FACTORS INFLUENCING THE HEALTH OF CANADIAN INUIT INFANTS

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Abstract

Inuit infants throughout the Arctic experience higher mortality and poorer health than their non-Inuit counterparts, and suffer disproportionately from bacterial and viral infections. This research initially reviews the health status of these infants, with a focus on Canadian Inuit communities and reference to other circumpolar regions, as appropriate. It also discusses the wide range of inter-related factors that affect their health and their susceptibility to infection: their demographic, social, economic and physical environment, as well as personal health practices and the availability of high quality, culturally-appropriate health services within their communities.

Data were then analyzed from a cohort study of 46 healthy Inuit infants that had been previously conducted in Iqaluit, Nunavut from December 1995 to November 1997. Hospitalization and morbidity patterns were examined over their first year of life. Infants experienced an average of four respiratory tract infections (RTIs) annually, which accounted for half of the hospitalizations in the cohort. Some interesting trends were evident from assessment of risk factors for hospitalization and infections using multiple linear regression. Infants of mothers with higher educational attainment spent six fewer days in hospital per year (95% CI: -14.6, 2.9), after adjustment for confounding variables. Adoption appeared to have adverse health effects in addition to those that would be expected due to lack of breastfeeding alone; among infants who were not breast-fed, adopted infants had three more RTIs per year than non-adopted infants (95% CI: 0.5, 5.1). These results provide support for undertaking larger epidemiological studies in order to clarify the role of these risk factors, so that future preventive efforts can be informed and effective.

Résumé

Les enfants Inuits à travers l'arctique souffre de mortalité plus élevée et de santé moins bonne que les enfants non-Inuit et souffrent donc de plus d'infections bactériennes et virales. Cette recherche résume l'état de santé de ces enfants en se concentrant sur les communautés Inuits Canadiennes en les comparant à d'autres régions polaires qui ont les même caractéristiques. Cette étude discute aussi de la grande variété de facteurs inter-reliés qui affectent leur santé et leur susceptibilité aux infections : l'environnement démographique, social, économique et physique ainsi que les pratiques personnelles de santé et la disponibilité de services de santé dans leurs communautés appropriés à leur culture.

Les données d'une étude cohorte de 46 enfants Inuits en santé qui avaient été exécutée à Iqaluit, Nunavut de décembre1995 à novembre 1997 ont été analysées. L'hospitalisation et la morbidité ont été examinées pour leur première année de vie. Les enfants ont expérimenté en moyenne quatre infections respiratoires annuellement, ce qui représente la moitié des hospitalisations dans la cohorte. Certaines tendances étaient évidentes lorsque les taux d'hospitalisation et infection étaient ajustés pour les facteurs de risques en utilisant une régression multiple linéaire. Les enfants de mères plus éduquées ont passé six fois moins de jour à l'hôpital par année (95% IC : -14.6, 2.9), après ajustement pour variables confondantes. Il est apparu que l'adoption avait des effets néfastes sur la santé en plus des effets dus à l'absence d'allaitement. Parmi les enfants qui n'avait pas reçu l'allaitement, les enfants adoptés avaient trois infections respiratoires de plus par année que les enfants non-adoptés (95% IC : 0.5, 5.1). Ces résultats supportent l'entreprise d'études épidémiologiques plus grandes ayant pour but de clarifier les rôles de ces facteurs de risques; ceci afin que les efforts préventifs soient efficaces et informatifs.

Preface

This thesis was written as a collection of two manuscripts that will be submitted for publication. The manuscripts are logically joined and integrated in the thesis through supplementary, connecting text.

The first manuscript comprises the literature review of the thesis (Section 2). To conform to journal requirements and suitability, a detailed assessment of epidemiological limitations of studies from the literature review was not included in the first manuscript. Instead, this critical appraisal is found in Section 5.1.

Epidemiological data from a previously-conducted cohort study were analyzed for the second manuscript, which comprises the methods, results and discussion of the thesis (Section 4). A more detailed assessment of limitations of this cohort study is discussed in Section 5.2. Additional data tables that were excluded from the second manuscript due to word limitations are provided in Appendices 4-8.

Contributions of Authors

Alison L. Jenkins Ph.D. (ALJ) wrote this thesis and was the principal author of both manuscripts. ALJ performed all of the data analysis for the cohort study of Inuit infants in Iqaluit, Nunavut, but had no involvement in study design, questionnaire design or data collection. Prior to analyzing the data, ALJ cleaned the database, reorganized variables, confirmed data validity and communicated with co-investigators to clarify data collection and data entry methods. As the thesis supervisor for ALJ, **Theresa W. Gyorkos Ph.D.** oversaw all aspects of the development and completion of the thesis and manuscript preparation and provided epidemiological expertise. TWG also had no involvement in study design, questionnaire design or data collection. As the statistical consultant for ALJ, **Lawrence Joseph Ph.D.** provided substantive feedback on the statistical aspects of the thesis, and also had no involvement in study design or data collection. **Brian J. Ward M.D.** was a co-investigator for the cohort study and a member of the thesis supervisory committee who was involved in study design. **Kate N. Culman M.D. (KNC)** was a co-investigator for the cohort study who was involved in study design and data collection in Iqaluit, Nunavut between December 1995 and November 1977. **Elaine L. Mills M.D. (ELM)** was the principal investigator of the NHRDP-funded project who was involved in study design and all aspects of study conduct up to the completion of data collection. All co-authors reviewed the manuscripts and assisted in the interpretation of the data.

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Table of Contents

List of Acronyms

ALJ	Alison L. Jenkins
CI	confidence interval
ELM	Elaine L. Mills
GI	gastrointestinal
Hib	*Haemophilus influenzae* type b
KNC	Kate N. Culman
LRTI	lower respiratory tract infection
NWT	Northwest Territories
OM	otitis media
PCB	polychlorinated biphenyl
RTI	respiratory tract infection
SIDS	sudden infant death syndrome
TB	tuberculosis
URTI	upper respiratory tract infection

List of Tables

Manuscript #1: An overview of factors influencing the health of Canadian Inuit infants

Manuscript #2: Risk factors for hospitalization and infection in Canadian Inuit infants over the first year of life

List of Figures

Manuscript #1: An overview of factors influencing the health of Canadian Inuit infants

List of Appendices

1. INTRODUCTION

According to the 1996 Canadian Census, there are 41,000 Inuit in Canada (Statistics Canada, 1998a); this population is younger than the general Canadian population and is growing more rapidly (Indian and Northern Affairs Canada, 1996; Statistics Canada, 2001b). Despite important improvements in health outcomes over the last 30 years in Inuit communities in terms of life expectancy, maternal and infant mortality and morbidity, disparities between their health status and that of other Canadians remain. Life expectancy at birth for Inuit is considerably lower than other Canadians (Statistics Canada, 2001f). Among other factors, high infant mortality contributes to this shorter life expectancy: infant mortality rates in Nunavik and Nunavut are over three times the overall Canadian rate (Statistics Canada, 2001e). Infections, both bacterial and viral, account for much of the higher mortality and morbidity Inuit infants suffer compared to other infants in Canada (Banerji, 2001; Banerji *et al*, 2001; Bjerregaard, 1988; Harrison, 1990; Hodgins, 1997; Maynard and Hammes, 1970; Pekeles, 1988; Postl *et al*, 1982; Thouez *et al*, 1990). A wide range of inter-related factors affect the health of Inuit infants: their demographic, social, economic and physical environment, as well as personal health practices and the availability of high quality, culturally-appropriate health services within their communities. Some of these factors, including subtle nutritional deficits, environmental contaminants, household crowding and associated socioeconomic factors, prenatal and second-hand exposure to tobacco smoke, adoption status, breastfeeding status and history of viral infection, might influence the susceptibility of Inuit infants to infection. Given the continuing disproportionate burden of infectious illness in Canadian Inuit infants, there is an urgent need to investigate the role of these risk factors in a systematic manner, so that future preventive efforts can be informed and effective.

2. LITERATURE REVIEW

The following manuscript comprises the literature review of the thesis. First, it examines the health status of Inuit infants in Canada, by reviewing data from studies conducted in Inuit communities both in Canada and in other regions of the circumpolar North, where appropriate. Then, using a 'determinants of health' approach, the various factors that affect their health are outlined: the demographic, social, economic and physical environment, as well as personal health practices and the availability of high quality, culturally-appropriate health services within their communities. Finally, how such factors might influence the susceptibility of Inuit infants to infection is discussed.

The manuscript will be submitted to the *Pediatric Infectious Disease Journal*. The subject matter presented is timely and original in content, since a recent, comprehensive review of the health of Inuit infants, and the factors that influence their health and susceptibility to infection, is lacking in the medical literature. This review will bring key gaps in knowledge and health information to the attention of researchers, clinicians and policymakers, which, if addressed, could lead to more appropriate and effective preventive strategies to improve the health of Inuit infants and their communities.

2.1 AN OVERVIEW OF FACTORS INFLUENCING THE HEALTH OF CANADIAN INUIT INFANTS

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ABSTRACT

Inuit infants throughout the Arctic experience higher mortality and poorer health than their non-Inuit counterparts in Canada, the United States, Denmark and Russia, and suffer disproportionately from bacterial and viral infections. This review examines the health status of these infants, with a focus on Canadian Inuit communities and reference to other circumpolar regions, as appropriate. A wide range of inter-related factors affect the health of Inuit infants: their demographic, social, economic and physical environment, as well as personal health practices and the availability of high quality, culturally-appropriate health services within their communities. Some of these factors, such as subtle nutritional deficits, environmental contaminants, household crowding and associated socioeconomic factors, prenatal and second-hand exposure to tobacco smoke, adoption status, breastfeeding status and history of viral infection may influence the susceptibility of Inuit infants to infection. Smoking is highly prevalent in Inuit communities, and its indisputable negative effects on health, including increased risk of respiratory tract infection in infants, represents an urgent public health challenge. Locally-driven, focused and methodologically sound epidemiological research that addresses key gaps in knowledge could lead to more appropriate and effective preventive strategies to improve health and well-being in Northern communities.

INTRODUCTION

The Inuit are an Aboriginal people in northern Canada who are part of a larger circumpolar Inuit population that includes Alaska, Greenland and Russia. There are four Inuit regions in Canada: Inuvialuit (northern Northwest Territories (NWT)), Nunavut (a new territory created through federal law that split from NWT in 1999), Nunavik (northern Quebec) and Nunatsiavut (northern Labrador) (Figure 1). Of the 799,010 people in Canada who identified themselves as Aboriginals (i.e. First Nations, Inuit or Métis) in the 1996 Census, approximately 41,000 are Inuit [(1)]. The vast majority (94%) resides outside of Canada's 25 Census metropolitan areas and about 60% of Inuit people live in NWT and Nunavut.

While the gender distribution of the Inuit population is similar to that of the general Canadian population, the Inuit population is considerably younger: in 1996, 15%

of the Inuit population was under the age of four, compared to 7% of the total population; only 3% of the Inuit population was over age 65, compared to 12% of the total population [2]. The Inuit population is also growing more rapidly: its fertility rate is more than twice that of the general Canadian population [3]. There are few reliable statistics on adoption rates, but adoption appears to be becoming more widespread in Inuit communities. Surveys conducted in the 1970's in NWT indicated that between 16 to 24% of Inuit children were adopted, usually by relatives at birth [4,5], while less than 5% of persons over 19 years of age had been adopted [5]; more recent statistics in Nunavik (1994/1995) indicate that, of those aged 15 to 24, 30% were adopted, while of those aged 25 and older, about 15% were adopted [6].

In Canada, all citizens and permanent residents are entitled to medical care with universal coverage. There are a variety of additional services provided free to the Inuit population, including prescription medications, eyeglasses and other medical devices, dental care, individual mental counseling and transportation to access medical services [7]. In practice, however, some of these additional health services are not available in remote communities, where the majority of Inuit live, and there can be great distances to the nearest hospital or tertiary care centre. As an example, the distance from Iqaluit, Nunavut to Ottawa, the major tertiary care referral site for Iqaluit, is over 2000 km (Figure 1). Most remote Inuit communities are served by nursing stations that are staffed by a nurse or community health representative, with physicians and other specialists flying in periodically. A recurring problem in the provision of culturally-appropriate health services in the North is the issue of medical transfers, where Aboriginal patients are transferred to southern Canada for more advanced medical care.

Despite important improvements in health outcomes over the last 30 years in Inuit communities such as life expectancy, maternal and infant mortality and morbidity, disparities between their health status and that of other Canadians remain. Life expectancy at birth for Inuit is considerably lower than other Canadians. In 1996, life expectancy at birth for Canada as a whole was 78.4 years (75.4 for men and 81.2 for women), compared to 64.8 years in Nunavik (60.7 for men and 70.0 for women), where 90% of the population is Inuit [6] and 70.1 years in Nunavut (68.3 for men and 71.3 for women), where 75% of the population is Inuit [8,9]. Among other factors, high infant

mortality contributes to this shorter life expectancy: infant mortality rates in Nunavik and Nunavut are over three times the overall Canadian rate [10].

Inuit infants have much higher rates of morbidity and mortality compared to other infants in Canada, and infections, both bacterial and viral, account for much of this illness and death [6,11-18]. These trends have persisted despite significant advances in living standards and health care delivery. This paper first examines the health status of Inuit infants in Canada, by reviewing data from studies conducted in Inuit communities both in Canada and in other regions of the circumpolar North, where appropriate. Then, using a 'determinants of health' approach, the various factors that affect their health are outlined: the demographic, social, economic and physical environment, as well as personal health practices and the availability of high quality, culturally-appropriate health services within their communities. Finally, how such factors might influence the susceptibility of Inuit infants to infection is discussed.

MATERIALS AND METHODS

Relevant scientific literature was identified using Medline (1965 to present) and supplemented by manual searches of pertinent journals and contact with experts. In addition to peer-reviewed publications, the following data sources were used: 1) The 1996 Census of Canada, which suffered from under-coverage of Aboriginal populations, owing to incomplete enumeration of approximately 44,000 people living in 77 First Nations reserves and settlements [1] and other factors related to possible under-reporting of Aboriginal status and increased mobility of Aboriginal populations [19]; 2) The National Public Health Survey; and 3) the National Longitudinal Survey of Children and Youth; both are conducted every two years by Statistics Canada, starting in 1994 with samples of approximately 22,000 and 25,000 Canadian households, respectively. The sampling frame for both surveys excluded on-reserve First Nations people and Inuit in the provinces, but did include Aboriginal peoples in Yukon, NWT and Nunavut; 4) The First Nations and Inuit Regional Health Survey (1995/1996), developed to provide comparable data on Aboriginal communities outside of the Territories. Data were collected from 183 First Nations communities across the country and five Inuit communities in Labrador [20,21]; 5) Report from the Nunavik Regional Board of Health

and Social Services entitled "Health and what affects it in Nunavik: how is the situation changing?" [6], based largely upon the 1992 Santé Québec Health Survey, which reached 22% of the Inuit population of Nunavik [22]; 6) Statistics Canada, Indian and Northern Affairs Canada, Health Canada internet sites (www.statcan.ca, www.ainc-inac.gc.ca and www.hc-sc.gc.ca) and government-housed published reports [3,23-27].

DISCUSSION

I. HEALTH STATUS OF CANADIAN INUIT INFANTS

Health Indicators

Infant mortality

Infant mortality rate is used as a measure of a population's health and is influenced by living conditions and by access to quality health care services. Higher rates of infant mortality persist in Inuit communities compared to the general Canadian population. In 1996, the infant mortality rate was 20.9 and 17.9 deaths per 1000 live births in Nunavik and Nunavut, respectively, compared to the national rate of 5.8 deaths per 1000 live births [10]. In Nunavik, deaths due to congenital causes, infection, and sudden infant death syndrome (SIDS) each accounted for approximately one third of total infant deaths [6]. The post-neonatal death rate was 16 per 1000 live births in Nunavik (1990 to 1994): eight times the national average [6]. Over one half of post-neonatal deaths were attributed to SIDS, a rate 20 times that for the rest of Quebec [6].

Birthweight

Although fetal growth and birthweight are important determinants of infant health, there are no standardized data available for Inuit infants. The rate of low birthweight in Inuit communities, using norms based on non-Aboriginal infants (i.e. < 2500g, as per the World Health Organization), appears to be similar to that for the rest of Canada; (7.4% in Nunavut and 6 % in Nunavik, compared to the national average of 5.8% in 1996 [28]). However, the rate of prematurity was found to be higher in Nunavik (8.4% in 1991 to 1993) than Quebec (6.8%) for the same time period [6].

