criteria of Surveillance and Control of Confounders Respiratory Disease

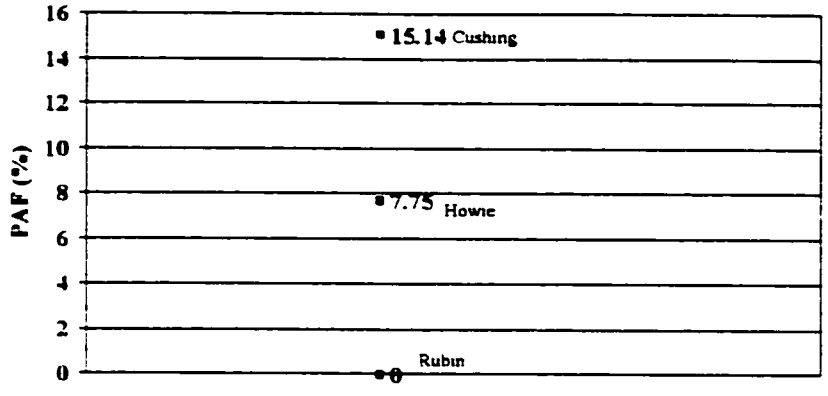


TABLE TEN: POPULATION ATTRIBUTABLE FRACTION LOWER RESPIRATORY DISEASE					
Study	**ANOS Score**	**Feeding Category**	**Effect (RR)***	**Prevalence** of Breastfeeding**	**PAF**
Cushing et al. [74] 1998	8	Full breast: Partial breast: No breast:	1.00 1.20 1.26	17.3% 58.8% 23.8%	15.14%
Howie et al. [25] 1990	8	Breast feeders: Early weaners: Bottle feeders:	1.00 1.18 1.21	56.1% 23.2% 20.6%	7.75%
Rubin et al. [80] 1990	6	Breast: Formula:	1.00 1.00	27.6% 72.4%	0%

* Relative Risk, taken from study

** Taken from the 1994 National Longitudinal Survey of Children and Youth, Statistics Canada

4.0 COSTING THE ADVERSE EFFECTS OF BOTTLE FEEDING

4.1 Methods

4.1.1 Estimating Health Care Utilization and Costs

Two databases accessed through the Institute for Clinical Evaluative Sciences (ICES) were used to estimate the direct costs of care (physician visits and hospitalizations) among Ontario infants for the first year of life. The data were for fiscal year 1994-1995 (April through March), and the age group was all children under the age of one. Physician data were taken from the ICES OHIP database, and hospitalization data were taken from the Canadian Institute of Health Information (CIHI) Discharge Abstract Database (DAD).

It is important to note that these two data sets are administrative in origin, that is, they are collected for financial or other administrative purposes. Despite the nature of collection, administrative databases are widely used for epidemiologic research with several advantages. Administrative databases:

- cover an entire population or geographic area;
- can be accessed at a low cost (relative to specially collected data);
- comply with standard coding systems (such as the ICD-9);
- have quality and verification checks (such as logic checks) built in to ensure the accuracy of data; and,
- are amenable to record linkage.

An ICES review [96] of the quality of health care administrative databases in Canada reports that the quality of such databases can be evaluated by the completeness of data (defined by the coverage of the population and available information on demographic

characteristics), agreement of information between data on the database and information that appears on the original records, and the agreement of diagnosis with diagnosis criteria as defined by expert groups with the actual coded diagnosis on the record. Although a formal systematic review of studies on the quality of health care data in Canada does not exist, a summary of smaller studies (by ICES [96]) reveals that:

- demographic information on patient age, sex and residence is complete and reliable;
- hospital data on the most responsible diagnosis vary in completeness and accuracy; and that the greatest disagreements with expert criteria-based reviews occurs with diagnoses where clinicians themselves may diagree;
- clinical data on secondary diagnoses, comorbidities and complications are less likely to be recorded accurately and comprehensively in hospital discharge abstracts; and,
- billing claims for physician services typically provide complete capture of procedure codes but these codes may not necessarily match those used in hospital records.

The most important caveat for the costs of care data used in this thesis is that all data reflect the number of events such as physician visits or hospital separations. Because visits (rather than patients) are counted, the potential exists for the same patient to have more than one physician visit or hospitalization. Therefore, these data sets cannot accurately assess the incidence of disease and require adjustment to achieve data at the individual level. For this thesis, it was impossible to determine the incidence of disease

among babies under the age of one for the time period under study.

4.1.1.1 Utilization and Costs: Physician Services

The ICES OHIP data set contains information associated with the reimbursement fees paid to physicians working in the fee-for-service sector. The five per cent of physicians who are on salary or paid by a third party billing service are not included. Database completeness is good in that less than one per cent of demographic information for the Ontario population are missing.

ICES provided data on the number of patients, number of billings and billing cost broken down according to seven broad physician visit types: Diagnostic and Therapeutic Procedures, Hospital Visits, Laboratory Medicine, Assessment and Consultation, Psychotherapy and Counselling, Surgery and Special Premiums/Other. An OHIP billing is equal to one service rendered. In one visit to a physician, there may be multiple services (for example, intermediate assessment and immunization) with multiple billing codes as appropriate [97]. The OHIP data set utilizes diagnostic codes that translate fairly well into ICD-9 codes. The following OHIP diagnostic codes were chosen to represent the three illnesses represented in this thesis:

Diarrhea:
003 Salmonella Infections-Other
009 Diarrhea

Otitis Media
381 Eustachian Tube Disorders
381 Serous Otitis Media
382 Suppurative Otitis Media

Respiratory Disease
460 Common Cold
460 Nasopharyngitis-Acute
461 Sinusitis-Acute
463 Tonsillitis-Acute
464 Croup
464 Epiglottis-Acute
464 Laryngitis-Acute
464 Tracheitis-Acute
466 Bronchitis-Acute
486 Pneumonia - All Types
487 Influenza

4.1.1.2 Utilization and Costs: Hospitalizations

The CIHI Discharge Abstract Database (DAD) contains data on Canadian hospital discharges. This database covers approximately 85% of all hospital inpatient discharges in Canada and contains demographic, administrative and clinical data for hospital discharges (inpatient acute, chronic, rehabilitation) and day surgeries. It is estimated that less than half of a per cent of all procedures and less than one per cent of records have missing information. As with other administrative databases, there is the potential for coding errors, and the coding methods and data fields used may vary across hospitals, affecting the final database. The data contained in this thesis reflect the number of hospitalizations (not number of patients) by most responsible diagnosis. The hospitalization data provided by ICES included number of separations, days of care and the total cost of hospitalizations.

The cost data provided by ICES were derived using CIHI's resource intensity weights (RIW) system. The RIW system is a resource allocation method for estimating a hospital's inpatient-specific costs for both acute and day procedure care [98]. RIW

standardizes the expression of hospital case volumes, recognizing that not all patients require the same health care resources. An RIW is associated with each Case Mix Group (CMG) and does not vary across hospitals. Case Mix Groups aggregate patients with similar clinical and resource utilization characteristics [98]. Within each CMG, RIWs can be further stratified by a complexity overlay (where applicable) which enhances the prediction of resource utilization and length of stay (LOS).

After grouping diagnoses into CMGs, the actual resource utilization of the CMGs are estimated using case-costing studies conducted in a sample of hospitals. Case-costing studies measure the actual costs incurred by a particular RIW. Prior to 1998, RIWs were calibrated using American case cost data (out of Maryland). Applying such case-cost data to Canadian CMGs depends on the generalizability of the American cost data (that is, American CMG resource utilization representative of Canadian CMG resource utilization) to the Canadian experience. The quality of the RIW data would thus depend on this.

RIWs are adjusted for hospital-specific factors (such as teaching status, size, factor input prices, and demographics of referral populations) using a Hospital Specific Relative Value (HSRV) method. RIWs are calibrated such that a value of one represents the average inpatient care across all participating hospitals. A value of less than one indicates those conditions which consume fewer resources than the average, and an RIW of greater than one indicates a CMG that consumes more resources than the average.

For costing purposes, the RIW value is applied to the number of cases within a CMG. This gives rise to "weighted case volume", which is how volume is expressed under the RIW system. This weighted case volume is then multiplied by the cost per RIW

to determine the expected approximate cost to the hospital for the CMG, program or service. The cost per RIW is calculated as the total net inpatient cost divided by the total number of RIWs for a specific hospital. Unlike RIWs, the cost per RIW varies among hospitals and depends on hospital-specific factors.

The following ICD-9 codes were chosen to represent the three diseases studied in this thesis:

Diarrhea

003 Salmonella Infections-Other
008 Intestinal Infections due to other organisms

Otitis Media

381 Nonsuppurative otitis media and Eustachian tube disorders
382 Suppurative and unspecified otitis media

Respiratory Disease

460 Acute nasopharyngitis (common cold)
461 Sinusitis-Acute
462 Acute pharyngitis
463 Tonsillitis-Acute
464 Acute laryngitis and tracheitis
465 Acute URI -multiple or unspecified
466 Bronchitis & Bronchiolitis -Acute
480 Viral pneumonia
481 Pneumococcal pneumonia
482 Other bacterial pneumonia
483 Pneumonia -Other specified organism
484 Pneumonia in infectious diseases classified elsewhere
485 Bronchopneumonia, organism unspecified
486 Pneumonia, organism unspecified
487 Influenza

4.1.2 Cost of Illness Estimation

To estimate the direct costs of illness attributable to bottle-feeding, a cost-of-illness study design was employed. Cost-of-illness studies seek to quantify, in economic terms, the impact of illness and injury on individuals and society [99]. Essential to any cost-of-illness study is the definition and measure of costs. Direct costs reflect the value of goods and services for which payment was made and resources used that could have been used for other purposes in the absence of illness. Direct costs include the costs of care provided by physicians and other health professionals, care in hospitals and other health care institutions, drugs and appliances, health sciences research, capital, administration and other health care expenditures. The direct costs estimated in this thesis were the costs of physician care and hospitalizations as these data sources were most readily available to the investigator. Direct costs such as drugs and research were not estimated.

