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What Factors Influence Parent Compliance with the Respiratory Syncytial Virus (RSV) Prevention Program?

by

Jing Xu

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled "What Factors Influence Parent Compliance with the Respiratory Syncytial Virus (RSV) Prevention Program?" submitted by Jing Xu in partial fulfilment of the requirements of the degree of Master of Science.

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Abstract

Background: Optimal prophylaxis against RSV requires monthly injections of palivizumab though the RSV season and precise compliance.

Objective: To determine compliance rates in an RSV prevention program, to describe characteristics of compliers compared to non-compliers, and to identify factors that influence parental compliance.

Methods: The Alberta Children's Hospital RSV program database was used to identify study participants and calculate compliance rate. Participants in the 2001-2002 RSV season participated in a telephone interview.

Results: The telephone interview response rate was 79.6%. Using 90% compliance as the definition of 'complier', 72.8% of families were compliers and 27.2% were non-compliers. Compliance was significantly higher among families of non-smokers (OR=3.3), and among those with household incomes greater than $50,000 (OR=3.2).

Conclusions: Families of non-smokers and those with higher incomes are more likely to be compliant. Compliance rates may be improved by understanding and addressing barriers to clinic attendance among lower income families and among smokers.

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Dedication

To my love - Bnbn

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CHAPTER ONE: INTRODUCTION

This chapter provides background information and the research rationale for the research purposes and questions. The background serves only as a brief introduction and a detailed literature review can be found in the next chapter.

1.1 Background

Respiratory Syncytial Virus (RSV) is a leading cause of hospitalization for respiratory tract infection during the first 2 years of life (Meissner et al., 1999). RSV is associated with substantial direct and indirect cost to the health care system and families (Joffe, Ray, Escobar, Black, & Lieu, 1999). A potential vaccine for RSV was developed and tested in clinical trials in the1960s, but the clinical trials revealed adverse events which led to death of 2 infants. Consequently, the most commonly manufactured prophylactic compounds for passive immunization are RSV-IVIG and palivizumab. Palivizumab has been found to reduce the risk of infant hospitalization and is currently the most effective method of passive immunization from RSV infection (The IMpact-RSV Study Group, 1998).

Since the fall of 1998, the Calgary Health Region (CHR) has offered an RSV prevention program. Parents of high risk infants are invited to have their infants receive palivizumab. High risk infants are defined by a gestational age of less than or equal to 32 weeks and less than or equal to 6 months of age with or without bronchopulmonary dysplasia (BPD) at the start of the RSV season, or who are less than or equal to 2 years of age with BPD and have required oxygen within the 6 months preceding the RSV season. The RSV prevention program for Southern Alberta (Red Deer South) and the British

Columbia corridor (Cranbrook, Golden and Kamploops) has been centralized at the Alberta Children's Hospital (ACH) in Calgary.

1.2 Research Rationale

The RSV prevention program is resource-intensive as palivizumab must be administered every 28 days (monthly) throughout the RSV season, and the season may be up to seven months in duration. Furthermore, albeit effective, palivizumab is expensive. Although there is no cost to eligible infants/families as it is covered by the provincial government health care plan, the average cost of one dose of palivizumab is USD900 (2003 dollars). Thus, the per patient cost of palivizumab ranges from USD900 to USD6,300 per RSV season, exclusive of the costs associated with personnel and administration for running the prevention program. If infants do not complete the prevention program as recommended, they may not be sufficiently protected against RSV and are at risk for RSV infection. Inpatient medical services for infants who contract RSV may be required despite previous passive immunization if an infant does not adhere to the monthly palivizumab schedule. Therefore, high compliance rates are critical to the reduction in risk of RSV infection and the success of the program.

Given the resources required for the program and the need for compliance, it is important to examine the compliance rates of the RSV prevention program and to understand characteristics of program participants (both infants and their families) that influence compliance. There are numerous theoretical frameworks that have been applied to explain health behaviour, including compliance to medical advice. The questionnaire upon which this study was based was originally developed based on the Health Belief

Model (HBM) which offers a framework to understand factors that influence parental compliance with the RSV prevention program. The HBM was initially developed to explain why people did not act on disease prevention or screening tests for the early detection of asymptomatic diseases. Later, the HBM was applied to the concept of compliance with prescribed medical regimens (Rosenstock IM, 1974).

The results from this study will contribute to understanding factors which may influence compliance to a pediatric RSV prevention program including participant characteristics, health beliefs, program satisfaction, information sources and geographical distribution of participants. The information from this study will be of value to those involved in health policy and program development and may inform strategies designed to improve program compliance. Furthermore, these data provide baseline information that can be used to assess the impact of changes in service delivery.

1.3 Research Purposes

This study is designed to (1) determine the compliance rate for the RSV prevention program in Calgary during the 2001-2002 season; (2) to describe the population/participants of the program with regard to compliance; and (3) to identify the factors that influence compliance with RSV prevention program.

1.4 Research Questions

1.4.1 Primary questions

1. What was the compliance rate for the 2001-2002 RSV prevention program in Calgary?

2. What are the characteristics of the program participants?

3. Do patient or family characteristics influence compliance with the RSV prevention program?

1.4.2 Secondary questions

1. Where did the parents obtain information about RSV and RSV prevention program?

2. Where is the preferred location of RSV prevention program for the participants?

3. What is the geographical distribution of the program participants?

CHAPTER TWO: LITERATURE REVIEW

This chapter reviews the literature relevant to this study from a clinical, epidemiologic, and sociological context, including RSV and its prevention, health behavior and compliance.

2.1 RSV

The following review of RSV consists of a general description of the disease, transmission of the disease, and the epidemiology and risk factors of the disease.

2.1.1 What is RSV

Respiratory syncytial virus (RSV), first identified in 1956 (Blount, Jr., Morris, & Savage, 1956), is a single-stranded enveloped RNA pneumovirus in the family *Paramyxoviridae* (Hall, 2001). Other family members include the mumps, measles, and parainfluenza viruses. RSV can be divided into two broad serological subgroups, strain A and strain B, which reflect the reactivity of different immunogenic viral envelope proteins detected by monoclonal antibodies (Ermak et al., 1998). RSV has two major surface glycoproteins: F and G proteins (Groothuis & Nishida, 2002).

RSV infects humans through the mucous membranes of the eyes, nose and mouth, and via the respiratory mucosa. Such infections are characterized by rhinitis, cough, and sometimes fever (Chavez-Bueno, Mejias, Jafri, & Ramilo, 2005; Sagai et al., 2004; Sato et al., 2005; Welliver, 2003). The replication of RSV is usually restricted to the upper airways; however, in vulnerable individuals (e.g., young infants and the elderly) who comprise approximately 30% of those infected, the virus may spread to the lower respiratory tract and cause serious disease (Domachowske & Rosenberg, 1999).

RSV is a seasonal virus, with peak rates of infection occurring in the cold season in temperate zones and in the rainy season in tropical climates, as temperatures fall. In Canada, the RSV season usually begins between October and December and ends the following March to May (Paes, 2003).

2.1.2 Epidemiology of RSV

RSV infection is one of the leading causes of hospitalization for infants in North America (Meissner et al., 1999). Most infants will develop an RSV infection during their first year of life and nearly one-fifth of infected infants will have RSV-associated symptoms, such as wheezing and cough. In Canada, RSV infections account for 5,800 hospitalizations annually (Langley et al., 1997). In the United States, an estimated 120,000 infants are hospitalized, and 200 infants die annually as a result of RSV infection (Shay, Holman, Roosevelt, Clarke, & Anderson, 2001; Simoes, 1999).

Several risk factors have been associated with the development of more severe disease, including: low socio-economic status (SES), crowded living conditions, indoor smoke, and a family history of asthma or atopy (Bradley et al., 2005; Carbonell-Estrany, Figueras-Aloy, & Law, 2004). In a prospective, multi-center, cohort study conducted by PICNIC (The Pediatric Investigators Collaborative Network on Infections in Canada) in 16 regions across Canada during 2 successive RSV seasons from 2000 to 2002, more than 5 inhabitants in household and more than 2 smokers at home were identified as risk factors by multivariate logistic regression analysis (Carbonell-Estrany et al., 2004).

In most cases, RSV infections are relatively mild and responsive to supportive therapies such as ventilation, which provide a measure of comfort and symptom relief without the use of medications. Some infants are at increased risk of developing severe forms of RSV as a consequence of compromised physical health, which may result in hospitalization, mechanically assisted ventilation, intensive care, or, in the worst case, death (Welliver, 2003). These high risk infants have been identified to include those with chronic lung disease (CLD) (Wang et al., 1996), congenital heart disease (CHD), immune deficiency or those born preterm (Carbonell-Estrany & Quero, 2001).

The direct costs for acute care of RSV infection are substantial. During the 2001-2002 RSV season (from Dec 18, 2001 to Jul 3, 2002), the total direct costs to the Calgary Health Region associated with 266 RSV admissions was $2,266,890, with an average cost per case of $8522. The total length of stay for these 266 cases was 1421 days, thus the average cost per day was $1595. These costs did not include the indirect cost such as time away from work to be with an ill child, or any costs associated with those whose RSV infection did not require hospitalization but may have required isolation at home.

2.2 Prevention of RSV

The ultimate aim of an RSV prevention strategy would be to develop a vaccine that produced effective immunity for those who are at high risk such as premature infants and the elderly (Paes, 2003). The definition of a *vaccine* (American Heritage Dictionaries, 2000) is: “A preparation of a weakened or killed pathogen, such as a bacterium or virus,

or of a portion of the pathogen's structure that upon administration stimulates antibody production or cellular immunity against the pathogen but is incapable of causing severe infection."

2.2.1 Immunization and vaccination

Although the terms "vaccination" and "immunization" are sometimes used interchangeably; they are nonetheless different (Janeway CA Jr., Travers P, Walport M, & Shlomchik MJ, 2001). Vaccination is the deliberate induction of adaptive immunity to a pathogen by injecting a vaccine into the body. In contrast, immunization is the deliberate provocation of an adaptive immune response by introducing either an antigen or antibody against a pathogen into the body. Immunization with an antigen is called active immunization to distinguish it from the injection of an antibody or immune serum into a naive recipient (an unimmunized individual), which is called passive immunization, as exemplified by palivizumab. Vaccination is a type of active immunization.

2.2.2 Active immunization for RSV in the 1960s

In the mid-1960s, the National Institutes of Health (NIH) in the United States sponsored clinical trials in infants using a formalin-inactivated, 100-fold concentrated, alum precipitated RSV vaccine in both Washington DC and California. The vaccine was administered as two or three intramuscular doses in 1 to 3 month intervals to preterm, high risk infants and children between the ages of 2 months and 7 years. There were no immediate health related side-effects. Nine months after the completion of the three-dose immunization schedule, vaccinated infants experienced RSV infections at rates similar to

control patients who had received a formalin-inactivated parainfluenzae vaccine. Eighty percent of those who were vaccinated and became infected, however, developed pneumonia or bronchiolitis and required hospitalization as compared to just 5% of control patients. Further, two of the vaccine recipients who were hospitalized with RSV died at the Children's Hospital in Washington, DC (Crowe, Jr., 1995; Kapikian, Mitchell, Chanock, Shvedoff, & Stewart, 1969; Kim et al., 1969). Consequently, active immunization for RSV in the 1960s was described as a failure. Valuable lessons were learned, however. First, vaccine-induced immune responses do not protect against natural RSV infection. Second, disease severity after vaccination markedly increased. The reason behind these observations has not been fully understood. (Paes, 2003).

Since this 1960 trial, the development of RSV vaccines has proceeded cautiously.

2.2.3 RSV Intravenous Immune Globulin (RSV-IVIG)

Although a safe and effective vaccine is not currently available, passive immunity using immunoglobulins (Ig) has been extensively investigated (Sastre, Melero, Garcia-Barreno, & Palomo, 2004; Subramanian et al., 1998; The IMpact-RSV Study Group, 1998; The PREVENT Study Group, 1997). RSV intravenous immune globulin (RSV-IVIG) is an intravenously administrated, human-derived polyclonal product containing a concentrated neutralizing antibody to RSV. RSV-IVIG was proven to be effective disease prophylaxis in two large-scale studies (Groothuis et al., 1993; The PREVENT Study Group, 1997).

In the first study, RSV-IVIG was administrated monthly throughout the RSV season to 249 infants with a mean age of 8 months. The study included infants with

bronchopulmonary dysplasia (BPD) (n=102), CHD (n=87), or who were born preterm (n=60) (Groothuis et al., 1993). There were significantly fewer RSV hospital admissions (p=0.02) and fewer RSV hospital days (p=0.02) in the group who received the high dose (750 mg/kg RSV-IVIG) compared to controls. The second study was a randomised, double-blind, placebo-controlled trial involving 54 centres and 510 infants in the United States between 1994 to 1995 (The PREVENT Study Group, 1997). The intervention group included 250 infants with BPD, who either were or were not premature, who received high-dose RSV-IVIG (750 mg/kg) every 30 days. The control group included 260 infants who received a placebo of 1% albumin every 30 days. Treatment with RSV-IVIG not only reduced hospitalization by 41%, but also reduced the severity of RSV illness. Of note, the PREVENT study group was funded by MedImmune, (MedImmune, Inc, Gaithersburg, MD), which should be considered in interpreting the findings.

Although monthly infusions of RSV-IVIG have been shown to be effective in the prevention of RSV hospitalizations, the routine use is limited by a few factors. RSV-IVIG has to be intravenously administered under medical surveillance, which is time-consuming. Further, it is a blood-derived product, which introduces the possibility of transmission of infectious pathogens. Finally, its high viscosity, together with the necessary large-volume dosage of 750 mg/kg, has the potential to precipitate fluid overload in infants with BPD or CHD, which can lead to severe consequences (Simoes et al., 1998). These concerns regarding the use of monthly RSV-IVIG infusions have led to the search for better prophylaxis, which has resulted in the most recent achievement in RSV prevention: palivizumab.

2.2.4 Palivizumab

2.2.4.1 What is palivizumab

Experimental trials have focused on the development of an antibody specific to the F protein which is conserved among all RSV strains. This focus has led to the invention of palivizumab (trade name is Synagis®) (Hall, 2001).

Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, is currently used to immunize high-risk infants to protect against RSV infection. The generic name, palivizumab, is derived from 'pali' meaning palliation, 'viz' for virus, 'u' for humanized, and 'mab' for monoclonal antibody.

Palivizumab was first developed in mouse models (Young, 2002). It has been suggested that palivizumab neutralizes RSV by preventing the RSV fusion domain from binding to the host cell membrane or by inducing a structural change in the fusion domain. The detailed mechanism is unclear (Johnson et al., 1999).

2.2.4.2 Efficacy of palivizumab

The efficacy of palivizumab has been well documented and consistent across many study designs. Efficacy has been demonstrated in *in vitro* studies, in animal models, and in clinical trials. In one *in vitro* study, palivizumab was shown to be effective against more than 500 clinical strains of RSV (Saez-Llorens et al., 1998). In a separate study, palivizumab was shown to be 20 times more active than RSV-IVIG in an RSV neutralization assay (Johnson et al., 1999).

Trials have been conducted for palivizumab to determine its clinical pharmacological, pharmacokinetic effects, and to identify any adverse reactions as well

as to assess safety and efficacy. There are four phases of clinical trials. Phase I studies are designed to establish the effects of a new drug in humans, which are usually conducted on small populations of healthy humans specifically to determine a drug's toxicity, absorption, distribution and metabolism. Phase II is to test for safety and efficacy in a slightly larger population of individuals who are afflicted with the disease or condition for which the drug was developed. The third phase and last pre-approval round of testing of a drug is conducted on large populations of afflicted patients. Phase III studies usually test the new drug in comparison with the standard therapy currently being used for the disease in question. The results of these trials usually provide the information that is included in the package insert and labeling. After a drug has been approved by the governing authorities such as Food and Drug Administration (FDA) and Health Canada, phase IV studies are conducted to compare the drug to a competitor, explore additional patient populations, or to further study any adverse events.

The safety, tolerance and pharmacokinetics of palivizumab has been primarily established in phase II trials in premature infants and infants with BPD (Saez-Llorens et al., 1998; Subramanian et al., 1998). In these phase II trials multi centred studies in the USA, Costa Rica and Panama, RSV-infected premature infants (born at less than 35 weeks gestational age) who were less than 6 months of age at the time of the trial and infants with BPD who were less than 2 years age at the time of the trial were administrated 15 mg/kg of palivizumab intramuscularly every month. This dose was determined to be adequate to sustain a preventive serum level (40 ug/ml) against RSV. Although between 0 and 15% of the infants who participated in the study developed transient low levels of anti-palivizumab antibodies, no further adverse effects were

observed. Only 3% of the patients assigned to the low dose group (5-mg/kg) developed an RSV illness that required hospitalization. Palivizumab is absorbed slowly after intramuscular administration, with the maximum serum concentration occurring after 5 days. The mean serum elimination half-life of palivizumab in infants less than 2 years of age is 20 days, varying from 19.3-26.8 days.