Health Status

In the 1980's, the incidence of infection in Canadian Inuit infants was extremely high relative to other diseases, and accounted for up to 80% of outpatient illness visits

[11]. Pneumonia/bronchiolitis, gastroenteritis and bacterial meningitis have been the most common infectious causes of early childhood morbidity and mortality in the Inuit throughout the Arctic[6,11,13-16,29]. The reasons for the high incidence of infection are unknown but have been attributed generally to socioeconomic factors, poor access to health care, harsh environment and crowded living conditions [12,18,30-33]. Exposure to environmental contaminants and tobacco smoke have also been proposed as risk factors [14,34]. A summary of published epidemiological studies on the health of Canadian Inuit infants is presented in Table 1.

Lower respiratory tract infections

Lower respiratory tract infections (LRTIs) are a major health concern for Inuit infants. In 1973, a retrospective review of the medical records of 260 Inuit infants from the Keewatin/Baffin regions, which represented 83% of the 314 live births from this geographic area during the study period, found that 41% had been hospitalized for LRTI in the first year of life [29], despite good adherence to recommended well-child care practices [11]. More recent studies (1997/1998) in the Baffin region, although limited by the small numbers of infants studied, suggest that high rates of LRTI are persisting: a retrospective chart review yielded a rate of 306 hospital admissions for bronchiolitis per 1000 infants during the first year of life and identified respiratory syncytial virus as a pathogen in a significant proportion of admissions [15]. A prospective study in the same region found an annualized incidence rate of hospital admission for LRTI of 484 per 1000 infants [14], based on 51 hospital admissions over an eight month period of 42 infants less than six months of age. Similarly, in Nunavik, one baby is hospitalized for bronchitis and pneumonia in the first year of life for every three born [6]. Parallel trends have been observed in Alaska: a retrospective analysis of hospital discharge records has shown that the bronchiolitis-associated hospitalization rates for Alaskan Native infants less than one year old are more than two times greater than the rates estimated for all US infants [35]. A prospective study conducted from 1993 to 1996 of infants in the Yukon-Kuskokwim Delta in southwestern Alaska showed that respiratory syncytial virus infection was the single most frequent cause of infant hospitalization, with hospital admission rates ranging from 53 to 249 per 1000 infants [36]. A chart review in the same region yielded comparable results [37].

Risk factors for LRTI have been examined in studies in Inuit populations. One study conducted in the 1970's in NWT found that breastfeeding was associated with a reduction in LRTI hospitalization rates in the first eight years of life, while birthweight, sex, adoption, number of siblings and maternal smoking were not [29]. A 1989 study in Nunavik also found that ever-breastfed Inuit infants contracted fewer pulmonary infections in the first year of life than bottle-fed infants (mean 1.2 (95% CI: 0.9, 1.6) versus 2.0 (95% CI: 1.3, 2.6)); although information on smoking or crowding was apparently not collected [34]. Additional risk factors that have been proposed include household crowding [37], defects in cell-mediated immunity [38-40], adoption [14] and exposure to tobacco smoke [14].

Otitis media

A recent literature review concluded that Aboriginal peoples from diverse geographic regions (Canada, the United States, Greenland and Australia) were at highest risk of developing chronic suppurative otitis media (OM) [41]. Studies in Canadian Inuit infants and children reported a prevalence of OM of between 7 and 31%, compared to less than 1% in the United States, the United Kingdom, Denmark and Finland [41]. OM is endemic in the Inuit populations across the Arctic [42-50] and a 1989 study, designed to assess the impact of environmental contaminants on infant health, found that OM was still the most frequent health problem among Inuit infants in Nunavik [34]. Of 118 of the 213 infants in the cohort for whom follow-up was complete, 80% had one or more episodes and 40% had three or more episodes of OM in the first year of life. Repeated infections can result in perforation, scarring and permanent hearing loss [6]. Indeed, one quarter of children in Nunavik have significant hearing loss in at least one ear by the age of five [6].

Risk factors for OM have been examined in Inuit populations. One retrospective study of 285 children (238 Inuit and 47 non-Inuit) conducted in Labrador in 1977 found a decrease in the prevalence of OM with increasing age at the onset of bottle-feeding [43]; comparable trends were observed in another study conducted among 536 Inuit randomly selected from five communities across the Canadian Arctic in 1965 [50]. Other, more recent studies have failed to show a relationship between OM and breastfeeding in the Inuit [34,51]. Moreover, results from studies conducted in the Arctic region of the

association between household crowding and OM have been contradictory [49,51-53]. Exposure to environmental organochlorines through breastfeeding may also be associated with increased risk of OM in the Inuit [34], although further studies are required to clarify the nature and strength of this relationship, given the benefits of breastfeeding in general.

Gastrointestinal illness

Epidemiologic data on the incidence of gastrointestinal (GI) illnesses in Inuit infants are surprisingly scarce. A longitudinal study of infectious diarrhea in northern Canada conducted in the late 1970's on 98 families in urban Winnipeg and 15 families in remote Inuit settlements found that the rate of infection due to rotavirus in neonates was significantly higher in the Inuit settlements than in Winnipeg (1.07 versus 0.36 episodes per child per year); re-infections also occurred more frequently in the first six months of life in Inuit infants [54]. Risk factors hypothesized to play a role were household crowding and lack of outdoor activity in the colder season. Among American Indian and Alaskan Native infants in the first year of life, retrospective analysis of hospital discharge records revealed that diarrhea-associated hospitalization rates in 1980 to 1982 were 230% greater than that of the national population and remained 45% higher in 1993 to 1995; rotavirus appeared to be an important contributor to diarrheal morbidity in this population [55].

Meningitis

Meningitis has also been a major health problem affecting the Inuit in Canada and the United States [56-59]and has caused more infant and child deaths over the past 20 years in Nunavik than any other type of infection [6]. A prospective study conducted from 1972 to 1977 at the Churchill Health Centre, which serves northern Manitoba and the Keewatin region, found an annual incidence of meningitis of 202 per 100,000 in the Inuit population, compared to 157 and 19 per 100,000 in the Indian and Caucasian populations, respectively [57]. A community-based surveillance study, carried out in Manitoba and the Keewatin region between 1981 and 1984, found an annual incidence rate of *Haemophilus influenzae* type b (Hib) meningitis of 530 per 100,000 population less than five years of age among the Keewatin Inuit, compared to rates of 32.1 and 20 in the overall Manitoban and Canadian population, respectively [56]. A recent review of worldwide trends in Hib disease found that the Aboriginal populations of Alaska, northern Canada and central and northern Australia had the highest recorded annual incidence rates of Hib meningitis in

the pre-vaccination era; indeed, the rate reported among the Keewatin Inuit in the 1980's was found to be the highest ever recorded [60]. Prior to vaccine availability, the annual incidence of invasive Hib disease (e.g. all invasive diseases attributable to Hib, including meningitis, septicemia, pneumonia, epiglottitis, cellulitis, arthritis, osteomyelitis and pericarditis) among Alaskan Natives in the United States was much higher than the general population: 491 per 100,000 population under five years old from 1971 to 1977 [58], compared to between 40 to 100 per 100,000 in the general population [61]. After a vaccine was introduced, the rate of invasive Hib disease in Alaskan Natives dropped to 17 per 100,000 population (1992 to 1995), but still remains high in remote parts of the state, despite widespread vaccination [62,63]. In Canada, the incidence of Hib disease has decreased significantly in the general population and among Aboriginal populations since Hib vaccines were introduced in 1992 [64]. Although immunization has succeeded in virtually eliminating Hib meningitis from Nunavik, meningitis due to other bacterial organisms persists [6].

Risk factors for Hib infection in the Alaskan Inuit were assessed in an age-matched case-control study undertaken in 1983 [30]. Univariate analyses suggested that breastfeeding was protective in this population (OR 0.53; 95% CI: 0.27, 0.98) and that living in extended families was a risk factor for Hib disease (OR 1.8; 95% CI: 0.87, 3.25). After multivariate analysis, however, only the number of extended family members predicted case or control status as outcome. A 1999 study examining risk factors of Hib carriage in a vaccinated Alaskan Native population found that day care attendance, increasing age and household crowding were associated with Hib carriage in univariate analyses; crowding remained a risk factor (OR 1.2; 95% CI: 1.1, 1.5) after controlling for day care attendance in logistic regression analysis [62].

Tuberculosis

In the 1960's tuberculosis (TB) case rates in Canadian Inuit were among the highest ever recorded in a human population [65]; and the rates remained 24 times higher among Inuit than the general Canadian population from 1970 to 1984 [66] and 11.5 times higher among the Inuit of Quebec than in Canada from 1990 to 1994 [67]. In 1998, the incidence of new active and relapsed TB among the Inuit was 58.7 per 100,000 compared to 21.3 and 1.5 among foreign-born and Canadian-born non-Aboriginals, respectively [27].

There were no cases of new active or relapsed TB in Inuit infants less than one year old reported in 1998, while the rate for Canada as a whole was three cases per 100,000 population in this age group [27]. Alaska has a high rate of pediatric TB: a population-based, retrospective analysis of all reported cases of TB among children aged 0 to 14 during 1987 to 1994 found that Alaskan Natives have a relative risk of clinical TB of 65 (95% CI: 20, 207) compared to Caucasians [68]. Risk factors proposed for pediatric TB in Inuit communities include inadequate housing conditions, differences in access to health care, genetic susceptibility and nutritional deficiencies [68].

Nutritional deficiencies

Although clinical evidence of nutritional deficiencies has not been documented systematically in Arctic populations, some studies have shown that intake of iron, folacin, calcium, and vitamin A are below dietary standards established by Health Canada, especially among women of reproductive age [69-71]. There is also accumulating evidence that Inuit infants may be deficient in iron [69,72,73] and vitamin A [74].

A small study conducted in the western Canadian Arctic found that of 31% (9 of 29 infants) were iron deficient four months after delivery (from a total of 178 Inuit, White, Indian and Métis mother-infant pairs enrolled in the study) [72]. More recent prevalence data for anemia in Inuit infants from Nunavik, gathered in 1989 as a part of a population-based study to assess the impact of environmental contaminants on infant health, support these findings [69,73]. Twenty-one percent of infants aged two months, 47% aged six months and 38% aged 12 months were found to be anemic in this population, well exceeding the 2.5% prevalence anticipated in a population of infants not experiencing iron deficiency [73]. One quarter of Inuit infants in this study had iron-deficiency anemia by six months of age [73]. Using the same data source, another analysis found that 49% of infants aged four to nine months (123 of a total of 213 infants in the study population) were at least moderately anemic (hemoglobin < 105 g/L), and half of these were definitely or probably iron deficient [69]. In addition, this study also reported that 40% of pregnant women in Nunavik were iron deficient at term.

A study carried out between 1988 and 1991 of over 100 infant-mother pairs in NWT found no clinical evidence of vitamin A deficiency among the infants, but 18% of Inuit infants in the study had mean plasma retinol concentrations in the 'deficient' range,

compared to 11% of non-Inuit infants; while 41% had concentrations in the 'depleted' range, compared to 15% of non-Inuit infants [74]. Nunavik babies were found to have serum vitamin A levels about a third lower than babies in southern Quebec at birth [6].

There is abundant evidence of continued disparities between the health of Inuit infants and that of other infants in Canada. The next section explores some of the factors in the social, economic, physical, behavioural and cultural environment of the Inuit that are most likely to influence the health of their infants.

II. SELECTED DETERMINANTS OF HEALTH PERTINENT TO THE CANADIAN INUIT POPULATION

Social and economic environment

The socioeconomic environment of a population is a strong predictor of health status. Although there is no recognized single index of socioeconomic status [75], three inter-related variables: education, employment and income, are often used as measures. Poverty, low educational attainment and unemployment can all adversely affect health outcomes, in part by influencing personal health practices [26].

Education

In many populations around the world, increased access to schooling, especially for girls, has led to improvements in health and well-being. Educational attainment is often associated positively with health status and healthy behaviours [26]. In 1996, the proportion of high school graduates (among respondents aged 25 to 29) was 33.3% and 28.6% in Nunavik and Nunavut, respectively, compared to 71.8% nationally [76]. The percentage of Inuit women aged 15 and older who reported less than grade nine education was more than double (41%) the percentage of non-Aboriginal women (14%), and only 5% of Inuit women reported university as their highest level of education, compared to over 21% of the general female Canadian population [24]. Remoteness appears to be a barrier to education: a higher percentage of women with a university education was reported in urban Aboriginal populations compared to more rural and remote populations.

Employment and income

Income is strongly associated with health status as well as with other determinants of health [26]. In 1995, the average employment income of the Inuit was $16,378, about

1.5 times lower than the national average of $26,474 [25], although cost of living and income tax status should be taken into consideration in this comparison. According to the 1996 Census, the unemployment rate for Inuit women (20%) and men (23%) were more than double their respective national counterparts (both 10%) [77]. Among Inuit women with a university education, the unemployment rate of Inuit women was still higher than that of non-Aboriginal women, illustrating that many factors play a role in the socioeconomic environment of Inuit families [24].

Physical environment

Environmental contaminants, as well as inadequate housing, water supply and waste disposal, can have a negative impact on the health status of individuals and communities.

Environmental contaminants

Inuit people are more at risk of exposure to environmental contaminants through their traditional diet of fish and marine mammals, where many contaminants tend to accumulate [78,79]. The most recent data on exposure to polychlorinated biphenyls (PCBs) and mercury indicate that some Inuit infants have concentrations beyond the threshold for the appearance of adverse health consequences: mercury was found to be more than 14 times higher in Inuit infants from Nunavik, at an average concentration of 14.2 μg/L, than in the southern Quebec general population; PCB levels were four times higher, at a concentration of 2 μg/L; and similar, albeit slightly lower, levels of both contaminants were also observed among the Inuit living in the Baffin region of NWT [80]. The breast milk of Inuit women in northern Quebec has been found to contain levels of PCBs two to ten times higher than those measured in their southern counterparts [81]. Mean umbilical cord-blood levels of lead were three-fold higher in Nunavik than comparison samples from Toronto and Quebec City (5.2 μg/dL versus 1.7 and 1.8 μg/dL respectively) [82], although these levels are below the concentration thought to put a foetus at risk (10μg/dL) . Studies in Inuit adults from Nunavik [83] and across Canada [84] suggest that a significant proportion of women of reproductive age may have lead and mercury concentrations exceeding those that have been associated with subtle neurodevelopmental deficits in other populations [85].

Housing

Inadequate housing and overcrowding are major problems for the Inuit living in the North [19]. It was estimated in 1995 that between 25 and 30% of households in Nunavik were overcrowded [6]. The mean number of members per household in Nunavut is 3.9 [14], compared to the national mean of 2.6 [86].

Inadequate water supply and sewage disposal systems also pose a risk to the health of Canadian Inuit populations. In Nunavik, water is pumped from rivers or lakes into holding reservoirs and chlorinated, or taken directly from lakes, chlorinated and delivered to homes; sewage is not treated, but released into river systems not used by local residents. Chlorination and testing of water, and cleaning of municipal water equipment and household tanks do not appear to be regulated adequately; in 1996 almost one in five household water specimens was found to contain fecal coliforms [6]. *Helicobacter pylori* has also been detected in local water supplies of Inuit communities in the central Canadian Arctic [87].

Personal health practices

Lifestyle behaviours such as smoking, alcohol dependence and breastfeeding practices can affect an individual's health as well as that of his/her dependents [26]. Health-seeking behaviours in the Inuit may also be adversely affected by the loss of traditional cultural values and lifestyles. Changing knowledge and attitudes about health brought about by the displacement of traditional health teachings by Western medical approaches, together with a host of other factors, may play a role: interviews with older Inuit women in Keewatin and other regions indicate a perceived decrease in knowledge about female sexuality and reproductive health [88-90] and a reduced sense of personal responsibility for healthy childbirth [91].