As a complement to direct costs, indirect costs are the costs to society additional to those associated with the treatment of disease [99 100]. An example of an indirect cost attributable to artificial feeding is the lost productivity arising from missed days of work to care for a sick child. This thesis focused only on the estimation of direct costs for the three illness under study, since data to support the estimation of indirect costs were not available. Indirect costs attributable to artificial feeding will be discussed in light of the direct costs estimates.

Cost-of-illness studies can be conducted from two perspectives: prevalence or incidence. Prevalence-based studies estimate the costs incurred during a given time period, regardless of the time of disease onset, whereas incidence-based studies represent

all future costs associated with onset of illness in the base year [99]. Incidence-based studies measure the savings or benefits of reducing the incidence of disease or preventing new cases, or of successful intervention during the course of the disease. To conduct an incidence-based study, information on the likely course of disease and the utilization and cost of medical resources during the course of illness is required. The distinction between prevalence and incidence-based perspectives was not relevant to this thesis as it was conducted on a specific population cohort (infants under the age of one year) for a specific base year (1994). Adopting a prevalence or incidence-based perspective is most relevant for cost of illness studies that examine more than one cohort (age group) or more than one base year.

4.1.2.1 Calculation of the Direct Costs of Bottle Feeding

The direct costs attributable to bottle feeding were determined by multiplying the PAF by the total direct costs of the three illnesses studied. This method was used in 1999 by Birmingham et al. [101] who estimated the cost of obesity in Canada. In the instance where a PPF was calculated for this thesis, the cost savings of bottle feeding were derived by subtracting the costs of care among the total population of infants under the age of one (ICES OHIP and hospitalization data) from the hypothetical costs of care among the population in absence of bottle feeding. Because this hypothetical cost estimate was not available, it was necessary to derive it. Given that the PPF and total costs of care were known, both of these values were applied to the PPF equation to solve for the costs of care in the absence of bottle feeding. This derivation is shown in Appendix N.

The overall impact of bottle feeding for the three diseases was estimated as the sum of the PAF-weighted costs of bottle feeding minus the cost savings of bottle feeding for diarrhea, otitis media and respiratory illness among children under the age of one.

Discounting, which allows for differential timing of costs, was not pertinent to the cost estimates as costs were estimated for only the first year of life.

4.1.2.2 Sensitivity Analysis

Given the assumptions made in the estimation of direct costs, a sensitivity analysis was performed to assess the influence of variations in the PAF. The parameters thought to be the most uncertain and susceptible to error were the relative risks from each of the individual studies that were used to calculate the PAFs. Previous sections of this thesis have discussed the methodologic issues that apply to studies that examine the risk of disease among bottle versus breast fed babies. Any bias in these studies would affect the resulting relative risks. Biased relative risks when combined with prevalence data (which themselves carry some degree of sampling error) would bias the PAF.

The sensitivity analysis was conducted in two ways:

1. As the median PAF were taken as the point estimate for the main analysis, the range of PAFs was used in the sensitivity analysis as a way of testing the robustness of the economic analysis and to provide a range of values around this estimate. Upper and lower bounds were derived using PAFs calculated from relative risks taken from the studies. This analysis provided extreme values of the economic burden of bottle feeding.

2. The costs of care attributable to formula feeding were calculated for each study that scored full stars for surveillance and confounding on the ANOS. Not all studies examined all three outcomes studied as part of this thesis.

Other approaches to sensitivity analysis were considered but abandoned due to a general lack of data. Calculation of confidence intervals around the PAF values was considered as a way of quantifying chance error. Confidence intervals for the PAF could be calculated by using the confidence intervals of the relative risk measures and then inserting them into the PAF formula. This was not feasible as not all studies used in the economic analysis provided confidence intervals for their relative risk estimates. An approximate variance of the PAF as derived by Birkett [102] was considered as an alternative method of calculating confidence intervals around the PAF but this method was inappropriate for use with PAFs calculated with more than two exposure levels.

Monte Carlo simulation methods were explored as a way to incorporate simultaneous error in the relative risks and the prevalence of bottle-feeding, but only for dichotomous exposures. These methods were clearly inappropriate as most of the exposures in this thesis were polychotomous.

4.2 Results

4.2.1 Utilization and Costs: Physician Services

The population of Ontario infants less than one year of age for fiscal year 1994/1995 was 147,176 (Provincial Health Planning Database, Ontario Ministry of Health and Long-term Care, 2001). Table Eleven breaks down the OHIP billings and costs among this population for each of the three illnesses under study.

Among this population, there were 3,508,025 OHIP billings at a total cost of $90,393,292.35 for the fiscal year 1994/1995. Of these billings, 70,108 were for diarrhea, 159,255 were for otitis media, and 101,545 were for lower respiratory illness. Assessment and Consultation billings accounted for the largest proportion of OHIP billings in this group of diseases: 85% for diarrhea, 90% for otitis media, and 88% for all respiratory illness. The three diseases combined cost the health care system $8,646,588.55 in OHIP billings. Collectively, diarrhea, otitis media and lower respiratory illness accounted for just under 10% of all OHIP billings for this age group.

TABLE ELEVEN: OHIP BILLINGS AND COSTS AMONG ONTARIO INFANTS LESS THAN ONE YEAR OF AGE 1994/1995		
	Number of Billings	**Cost**
Diarrhea	70108	$1,996,402.03
Otitis Media	159255	$3,880,316.76
Lower Respiratory Illness	101545	$2,769,869.76
Total	330908	$8,646,588.55
Data Source: ICES OHIP Database, 1994/1995		

4.2.2 Utilization and Costs: Hospitalizations

For the 1994/1995 fiscal year, there were 28,987 hospital separations among Ontario infants under the age of one (not including separations for delivery) at a cost of $80,420,180.93. Collectively, diarrhea, otitis media and lower respiratory illness

accounted for 22% of all hospital separations and 14% of costs. Lower respiratory illness alone accounted for 20% of hospital separations and 12% of costs for this age group. Table Twelve summarizes the hospital separations, days of care, length of stay, and costs among Ontario infants under the age of one.

TABLE TWELVE:
HOSPITALIZATIONS AND COSTS AMONG ONTARIO INFANTS LESS THAN ONE YEAR OF AGE, 1994/1995

	Hospital Separations	Days of Care	Average Length of Stay	Total Cost
Diarrhea	429	1323	3.08	$672,075.24
Otitis Media	247	531	2.15	$318,857.77
Lower Respiratory Illness	5724	20694	3.61	$9,868,836.34
Total	6400	22548	3.52	$ 10,859,769.35

Data Source: Discharge Abstract Database, 1994/1995
Canadian Institute for Health Information

4.2.3 Direct Costs of Bottle Feeding

Table Thirteen summarizes the PAFs/PPF for each of the diseases under study, and presents the PAF weighted costs of care (or cost savings as derived by use of the PPF). The resultant costs minus cost savings represent the direct economic burden of bottle feeding among Ontario infants under the age of one for each of the three diseases under study.

TABLE THIRTEEN:
OHIP AND HOSPITALIZATION COSTS ATTRIBUTABLE TO BOTTLE-FEEDING AMONG ONTARIO INFANTS UNDER THE AGE ONE, 1994/1995

Estimate	Study	PAF	OHIP Costs Attributed to Formula Feeding (PAF x OHIP Costs)	Hospital Costs Attributed to Formula Feeding (PAF x Hosp Costs)	Total Costs Attributed to Formula Feeding
DIARRHEA OHIP Costs: $1,996,402.02, Hospitalization Costs: $672,075.24					
Median	Scariati	21.12%	$421,640.11	$141,942.29	$563,582.40
Lower Bound	Rubin	4.36%	$87,043.13	$29,302.48	$116,345.61
Upper Bound	Howie	30.92%	$617,287.50	$207,805.66	$825,093.16
OTITIS MEDIA OHIP Costs: $3,880,316.76, Hospitalization Costs: $318,857.77					
Median	Rubin	16.86%	$654,221.41	$53,759.42	$707,980.83
Lower Bound	Howie	PPF= 4.66%	-$189,660.97	-$15,585.03	-$205,246.00
Upper Bound	Scariati	29.60%	$1,148,573.76	$94,381.90	$1,242,955.66
LOWER RESPIRATORY DISEASE OHIP Costs: 2,769,869.76, Hospitalization Costs: $9,868,836.34					
Median	Howie	7.75%	$214,664.91	$764,834.82	$979,499.73
Lower Bound	Rubin	0%	$0	$0	$0
Upper Bound	Cushing	15.14%	$419,358.28	$1,494,141.82	$1,913,500.10

Table Fourteen summarizes the direct costs as estimated for diarrhea, otitis media and lower respiratory disease among Ontario infants under the age of one. Collectively, the total direct costs (OHIP billings and hospitalizations) attributed to bottle feeding for the three diseases was estimated to be $2,251,062.96. Sensitivity analysis demonstrated that bottle feeding could be responsible for a health care cost savings of $88,900.39 to a cost of $3,981,548.92.

TABLE FOURTEEN:
ESTIMATED DIRECT COSTS OF BOTTLE-FEEDING FOR DIARRHEA, OTITIS MEDIA AND LOWER RESPIRATORY DISEASE, AMONG ONTARIO INFANTS UNDER AGE ONE 1994/1995

Outcome	Economic Burden of Bottle Feeding	Lower Bound	Upper Bound
Diarrhea	$563,582.40	$116,345.61	$825,093.16
Otitis Media	$707,980.83	-$205,246.00	$1,242,955.66
Lower Respiratory Disease	$979,499.73	$0	$1,913,500.10
Total	$2,251,062.96	-$88,900.39	$3,981,548.92

4.2.4 Sensitivity Analysis

The extreme values of the economic effects of bottle feeding comprised the first part of the sensitivity analysis and is summarized as part of Table Fourteen.