In the late 1990s, the IMpact RSV study group conducted the largest, international multi-center, randomized, double-blind, placebo-controlled trial of RSV prophylaxis in 139 centres across the United States, the United Kingdom and Canada (The IMpact-RSV Study Group, 1998). Premature infants (born at less than 35 weeks gestational age) who were less than 6 months of age prior to study entry and infants who were less than 24 months of age prior to study entry and who had BPD requiring supportive medical treatment for 6 months at the time of enrolment were randomized to receive either five monthly injections of 15 mg/kg of palivizumab (n=1002) or placebo (n=500). Infants treated with palivizumab had an overall reduction of 55% in the number of hospital admissions resulting from RSV infection as compared to the control group ($p<0.001$). A subgroup analysis showed a similar 59% reduction in hospitalizations for infants with BPD (n=762), a 78% reduction for all infants without BPD (n=740), a 47% reduction for infants born at less than 32 weeks gestational age (n=1111), and an 80% reduction for preterm infants born between 32 and 35 weeks gestational age (n=373). This trial confidently established the efficacy of palivizumab in the prophylaxis of RSV. The clinical benefits observed with this palivizumab trial far surpassed those of the RSV-IVIG trial (The PREVENT Study Group, 1997).

Following the IMpact trial, which was considered a gold standard because of its rigorous methodology, palivizumab received approval from the United States' Food and Drug Administration (FDA) in June 1998 and was recommended by the American Academy of Pediatrics for: 1) infants born at less than 32 weeks gestational age without CLD, 2) for infants less than 6 months of age at the start of RSV season, and 3) for infants less than 2 years of age with CLD who required medical support for 6 months prior to the start of RSV season (American Academy of Pediatrics Committee, 1998b). These criteria were soon adopted by the Canadian Paediatric Society (A joint Canadian Paediatric Society statement with the Fetus and Newborn Committee, 1999).

Following the adoption of these criteria, several post-market studies were conducted. In a large Spanish trial, RSV hospitalization was found to be reduced by 70% in infants born at 29-32 weeks gestational age who received palivizumab as compared to non-prophylaxis recipients (4.0% versus 13.3%) (Pedraz, Carbonell-Estrany, Figueras-Aloy, & Quero, 2003). In a Canadian study of 444 infants with a mean gestational age of 29.4 weeks, only 2.0% of infants receiving palivizumab were hospitalized due to RSV infection (Oh et al., 2002). In addition to reducing hospitalization, palivizumab was well-tolerated and had few very mild side effects. (MacConnachie, 2000)

2.2.4.3 Cost of palivizumab

In spite of the high efficacy, the high cost of palivizumab prophylaxis has been identified as a substantial concern (American Academy of Pediatrics Committee, 1998a) and consequently guidelines for use are stratified by risk (Law et al., 2004).

Each patient requires a minimum of five monthly doses dispensed as single, 50 mg or 100 mg vials, and costs are approximately USD$4,500 per patient per year. A few studies have been undertaken to evaluate the cost effectiveness of palivizumab, however, these focused on the direct costs, such as hospital-based charges which may vary significantly between institutions, and they ignore the indirect costs and productivity losses incurred per patient.

2.3 Theoretical Framework for Health Behavior

Theories of health behavior provide explicit statements of proposed structural and psychological processes that influence individual behavior. Several theories and conceptual models have been proposed to both explain and predict the health behavior of individuals. Three well known models relevant to this study and a rationale for selection of the HBM are discussed below.

2.3.1 Social Cognitive Theory (SCT)

In 1977, Albert Bandura, a psychologist at Stanford University, introduced the concept of perceived self-efficacy in the context of cognitive behaviour modification and in 1986, he proposed Social Cognitive Theory (SCT) in his book *Social Foundations of Thought and Action: A Social Cognitive Theory* (Bandura A, 1986).

According to SCT, behavioral change depends on factors related to environment, people and behavior which constantly influence one another. The theory posits that people plan courses of action, anticipate the likely consequences of these actions, and set goals and challenges for themselves in order to motivate, guide and regulate their actions. In this process, there are three types of expectancies: (a) situation-outcome expectancies,

in which consequences are cued by environmental events without personal action; (b) action-outcome expectancies; in which outcomes flow from personal action and (c) perceived self-efficacy. Self-efficacy is concerned with an individual's belief in his/her capability to perform a specific action required to attain a desired outcome (Conner & Norman, 1995).

SCT emphasizes the interactions between an individual's cognition and his/her behavior through processes such as self-efficacy and outcome expectancies (Akers RL & Lee G, 1996; Clark et al., 1988).

2.3.2 Transtheoretical, or Stages-of-Change (SOC), Model

The Transtheoretical Model of Behavior Change was developed by Dr. James Prochaska and his colleagues of the University of Rhode Island Cancer Prevention Research Center in 1983. One of the model's major contributions is the recognition that behavior change unfolds through a series of stages; therefore, it is also called the Stages-of Change (SOC) Model (Prochaska & DiClemente, 1983).

The SOC Model suggests that cognitive/behavioral change progresses as an individual moves through the following stages: precontemplation (benefits of lifestyle or behaviour change are not being considered); contemplation (starting to consider change but not yet begun to act on this intention); preparation (ready to change the behavior and preparing to act); action (making the initial steps toward behavior change); and maintenance (maintaining behaviour change while often experiencing relapses). Recent revisions of the SOC model further categorize the precontemplation stage into an unaware stage (no idea that there is problem behavior), an uninvolved stage (knows that

the behavior needs to be changed but does not perceive the problem as salient), and an undecided stage (considering the positive and negative consequences of the behaviour change) (Prochaska & Velicer, 1997).

The SOC Model has been used extensively to design programs that promote healthy lifestyle choices by promoting behavior change in areas such as smoking, diet, alcohol and substance use, and eating disorders (Prochaska et al., 1997).

2.3.3 Health Belief Model (HBM)

The Health Belief Model (HBM) was developed in the early 1950s by a group of social psychologists at the United States Public Health Services in an attempt to understand why people would not accept disease prevention or screening tests for the early detection of asymptomatic diseases. Later, the HBM was applied to the concept of compliance with prescribed medical regimens (Rosenstock IM, 1974).

The HBM combines individual perceptions, personal characteristics and situational variables to predict the likelihood of taking preventive health action. Four dimensions lie at the core of the HBM: (1) a person's belief about his/her susceptibility to a problem - perceived susceptibility; (2) the severity of a problem or illness - perceived severity; (3) the benefits of a preventive action - perceived benefits; and (4) the barriers to the desired action - perceived barriers. An internal or external stimulus that triggers the decision-making process labeled "cues to action" has been subsequently added to the HBM. In the presence of "cues to action" the likelihood of preventive action is the result of perceived benefits minus perceived barriers to the action (Janz & Becker, 1984).

Among the four dimensions of HBM, perceived barriers have been shown to be the most dominant predictor of behavior, and perceived severity to be the least helpful in understanding behavior, across a variety of study designs and behaviors (Janz et al., 1984).

The HBM has been a major organizing framework for explaining and predicting the acceptance of health and medical care recommendations, and has been used in variety of study designs, especially in regards to preventive health behaviors.

2.3.4 The Relevance of the HBM as a Theoretical Framework for This Study

The three theories, SCT, SOC and HBM, have considerable overlap. Although labelled differently in each theory, each theory incorporates some element of: an intent to behave or act; environmental constraints impeding a behavior; beliefs regarding a behavior; perceived threats to health; individual skills; outcome expectancies related to a behaviour or action; self-confidence with respect to the behavior; and stages and processes of change (Kretzer & Larson, 1998; Morrow, Hickok, & Burish, 1994).

The Health Belief Model is the most widely used and respected framework for compliance studies (Roden, 2004; Trick, 1993). For the current study, the HBM is the most relevant behavioral model as the theoretical framework for the following reasons: (1) The core of Social Cognitive Theory is self-efficacy. Over the years, the notion of self-efficacy has been adopted as a part of most health behaviour theories (Elder, Ayala, & Harris, 1999), including the HBM as part of the *perceived barriers* dimension. Thus,

the core component of SCT is no longer truly independent from other theories as the key component has proven to be an essential for all major models.

(2) The transtheoretical, or Stages-of-Change (SOC) Model was created for and has been mainly applied to smoking cessation behaviors. The SOC model has dissected the decision-making process for such behaviors into many steps and with great detail (Lawrence, Aveyard, Evans, & Cheng, 2003). The preventive behavior being explored through the current study is in regards to keeping medical appointments for one's own infant. This behaviour requires less self discipline and behaviour change than smoking cessation or maintaining a healthy diet. The staged approach to behaviour change, including consideration of issues of addiction and dependence, differs in concept from this study where the focus relates to the initiation of a health promotion behaviour for a vulnerable infant and a parent.

2.4 Palivizumab Compliance

Compliance describes willingness to follow a prescribed course of treatment (American Heritage Dictionaries, 2000), or the degree to which a person adheres to advice (Evans CE & Haynes RB, 1990). For children's treatment protocols or health programs such as immunization, it is important to have the adherence of both children and their parents (Fotheringham & Sawyer, 1995). However, as the RSV prevention program is established to serve high-risk infants less than 2 years old, the compliance with the program depends on infants' caregivers.

As recommended by American Academy of Pediatrics Committee and Canadian Pediatric Society, palivizumab must be administered every 30 days by intramuscular injection throughout the RSV season to maintain the serum concentration at a level sufficient to provide protection against RSV (Fenton, Scott, & Plosker, 2004; Oh et al., 2002; Paes, 2003). Consequently, the effectiveness of palivizumab in the clinical setting is dependent on compliance with this regimen of monthly injections. As the RSV season is usually from late fall to early spring, five doses are typically required.

There are two published studies that have particular importance to this study. One was conducted in Ohio, United States in 1998 (Langkamp & Hlavin, 2001) which was the first compliance study on palivizumab and was based on the Health Belief Model; the other was conducted in Canada by COMPOSS group in 2000 (Oh et al., 2002) which was a comprehensive multi-centered palivizumab utilization and outcomes study that used a similar concept of compliance to this study.

In the Langkamp study, a 2-page questionnaire was mailed out to the families of 385 infants who met criteria to receive palivizumab in two outpatient clinics after the 1998-1999 RSV season, with a response rate of 55%. The survey instrument included questions based on Health Belief Model, use of health-care services and demographic characteristics. Based on a chart review, the total compliance rate to the palivizumab program was 78% which was defined as receipt of all recommended doses of palivizumab, regardless of time interval between injections. Survey results showed the strongest predictor of compliance was parent's perception that palivizumab would protect their child from RSV (67% in compliant group vs. 48% in noncompliant group). There

was no difference between the compliant and noncompliant families in distance traveled to clinic, out-of-pocket expenses for palivizumab, and whether someone who smoked lived in the home; but noncompliant families had more difficulty with transportation. The information on family income was not collected, but all families had private insurance or Medicaid that would have covered at least some of the cost for palivizumab. As the first study of its kind, it provided valuable information on factors that influence compliance, however, the generalizability of the results was compromised because there was a significant difference of response rates between compliers (84%) and noncompliers (70%), and because the response rate was only 55%.

In the COMPOSS group study, there were eighteen (18) sites in six (6) Canadian provinces which included both neonatal and pediatric tertiary care facilities and community settings. It was a prospective, observational study that enrolled 480 infants at the beginning of 1999-2000 RSV season of which 444 infants (92.5%) were followed up successfully until the end of the RSV season. All infants enrolled by their physician through the 1999-2000 Special Access Programme of the Canadian Therapeutic Products Programme to receive palivizumab prophylaxis were eligible for the study. Information on palivizumab compliance, clinical respiratory events and infant's characteristics were obtained through chart reviews and monthly telephone follow-up with parents/caregivers. With palivizumab prophylaxis, low hospitalization rates (2.4%) from RSV infection were found, which was consistent with previous studies. Regarding palivizumab utilization, not only the total number of doses each infant received was considered, the time intervals between palivizumab injections were also calculated. Product guidelines indicate that

palivizumab injection should be given 30 ± 5 days after the previous dose, and the majority of doses (77%) were delivered within the timeframe. The clinical results from this multi-centered study provided a comprehensive picture of palivizumab utilization and outcomes in Canada which was consistent with other palivizumab studies around the world. The concept of counting the days of injection intervals was used to define compliance for the author's study which will be explained in next chapter.

2.5 Gaps in the Literature

There was no information on the compliance rate of the RSV prevention program since its inception in Calgary, and no study has applied the definition of compliance as stringently as in this study. The study would be able to determine the compliance rate and to better understand the population the program served during 2001-2002 RSV season and to identify the factors which may influence compliance. The information from this study will be of value to those involved in health policy and program development and may inform strategies designed to improve program compliance. Furthermore, these data provide baseline information that can be used to assess the impact of changes in service deliver.

CHAPTER THREE: METHODOLOGY

This chapter describes the study design and methods, including a definition of the study population and the sample, definitions of compliance and complier, data collection procedures, questionnaire development, and data analysis strategies. Ethical considerations are also included.

3.1 Study Design

This is a descriptive study of the experience of infants' primary caregivers with the RSV prevention program at the Alberta Children's Hospital (ACH).

3.2 Study Population and Sample

3.2.1 Study population

The study population included all of the families with infants who participated in the RSV prevention program during the 2001-2002 RSV season in Calgary, Alberta. To be eligible for the RSV prevention program at the Alberta Children's Hospital (ACH), infants must have met one of the following criteria:

(1) Infants born at less than or equal to thirty-two (32) gestational weeks and who were less than or equal to six (6) months of age (with or without BPD) at the start of the RSV season;

(2) Infants less than two (2) years old with BPD who required respiratory support with oxygen within the six (6) months preceding the RSV season; or

(3) Approved special cases, such as infants from multiple births or infants with cystic fibrosis.

The study population included both the infants who participated in the Calgary 2001-2002 RSV prevention program and their primary caregivers.

3.2.2 Study Sample

The study sample consisted of members of the study population minus those who met the exclusion criteria, as follows.

Exclusion criteria:

(1) the eligible infant was deceased;

(2) the primary caregiver of the eligible infant was unable to respond to the telephone questionnaire in English;

(3) eligible infants who received one dose of palivizumab at the end of the RSV season, therefore were not required to return for repeat injections. For example, an eligible infant born at the end of the RSV season would receive one injection of palivizumab before being discharged from the birth hospital. In this situation, the primary caregiver would not be required to return to ACH for repeat palivizumab injections. Therefore, questions regarding factors influencing the primary caregiver's decision to return to the ACH for future palivizumab appointments were not applicable.

3.3 Definition of Compliance and Complier

In most immunization or vaccination program compliance studies, compliance is defined as whether or not the study subjects received the intervention, such as the injection, without any consideration of the timing of the intervention (Fotheringham et al., 1995). For instance, if the patient received the intervention two weeks late, he or she

was still considered compliant. As timing is critical to the effectiveness of palivizumab, a more stringent definition of compliance was developed for this study.

3.3.1 Definition of compliance

Compliance to palivizumab injections was defined as a percentage, calculated as the number of actual days infants were protected divided by the maximum possible protected days, using 28 days as a standard interval.

3.3.2 Palivizumab injections interval at the ACH

As previously reviewed, it is universally recommended that palivizumab be administered every 30 days during the RSV season to maintain the serum concentration at a level sufficient to provide protection against RSV infection. In addition, the RSV clinic at the ACH was open two days per week (Mondays and Wednesdays) during RSV season. It was therefore decided by the RSV clinic staff that the best scheduling system for appointments was every 4 weeks, i.e. every 28 days. It was felt that it would be easier for the primary caregivers to remember a scheduled appointment on a fixed day (e.g. Monday) every four weeks or 28 days, as opposed to every 30 days. This scheduling practice did not compromise the effectiveness of palivizumab.

3.3.3 An example of calculating the compliance

The 2001-2002 RSV season was defined as occurring between December 18, 2001 to June 3, 2002, for a total of 168 days. Compliance was calculated as illustrated in the following example: an infant was considered eligible for the RSV Prevention program

and received the first injection on December 18, 2001. This infant was scheduled to receive palivizumab every 28 days following the first injection, i.e. on January 15, February 12, March 12, April 9, and May 7, 2002. There was no injection scheduled in June as the 2001-2002 RSV season ended on June 3, 2002. If this infant received all of the five injections exactly on the scheduled days, then the infant was protected for the entire 2001-2002 RSV season (168 days) and compliance would be 100%. If this infant stopped participating in the RSV Prevention program after receiving the third injection on Feb 12, 2002, then the infant was protected for only 84 days and compliance would be 50%. If the infant received all of the following five injections but two injections were late (one by seven days and the other by one day), then the infant was protected for 160 days (168 minus 8) and compliance would be 95%.

