OPEN ACCESS

Ology Press

Research

Vaccines and Immunology Open Access Journal

RSV Infection in Nunavut - cost analysis and associated risk factors: implication of vaccination program and public health planning

Sana Sharif MSc MPH,[1] Hina Sharif D-Pharm MBA,[2] Nadia Sharif MBBS FCPS,[3] Yingying Su BS PhD,[4] Rafay Sharif BS ME,[5]

[1]School of Public Health, University of Saskatchewan, Canada

[2]Department of Procurement, Marie Stopes Society, Pakistan

[3]Department of Pulmonary Medicine, Agha Khan University Hospital, Pakistan

[4]Department of Epidemiology, University of Saskatchewan, Canada

[5]Department of Bio-medical Engineering, Zia-ud-din University, Pakistan

Correspondence: Sana Sharif, School of Public Health, University of Saskatchewan, Canada, Email sas399@mail.usask.ca

Received: August 28, 2018 | **Published:** September 05, 2018

Abstract

Background/ Objectives. Respiratory Syncytial Virus (RSV) is a major cause of lower respiratory tract infection in Nunavut, causes severe symptoms of bronchiolitis and pneumonia. Synagis® vaccine decrease the mortality and morbidity rate of RSV. There is only one hospital for the entire territory and necessity of evacuation to reach the hospital. RSV is cost burden on Government of Nunavut in two ways: (a) The frequent use of evacuation rises the cost in additional to treatment cost. (b) Vaccine is costly and multiple doses are required to maintain the protection. Characterized the burden of the RSV infection (2011-2016), assessing risk and protective factors associated with RSV, and cost-benefit analysis for widening or narrowing the Synagis® program.

Methods. (a) Descriptive statistics (b) Incidence rate analysis (c) Cost analysis (medical services and Synagis® (d) Factors associated with RSV.

RESULTS. The highest observed average incidence rate of RSV (8 per 100 population) during 2012/13 year. The higher average incidence rate analyzed in age group 0-11 month among male 9 per 100 population and female 8 per 100 population. The average medical services cost per RSV case was $12,203 which is higher than average cost per vaccine participant $7,414. The total cost incurred due to RSV was approximately $8 million. Breastfeeding showed significant protective association with RSV and prenatal/postnatal smoking exposure showed significant risk for increasing RSV.

Recommendations. Introduced Universal Synagis® Program (USP) by the cost comparison between analyzed medical services cost with vaccine cost. Promote breastfeeding. Try to encourage no prenatal and postnatal smoking.

Keywords: RSV, synagis®, nunavut, LRTI, bronchiolitis, cost-effective, treatment, immunization.

Introduction

Respiratory Syncytial Virus (RSV) was first outlaid from Chimpanzee with the symptoms of cold.[1] Geographically it's cleared that RSV is the major cause of pneumonia and bronchiolitis in early childhood and infants.[2] RSV is a predominant cause of viral LRTI in initial childhood, producing probably 33 Million LRTI among under the age of five children, till 2011 there were 3.4 million hospitalizations and among 66,000-199,000 deaths yearly, worldwide

Epidemiology: RSV comes up with distinct challenge for the epidemiologists; meanwhile this virus shows patterns of infection and illness dissimilar with those of any other known respiratory tract viral pathogen.[3] RSV has a global occurrence, with likely, epidemics annually. In moderate climates, RSV typically appears in November or December and continues until April or May.[4] It is one of the major sources of developing LRTI in Northern Canada especially Nunavut, which causes severe symptoms of respiratory tract infection such as Bronchiolitis, Pneumonia (5),[5] this also support by another previous investigation that rate of RSV infection observed peak in infants aged almost 3 months.[6] With primary cardiopulmonary ailments[7] the elderly population,[8] and the people with immune-suppressed, predominantly bone marrow transplant cases.[9,10]

Nunavut: It is the most recent, biggest, and northernmost territory of Canada. It was disjointed legitimately on April 1, 1999 from the Northwest Territories, through the Nunavut Act[11] and the Nunavut Land Claims Agreement Act.[11] According to 2015 statistics, the population in whole territory was 36,919. The access route to each community is either by plane or by boat (which couldn't possible during winter). There are community centers present in Nunavut for healthcare, one center present in each community, but only one hospital Qikiqtani General Hospital (QGH) situated in Iqaluit, having all sort of healthcare facilities for instance Emergency Department, Intensive Care Unit etc.

Risk/Protective Factors: Several factors were identified through the literature review as being associated with an increased or decreased risk of RSV infection in infants.

Citation: Sharif S, Sharif H, Sharif N, et al. RSV Infection in Nunavut - cost analysis and associated risk factors: implication of vaccination program and public health planning. *Vaccine Immunol Open Access J.* (2018);1(1):26–36. DOI: 10.30881/vioaj.00007

(a) Breastfeeding**:**

One study found that being exclusively breastfed for more than two months was protective against RSV infection [OR 3.26 (1.96-5.42][12] and Children who do not exclusively breastfeeds have higher chance of RSV. (P= 0.032; odds ratio, 0.256; 95% confidence interval, 0.074–0.892)[13].