Table Fifteen summarizes the results from the sensitivity analysis by study. Out of the four studies used in the sensitivity analysis, only two studies (Howie et al. [25], and Rubin et al. [80]) provided relative risks for all three of the outcomes examined in this thesis. Using the relative risks reported by Howie et al. [25], the costs of care attributable to formula feeding were approximately $1.6 million, even after the cost savings of formula

feeding (just over $200,000) were factored into the estimate. For the study completed by Rubin et al. [80], the costs of care attributable to formula feeding were $824,326.44. Although both studies scored full stars on the ANOS criteria thought to be most important, the study by Howie et al. [25] scored higher on the overall quality rating scale. The two high-ranking studies with only partial outcomes suggested higher costs, despite being less complete.

TABLE FIFTEEN: SENSITIVITY ANALYSIS BY STUDY

Study ANOS Score	Diarrhea	Otitis Media	Respiratory Disease	Total
Cushing [74] 8 Stars	Did not study outcome	Did not study outcome	$1,913,500.10	$1,913,500.10
Howie [25] 8 Stars	$825,093.16	-$205,246.00	$979,499.73	$1,599,346.89
Rubin [80] 6 stars	$116,345.61	$707,980.83	$0.00	$824,326.44
Scariati [30] 5 stars	$563,582.40	$1,242,955.66	Did not study outcome	$1,806,538.06

Although the estimation of the cost of drugs was not formally undertaken as part of this thesis, a very tentative estimate might be made. A recent publication by the Canadian Institute for Health Information (CIHI) [103] reported Canadian health expenditures from 1975 to 2001, aggregated into National estimates that included all provinces, all ages, both sexes, and all conditions. CIHI [103] reported that in 1994, hospital costs, physician costs, and drug costs (prescription and non-prescription drugs) accounted for 63% of all direct costs. When considering only these three costs, hospitalizations and physician costs accounted for approximately 79.8% of direct costs and drugs 20.2%. To

derive a direct cost estimate of formula feeding that included the cost of drugs, the PAF/PPF-weighted costs of hospitalizations and physicians was divided by 0.798. This calculation inflated the cost estimates found in Table Fourteen to include drug expenditures (assuming the health expenditure distribution presented by CIHI applied to the population and conditions under study). Including the crude estimates of drug expenditures, the economic burden of bottle feeding was estimated to be $2,820,880.90 with lower and upper bounds being savings of $111,404.00 and costs of $4,989,409.67.

5.0 DISCUSSION

The economic burden of bottle-feeding was smaller than expected. The 1994/1995 direct cost of illness attributed to bottle feeding in Ontario infants under the age of 12 months for three diseases (diarrhea, otitis media and respiratory disease) was estimated to be $2,251,062.96. The sensitivity analysis demonstrated considerable uncertainty in this estimate ranging from a cost saving of $88,900.39 to an economic burden of as much as $3,981,548.92. Among those studies selected for the economic analysis, two generated relative risks for all three conditions: Rubin et al. [80] and Howie et al. [25]. When estimating the cost of illness using the results from these individual studies, the relative risks by Rubin et al. [80] generated a direct cost estimate of $824,326.44 and the study by Howie et al. [25] generated a cost of illness estimate of $1,599,346.89 (even after the protective effect of bottle feeding against otitis media was factored in). Of the remaining studies used for the economic analysis, Cushing et al. [74] (who studied only respiratory disease) generated a cost estimate of $1,913,500.10 (for lower respiratory infection) and Scariati et al. [30], (who studied all of the diseases except respiratory disease) generated a cost estimate of $1,806,538.06.

The above results must be interpreted in the context of the three components that generated the potential cost savings: the systematic review, the calculation of the population attributable fraction, and the costing of the adverse effects.

5.1 Methodologic Considerations

5.1.1 Systematic Review

Since a pre-existing systematic review of the literature was not available at the time of this research, one was undertaken. The goal of the systematic review was to identify relevant studies that would yield valid relative risks for the three diseases under study in bottle-fed babies. The systematic review was qualitative in nature; no summary measure of relative risk was calculated.

The systematic review may have been subject to publication bias, since the search for studies was limited to electronic databases and the references of those studies identified through the electronic search. The Cochrane Handbook [32] reports that publication bias is a phenomenon in the published literature, where the probability of publication of research depends on the nature and direction of the study results. Editors (and authors) tend to publish articles containing positive findings in contrast to reports that do not yield significant results [104]. Pettiti [34] reports that publication bias exerts its effect by distorting the general belief about associations.

Because a quality rating tool for observational studies was not available, the investigator relied on the Newcastle-Ottawa Scale (NOS) and adapted it (producing the Adapted Newcastle Ottawa Scale, the ANOS) to suit the needs of this research. To date, the face/content validity of the NOS has been established but continues to undergo evaluation for reliability and validity [41]. It was encouraging that the strength of agreement between raters (as measured by Kappa) was almost perfect for five of seven ANOS criteria.

The actual quality rating of studies was completed by the principal author of this thesis and one of the thesis advisors (RAS). This was a limitation as the second rater had seen the principal author's quality ratings some time before completing his own review. It is thus possible that the second rater's approach to the appraisal process was biased, although he claimed to remember no details of the ratings of the individual studies.

The main deficiency of the NOS and the ANOS, found during data abstraction, was that there was no star awarded for the quality or appropriateness of data analysis. This lack of an important criterion was an issue for the study by Rubin et al. [80], whose relative risk estimates were selected for the economic analysis. This study initially classified babies into five feeding groups 1) exclusively breastfed, 2) breastfed more than formula fed, 3) breastfed and formula fed in equal amounts, 4) breastfed less than formula fed and 5) exclusively formula fed. For the statistical analysis, the authors dichotomized the exposure, collapsing groups one and two into the breastfeeding group, and the remaining groups into the bottle fed group. Grouping the infants in this manner likely introduced some misclassification as the "bottle-fed" group contained babies who had received a substantial amount of breast milk (comprising as much as half of some infants' diets). The presence of breastfed babies in the bottle fed group may have reduced the apparent effect size found in the study. Rubin et al. [80] consistently generated relative risk estimates close to 1.00 and below those estimated in other studies. In fact, the proportion of children who received both breast milk and formula at any given time during the study was below 20% of the entire sample, so if there was a reduction in the effect measure due to misclassification, it was likely minimal. But this example demonstrates the need to

evaluate the statistical analysis completed by investigators when relative risks are to be used in the context of an applied epidemiologic study or for meta-analysis.

5.1.2 The Population Attributable Fraction

The PAF quantified the impact of formula feeding on the Ontario population of infants less than one year of age. The most important feature of measures of potential impact (such as the PAF) is that the link between exposure and outcome must be causal. Calculation of the PAF when there is no causal relationship between exposure and outcome would be a meaningless measure as there would be no change in the frequency of outcome/disease if the exposure was completely eliminated. In the relationship between formula feeding and the childhood diseases studied in this thesis, evidence of a causal relationship exists through the fulfilment of criteria for causation such as: biologic plausibility (as evidenced in the introduction), consistency of evidence (studies summarized in this study consistently found protective effects of breastfeeding), and dose-response relationship as demonstrated by Raisler et al. [79] and Scariati et al. [30]. The only two criteria for causation that may have been questionable were: the strength of association and correct temporal sequence. In the studies reviewed for this thesis, relative risks were consistently estimated to be between 1.0 and 1.5. A relative risk of 2.0 is generally thought to be a strong association indicative of a causal relationship. Earlier literature suggests that the health of an infant may dictate feeding choice (that is, sick babies, generally receive formula, particularly in the case of premature babies), but as the benefits of breastfeeding continue to be acknowledged, it seems unlikely in the 1990's that many mothers stopped breastfeeding because of the three diseases studied in this thesis.

5.1.2.1 Relative Risks

There was little consistency between the studies with respect to relative risk estimates, even when stratified by quality rating score (that is, studies with the same quality rating score did not necessarily yield similar relative risk estimates). Relative risk estimates for bottle fed babies for gastrointestinal disease ranged from 1.07 (Rubin et al. [80]) to 2.13 (Howie et al. [25]) with the rest falling between 1.5 and 2.0. Relative risk estimates for otitis media ranged from 0.97 (Howie et al. [25]) to 3.06 (Duffy et al. [75]) with the remaining studies ranging between 1.5 and 2.0. For lower respiratory disease (there was not compelling evidence that bottle feeding was a risk factor for upper respiratory disease) the relative risks ranged from 1.00 (Rubin et al. [80]) to 1.26 (Cushing et al. [74]) with the remaining estimates falling in between.

The discrepancies in the relative risk estimates could likely be attributed to differences in the underlying study designs such as: varying lengths of exposure observation (some studies observed breast/bottle feeding for the first six months of life while others observed the exposures for the entire first year of life), the time of observation for each study (some only studied their populations for the first six months of life), definitions of breastfeeding (some used the WHO categorization of breastfeeding [94], others did not), subtle differences in the definitions of the diseases under study, data collection methods and data analysis. Even when studies were selected using the most salient methodologic standards (regular surveillance and control for confounding factors) there was not a lot of consistency in the relative risk estimates.

The method of selecting relative risk estimates from studies fulfilling salient

methodologic standards requires further development before in can be generalized for use in other systematic reviews. The variability among results of studies was astounding, and there was no obvious method to resolve discrepancies between the study results. In the absence of guidance (from the literature) on how to handle disparate study results in the conext of a qualitative systematic review, the author of this thesis proceeded as systematically as possible in selecting relative risks for use in the economic analysis.