Smoking

Smoking is an extremely important determinant of ill health in Inuit communities. Rates of smoking among the Inuit are more than twice the national average, and smoking begins at a young age: 69% of Inuit youth reported smoking by the time they are teenagers [92]. A national database on breastfeeding among First Nations and Inuit women in Canada found that 80% of women smoked during pregnancy [93]. More recently, the prevalence of smoking during pregnancy in Nunavik and Nunavut has been estimated at

75% and 73% respectively [6], (Roberts, A., Medical Officer of Health, Nunavut, personal communication). Inuit infants thus have a very high risk of exposure to tobacco *in utero* and to second-hand smoke in the home, especially given the amount of time people spend indoors due to adverse weather conditions.

Alcohol dependence

Although some studies have suggested that fetal alcohol syndrome is more prevalent among Canadian Aboriginal children than non-Aboriginal children, the evidence does not appear to be conclusive [94]. There are no reliable statistics on the prevalence of fetal alcohol syndrome and fetal alcohol effects in northern Inuit communities.

Twenty-five to 30% of women surveyed in Nunavik and 18% in Nunavut reported alcohol use during pregnancy [6], (Roberts, A., Medical Officer of Health, Nunavut, personal communication). Similar percentages of women aged 15 to 34 (including pregnant women) in Nunavik reported a "binge" pattern of drinking: at least monthly drinking sessions of five drinks or more [6]. National data from the 1996/1997 National Population Health Survey indicate that 17.5% of all Canadian women reported consuming alcohol during their pregnancy, with only 2.5 % of these women reporting "binge" drinking [26].

Breastfeeding

Surveys conducted in 1996 show that Aboriginal mothers are less likely to initiate breastfeeding than mothers in Canada overall (54% versus 75%), but more likely to breastfeed six months or more (39% versus 24%) [20,95]. Unfortunately, rates specific to Inuit mothers and infants were not reported. Breastfeeding rates have traditionally been high in Inuit communities [4,6,93]. A study conducted in 1978/1979 in NWT found that 70% of Inuit mothers initiated breastfeeding (partial or full), 58% were breastfeeding at three months, and 44% at six months, with a mean duration of breastfeeding of 8.4 months [4]. Adoption appeared to play an important role in breastfeeding in this survey population: of those Inuit infants remaining with their natural mother, 91% were initiated on breastfeeding, and 88% continued beyond the first month [4]. A national database on breastfeeding among First Nations and Inuit women in Canada was started in 1983 (that excluded NWT and Saskatchewan) and found that, overall, 60.7% of mothers initiated

breastfeeding (partial or full), 42% were breastfeeding at three months, and 30.6% at six months [93], although there was considerable variation in breastfeeding rates among regions: rates were highest in the Yukon (91% at birth, 53% at six months) and northern Quebec (79% at birth, 54% at six months). In the Nunavik region, almost half of the infants in this survey were still breastfed at six months; this prevalence jumped to 65% when adopted babies were excluded [93]. A cohort study of Inuit infants in Nunavik conducted in 1989 found that 57% were breastfed (partial or full) versus 43% bottle-fed [34].

Health Services

Access to high quality, culturally-appropriate health services also contributes to the health of a population. In the Inuit context, both geographic and cultural obstacles can act as barriers to such access and can also render health services less effective. Physical barriers include geographic remoteness, while cultural obstacles include communication problems, differences in values, attitudes and beliefs, and the existence of racism and prejudice [96].

Health service utilization

The National Population Health Survey in 1994/1995 indicated few barriers to health care in the Yukon and NWT, where only 6 to 7% of residents reported difficulty receiving needed health care or advice, compared to 4% for the rest of Canada [97]. The sources of care sought, however, differed from the rest of Canada: 36% of Aboriginal people in the territories had consulted general practitioners in the previous year, compared to 60% for non-Aboriginal northerners and 77% for the rest of Canada; while 41% of Aboriginals had consulted a nurse, compared to 18% of non-Aboriginal northerners and 7% for the rest of Canada. Similar trends were observed in data drawn from the 1991 Aboriginal Peoples Survey [23] and in Nunavik [6]. According to a Santé Québec survey conducted in the early 1990's, the overall frequency of medical consultation was similar, but the types of professionals consulted were different: nurses were consulted more frequently in Nunavik, while specialists were consulted more frequently in southern Quebec [6]. These differences reflect in large part how health services are organized in the North.

Satisfaction with health services

Almost half of the First Nations and Labrador Inuit respondents of the First Nations and Inuit Regional Health Survey in 1995 thought that their health services were not at the same level as the rest of Canada; those living in isolated communities were more likely to believe that services are unequal [21]. Those who felt that services were not equal expressed a clear desire for improved services on the whole. The largest percentage (86%) thought that pediatric services needed improvement.

III. FACTORS THAT MAY INFLUENCE SUSCEPTIBILITY OF THE INUIT INFANT TO INFECTION

Among the various determinants of health discussed above, which might influence the susceptibility of Inuit infants to infection?

Nutritional deficiencies

Subtle nutritional deficiencies may affect immune function among Inuit infants. Among Alaskan Native children, anemia has long been associated with the occurrence of respiratory infections [16,98]. Whether anemia predisposes to infections, or vice versa, was explored in a historical cohort born in the 1960's: 308 of 643 Alaskan Native infants enrolled in the study had a hemoglobin measurement made during the first year of life which was related to infectious episodes recorded during the previous or subsequent three months [99]. The results indicated that low hemoglobin levels were not predictive of infection but that a history of previous infections was associated with subsequent low hemoglobin levels. This relationship has not yet been studied in Canadian Inuit populations, but preliminary evidence suggests a high prevalence of iron-deficiency anemia in Nunavik infants [69,73]. Vitamin A deficiency is also thought to increase the risk of infection [100,101]. Studies indicate that serum vitamin A levels are lower in Inuit infants compared to their non-Inuit counterparts [6,74], but the significance of these observations is difficult to interpret since random serum levels do not always correlate with total body stores of vitamin A.

Environmental Contaminants

In Nunavik, prenatal organochlorine exposure was found to be associated with increased risk of acute OM in Inuit infants in their first year of life, but no increased risk

was observed for bronchopulmonary diseases [34]. However, these risk estimates were made on the basis of 65 of a total of 213 infants enrolled in the study. Current research efforts are focused on evaluating the possible adverse health and developmental effects of environmental contaminants on Inuit infants. Thus far, the health benefits of breastfeeding and consuming traditional food appear to far outweigh the risks posed by contaminants [83,84].

Housing

Inadequate housing is also a determinant of infection in the North [25]. The cold Northern climate keeps people indoors a great deal of the time, amplifying the effects of household crowding, smoking and inadequate ventilation. Crowded living conditions favour transmission of infectious diseases, such as respiratory infections, including TB, gastroenteritis and skin infections, and could contribute to the overall higher rates of infectious diseases in Aboriginal people [32]. In addition, caregiving practices may play a role in transmission of infectious disease, given that children usually circulate among several homes, usually within the same extended family [6]. Household crowding has been proposed as a risk factor for lower respiratory tract infections in Alaskan Natives[37,98]. While some studies in the Arctic region have shown a link between episodes of OM and crowding [43,50,51], others have failed to confirm this association [49,52,53]. An ecologic study of 49 predominantly Native communities in NWT showed that the rate of health centre visits, as a measure of morbidity, was negatively correlated with housing and socioeconomic status indicators [33]. However, since poor housing is associated with low socioeconomic status, any conclusion that housing is associated with health must control for socioeconomic status. When both variables were considered jointly in a multiple regression model, socioeconomic status was by far the stronger factor predicting the rate of health centre visits.

Inadequate water supply and sewage disposal may also influence the health status of Inuit infants. Two major epidemics of fecal-oral transmitted diseases were reported in NWT in the 1990's: a large epidemic of hemorrhagic enterocolitis (caused by *Eschirichia coli* 0157:H7) in the Keewatin region in 1991 [102], and a large hepatitis A outbreak in the Baffin region in 1992; in both epidemics person-to-person spread was the most important mode of transmission [6].

Smoking

Despite the high prevalence of smoking in Inuit communities and the strong epidemiological evidence of increased risk of respiratory infections in infants exposed to environmental tobacco smoke [103,104], research on the effect of maternal and environmental tobacco exposure on infant health within Inuit populations has been limited. A small study in NWT confirmed a high prevalence of maternal smoking among Inuit women (70%; 39 of 56 women), as well as an association between smoking and decreased birthweight [105]. A role for tobacco exposure in the high rates of LRTI in Inuit infants has recently been suggested [14]. Furthermore, over half of post-neonatal deaths reported in Nunavik from 1990 to 1994 were attributed to SIDS. Based on existing high smoking rates during pregnancy and a relative risk for SIDS of three to four for infants born to mothers smoking during pregnancy, passive smoke exposure likely accounts for most of these deaths [6].

Breastfeeding

In general, studies conducted in Inuit populations confirm the importance of breastfeeding in preventing infections. A study of Inuit infant health in the Keewatin/Baffin districts of NWT found that breastfeeding was associated with a significant reduction in hospitalization for lower respiratory tract infections [29], and another demonstrated a strong inverse relationship between the duration of breastfeeding (partial or full) and the duration of hospitalization for non-congenital conditions in the first year of life in Inuit children [4]. In Nunavik, ever-breastfed infants contracted fewer pulmonary infections over the first year of life than bottle-fed infants [34] and were better protected against iron deficiency [73]. Some studies have found an association between lack of breastfeeding and increased risk of OM in Inuit infants [43,50], while others have failed to show such a relationship [34,51]. Breastfeeding appeared to be protective against pneumococcal illness [106] and Hib disease [30] in Alaskan Native children less than two years of age.

Impaired immune function

While immune abnormalities may help to explain the increased incidence and severity of disease in Inuit populations, there are little published data examining immune function in the Inuit. In one study, 23 Inuit children aged between three and 18 months

were examined when they were clinically well but recovering from recurrent pneumonia, OM, severe diarrhea or failure to thrive [107]. They were found to have low percentages of T cells, increased levels of B cells and impaired mitogen responses compared to non-Inuit controls. However, it was recognized that these children represented a highly selected group that may have been more likely to demonstrate immunologic aberrations.

Other preliminary data have shown that Inuit infants on Baffin Island may have defects in cell-mediated immunity [39,40]. In a study comparing immune cell phenotypes, Inuit infants were found to have lower CD4+ T cells and higher CD8+ T cells than their non-Inuit counterparts, leading to lower CD4:CD8 ratios [39]. The significance of this observation is unclear, but may reflect exposure to viral infection, to which CD8+ cell populations are known to expand considerably but transiently [108]. Inuit infants also had a larger percentage of memory cells (CD45RO), indicating exposure and response to foreign antigens, greater expression of activation markers on CD8+ T cells, and an intermittedly elevated expression of a putative Th 2 phenotype marker CD30 [39]. Inuit infants also had higher expression of CTLA-4 on CD4+ T cells and CD86 on B cells after mitogen stimulation, perhaps reflecting a state of heightened immunological reactivity [40]. Further analysis is required to determine the clinical relevance of these findings.

Several viral infections are known to cause immunosuppression through direct and indirect effects on cell-mediated immunity [107,109,110], which has led to the hypothesis that exposure to viruses in early life may pre-dispose Inuit infants to more frequent or severe infections with other organisms. Serologic studies of the herpesviruses, hepatitis A virus and hepatitis B virus have been performed in various regions of the Arctic [111-116] and seroconversion rates for hepatitis A [115], Epstein Barr virus [111], cytomegalovirus [113,114] and herpes simplex virus [114] have all been documented to occur at an earlier age than seen typically in non-Inuit populations. Whether early seroconversion reflects earlier exposure to viruses in infancy, or environmental or genetic factors that heighten susceptibility to viral infection, has not been investigated. Preliminary data demonstrate that Inuit infants are much more likely to be infected with Epstein Barr virus, cytomegalovirus and herpes simplex virus in the first year of life compared to non-Inuit infants, with the majority of infections occurring between four and 13 months of life [117]. Several of the herpesviruses are known to exert immunosuppressive effects [107,109,110]and

therefore may affect the development and/or the functional activity of the immune systems of infected infants.

IV. FUTURE RESEARCH

This paper has summarized some important factors that influence the health of Inuit infants in Canada, and has revealed gaps in knowledge that, if addressed, could lead to more effective and focused preventive approaches. Potential areas of future research could include: 1) assessing the potential relationship between iron-deficiency anemia and/or vitamin A deficiency and immune function in Inuit infants; 2) evaluating the potential role of environmental contaminants in increasing susceptibility to infection; 3) measuring the contribution of household crowding to infection rates; 4) clarifying the role of tobacco smoking as a risk factor for infections and SIDS in Inuit communities; 5) determining the potential impact of infant adoption and subsequent lack of breastfeeding on infection rates in Inuit infants; 6) exploring whether early acquisition of viral infections predisposes Inuit infants to secondary infections. There appears to be a clear need to focus on anti-tobacco preventive programs in Inuit communities, given the high prevalence of smoking and its proven adverse health effects.

Subtle nutritional deficits, environmental contaminants, household crowding and associated socioeconomic factors, prenatal and second-hand exposure to tobacco smoke, breastfeeding status, and history of viral infection may all contribute to making Inuit infants more susceptible to infectious illness. Complex inter-relationships among these various risk factors underline the importance of taking a methodologically sound approach to research in Inuit communities that accounts for confounding and interaction effects. Studies conducted in the North often lack the statistical power to take such an approach. This shortcoming needs to be addressed, but is only part of the challenge. Steps need to be taken, together with Inuit communities and health professionals, to identify and overcome barriers to research so that clear and meaningful results can be achieved. Continuing to raise research capacity within Inuit communities, to ensure local ownership of and participation in research in the North, is a critical part of this process. Epidemiological studies that are not only well-designed, but also driven and managed

locally are urgently required to clarify factors contributing to increased incidence of infection in Canadian Inuit infants, so as to shape and inform future preventive efforts.

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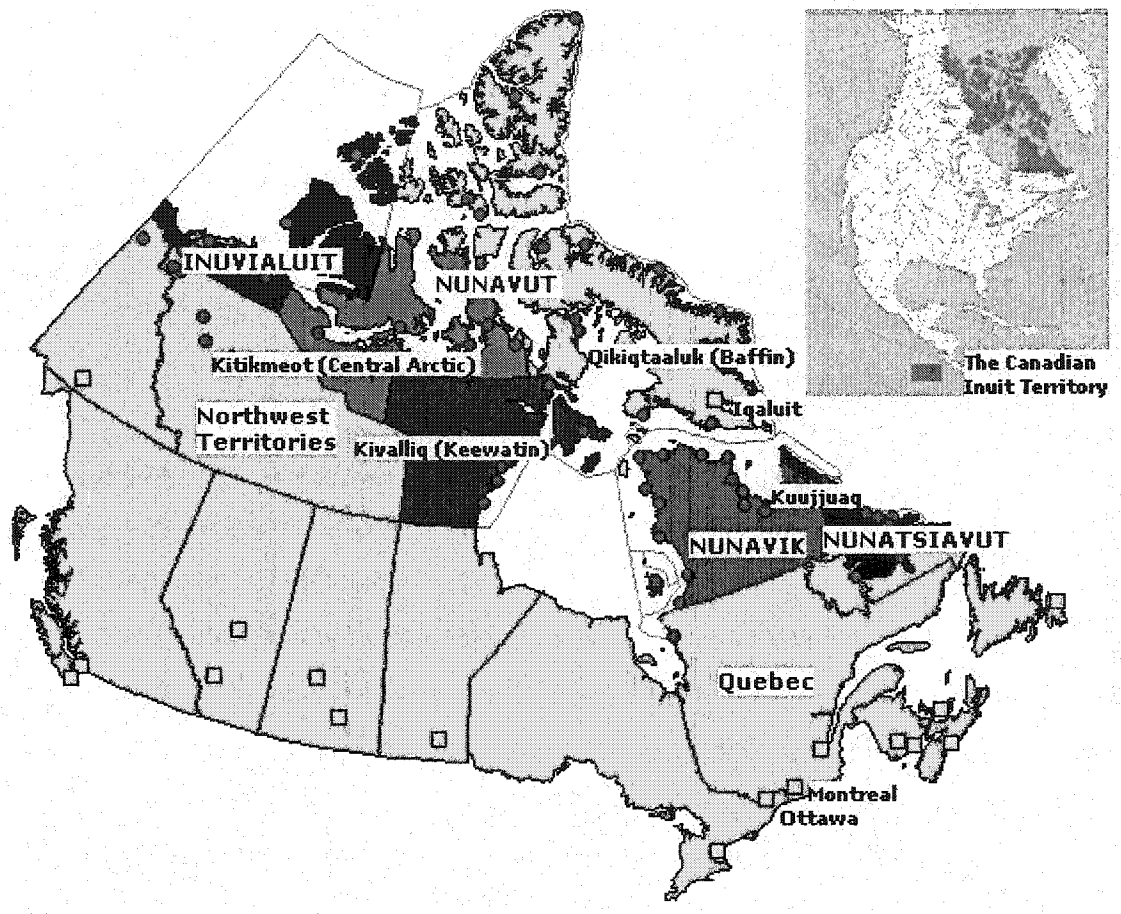
Table 1: Epidemiological Studies on the Health Status of Canadian Inuit Infants