As a second example, if an infant was born after the 2001-2002 RSV season began, in April 2002 for instance, the infant was still eligible for the RSV Prevention program. If the infant was scheduled to receive injections on April 16 and May 14, 2002, the maximum period the infant could be protected within the 2001-2002 RSV season was 49 days. If the infant received the two injections on the scheduled days, compliance would be 100%. If the infant was on time for the first injection but eight days late for the second injection, the infant was protected for 41 days (49 minus 8) within the 2001-2002 RSV season and compliance would be 84%.

As a final example, if an infant moved out of Alberta after one or more injections and was thus no longer eligible for the RSV prevention program in Calgary, then the maximum possible protection days is calculated from the date of the infant's first injection to the date of the last injection before the infant moved.

3.3.4 Definition of Complier and Non-complier

Based on clinical importance, the paediatricians on the research team predetermined the definition of 'compliant' as ninety percent (90%) or greater.

3.4 Data Collection

The study data were obtained through the RSV prevention program database and through telephone interviews.

3.4.1 Database review

The RSV prevention program database was set up by the program nurses to record basic information on the participating infants, which included: date of birth, birth weight, gestational age, family and medical history, and the time, dosage and side-effects of each palivizumab injection.

The database was reviewed with the purpose of retrieving the following information:

(1) The number of families who brought their infants to participate in the 2001-2002 RSV prevention program and their contact information;

(2) The dates of injections and the doses of palivizumab actually received by each infant;

(3) Infant information, including birth weight, birth outcome and gestational age.

In summary, the program database was used to identify study participants, retrieve basic information about each study participant as well as to determine the length of the interval between each palivizumab injection. Compliance rates were then calculated and participants were classified as either a non-complier (<90%) or a complier (>=90%).

3.4.2 Telephone interview

The primary caregivers of infants who participated in the 2001-2002 RSV season were contacted by nurses for a questionnaire based telephone interview to obtain demographic information and information regarding factors related to the RSV program. Questions related to compliance or non-compliance were developed using the Health Belief Model as a framework and based on the work of Langkamp (Langkamp et al., 2001). Three nurses from the RSV prevention program conducted the telephone interviews using a structured format and closed ended questions. All three nurses were knowledgeable about RSV and palivizumab and had been employed by the RSV clinic. The nurses were chosen to conduct the telephone interviews as a means to increase the response rate, as the nurses were acquainted with most of the eligible families. All nurses were trained in interview techniques. A database was created to store the information collected from these interviews.

The primary caregivers of the eligible infants were interviewed. It was planned that if there was more than one eligible infant in a family, such as twins, a separate questionnaire would be used for each infant, while the demographic information of the primary caregiver would only be answered once. During the study however, it was found that all but one primary caregiver responsible for more than one eligible infant indicated that they had the same level of concern about the health condition of each of their children and thus only one questionnaire was needed for each family. For the particular family where the primary caregiver (the mother) worried unequally about her twins'

health conditions, the data was analyzed with reference to the infant with the worse condition.

Up to six attempts were made to reach each of the eligible families. If multiple attempts were required, at least one attempt was made in the morning, one in the afternoon and one in the evening. The outcomes of the calls can be categorized as below, followed by the corresponding actions:

(1) Complete: The respondent completed the entire questionnaire. Do not call again.

(2) Refused: The respondent explicitly refused to participate. Do not call again.

(3) Soft Callback: The respondent gave an estimated time to call back. Call back.

(4) Hard Callback: The respondent gave a specific time to call back. Call back.

(5) Partial Complete; Answering Machine; No Answer; Busy Tone: Call back.

(6) Wrong Number: The respondent did not live there. If a new number is given, try again. If no new number was obtained, record as lost to follow-up. The phone directory and medical records were searched in an effort to locate those who had moved.

3.4.3 Questionnaire development

The questionnaire development determined what information would be collected through telephone interviews.

3.4.3.1 Reference questionnaire from the United States

The first published compliance study on palivizumab was conducted in Ohio, United States by Langkamp DL and Hlavin SM and published in 2001 (Langkamp et al., 2001). The authors provided permission to use their questionnaire as a guideline for developing the questionnaire for the current study. The Langkamp questionnaire was two

pages in length. Modifications were made when designing the questionnaire for the current study for the following reasons. Firstly, in the United States palivizumab is only offered to families who are covered through private insurance or Medicaid for at least some of the cost for the medication and its administration. In Canada the RSV prevention program is offered at no cost to all eligible infants. Therefore, questions on the Langkamp questionnaire regarding direct costs, indirect costs or perceived costs were revised. Secondly, in the United States there is a home visitation program, which is offered through private companies, that enables palivizumab to be administered at the infant's residence by a nurse. The RSV prevention program offered at the ACH is centralized and almost all palivizumab injections are given at the ACH. In a few circumstances, an infant may receive their first injection before they are discharged from their birth hospital. Currently, there is no service in Calgary that allows palivizumab to be administered at an infant's home. Questions regarding program delivery were therefore modified. Finally, the Langkamp questionnaire did not collect any demographic information, information regarding the smoking status of residents at the infant's home, daycare attendance, program satisfaction, and information sources. Questions designed to collect this information were added to the questionnaire for the current study.

3.4.3.2 Pilot telephone interview

The first ten (10) successful telephone interviews were used to pilot test the questionnaire to determine if the questions were asked in a clear, easy-to-understand way both in content and wording. The pilot process resulted in the modification of a question. The original question was: "In your opinion, how much do you know about RSV

infection? There was confusion to the primary caregivers with regards to when it referred to: at the time of enrolment or at the end of the program? To clarify the confusion, this question was divided into two in the final questionnaire: "In your opinion, how much did you know about RSV infection before your infant had his/her first injection?" and "In your opinion, how much did you know about RSV infection after your infant had his/her last injection?" The same adjustments were made to the question regarding palivizumab. The research team agreed to include data from the ten pilot interviews in the final analysis due to minimal changes in the final questionnaire.

3.4.3.3 Questionnaire structure scan

The final questionnaire was eight pages (see Appendix 1) and could be completed in 15 to 20 minutes. The questionnaire consisted primarily of yes-or-no questions and 4-point Likert scale questions using "1=not at all", "2=a little", "3=somewhat" and "4=a great deal". All questions were referred to the time frame of "during the winter of 2001-2002".

Part One: Four dimensions of Health Belief Model

The four dimensions of the Health Belief Model (HBM) include: 1) perceived susceptibility; 2) perceived severity; 3) perceived benefits; and 4) perceived barriers. Although questions were asked to reflect all domains of the HBM, the focus was on *perceived barriers,* as this construct has been demonstrated to be the most dominant factor of the HBM across variety of study designs and behaviors (Janz et al., 1984).

There were one to ten questions to address each of the elements of the HBM.

Sample questions designed to address the first three dimensions of the HBM included: “In your opinion, how susceptible is your infant to general illness?”; “How great was your infant’s risk of getting RSV?”; “How much did you feel the health of your infant’s lungs would be worse if your infant got RSV infection?”; and “How much did you feel that palivizumab would help protect your infant against RSV infection?” Sample questions to address perceived barriers included: “How much did you worry about your infant having side-effects from palivizumab?” and “How much difficulty did you have with transportation for your palivizumab appointment?”

Part Two: Knowledge of RSV and palivizumab (based on self-report)

The primary caregivers were asked about their knowledge of RSV and palivizumab before and after participating in the RSV prevention program. A sample question was: “In your opinion, how much did you know about palivizumab before your infant had his/her first injection?”

Part Three: Use of health care services for respiratory illnesses during the RSV season

A sample question to understand health care service utilization was: “During the winter of 2001-2002, did your infant go to an emergency department for any respiratory or breathing concerns?”

Part Four: Information sources about RSV and RSV prevention program

A sample question to explore information sources was: “Where did you get the information about palivizumab? Please tell me all that apply from the following list.”

Part Five: Preferred location of palivizumab injections

A sample question to understand preferences regarding the RSV program was: "Where would you prefer the palivizumab injections to be given to your infant? Please choose from the following list."

Part Six: Demographic information

Standard demographic information was obtained on the primary caregiver's age group, educational level, marital status, ethnic background and household income.

Part Seven: Other factors

The final questionnaire also included questions regarding other related factors, such as program satisfaction, program convenience, palivizumab cost estimation, receiving other baby shots, daycare attendance and whether there is a smoker at home. This last question was added because passive exposure to tobacco smoke has been identified as a risk factor for RSV (Paes, 2003).

3.5 Sample Size

Based on Langkamp's previous work, it was anticipated that 67% of primary caregivers who complied believed that the immunization was effective, compared to 48% of those who did not comply. With an alpha of 0.05 and power of 80%, and an estimated 80% response rate, 50 participants per group would be required to detect as significant a 14% difference in health attitudes between compliers and non-compliers.

3.6 Data Analysis

Data obtained from the RSV prevention program database and responses to the telephone interviews were first entered into Microsoft Excel for simple calculations, sorting and graphing. The data were then exported to SPSS 12.0 (SPSS Inc., Chicago, IL, USA) for statistical analysis.

Two denominators were used for calculations: the first was the total number of infants, which was used when analysing infant characteristics; the second was the total number of families, which was used when analysing primary caregiver characteristics and HBM related questions.

Descriptive analysis with means and proportions were used to characterize study participants overall and to describe differences between compliers and non-compliers (e.g. infant's gestational age and primary caregivers' socio-demographic profile). Continuous variables such as infant's gestational age and birth weight were described using the mean, median and standard deviation. Most variables were recoded into dichotomous variables based on frequency and clinical importance. Categorical variables were described using frequencies and percentages, and χ^2 tests were used to detect significant relationships between the outcome variable—compliance—and all other independent variables. Fisher's exact test was used in place of the χ^2 test for those variables that had a cell count less than 5 in the corresponding 2x2 table. For the multivariate analysis, logistic regression using the forward enter approach was carried out to identify factors that influence compliance. Variables that had $p<0.05$ in χ^2 tests were eligible for inclusion into the regression model. Potential confounders and interactions were examined by logistic regression.

Logistic regression techniques were used to analyze this data because the outcome variable – complier Yes/No (i.e. complier or non-complier) – was dichotomous not continuous. Thus the dependent variable violated the assumptions of multiple regression such as data normality, linearity of relationships, interval data or data whose range is not truncated. Logistic regression is appropriately used when the dependent variable is dichotomized (or categorical) and allows for the independent variables to be of any type. Furthermore, logistic regression yields odds ratio (OR) which is a measure of effect size, or the magnitude of the relationships between variables which can be useful to program planners, policy and decision makers as well as clinicians.

All tests were two-tailed, with p values of less than 0.05 considered as statistically significant. Missing data were omitted and the numbers of the corresponding variables are reduced and noted in data presentation and analysis.

To address the secondary research question: "How do the program participants distribute geographically?" A Geographic Information Systems (GIS) software, ArcView 8.1, was used for all mapping functions.

3.7 Ethical Considerations

This study was carried out in compliance with the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (Tri-Council Policy Statement, 1998) and was approved by the Conjoint Health Research Ethics Board (CHREB), University of Calgary, Calgary Health Region and Child Health Research Committee (Appendix 2).

Data were collected through telephone interviews and verbal consent was obtained prior to each interview. All information required to obtain informed consent was scripted

for the telephone interviewers as in the *Study Invitation* (see Appendix 3) and was provided verbally before each interview began. Participation was completely voluntary and the collected information was kept confidential. Data were grouped and generalized for reporting, so that no individual participant could be identified. Identifying information, such as participants' name and address, will be deleted and destroyed once the study is complete. Should any participants have questions or concerns, the researcher's telephone number and email address were provided upon request through the study invitation. The collected information was saved in databases created for this study and could only be accessed by the study investigators.

CHAPTER FOUR: RESULTS

This chapter reports the findings of the study, including: the compliance rate for the 2001-2002 season of the RSV prevention program; response rates; and characteristics of the infants and their primary caregivers. Detailed descriptive results from the questionnaire are presented to allow for an understanding of the study population, before statistical analysis using χ^2 tests and logistic regression. In addition, secondary questions of the study (i.e., where did the primary caregivers obtain information regarding the RSV prevention program; what is the participants' preferred location of the RSV prevention program; and what is the geographical distribution of the program participants) are answered.

4.1 Compliance Rate for the 2001-2002 RSV Prevention Program

Data were obtained for the 2001-2002 RSV season from the RSV prevention program Database and analyzed to determine the compliance rate of all participating families with infants.

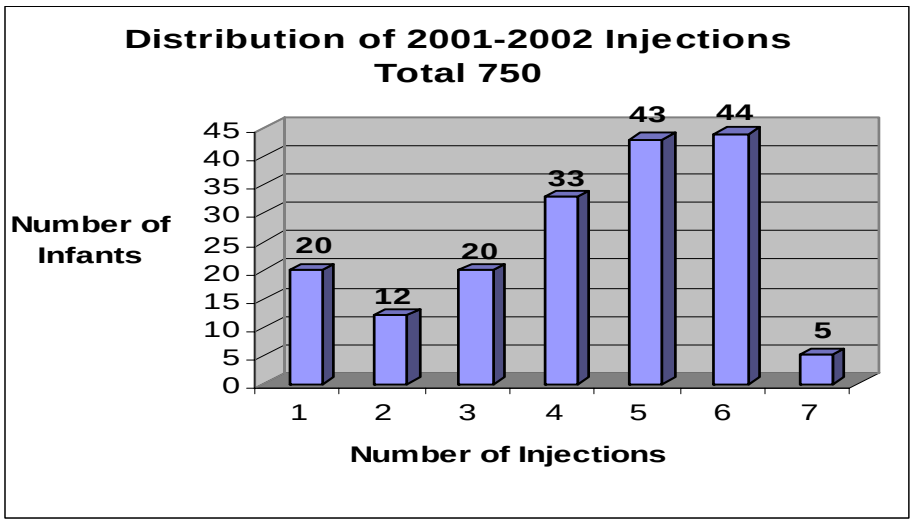
4.1.1 Overview of 2001-2002 RSV Prevention Program

The 2001-2002 RSV season was between December 18, 2001 and June 3, 2002. There were 177 infants who attended the 2001-2002 RSV prevention program, representing 151 separate families. The birth outcomes among these 151 families were: 119 singleton deliveries, 29 twin deliveries and 3 triplet deliveries. The 177 infants include 3 sets of triplets (3x3=9), 20 sets of twins (2x20=40), 9 single infants of a twin

birth (1x9=9) and 119 singletons. The infant gender ratio was 1:1 with 89 females and 88 males.

The 177 infants received a total of 750 doses of palivizumab during the 2001-2002 RSV season. Twenty infants received one injection, 12 infants received two injections, 20 infants received three injections, 33 infants received four injections, 43 infants received five injections, 44 infants received six injections, and 5 infants received seven injections (Figure 1).

Figure 1: Distribution of 2001-2002 palivizumab injections



4.1.2 Compliance Rate for the 2001-2002 RSV Prevention Program

Compliance was calculated for each of the 177 infants in the program and per family unit, following the methods described in Chapter Three-Methodology. Based on individual compliance, the program participants were divided into two groups. Those with 90-100% compliance were categorized as compliers, and those with less than 90% compliance were categorized as non-compliers.

There were 130 infant compliers from 110 families and 47 infant non-compliers from 41 families, resulting in a total infant compliance rate of 73.4% and total family compliance rate of 72.8% (Table 1).

Table 1 Compliance rate for the 2001-2002 RSV prevention program

	Infant N=177	**Percentage**	**Family N=151**	**Percentage**
90—100% (complier)	130	73.4%	110	72.8%
Less than 90% (non-complier)	47	26.6%	41	27.2%

A more detailed program compliance distribution is listed in Table 2.

Table 2 Distribution of 2001-2002 RSV prevention program compliance rate

	Infant N=177	**Percentage**	**Family N=151***	**Percentage**
100%	65	36.7%	54	35.8%
90—99%	65	36.7%	58	38.4%
80—89%	16	9%	14	9.3%
70—79%	17	9.6%	16	10.6%
60—69%	8	4.5%	6	4.0%
15—59%	6	3.4%	6	4.0%

* Number of twins fell in different percentage = 3 sets.

4.2 Response Rate

Three nurses who had worked with the RSV prevention program at the Alberta Children's Hospital conducted telephone interviews between January and May 2003 using the questionnaire developed for this study.

Some of the 177 infants from the 151 families in the 2001-2002 RSV prevention program were not eligible for the telephone interview based on the exclusion criteria for the study. The reasons for exclusion included: 2 infants were deceased, 7 infants' primary caregivers had an English language barrier, and 8 infants only received one injection at the end of the RSV season. Thus 17 infants from 14 families were excluded from the study sample.