The relative risks used in the calculation of the impact fractions were for disease incidence in breast and bottle-fed babies. Population attributable fractions using these relative risks thus estimated the proportion of cases attributable to bottle-feeding rather than the proportion of costs. It is important to make this distinction as use of these relative risks assumes equal severity in the breast and bottle-fed babies and thus equal utilization and care. It is plausible that in those instances where breast and bottle-fed babies had similar disease incidence the illness experienced by bottle-fed babies was more severe, and required more/specialized care. Thus, the relative risk for disease does not necessarily translate into the relative risks of physician visits or hospitalizations, and the proportion of costs attributable to bottle-feeding may have been different if the relative risk of visiting a physician or being hospitalized had been available.

For the purposes of this research, it was necessary for the investigator to manipulate many of the relative risks. The main adjustment for many of the relative risks as presented in the original studies was to rescale them such that relative risk associated with breastfeeding was set to one. In other cases, relative risks were not provided as part of the reference studies and it was necessary to derive them from adjusted cumulative

incidence of disease among breast and formula fed infants. It is necessary to acknowledge that such manipulation may have introduced some error into the relative risks used in the calculation of the PAF.

The relative risk estimates for otitis media generated by Howie et al. [25] were anomalies. This study found bottle feeding to be protective against otitis media, with relative risks of 0.83 and 0.97 for early weaners (infants weaned before 13 weeks of age) and bottle feeders (infants bottle fed from birth) respectively. Out of all of the studies which were evaluated using the ANOS, this study achieved a perfect score, and was the only one that found bottle feeding to be protective against otitis media. All others generated relative risks of greater than one. This lack of consistency with the other studies was curious as the study appeared to be internally valid. The authors of the study did not offer explanation of this finding. This study did not include relative risks so the author of this thesis manipulated the study data (quarterly cumulative incidence measures) in order to derive relative risks. It is doubtful that this manipulation accounted for the protective relative risks as the cumulative incidence of otitis media among bottle feeders and early weaners was consistently lower than that of breastfed babies. Confidence intervals were presented for cumulative incidence differences between breast and bottle-fed babies only (confidence intervals were not included for early weaners), which demonstrated no significant differences in cumulative incidence between the two groups. The apparent effect of bottle feeding in this study may have been due to chance alone.

For all of the PAF calculations, it is important to note that the relative risks used were adjusted for confounding factors. Some variation in the PAF values was thus

expected as relative risks would vary according to what other exposures (such as day care, environmental tobacco smoke etc.) were included in the analysis.

5.1.2.2 Prevalence Data

The data source used for the prevalence of bottle-feeding among Ontario infants was the 1994 NLSCY. These data showed that approximately 80% of Ontario infants were breastfed at birth. By six months of age, the proportion of infants still breastfeeding had decreased to 28%. When compared to estimates derived from other Canadian surveys, the results taken from the NLSCY were found to be consistent, and added to the evidence of an increasing trend in breastfeeding initiation rates over time. The 1990 Ontario Health Survey, as analyzed by Nolan & Goel [28], found that 69% of women who reported having had a baby in the year preceding the survey had breastfed their babies after birth. Just over half of these women (55%) were still breastfeeding when their babies were four months of age. The 1994/1995 National Population Health Survey found that 78% of Ontario mothers reported that they had breastfed their youngest child, and of those, 33% continued breastfeeding for six months or more [105]. The 1996 Ontario Health Survey found that 84% of women reported that they had initiated breastfeeding, but information on duration of breastfeeding was not collected as part of this survey.

When comparing the results of the NLSCY with estimates from these other surveys, it is important to note that all these data sources are based on reports of the mothers. In all of the surveys except the NLSCY, the parent/mother is the sampling unit, and the population weights have been applied to the mother rather than to the child despite the fact that the mother's youngest child might be several years old. It is not

possible to derive weighted estimates of *children* who have been breastfed from these surveys as the estimates truly reflect the experience of the cohort of mothers. The NLSCY is a superior data source in this regard as children were the sampling unit and the breastfeeding estimates were based on a population of children under the age of two.

A limitation of the NLSCY as a data source was that it did not inquire about bottle feeding directly. The estimates of the proportion of bottle fed infants used in this thesis were derived from the breastfeeding estimates (for example, if the prevalence of breastfeeding was 60%, the prevalence of bottle feeding was assumed to be 40%). Deriving the proportion of bottle fed babies in this manner was likely sufficient but if mothers were queried about bottle feeding directly, the proportions may have been slightly different than what were derived for the purpose of this thesis.

Another limitation associated with the NLSCY was that it did not inquire about the exclusivity of breastfeeding. Mothers were asked if they breastfed their infants but were not asked about supplemental bottles. It is probable that a proportion of the breastfeeding infants were bottle fed to some degree, but this occurrence could not be quantified. The lack of exclusivity data exerted its largest effect when prevalence data were aligned with relative risks from the various studies. Calculation of the PAF required that prevalence data be available corresponding to each relative risk estimate. Most of the relative risks were estimated according to the duration and exclusivity of breast/bottle feeding. Given the deficiency of exclusivity data in the prevalence data, the alignment of NLSCY estimates with study results was often somewhat arbitrary and may have impacted on the PAF estimate: if the wrong proportion of infants were assigned to a particular

feeding group/level of exposure, the resultant PAF could be over or under-estimated.

5.1.3 Costing the Adverse Effects of Bottle feeding

5.1.3.1 Health Care Utilization and Costs

The cost data to which the PAFs/PPF were applied were accessed through the Institute for Clinical Evaluative Sciences. These data enumerate utilization and cost, with the main source of error coming from systematic and random inconsistencies that appear in coding. The degree to which these inconsistencies over or underestimate utilization and costs is unknown but ICES reported that out of the three illnesses, diarrhea was most susceptible to coding errors and inconsistencies [97].

In addition to the above inconsistencies in the data, it must also be acknowledged that in the case of the OHIP billing data only one diagnosis on the billing claim is made, and that for the hospitalization data, the most responsible diagnosis code is used. The implication of using only one diagnosis code is the potential for undercounting of disease. Since the diseases studied in this thesis are acute in nature, and are most likely to appear as the most responsible diagnosis (particularly in the case of otitis media and respiratory disease), error due to undercounting should be small. It must also be noted that the way in which the coding occurs may not reflect the actual diagnosis. For example in the case of diarrhea, a diagnosis of failure to thrive syndrome may mask some diarrhea cases.

5.1.3.2 Direct costs attributed to Formula Feeding

The direct costs attributed to bottle feeding estimated in this thesis are significantly lower than those found in other studies. Other studies have found cost savings that range between $3 million USD (among Australian infants under the age of one for

gastrointestinal disease hospitalizations alone) as estimated by Drane et al. [24] to $1 billion USD (for diarrhea, otitis media and respiratory disease) as estimated by Riordan [4]. Ball and Wright [5] found the cost per never breastfed infant to be in excess of $331.00 to $475.00 (US dollars) in direct and indirect costs for diarrhea, otitis media and respiratory disease.

It is difficult to compare Canadian cost-of-illness estimates with those reported for the United States, as adjustments would need to be made for differences in the financing and delivery of services, which result in larger US administrative costs, higher US physician fees, and greater US daily service intensity [106].

This thesis drastically underestimates the true cost of illness attributed to bottle feeding for the three diseases studied in two ways. First, the direct costs of only physician visits and hospitalizations were estimated. Other direct costs such as drugs and health science research were not formally estimated. While there are few medication costs associated with the treatment of diarrhea, the cost of oral rehydration solution and extra diapers would need to be considered as a direct cost of illness. For otitis media, medication costs would account for a substantial proportion of direct cost: Ball and Wright [5] estimated that each episode of otitis media would require treatment with an antibiotic at an average cost of $13.05 (US dollars) per course of treatment. In a study of the economic cost of otitis media in Canada, Coyte et al. [106] estimated that drugs accounted for 18.4% of the direct costs of treatment of childhood (under age 14) otitis media. For lower respiratory infections, Ball and Wright [5] noted albuterol as the drug of choice for treatment, and was estimated to cost $3.80 (US dollars) for a ten day course of

treatment.

An approximation of the direct costs attributable to bottle feeding which included the cost of drugs was completed using the distribution of expenditures presented by CIHI [103]. When the direct costs of physician visits, hospitalizations and drugs were considered together, direct cost estimates ranged from a cost saving of $111,404.00 to a burden of $4,989,409.67, with the point estimate being $2,820,880.90. While drugs are a substantial component of the direct costs of illness, the estimates generated using the CIHI data must be interpreted with caution, as the use of the distribution assumes that the national estimate that was based on all provinces, all ages, both sexes, and all conditions applies to the population and conditions studied in this thesis. The estimate generated by Coyte et al. [106] is encouragingly similar, but this estimate is a proportion of all direct costs (over and above hospital, physician and drug costs), and is based on a larger age cohort of 14 years of age and under.

The other way in which this study underestimates the cost of illness attributed to bottle feeding is the lack of estimation of the indirect costs. Indirect costs of illness attributable to formula feeding deserve some discussion since medical expenses alone are not a complete evaluation of the cost of illness. Indirect costs represent the value of output lost because of cessation/reduction of productive activity [99 100]. The main indirect cost associated with illness attributable to bottle feeding is missed time from work for parents/guardians to care for a sick child. Two American studies estimated the burden of illness in terms of lost work time to care for sick children. In 1995, Cohen et al. [107] conducted a comparison of maternal absenteeism among breastfeeding and formula

feeding women in two corporations that had on-site lactation programs. Out of 101 babies (59 breastfed and 42 bottle-fed) studied, the bottle-fed infants experienced more episodes of illness than breastfed infants which translated into increased rates of maternal absenteeism. Mothers of formula fed infants had three times as many one-day absences as breastfeeding mothers (30 versus 10), a difference which was statistically significant [107]. For maternal absences of greater than one day, there was no significant difference: mothers of formula fed infants had 20 such absences compared with 13 among breastfeeding mothers [107]. This study is particularly relevant to this thesis as the authors concentrated on three illnesses (upper respiratory infections, gastrointestinal infections and otitis media).