First Author	Year	Location	Study Population	Description
Banerji [14]	Oct 1997-June 1998	Iqaluit, Nunavut	42 Inuit infants (under six months) admitted to Baffin Regional Hospital for LRTI	Prospective case study of LRTI* in Inuit infants
Banerji [15]	Mar 1995-Feb 1996	Iqaluit, Nunavut	78 Inuit children (birth to 48 months) admitted to Baffin Regional Hospital for bronchiolitis	Retrospective chart review of bronchiolitis in Inuit infants
Dewailly [34]	July 1989-Sept 1990	Puvirnituq and Kuujjuaq, Nunavik	171 Inuit infants (birth to one year) born in one of Nunavik's two community hospitals	Prospective cohort study examining association of organochlorine exposure and susceptibility to infections
Willows [73]	July 1989-Sept 1990	Nunavik	Inuit infants from the Dewailly *et al.* study [34]	Anemia and iron status in Inuit infants
Hodgins [69]	July 1989-Sept 1990	Nunavik	Inuit infants from the Dewailly *et al.* study [34]	Iron status in pregnancy and infancy
Godel [74]	1988-1991	Ten communities in western NWT	135 mother-infant pairs, 53 of whom were Inuit, who presented for prenatal care in their community and gave birth in Inuvik	Perinatal vitamin A status in mothers and infants
Godel [72]	Not stated likely 1988-1991	Ten communities in western NWT	171 mother-infant pairs, 37 of whom were Inuit	Iron status in pregnancy and infancy
Godel [105]	Sept 1987-Jan 1990	Ten communities in western NWT	162 women, 56 of whom were Inuit, who presented for prenatal care in their community and gave birth in Inuvik	Effect of maternal smoking, caffeine and alcohol intake on fetal growth
Hammond [56]	Apr 1981-Mar 1984	Manitoba and Keewatin, NWT	90 children (under 5 years) with *H. influenzae* meningitis, 9 of whom were Inuit	Community-based surveillance study for *H. influenzae* meningitis

First Author	Year	Location	Study Population	Description
Carson [29]	1982	Keewatin and Baffin districts of NWT	260 Inuit children (birth to eight years)	Retrospective survey of Inuit children from 1973-1974 PIMM cohort [118], examining LRTIs
Postl [11]	Jan-July 1982	Keewatin and Baffin districts of NWT	584 children (birth to eight years), 353 of whom were Inuit	Retrospective survey of Inuit children from 1973-1974 PIMM cohort [118], examining health care utilization, morbidity and mortality
Gurwith [54]	1976-1979	Winnipeg, Berens River and Eskimo Point, Manitoba	144 families, at least 15 of whom were Inuit	Longitudinal study of diarrhea among infants and small children in three northern communities
Timmermans [43]	1977	Nain, Labrador	238 Inuit and 47 Caucasian children (birth to 15 years)	Prevalence of OM, history of breastfeeding
Spady [118]	Apr 1973-Mar 1974	NWT	All infants (1191) born over calendar year, 449 of whom were Inuit	PIMM study
Wotton [57]	Oct 1972-Feb 1977	Northern Manitoba, Keewatin and Baffin districts of NWT	36 cases of bacterial meningitis (two months to 20 years), 30 of whom were Inuit, in catchment area of the Churchill Health Centre	Prospective surveillance study examining incidence of bacterial meningitis
Schaefer [50]	1965-1966	Five areas of the Canadian Arctic	536 Inuit of all ages	Survey of infant feeding habits and incidence of chronic OM

* LRTI, lower respiratory tract infection; OM, otitis media; PIMM, Perinatal and Infant Morbidity and Mortality.

Figure 1: Inuit Settlement Areas in Canada



Adapted from Map of Canada's north (Pan Arctic Inuit Logistics Corporation) and the North America Map (Makivik Corporation) (http://www.makivik.org/eng/media_centre/nunavik_maps.htm and http://inuit.pail.ca/maps.html; accessed January 11, 2002)

Figure Legend

Figure 1: Inuvialuit is found in northern Northwest Territories (NWT). In 1993, the new territory of Nunavut was created through federal law and split from the NWT on April 1, 1999. Nunavut is comprised of three regions: Qikiqtaaluk (or Baffin) Region in eastern and northern Nunavut, the Kivalliq (or Keewatin) Region in the south and central portions of Nunavut near Hudson Bay, and the Kitikmeot Region in central and western Nunavut. Nunavik is located in northern Quebec, and Nunatsiavut in northern Labrador.

3. STUDY OBJECTIVES

The literature review reveals a need for focused, epidemiological research on factors that influence the health of Inuit infants and their susceptibility to infection. Recent studies provide evidence that Inuit infants in Canada continue to suffer from high rates of RTIs in early life (Banerji, 2001; Banerji *et al*, 2001; Dewailly *et al*, 2000), but detailed investigation of risk factors that are associated with ill health and infection has been limited.

Therefore, a study was designed to examine infectious morbidity, hospitalization and associated risk factors in a cohort of 46 Inuit infants from Iqaluit, Nunavut over their first year of life. Data were collected previously (September 1995 to October 1997) by a study co-investigator (KNC) and provided to the author of the thesis (ALJ) by the study's primary investigator (ELM).

The objective of the database research presented in this thesis was twofold: 1) to document hospitalization and infection patterns in this cohort of Inuit infants; and 2) to determine the association between hospitalization and infection patterns and key risk factors (season at birth, sex, maternal education, maternal smoking during pregnancy, household smoking, household crowding, breastfeeding and adoption status).

Although this thesis does not seek to compare these hospitalization rates to those in other parts of Canada, differences between Northern communities and the rest of Canada should be noted when using hospitalization rates as a measure of health. For example, the decision to hospitalize an infant for observation and care can be easier in the North, where there might be less opportunity for families to return to hospital if the infant gets worse, and there is less pressure on hospital beds.

4. METHODS, RESULTS AND DISCUSSION

The following manuscript, which will be submitted to *Canadian Medical Association Journal*, describes the results of the analysis of risk factors for hospitalization and infection in a cohort of 46 Inuit infants from Iqaluit, Nunavut over their first year of life. This manuscript comprises the methods, results and discussion sections of the present thesis. Due to journal requirements (i.e. word limitations), some data were not shown in the manuscript. For clarity, these additional data tables are found in Appendices 4-8.

4.1 RISK FACTORS FOR HOSPITALIZATION AND INFECTION IN CANADIAN INUIT INFANTS OVER THE FIRST YEAR OF LIFE

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ABSTRACT

Background: Inuit infants experience higher mortality and poorer health than other Canadian infants, and suffer disproportionately from bacterial and viral infections. A wide range of inter-related factors affect their health and susceptibility to infection.
Methods: This study describes hospitalization and morbidity patterns in a cohort of 46 healthy Inuit infants from Iqaluit, Nunavut over their first year of life. Risk factors for hospitalization and infections, such as season at birth, sex, maternal education, maternal smoking during pregnancy, household smoking, household crowding, breastfeeding and adoption status, were assessed using multiple linear regression.
Results: Infants experienced an average of four respiratory tract infections (RTIs) annually, which accounted for half of the hospitalizations in the cohort. Some interesting trends were evident from assessment of risk factors using multiple linear regression. Infants of mothers with higher educational attainment spent six fewer days in hospital per year, after adjustment for confounding variables. Adoption appeared to have adverse health effects in addition to those that would be expected due to lack of breastfeeding alone; among infants who were not breast-fed, adopted infants had three more RTIs per year than non-adopted infants.
Interpretation: These results provide support for undertaking larger epidemiological studies in order to clarify the role of these risk factors, so that future preventive efforts can be informed and effective.

INTRODUCTION

Historically, Inuit infants have had much higher rates of morbidity and mortality compared to other infants in Canada, and have suffered disproportionately from infections[1-10]. Today, lower respiratory tract infections (LRTIs) and otitis media (OM) are still major health concerns for Inuit infants[5,6,11]. The reasons for the high incidence of infection have not been investigated systematically but have been attributed generally to socioeconomic factors, harsh environment and crowded living conditions[3,10,12-15].

This prospective study describes hospitalization and morbidity patterns and examines associated risk factors in a birth cohort of healthy Inuit infants from Iqaluit, Nunavut over their first year of life.

METHODS

A birth cohort of Inuit infants was enrolled over a 22 month period from September 1995 to October 1997. Each infant was followed for one year. Healthy infants between one and three months of age who resided in the study area, were of at least 50% Inuit ancestry, and were not born prematurely, were eligible for recruitment. Of 196 infants born at Baffin Regional Hospital in Iqaluit, Nunavut during this period, 100 were eligible, of which 52 enrolled in the study; 37 declined to participate and 11 could not be contacted. Of the 96 infants who were not eligible, 53 were non-Inuit, 13 were less than 50% Inuit ancestry, 20 had moved from Iqaluit and 10 were premature.

The infants were identified from the Iqaluit Birth Register or Baffin Regional Hospital records and their primary caregivers were contacted by an Inuit research assistant. Infants were enrolled by the study investigator (KNC) after review of their medical histories and after informed consent forms were signed by their primary caregivers.

Data were collected using a series of specifically-designed questionnaires administered at enrolment by a trained health worker, with the assistance of an Inuit interpreter if necessary. Information was collected from the primary caregiver on general demographics (ethnicity of mother and father), household demographics (number of rooms in the house, number of people living in household, number of smokers in the household, education and employment of mother and father), prenatal history (history of

maternal infection, maternal use of drugs, alcohol and cigarettes), perinatal history (APGAR score, birthweight, length, head circumference), infant's past medical history (medical illnesses and hospitalizations from birth to enrolment) and nutritional history (breastfed or not at enrolment). Complete physical evaluations were also performed at enrolment.

The infants were followed up at three month intervals for one year, by questionnaire and physical examination as per the first visit. Monthly phone calls to the primary caregiver were made by the Inuit research assistant to obtain interim infant health information, including date and type of medical illnesses, clinic visits and hospitalizations. Data were verified by examining medical records. The number of infections for each infant during the first year of life was determined from the medical records and episodes were grouped in the following categories: 1) LRTI with or without OM, with or without upper respiratory tract infection (URTI); 2) OM without LRTI, with or without URTI; 3) URTI without LRTI and without OM; 4) total RTIs (sum of categories 1, 2 and 3); 5) total gastrointestinal (GI) infections; 6) total "other" infections (skin, mouth, eye and urinary tract infections); and 7) total infections (sum of categories 4, 5 and 6). If there was more than one infection in a given category in any seven day period, only one infection was counted. If there was more than one category of RTI in any seven day period, only the more severe infection was counted.

The outcomes considered were: 1) annualized number of hospitalizations for infections; 2) annualized total number of days hospitalized due to infections; and 3) annualized number of LRTI, OM, URTI, total RTI, GI, "other" and total infections; all determined from birth to end of follow-up. Annualized rates were used rather than counts, because there were slight variations in length of follow-up of study infants. Independent variables season at birth, sex, maternal education, maternal smoking during pregnancy, household smoking (smokers per household), household crowding (persons per room) at enrolment, breastfeeding (any/none) at enrolment, and adoption status. Birthweight was not considered as an independent variable since premature infants were excluded from this study. Outcome data were complete for the infants who completed the study, as were data on independent variables, except that two mothers did not report their smoking status during pregnancy.

Ethics approval for this study was obtained through the ethics committee and institutional review board of the Montreal Children's Hospital and the Baffin Regional Inuit Health Board.

Means, standard deviations, medians, and range for continuous variables and proportions for categorical variables were calculated. Relationships between independent variables and outcomes were investigated by standard linear regression. Independent variables were included in multiple linear regression models if 1) there was *a priori* evidence that they could be independent predictors of the outcome, or 2) if correlations or results of simple linear regressions suggested that the given variable was a predictor or confounder. 95% confidence intervals were reported for all regression parameters. SAS® software (version 8) was used for statistical analyses (SAS Institute Inc., Cary, NC, USA).

RESULTS

Forty six of 52 Inuit infants from Iqaluit, Nunavut who were enrolled in the study completed the one year follow-up, with a mean age at enrolment of 61.9 ± 31.2 days. Of these infants, 16 were female (35%), one quarter were adopted, and 54% were breastfed at time of enrolment into the study. Tobacco exposure was extremely high in the study population: 85% of infants were exposed to tobacco smoke *in utero* and 94% exposed to second-hand smoke in the home.

Hospitalization and morbidity patterns for the 46 infants who completed follow-up are summarized in Table 1. There were 51 hospitalizations for all causes involving 18 infants; three quarters of these hospitalizations (39 of 51) were for infection, 64% of which were RTIs (25 of 39). Thirty-seven percent of the infants in the study (17 of 46) were hospitalized for infection at least once in their first year of life, spending a median of 6.0 days in hospital (range 1.0– 114.0) over their length of follow-up. The infants experienced a median of 7.1 total infections per year (range 1.6-16.9), of which 4.1 (range 0-13.2) were RTIs. Fifty-two percent of infants (24 of 46) experienced at least one LRTI annually, of whom 42% (10 of 24) had more than two episodes per year. One fifth of the study infants (9 of 46) experienced three or more OM episodes per year and

over half suffered a GI infection during the course of the study, with 10% of infants (5 of 46) having more than two episodes.

Risk factor-outcome relationships in this study were examined by multiple linear regression, but these results were generally inconclusive due to the small sample size of the study. Particular attention should be paid to the 95% confidence intervals of the regression coefficients for the various risk factors: many included both zero and potentially interesting effects. Infants born in winter months (November to April), on average, had 0.6 (95% CI: -1.3, -0.03) fewer hospitalizations for infections and spent 4.9 (95% CI: -12.5, 2.7) fewer days in hospital due to infections annually than infants born in summer months. Infants of mothers who attended grade eight or higher, on average, had 0.6 (95% CI: -1.3, 0.04) fewer hospitalizations and 7.0 (95% CI: -14.8, 0.7) fewer days of hospitalization annually. For each unit increase in household crowding (persons per room), infants experienced, on average, 0.5 (95% CI: -0.6, 1.6) more hospitalizations and spent 5.2 (95% CI: -7.5, 17.9) more days in hospital annually. Since season at birth, maternal education and household crowding were inter-correlated, multiple linear regression analyses were necessary to determine the effect of confounding. Protective trends of higher maternal education were still evident when season at birth and household crowding were included in the regression model; infants of mothers who attended grade eight or higher, on average, spent 5.8 (95% CI: -14.6, 2.9) fewer days in hospital annually. The parameter estimates for season at birth and household crowding were diminished by more than 20% in the three variable model (data not shown), suggesting that they were highly confounded and their effects could not be separated in this study.

Sex differences in RTI rates were observed: girls experienced, on average, 1.6 (95% CI: -3.2, -0.05) fewer RTIs and 1.0 (95% CI: -1.8, -0.2) fewer URTIs per year than boys. Results for maternal smoking and RTIs were inconsistent with strong epidemiological evidence from published studies: infants in this study who were exposed to tobacco *in utero* experienced, on average, 1.4 (95% CI: -2.7, -0.1) fewer episodes of OM annually than unexposed infants. Household smoking appeared to have no important effect on RTI rates; this observation may be due to lack of variability in the exposure, since 85% of mothers in the study reported smoking during pregnancy and 94% of infants were exposed to tobacco smoke in the household.