Among the 160 (177 minus 17) eligible infants from 137 (151 minus 14) families, 107 primary caregivers representing 123 infants completed the telephone interview. There were 23 primary caregivers representing 27 infants lost to follow-up and 7 primary caregivers representing 10 infants refused to participate in the telephone interview.

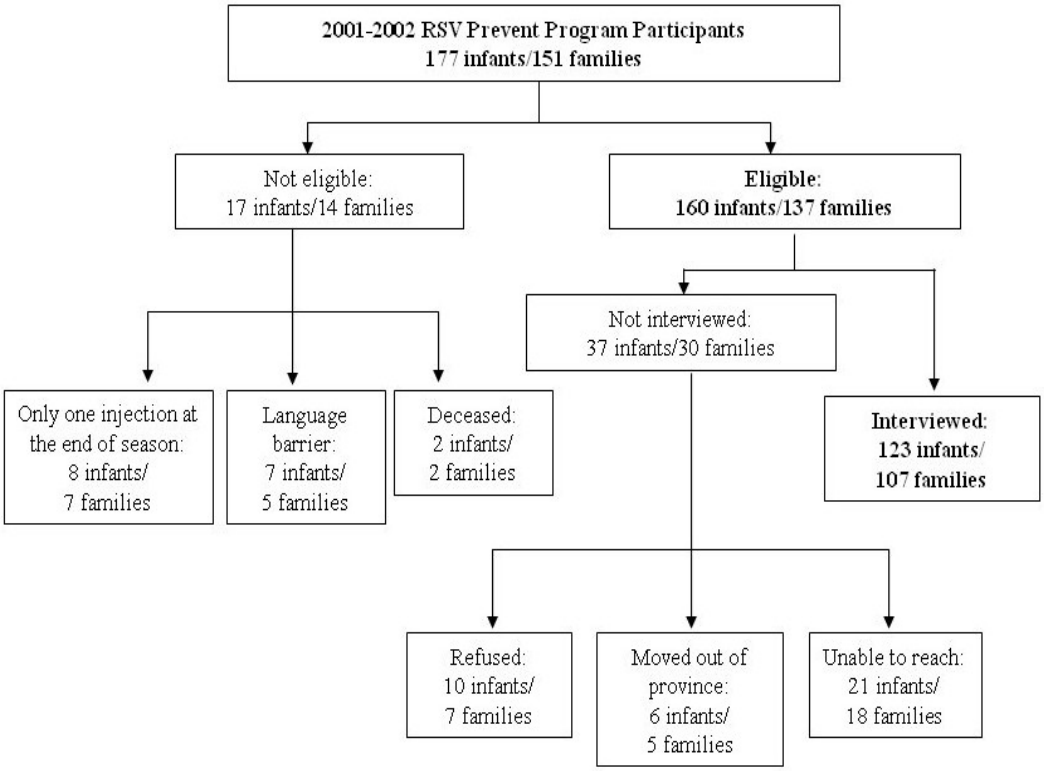
As there were both twins and triplets participating in the RSV prevention program, the number of families who completed the telephone interview and the number of infants who were included in this study differed. Therefore, two response rates were calculated: one based on the number of infants and the other based on the number of families.

Response rate based on infants was 123/160=76.9%

Response rate based on families was 107/137=78.1%

Refer to Figure 2 for a graphic presentation of the telephone interview workflow.

Figure 2: Telephone interview workflow of the 2001-2002 RSV prevent program participants



4.3 Compliance Rate for the Interviewed Sample

Among the 123 infants whose primary caregivers participated in the telephone interview, 92 infants from 79 families were compliers and 31 infants from 28 families were non-compliers, resulting in an infant compliance rate of 74.8% and a family compliance rate of 73.8% (Table 3).

Table 3 Compliance rate of the interviewed sample for the 2001-2002 RSV prevention program

	Infant N=123	Percentage	Family N=107	Percentage
90—100% (complier)	92	74.8%	79	73.8%
Less than 90% (non-complier)	31	25.2%	28	26.2%

The compliance rates of the interviewed sample (infant: 74.8%, family: 73.8%) were only slightly higher than the compliance rates of the population of families and infants in the 2001-2002 RSV prevention program (infant: 73.4%, family: 72.8%).

4.4 Description of the Study Participants

The study results were obtained from telephone interviews were based on 123 infants from 107 families. To ensure that the opinions of primary caregivers of twins and triplets did not contribute more than the opinions from the primary caregivers of singletons, the unit of analysis was the family, unless infant characteristics were being analyzed. Therefore, the number of subjects in the majority of the analyses was 107 families.

4.4.1 Characteristics of the infants

These 123 infants included 3 sets of triplets (n=9), 10 sets of twins (n=20), 5 single infants of a twin (n=5) and 89 singletons, coming from 107 families. Nearly half of the infants (48.8%, n=60) were first parity. Both mean and median gestational age (GA) at birth were 31 weeks. Mean birth weight (BW) was 1642g and median birth weight was 1490g. There were eight (6.5%) term babies (GA>=37 wks) among these 123 infants, therefore the mean GA at birth and the mean BW were relatively high (Table 4).

Table 4 Characteristics of infants

	Mean	**Median**	**SD**	**Min**	**Max**
Gestational age (wks)	31	31	3.8	23	40
Birth weight (g)	1642	1490	861	470	4140

Health care utilization for respiratory concerns during the winter of 2001-2002 was assessed based on the primary caregivers' self report. About 25% of all infants went to an emergency department and 12% of the infants were admitted to hospital. The ACH was the primary site in both situations. Less than 40% of the infants were taken to a doctor's office or the Respiratory Home Care Clinic (RHCC) for respiratory concerns, and most (55.5%) of these only required one visit (Table 5).

Table 5 Health care utilization during winter 2001-2002 for respiratory concerns

Health care utilization	Frequency	Percentage
Visited doctor's office or Respiratory Home Care Clinic	**45**	**36.6%**
Once	*25*	*55.5%*
More than once	*20*	*44.5%*
Visited emergency department	**31**	**25.2%**
At ACH	*27*	*87.1%*
At other hospital	*4*	*12.9%*
Admitted to hospital	**15**	**12.2%**
At ACH	*12*	*80%*
At other hospital	*3*	*20%*

4.4.2 Characteristics of primary caregivers

The 107 primary caregivers of the 123 infants completed the telephone interview; 98 (91.6%) were mothers. No primary caregivers were between the ages of 15 and 20 years and over 80% were at least 30 years old.

The majority of primary caregivers were married or living with a partner (91%), Caucasian (77%), had more than a high school education (79%), and had an annual household pre-tax income greater than $50,000 (67%). Nineteen families had a smoker at home (Table 6).

Table 6 Characteristics of primary caregivers

Characteristics	Frequency	Percentage
Relationship to the infant		
Mother	98	91.6%
Father	5	4.7%
Foster parents	3	2.8%
Legal guardian	1	0.9%
Age group		
15-20 years old	0	0%
21-29 years old	21	19.6%
30-39 years old	73	68.2%
40 or above years old	13	12.1%
Marital status		
Married or living with a partner	97	90.7%
Other	10	9.3%
Ethnicity		
Caucasian	82	76.6%
Non-Caucasian	25	23.4%
Education level		
> High school	84	78.5%
≤ High school	23	21.5%
Household income		
≥ $50,000/year	72	67.3%
< $50,000/year	35	32.7%
Smoker at home		
Yes	19	17.8%
No	88	82.2%

4.5 Other Descriptive Results from the Questionnaire

The following section describes primary caregivers' opinions regarding their infants' health; primary caregivers' knowledge about RSV and palivizumab; perceived barriers to participation in the RSV prevention program; and perceptions about the RSV prevention program.

4.5.1 Primary caregivers' opinions regarding their infants' health

Guided by the Health Belief Model, the primary caregivers were asked about their opinions regarding their infants' health. All of the questions were stated in the time frame "during the winter of 2001-2002". Less than 25 % of primary caregivers were very concerned that their infants would become infected with RSV; however, 45% worried a great deal about the physical health of their infants. The majority (62%) of primary caregivers felt the health of their infant's lungs would be "a great deal" worse in either the short or long term if their infants got an RSV infection (Table 7).

Table 7 Primary caregivers' opinions regarding their infants' health

Primary caregivers worried about: (N=107)	**Not at all/ A little/ Somewhat**	**A great deal**
Infants' physical health	59 (55.1%)	48 (44.9%)
Infants' susceptibility to general illness	65 (60.7%)	42 (39.3%)
Infants would get RSV infection	81 (75.7%)	26 (24.3%)
Infants had high risk of getting RSV	72 (67.9%)	34 (32.1%)
Health of infants' lungs would be worsen if got RSV infection	41 (38.3%)	66 (61.7%)

Many of the infants were less than one year old and therefore not eligible for the flu shot; however, 100% of the primary caregivers of these infants self reported that their infants had received all of the recommended baby shots.

4.5.2 Knowledge about RSV and palivizumab

The Health Belief Model emphasizes *perceived* susceptibility, *perceived* severity, *perceived* benefits and *perceived* barriers. What people "perceive", however, may depend on their knowledge about a disease and its prophylaxis. Primary caregivers were asked to report on their level of knowledge about RSV and palivizumab.

4.5.2.1 Self-reported knowledge level

During the pilot testing stage, data were collected from the first ten primary caregivers regarding their knowledge about RSV and palivizumab after program participation. For the remaining study participants the question was expanded to include knowledge both before and after program participation, to better understand how knowledge changed as a consequence of attending the RSV prevention program. Sixty-nine percent of the primary caregivers knew nothing or very little about RSV before participating in the program, while only 19.6% knew nothing or very little after participating in the program. Only 9.3% of the primary caregivers knew somewhat or a great deal about palivizumab before participation in the program, while 59.8% felt they knew somewhat or a great deal after participation in the program (Table 8).

Table 8 Self-reported knowledge level about RSV and palivizumab

Knowledge about:	Not at all/ A little	Somewhat/ A great deal
RSV		
Before infant received first injection (n=97)	67 (69.1%)	30 (30.9%)
After infant received last injection (n=107)	21 (19.6%)	86 (80.4%)
Palivizumab		
Before infant received first injection (n=97)	88 (90.7%)	9 (9.3%)
After infant received last injection (n=107)	43 (40.2%)	64 (59.8%)

4.5.2.2 Knowledge about the cost of palivizumab

Under the Canadian system of universal health care, palivizumab is offered to eligible high-risk infants at no direct cost to the family. We sought to determine if primary caregivers were aware of the costs of palivizumab.

The cost of palivizumab for each dose (or each infant) varies, because the dosage is determined by the infant's weight. As mentioned in the literature review, the standard is 15mg/kg and the average cost per dose is USD900. For the purpose of this study, it was decided prior to analysis that answers between CAD1000 to CAD1500 inclusive per injection were considered to be correct.

The primary caregivers were encouraged to provide their best guess as to the cost of a single palivizumab injection. Among respondents, 22 (20.6%) people refused to guess because they "had no idea at all". Among the remaining 85 respondents, 41 (48.2%) answered correctly; 5 (5.9%) guessed too high (at up to CAD4000); while 39 (45.9%) gave an answer lower than the true cost, with some responses less than CAD10 (Table 9).

Table 9 Knowledge about the cost of palivizumab

Best estimates of the cost of a single dose of palivizumab (n=85)	Frequency	Percentage
< $50	4	4.7%
≥ $50 and < $100	8	9.4%
≥ $100 and < $500	16	18.8%
≥ 500 and < $1000	11	12.9%
≥ $1000 and ≤ $1500	41	48.2%
> $1500	5	5.9%

4.5.3 Barriers to participation in the RSV prevention program

The identified barriers to participation in the RSV prevention program included psychological barriers, such as worry about side-effects and infant discomforts, as well as logistical barriers, such as difficulty in transportation and long distance travel.

The majority (80.4%) of primary caregivers worried about the side-effects of palivizumab "not at all" or "a little". Consistently over 90% of the participants considered repeated hospital visits, difficulty in scheduling time, transportation, and poor weather as "not at all" or "a little" barriers. Only seven (6.7%) people agreed that the distance required to travel to the ACH had affected their compliance. Typically, 95% participants were able to reach the ACH within one hour, including parking time. Three fourths of the participants waited on-site at the ACH for the infants palivizumab injections for less than 15 minutes.

The number of primary caregivers who reported psychological barriers to participating in the RSV prevention program was more than double the number of primary caregivers who reported logistical barriers (Table 10 and Table 11).

Table 10 Barriers to participation in the RSV prevention program

Barriers	Not at all/ A little	Somewhat/ A great deal
Worry about side-effects of palivizumab (n=107)	86 (80.4%)	21 (19.6%)
Worry about discomfort of palivizumab (n=107)	81 (75.7%)	26 (24.3%)
Repeated (monthly) hospital visits (n=104)	94 (90.4%)	10 (9.6%)
Difficulty in scheduling time for visits (n=104)	94 (90.4%)	10 (9.6%)
Difficulty in transportation (n=104)	95 (91.3%)	9 (8.7%)
Poor weather (n=104)	96 (92.3%)	8 (7.7%)

Table 11 Travelling and waiting time for palivizumab appointment

	Frequency	Percentage
One way travelling and parking time to the ACH (n=101)		
< 30 minutes	38	37.6%
30 to 60 minutes	58	57.4%
> 60 minutes	5	5%
Length of wait on-site at the ACH for palivizumab injection (n=107)		
< 15 minutes	80	74.8%
15 to 30 minutes	25	23.4%
> 30 minutes	2	1.8%

4.5.4 Perceptions of the RSV prevention program

4.5.4.1 Program satisfaction

All of the primary caregivers were “somewhat” or “very satisfied” with the RSV prevention program, with 90% being “very satisfied”. Ninety two percent of primary

caregivers (n=98) felt that the program was “somewhat” or “very convenient”. The primary inconvenience experienced by caregivers was difficulty in parking. All but one primary caregiver believed this program would help their infants “somewhat” or “greatly”; 92.4% (n=97) of the primary caregivers would be “somewhat” or “very much” likely to participate in similar programs in the future.

4.5.4.2 Qualitative information

There was consensus among primary caregivers regarding reasons for enrolling their infants in this program. “It was what the infant needed” was determined to be the number one reason, followed by a measure of “prevention” and “protection” to “keep the baby healthy”.

Primary caregivers were very grateful that the RSV prevention program was available and perceived it as a “wonderful program” with friendly, caring and knowledgeable nurses. It allowed them to have “peace of mind” knowing that the program would keep their infant(s) healthy, or that their infant(s) would have less severe symptoms if they became infected with RSV. The primary caregivers generally had a very positive experience.

4.6 Differences in Characteristics and Health Beliefs among Study Participants

Bivariate Analyses

While the previously presented analyses have all described the study population, the following section presents analyses comparing the characteristics and health beliefs of

compliers and non-compliers. All variables were dichotomized and χ^2 or Fisher's Exact Tests were applied, as appropriate.

4.6.1 Statistically non-significant variables

To address the study objectives, many variables were analyzed to determine their relationship to program compliance. Results of χ^2 tests revealed that many variables were not significantly related to program compliance (Table 12), including: infant characteristics, demographics of primary caregivers, knowledge about RSV and palivizumab before and after participation in the RSV prevention program and variables related to the HBM.

Table 12 Variables not significantly related to compliance – Bivariate analyses

Variables	Complier N=79	Non-complier N=28	P-value	OR	95% CI
Infants' characteristics					
Gestational age <31 weeks	37 (48.1%)	10 (38.5%)	0.396	1.5	0.6, 3.7
Multiple birth	10 (12.7%)	3 (10.7%)*	1.0	1.2	0.3, 4.7
Other children at home	46 (58.2%)	20 (71.4%)	0.217	0.6	0.2, 1.4
Primary caregivers' characteristics					
Education above high school	63 (79.7%)	20 (71.4%)	0.365	1.6	0.6, 4.2
Married or living with partner	73 (93.6%)	23 (82.1%)	0.075	0.3	0.1, 1.2
Caucasian	63 (79.7%)	19 (67.9%)	0.201	0.5	0.2, 1.4
Knowledge about RSV and palivizumab					
Good knowledge about RSV before program	21 (29.6%)	9 (34.6%)	0.634	0.8	0.3, 2.1
Good knowledge about RSV after program	65 (82.3%)	21 (75%)	0.405	1.5	0.6, 4.3
Good knowledge about palivizumab before program	9 (12.7%)	0*	0.107		
Good knowledge about palivizumab after program	47 (59.5%)	17 (60.7%)	0.910	0.95	0.4, 2.3
HBM related					
Believe program very helpful	60 (75.9%)	21 (75%)	0.920	1.1	0.4, 2.9
Scheduling time barrier	5 (6.5%)	5 (18.5%)	0.068	0.3	0.1, 1.2
Transportation barrier	5 (6.5%)	4 (14.8%)*	0.234	0.4	0.1, 1.6
Distance was a barrier	4 (5.2%)	3 (11.1%)*	0.372	0.4	0.1, 2.1
Poor weather was a barrier	5 (6.5%)	3 (11.1%)*	0.425	0.6	0.1, 2.5
Worried about infant's discomfort	21 (26.6%)	5 (17.9%)	0.355	1.7	0.6, 4.9
Worried about palivizumab's side effect	16 (20.3%)	5 (17.9%)	0.784	1.2	0.4, 3.6

* Fisher's exact test

4.6.2 Statistically significant variables

Both annual household income and the presence of a smoker at home were significantly related to compliance. Primary caregivers with an annual household income of greater than $50,000 were 4 times more likely to be compliant than primary caregivers with an annual household income of less than $50,000. If no one in the home smoked, the primary caregivers were almost 5 times more likely to be compliant than primary caregivers who reported smoking in the home (Table 13).