(b) Prenatal exposure to tobacco:

Exposure to tobacco smoke during pregnancy has been associated with an increased risk of RSV with [OR= 1.6(95% CI, 1.0–2.60].[14] It's revealed in another study that smoking during pregnancy increases the chance of RSV infection among infants [OR 1.61(1.16-2.25)].[15]

(c) Postnatal exposure to tobacco:

Maternal smoking increases the chance of risk of severe RSV infection (OR, 2.33 (95% CI, 1.19–4.57)[16]. Exposure to tobacco smoke inside the home has been associated with an increased risk for RSV infection in several studies.[17–19] More than two smokers in the household is significant risk for RSV infection [OR 1.71 (0.97-3.00)][19]. It is found an increased risk associated with a parent who smokes, even if the smoking takes place outside[17].

(d) Presence of Older Children in the Home:

Having school-aged siblings in home was associated with a significantly greater risk of RSV infection [OR 2.04 (1.53-2.74][17,20], and also pre-school age siblings or children at home is also one of the increasing risk factor of RSV [OR: 2.76 (1.51-5.03)][19].

(d) Crowding living condition:

The presence of more than five individuals residing in one household was found to increase the risk for RSV hospitalization [OR 1.69 (0.93-3.10)][19]. The presence of more than 4 residents and visitors in one household was to found to increase the RSV risk [OR 1.91 (1.19-3.07)][12]. The risk of RSV infection also increased among children sharing a bedroom with other people[17].

(e) Premature birth and low birth weight:

Both prematurity and low birth weight are associated with more severe RSV infections.[17,21] This relationship has been found to continue up to six months after birth for preterm babies with extremely low birth weights [0.40 + 0.24 infections per infant per month].[22]

Immunization against RSV- Synagis®

Palivizumab) is a humanized monoclonal antibody to neutralize the RSV effect. Synagis® inhibits the RSV actions and supports to avert the disease. It is used to stop serious lung disease caused by RSV in premature children, and those with certain lung disorders or heart disease. This will not beneficial for children who are already sickening with RSV disease[23]. Previous research revealed that the premature born children who had Broncho Pulmonary Dysplasia (BPD), Synagis® reduced hospitalization by 55% among RSV cases; however, Synagis® efficacy was higher among children without BPD i.e. 78% as compared among those with BPD i.e. 38% [24].

In Nunavut, RSV season typically in peak winter from January through May, and therefore this duration is for Synagis® immunization as well. RSV infection in infants is a frequent cause of medical evacuations to receive care. Children obliging intensive care must be travelled either to QGH in Iqaluit, or have to travel to other jurisdiction's hospitals (frequently Ottawa, Winnipeg, Yellowknife, Edmonton) via Medevac or Schedevac. RSV is the major cost burden on Government of Nunavut (GN), the travel for RSV elevates the cost of RSV in additional to treatment cost. Synagis® immunization program is to reduce morbidity and mortality rate related to RSV in infants. But again, vaccine is so costly and multiple doses are required over the RSV season to maintain protection and boost up the immunity against RSV. Therefore, there are limited criteria eligibility for children (See Appendix for Synagis® criteria in Nunavut).

The purpose of the study is to characterize the burden of disease due to RSV among infants in Nunavut from 2011 to 2016; also, determine the costs related to RSV to the GN which includes medical services, evacuation as well as Synagis® cost. In this study, also interested to assess risk factors associated with more severe RSV infections in infants to inform public health programming, including enrolment criteria of the Synagis® program.

Methodology

Sample: All the children in Nunavut from 0 to 24 months of age at the date of swab collection with a laboratory- confirmed RSV infection between September 2011 to August 2016 (5 years) were included in this analysis. The population was selected as it has the highest risk for serious health outcomes due to RSV. According to the above criteria, the total of 461 cases of RSV included in this study.

Data Sources: (a)Records of the lab-confirmed RSV cases, including demographic information were obtained from the Nunavut Influenza and RSV Enhanced Surveillance Database, located in the Health Protection Unit, GN. (b) The Nunavut's Health Insurance Registry was used to obtain health card numbers or birthdates if they were missing in the database. (c) Hospitalization records, including indicator of intubation and costs, were obtained from the Discharge Abstract Database (DAD), a database collected by the CIHI that includes information on patient discharges in all health care facilities in Canada. (d) Information on medical travel, including cost, was obtained from a database of all medical travel funded through the Nunavut Health Insurance Program. (e) Synagis® information was obtained from the Nunavut Synagis® Database, held in the Health Protection Unit, GN. (f) Cost of Synagis® taken from Health Protection Unit, GN. (g) Emergency Department visits; Temporary HCN and risk factor information was obtained from MEDITECH, an electronic medical health record system maintained by the Government of Nunavut. Health care visits as well pediatrician consultation reports, discharge summaries, well-baby records and other reports entered in patient's MEDITECH file were reviewed for relevant information. (h) Population estimates were obtained from the Nunavut Bureau of Statistics. (i) Average Cost of a Standard Hospital Stay, by province/territory taken from Canadian Institution of Health Information. (Note: Cost is in Canadian dollars' currency)

Variables: There are multiple variables included in this study based on Demographic information, Medical care services received including medical travel information and associated cost, Synagis® doses received and cost, risk/protective factors for severe infection, also considered different levels of Infection. See Table 1 for detail of the variables.