Most risk factors had no effect on GI and "other" infection rates. However, for each unit increase in household crowding (persons per room), infants experienced, on average, 1.1 (95% CI: -1.9, -0.4) fewer GI infections annually. Although household crowding, household smoking and breastfeeding were inter-correlated, the regression coefficient for household crowding did not change in the model containing the three variables (data not shown). This result suggests that the crowding-GI infection rate relationship was not confounded by these variables. On the other hand, the parameter estimate for household smoking was altered by more than 20% in the three variable model (data not shown). Since the magnitude of the relationship between household smoking and outcome was not clinically important in either the univariate model or models containing other combinations of variables (data not shown), it is more plausible that this effect was not due to confounding but rather due to random changes in numerical estimates in the small data set. Sex and seasonal differences in "other" infections were observed: girls, on average, had 1.3 (95% CI: 0.5, 2.0) more "other" infections annually than boys; infants born in winter had, on average, 0.9 (95% CI: -1.6, -0.1) fewer "other" infections annually compared to those born in summer. Although sex and season at birth were correlated, both remained independent predictors of "other" infections when tested together in a multiple linear regression model (data not shown).

Infants who were breastfed at enrolment, on average, had 0.33 (95% CI: -1.0, 0.3) fewer hospitalizations, 1.0 (95% CI: -2.5, 0.5) fewer RTIs, 0.7 (95% CI: (-1.7, 0.3) fewer LRTIs and 0.7 (95% CI: (-1.6, 0.3) fewer episodes of OM, and spent 4.2 (95% CI: -11.9, 3.5) fewer days in hospital annually, compared to infants who were not breastfed. Adopted infants experienced, on average, 0.4 (95% CI: -0.3, 1.1) more hospitalizations, 2.4 (95% CI: 0.8, 4.0) more RTIs, 1.4 (95% CI: 0.3, 2.4) more LRTIs and 1.1 (95% CI: 0.05, 2.1) more episodes of OM, and spent 7.9 (95% CI: -0.6, 16.4) more days in hospital annually than non-adopted infants.

There was a strong, inverse relationship between breastfeeding and adoption; none of the 12 adopted infants who participated in this study were breastfed. In multiple linear regression analyses, controlling for breastfeeding had little effect on the magnitude of the relationships between adoption and hospitalization and RTI rates; regression coefficients for adoption remained essentially unchanged, with 95% confidence intervals

widened only slightly in models containing the breastfeeding variable (Table 2). Stratifying by breastfeeding gave similar results; among the 20 infants who were not breast-fed, those who were adopted still had, on average, 2.8 (95% CI: 0.5, 5.1) more RTIs per year than non-adopted infants. Controlling for adoption, however, reduced the magnitude of the regression coefficient for breastfeeding (Table 2). Although it was impossible to separate the effects of these two variables in this study, it appeared that adoption exerted adverse effects on infection rates in addition to those that would be expected due to lack of breastfeeding alone.

INTERPRETATION

While the summary statistics presented here are similar to those observed in other studies and surveys[5,7,11,16], the Inuit population is not homogeneous; their health status and needs can vary greatly from community to community. The extremely high rate of maternal smoking during pregnancy that was reported in this study (85%) was evident in another recent study in the same region[5] and in prevalence estimates from Nunavik and Nunavut (75% and 73% respectively)[7], (Roberts, A., Medical Officer of Health, Nunavut, personal communication). The mean number of members per household was 5.7 ± 2.4 in this study, compared to 3.9 in Nunavut[5] and 2.6 nationally[17]. The breastfeeding rate reported here (54%) corroborates that observed in a 1989 cohort study of Inuit infants in Nunavik (57%)[11], and the adoption rate seen in the present study (25%) is comparable to that reported recently in Nunavik[7]. Adoption exerted a negative impact on breastfeeding prevalence, as previously observed[16].

The high rates of hospitalization and the morbidity patterns in this study demonstrate that RTIs continue to be a major health problem for Inuit infants. A 1997/1998 prospective case study in Iqaluit, Nunavut reported an annualized incidence rate of hospital admission for LRTI of 484 per 1000 infants[5]. A 1989 study in Nunavik, designed to assess the impact of environmental contaminants on infant health, found that OM was still the most frequent health problem among Inuit infants, with 40% of infants (47 of 118) having three or more episodes of OM in the first year of life[11].

Relationships between risk factors and outcomes in this study were examined by multiple linear regression, but the results should be interpreted with caution given the

relatively small sample size. With few exceptions, regression results were inconclusive since the 95% confidence intervals of the regression coefficients for the various risk factors included both zero and potentially interesting effects. Further evidence needs to be collected, in a larger study, to better estimate the magnitude of these potential effects and determine their clinical importance. However, given the heterogeneous nature of northern populations and the relatively small size of individual communities, large sample sizes can be difficult to achieve. In the current study, over half of the eligible birth cohort of Iqaluit was enrolled over a two year period. Additional study limitations included potential selection bias due to loss to follow-up and voluntary enrolment. Although the reasons for the withdrawal of the six infants from the study are unknown, they experienced higher annualized rates of hospitalization than infants who completed follow-up. Since their withdrawal from the study appears to be related to outcome, the exclusion of these infants from the analysis, while necessary, was likely to introduce selection bias. The refusal of caregivers to enroll infants who met the eligibility criteria may have introduced additional selection bias, if refusal was related to the various outcomes. It is difficult to predict the effect of these potential biases on the study results.

Infants of mothers who attended grade eight or higher spent fewer days in hospital per year, even after controlling for confounders. Breastfeeding effects were inconclusive but protective trends could be noted for hospitalization outcomes, LRTI, OM and GI infection rates. Complex inter-relationships among risk factors, both measured and un-measured, could have diminished the association between breastfeeding and outcomes. Notably, there appeared to be additional, negative effects of adoption on RTI rates and days hospitalized that could not be accounted for by lack of breastfeeding. Although very preliminary, these findings warrant further research to determine whether increased health support should be targeted to adoptive families. That adopted children stayed longer in hospital could, for example, be due to differences in living and caregiving arrangements.

The results demonstrating an apparent protective effect of maternal smoking during pregnancy on OM rate were not observed for LRTI and URTI rates or hospitalization outcomes, and, importantly, were not consistent with strong, previously published epidemiological evidence for increased risk of respiratory infections in infants

exposed to tobacco smoke[18,19]. Taken together with the extremely high tobacco smoke exposure in the study population, health education programs to diminish smoking rates in Inuit communities are in clear need. Household crowding was associated negatively with GI infection rates in this study. The regression coefficient for maternal smoking and household crowding did not change when other combinations of independent variables were included in models, suggesting that their relationships with OM rate and GI infection rate, respectively, were unlikely to be confounded by other variables that were measured in this study. Nonetheless, some or all of the following factors could have exerted unpredictable effects on the association of maternal smoking with OM rate and that of household crowding with GI rate: 1) association of these risk factors with confounders that weren't considered in this study; 2) complex inter-relationships among the risk factors that were considered; 3) lack of variability in exposure (85% of mothers reported smoking during pregnancy); 4) measurement error (due to inadequate measurement or under-reporting); and 5) missing data (one missing maternal smoking value represented the infant with the highest hospitalization rate and very high infection rates).

Risk factors for RTIs have been examined previously in Canadian Inuit populations. Breastfeeding was associated with lower hospitalization rates for LRTI in the first eight years of life[2], lower rates of pulmonary infection in the first year of life[11], and decreased prevalence of OM[20,21]. Other studies failed to show a relationship between OM and breastfeeding[11,22], and results concerning the association between household crowding and OM have been contradictory[22-25]. Exposure to environmental organochlorines through breastfeeding may also be associated with increased risk of OM in the Inuit[11], although further study is required to clarify the nature and strength of this relationship, given the benefits of breastfeeding in general.

This study demonstrates that RTIs remain an important source of morbidity in Canadian Inuit infants and underscores the need for larger epidemiological studies that have sufficient statistical power to account for the complex inter-relationships among risk factors. Future studies that are not only well-designed, but also driven and managed locally, should help to clarify the role of risk factors such as adoption and tobacco smoking, among others, on infection rates in Inuit infants.

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CONTRIBUTION OF AUTHORS

Alison L. Jenkins Ph.D. was the principal author of the manuscripts and performed all of the data analysis for the cohort study of Inuit infants in Iqaluit, Nunavut. **Theresa W. Gyorkos Ph.D.** oversaw all aspects of manuscript preparation and provided epidemiological expertise. **Lawrence Joseph Ph.D.** provided substantive feedback on the statistical aspects of the manuscript. **Gary S. Pekeles M.D.** and **Brian J. Ward M.D.** were involved in study design. **Kate N. Culman M.D.** was involved in study design and data collection in Iqaluit, Nunavut between December 1995 and November 1977. **Elaine L. Mills M.D.** was the principal investigator and was involved in study design and all aspects of study conduct up to the completion of data collection. All co-authors reviewed the manuscript.

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Table 1: Hospitalization and morbidity patterns for Inuit infants from Iqaluit, Nunavut who completed follow-up for one year[§]

OUTCOMES	Mean (SD)	Median	Min	Max
Length of follow-up (days)	451.50 (39.00)	457.00	357.00	524.00
Hospitalization rate[*]	0.66 (1.08)	0	0	5.13
Days hospitalized per year	4.10 (12.88)	0	0	83.55
LRTI[¶] rate	1.13 (1.68)	0.72	0	8.80
OM rate	1.58 (1.61)	0.91	0	6.39
URTI rate	1.73 (1.33)	1.48	0	5.18
Total RTI rate	4.49 (2.58)	4.09	0	13.19
GI infection rate	0.68 (0.81)	0.72	0	2.83
"Other" infection rate	1.82 (1.33)	1.63	0	5.82
Total infection rate	6.87 (3.22)	7.12	1.57	16.86

[§] n = 46

[*] Overall rates are expressed per year

[¶] LRTI, lower respiratory tract infection; OM, otitis media; URTI, upper respiratory tract infection; GI, gastrointestinal.

Table 2: Investigation of effects of adoption and breastfeeding on RTI rates and hospitalization outcomes[§]

Outcome	Independent variable	Simple linear regression coefficient (95% CI)	Multiple linear regression coefficient (95% CI)	Variables in model
Hospitalization rate[*]	adoption	0.39 (-0.34, 1.12)	0.26 (-0.71, 1.22)	adoption breastfeeding
	breastfeeding	-0.33 (-0.97, 0.32)	-0.18 (-1.03, 0.67)	adoption breastfeeding
Days hospitalized	adoption	7.91 (-0.57, 16.39)	8.30 (-2.97, 19.57)	adoption breastfeeding
	breastfeeding	-4.21 (-11.87, 3.45)	0.53 (-9.40, 10.47)	adoption breastfeeding
LRTI rate	adoption	1.36 (0.29, 2.44)	1.44 (0.02, 2.87)	adoption breastfeeding
	breastfeeding	-0.72 (-1.71, 0.27)	0.11 (-1.15, 1.37)	adoption breastfeeding
OM rate	adoption	1.10 (0.05, 2.14)	1.05 (-0.34, 2.45)	adoption breastfeeding
	breastfeeding	-0.66 (-1.61, 0.29)	-0.06 (-1.28, 1.17)	adoption breastfeeding
Total RTI rate	adoption	2.37 (0.76, 3.98)	2.69 (0.62, 4.76)	sex adoption breastfeeding
	breastfeeding	-1.01 (-2.53, 0.51)	0.69 (-1.14, 2.51)	sex adoption breastfeeding

[§] RTI, respiratory tract infection, LRTI, lower respiratory tract infection; OM, otitis media; URTI, upper respiratory tract infection. [*] Rates are expressed per year.

5. GENERAL DISCUSSION

5.1 Limitations of studies on Inuit infant health

An overall review of the medical literature and government-housed documents revealed a shortage of Inuit-specific health research and statistics. Without this information, individuals, communities and governments are limited in their abilities to address the health needs of Inuit (Mailloux and Gillies, 2001). Existing data collection mechanisms in Canada (i.e. Census, surveillance systems) are not designed to produce Inuit-specific data and have been faulty in other respects; for example, in addition to the problem of undercoverage (Smylie, 2000), there have been inconsistencies in the wording for questions concerning ethnicity in the Canadian Census (Mailloux and Gillies, 2001). Moreover, critical examination of epidemiological studies on the health of Canadian Inuit infants revealed some study limitations that threatened the validity of their results. Threats to validity can be divided in two main groups: selection bias due to nonrandom sampling, loss to follow-up and volunteer bias; and information bias due to use of untested questionnaires, lack of adequate and rigorous analyses (i.e. poor or absent measurement and control of confounders) and social desirability bias. In addition, some studies did not appear to have a defined study base, from which results could be generalized to an external population.

Selection bias is a systematic error in the estimation of the exposure-outcome relationship caused when a study sample is unrepresentative of the intended target population in a way that is differential with respect to exposure or outcome. For example, in a 1989 study in Nunavik, designed to assess the impact of environmental contaminants on infant health, follow-up was complete for 53% of the infants who were eligible for the study (118 of 222) (Dewailly *et al*, 2000). If the infants who withdrew from the study or missed study visits were sicker or healthier than those who completed follow-up, or had different exposure levels to environmental contaminants, selection bias would have been introduced. In another study using these same data, prevalence estimates for anemia were determined from hemoglobin measurements obtained from 109, 116 and 122 of the infants at the two, six and 12 month examinations, respectively (Willows *et al*, 2000).

Twenty-one percent of infants aged 2 months, 47% aged 6 months and 38% aged 12 months were found to be anemic based on hemoglobin concentrations below age-specific cut-off points. These estimates were likely underestimated since blood was drawn only from infants who were free from apparent illness. Anemia has long been associated with increased rates of infections in Inuit populations (Brody, 1965; Maynard and Hammes, 1970). An earlier study conducted in the western Canadian Arctic found that 31% of infants were iron deficient four months after delivery (Godel *et al*, 1992a). However, this prevalence estimate was based on measurements taken from only 29 infants, of unstated background, from a total of 178 Inuit, White, Indian and Métis mother-infant pairs who were enrolled in the study. There was no discussion about potential differences between these 29 infant and the 149 other infants who were not included in the calculation of this estimate. The validity of this particular prevalence estimate is questionable, and these results should not be generalized to any external population given the doubtful internal validity and the lack of an apparent defined study base. While avoiding selection bias is difficult in any epidemiological study, the challenges to encourage participation and minimize loss to follow-up are particularly great in remote and scattered Inuit communities. There is also an understandable apprehension about health research conducted by outsiders, given the history of European and Inuit relations over the past 500 years (Mailloux and Gillies, 2001).

Measurement error can occur through inadequate measurement, underreporting or misclassification of exposure or outcome. In a study conducted between 1987 and 1990 in NWT to assess the effect of smoking and caffeine and alcohol consumption during pregnancy on fetal growth, these risk-taking behaviours were likely underreported (Godel *et al*, 1992b). Not only do individuals tend to bias their response towards a socially acceptable answer when asked sensitive questions about, for example, alcohol consumption, but apparent errors in questionnaire design meant that the required data were not captured: no information was obtained about irregular smoking or consumption of caffeine and alcohol, and former smokers were classified as nonsmokers without determining whether smoking had ceased before or during pregnancy. These errors likely resulted in underestimation of the prevalence of the undesirable behaviours and lessened the magnitude of the relationship between exposure and outcome.

Another limitation endemic to studies conducted in the North is the (often unavoidable) use of small study populations, such that conclusions are sometimes based on data from very few study subjects. As an example, a recent prospective study in Iqaluit, Nunavut found an annualized incidence of hospital admission for LRTI of 484 per 1000 infants (Banerji *et al*, 2001), but this rate was based only on 51 hospital admissions over an eight month period incurred by 42 infants less than six months of age. Small sample sizes can also result in the lack of power to demonstrate an association that truly exists between an exposure (or risk factor) and outcome. Such studies can suffer from wide 95% confidence limits that, rather than demonstrating evidence of "no effect", are inconclusive since they encompass both the null effect and potentially clinically important effects. For example, organochlorine exposure through breastfeeding was hypothesized to increase the susceptibility of Inuit infants to infections in a 1989 study in Nunavik, but the 95% confidence intervals for relative risks of infection in breastfed infants compared to bottle-fed infants were too wide to be informative about group differences (Dewailly *et al*, 2000). Even if these estimates had been conclusive, they may not have been valid, since potential confounders of the association between breastfeeding and infections, such as maternal education, maternal smoking during pregnancy and adoption status, were not controlled for in the analyses. Similarly, a 1965 Canadian study randomly sampled 536 Inuit of all ages from a well-defined study base, and found a clear association between history of bottle-feeding and chronic OM (Schaefer, 1971), but did not control for potential confounders. Indeed, bottle-feeding rates were associated closely to degree of urbanization, and hence other socioeconomic factors.