Table 13 Variables significantly related to compliance - Bivariate analyses

Variables	Complier N (%)	Non-complier N (%)	P-value	OR	95% CI
Household income (≥ $50,000)	60 (75.9%)	12 (42.9%)	0.001	4.2	1.7, 10.5
No smoker at home	71 (89.9%)	18 (64.3%)	0.002	4.9	1.7, 14.3

4.7 Predictors of Compliance – Multivariate Analysis

Logistic regression was used to identify predictors of compliance and to identify interaction and confounding variables. The results of the regression analysis were consistent with the result of χ^2 tests as reported above. No interaction between household income and smoker status at home was found. Logistic regression was used to describe the relationship of several predictor variables (e.g. income and smoker at home) to the dichotomous dependent variable (compliant or not). The goal of logistic regression was

to obtain a valid estimate of the relationship (the odds ratio) between a specified independent variable and dependent variable, while controlling for or adjusting other covariates, hence somewhat smaller odds ratios and narrower 95% confidence intervals were obtained compared to the bivariate analyses (Table 14).

Table 14 Predictors of compliance – Logistic regression results

Variables in equation	N (%)	P-value	OR	95% CI
Household income ≥ $50,000	72 (67.3%)	0.018	3.2	1.2, 8.3
No smoker at home	89 (83.2%)	0.037	3.3	1.1, 10.4

4.8 Information Sources Regarding the RSV Prevention Program

As knowledge is an important factor related to compliance, we explored primary caregivers' information sources regarding the RSV prevention program.

Primary caregivers were asked where they obtained information regarding the RSV prevention program. The majority of primary caregivers provided responses within the list provided in the questionnaire (ACH clinics, pediatrician, family physician, discharge physician, nurse, friend/family member and reading materials). Primary caregivers could select as many sources from this list as applied to their situation and were not asked to rank their choices.

Nurses were identified as the primary source of information (68.2%). Among nurses, the neonatal intensive care unit (NICU) nurse was the most-frequently mentioned (42.1%), followed by the RSV nurse (18.7%) and the transitional care nurse (12.1%). Many primary caregivers also received information from ACH clinics (to be exact, the G clinic) and other reading materials such as books, pamphlets, posters and the Internet.

Other less frequently mentioned information sources include discharge physician, pediatrician, friend/family member and television advertisements (Table 15).

Table 15 Information source regarding the RSV prevention program

Information source	Frequency	Percentage
Nurses	**73**	**68.2%**
NICU nurse	45	42.1%
RSV nurse	20	18.7%
Transitional care nurse	13	12.1%
Community nurse	1	0.9%
Reading materials	50	46.7%
ACH clinics	40	37.4%
Discharge physician	30	28%
Pediatrician	19	17.8%
Friend/family member	11	10.3%

4.9 Preferred Location to Receive Palivizumab

To better understand the needs of program participants, primary caregivers were asked about where they would prefer their infant to receive their palivizumab injections. The following four locations were provided as options: family doctor's office, community health center, their own home and the ACH.

Over half of the primary caregivers (56.7%) would have preferred to have their infants receive the palivizumab injection at home. Sixteen primary caregivers (16.5%) indicated that their preference was the community health center; the ACH and family doctor's office were each preferred by 13 primary caregivers (13.4%).

If the most preferred location was not available, the second best location chosen by 36 primary caregivers (36.4%) was family doctor's office, follow by the community health center (28.3%), the ACH (21.2%) and at home (14.1%).

4.10 Geographical Distribution of Program Participants

In order to have a better understanding of how the 2001-2002 RSV prevention program participants were distributed geographically, their postal codes (PC) were used to locate them on the following maps using ArcView 8.1. ArcView is a Geographic Information Systems (GIS) software package that allows for the processing of spatial data and is used to support decisions about a geographic area (Fotheringham A, Brunsdon C, & Charlton M, 2000).

4.10.1 Mapping of program participants in the City of Calgary

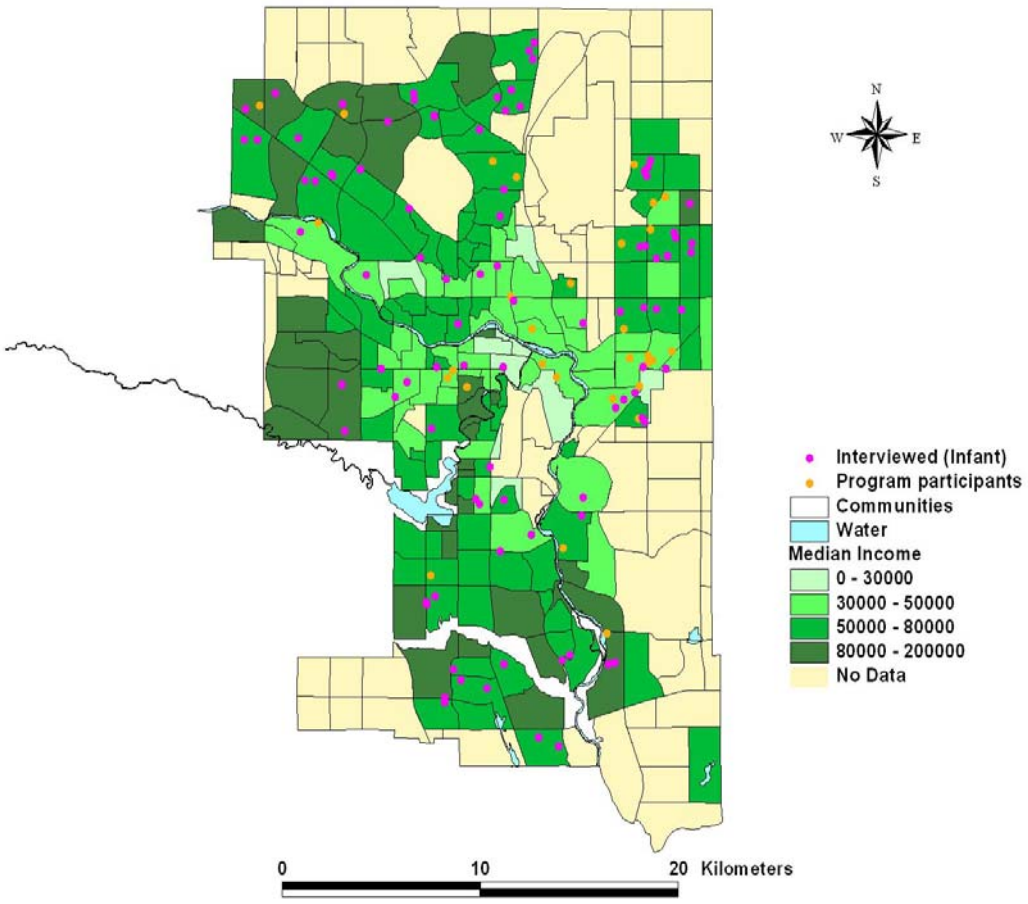
The RSV prevention program is a centralized program and consequently, with few exceptions, palivizumab is provided and administered at the ACH in the Calgary Health Region. A few exceptions can occur, such as when the first dose of palivizumab is administered at the infant's birth hospital before he or she is discharged home. The following map of the City of Calgary (Figure 3) shows that the program provided services to families who resided in all areas of the city. The few families who live outside of the City of Calgary will be showed in the subsequent map (Figure 4).

Each dot on the map represents an infant who was enrolled in the 2001-2002 RSV prevention program. Pink dots represent infants whose primary caregivers had completed

the telephone interviews. Yellow dots represent infants whose primary caregivers did not complete the telephone interview.

The distribution of the survey participants reflects all social districts within the CHR. The small sample size prevents more specific neighbourhood analysis.

Figure 3 RSV prevention program participants in the City of Calgary

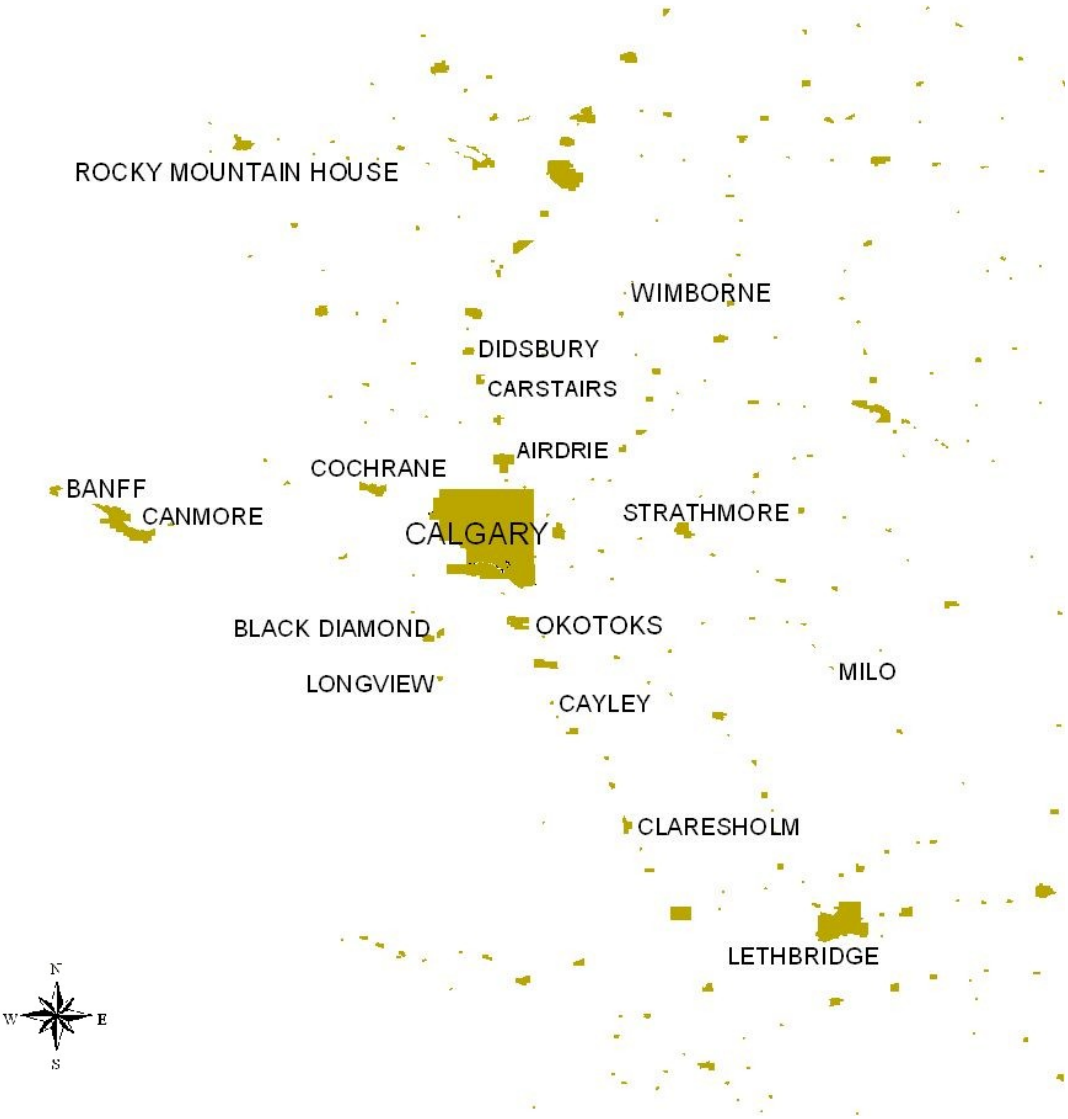


4.10.2 Mapping of program participants in Southern Alberta

The RSV prevention program serves the Calgary Health Region and surrounding areas. Medicine Hat, in southern Alberta, has a similar RSV prevention program.

Each of the 17 cities, town or villages that appear on the following map had at least one infant who participated in the 2001-2002 RSV prevention program. The distribution of program participants indicates the range of communities served by the program.

Figure 4 RSV prevention program participants in Southern Alberta



CHAPTER FIVE: DISCUSSION AND CONCLUSION

This chapter discusses the most salient study results and their implications for the RSV prevention program. The discussion will focus on the perceived barriers to program participation; participants' information sources; preferred location for the RSV prevention program; the relationship between household characteristics and program compliance; perceptions regarding the RSV prevention program; and making a comparison between the RSV prevention program and the Respiratory Home Care Clinic. The study strengths and limitations, future directions and conclusions are also presented.

5.1 Implications for the RSV Prevention Program

Between 1998 and the end of the 2003-2004 RSV season, the RSV prevention program in Calgary provided immunization to about 1000 vulnerable infants. A recent population-based study compared the impact of palivizumab on confirmed RSV hospitalizations within the Calgary Health Region (CHR) to those in the Capital Health Authority of Edmonton (CHA). Between 1999 and 2002, CHR offered palivizumab to high risk infants, while CHA did not. The study demonstrated demographic similarity in infants' between health regions, and that post implementation of palivizumab, CHA high risk infants were 2.4 times more likely to be hospitalized with RSV than their counterparts in CHR (Mitchell, Gillis, Majaesic, & Tough, 2004).

The RSV prevention program has been well received by most program participants based on the first-hand experiences of RSV nurses and the telephone interview results of this study. This study provides information about the population served by the program; and allows for improved understanding of the factors associated with program

participation and compliance. Understanding variables that influence compliance will allow for the development of strategies to improve program compliance, which is critical to program success. This study has also established a baseline for future research including compliance studies in subsequent RSV seasons and comparison studies to explore the impact of changes in service delivery.

5.1.1 Barriers to program participation

Among the four dimensions of the Health Belief Model, perceived barriers have been shown to be the most dominant predictor of behavior under the HBM across a variety of study designs and behaviors (Janz et al., 1984). "Perceived barriers" is also the most important dimension of this study, because it can inform our understanding of where strategies for improved compliance could be introduced.

Although not statistically significant, non-compliers had a tendency (10% or greater difference between groups) to have older infants, other children at home, to be non-Caucasian, unmarried, less knowledgeable about RSV both before and after the prevention program, and to note structural barriers. The trend that primary caregivers who were married or living with a partner, and who had only one child, were more likely to be compliant may be explained by potentially the ease in arranging time for at least one of them to take the infant to the ACH and needlessness to worry about child care for other children at the same time. Another trend was the primary caregivers who reported having difficulty in scheduling time for palivizumab appointment were more likely to be non-compliant.

Even though transportation and time were not found to be statistically significantly related to compliance in this study, they were identified as barriers in the Langkamp study (Langkamp et al., 2001) and in other studies related to infants' vaccination visits (Bardenheier et al., 2004; Jhanjee, Saxeena, Arora, & Gjerdingen, 2004). The small number of primary caregivers who were included in this study may have influenced these finding as the trend toward decreased compliance with increase report of barriers was noted (twice as many non-compliers reported these barriers compared to non-compliers). Consequently, it may be of value for program providers to continue to inquire of participants about transportation or time arrangement barriers.

The major caveat to high levels of program satisfaction was identified as difficulty in finding parking. Parking was often referred to as "terrible" and as a "stress-inducer". This obstacle was anticipated because parking has been a well-recognized problem in the Calgary Health Region and is difficult to address for patients and families. Fortunately, the new Alberta Children's Hospital will be open by the fall of 2006, and the parking pressures may be relieved to some extent.

5.1.2 Information sources

Knowledge does not necessarily lead to behavioral change (Bettinghaus, 1986), however, it is believed to be a pre-requisite for behavioral change (Kennedy, Regehr, Rosenfield, Roberts, & Lingard, 2004). Providing relevant and accurate information about the consequences of RSV infection and the purpose of the program may encourage positive behavioral change and improve compliance. As nurses were identified as the

primary information source for participants in the RSV prevention program, higher compliance may be achieved through 1) NICU nurses spending sufficient time in explaining the short and long term consequences of RSV infection to caregivers of eligible infants; 2) NICU nurses spending more time in explaining the importance and effectiveness of palivizumab to the caregivers of eligible infants; 3) NICU nurses having access to translators to ensure families understand RSV and its consequences; 4) RSV nurses emphasize the special monthly injection requirement at the time of program enrolment (i.e. when the first dose of palivizumab was given to the infant) and answer related questions throughout the program enrolment. Over a quarter of primary caregivers also received information from the infant's discharge physician, therefore, brief endorsement of the program before discharge from the physician may help increase the compliance, because physician endorsement has been identified as a positive factor for compliance even when it is brief and verbal (Delichatsios, Hunt, Lobb, Emmons, & Gillman, 2001).