Ethics approval was obtained by taking licensed through the Nunavut Research Institute. This project is being conducted as an internal program review with the Department of Health, GN and is therefore subject to the territory's Scientist Act and other relevant legislation, including the Access to Information and Privacy

Citation: Sharif S, Sharif H, Sharif N, et al. RSV Infection in Nunavut - cost analysis and associated risk factors: implication of vaccination program and public health planning. *Vaccine Immunol Open Access J.* (2018);1(1):26–36.
DOI: 10.30881/vioaj.00007

Protection Act (ATIPP) which has provisions for the collection of medical information for the purpose of public health protection and planning. The study was administrative through Public Health Agency of Canada.

Table 1 The study variables & their descriptions[25,26]

Variables	Valid values	Description
Patient's Demographic Information		
HCN	Unique numeric identifier, nine digits in length	Patient's unique lifetime identifier for Nunavut Health Insurance Registry. If unknown, unique dummy HCN assigned.
Last Name	Name up to 25 characters in length	Patient's family name of patient linked to Health Insurance Registry file. Used to help identify clinical utilization records related to patient but recorded under caregiver's HCN.
First Name	Name up to 25 characters in length	Patient's given name of patient linked to Health Insurance Registry file.
Sex	Male, Female, Unknown	Biological sex of patient
Date of Birth	DD-MM-YYYY	The calendar day, month and year in which patient was born. Used to calculate age.
Age	0-5 month, 6-11 month, 12-17 months, 18-23 months	Patient's age in months on date of swab collection, calculated based on date of birth
Community	Community name (25 valid values)	Patients, or primary caregiver's, community of residence at time of infection.
Region	Qikiqtaaluk, Kivalliq, Kitikmeot	Patients, or primary caregiver's, region of residence at time of infection, based on community.
Ethnicity	Inuit, Non-Native, Non-Registered Metis, Registered Metis, Dene, Out of Territory	Identified using last digit of patient's valid HCN
Caregiver's HCN	Unique numeric identifier, nine digits in length	Patient's caregiver's unique lifetime identifier for Nunavut Health Insurance Registry, used to identify clinical utilization records for patient prior to being assigned own HCN
RSV Infection Information		
Symptom's Onset Date	DD-MM-YYYY	Symptoms onset date for RSV infection, prior to positive swab collection. If not available, date four days prior to swab collection date was used as proxy based on literature review 1
Swab Collection Date	DD-MM-YYY	The calendar day, month and year in which laboratory-confirmed RSV swab collected. Used to calculate age and year of infection.
Year of RSV Infection	(2011/12), (2012/13), (2013/14), (2014/15), (2015/16)	Respiratory season during which patient's RSV infection took place. Calculated based on swab date.
Severity of Infection	Mild, Moderate, Severe	Proxy based on hospitalization and intubation records (see below). • Mild – no hospitalization • Moderate – hospitalization due to RSV, no intubation • Severe – hospitalized and intubated due to RSV infection
Clinical Utilization		
Hospitalized	Yes or No	Indicator for whether patient was admitted to a hospital for care related to laboratory-confirmed RSV infection.
Length of Stay	Number	Number of day's patient was hospitalized for as indicated in hospital record. Used to calculate estimated hospitalization cost if no hospital cost included in record.
Province/Territory of Hospitalization	Province/Territory name	Province or Territory in which patient was hospitalized, as indicated in hospital record. Used to calculate estimated hospitalization cost if no hospital cost included in record.

Citation: Sharif S, Sharif H, Sharif N, et al. RSV Infection in Nunavut - cost analysis and associated risk factors: implication of vaccination program and public health planning. *Vaccine Immunol Open Access J.* (2018);1(1):26–36. DOI: 10.30881/vioaj.00007