Due to inherent difficulties of conducting well-designed epidemiological studies in the North, studies from diverse Arctic regions and from different time periods are often compared inappropriately. As an example, the epidemiological evidence from studies of risk factors for OM in Inuit communities, when examined on a superficial level, seems contradictory. This lack of clarity is perhaps not surprising, taking into account the wide range of communities and time periods in which the various studies were conducted, as well as study limitations such as confounding bias. A 1965 study in five areas in the Canadian Arctic (Schaefer, 1971) and a 1977 study in Nain, Labrador (Timmermans and Gerson, 1980) both demonstrated protective effects of breastfeeding on OM but

unfortunately did not take into account the effect of potential confounders. A cross-sectional study of 740 Greenlandic children conducted in 1993 reported that episodes of acute OM were more frequent in infants who were breastfed exclusively for more than four months (OR 2.47; 95% CI: 1.26, 4.83) (Homoe *et al*, 1999). Such breastfeeding patterns were thought to be a surrogate parameter for low socioeconomic status, and after controlling for other risk factors in multiple logistic regression analysis, duration of exclusive breastfeeding was no longer a strong predictor of OM (OR 1.14; 95% CI: 1.01, 1.27). In the same study, crowded households were also a risk factor for acute OM (OR 5.55; 95% CI: 1.72, 17.89), but controlling for breastfeeding and parental history of OM abolished this effect (OR = 1.24; 95% CI: 0.88-1.74). A survey from 1984 in 142 Greenlandic children did not find household crowding to be a risk factor for OM, corroborating results from another study (Bjerregaard, 1983), but that low socioeconomic status was a determinant of middle ear disease (Pedersen and Zachau-Christiansen, 1986). In a 1965 study of 641 Inuit children living in six Alaskan settlements, breastfeeding was not considered as a risk factor, and no relationship between crowding and incidence of OM was demonstrated over the one year study period (Reed and Dunn, 1970). Even at a given time, Inuit communities are not homogeneous; they can differ with respect to location, environment, socioeconomic opportunities, and exposure to non-Inuit customs and values; thus it is unlikely that the health situation in one region would be representative of all Inuit (Mailloux and Gillies, 2001).

5.2 Limitations of the cohort study analyzed in this thesis

Extreme caution should be used in interpreting the results of the data analysis in this thesis, even though the 46 Inuit infants who participated represented over half of the eligible birth cohort of Iqaluit enrolled over a two year period. Firstly, there were complex intercorrelations among the risk factors and outcomes considered in this study, with several potential candidates for confounding (Appendices 4 and 5). Unfortunately, the ability to control for complex confounding relationships using multiple linear regression in this study (Appendix 6) was limited by the small sample size. Secondly, selection bias may have occurred in this study, since enrolment was voluntary and there was, albeit minimal, loss to follow-up. The six infants who withdrew were likely different

from the 46 who completed the study with respect to outcome, since the former group had higher hospitalization rates prior to enrolment (Appendix 7). It was not appropriate to use statistical inference to compare these groups for possible bias, because such inference depends as much on the sample size as it does on any observed differences; with small sample sizes, even huge biases may not look "significant". Thirdly, the study's small sample size also resulted in wide 95% confidence intervals for simple linear regression coefficients that included zero and potentially important effects (Appendix 8). Lastly, the results cannot necessarily be generalized to the Canadian Inuit infant population at large, since the study base was limited to families living in Iqaluit who may not be representative of families from outlying regions.

In light of these limitations, it is not surprising that there were some differences in the results observed in this thesis and those of epidemiological studies in other populations. Although it can be very useful to compare the two, findings cannot necessarily be generalized beyond their intended target populations.

5.3 Risk factors for LRTI

Proposed risk factors for LRTI in infants include exposure to cigarette smoke (Li *et al*, 1999; Strachan and Cook, 1997), lack of breastfeeding (Golding *et al*, 1997a), vitamin A deficiency (Humphrey *et al*, 1996) and household crowding (Simoes *et al*, 1993). There is strong evidence that parental smoking causes adverse respiratory health outcomes such as hospitalization for LRTI in a child's early life. A recent systematic quantitative review of 38 studies that examined this relationship during the first three years of life yielded a pooled odds ratio of 1.57 (95% CI: 1.42, 1.74) for smoking by either parent, and 1.72 (95% CI: 1.55, 1.91) for maternal smoking; the associations with parental smoking were robust to adjustment for confounding factors and showed evidence of a dose-response relationship (Strachan and Cook, 1997).

In the present study, results for maternal smoking during pregnancy were inconclusive, and household smoking did not appear to influence LRTI rates. This observation may have been due to lack of variability in exposure, since 85% of mothers in the study smoked during pregnancy and 94% of infants were exposed to tobacco smoke in the household. Indeed, tobacco smoking is a particularly important risk factor to

consider in the Inuit context, given: 1) the high rates of LRTI observed in the present study and by others (Banerji, 2001; Banerji *et al*, 2001); 2) the extremely high prevalence of smoking in Inuit communities; and 3) the indisputable negative effects of tobacco smoke exposure on the health of infants and children. In addition to increased risk of LRTI (Li *et al*, 1999; Strachan and Cook, 1997), the consequences of tobacco smoke exposure include perinatal death (Meyer and Tonascia, 1977), low birthweight (Brooke *et al*, 1989), reduced respiratory function after birth (Stick *et al*, 1996) and increased risk of SIDS (Anderson and Cook, 1997).

5.4 Risk factors for OM

URTI is an important risk factor for OM (Arola *et al*, 1990); other factors of importance may include immaturity of Eustachian tube function, impaired or immature immune function, household crowding, exposure to household tobacco smoke, poor nutrition, lack of breastfeeding, family history of OM and high rates of nasopharyngeal colonization with potentially pathogenic bacteria (Bluestone, 1998). A 1995 meta-analysis of 22 studies conducted from 1966 to 1994 found that risk of acute OM increased with a family history of the disease (RR 2.63; 95% CI: 1.86, 3.72); with parental smoking (RR 1.66; 95% CI: 1.33, 2.06); and with day care outside the home (RR 2.45; 95% CI: 1.51, 3.98) (Uhari *et al*, 1996). Although this meta-analysis provides strong epidemiological evidence of increased risk of OM in infants and children due to parental smoking, it did not differentiate between the effects of pre- and postnatal maternal smoking. A prospective study of 8556 pregnant women in Australia showed that maternal smoking during pregnancy was a predictor of middle ear disease five years post-delivery, independent of smoking at six months and at five years, age and sex of the child, breastfeeding history, maternal age, education and employment at five years, socioeconomic status, use of day care, and the number of siblings or children in the household (Stathis *et al*, 1999). A study of 1013 American infants followed prospectively over the first year of life demonstrated that heavy maternal smoking of over 20 cigarettes per day was an important risk factor for OM in the first year of life (Ey *et al*, 1995).

The present study found that maternal smoking during pregnancy was associated with lower rates of OM over the first year of life, even after controlling for the potential

confounders that were measured in this study. Similar protective trends were not, however, noted for LRTI, RTI or hospitalization rates. It is difficult to interpret these results owing to the lack of variability in tobacco smoke exposure. A larger epidemiological study is required to clarify these observations among Inuit, especially given the overwhelming weight of evidence from studies in other populations that points to maternal smoking as a risk factor for OM (Ey *et al*, 1995; Stathis *et al*, 1999; Uhari *et al*, 1996).

Breastfeeding for at least three months reduced the risk of acute OM (RR 0.87; 95% CI: 0.79, 0.95) (Uhari *et al*, 1996). A recent review of the epidemiological evidence found that OM was less common among breastfed children and that the longer the duration of breastfeeding, the lower the risk of developing OM (Golding *et al*, 1997a). In the present study, breastfeeding appeared to protect against OM and LRTI, while adoption had the opposite effect; breastfeeding and adoption were highly confounded and their effects on these outcomes could not be separated. However, among infants who were not breastfed, adopted infants experienced three more RTIs in total (i.e. LRTI + OM + URTI) over the first year of life than non-adopted infants. Although these effects could not be teased apart for LRTI and OM alone, the results suggest that adoption had negative health effects on overall RTI rates in addition to those that would be expected due to lack of breastfeeding. The impact of household crowding on OM rates in this study was inconclusive.

5.5 Risk factors for GI infections

Household crowding was associated negatively with GI infection rates in this thesis, even after controlling for the potential confounders that were measured in the study. A larger study will be required to prove or disprove this finding. While poor quality housing is generally accepted to be an important contributor to ill health (United Nations Centre for Human Settlements, 1996), few epidemiological studies have quantified the impact. A recent study in Malawi demonstrated that children in improved homes were less likely to have respiratory, gastrointestinal, or malarial illnesses (OR 0.56; 95% CI: 0.35, 0.91) after confounding factors were controlled for, but the particular contribution of crowding was not examined (Wolff *et al*, 2001).

Breastfeeding was protective against GI infection in this study, but the magnitude of the effect did not appear to be clinically important. The protective effect of breastfeeding against infection has long been recognized and can be attributed to anti-inflammatory substances and specific maternal antibodies in human breast milk, which act on the respiratory and gastrointestinal tract of the infant (Wold and Adlerberth, 2000). There is strong evidence from reviews of epidemiological studies and meta-analyses that breastfeeding protects against gastric infections (Golding *et al*, 1997b).

5.6 Other potential risk factors for infection not measured in this study

Although measures of nutritional deficiencies were not considered as risk factors in this study, they also have serious health consequences related to infection. Iron-deficiency anemia has been associated with impaired cell-mediated immunity, which may increase susceptibility to infection (Bhaskaram and Reddy, 1975; Dallman, 1987). A link between vitamin A deficiency and adverse health outcomes related to the immune response was first recognized over 30 years ago (Scrimshaw *et al*, 1968) and has been followed up with supporting data from animal models, observational studies in humans and intervention trials (Sommer and West, 1996). Since preliminary evidence suggests that Inuit infants have subtle nutritional deficiencies (Godel *et al*, 1992a; Godel *et al*, 1996; Willows *et al*, 2000) and defects in cell-mediated immunity (Culman *et al*, 1999a; Pekeles *et al*, 1999; Reece and Brotton, 1982), larger studies in this population should assess the role of these risk factors in increasing susceptibility to infection.

Environmental contaminants such as PCBs and heavy metals were also not measured as risk factors in this study. These substances pass through the placental barrier and during breastfeeding, putting the developing fetus and newborn infant at risk. Exposure to environmental sources of PCBs and associated microcontaminants can result in altered immune status (Dewailly *et al*, 2000; Tryphonas, 1998; Weisglas-Kuperus *et al*, 1995). While studies in non-human primates have shown that chronic exposure to low levels of PCBs lead to changes in several parameters of the immune system, which may lead to diminished resistance to microbial infection (Tryphonas, 1998), comparable data in humans are scarce. A study in Dutch infants showed no significant correlations between pre- and postnatal PCB/dioxin exposure and the incidence of infection during

the first 18 months of life, nor the antibody levels to common childhood vaccines (mumps, measles and rubella) considered to be direct measurements of immune function (Weisglas-Kuperus *et al*, 1995). Higher prenatal PCB/dioxin exposure was, however, associated with an increase in the total number of T cells as well as with an increase in the number of CD8+ T cells at 18 months of age, and with lower monocyte and granulocyte counts, but only at three months of age (Weisglas-Kuperus *et al*, 1995). The clinical importance of these differences are unclear, since all the values observed for these leukocyte subpopulations in high and low PCB/dioxin-exposed infants were within the normal range. Furthermore, since it seems plausible that higher exposures to environmental contaminants could be associated with lower socioeconomic status, results of studies that are not controlled adequately for potential confounding variables should be interpreted with caution (Baghurst *et al*, 1987).

5.7 Conclusions

Despite the inherent challenges, future studies that investigate risk factors for infection in Inuit infants must be adequately sized and methodologically-sound. Many factors, including subtle nutritional deficits, environmental contaminants, household crowding and associated socioeconomic factors, prenatal and second-hand exposure to tobacco smoke, breastfeeding status, and history of viral infection could contribute to making Inuit infants more susceptible to infectious illness. As observed and discussed, these risk factors are intimately interrelated; if potential confounding relationships are not taken into account in epidemiological studies, their findings will not be valid. Barriers to conducting research to address these risk factors must be identified and overcome. Research capacity must continue to be raised within Northern communities, to ensure ownership of and participation in research that concerns them, with the goal of improving the health and well-being of all Inuit.

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7. APPENDICES

Appendix 1: Questionnaires

IMMUNE FUNCTION IN THE INUIT INFANT:
ROLE OF VIRUSES IN IMMUNE INJURY
INITIAL EVALUATION

Baby's name

_____
(last) (first) (middle)

Address_____

_____

Date of birth ___/___/___ Baby's sex ☐ f (1)
d m Y ☐ m (2)

GENERAL DEMOGRAPHICS

Spoken language

☐ (1) english	☐ (1) english
☐ (2) inuktituk	☐ (2) french
☐ (3) both	☐ (3) both

Race:

Mother

☐ (1) Inuit	☐ (1) Native
☐ (2) Caucasian	☐ (2) Caucasian
☐ (3) 1/2 Inuit 1/2 caucasion	☐ (3) Black
☐ (4)other_____	☐ (4)other_____
	Country of origin:
	_____

Father

☐ (1)Inuit	☐ (1) Native
☐ (2) Caucasian	☐ (2) Caucasian
☐ (3) 1/2 Inuit 1/2 Caucasion	☐ (3) Black
☐ (4)other _____	☐ (4)other_____
	Country of origin:
	_____

Adopted

☐ (1) Yes
☐ (2) No

If the parents have agreed to participate, complete the following.

PRENATAL HISTORY

1. History of maternal infection Specify_____ ☐ (1) 1st trimester ☐ (2) 2nd trimester ☐ (3) 3rd trimester ☐ (4) unknown	☐ (1)yes ☐ (2) no ☐ (3) unknown
2. History of maternal medications Specify_____	☐ (1) yes ☐ (2) no ☐ (3) Unknown
3. History of chronic maternal illness Specify_____ _____	☐ (1) yes ☐ (2)no ☐ (3) Unknown
4. History of maternal alcohol use If yes, specify quantity ☐ (1) Daily ☐ (a) < 1 glass ☐ (b) > 1 glass ☐ (2) Weekly ☐ (a) < 1 glass ☐ (b) > 1 glass ☐ (3) Monthly ☐ (a) < 1 glass ☐ (b) > 1 glass ☐ (4)Binge ☐ (a) occasional ☐ (b) None	☐ (1)yes ☐ (2) no ☐ (3) Unknown
5. History of maternal drug use, IV or other If yes, Specify_____ ☐ (1) 1st trimester ☐ (2) 2nd trimester ☐ (3) 3rd trimester	☐ (1) yes ☐ (2) no ☐ (3) unknown
6. History of maternal cigarette use No. of cigarettes per day ☐ (1) <10 ☐ (2) 10-20 ☐ >20 No. Months (1-9)	☐ (1) yes ☐ (2) no ☐ (3) Unknown
7. Other maternal history Specify_____ _____	☐ (1) yes ☐ (2) no ☐ (2) Unknown

PERINATAL HISTORY

1. Type of delivery If C-sxn, specify reason ☐ (1) Repeat ☐ (2) Breech ☐ (3) C-P disproportion ☐ (4) Failure to progress ☐ (5) Other	☐ (1)vag ☐ (2)c-sxn ☐ (3) Unknown
2. APGAR Score	(1-10) 1min _____ (1-10) 5 min _____
3. Perinatal complications Specify_____	☐ (1) yes ☐ (2) no ☐ (3) Unknown
4. Infant's birth weight	☐ (1)<2.5 kg ☐ (2) 2.5-3.0 kg ☐ (3) 3.1-3.5 kg ☐ (4) 3.6-4.0 ☐ (5) > 4.0
5. Infant's length	☐ (1) <5th% ☐ (2) 5th-10th ☐ (3) 11th-25th ☐ (4) 26th-50th ☐ (5) 51st-75th ☐ (6) 76th-95th ☐ (7) > 95th
6. Infant's head circumference (%)	☐ (1) <5th% ☐ (2) 5th-10th ☐ (3) 11th-25th ☐ (4) 26th-50th ☐ (5) 51st-75th ☐ (6) 76th-95th ☐ (7) > 95th
7. Number of days in hospital If > 2 days for vag delivery, why _____ _____ If > 7 days for C-sxn, why_____ _____	vaginal delivery ☐ (1) <48 hours ☐ (2) >48 hours C-sxn ☐ (1) < 7 days ☐ (2) > 7 days
8. Comment	