In a 1996 study that estimated the community burden of otitis media, Yawn et al. [108] found that of the 1,810 families who reported episodes of otitis media in their children, 568 (just over one third) also reported parental work absences totaling 891 days in the study year. Families also made special child care arrangements (other than the ususal day care or babysitter) for another 141 days over the year [108]. The majority of the work absences were reported to be a half to one day each, averaging out to approximately three hours per affected child. This study was conducted among families with children younger than 13 years of age. Among a population of babies under one year of age, this three hour average would be higher, as babies who require antibiotics in the treatment of otitis media cannot be returned to day care until they have had 24 hours of treatment. Although relevant to this thesis, the estimates taken from this study cannot be directly applied to the population studied in this thesis as the age groups studied are not

comparable.

In addition to the costs associated with the management of excess illness attributed to bottle feeding are the costs borne by families who purchase formula. The Sudbury and District Health Unit [109] estimated the cost of formula for the first year of life to range from $993 for powdered cow's milk based formula to as much as $3,312 for ready-to-serve soy based or lactose free formula. In contrast, the cost of breastfeeding was estimated to be $365 per year which included extra food for the lactating mother and infant vitamin D supplement [109]. This cost of breastfeeding did not include such costs as: fees for a Lactation Consultant (when needed), nursing bras, nursing pads, nipple shields (when needed), breast pumps and accessories as well as the indirect cost of extended maternity leaves to pursue longer breastfeeding relationships approaching or exceeding one year.

5.2 Conclusions and Future Research Considerations

This thesis is the first known Canadian study to examine the economic burden of illness attributable to bottle-feeding. To date, studies of this kind have been conducted in other jurisdictions which cannot be directly applied to Canadian populations. Although the direct cost estimate of $2 million attributed to bottlefeeding for the entire population of Ontario infants under the age of one seems relatively small, it is important to note that this thesis was limited in its ability to provide a complete estimation of the economic burden of bottle-feeding. Only three conditions were studied (albeit those childhood diseases thought to account for the largest burden of illness in the age group studied), direct costs such as drugs were not formally estimated, and the costs of illness were only studied for one year. It is thus impossible to make policy recommendations that are based

on such a small component of the economic burden of bottle-feeding. What the results of this study do call for is the need for further research on the economic burden of bottle-feeding.

Future research efforts in this area should take the form of an observational study that follows a population of infants and tracks utilization of health care resources (including drugs) by feeding status. As such, the feasibility of conducting an incidence-based cost-of-illness study should be explored, as there is general agreement in the literature that the protective effect of breastfeeding extends beyond the first year of life and beyond weaning. A follow-up [70] of the study by Howie et al. [25] found that the benefits of breastfeeding persisted beyond the original one-year study period, and even at the seven year follow-up point the probability of respiratory illness occurring at any time during childhood was significantly reduced by prolonged breastfeeding and the delay of solid foods.

As observational studies are often time-consuming and expensive to conduct, the economic burden of bottle-feeding seems to be amenable to record linkage research. The linkage between the results of health surveys such as the NLSCY with health administration databases would enable the tracking and comparison of health care utilization and costs among breast and bottle-fed babies.

In addition to refining the methodology to generate accurate direct cost estimates, research must also be devoted to the investigation of indirect costs attributed to bottle feeding.

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APPENDIX A
Search Strategy for Identification of Morbidity Studies

1. Breast feeding/ or "breast feeding".mp
2. Bottle feeding/ or "bottle feeding".mp
3. 1 or 2
4. "Infant"/
5. Morbidity/ or "morbidity".mp
6. "Comparative Study"/
7. Prospective studies/ or "prospective studies".mp
8. Follow-up studies/ or "follow-up studies".mp
9. Cohort studies/ or "cohort studies".mp
10. Longitudinal studies/ or "longitudinal studies".mp
11. Case-control studies/ or "case-control studies".mp
12. Meta-analysis/ or "meta-analysis".mp
13. 6 or 7 or 8 or 9 or 10 or 11 or 12
14. Otitis media/ or "otitis media".mp
15. Respiratory tract infections/ or "respiratory tract infections".mp
16. Respiratory syncytial viruses/ or "respiratory syncytial virus".mp
17. Diarrhea/ or Diarrhea, infantile/
18. Gastroenteritis/
19. 14 or 15 or 16 or 17 or 18
20. 3 and 4 and 5 and 13 and 19
21. 3 and 13 and 19

APPENDIX B
NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort
   - a) truly representative of the average _____ (describe) in the community ★
   - b) somewhat representative of the average _____ in the community ★
   - c) selected group of users eg nurses, volunteers
   - d) no description of the derivation of the cohort

2) Selection of the non exposed cohort
   - a) drawn from the same community as the exposed cohort ★
   - b) drawn from a different source
   - c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure to implants
   - a) secure record (eg surgical records) ★
   - b) structured interview ★
   - c) written self report
   - d) no description

4) Demonstration that outcome of interest was not present at start of study
   - a) yes ★
   - b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis
   - a) study controls for _____ (select the most important factor) ★
   - b) study controls for any additional factor ★ (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome
   - a) independent blind assessment ★
   - b) record linkage ★
   - c) self report
   - d) no description

2) Was follow-up long enough for outcomes to occur
   - a) yes (select an adequate follow up period for outcome of interest) ★
   - b) no

3) Adequacy of follow up of cohorts

a) complete follow up - all subjects accounted for ★

b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) ★

c) follow up rate < ____% (select an adequate %) and no description of those lost

d) no statement

APPENDIX C
NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
CASE CONTROL STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

1) Is the case definition adequate?
   a) yes, with independent validation ★
   b) yes, eg record linkage or based on self reports
   c) no description

2) Representativeness of the cases
   a) consecutive or obviously representative series of cases ★
   b) potential for selection biases or not stated

3) Selection of Controls
   a) community controls ★
   b) hospital controls
   c) no description

4) Definition of Controls
   a) no history of disease (endpoint) ★
   b) no description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis
   a) study controls for _____ (Select the most important factor.) ★
   b) study controls for any additional factor ★ (This criteria could be modified to indicate specific control for a second important factor.)

Exposure

1) Ascertainment of exposure to breast implants
   a) secure record (eg surgical records) ★
   b) structured interview where blind to case/control status ★
   c) interview not blinded to case/control status
   d) written self report or medical record only
   e) no description

2) Same method of ascertainment of implants for cases and controls
   a) yes ★
   b) no

3) Non-Response rate
   a) same rate for both groups ★
   b) non respondents described
   c) rate different and no designation

APPENDIX D
ADAPTED NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
COHORT STUDIES

This scale has been modified from its original version to incorporate methodologic standards put forth by:
Bauchner H, Leventhal JM & Shapiro ED. Studies of breast-feeding and infections. How good is the evidence? *Journal of the American Medical Association* 1986; 256:887-892

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Definition of breastfeeding
   a) definition takes into account both duration and exclusivity ★
   b) definition based on duration only
   c) definition not provided

2) Ascertainment of feeding status
   a) structured interview ★
   b) medical records
   c) written self report (self-administered questionnaire)
   d) no description

Comparability

1) Comparability of cohorts on the basis of the design or analysis
   a) study controls for socioeconomic status (which can include any one of the following: income, maternal education, or occupation) ★
   b) study controls for any additional factor(s): maternal age, maternal smoking, use of day care, size of family (number of siblings) ★

Outcome

1) Definition of outcome
   a) diagnosis defined according to specific predetermined criteria (ie: Otitis media includes....) ★
   b) diagnostic criteria not provided

2) Assessment of outcome/Avoidance of detection bias
   a) active surveillance at least once per month via structured interview (ie: interview by telephone), diary, or self-completed questionnaire ★
   b) assessment based on visits for infectious illness (ie: counts of sick visits)

3) Was follow-up long enough for outcomes to occur
   a) yes (≥ 6 months of follow-up) ★
   b) no

4) Adequacy of follow up of cohorts (Note: Only one star can be awarded for this category)
   a) subjects lost to follow up unlikely to introduce bias - small number lost - <20% ★
   b) person-time analysis with reasonable proportion of subjects followed to ≥6 months ★
   c) no statement

APPENDIX E
ADAPTED NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
CASE CONTROL STUDIES

This scale has been modified from its original version to incorporate methodologic standards put forth by:
Bauchner H, Leventhal JM & Shapiro ED. Studies of breast-feeding and infections. How good is the evidence? *Journal of the American Medical Association* 1986; 256:887-892

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

1) Is the case definition adequate?/Definition of outcome
   a) yes, with clear diagnostic criteria ★
   b) yes, ie: record linkage or based on self reports
   c) no description

2) Representativeness of the cases/Avoidance of detection bias
   a)consecutive or obviously representative series of cases (cases of disease equally likely to be enrolled in study independent of feeding group) ★
   b) potential for selection biases or not stated

3) Selection of Controls
   a) selection of controls fulfills the study base principle (Wacholder et al.) that cases and controls are representative of the same base experience ★
   b) selection of controls does not fulfill the study base principle

4) Definition of Controls
   a) controls do not currently have disease of interest ★
   b) no description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis
   a) study controls for socioeconomic status (which can include any one of the following: income, maternal education, or occupation) ★
   b) study controls for any additional factor(s): maternal age, maternal smoking, use of day care, size of family (number of siblings) ★

Exposure

1) Definition of breastfeeding
   a) definition takes into account both duration and exclusivity ★
   b) definition based on duration only
   c) definition not provided

2) Ascertainment of feeding status
   a) structured interview ★
   b) medical records
   c) written self report (self-administered questionnaire)
   d) no description

3) Same method of ascertainment of feeding status for cases and controls
   a) yes ★
   b) no

4) Non-Response rate
   a) subjects lost unlikely to introduce bias- <20% in both groups and description provided of those lost ★
   b) no statement