Table Continued

Variables	Valid values	Description
Resource Intensity Weighting	Number	A comparative value listed in hospital record that refers to the estimated resource utilization of an average patient during hospitalization, as defined by the Canadian Institution of Health Information. Used to calculate estimated hospitalization cost if no hospital cost included in record.2
Medical Travel	Yes or No	Indicator for whether medical travel dataset indicates travel for patient related to laboratory-confirmed RSV infection.
Emergency Department Visit	Yes or No	Indicator for whether patient was seen in the Qikiqtani General Hospital Emergency for care related to laboratory-confirmed RSV infection.
Intubated	Yes or No	Indicator for whether patient was intubated during hospital stay based on hospital records.
Cost of Hospitalization	Numeric	Cost of patient's hospital admissions related to RSV infection as listed in DAD or, if no cost included in record, estimated as per calculations outlined in cost table (below). Cost was rounded off to nearest dollar.
Cost of Medical Travel	Numeric	Cost of patient's medical travel, including accompanying persons, related to RSV infection as listed in the medical travel database. Cost was rounded off to nearest dollar.
Estimated Cost of Emergency Department Visit	Numeric	Estimated cost of patient's Emergency Department visit related to RSV. Calculations detailed in cost Table 2 (below). Cost were rounded off to nearest dollar.
Average Cost of Standard Hospital Stay in Province/ Territory	Numeric	Used to calculate estimated hospitalization cost if no hospital cost included in record.
Synagis® History		
Synagis®	Yes or No	Indicator whether patient was enrolled in Nunavut Synagis® Program during the respiratory season in which RSV infection occurred and received at least one dose prior to swab collection date.
Date of last dose	DD-MM-YYYY	The calendar day, month and year in which the last Synagis® dose was administered to patient immediately prior to the swab collection date.
Up-to-Date dose	Yes, on time (≤ 28 days) Yes, not on time (>28days) No, on time (≤ 28 days) No, not on time (>28days)	Indicator of whether patient was up-to-date with Synagis® vaccination at time of RSV infection. Determined by the number of days between date of last dose and date of swab collection.
Cost of Synagis®	Numeric	Total cost of Synagis® doses administered to patient during the respiratory season in which RSV infection occurred. Further information on cost calculation included in cost Table 2 (below).
Child's Risk Factors For severe RSV/Clinical		
Breastfeeding	Exclusively/ Not Exclusively / Never / Less than 2 months of age	For infants, older than 2 months, indicator of breastfeeding history of patient as reported by caregiver. From the birth, up to the time of infection • Exclusively: only breastmilk, no formula fed to patient for more than two months • Not exclusively: breastmilk fed to patient in addition to formula and/or other milk products, or exclusive breastfed for less than two months. • Never: No breastmilk fed to child, only formula and/or other milk products

Citation: Sharif S, Sharif H, Sharif N, et al. RSV Infection in Nunavut - cost analysis and associated risk factors: implication of vaccination program and public health planning. *Vaccine Immunol Open Access J.* (2018);1(1):26–36.
DOI: 10.30881/vioaj.00007

Table Continued

Variables	Valid values	Description
Prenatal Exposure to Tobacco	Yes or No	Indicator of whether biological mother reported smoking tobacco while pregnant with patient.
Postnatal Exposure to Tobacco Inside the Home	Yes or No	Indicator of whether patient lives with individuals who smoke tobacco inside of the accommodation, reported at any time prior to swab collection date.
No. of Household	2-5, 6-9, ≥10	Number of people who typically reside at patient's primary residence as reported by caregiver.
Presence of older children in the home	Yes or No	Whether older children are regularly present in the patient's primary residence.
Gestational Age at Birth	<36 weeks or >36	Patient's gestational age at birth in completed weeks.
Birth weight	<2500g or >2500g	Patient's weight at birth in grams.
Type of Accommodation	Private or Shared	Private: only patient's immediate family shared the primary accommodation; Shared: patient's primary accommodation shared by individuals other than patient's immediate family.

Data analysis

Sample Characteristics

RSV cases will be summarized by descriptive statistics (case counts and proportions) by age group (0-5 months, 6-11 months, 12-17 months, and 18-23 months); Sex; RSV year of infection (September to August; 2011/12, 2012/13, 2013/14, 2014/15, 2015/16; and Ethnicity. Bivariate analysis will be conducted based on Severity of Infection to explore potential confounders or effect modifiers.

Synagis®

Bivariate analysis of Up-to-Date and Severity of Infection to examine whether relationship exists Synagis® program participants who did not have a laboratory-confirmed RSV infection in the same respiratory season as receiving Synagis® will be categorized as "None" for Severity of Infection Age category, sex, respiratory season and region will be examined as possible confounders.

Costs consist of average cost of medical services will be calculated using costs of hospitalization, medical travel, and emergency department visits by respiratory season. Average cost of medical services will be stratified by age group, sex and region to explore potential confounders or effect modifiers See Table 2 for cost calculation criteria. Synagis® program consist of the cost of care for Synagis® participants who developed an RSV infection in the same respiratory season will be calculated using hospitalization, medical travel and emergency department costs.

Incidence rates for each of the following by year, age group (0-11 months, 12-23 months), sex, year of infection and Region. Average incidence rates will also be calculated.

Availability of risk factor information in MEDITECH which include the percentage of cases with information on each risk factor variable recorded in MEDITECH will be calculated for the Qikiqtaaluk region in order to inform data collection planning for future risk factor analysis. Depending on availability of data, bivariate analysis between risk factors and Severity of Infection will be conducted for cases from the Qikiqtaaluk region.

Analysis will be conducted using IBM SPSS Statistics 22 and Microsoft Excel 2010.