INFANT'S PAST MEDICAL HISTORY

1. Medical illness and dates (d/m/y) If yes: ☐ (1) URI __/__/__ ☐ (2) meningitis __/__/__ ☐ (3) Sepsis __/__/__ ☐ (4) fever __/__/__ ☐ (5) gastro __/__/__ ☐ (6) OM __/__/__ ☐ (7) pneumonia (LRI__/__/__ ☐ (8) other non-infection __/__/__ ☐ (9) other infection __/__/__ Specify	☐ (1) yes ☐ (2) no ☐ (3) Unknown
2. Previous hospitalisations 1) Date of admission _________ (d m y) Date of discharge _________ (d m y) Number of days _____ Diagnosis_____ 2) 1) Date of admission _________ (d m y) Date of discharge _________ (d m y) Number of days _____ Diagnosis_____ Transfer to referral hospital ☐ (1) yes ☐ (2) no Number of days in referral hospital _____	☐ (1) yes ☐ (2) no ☐ (3) Unknown
3. Previous surgery Specify_____ Date _________ d m y	☐ (1) yes ☐ (2) no ☐ (3) unknown
4. Has the infant received any medications? Specify_____Reason_____ Date R'cd ___/___/___	☐ (1) yes ☐ (2) no ☐ (3) unknown
5. Has the infant received any blood products? Specify_____Reason_____ Date R'cd ___/___/___	☐ (1) yes ☐ (2) no ☐ (3) unknown

INFANT'S PAST MEDICAL HISTORY

6.	Allergies Specify_____	☐ (1)yes ☐ (2) no ☐ (3) Unknown
7.	Comment_____ _____ _____	

FAMILY MEDICAL HISTORY

1. Major illnesses -Mother Specify_____	☐ (1) yes ☐ (2) no ☐ (3) Unknown
2. Major illnesses -Father Specify_____	☐ (1)yes ☐ (2) no ☐ (3) Unknown
3. Major illnesses -Siblings Specify_____	☐ No sibling Sib 1 ☐ (1) yes ☐ (2) no ☐ (3) Unknown Sib2 ☐ (1) yes ☐ (2) no ☐ (3) unknown sib 3 ☐ (1)yes ☐ (2) no ☐ (3) unknown
4. Major illnesses -Grandmother Specify_____	mat ☐ (1) yes ☐ (2) no ☐ (3) unknown pat ☐ (1) yes ☐ (2) no ☐ (3) unknown
5. Major illnesses-Grandfather Specify_____	mat ☐ (1) yes ☐ (2) no ☐ (3) unknown pat ☐ (1) yes ☐ (2) no ☐ (3) unknown
6. History of recurrent infections in any family member If yes: Specify family member_____ Type of infection ☐ (1) URI (sinusitis, OM) ☐ (2) pneumonia ☐ (3) meningitis ☐ (4) Sepsis ☐ (5) skin abscess ☐ (6) other, specify _____	☐ (1) yes ☐ (2) no ☐ (3) unknown
7. Major illnesses-other family member Specify: _____	☐ (1) yes ☐ (2) no ☐ (3) unknown

HOUSEHOLD DEMOGRAPHICS

1. How many people live in the household and sleep over night?	No. people ___(no.) <15 years ___(no.) >15 years
2. How many people share the infant's bedroom?	___ (no.) <15 years ___ (no.) >15 years
3. How many smokers are there in the household? What is the total packs per day smoked?	_____ no. Of smokers ☐ (1) <1 ☐ (2) 1-2 ☐ (3) 2+-3 ☐ (4) >3
4. Is the infant cared for during the day by someone other than a parent?	☐ (1) yes ☐ (2) no ☐ (3) unknown
5. If yes to the above question, what type of care?	☐ (1) babysitter at home ☐ (2) family day care ☐ (3)day care ☐ (4) family member at home ☐ (5) other specify_____
6. How many other children are with the child during the day? What is the age range?	____ no. Children age range, can tick more than 1 ☐ (1) < 5 years ☐ (2) 5-10 years ☐ (3) 11-15 years
7. Does another child in the family go to day care or school?	☐ (1) yes ☐ (2) no ☐ (3) unknown
8. How many rooms in the house (exclude bathroom)?	____ no. Of rooms

HOUSEHOLD DEMOGRAPHICS (con't)

9. Highest educational level-mother	☐ (1) less than grade 8 ☐ (2) some high school ☐ (3) completed high school ☐ (4) some technical school ☐ (5)technical school diploma ☐ (6) some university ☐ (7) university diploma ☐ (8) post graduate degree
10. Highest educational level-father	☐ (1) less than grade 8 ☐ (2) some high school ☐ (3) completed high school ☐ (4) some technical school ☐ (5)technical school diploma ☐ (6) some university ☐ (7) university diploma ☐ (8) post graduate degree
11. Is the mother employed or in school? Employed? School? If yes, does she work more than 20 hours per week?	☐ (1) yes ☐ (2) no ☐ (3) uk ☐ (1) yes ☐ (2) no ☐ (3) uk ☐ (1) yes ☐(2) no ☐ (3) uk
12. Is the father employed or in school? Employed? School? If yes, does he work more than 20 hours per week?	☐ (1) yes ☐ (2) no ☐ (3) uk ☐ (1) yes ☐ (2) no ☐ (3) uk ☐ (1) yes ☐ (2) no ☐ (3) uk
13. If Mother employed, specify type	☐ (1) professional ☐ (2) trade specify_____
14. If Father employed	☐ (1) professional ☐ (2) trade specify_____

NUTRITIONAL HISTORY

☐(1) 0-3 MONTHS
☐ (2) 3-6 MONTHS
☐ (3) 6-9 MONTHS
☐ (4) 9-12 MONTHS
☐ (5) > 12 MONTHS

1. Is the infant breastfeeding? Go to question 3 if no, go to que.2 if yes	☐ (1) yes ☐ (2) no ☐ (3) unknown
2. If yes,	☐ (1) breastmilk alone ☐ (2) breastmilk and formula ☐ (3) breastmilk and other milk, spec_____ ☐ (4) unknown
3. If no,	☐ (1) Accepted formula ☐ (2) Cow's milk ☐ (3) carnation evaporated milk concoction ☐ (4) other Specify_____
4. How many feeds per day? How many ounces per day?	____ (1-2 digit number) ☐ Unknown ____ (2 digit number) ☐ Unknown
5. Cereals? Vegetables? Fruits? Meats? Fish? Raw meats/fish? Dairy (non-milk)? Other? Specify: _____	☐ (1) Daily ☐ (2) occasional ☐ (3) never ☐ Unknown ☐ (1) Daily ☐ (2) occasional ☐ (3) never ☐ Unknown ☐ (1) Daily ☐ (2) occasional ☐ (3) never ☐ Unknown ☐ (1) Daily ☐ (2) occasional ☐ (3) never ☐ Unknown ☐ (1) Daily ☐ (2) occasional ☐ (3) never ☐ Unknown ☐ (1) Daily ☐ (2) occasional ☐ (3) never ☐ Unknown ☐ (1) Daily ☐ (2) occasional ☐ (3) never ☐ Unknown ☐ (1) Daily ☐ (2) occasional ☐ (3) never ☐ Unknown
6. Date solids first introduced	___/___/___ day/mo/year ☐ Unknown

INITIAL EVALUATION
PHYSICAL EXAMINATION

☐ (1) 0-3 MONTHS ☐ (2) 3-6 MONTHS
☐ (3) 6-9 MONTHS ☐ (4) 9-12 MONTHS
☐ (5) >12 MONTHS

If abnormal, describe below	☐ (1) NORMAL	☐ (2) ABNORMAL
Growth **weight**	☐ (1) < 5% ☐ (2) 5-10% ☐ (3) 11-25th ☐ (4)26-50th% ☐ (5) 51-75th ☐ (6) 76-95th% ☐ (7) >95th %	
length	☐ (1) < 5% ☐ (2) 5-10% ☐ (3) 11-25th ☐ (4)26-50th% ☐ (5) 51-75th ☐ (6) 76-95th% ☐ (7) >95th %	
HC	☐ (1) < 5% ☐ (2) 5-10% ☐ (3) 11-25th ☐ (4)26-50th% ☐ (5) 51-75th ☐ (6) 76-95th% ☐ (7) >95th %	
System		Description of findings
Skin, mucous membranes	☐ 1 ☐ neg	
Head, eyes, neck	☐ 2 ☐ neg	
Ears, nose	☐ 3 ☐ neg	
Throat, teeth, mouth	☐ 4 ☐ neg	
Lymph nodes	☐ 5 ☐ neg	
Chest	☐ 6 ☐ neg	
Heart	☐ 7 ☐ neg	
Abdomen	☐ 8 ☐ neg	
Genitalia, pelvis	☐ 9 ☐ neg	
Musculoskeletal	☐ 10 ☐ neg	
Neurological	☐ 11 ☐ neg	
Development	☐ 12 ☐ neg	

INTERVAL HISTORY

Interval History # _____

GENERAL DEMOGRAPHICS

1. Has the family moved or changed the phone number? If yes, new address_(Change original database) _____	☐ (1) yes ☐ (2) no
2. How many people live in the house?	____>15 years ____<15 years
3. How many people share the infant's bedroom?	____> 15 years ____<15 years
4. How many smokers are in the household? What is the total packs per day smoked?	____no. of smokers ☐ (1) <1 ☐ (2) 1-2 ☐ (3) 2+-3 ☐ (4) >3
5. Is the infant cared for during the day by someone other than a parent? If yes, what is the type of care	☐ (1) yes ☐ (2) no ☐ (3) unknown ☐ (1) babysitter at home ☐ (2) family day care ☐ (3) day care ☐ (4) family member at home ☐ (5) other specify_____
Is there another child at home who attends day care or school?	☐ (1) yes ☐ (2) no

INTERVAL HISTORY

Interval History # _____

NUTRITIONAL HISTORY

☐(1) 0-3 MONTHS
☐ (2) 3-6 MONTHS
☐ (3) 6-9 MONTHS
☐ (4) 9-12 MONTHS
☐ (5) > 12 MONTHS

1. Is the infant breastfeeding? Go to question 3 if no, go to que.2 if yes	☐ (1) yes ☐ (2) no ☐ (3) unknown
2. If yes,	☐ (1) breastmilk alone ☐ (2) breastmilk and formula ☐ (3) breastmilk and other milk, spec_____ ☐ (4) unknown
3. If no,	☐ (1) Accepted formula ☐ (2) Cow's milk ☐ (3) carnation evaporated milk concoction ☐ (4) other Specify_____
4. How many feeds per day? How many ounces per day?	____ (1-2 digit number) ☐ unknown ____ (2 digit number) ☐ unknown
5. Cereals? Vegetables? Fruits? Meats? Fish? Raw meats/fish? Dairy (non-milk)? Other? Specify_____	☐ (1) Daily ☐ (2) occasional ☐ (3) never ☐ unknown ☐ (1) Daily ☐ (2) occasional ☐ (3) never ☐ unknown ☐ (1) Daily ☐ (2) occasional ☐ (3) never ☐ unknown ☐ (1) Daily ☐ (2) occasional ☐ (3) never ☐ unknown ☐ (1) Daily ☐ (2) occasional ☐ (3) never ☐ unknown ☐ (1) Daily ☐ (2) occasional ☐ (3) never ☐ unknown ☐ (1) Daily ☐ (2) occasional ☐ (3) never ☐ unknown ☐ (1) Daily ☐ (2) occasional ☐ (3) never ☐ unknown
6. Date solids first introduced	___/___/___ day/mo/year ☐ unknown

INTERVAL HISTORY

Interval History # _____

MEDICAL HISTORY

Has the infant had any illnesses that did not require a visit to the doctor? If yes, specify_____	☐ (1) Yes ☐ (2) No
Has the infant had an illness for which he/she went to the doctor? If (1) Yes, specify_____ _____ #1 Date ___/___/___ d m y #2 Date ___/___/___ d m y #3 Date ___/___/___ d m y	☐ (1) Yes ☐ (2) No
Has the infant been hospitalized? Date ___/___/___ d m y Diagnosis_____	☐ (1) Yes ☐ (2) No
Has the infant been transferred out of Iqaluit to a major medical center? Date ___/___/___ d m y Diagnosis_____	☐ (1) Yes ☐ (2) No

INTERVAL HISTORY

Interval History # _____

MEDICAL HISTORY

Has the infant been on any medications? Name of medication_____ Reason for use _____	☐ (1) Yes ☐ (2) No
Comments_____ _____ _____ _____ _____ _____ _____ _____	

FOLLOW-UP PHYSICAL EXAMINATION

Follow-up # _____

☐ **(1) 0-3 MONTHS** ☐ **(2) 3-6 MONTHS**

☐ **(3) 6-9 MONTHS** ☐ **(4) 9-12 MONTHS**

☐ **(5) >12 MONTHS**

If abnormal, describe below	☐ (1) NORMAL	☐ (2) ABNORMAL
Growth **weight**	☐ (1) < 5% ☐ (2) 5-10% ☐ (3) 11-25th ☐ (4)26-50th% ☐ (5) 51-75th ☐ (6) 76-95th% ☐ (7) >95th %	
length	☐ (1) < 5% ☐ (2) 5-10% ☐ (3) 11-25th ☐ (4)26-50th% ☐ (5) 51-75th ☐ (6) 76-95th% ☐ (7) >95th %	
HC	☐ (1) < 5% ☐ (2) 5-10% ☐ (3) 11-25th ☐ (4)26-50th% ☐ (5) 51-75th ☐ (6) 76-95th% ☐ (7) >95th %	

System		Description of findings
Skin, mucous membranes	☐ 1 ☐ neg	
Head, eyes, neck	☐ 2 ☐ neg	
Ears, nose	☐ 3 ☐ neg	
Throat, teeth, mouth	☐ 4 ☐ neg	
Lymph nodes	☐ 5 ☐ neg	
Chest	☐ 6 ☐ neg	
Heart	☐ 7 ☐ neg	
Abdomen	☐ 8 ☐ neg	
Genitalia, pelvis	☐ 9 ☐ neg	
Musculoskeletal	☐ 10 ☐ neg	
Neurological	☐ 11 ☐ neg	
Development	☐ 12 ☐ neg	

Appendix 2: Ethics approval

L'Hôpital de Montréal pour Enfants
The Montreal Children's Hospital

UN HÔPITAL D'ENSEIGNEMENT - McGILL UNIVERSITY - A TEACHING HOSPITAL

INSTITUTIONAL REVIEW BOARD

November 1997

ANNUAL REAPPROVAL OF RESEARCH PROJECT

PROJECT NUMBER/TITLE: Dr. E. Mill's protocol: Viruses as Agents of Immune Injury in the Inuit

Date of original approval: September 27, 1993 Date of last approval: November 29, 1996

Total number of patients recruited at this site: a) since last approval _____ b) since original approval 156

Projected date of study completion Dec. 1998 Answer all of the following questions:

YES	NO	
X		Have there been any amendments to the proposed research plan or consent form? (If yes, ensure that the details have been provided to the IRB and that the revised consent form has been approved.)
	X	Are drugs or diagnostic reagents to be administered to human subjects?
	X	Are subjects exposed to any source of radiation?
	X	Are human tissues used? Source
	X	Are investigational medical devices or drugs used?
	X	Have any unexpected side effects, adverse events, or findings been noted? (If yes, describe the effects, adverse events, or findings.)
		Has the IRB been informed of the adverse events? Date
X		Written informed consent has been obtained and will continue to be obtained from all participants.

BRIEFLY DESCRIBE THE PROGRESS OF THE STUDY TO DATE. We have enrolled 104 montreal infants and 52 inuit infants. ½ of the infants have now completed the study. Laboratory investigations are underway T cell enumeration and mitogen proliferation are complete on 30 infants.

Please forward this information to Room A-327.