Only 2 infants' primary caregivers indicated that they received information from their family doctor. Because most of the infants who are enrolled in the RSV prevention program are premature and/or have other health problems, they are typically under the care of ACH clinics and/or pediatricians, and are not typically cared for by their family doctor. Consequently, family doctors were not expected to be a primary information source for the RSV prevention program.

5.1.3 Preferred location

Centralized administration of the RSV prevention program allowed for coverage of the City of Calgary and surrounding areas, as noted by the mapping exercise. It is understandable that the primary caregivers would prefer to have palivizumab administered at their home; however, neither the requirement to travel to the ACH nor the distance between their home and the ACH were identified as barriers to program participation. It is assumed that these logistical barriers are less relevant in the context of program relevancy and importance of infants' health. Moreover, the RSV prevention program appointments are often scheduled in conjunction with other medical appointment at ACH – which may serve as an incentive to attend and contribute to high program satisfaction scores.

Satisfaction to the centralized RSV prevention program was high; however, if the resources were available, care givers indicated that it would be desirable for the program to be offered through a few community health clinics covering each quadrant of the city. More locations may be appropriate if the criteria for immunization was expanded or changed, or if population growth warranted. At this time, the current central location of the ACH does not appear to be a significant drawback for program participation.

5.1.4 Relationship between smokers and high-income families with compliance

Families that have a smoker in the house and families with lower household incomes were identified as less compliant to the RSV prevention program. These results are consistent with the literature on compliance in medical regimen (McCaw-Binns, La Grenade, & Ashley, 1995; Navaie-Waliser et al., 2000; Senturia et al., 1998).

In the study Navaie-Waliser published in 2000, the data was analysed to determine characteristics of program completers enrolled in a home visitation program which targeted high-risk pregnant woman in North Carolina, USA. 373 pregnant women were enrolled because they either had high medical risk, and/or had high social/environmental risk such as inadequate social support or lack of housing. Similar to the current study, no socio-demographic characteristics such as age, education, marital status were found different between those who completed the program and who did not, and yet multivariate logistic modelling revealed that those who were non-smoker were 1.8 times more likely to complete the program. Another study designed to determine the compliance of a 9-month follow-up with the caregivers of children with asthma in multi-centers in USA (Senturia et al., 1998) and a study on under-users of antenatal care in Jamaica (McCaw-Binns et al., 1995) have also identified smoking as a factor for non-compliance.

Second hand smoke exposure increases risk of asthma and respiratory illness (Carbonell-Estrany et al., 2004). Thus infants from families with a smoker at home are at multiple risks of poor outcomes as a consequence of preterm birth, with additional risks related to exposure to second hand smoke, and with less compliant caregivers.

Higher income has been identified as positively associated with compliance in medical regimen (Katz et al., 2001; La Greca, 1990). Women with lower income have been found to be less likely to use pre-natal care which may precede, and/or predict lower service utilization for their infants and children (Tough SC et al., 2003). Even though Navaie-Waliser's study did not find family income had impacted completion of home

visit program, the annual family incomes in this sample were low with categories of under or above $12,000 USD. This low income sample may have influenced the interpretation of the findings and is difficult to generalize to a community based sample not living in poverty. Calgary is one of the fastest growing and prosperous cities in Canada with median annual household income almost 9% higher than national average (Statistics Canada, 2001). This sample's income profile was high and was dichotomized at under or above 50,000 CAD based on the median annual household income in Alberta in 2003, thus not comparable to Navaie-Waliser's study.

Based on these results, there may be opportunity for RSV nurses to pay increased attention to families of lower income and to parents who smoke and devoted additional effort to prevent such families from missing appointments, for example through reminder phone calls/post cards.

5.1.5 Perceptions regarding the RSV prevention program

An important feature of the RSV prevention program is the therapeutic alliance between the RSV nurses and the primary caregivers. Almost all of the primary caregivers in this study had expressed their gratitude to the nurses and described them as friendly, caring, supportive, well organized, helpful and flexible. According to qualitative feedback from the primary caregivers, the RSV nurses were competent in working with the infants and managed the injections efficiently and quickly, and they were willing to answer questions regarding RSV and other health issues. This kind of therapeutic relationship has been reported to be helpful with increasing compliance or response in

treatment programs for children (Karver, Handelsman, Fields, & Bickman, 2006; Kazdin, Marciano, & Whitley, 2005).

Moreover, families appreciated that the palivizumab appointments were accommodated with other appointments at the Respiratory Home Care Clinic (G clinic) as much as possible. Because infants in the RSV prevention program were predominantly premature and had other health concerns, many of them had regular follow-up appointments at the Respiratory Home Care Clinic in addition to appointments for the RSV prevention program. Receiving a palivizumab injection while waiting for, or soon after, the infant's appointment would save an extra trip to the ACH and also make efficient use of the time spent at ACH.

5.2 Mapping comparison between RSV prevention program and Respiratory Home Care Clinic

John Snow first demonstrated the value of mapping data for public health analysis in his classic illustration of London's cholera outbreak and contaminated water of the Broad Street pump (The Commonwealth Fund, 1936). After observing, mapping the location of deaths, and interviewing the survivors, Snow successfully tracked down the source of cholera outbreak in Soho (a district of London, UK) as a contaminated water pump in Broad Street. Removal of the pump handle at the source of contamination ended the outbreak which had claimed over 600 lives during August and September in 1854.

Spatial data, such as postal codes, provide the opportunity to map the occurrence of an event on a map. The Geographic Information System produces a picture, which is

more intuitive and accessible than pages of data (Richards, Croner, Rushton, Brown, & Fowler, 1999).

As the Alberta Children's Hospital serves not only the CHR but also Southern Alberta, many patients visit the ACH from other health regions. The Respiratory Home Care Clinic (RHCC) is another example of a program with a wide distribution of program participants, as shown in Figure 5 and Figure 6. A superficial comparison between the RHCC and the RSV maps suggests that both programs have broad and similar reach and there is no apparent reason to suggest that the RSV program is not reaching a specific social district.

Figure 5 Respiratory Home Care Clinic (HRCC) program participants in the City of Calgary

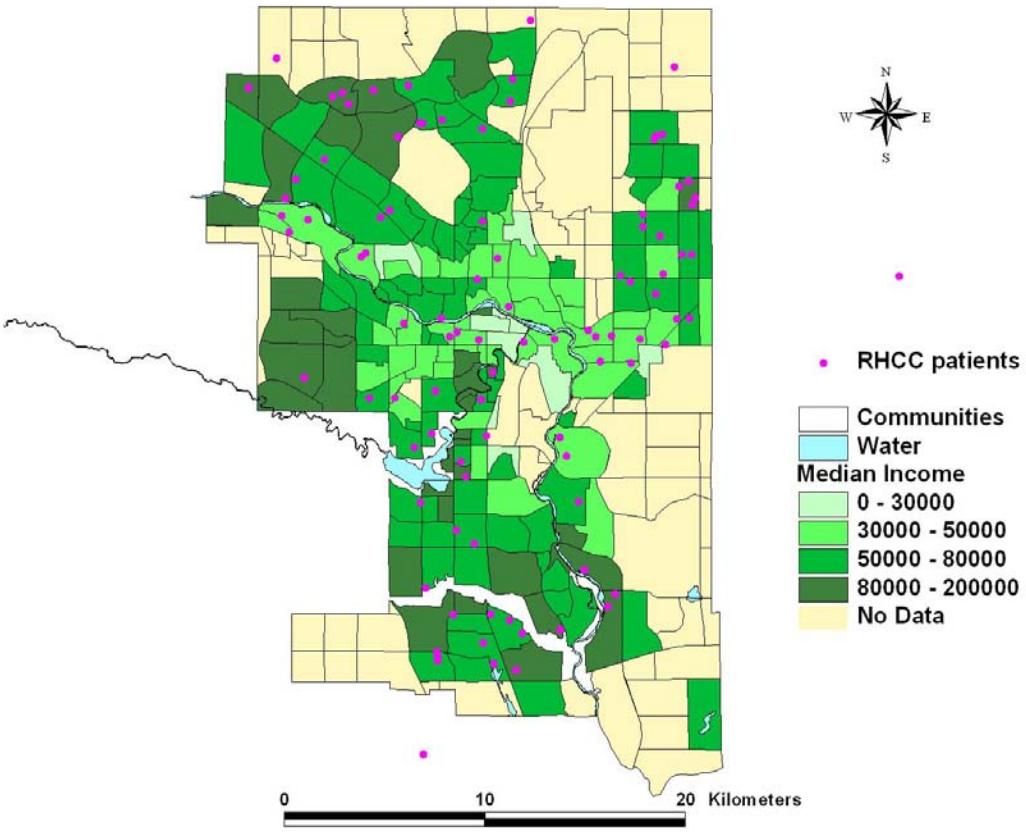
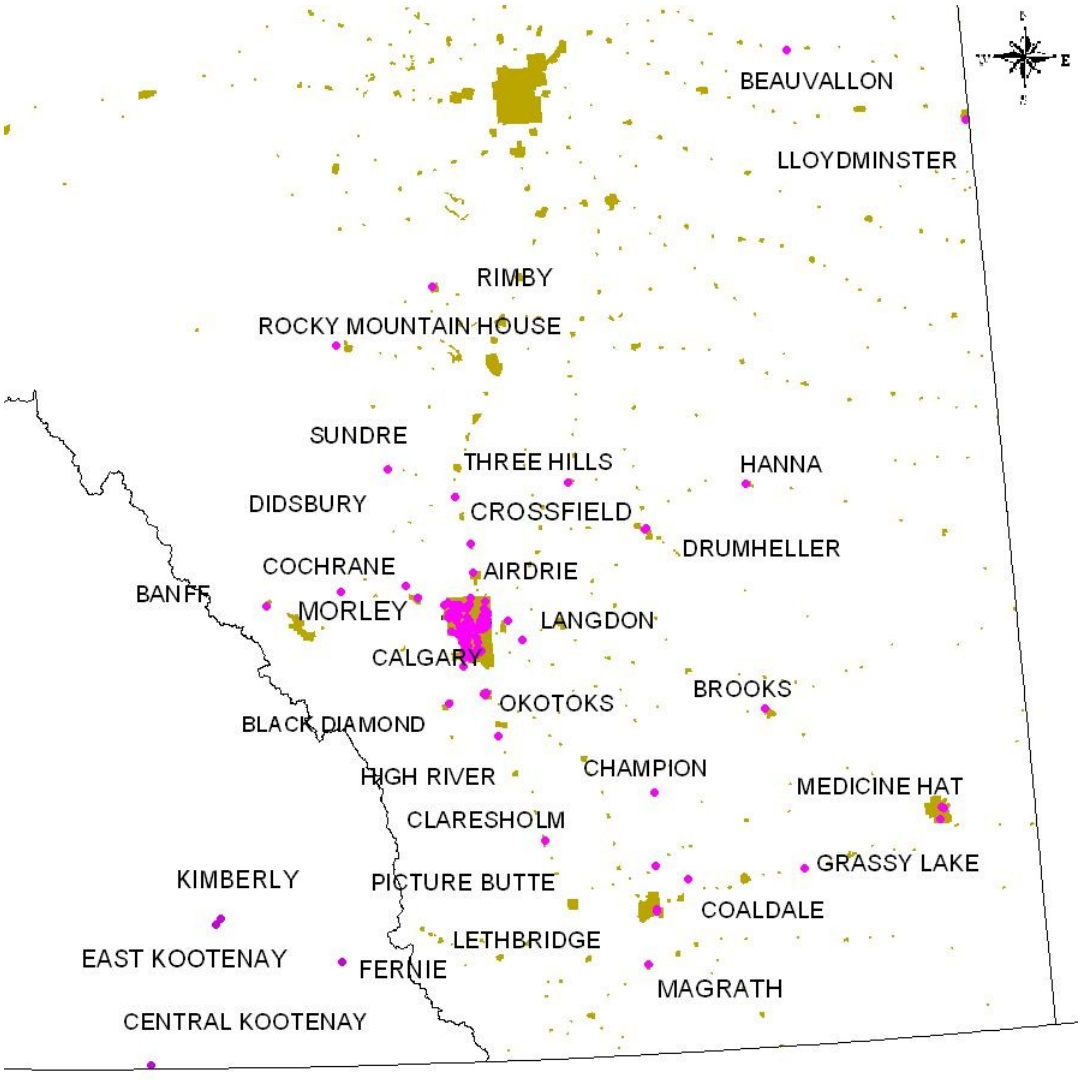


Figure 6 Respiratory Home Care Clinic (RHCC) program participants in Southern Alberta



5.3 Study Strengths and Limitations

5.3.1 Study strengths

5.3.1.1 Selection bias

Selection bias has been identified as an issue in survey research because non-respondents may differ systematically from respondents (Sackett, 1979). Common techniques to minimize selection bias include increasing the response rate and trying to identify if there are important difference between respondents and non-respondents.

Response rates for telephone surveys are usually between 50% and 60% (Robertson, Sinclair, Forbes, Kirk, & Fairley, 2000; Smith, Chey, Jalaludin, Salkeld, & Capon, 1995). For this study, the response rate based on infants and their families were 76.9% and 78.1% respectively. The relatively high response rate may be attributed to already established positive relationships between the interviewers (RSV nurses) and the interviewees (primary caregivers of the infants). In addition, the study sought the opinions regarding an interesting and important topic to the interviewees, which may have contributed to a higher response rate (Groves, Presser, & Dipko, 2004).

The compliance rates of the interviewed sample (infant 74.8%; family 73.8%) were only slightly higher than those of all participants in the 2001-2002 RSV prevention program (infant 73.4%; family 72.8%), indicating that the interviewed sample is likely a good representation of all program participants, and that selection bias due to disproportional follow-up was minimal.

5.3.1.2 Multi-dimensional study engagement

This study is relevant for all dimensions of the RSV prevention program: program participants – infants and caregivers, program providers – RSV nurses, administrator – program Head, and the process of health service delivery.

The RSV program is aligned with regional priorities to meet the needs of vulnerable families, and the high response rates reflect families' willingness to participate. This study provided an opportunity to engage clinical service providers in creating and using evidence. By involving all key stakeholders, the study offered evidence on practice and service delivery that can be used to improve processes for identification and communication with families at risk of poor compliance and is an example of collecting evidence to inform practice.

5.3.2 Study limitations

Although the study had a high response rate overall (78.1% based on families), the response rate from families with twins was quite low (15/29=51.7%) compared with the response rate from families with singletons (89/119=74.8%) and triplets (3/3=100%). Thus the generalizibility of the study results to families with twins may not be as strong as to other families.

The major limitation of this study is the small sample size and consequently odds ratios less than 4.0 would not reach statistical significance. Proportionate differences between compliers and non compliers needed to be greater than 25% to reach statistical

significance at $p<0.05$. With a larger sample size, smaller differences between groups which might be clinically meaningful may have become statistically significant. Odds ratios greater than 2 (or less than 0.5) may be clinically important and this sample was too small to detect this small a difference (Sackett DL & Haynes RB, 1991).

Had a larger sample been available, at an odds ratio of 2.0 or greater we would have found a significant difference between compliers and non-compliers in marital status, ethnicity, scheduling time, transportation, and distance. A higher proportion of non-compliers were single, non-Caucasian and to indicate that scheduling time, transportation, and distance were barriers. However, as a descriptive study, we sampled the total population of target program.

5.4 Future Directions

It is foreseeable that although palivizumab is currently the best prophylactic strategy available, the following changes would be desirable: reduction of palivizumab cost with better production lines; new humanized antibodies that are more effective than palivizumab; or a new RSV vaccine that is safe and effective in preventing RSV.

To improve the delivery and operation of the RSV prevention program, the following methods have been suggested: active follow-up of high-risk infants and bulk purchasing or lot preparation and dispensing of palivizumab (Fenton et al., 2004). From a research perspective, further compliance studies in RSV seasons and comparison studies to explore the impact of changes in service delivery over time are recommended.

5.5 Conclusion

It is vital to maintain high levels of compliance with monthly palivizumab injections during the RSV season to achieve therapeutic serum levels and reduce the incidence of breakthrough infection. Families of non-smokers and those with higher household incomes are more likely to be compliant. Specialized efforts to recruit and retain infants born in low income home and to smokers may warrant attention. As well, larger studies with increased sample size will allow for an improved understanding and confidence in the potential barriers to compliance. Caring and resourceful NICU and RSV nurses who establish personal connections with the primary caregivers of the infants prior to discharge to ensure recruitment and retention in the RSV prevention program are likely to encourage compliance and therefore critical to the success of the program.