Results

Descriptive statistics

See table 3, in which all the demographic information, including Synagis® information are summarized in the form of case count and proportion. As mentioned previously there were 461 total cases of RSV included in this study. among 461 cases mostly cases were Inuit and rest were unknown identity. The male sex cases were more than female cases from five-year data. The most represented age group of having RSV is "0-5 months". There were 3% participants of Synagis® developed RSV infection during immunization program. Table 4 showing the bivariate analysis between the level of infection with respect to demographic information, Synagis® as well as risk or protective factors associated with RSV infection. According to level of infection, there were more cases of medium level of infection than severe and mild cases. Qikiqtaaluk is the region having more number of cases than other two regions of Nunavut. Among risk/protective factors, the breastfeeding is the protective factor against the RSV cases, there were more cases among those who never breastfed and developed severe infection of RSV. Prenatal and Postnatal are the strongest risk factors for RSV. According to the analysis, the 6-9 people at home and other children present in the house, there was a chance to developed RSV infection. Gestational birth age and birthweight doesn't show significant association with RSV infection.

Incident rates

See Figure 1, showing the incident rates with respect to year of infection. the higher average incidence rate for age groups observed during 2012/13 season of infection i.e. 7.8~8 per 100 population. See Table 5, the incidence rate of male under age group of 0-11months

Citation: Sharif S, Sharif H, Sharif N, et al. RSV Infection in Nunavut - cost analysis and associated risk factors: implication of vaccination program and public health planning. *Vaccine Immunol Open Access J.* (2018);1(1):26–36.
DOI: 10.30881/vioaj.00007

higher during 2012/13 and 2013/14 which was 12 and 11 per 100 population respectively, analyzed incident rates were higher among male gender than female. As far as region is concerned, the higher incidence rate of RSV among age group of 0-11 months during 2011/12 season of infection in Qikiqtaaluk region was observed, which was about 18 per 100 population while in 2013/14 the incidence rate was 11.9~12 per 100 population, which were higher than other two regions.

Table 2 Cost Calculation

Variable	Source	Calculation
Cost of Hospitalization	DAD	Cost of patient's hospital admissions related to RSV infection as listed in DAD or, if no cost included in record, estimated with following formula: Length of Stay X Resource Intensity Weight (RIW) X Average Cost of Standard Hospital Stay in Province/Territory
Estimated Cost of Emergency Department Visit	CIHI – average cost of stay	Estimated cost of an ED visit was calculated by multiplying the average cost of a standard one-day hospital stay in Nunavut by the Resource Intensity Weight (RIW) of a one-day hospital stay with only one procedure for a child under 2 years old age. This cost was calculated for each respiratory season as the average cost of a standard hospital stay changes from year to year.
	DAD - RIW	Average Cost of Standard Hospital Stay in Nunavut X Resource Intensity Weight (patient under 2 years of age, one procedure during stay)
Cost of Synagis®	Nunavut Synagis® Database – number of doses, dose size Cost of Synagis® is taken from Health Protection unit, GN.	Cost of Synagis® per patient was calculated by multiplying the number of vials used for the patient by the vial price (2015/16 price list). Number of doses and size of doses were listed in Nunavut Synagis® Database for 2011/12, 2012/13 and 2013/14. When no dose sizes were listed for a patient, cost was estimated using the average cost for patients who received the same number of doses in a respiratory season. Estimated Cost of Synagis® is calculated by the average Cost of Synagis® in a year divided by the No. of participants in the same year.

(Note: See table in Appendix for Inclusion and Exclusion criteria of the variables.)