APPENDIX F: COHORT STUDIES EXCLUDED FROM SYSTEMATIC REVIEW						
Study, Year	**Setting, Study period**	**Study Design, Follow-up period**	**Outcome Studied**	**N**	**Effect of Breast-feeding**	**Reason for Exclusion**
Aniansson et al. [46] 1994	Göteborg, Sweden Nov. 1985 to Jan. 1988	prospective cohort first 10 mos of life	acute otitis media	400	protective	-no multivariate analysis or control for confounders
Chandra [55] 1979	St. John's Newfoundland	prospective cohort first 24 mos of life	respiratory infection otitis media diarrhea dehydration	breast: 30 bottle: 30	protective	-small sample
Cunningham [47] 1977	Mary Imogene Bassett Hospital, Cooperstown New York Feb. 1974 to Jan. 1975	retrospective cohort first year of life	otitis media lower respiratory illness vomiting, diarrhea hospital admissions	326	protective	-no adjusted incidence measures presented
Cunningham [48] 1979	Mary Imogene Bassett Hospital, Cooperstown New York Feb. 1974 to Jan. 1975	retrospective cohort first year of life	otitis media lower respiratory illness vomiting, diarrhea hospital admissions	503	protective	-no adjusted incidence measures presented
Cushing & Anderson [56] 1982	University of New Mexico Hospital Feb-Dec 1979	prospective cohort first 12 mos of life	diarrhea	40 women	no effect	-small sample -no control for confounders

APPENDIX F: COHORT STUDIES EXCLUDED FROM SYSTEMATIC REVIEW						
Study, Year	**Setting, Study period**	**Study Design, Follow-up period**	**Outcome Studied**	**N**	**Effect of Breast-feeding**	**Reason for Exclusion**
Dewey et al.[57] 1995	Davis, California DARLING study (Davis Area Research on Lactation, Infant Nutrition and Growth)	prospective cohort first 2 years of life	respiratory symptoms diarrhea otitis media other	87 breast: 46 bottle: 41	-no effect for resp. - protective against diarrhea and otitis	-small sample
Duffy et al.[68] 1986	Public health clinics affiliated with Children's Hospital Buffalo, New York Oct 1983-Jan 1984	prospective winter diarrhea season	rotavirus-induced gastroenteritis	197 maternal-infant pairs	no effect; breast-feeding mediated severity of illness	-participants from Women, Infant and Child (WIC) Supplementation Program (low income) -54% participants black: limited generalizability -follow-up period ill-defined -smallish
Fosarelli et al.[69] 1985	Johns Hopkins Primary Care Clinic October-December 1981	retrospective	infectious illness including: otitis media upper respiratory illness gastroenteritis	279 inner-city infants	no effect; bottle feeding associated with multiple episodes of OM	-85.7% participants black: limited generalizability

APPENDIX F: COHORT STUDIES EXCLUDED FROM SYSTEMATIC REVIEW						
Study, Year	**Setting, Study period**	**Study Design, Follow-up period**	**Outcome Studied**	**N**	**Effect of Breast-feeding**	**Reason for Exclusion**
Frank et al. [58] 1982	Houston Family Study Houston, Texas May 1976-June 1980	prospective birth to 4 years	respiratory virus infection	81 breast: 39 bottle: 42	no effect; breast-feeding mediated severity of illness	-small sample size
Hakansson & Cars [59] 1991	Teleborg Health Centre Växjö, Sweden Nov. 1983- Dec. 1984	prospective first 18 months of life	respiratory tract infection	28 matched pairs	not applicable (data not provided)	-small sample size -outcome not defined for feeding status (outcome defined according to smoking status of mother)
Hakansson & Carlsson [49] 1992	Teleborg Health Centre Växjö, Sweden Nov. 1983 to Dec. 1984; Jan. to Dec. 1986	prospective first 18 months of life	respiratory tract infection	192 infants	no effect	-no adjustment for covariates beyond maternal smoking status
Harsten et al. [50] 1989	University Hospital, Lund, Sweden Nov. 1982 to Feb. 1984	prospective first 3 years of life	recurrent acute otitis media	113	no effect	-incidence measures not presented according to breastfeeding status/duration -no multivariate analysis to control for confounding -smallish

APPENDIX F: COHORT STUDIES EXCLUDED FROM SYSTEMATIC REVIEW						
Study, Year	**Setting, Study period**	**Study Design, Follow-up period**	**Outcome Studied**	**N**	**Effect of Breast-feeding**	**Reason for Exclusion**
Holberg et al. [63] 1991	Health Maintenance Organization Tucson, Arizona Enrollment: May 1980 to January 1984 Part of the Tucson Children's Respiratory Study	prospective cohort first year of life	respiratory syncytial virus	1,179	protective	-RSV as an outcome too narrow focus -interaction between breastfeeding and maternal education; the direct effect of breastfeeding could not be reported
Holmes et al. [51] 1983 (study funded by Mead Johnson)	University of Kansas Medical Centre Kansas City, Missouri March 1973-Aug 1975	prospective first 12 mos of life	upper respiratory infection lower respiratory infection acute otitis media gastroenteritis	251 breast: 127 bottle: 124	no effect	-inadequate adjustment for confounders
Myers et al. [60] 1984	Iowa City April 1979-Jan 1980	prospective first 112 days of life	upper respiratory tract illness lower respiratory tract illness gastroenteritis	breast: 10 bottle: 10	no effect	-small sample

APPENDIX F: COHORT STUDIES EXCLUDED FROM SYSTEMATIC REVIEW						
Study, Year	**Setting, Study period**	**Study Design, Follow-up period**	**Outcome Studied**	**N**	**Effect of Breast-feeding**	**Reason for Exclusion**
Nafstad et al. [64] 1996	Oslo, Norway	prospective cohort first 12 mos of life	lower respiratory tract infection	3,238 infants	protective	-ORs presented according to smoking status, unable to derive ORs on feeding status alone -effect diluted by lumping infants who received no breastfeeding with those who breastfed for 1-6 mos
Owen et al. [65] 1993	Galveston County, Texas	prospective first 24 mos of life	otitis media with effusion	698 infants	protective	-insufficient incidence data provided -RR's cannot be derived from structured equation model
Paine et al. [61] 1982	family practice office in Williamsburg, Iowa Aug. 1973-Jan. 1978	retrospective cohort first 12 mos of life	upper respiratory tract infection lower respiratory tract infection otitis media gastrointestinal illness	106 infants	protective	-small sample -rural population: limited generalizability

APPENDIX F: COHORT STUDIES EXCLUDED FROM SYSTEMATIC REVIEW						
Study, Year	**Setting, Study period**	**Study Design, Follow-up period**	**Outcome Studied**	**N**	**Effect of Breast-feeding**	**Reason for Exclusion**
Paradise et al.[66] 1997	Greater Pittsburgh area (Children's Hospital, two rural hospitals, four suburban hospitals) enrollment: June 1991 to August 1992	prospective first two years of life	otitis media	2,253	protective	-multivariate logistic regression analysis completed; adjusted relative risks not presented (only univariate available)
Ruuska & Vesikari[52] 1991	University Central Hospital of Tampere, Finland	prospective cohort first 24-32 mos of life	diarrhea	336	protective	-incidence of diarrhea assessed according to day care use and maternal education (univariate); no multivariate assessment of breastfeeding with covariates
Saarinen[62] 1982	Helsinki University Central Hospital Helsinki, Finland Jan.1975-1978	prospective first 3 years of life	otitis media	237 infants	protective	-small numbers in relevant groups to enable multivariate analysis and control of confounders

APPENDIX F: COHORT STUDIES EXCLUDED FROM SYSTEMATIC REVIEW						
Study, Year	**Setting, Study period**	**Study Design, Follow-up period**	**Outcome Studied**	**N**	**Effect of Breast-feeding**	**Reason for Exclusion**
Sassen et al. [71] 1994	Three health care centres (2 rural, 1 urban) in the Netherlands July 1987-October 1988	prospective first 24 months	acute otitis media	289 infants	not applicable	-study modelled the changes to risk of otitis media after the discontinuation of breastfeeding
Sipila et al. [53] 1988	Three geographically separate urban areas Tampere, Finland	prospective 17-32 months	acute and recurrent otitis media	1,294 infants	protective	-adjusted incidence measures not presented
van den Bogaard et al. [54] 1991	Nijmegen, the Netherlands	retrospective cohort first three years of life	early childhood morbidity (including but not limited to): upper respiratory tract lower respiratory tract	1,347	protective	-no adjustment for potential confounders -four cohorts analysed simultaneously: 1967-1970, 1971-1974, 1975-1978, 1979-1983 without consideration of historical effects (ie: 1967 cohort is likely to differ from 1979 cohort)

APPENDIX F: COHORT STUDIES EXCLUDED FROM SYSTEMATIC REVIEW						
Study, Year	**Setting, Study period**	**Study Design, Follow-up period**	**Outcome Studied**	**N**	**Effect of Breast-feeding**	**Reason for Exclusion**
Wright et al. [67] 1989	Health Maintenance Organization Tucson, Arizona Enrollment: May 1980 to October 1984 Part of the Tucson Children's Respiratory Study	prospective cohort first year of life	lower respiratory tract illness	1,246 infants	protective	-effect modification: strong interaction found between minimal breastfeeding and sharing a room: RR's cannot be attributed to effect of feeding alone
Wilson et al. [70] 1998	Dundee, Scotland	prospective cohort	respiratory tract infection	545 children	protective	-seven year follow-up to study conducted by Howie et al. -earlier study most applicable to children age 12 months and under