REFERENCES

A joint Canadian Paediatric Society statement with the Fetus and Newborn Committee (1999). Palivizumab and respiratory syncytial virus immune globulin intravenous for the prophylaxis of respiratory syncytial virus infection in high risk infants. *Paediatr Child Health, 4,* 474-480.

Akers RL & Lee G (1996). A longitudinal test of social learning theory: Adolescent smoking. *Journal of Drug Issues, 26,* 317-343.

American Academy of Pediatrics Committee (1998a). American Academy of Pediatrics Committee on Infectious Diseases and Committee of Fetus and Newborn, Prevention of respiratory syncytial virus infections: indications for the use of palivizumab and update on the use of RSV-IGIV. *Pediatrics, 102,* 1211-1216.

American Academy of Pediatrics Committee (1998b). American Academy of Pediatrics Committee on Infectious Diseases and Committee of Fetus and Newborn, Prevention of respiratory syncytial virus infections: indications for the use of palivizumab and update on the use of RSV-IGIV. *Pediatrics, 102,* 1211-1216.

American Heritage Dictionaries (2000). *The American Heritage Dictionary of the English Language, Fourth Edition*.

Bandura A (1986). *Social Foundations of Thought and Action: A Social Cognitive Theory*.

Bardenheier, B. H., Yusuf, H. R., Rosenthal, J., Santoli, J. M., Shefer, A. M., Rickert, D. L. et al. (2004). Factors associated with underimmunization at 3 months of age in four medically underserved areas. *Public Health Rep., 119,* 479-485.

Bettinghaus, E. P. (1986). Health promotion and the knowledge-attitude-behavior continuum. *Prev.Med., 15,* 475-491.

Blount, R. E., Jr., Morris, J. A., & Savage, R. E. (1956). Recovery of cytopathogenic agent from chimpanzees with coryza. *Proc.Soc.Exp.Biol.Med., 92,* 544-549.

Bradley, J. P., Bacharier, L. B., Bonfiglio, J., Schechtman, K. B., Strunk, R., Storch, G. et al. (2005). Severity of respiratory syncytial virus bronchiolitis is affected by cigarette smoke exposure and atopy. *Pediatrics, 115,* e7-14.

Carbonell-Estrany, X., Figueras-Aloy, J., & Law, B. J. (2004). Identifying risk factors for severe respiratory syncytial virus among infants born after 33 through 35 completed weeks of gestation: different methodologies yield consistent findings. *Pediatr.Infect.Dis.J., 23,* S193-S201.

Carbonell-Estrany, X. & Quero, J. (2001). Hospitalization rates for respiratory syncytial virus infection in premature infants born during two consecutive seasons. *Pediatr.Infect.Dis.J., 20,* 874-879.

Chavez-Bueno, S., Mejias, A., Jafri, H. S., & Ramilo, O. (2005). Respiratory syncytial virus: old challenges and new approaches. *Pediatr.Ann., 34,* 62-68.

Clark, N. M., Rakowski, W., Wheeler, J. R., Ostrander, L. D., Oden, S., & Keteyian, S. (1988). Development of self-management education for elderly heart patients. *Gerontologist, 28,* 491-494.

Conner, M. & Norman, P. (1995). Predicting Health Behaviour: Research and Practice with Social Cognition Models. *Buckingham: Open University Press.*.

Crowe, J. E., Jr. (1995). Current approaches to the development of vaccines against disease caused by respiratory syncytial virus (RSV) and parainfluenza virus (PIV). A meeting report of the WHO Programme for Vaccine Development. *Vaccine, 13,* 415-421.

Delichatsios, H. K., Hunt, M. K., Lobb, R., Emmons, K., & Gillman, M. W. (2001). EatSmart: efficacy of a multifaceted preventive nutrition intervention in clinical practice. *Prev.Med., 33,* 91-98.

Domachowske, J. B. & Rosenberg, H. F. (1999). Respiratory syncytial virus infection: immune response, immunopathogenesis, and treatment. *Clin.Microbiol.Rev., 12,* 298-309.

Elder, J. P., Ayala, G. X., & Harris, S. (1999). Theories and intervention approaches to health-behavior change in primary care. *Am.J.Prev.Med., 17,* 275-284.

Ermak, T. H., Giannasca, P. J., Nichols, R., Myers, G. A., Nedrud, J., Weltzin, R. et al. (1998). Immunization of mice with urease vaccine affords protection against Helicobacter pylori infection in the absence of antibodies and is mediated by MHC class II-restricted responses. *J.Exp.Med., 188,* 2277-2288.

Evans CE & Haynes RB (1990). Patient compliance. In Rakel RE (Ed.), *Textbook of family practice.4th ed.* (pp. 371-379). Philadelphia: WB Saunders.

Fenton, C., Scott, L. J., & Plosker, G. L. (2004). Palivizumab: a review of its use as prophylaxis for serious respiratory syncytial virus infection. *Paediatr.Drugs, 6,* 177-197.

Fotheringham A, Brunsdon C, & Charlton M (2000). Spatial Data. Quantitative Geography: Perspectives on spatial data analysis. *London: Sage Publications,* 15-29.

Fotheringham, M. J. & Sawyer, M. G. (1995). Adherence to recommended medical regimens in childhood and adolescence. *J.Paediatr.Child Health, 31,* 72-78.

Groothuis, J. R. & Nishida, H. (2002). Prevention of respiratory syncytial virus infections in high-risk infants by monoclonal antibody (palivizumab). *Pediatr.Int., 44,* 235-241.

Groothuis, J. R., Simoes, E. A., Levin, M. J., Hall, C. B., Long, C. E., Rodriguez, W. J. et al. (1993). Prophylactic administration of respiratory syncytial virus immune globulin to high-risk infants and young children. The Respiratory Syncytial Virus Immune Globulin Study Group. *N.Engl.J.Med., 329,* 1524-1530.

Groves, R. M., Presser, S., & Dipko, S. (2004). The Role of Topic Interest in Survey Participation Decisions. *Public Opinion Quarterly (American Association for Public Opinion Research), 68,* 2-31.

Hall, C. B. (2001). Respiratory syncytial virus and parainfluenza virus. *N.Engl.J.Med., 344,* 1917-1928.

Janeway CA Jr., Travers P, Walport M, & Shlomchik MJ (2001). *Immunobiology, 5th ed*. Garland Publishing.

Janz, N. K. & Becker, M. H. (1984). The Health Belief Model: a decade later. *Health Educ.Q., 11,* 1-47.

Jhanjee, I., Saxeena, D., Arora, J., & Gjerdingen, D. K. (2004). Parents' health and demographic characteristics predict noncompliance with well-child visits. *J.Am.Board Fam.Pract., 17,* 324-331.

Joffe, S., Ray, G. T., Escobar, G. J., Black, S. B., & Lieu, T. A. (1999). Cost-effectiveness of respiratory syncytial virus prophylaxis among preterm infants. *Pediatrics, 104,* 419-427.

Johnson, S., Griego, S. D., Pfarr, D. S., Doyle, M. L., Woods, R., Carlin, D. et al. (1999). A direct comparison of the activities of two humanized respiratory syncytial virus monoclonal antibodies: MEDI-493 and RSHZl9. *J.Infect.Dis., 180,* 35-40.

Kapikian, A. Z., Mitchell, R. H., Chanock, R. M., Shvedoff, R. A., & Stewart, C. E. (1969). An epidemiologic study of altered clinical reactivity to respiratory syncytial (RS) virus infection in children previously vaccinated with an inactivated RS virus vaccine. *Am.J.Epidemiol., 89,* 405-421.

Karver, M. S., Handelsman, J. B., Fields, S., & Bickman, L. (2006). Meta-analysis of therapeutic relationship variables in youth and family therapy: the evidence for different relationship variables in the child and adolescent treatment outcome literature. *Clin.Psychol.Rev., 26,* 50-65.

Katz, K. S., El Mohandes, P. A., Johnson, D. M., Jarrett, P. M., Rose, A., & Cober, M. (2001). Retention of low income mothers in a parenting intervention study. *J.Community Health, 26,* 203-218.

Kazdin, A. E., Marciano, P. L., & Whitley, M. K. (2005). The therapeutic alliance in cognitive-behavioral treatment of children referred for oppositional, aggressive, and antisocial behavior. *J.Consult Clin.Psychol., 73,* 726-730.

Kennedy, T., Regehr, G., Rosenfield, J., Roberts, S. W., & Lingard, L. (2004). Exploring the gap between knowledge and behavior: a qualitative study of clinician action following an educational intervention. *Acad.Med., 79,* 386-393.

Kim, H. W., Canchola, J. G., Brandt, C. D., Pyles, G., Chanock, R. M., Jensen, K. et al. (1969). Respiratory syncytial virus disease in infants despite prior administration of antigenic inactivated vaccine. *Am.J.Epidemiol., 89,* 422-434.

Kretzer, E. K. & Larson, E. L. (1998). Behavioral interventions to improve infection control practices. *Am.J.Infect.Control, 26,* 245-253.

La Greca, A. M. (1990). Issues in adherence with pediatric regimens. *J.Pediatr.Psychol., 15,* 423-436.

Langkamp, D. L. & Hlavin, S. M. (2001). Factors predicting compliance with palivizumab in high-risk infants. *Am.J.Perinatol., 18,* 345-352.

Langley, J. M., Wang, E. E., Law, B. J., Stephens, D., Boucher, F. D., Dobson, S. et al. (1997). Economic evaluation of respiratory syncytial virus infection in Canadian children: a Pediatric Investigators Collaborative Network on Infections in Canada (PICNIC) study. *J.Pediatr., 131,* 113-117.

Law, B. J., Langley, J. M., Allen, U., Paes, B., Lee, D. S., Mitchell, I. et al. (2004). The Pediatric Investigators Collaborative Network on Infections in Canada study of predictors of hospitalization for respiratory syncytial virus infection for infants

born at 33 through 35 completed weeks of gestation. *Pediatr.Infect.Dis.J., 23,* 806-814.

Lawrence, T., Aveyard, P., Evans, O., & Cheng, K. K. (2003). A cluster randomised controlled trial of smoking cessation in pregnant women comparing interventions based on the transtheoretical (stages of change) model to standard care. *Tob.Control, 12,* 168-177.

MacConnachie, A. M. (2000). Palivizumab (Synagis) for prevention of respiratory illness in children. *Intensive Crit Care Nurs., 16,* 123-124.

McCaw-Binns, A., La Grenade, J., & Ashley, D. (1995). Under-users of antenatal care: a comparison of non-attenders and late attenders for antenatal care, with early attenders. *Soc.Sci.Med., 40,* 1003-1012.

Meissner, H. C., Welliver, R. C., Chartrand, S. A., Law, B. J., Weisman, L. E., Dorkin, H. L. et al. (1999). Immunoprophylaxis with palivizumab, a humanized respiratory syncytial virus monoclonal antibody, for prevention of respiratory syncytial virus infection in high risk infants: a consensus opinion. *Pediatr.Infect.Dis.J., 18,* 223-231.

Mitchell, I., Gillis, L., Majaesic, C., & Tough, S. (2004). A population-based study assessing the impact of a prophylaxis program with palivizumab on outcomes and associated health care resource utilization in infants at high risk of severe respiratory syncytial virus infection. *Technical report*.

Morrow, G. R., Hickok, J. T., & Burish, T. G. (1994). Behavioral aspects of clinical trials. An integrated framework from behavior theory. *Cancer, 74,* 2676-2682.

Navaie-Waliser, M., Martin, S. L., Campbell, M. K., Tessaro, I., Kotelchuck, M., & Cross, A. W. (2000). Factors predicting completion of a home visitation program by high-risk pregnant women: the North Carolina Maternal Outreach Worker Program. *Am.J.Public Health, 90,* 121-124.

Oh, P. I., Lanctjt, K. L., Yoon, A., Lee, D. S., Paes, B. A., Simmons, B. S. et al. (2002). Palivizumab prophylaxis for respiratory syncytial virus in Canada: utilization and outcomes. *Pediatr.Infect.Dis.J., 21,* 512-518.

Paes, B. A. (2003). Current strategies in the prevention of respiratory syncytial virus disease. *Paediatr.Respir.Rev., 4,* 21-27.

Pedraz, C., Carbonell-Estrany, X., Figueras-Aloy, J., & Quero, J. (2003). Effect of palivizumab prophylaxis in decreasing respiratory syncytial virus hospitalizations in premature infants. *Pediatr.Infect.Dis.J., 22,* 823-827.

Prochaska, J. O. & DiClemente, C. C. (1983). Stages and processes of self-change of smoking: toward an integrative model of change. *J.Consult Clin.Psychol., 51,* 390-395.

Prochaska, J. O. & Velicer, W. F. (1997). The transtheoretical model of health behavior change. *Am.J Health Promot., 12,* 38-48.

Richards, T. B., Croner, C. M., Rushton, G., Brown, C. K., & Fowler, L. (1999). Geographic information systems and public health: mapping the future. *Public Health Rep., 114,* 359-360.

Robertson, B., Sinclair, M., Forbes, A., Kirk, M., & Fairley, C. K. (2000). The effect of an introductory letter on participation rates using telephone recruitment. *Aust.N.Z.J.Public Health, 24,* 552.

Roden, J. (2004). Revisiting the Health Belief Model: nurses applying it to young families and their health promotion needs. *Nurs.Health Sci., 6,* 1-10.

Rosenstock IM (1974). Historical origins of the health belief model. *Health Educ Monogr, 2,* 328.

Sackett DL & Haynes RB (1991). Clinical Epidemiology: A basic Science fore Clinical Medicine. *Little, Brown and Company,* 292.

Sackett, D. L. (1979). Bias in analytic research. *J Chronic.Dis., 32,* 51-63.

Saez-Llorens, X., Castano, E., Null, D., Steichen, J., Sanchez, P. J., Ramilo, O. et al. (1998). Safety and pharmacokinetics of an intramuscular humanized monoclonal antibody to respiratory syncytial virus in premature infants and infants with bronchopulmonary dysplasia. The MEDI-493 Study Group. *Pediatr.Infect.Dis.J., 17,* 787-791.

Sagai, S., Suetake, M., Yano, H., Yoshida, M., Ohyama, K., Endo, H. et al. (2004). Relationship between respiratory syncytial virus infection and acute otitis media in children. *Auris Nasus Larynx, 31,* 341-345.

Sastre, P., Melero, J. A., Garcia-Barreno, B., & Palomo, C. (2004). Comparison of antibodies directed against human respiratory syncytial virus antigens present in two commercial preparations of human immunoglobulins with different neutralizing activities. *Vaccine, 23,* 435-443.

Sato, M., Saito, R., Sakai, T., Sano, Y., Nishikawa, M., Sasaki, A. et al. (2005). Molecular epidemiology of respiratory syncytial virus infections among children with acute respiratory symptoms in a community over three seasons. *J.Clin.Microbiol., 43,* 36-40.

Senturia, Y. D., McNiff, M. K., Baker, D., Gergen, P., Mitchell, H., Joseph, C. et al. (1998). Successful techniques for retention of study participants in an inner-city population. *Control Clin.Trials, 19,* 544-554.

Shay, D. K., Holman, R. C., Roosevelt, G. E., Clarke, M. J., & Anderson, L. J. (2001). Bronchiolitis-associated mortality and estimates of respiratory syncytial virus-associated deaths among US children, 1979-1997. *J.Infect.Dis., 183,* 16-22.

Simoes, E. A. (1999). Respiratory syncytial virus infection. *Lancet, 354,* 847-852.

Simoes, E. A., Sondheimer, H. M., Top, F. H., Jr., Meissner, H. C., Welliver, R. C., Kramer, A. A. et al. (1998). Respiratory syncytial virus immune globulin for

prophylaxis against respiratory syncytial virus disease in infants and children with congenital heart disease. The Cardiac Study Group. *J.Pediatr., 133,* 492-499.

Smith, W., Chey, T., Jalaludin, B., Salkeld, G., & Capon, T. (1995). Increasing response rates in telephone surveys: a randomized trial. *J.Public Health Med., 17,* 33-38.

Statistics Canada. (2001). Census data. http://www.statcan.ca/english

Subramanian, K. N., Weisman, L. E., Rhodes, T., Ariagno, R., Sanchez, P. J., Steichen, J. et al. (1998). Safety, tolerance and pharmacokinetics of a humanized monoclonal antibody to respiratory syncytial virus in premature infants and infants with bronchopulmonary dysplasia. MEDI-493 Study Group. *Pediatr.Infect.Dis.J., 17,* 110-115.