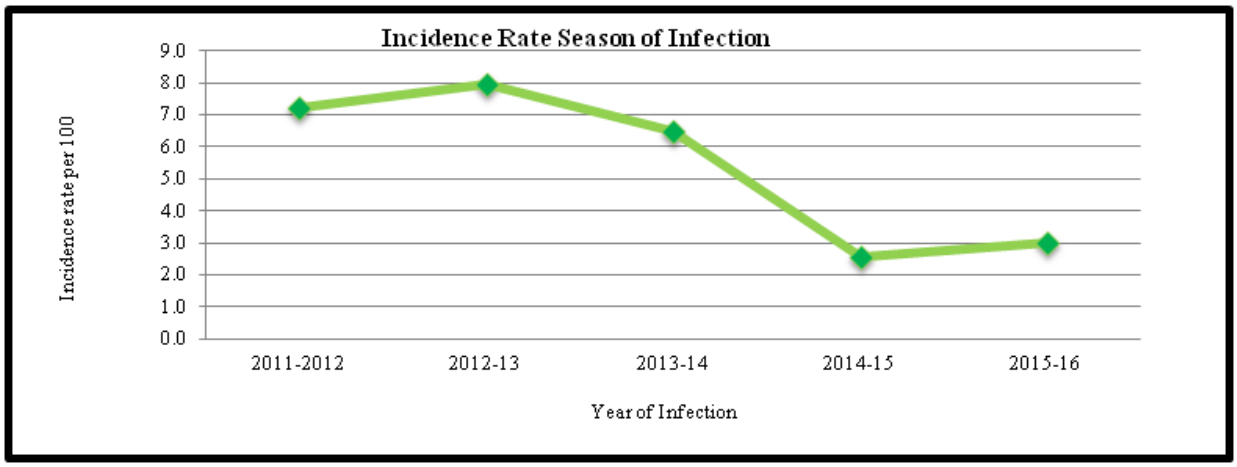

Figure 1 Average Incidence Rates by Seasons

Cost associated with RSV

See table 6, there is breakdown of Medical services Costs breakdown in between ER cost, travel cost and Hospitalization cost by year of Infection. The higher ER cost incurred in 2011/12 season of infection which were approximately $235,260, whereas higher travel cost incurred during 2012/13 season of infection which were approximately $638,201, however higher hospitalization cost incurred during 2013/14 which were approximately $783,026. See for all five seasons of infection with respect to medical services consumption proportion.

Medical Services Cost by Severity of Infection

After cost analysis, it was analyzed that severe cases incurred more hospitalization cost as well as travel cost i.e. $1,359,200 and $1,615,136 respectively, however Medium Severe cases incurred more ER cost than other two levels of infection i.e. $238,797, whereas higher average cost per case observed in mild cases i.e. $81,123. See table 7, for the entire cost breakdown between each level of infection with respect to different medical facilities.

Citation: Sharif S, Sharif H, Sharif N, et al. RSV Infection in Nunavut - cost analysis and associated risk factors: implication of vaccination program and public health planning. *Vaccine Immunol Open Access J.* (2018);1(1):26–36.
DOI: 10.30881/vioaj.00007

Table 3 Descriptive analysis of study variables

Descriptive Statistics (n= 461 cases of RSV	N (%)
Sex	
1. Male	219 (47.5)
2. Female	242 (52.5)
Age Group	
1. 0-5 months	218 (47)
2. 6-11 months	131 (28)
3. 12-17 months	75 (16)
4. 18-23 months	37 (8)
Ethnicity	
1. Inuit	456 (99)
2. Non-Native	4 (0.008)
3. NA	1 (0.002)
Region	
1. Qikiqtaaluk	248 (54)
2. Kivalliq	166 (36)
3. Kitikmeot	47 (10)
RSV Year of infection	
1. 2011/12	122 (26)
2. 2012/13	129 (28)
3. 2013/14	109 (24)
4. 2014/15	49 (11)
5. 2015/16	52 (11)
Synagis® Candidates per Year	
1. 2011/12	61 (16)
2. 2012/13	94 (25)
3. 2013/14	80 (21)
4. 2014/15	77 (20)
5. 2015/16	64 (17)
Synagis® participants developed RSV	
1. Yes	14 (3)
2. No	447 (97)

Table 4 Bivariate analysis between the variables and level of Infection

	Bivariate Analysis (n= 461 cases of RSV)		
	Level of RSV Infection N (%)		
Variable (N=no. of RSV cases)	**Severe**	**Medium**	**Mild**
Demographic Information			
Age Group			
1. 0-5 months (218)	17 (8)	102 (47)	98 (45)
2. 6-11 months (131)	4 (3)	47 (36)	81 (61)
3. 12-17 months (75)	2 (3)	22 (29)	51 (68)
4. 18-23 months (37)	-	14 (38)	23 (62)
Region			
1. Qikiqtaaluk (248)	12 (5)	113 (44)	128 (52)
2. Kivalliq (166)	9 (5)	63 (38)	94 (57)
3. Kitikmeot (47)	2 (4)	14 (30)	31 (66)
Synagis®			
Synagis® participant's			
1. Up-to-date & on time (5)	1 (20)	1 (20)	3 (60)
2. Up-to-date & not on time (2)	1 (50)	1 (50)	-
3. Not up-to-date & on time (5)	1 (20)	1 (20)	3 (60)
4. Not up-to-date & not on time (2)	-	1 (50)	1 (50)
Risk/ Protective Factors			
Breastfeeding History			
1. Exclusively (39)	1 (11)	23 (39)	15 (38)
2. Less Exclusively (28)	2 (26)	14 (24)	12 (30)
3. Never breastfed (41)	6 (67)	22 (37)	13 (33)
4. Unknown (54)	-	-	-
Prenatal Smoking			
1. Yes (107)	9 (9)	60 (58)	34 (33)
2. No (9)	1 (17)	3 (50)	2 (33)
No. of Household			
1. 2-5 (48)	6 (13)	21 (44)	21 (44)
2. 6-9 (60)	2 (3)	36 (60)	22 (37)
3. 10- greater (16)	3 (19)	10 (63)	3 (19)

Citation: Sharif S, Sharif H, Sharif N, et al. RSV Infection in Nunavut - cost analysis and associated risk factors: implication of vaccination program and public health planning. *Vaccine Immunol Open Access J.* (2018);1(1):26–36. DOI: 10.30881/vioaj.00007