APPENDIX G: COHORT STUDIES CONSIDERED FOR ECONOMIC ANALYSIS				
Study, Year	**Setting, Study Period**	**Study Design, Follow-up period**	**Outcome Studied**	**N Study Groups**
Alho et al. [72] 1990	Oulu, Finland Infants from 10 local government districts with a date of birth between July 1 1985 and June 30 1986	retrospective cohort first two years of life	acute otitis media acute respiratory tract infections	2,512
Beaudry et al. [73] 1995	New Brunswick Infants born in 1982 and 1983	retrospective cohort first 6 months of life	gastrointestinal disease respiratory illness	776 breast: 430 (at birth) bottle: 346 (at birth)
Cushing et al. [74] 1998	Albuquerque, New Mexico Infants born between January 1, 1998 and June 30, 1990	prospective cohort first 18 months of life	upper respiratory tract infection (URI) lower respiratory tract infection (LRI)	1,202
Duffy et al. [75] 1997	Buffalo, New York	prospective cohort first 24 months of life	acute otitis media otitis media with effusion	306

APPENDIX G: COHORT STUDIES CONSIDERED FOR ECONOMIC ANALYSIS				
Study, Year	**Setting, Study Period**	**Study Design, Follow-up period**	**Outcome Studied**	**N Study Groups**
Duncan et al. [76] 1993	Tucson, Arizona Health Maintenance Organization May 1980-October 1984	prospective cohort first 12 months of life	acute otitis media recurrent otitis media	1,013
Fergusson et al. [77] 1981	Christchurch, New Zealand (Christchurch Child Development Study) Infants born during the middle of 1977	prospective cohort first two years of life	gastrointestinal illness lower respiratory illness	1,210
Howie et al. [25] 1990	Community of Dundee, Scotland recruitment times: Sept. 1983 to Dec.1984; March to Aug. 1985; Dec. 1985 to May 1986	Prospective observational first two years of life	gastrointestinal disease respiratory illness ear infection	674 followed for two years breast: 227 early weaners: 180 bottle: 267
Kero et al. [78] 1987	University Central Hospital, Turku, Finland enrollment: June 1981 and May 1982	prospective cohort first 12 months of life	otitis media	5,261

APPENDIX G: COHORT STUDIES CONSIDERED FOR ECONOMIC ANALYSIS				
Study, Year	**Setting, Study Period**	**Study Design, Follow-up period**	**Outcome Studied**	**N Study Groups**
Raisler et al. [79] 1999	John Hopkins University School of Hygiene and Public Health	secondary analysis of the 1988 National Maternal and Infant Health Survey	diarrhea vomiting cough or wheeze	7,092
Rubin et al. [80] 1990	Copenhagen, Denmark Infants born at Gentofte University Hospital between February and June 1985	prospective cohort first 12 months of life	gastroenteritis upper respiratory illness lower respiratory illness otitis media	500
Scariati et al. [30] 1997	United States Infant Feeding Practices Panel Study Survey conducted between 1993 and 1994	first 7 months of life	diarrhea otitis media	1,743 mother-infant pairs
Teele et al. [81] 1989	Boston Massachusetts, two centres: urban health centre and a suburban private practice Enrollment from June 1975 to August 1977	prospective cohort first 7 years of life	otitis media	877

APPENDIX H: CASE-CONTROL STUDIES EXCLUDED FROM SYSTEMATIC REVIEW						
Study, Year	**Setting, Study period**	**Case-Control Design**	**Outcome Studied**	**N**	**Effect of Breast-feeding**	**Reason for Exclusion**
Dagan & Pridan [82] 1982	Pediatric emergency room, Soroka University Hospital Beer Sheba, Israel	cases: hospital-based controls: healthy infants visiting maternal-child health centres	gastroenteritis otitis media lower respiratory tract infection upper respiratory tract infection	cases: 480 controls: 502 infants under the age of 1	protective	-no control for confounders
Downham et al. [83] 1976	Newcastle, UK Winter 1973-1974	cases: hospital-based controls: infants in the waiting room of Newcastle city child health clinic	respiratory syncytial virus	cases: 115 controls: 167	protective	-inadequate control for confounders -feeding definitions not provided
Fallot et al. [84] 1980	Onondaga County, New York Jan - Dec 1978	cases: hospital-based controls: patients at University Hospital clinic, and private clinic	hospital admissions	cases: 136 controls: 224	protective	-no adjustment for confounding variables -small numbers in relevant groups

APPENDIX H: CASE-CONTROL STUDIES EXCLUDED FROM SYSTEMATIC REVIEW						
Study, Year	**Setting, Study period**	**Case-Control Design**	**Outcome Studied**	**N**	**Effect of Breast-feeding**	**Reason for Exclusion**
Koopman et al. [86] 1985	Private practice, Ypsilanti, Michigan August 1979-April 1981	prospective, pop'n based case-control study	gastrointestinal illness	143 case-control pairs matched by age, sex, geographic area	protective	-small numbers in relevant groups
Pukander [88] 1982	Jalasjarvi, Finland June 1978-May 1979	cases: identified through a communal health centre controls: community	acute otitis media	103 cases 97 controls	protective	-study conducted among individuals age 16 and under, children under the age of one not separated out for analysis -no adjustment for confounding variables
Pukander et al. 1985 [89]	Tampere and Oulu, Finland	cases: identified through out-patient clinic controls: community	acute otitis media	207 controls	protective	-study conducted among 2-3 year olds, no incidence data on the first year of life

APPENDIX H: CASE-CONTROL STUDIES EXCLUDED FROM SYSTEMATIC REVIEW						
Study, Year	**Setting, Study period**	**Case-Control Design**	**Outcome Studied**	**N**	**Effect of Breast-feeding**	**Reason for Exclusion**
Pullan et al. [85] 1980	Tyneside Hospital, Newcastle UK enrollment: Dec. 1977 to Mar. 1978	cases: hospital-based controls: community; 4 to a case; matched on age	respiratory syncytial virus	127 cases 503 controls	protective	-univariate analysis of confounders conducted, but no multivariate analysis
Tainio et al. [87] 1988	Helsinki, Finland	nested case-control	recurrent otitis media	cases: 28 controls: 80		-small number of cases

APPENDIX I: INDIVIDUAL ANOS STUDY SCORES BY RATER, COHORT STUDIES								
Study			**COMPARABILITY**	**OUTCOME**				**NUMBER OF STARS**
	Definition of Breastfeeding	**Ascertainment of Exposure**	**Comparability of Cohorts on the Basis of Design or Analysis**	**Definition of Outcome**	**Ascertainment of Outcome (Surveillance)**	**Adequate Length of Follow Up**	**Adequacy of Follow Up**	
Alho et al. 1990 [72] JMP			★ ★	★		★	★	5
RAS			★ ★	★		★	★	5
No disagreement.								
FINAL SCORE			★ ★	★		★	★	5
Beaudry [73] et al. 1995 JMP			★ ★			★	★	4
RAS	★		★ ★			★	★	5
Breastfeeding definition (from article): "Breastfeeding was defined as the period of breastfeeding from birth until the infant was totally weaned, even if other foods were offered..." RAS agreeable to retracting star under Definition of Breastfeeding.								
FINAL SCORE			★ ★			★	★	4

APPENDIX I: INDIVIDUAL ANOS STUDY SCORES BY RATER, COHORT STUDIES								
Study			**COMPARABILITY**	**OUTCOME**				**NUMBER OF STARS**
	Definition of Breastfeeding	**Ascertainment of Exposure**	**Comparability of Cohorts on the Basis of Design or Analysis**	**Definition of Outcome**	**Ascertainment of Outcome (Surveillance)**	**Adequate Length of Follow Up**	**Adequacy of Follow Up**	
Cushing [74] et al. 1998 JMP	★	★	★ ★	★	★	★	★	8
RAS	★	★	★ ★	★	★	★	★	8
No disagreement.								
FINAL SCORE	★	★	★ ★	★	★	★	★	8
Duffy [75] et al. 1997 JMP	★	★	★ ★	★	★	★	★	8
RAS	★	★	★	★	★	★		6
No mention of SES as covariate in analysis. JMP willing to retract star under comparability. 86% of infants completed 9 or more of 13 scheduled visits over 24 months of follow-up. RAS willing to retract star given modification to NOS whereby a loss to follow-up of less than 20% is acceptable OR a description provided of those lost (under Adequacy of follow-up).								
FINAL SCORE	★	★	★	★	★	★	★	7

APPENDIX I: INDIVIDUAL ANOS STUDY SCORES BY RATER, COHORT STUDIES								
Study			**COMPARABILITY**	**OUTCOME**				**NUMBER OF STARS**
	Definition of Breastfeeding	**Ascertainment of Exposure**	**Comparability of Cohorts on the Basis of Design or Analysis**	**Definition of Outcome**	**Ascertainment of Outcome (Surveillance)**	**Adequate Length of Follow Up**	**Adequacy of Follow Up**	
Duncan[76] et al. 1993 JMP	★		★ ★			★	★	5
RAS	★		★			★	★	4
Maternal education provided as an SES covariate. RAS willing to award additional star to comparability.								
FINAL SCORE	★		★ ★			★	★	5
Fergusson et al.[77] 1981 JMP			★			★	★	3
RAS		★	★ ★			★	★	5
Study reports information about the child, his/her health history and family situation was collected from a structured interview. Assuming that breastfeeding information is collected in this manner, JMP willing to award star under ascertainment of exposure. Maternal education included as an SES covariate. JMP willing to award additional star to comparability.								
FINAL SCORE		★	★ ★			★	★	5

APPENDIX I: INDIVIDUAL ANOS STUDY SCORES BY RATER, COHORT STUDIES								
Study			**COMPARABILITY**	**OUTCOME**				**NUMBER OF STARS**
	Definition of Breastfeeding	**Ascertainment of Exposure**	**Comparability of Cohorts on the Basis of Design or Analysis**	**Definition of Outcome**	**Ascertainment of Outcome (Surveillance)**	**Adequate Length of Follow Up**	**Adequacy of Follow Up**	
Howie et al. [25] 1990 JMP	★	★	★ ★	★	★	★	★	8
RAS	★	★	★ ★	★	★	★		7
674/ 750 subjects were available for analysis, 618/ 674 were followed for 2 years. RAS willing to award star given modification to NOS scale.								
FINAL SCORE	★	★	★ ★	★	★	★	★	8
Kero [79] et al. 1987 JMP		★	★			★	★	4
RAS		★	★			★		3
4868/5261, 92.5% of cohort followed up. RAS willing to award star given modification of NOS scale.								
FINAL SCORE		★	★			★	★	4