The Commonwealth Fund (1936). *Snow on Cholera, New York*. Oxford University Press.

The IMpact-RSV Study Group (1998). Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. *Pediatrics, 102,* 531-537.

The PREVENT Study Group (1997). Reduction of respiratory syncytial virus hospitalization among premature infants and infants with bronchopulmonary dysplasia using respiratory syncytial virus immune globulin prophylaxis. *Pediatrics, 99,* 93-99.

Tough SC, Frick C, Faber AJ, Fraser-Lee NJ, White DE, , N.-C. C. et al. (2003). Do maternal characteristics and past pregnancy experiences predict preterm delivery among women aged 20 to 34? *J Obstet Gynaecol Can, 25,* 656-666.

Tri-Council Policy Statement (1998). *Medical Research Council of Canada, Natural Sciences and Engineering Research Council of Canada, Social Sciences and Humanities Research Council of Canada. Ethical Conduct for research involving humans.*

Trick, L. R. (1993). Patient compliance--don't count on it! *J.Am.Optom.Assoc., 64,* 264-270.

Wang, E. E., Law, B. J., Boucher, F. D., Stephens, D., Robinson, J. L., Dobson, S. et al. (1996). Pediatric Investigators Collaborative Network on Infections in Canada (PICNIC) study of admission and management variation in patients hospitalized with respiratory syncytial viral lower respiratory tract infection. *J.Pediatr., 129,* 390-395.

Welliver, R. C. (2003). Respiratory syncytial virus and other respiratory viruses. *Pediatr.Infect.Dis.J., 22,* S6-10.

Young, J. (2002). Development of a potent respiratory syncytial virus-specific monoclonal antibody for the prevention of serious lower respiratory tract disease in infants. *Respir.Med., 96 Suppl B,* S31-S35.

APPENDIX 1: QUESTIONNAIRE

Study ID:_____

Call attempt:_____ **Date (yy/mm/dd):**_____

SYNAGIS FOLLOW-UP QUESTIONNAIRE

Form One: for those children who got at least one Synagis injection during the 2001-2002 RSV season (from Dec. 18, 2001 to June 3, 2002.).

To be answered by the ***PRIMARY CARE GIVER*** of the child.

Please circle the answer for each question.

1	What is your relationship to the child? Are you: 1. Child's mother 2. Child's father 3. Other (please specify): _____				
	Most of the following questions can be answered on a scale which ranks responses from "not at all", to "a little", to "somewhat" and ends at "a great deal". Please answer the following questions using that scale. There are also some 'yes/no' questions.	NOT AT ALL	A LITTLE	SOME WHAT	A GREAT DEAL
2	On a scale from not at all to a great deal, how much do you worry about the health condition of your child?	1	2	3	4
3	In general, do you think it is easy for your child to encounter a health problem?	Yes		No	
4	Using the scale again, from not at all to a great deal, in your opinion, how much do you know about RSV (Respiratory Synctial Virus) infection?	1	2	3	4
	Interviewer: *if the answer is* ***1 or 2****, please read the following:* *RSV (Respiratory Synctial Virus) is a major cause of hospitalization for respiratory tract infection among infants under 2 years old. It mainly affects the lower respiratory tract including the lungs.*				

	Interviewer: add in "using the same scale" for the following questions if the respondent needs clarification, if not, continue.				
5	In your opinion, how much do you know about Synagis injections?	1	2	3	4
	Interviewer: *if the answer is* ***1 or 2****, please read the following:* Synagis is used for RSV immunization and is offered to high-risk infants free of charge. Synagis is usually given as an injection once every 28 days for 5 months on average in winter.				
6	During the past winter, how much did you worry about your child getting RSV (Respiratory Synctial Virus) infection?	1	2	3	4
7	During the past winter, how much did you worry about your child having side-effects from Synagis injections?	1	2	3	4
8	During the past winter, how much did you worry about the discomfort your child might have felt with monthly Synagis injections?	1	2	3	4
9	In your opinion, how great was your child's risk of getting RSV infection during the past winter?	1	2	3	4
10	During the past winter, how much did you think the health of your child's lungs would worsen if your child got RSV infection?	1	2	3	4
11	During the past winter, how much did you think that Synagis would help protect your child against RSV infection?	1	2	3	4
12	Synagis is usually given as an injection once every 28 days for 5 months. How much did the need for <u>monthly</u> injections affect your decision about whether your child would receive Synagis?	1	2	3	4
13	Do you know how much **one injection** of Synagis cost?	Yes		No	

	13a. If yes, how much per injection (your best guess is ok): $ _____ 13b. If no, please provide your best guess: $_____				
14	You don't need to pay for Synagis. Did you consider the price of Synagis when you decided your child would receive the injection?	Yes		No	
	14a. If yes, how much did the cost of the injections affect your decision that your child would receive Synagis?	1	2	3	4
15	During the past winter, how much difficulty did you have with scheduling **time** for your child to receive Synagis?	1	2	3	4
16	During the past winter, how much difficulty did you have with **transportation** in getting your child to the Alberta Children's Hospital to receive Synagis?	1	2	3	4
17	During the past winter, how much did the **poor weather** conditions affect your decisions about taking your child to receive Synagis on scheduled appointment days?	1	2	3	4
18	On average, how long did it take you to travel **one way** to Alberta Children's Hospital for your child to receive Synagis each time (e.g. by car, bus etc.)? 1 Less than 30 minutes 2 30—60 minutes 3 More than 1 hour, but less than 2 hours 4 2 hours or more				
19	On average, after you arrived at Alberta Children's Hospital, how long did you wait before your child received Synagis injections? 1 Did not need to wait 2 Less than 10 minutes 3 10--20 minutes 4 20--30 minutes] 5 More than 30 minutes				

20	Usually, who took your child to the hospital to receive Synagis injections? (If more than one person, please tell me all that apply.) Was this usually the child's: 1. Mother 2. Father 3. Other (please specify): _____			
21	Usually, did the person(s) specified in the above question need to take time off from work to take your child to hospital to receive Synagis?	Yes	No	N/A (not working)
22	Are there other children who live in your child's household?	Yes		No
	22a. If yes, what are their ages? child #1_____ child #2_____ child #3_____ child #4 _____			
23	Does anyone in your home smoke?	Yes		No
	23a. If yes, what is the relationship between the smoker and the child? (please tell me all that apply) ❑ Child's mother ❑ Child's father ❑ Other (please specify):_____			
24	How is smoking handled in your home? (If no one smokes in your home, please consider the times when your relatives, friends or guests visiting you.) Is smoking: *(circle one only)* 1. Permitted any where 2. Confined to certain areas of the home 3. Not allowed when children are present 4. Not allowed in the home ***(interviewer:** if smoking only allowed outside of house, check option #4)*			
25	During the past winter, did your child go to daycare or to a babysitter where there were other young children?	Yes		No

	25a. If yes, how often did your child go to daycare or to a babysitter? 1. Every day 2. 4-6 days per week 3. 2-3 days per week 4. Once a week 5. 2-3 times a month 6. Once a month 7. Less than once a month		
26	During the past winter, did you take your child to a **doctor's office** for any respiratory or breathing concerns? Such as a bad cold or wheezing?	Yes	No
27	During the past winter, did your child go to an **emergency department** for any respiratory or breathing concerns?	Yes	No
	27a. If yes, which emergency department did your child go? [ ]		
28	During the past winter, was your child admitted to Alberta Children's Hospital or Peter Lougheed Centre or any other **hospitals**?	Yes	No
	28a. If yes, which hospital was your child admitted to?		
	28b. If yes, was your child admitted to **ICU** (Intensive Care Unit)?	Yes	No
29	Does the **distance** you need to travel to the Alberta Children's Hospital influence your decision to get the monthly injections?	Yes	No
30	If Synagis injections were offered **at your home**, would this influence your likelihood of having your infant complete all recommended monthly injections?	Yes	No
31	Did your child receive all the recommended immunizations or baby shots (e.g. IE etc.)?	Yes	No
32	Did your child receive the **Flu** shot?	Yes	No

<table>
<tr><td>33</td><td colspan="3">Where did you get the information about Synagis? (please tell me all that apply)
❑ Clinic at Alberta Children's Hospital If yes, which clinic: [ ]
❑ Pediatrician
❑ Family physician
❑ Nurse
o NICU nurse
o Community nurse
o Other nurse (please specify):_____
❑ Friends
❑ Reading materials, such as books or posters
❑ Other, (please specify):_____</td></tr>
<tr><td>34</td><td colspan="3">On average, how satisfied were you with the Synagis injections program your child was in during the past winter?
1 Very satisfied
2 Somewhat satisfied
3 Somewhat dissatisfied
4 Very dissatisfied</td></tr>
<tr><td rowspan="2">35</td><td>Do you feel that your child experienced any side-effects from Synagis injections?</td><td>Yes</td><td>No</td></tr>
<tr><td colspan="3">34a. If yes, what side-effects:_____</td></tr>
<tr><td rowspan="2">36</td><td>Did you have to pay any significant out of pocket expenses for your child to receive Synagis injections?</td><td>Yes</td><td>No</td></tr>
<tr><td colspan="3">35a. If yes, what were the top three out of pocket expenses?

(1) _____ (2) _____ (3) _____

35b. In total, how much did each of them cost during the time your child receiving Synagis last winter?

(1) $_____ (2) $_____ (3) $_____</td></tr>
<tr><td>37</td><td colspan="3">In general, how convenient was it for your child to receive Synagis injections during the past winter?
1. Very convenient
2. Somewhat convenient
3. Somewhat inconvenient
4. Very inconvenient</td></tr>
</table>

38	If you could choose again, would you still participate in the RSV Prevention Program?	Yes	No	Don't know
	38a. If yes, do you think you would: 1. Make **much more effort** to bring your child to get Synagis injection on scheduled appointment days? 2. Make **somewhat more effort** to bring your child to get Synagis injection on scheduled appointment days? 3. Make **the same effort as last year** in bringing your child to get Synagis injection on scheduled appointment days? 4. Make **less effort** to bring your child to get Synagis injection on scheduled appointment days?			
	38b. If no, what are your top three reasons that you won't participate in RSV Prevention Program? (open-ended question) 1. 2. 3.			
39	In the future, if a similar program will be provided to your child to prevent your child from getting other health problems, how likely would you like to participate? 1. Very much likely 2. Somewhat likely 3. Very little likely 4. Not at all likely			

Now just a few more questions for statistical purposes, in order to classify your answers along with everyone else who has participated in the survey.

40	What is your age? _____ Years (***Interviewer:*** if the respondent refuses or is very reluctant to answer this question, offer the age ranges) 1. 15 to 20 years old 2. 21 to 29 years old 3. 30 to 39 years old 4. 40 and above years old

41	What is your highest level of education? 1 Some high school or grade school (Grades 1-11) 2 Graduated high school 3 Some trade, technical, vocational school or business/community college (e.g. SAIT, Mount Royal College) 4 Some university (e.g. University of Calgary) 5 Completed trade, technical, vocational school or business/community college (e.g. SAIT, Mount Royal College) 6 University undergraduate degree (e.g. B.A., B.SC., LL.B.) 7 Some post-graduate education 8 Post graduate degree (e.g. M.A., M.SC., M.ED., M.D., D.D.S., D.M.D., D.V.M., O.D., PH.D., D.SC., D.ED.) 9 Other, (please specify): _____
42	What is your current occupation (e.g. accountant, homemaker, auto-mechanic)? _____
43	What is your ethnic or cultural background? 1 African North American/Black 2 Caucasian/White (e.g. English, French, German, Irish, Polish, Scottish, Ukrainian) 3 Chinese 4 Filipino 5 Greek 6 Italian 7 Japanese 8 Korean 9 Latin American (e.g. Brazilian, Chilean, Mexican) 10 Native/Aboriginal peoples of North America (e.g. First Nations, North American Indian, Inuit) 11 South Asian (e.g. East Indian, Pakistani, Punjabi, Sri Lankan) 12 South East Asian (Cambodian, Indonesian, Laotian, Vietnamese) 13 West Asian/ Arab (e.g. Armenian, Egyptian, Iranian, Lebanese, Moroccan) 14 Other (please specify): _____ 15 No response
44	What language do you **mainly** speak at home? (one answer only) _____

45	What is your marital status? 1. Single 2. Living with partner 3. Married 4. Separated 5. Divorced 6. Widowed
46	What is your combined household income before taxes in the past 12 months (your best guess)? 1. Less than $10,000 2. $10,000--$29,999 3. $30,000--$49,999 4. $50,000--$69,999 5. $70,000--$89,999 6. $90,000 or over 7. I prefer not to answer this question

Finally, two more questions about yourself.

		Poor	Fair	Good	Excellent
47	How would you rate your own physical health over the past 6 months?	1	2	3	4
48	How would you rate your own emotional health over the past 6 months?	1	2	3	4

That concludes the questionnaire, thank you very much for your time and help! Do you have any suggestion or comments about this interview or the Synagis injection program (i.e. RSV prevention program)?

If I have any questions about the information you provided in this interview, can I contact you again?

☐ Yes ☐ No

APPENDIX 2: ETHICS APPROVAL

UNIVERSITY OF CALGARY

FILE COPY

FACULTY OF MEDICINE

Office of Medical Bioethics
Heritage Medical Research Building/Rm 93
Telephone: (403) 220-7990
Fax: (403) 283-8524

2002-11-08

Dr. S.C. Tough
Department of Paediatrics
ACH
Calgary, Alberta

Dear Dr. Tough:

RE: What Factors Influence Parent Compliance with Respiratory Syncytial Virus (RSV) Prevention Program?
Student: Ms. Jing (Tracy) Xu **Degree: MSc**

Grant-ID: 16753

The above-noted thesis proposal including, the Study Invitation (dated October 7, 2002), and the Questionnaires (dated October 7, 2002) have been submitted for Committee review and found to be ethically acceptable. Please note that this approval is subject to the following conditions:

(1) a copy of the informed consent form must have been given to each research subject, if required for this study;
(2) a Progress Report must be submitted by 2003-11-08, containing the following information:
    (i) the number of subjects recruited;
    (ii) a description of any protocol modification;
    (iii) any unusual and/or severe complications, adverse events or unanticipated problems involving risks to subjects or others, withdrawal of subjects from the research, or complaints about the research;
    (iv) a summary of any recent literature, finding, or other relevant information, especially information about risks associated with the research;
    (v) a copy of the current informed consent form;
    (vi) the expected date of termination of this project;
(3) a Final Report must be submitted at the termination of the project.

Please note that you have been named as a principal collaborator on this study because students are not permitted to serve as principal investigators. Please accept the Board's best wishes for success in your research.

Yours sincerely,

Christopher J. Doig, MD, MSc, FRCPC
Chair, Conjoint Health Research Ethics Board

c.c. Child Health Research Committee
Dr. B. Scott (information)
Ms. Jing (Tracy) Xu

APPENDIX 3: STUDY INVITATION

Hello, may I speak with *(usu. mother of the infant)*?

Good morning/afternoon/evening, this is *(name of interviewer)* calling from the Respiratory Home Care Clinic, RSV Prevention Program at the Alberta Children's Hospital. As you may know the RSV immunization is new, so we are conducting a follow-up survey to evaluate the RSV Prevention Program. I'd like to speak with the primary care giver of *(name of infant)*. Are you the primary care giver?

*(**Interviewer:** If yes, proceed. If no, ask to speak to the primary care giver and repeat except the last sentence. If the primary care giver is not available at this time, please* schedule an appropriate time to call back.)

The purpose of this study is to help us better understand how well the RSV Prevention Program meets YOUR needs, and what influences YOUR decision to bring your baby to the immunization program. The results from this study will allow us to develop recommendations to improve the delivery and availability of the RSV Prevention Program, so that the program can benefit more families.

I'd like to know your opinion on the program by doing a short telephone interview. The interview is about 15 to 20 minutes. Would you be able to speak with me now?

(Interviewer: If yes, proceed. If no, please schedule an appropriate time to call back.)

Before we begin, I would like to assure you that your participation in this interview is completely voluntary, and any information you provide will be kept confidential. You may refuse to answer any questions and you are free to withdraw from the interview at any time, and this will NOT affect the health care your child will receive. Once the study is finished, the identifying information such as name and address will be deleted and destroyed. Only grouped and non-identifying data will be used for academic reports of this research, and no one will know what information is from you.

If you have any questions or concerns related to this research, please feel free to contact the project researcher or the research supervisor. Would you like to have their telephone numbers?

(Interviewer: If yes, provide the contact information as following:

Project researcher: Ms. Tracy Xu, (403) 210-7486 or jmxu@ucalgary.ca

Research supervisor: Dr. Ian Mitchell, (403) 943-7818)

Your decision to answer this telephone interview will be interpreted as an indication of your consent to participate. Do you have any questions? Do I have your permission to begin the interview?