Table Continued

	Bivariate Analysis (n= 461 cases of RSV)		
	Level of RSV Infection N (%)		
Variable (N=no. of RSV cases)	**Severe**	**Medium**	**Mild**
Demographic Information			
No. of Other children at home			
1. Yes (87)	9 (10)	44 (51)	34 (39)
2. No (23)	1 (4)	17 (74)	5 (22)
Gestational Age			
1. ≤36 weeks (34)	4 (12)	17 (50)	13 (38)
2. >36 weeks (62)	6 (8)	41 (57)	25 (35)
Birthweight			
1. ≤2500g (20)	1 (5)	10 (50)	9 (45)
2. >2500g (102)	8 (8)	54 (53)	40 (39)

Table 5 Incident Rates between Sex and Age groups with respect to year of Infection

	Incident Rates (%)	
	Age Group	
Year of Infection	0—11 months	12—23 months
Sex		
Male		
2011/12	9.2	4.5
2012/13	12.0	3.6
2013/14	11.1	3.2
2014/15	5.5	1.1
2015/16	5.5	1.3
Average	**8.6**	**2.8**
Female		
2011/12	11.8	2.7
2012/13	11.5	4.3
2013/14	10.1	1.9
2014/15	2.9	2.0
2015/16	3.0	2.0
Average	**7.9**	**2.6**

Table Continued

	Incident Rates (%)	
	Age Group	
Year of Infection	0—11 months	12—23 months
Region		
Qikiqtaaluk		
2011/12	18.3	4.3
2012/13	7.7	3.3
2013/14	11.9	2.4
2014/15	4.0	2.2
2015/16	5.3	2.4
Average	**9.4**	**3.3**
Kivalliq		
2011/12	5.7	2.6
2012/13	12.9	6.3
2013/14	10.5	3.0
2014/15	4.0	1.2
2015/16	3.9	0.9
Average	**7.4**	**2.8**
Kitikmeot		
2011/12	7.7	1.5
2012/13	18.2	3.5
2013/14	4.9	0.8
2014/15	0.9	0
2015/16	1.0	0
Average	**6.5**	**1.2**

Cost Comparison of five years' medical services and Synagis® cost for RSV infection

In Table 8, there is cost summary for all five years cost of medical services due to RSV and cost of Immunization with respect to season of infection and cases for RSV and Participants of Synagis®. The average cost per participant of Synagis was approximately $ 7,414, whereas average cost per RSV case was approximately $12,203.

Citation: Sharif S, Sharif H, Sharif N, et al. RSV Infection in Nunavut - cost analysis and associated risk factors: implication of vaccination program and public health planning. *Vaccine Immunol Open Access J.* (2018);1(1):26–36.
DOI: 10.30881/vioaj.00007

Table 6 RSV Medical Services Cost by Year of Infection

Season of Infection	ER Cost	Travel Cost	Hospitalization Cost	Total Cost By years	Average total services cost per case (n)
2011-2012	22%	36%	42%	$984,570	**$ 12,542** (122)
2012-2013	5%	45%	50%	$1,409,723	**$ 10,928** (129)
2013-2014	3%	41%	56%	$1,367,104	**$ 12,542** (109)
2014-2015	10%	46%	44%	$813,314	**$ 16,651** (49)
2015-2016	4%	37%	59%	$887,627	**$ 15,641** (52)
Total Cost by Services	**$437,426 (8%)**	**2,264,764 (41%)**	**5,462,339 (51%)**	**$5,462,339**	**$ 11,849 (461)**

Table 7 Medical Services cost by Level of Infection

Level of Infection	ER Cost	Travel Cost	Hospitalization Cost	Average Cost By case (n)
Severe	-	$498,483	$1,355,089	$80,590 (23)
Medium	$164,793	$1,649,812	$1,405,060	$16,946 (190)
Mild	$272,633	$116,369	-	$1,569 (248)

Table 8 Comparison of Synagis® & Medical Services due to RSV by Year of Infection

Year	**Synagis®** participants	**Total Synagis®** Cost	**RSV cases**	**Cost of Medical Services & Travel**
2011/2012	61	$516,646	122	$984,570
2012/2013	94	$689,070	129	$1,409,723
2013/2014	80	$514,544	109	$1,367,104
2014/2015	77	$563,441	49	$813,314
2015/2016	64	$504,013	52	$887,627
Total	376	$2,787,713	461	$5,462,339