APPENDIX I: INDIVIDUAL ANOS STUDY SCORES BY RATER, COHORT STUDIES								
Study			**COMPARABILITY**	**OUTCOME**				**NUMBER OF STARS**
	Definition of Breastfeeding	**Ascertainment of Exposure**	**Comparability of Cohorts on the Basis of Design or Analysis**	**Definition of Outcome**	**Ascertainment of Outcome (Surveillance)**	**Adequate Length of Follow Up**	**Adequacy of Follow Up**	
Raisler et al.[79] 1999 JMP	★	★	★ ★			★		5
RAS	★		★ ★			★		4
Questionnaires were self-administered as part of National Maternal and Infant Health Survey. JMP willing to retract star under Ascertainment of Exposure.								
FINAL SCORE	★		★ ★			★		4

APPENDIX I: INDIVIDUAL ANOS STUDY SCORES BY RATER, COHORT STUDIES								
Study			**COMPARABILITY**	**OUTCOME**				**NUMBER OF STARS**
	Definition of Breastfeeding	**Ascertainment of Exposure**	**Comparability of Cohorts on the Basis of Design or Analysis**	**Definition of Outcome**	**Ascertainment of Outcome (Surveillance)**	**Adequate Length of Follow Up**	**Adequacy of Follow Up**	
Rubin et al. [99] 1990 JMP	★		★ ★	★	★	★		6
RAS	★	(★)	★ ★	(★)	(★)	★		6.5
Questionnaires were self-administered, RAS willing to retract score under Ascertainment of Exposure. Definition of outcome was suitable for gastroenteritis and lower respiratory infection. No diagnostic criteria presented for otitis media or lower respiratory infection. Stars for definition of outcome awarded to the gastroenteritis and respiratory infection. Subjects monitored on a monthly basis, RAS willing to award star given modification of the NOS to Ascertainment of Outcome whereby studies that include active surveillance of at least once per month via structured interview or self-administered questionnaire will be awarded the star.								
FINAL SCORE	★		★ ★	★-Gastro ★-URI	★	★		6 -Gastro 6 - URI 5 - LRI 5 - OM

APPENDIX I: INDIVIDUAL ANOS STUDY SCORES BY RATER, COHORT STUDIES								
Study			**COMPARABILITY**	**OUTCOME**				**NUMBER OF STARS**
	Definition of Breastfeeding	**Ascertainment of Exposure**	**Comparability of Cohorts on the Basis of Design or Analysis**	**Definition of Outcome**	**Ascertainment of Outcome (Surveillance)**	**Adequate Length of Follow Up**	**Adequacy of Follow Up**	
Scariati [30] et al. 1997 JMP	★		★ ★		★	★		5
RAS	★		★ ★			★		4
Ascertainment of Outcome completed via a series of 11 self-administered questionnaires. RAS willing to award star given modification of NOS to reflect that surveillance via this method is acceptable.								
FINAL SCORE	★		★ ★		★	★		5
Teele et al. [31]1989 JMP		★	★ ★	★		★	★	6
RAS			★ ★	★		★	★	5
Ascertainment of exposure completed via a 4 page encounter form completed at every office visit. This method of ascertainment was assumed to be self-administered, JMP willing to retract star.								
FINAL SCORE			★ ★	★		★	★	5

APPENDIX J
NATIONAL LONGITUDINAL SURVEY OF CHILDREN AND YOUTH, 1994
SURVEY QUESTIONS ON BREASTFEEDING

Note: This set of questions were asked of mothers to children age two and under at the time of the survey.

Are you currently breastfeeding (...children's name)?

- ☐ Yes
- ☐ No
- ☐ Don't Know

Note: If yes, go to next section

Did you breastfeed (...) even if only for a short time?

- ☐ Yes
- ☐ No
- ☐ Don't Know
- ☐ Not Applicable (women breastfeeding at the time of survey)

Note: If no, go to next section

For how long?

- ☐ Less than 1 week
- ☐ 1-4 weeks
- ☐ 5-8 weeks
- ☐ 9-12 weeks
- ☐ 3-6 months
- ☐ 7-9 months
- ☐ 10-12 months
- ☐ 13-16 months
- ☐ More than 16 months
- ☐ Don't Know
- ☐ Not Applicable (women breastfeeding at the time of survey, and women who never breastfed their child)

APPENDIX K

DETAILS OF STUDIES USED IN ECONOMIC ANALYSIS GASTROINTESTINAL DISEASE (DIARRHEA)				
Study/ ANOS Score/ n	**Definition of Outcome**	**Duration of Observation for Outcome**	**Feeding Groups**	**Feeding Duration**
Howie et al. [25] 1990 8 stars n=674	vomiting or diarrhea or both, lasting as a discrete illness for 48 hours or more vomiting: separate from persistent posseting or episodes of regurgitation diarrhea: distinguished from chronic diarrheal disease such as intolerance to cow's milk or malabsorption	first 24 months of life cumulative incidence provided by quarter for first 12 months relative risks derived for first 12 months of life	Breastfeeders: infants breastfed for 13 weeks or more Early weaners: infants who were breastfed, but stopped before 13 weeks of age Bottle-feeders: infants bottle-fed from birth	first 13 weeks of life
Rubin et al. [80] 1990 6 stars n=500	infants exhibiting ≥ 2 symptoms for at least 2-20 days, or ≥ 3 symptoms (no set time period), or called/visited MD for symptoms (confirmed by MD) symptoms: temperature ≥38.5°C, increased stool, loose stool, vomiting	first 12 months of life	Breastfeeders: 100% breastfeeding Breastfeeding >formula feeding Formula feeders: Breastfeeding=formula feeding Breastfeeding<formula feeding 100% formula feeding	assessed monthly, for the first 12 months of life
Scariati et al. [30] 1997 5 stars n=1,743	diarrhea defined as three or more watery or semiwatery stools in a 24 hour period	first 6 months of life	Full breast Breast>formula Breast=formula Breast<formula Full formula	assessed monthly, for first 6 months of life

APPENDIX L

DETAILS OF STUDIES USED IN ECONOMIC ANALYSIS OTITIS MEDIA				
Study **ANOS Score**	**Definition of Outcome**	**Duration of Observation for Outcome**	**Feeding Groups**	**Feeding Duration**
Howie et al. [25] 1990 8 stars n=674	painful or discharging ear lasting for 48 hours or more	first 24 months of life cumulative incidence provided by quarter for first 12 months relative risks derived for first 12 months of life	Breastfeeders: infants breastfed for 13 weeks or more Early weaners: infants who were breastfed, but stopped before 13 weeks of age Bottle-feeders: infants bottle-fed from birth	first 13 weeks of life
Rubin et al. [80] 1990 6 stars n=500	mother's report of otitis media diagnosis from a physician	first 12 months of life	Breastfeeders: 100% breastfeeding Breastfeeding >formula feeding Formula feeders: Breastfeeding=formula feeding Breastfeeding<formula feeding 100% formula feeding	assessed monthly, for the first 12 months of life
Scariati et al. [30] 1997 5 stars n=1,743	ear infection was not predefined	first 6 months of life	Full breast Breast>formula Breast=formula Breast<formula Full formula	assessed monthly, for first 6 months of life

APPENDIX M

DETAILS OF STUDIES USED IN ECONOMIC ANALYSIS LOWER RESPIRATORY DISEASE				
Study	**Definition of Outcome**	**Duration of Observation for Outcome**	**Feeding Groups**	**Feeding Duration**
Howie et al.[25] 1990 8 stars n=674	coryza, accompanied by cough or wheeze, or both, lasting for 48 hours or more	first 12 months of life	Breastfeeders: infants breastfed for 13 weeks or more Early weaners: infants who were breastfed, but stopped before 13 weeks of age Bottle-feeders: infants bottle-fed from birth	first 13 weeks of life
Cushing et al.[74] 1998 8 stars n=1,202	Lower respiratory infectious illness: 2 or more consecutive days of any upper respiratory symptoms and either wet cough or wheezing or both for at least 1 day	first 6 months of life	Full breast: breast milk the only source of milk in the diet Partial breast: other milk given in addition to breast milk No breast: no breast milk given	assessed bi-weekly for first 6 months of life
Rubin et al.[80] 1990 6 stars n=500	Lower respiratory infectious illness: pneumonia, bronchiolitis, croup, based mother's report of diagnosis made by a physician	first 12 months of life	Breastfeeders: 100% breastfeeding Breastfeeding >formula feeding Formula feeders: Breastfeeding=formula feeding Breastfeeding<formula feeding 100% formula feeding	assessed monthly, for the first 12 months of life

APPENDIX N

DERIVATION OF THE COST SAVINGS OF BOTTLE FEEDING

The study by Howie et al. found bottle feeding to be protective against otitis media. A Population Prevented Fraction was calculated, and used to derive the cost savings of bottle feeding.

C_{br} = Costs of care among breastfed population (in absence of bottle feeding)
C_{tot} = $4,199,174.53, Costs of care among total population for otitis media
PPF = 4.66%, Population Prevented Fraction

To solve for C_{br}:

$$PPF = \frac{C_{br} - C_{tot}}{C_{br}}$$

$$C_{br} = \frac{C_{tot}}{1\text{-}PPF}$$

$$C_{br} = \frac{\$4,199,174.53}{1\text{-}0.0466}$$

$$C_{br} = \$4,404,420.53$$

$$\text{Cost savings of bottle feeding} = C_{br} - C_{tot}$$

$$= \$4,404,420.53 - \$4,199,174.53$$

$$= \$205,246.00$$