Madeleine Hollingdrake

Madeleine Hollingdrake
Administrative Secretary for
Institutional Review Board

THE INSTITUTIONAL REVIEW BOARD

A Montreal Children's Hospital Committee consisting of:

Julie D. Paquin, M.D., Chairperson	
Patricia A. Forbes, M.B.	Paediatrics
Andrée Prendergast	Nonaffiliated
Rev. D. Meloche	Pastorial Service
Susan Drouin, M.Sc.N.	Nursing
Michael Shevell, M.D.	Neurology
Neil Sweezey, M.D.	Respiratory
Kathleen Glass	Clinical Ethicist
Carol Schopflocher	Psychology
Robert Hutcheon, M.D.	Palliative Care

has reviewed the clinical research project entitled:

Viruses As Agents of Immune Injury in the Inuit

submitted by: Dr. E. Mills

and consider it to be within acceptable limits of clinical investigation solely from the point of view of medical ethics. The following conditions apply to the ethical approval of the above-named study:

1. Proof of ethical approval of the IRB includes the dated and signed IRB stamp on the consent form(s).

2. The study is approved for a period of one year from the date shown below.

3. Prior to the end of the one-year period, the investigator(s) must advise the Institutional Review Board of the number and status of patients enrolled in the study. We wish to be advised promptly of any significant adverse outcomes.

4. The investigator(s) must inform the Institutional Review Board should any changes be made to the study protocol and/or consent form.

5. The IRB reserves the right to examine your study data, including signed consent forms.

Julie D. Paquin

September 30, 1993

Julie D. Paquin, M.D., Ch.B., F.R.C.P.(C)
Chairperson
Institutional Review Board

Date

cc: June Paterson,
MCH Research Institute

Appendix 3: Informed consent form

L'Hôpital de Montréal pour Enfants
The Montreal Children's Hospital

UN HÔPITAL D'ENSEIGNEMENT • McGILL UNIVERSITY • A TEACHING HOSPITAL

INFORMED CONSENT
VIRUSES AS AGENTS OF IMMUNE INJURY

We would like to enroll your infant into a study to help us understand why some infants get very severe infections and others not. If we understand why this happens, then we can work toward preventing infections in these children.

Many factors are known to increase the chance of getting an infection. The immune system in the body helps to fight infection, but if the immune system is not working properly, then one is more likely to get an infection. We would like to assess the immune system of your child. Many viruses cause a change in the immune system which may last for a few weeks without causing harm to the person. Some infants may get infected with certain viruses at an earlier age than others, often without getting sick. These viruses may change the immune system so that when the child is infected with another virus or with a bacteria, they may get very sick. If your child gets sick in the next year we would like to test him\her to see if a virus caused the illness and to see if there was any change in the immune system.

If you decide to be a part of this study, your child will have an initial evaluation by a nurse and a pediatrician from the Montreal Children's Hospital at your home. A medical history and physical exam will be performed. Your child will then be seen at your home every three months for three more evaluations by the research nurse. At each visit your child will have a small amount of blood drawn from a vein (2 teaspoons). The blood will be tested for immune function, genes that determine the nature of your child's immunity to the germs that are commonly found in your community, and for many viruses. Each month you will receive a phone call from a research assistant who will ask you questions about the health of your child. Your infants medical charts will also be reviewed. If your child has symptoms consistent with a viral infection, the research nurse will come to your home to obtain a sample of the secretions from the nose to culture for viruses and a sample of the stools if your child has vomiting and diarrhea. No other tests will be done and the blood cells will not be banked for future use other than that related to immune function. If your child is sick, you should bring your child to the doctor as you normally would. The results of your child's tests will be compared with the other infants in the study including a group of Inuit infants.

The risks to your child of being a part of this study are small. They are the risks of having blood drawn, which may be some temporary slight bruising where the blood was drawn.

There are some immediate benefits to being a part of this study. We will be able to tell you if your child's immune system is working properly. We will be able to tell you if your child has been infected with certain viruses. We will be following your infant's health closely for the year he\she is in the study. Any illnesses your child gets during the the study period will be treated in the usual way by your doctor.

All of the medical information obtained from the study about your child will be confidential. Your child's name or picture will not be used in any publications, but the information obtained may be used.

Should there be any questions about the study, you can contact Teena Marie Johns, the research nurse on her beeper. Drs. Kate Culman, Gary Pekeles and Elaine Mills at the Montreal Children's Hospital are the investigators of the study and can also be contacted at (514) 934-4485. Should you have any questions about the health of your child you should continue to see your doctor.

Participation in this study is entirely voluntary. If you wish to no longer be a part of the study you can stop at any time without being penalized or having a change in the health care that you were getting before the study.

I, the undersigned, have read and understood the above explanations. I give consent for

_____ to participate in this study.
(child's name)

_____ _____
(parent's signature) (date)

_____ _____
(witness) (date)

INSTITUTIONAL REVIEW BOARD
approved for 12 months
from date below
Oct 31/97
signed

INSTITUTIONAL REVIEW BOARD
approved for 12 months
from date below
6/97
signed

L'Hôpital de Montréal pour Enfants
The Montreal Children's Hospital

UN HÔPITAL D'ENSEIGNEMENT • McGILL UNIVERSITY • A TEACHING HOSPITAL

INFORMED CONSENT-AMENDMENT

VIRUSES AS AGENTS OF IMMUNE INJURY

We would like to inform you of a modification to the study that your child is enrolled in. For the remainder of the home evaluations, the research nurse, Teena Marie Johns, will perform the full evaluation. This will include a history, physical examination, and blood procurement. A nursing student will accompany her to assist in holding your child during the blood drawing.

Teena Marie has extensive clinical experience from the Montreal Children's Hospital emergency room and will be able to provide a complete assessment. Any questions she has on her physical findings will be discussed with the research physicians at the Montreal Children's Hospital.

I, the undersigned, have read and understand the above changes to the study. I give consent for _____ (child's name)

to continue in the study.

_____ (parent's signature) _____ (date)

_____ (witness) _____ (date)

INSTITUTIONAL REVIEW BOARD
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from date below
Oct 31/97
signed

INSTITUTIONAL REVIEW BOARD
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from date below
June 6/97
signed

Appendix 4: Description of variables measured in the study population of Inuit infants in Iqaluit, December 1995 to November 1997

Variable	Details
Dependent[§]:	
Hospitalization rate	Number of hospitalizations for infections per year
Days hospitalized	Number of days hospitalized for infections per year
LRTI[*] rate	Number of LRTI per year
OM rate	Number of OM episodes per year
URTI rate	Number of URTI per year
Total RTI rate	Number of respiratory tract infections per year (LRTI + OM + URTI)
GI infection rate	Number of GI tract infections per year
"Other" infection rate	Number of "other" infections per year
Total infection rate	Number of total infections per year
Independent:	
Season at birth	0=summer (May-Oct); 1= winter (Nov-Apr)
Sex	0=male, 1=female
Maternal education	0=less than grade 8, 1=grade 8 and higher
Maternal smoking during pregnancy	0=no, 1=yes
Household smoking at enrolment	Number of people smoking in house
Household crowding at enrolment	Number of people living in house / number of rooms in house
Breastfeeding status at enrolment	0=no, 1=yes
Adoption status	0=no, 1=yes

[§] Complete information was obtained for each variable for all 46 infants except for maternal smoking during pregnancy where there were two missing values.

[*] Rates are expressed per year.

[¶] LRTI, lower respiratory tract infection; OM, otitis media; URTI, upper respiratory tract infection; GI, gastrointestinal.

Appendix 5: Correlation matrix (Pearson correlation coefficients > ±0.2 are shown) [§]

	Season at birth	Sex	Maternal education	Household crowding at enrolment	Household smoking at enrolment	Maternal smoking during pregnancy	Breast-feeding status at enrolment	Adoption status
Season at birth	1	-0.18	0.32	-0.19		-0.31		
Sex	-0.18	1				0.20		
Maternal education	0.32		1	-0.35		-0.20		
Household crowding at enrolment	-0.19		-0.35	1	0.56	0.21		
Household smoking at enrolment				0.56	1		-0.31	
Maternal smoking during pregnancy	-0.31	0.20	-0.20	0.21		1		
Breastfeeding status at enrolment					-0.31		1	-0.65
Adoption status							-0.65	1
Hospitalization rate*	-0.30		-0.27		0.21			
Days hospitalized	-0.20		-0.27					0.27
LRTI[¶] rate							-0.21	0.36
OM rate						-0.31	-0.21	0.30
URTI rate		-0.37						
Total RTI rate		-0.30				-0.24	-0.20	0.41
GI infection rate				-0.43	-0.21		-0.20	
"Other" infection rate	-0.32	0.46						
Total infection rate								0.25

[§] Complete information was obtained for each variable for all 46 infants except for maternal smoking during pregnancy where there were two missing values.

* Rates are expressed per year.

[¶] LRTI, lower respiratory tract infection; OM, otitis media; URTI, upper respiratory tract infection; GI, gastrointestinal.

Appendix 6: Investigation of confounding relationships

A) Season at birth, maternal education and household crowding with hospitalization outcomes

Outcome	Independent variable	Single linear regression coefficient (95% CI)	Multiple linear regression coefficient (95% CI)	Variables in model
Hospitalization rate[§]	season at birth	-0.64 (-1.26, -0.03)	-0.51 (-1.16, 0.15)	season at birth maternal education household crowding
	maternal education	-0.60 (-1.25, 0.04)	-0.42 (-1.13, 0.30)	season at birth maternal education household crowding
	household crowding	0.49 (-0.57, 1.55)	0.10 (-1.00, 1.20)	season at birth maternal education household crowding
Days hospitalized	season at birth	-4.89 (-12.48, 2.70)	-3.00 (-11.03,5.03)	season at birth maternal education household crowding
	maternal education	-7.04 (-14.77, 0.68)	-5.84 (-14.56, 2.87)	season at birth maternal education household crowding
	household crowding	5.20 (-7.49, 17.92)	1.00 (-12.46, 14.45)	season at birth maternal education household crowding

B) Breastfeeding, household crowding and smoking with GI rates

Outcome	Independent variable	Single linear regression coefficient (95% CI)	Multiple linear regression coefficient (95% CI)	Variables in model
GI rate	breastfeeding at enrolment	-0.31 (-0.79, 0.16)	-0.46 (-0.95, 0.02)	breastfeeding household smoking
		-0.31 (-0.79, 0.16)	-0.34 (-0.78, 0.09)	breastfeeding household crowding
		-0.31 (-0.79, 0.16)	-0.37 (-0.84, 0.10)	breastfeeding household smoking household crowding
	household smoking at enrolment	-0.13 (-0.31, 0.05)	-0.18 (-0.37, 0.00)	household smoking breastfeeding
		-0.13 (-0.31, 0.05)	0.03 (-0.18, 0.23)	household smoking household crowding
		-0.13 (-0.31, 0.05)	0.03 (-0.25, 0.18)	household smoking household crowding breastfeeding
	household crowding at enrolment	-1.13 (-1.86, -0.41)	-1.20 (-2.08, -0.31)	household crowding household smoking
		-1.13 (-1.86, -0.41)	-1.16 (-1.87, -0.45)	household crowding breastfeeding
		-1.13 (-1.86, -0.41)	-1.08 (-1.96, -0.20)	household crowding household smoking breastfeeding

[§] LRTI, lower respiratory tract infection; OM, otitis media; URTI, upper respiratory tract infection; GI, gastrointestinal.

[*] Rates are expressed per year

Appendix 7: Characteristics of infants from the study who completed follow-up (n=46) compared to those who withdrew (n=6)

A)

CATEGORICAL VARIABLES		Infants who completed follow-up (%); n=46	Infants who were withdrawn (%); n=6
Season at birth	Summer (May-Oct)	50	17
	Winter (Nov-Apr)	50	83
Sex	M	65	67
	F	35	33
Maternal education	Less than grade 8	37	67
	Grade 8 and higher	63	33
Maternal smoking during pregnancy	No	16	0
	Yes	84	100
Breastfeeding status at enrolment	No	46	50
	Yes	54	50
Adoption status	No	74	83
	Yes	26	17

B)

CONTINUOUS VARIABLES		Infants who completed follow-up; n=46		Infants who were withdrawn; n=6		Difference between two means
		Mean	SD	Mean	SD	
Household smoking at enrolment (smokers/house)		2.17	1.32	1.83	1.72	0.34
Household crowding at enrolment (persons/room)		1.01	0.31	0.83	0.20	0.18
Hospitalization rate[§]		0.66	1.08	1.93	2.10	-1.27
Pre-enrolment infection rate	Total RTI[*]	4.12	5.70	4.09	3.33	0.03
	GI	0.30	1.19	0	0	0.30
	Other	1.40	3.20	2.03	4.97	-0.63
	Total	5.14	5.62	6.12	7.44	-0.98

[§] Rates are expressed per year. [*] RTI, respiratory tract infection; GI, gastrointestinal.

Appendix 8: Simple linear regression coefficients for all independent variables[§]

	Regression coefficients (95% CI)								
	Hospital-ization rate*	**Days hospital-ized**	**LRTI[¶] rate**	**OM rate**	**URTI rate**	**Total RTI rate**	**GI infection rate**	**Other infection rate**	**Total infection rate**
Season at birth	**-0.64 (-1.26, -0.03)**	-4.9 (-12.48, 2.70)	-0.24 (-1.25, 0.77)	0.34 (-0.62, 1.30)	-0.08 (-0.87, 0.72)	-0.08 (-1.63, 1.47)	0.06 (-0.43, 0.54)	**-0.85 (-1.61, -0.09)**	-0.64 (-2.57, 1.29)
Sex	-0.13 (-0.81, 0.55)	-2.93 (-11.00 5.15)	-0.17 (-1.23 0.89)	-0.33 (-1.34, 0.68)	**-1.02 (-1.80, -0.24)**	**-1.60 (-3.15, -0.05)**	0.14 (-0.37, 0.65)	**1.29 (0.54, 2.03)**	0.01 (-2.03, 2.04).
Maternal education	-0.60 (-1.25, 0.04)	-7.04 (-14.77, 0.68)	-0.36 (-1.40, 0.68)	0.20 (-0.80, 1.20)	-0.13 (-0.96, 0.70)	-0.21 (-1.81, 1.39)	0.18 (-0.31, 0.68)	0.12 (-0.71, 0.95)	-0.01 (-2.10, 1.91)
Maternal smoking during pregnancy	0.27 (-0.44, 0.99)	1.41 (-2.63, 5.45)	0.32 (-0.73, 1.36)	**-1.39 (-2.70, -0.08)**	-0.47 (-1.60, 0.67)	-1.48 (-3.33, 0.38)	-0.17 (-0.86, 0.52)	-0.18 (-1.31, 0.95)	-1.98 (-4.35, 0.40)
Household smoking at enrolment	0.17 (-0.07, 0.41)	0.50 (-2.46, 3.45)	0.12 (-0.27, 0.50)	0.03 (-0.34, 0.40)	-0.18 (-0.48, 0.12)	-0.04 (-0.63, 0.55)	-0.13 (-0.31, 0.05)	0.19 (-0.11, 0.49)	0.029 (-0.71, 0.77)
Household crowding at enrolment	0.49 (-0.57, 1.55)	5.2 (-7.49, 17.92)	0.28 (-1.39, 1.95)	-0.26 (-1.85, 1.34)	-0.55 (-1.86, 0.77)	-0.18 (-2.75, 2.38)	**-1.13 (-1.86, -0.41)**	0.35 (-0.98, 1.67)	-1.61 (-4.78, 1.56)
Breastfeeding status at enrolment	-0.33 (-0.97, 0.32)	-4.21 (-11.87, 3.45)	-0.72 (-1.71, 0.27)	-0.66 (-1.61, 0.29)	0.48 (-0.31, 1.27)	-1.01 (-2.53, 0.51)	-0.31 (-0.79 0.16)	-0.15 (-0.95, 0.65)	-1.28 (-3.18, 0.63)
Adoption status	0.40 (-0.34, 1.12)	7.91 (-0.57, 16.39)	**1.36 (0.29, 2.44)**	**1.10 (0.05, 2.14)**	-0.29 (-1.19, 0.62)	**2.37 (0.76, 3.98)**	-0.06 (-0.50, 0.61)	-0.24 (-1.14, 0.68)	1.82 (-0.32, 3.96)

[§] Complete information was obtained for each variable for all 46 infants except for maternal smoking during pregnancy where there were two missing values.

* Rates are expressed per year.

[¶] LRTI, lower respiratory tract infection; OM, otitis media; URTI, upper respiratory tract infection; GI, gastrointestinal.