Conclusion & discussion

By the analysis it is found out that there was no any extreme difference between males and female's positive swabs cases, the higher number of cases among 0-5months aged group children, this might be that they are more likely to be tested, more likely to see a health care professional, could also be of the fact that under six-month age group the children have low immunity compared with the other age group children, and have more potential to infect by RSV during respiratory season. As far as region is concerned, Qikiqtaaluk is a larger than other two regions in Nunavut, so the proportion of cases in Qikiqtaaluk genuinely more than Kivalliq and Kitikmeot because of higher population difference, more population more number of cases expected. In analysis of ethnicity it is also very obvious that the more than 85% population in Nunavut are Inuit's and rest are Non-natives, Metis, Deans, which is a reason to increase number of cases (456 cases) among Inuit's than others, but on the other side if we see in non-native population which could be less than 5% and among them 4 cases would be a higher incidence rate than among Intuits. In bivariate analysis between the level of infection and regions, the reason behind the higher no. of severe or mild cases from Qikiqtaaluk region would be the presence of QGH situated inside the region, which could be reason that children had belonged from this region treated with intensive care, and as per definition of levels of infection those who were hospitalized were considered as medium level of infection, and might be there were more number of mild cases than medium but for presence of hospital in this region they hospitalized and was categorized under medium level of infection, while children from other regions got initial care more inside the other communities so they couldn't categorize properly in this study and again the higher population size in Qikiqtaaluk higher the ratio of severe, mild and medium level of cases. As far as bivariate analysis between the level of infection and children aged group, it is quite obvious that more number of cases belonged from 0-5month aged group, so the proportion of severity is higher than other age group, which is due to low immunity level, so this may be a reason more severe cases observed, and more complications experienced by children under the age of 6 months.

Higher incidence rate among male and females in between 0-11months age group, which again showed that newborn infants and young children under age of 1 were maybe have more severe infections, showed more symptoms, and ultimately tested more. The higher incidence rate in Qikiqtaaluk was observed during 2011/12 season of infection, whereas in Kitikmeot and Kivalliq the higher incidence rate was observed during 2012/13 season of infection, which could be the reason that during 2012/13 season of infection, the outbreak mostly covers children from Kitikmeot and Kivalliq region, and therefore the average incidence rate between the season of infection was observed during same 2012/13 season.

Citation: Sharif S, Sharif H, Sharif N, et al. RSV Infection in Nunavut - cost analysis and associated risk factors: implication of vaccination program and public health planning. *Vaccine Immunol Open Access J.* (2018);1(1):26–36.
DOI: 10.30881/vioaj.00007

According to analysis, the higher cost observed with respect to year of infection during 2012/13, this is due to higher number of cases in that season (129 cases). But average cost per case higher in season 2015/16 and 2014/15 ($ 17,587 &$ 16,122 respectively), the reason behind this cost due to higher travel cost as well as hospitalization cost, and it is also showing a greater number of cases treated outside of territory. The cost stratification as per aged groups, the average cost per case was higher among 12-17 months age group although the number of cases under this age group were 24 of total RSV cases, this is due to the reason of longer hospitalization stays as well as estimated all of them out of territory for receiving treatment and as it already explained in background and methodology of the study that all the hospitals have different cost of hospitalization stay with respect to different province, so that cost varied and increased among this age group. A part from age group, if we talk about the cost per medical services by level of infection, the higher average cost per case noted in Severe level of infection, although the number of cases under this level were limited, i.e. 23 cases but due to large number of procedures during hospital stay as well as longer stays in hospital, mostly went out of territory for receiving intensive care so that travel cost was also higher among those 23 cases.

The range of the days between the late dose of Synagis® to the missed dose of Synagis® is between 4 to 28 days, after 4 days from expected date of dose consider late dosage whereas 28 days' duration from one dose of Synagis® to the next dose and after 28 days consider late missed dose. After analyzing the Synagis® participants, there were fourteen participants (3%) who got infected with RSV during Synagis® program, the main reason for having infection among them was missed or late doses which ultimately developed infection but few of them under protective range of Synagis® but developed RSV, this might could be differences in dosage quantity or other risk factors could be more dominant with those participants of Synagis®. After bivariate analysis between the up to date participants of Synagis® with level of severity, it is found out that, two candidates who were actually up to date but developed severe RSV infection, there might be a reason those two patients didn't received dosages in time, although they both didn't miss any dosages, but no. of days should be accurate while receiving Synagis®.

In this study only considered those cases charts review, lab reports which was present electronically, only 33% (154 cases) information documented under Meditech, so among them, it was hard to decide about actual significant result regarding those risk factors. As far as this study analysis is concerned, Breastfed history showed significant association, those cases who never breastfed developed more no. of severe level of infection (6 cases, 67%) and among those who were breastfeeding exclusively, one case developed severe infection, this might be due to the effect of other risk factors would be dominant. Prenatal smoking exposure also showed significant result, those cases whose mother used tobacco during pregnancy developed more cases of Infection of RSV (107 cases) than those who didn't prenatal expose with tobacco (9 cases), this was studied in peer-literature, that children who prenatal expose to smoking developed respiratory infections in early life years. Postnatal smoking also showed significant results; those cases that exposed with tobacco or other smoke inside home developed RSV (103 cases) were higher in number than those who were not postnatal exposed with smoking (6 cases). The no. of household of the cases also showed significant relation with RSV, the higher number of cases among those cases who were living with 6-9 people inside the household (60 cases) than those who were living 2-5 people (48 cases). Other children living with the cases at home also showed noteworthy result as per mentioned in previous literature that if number of children are present with child, chances of RSV would be higher, so in this study with limited data, 87 cases developed RSV compared with those who didn't live with other children (43 cases). Gestational Age of birth and Birthweight showed insignificant relation with RSV infection, those who were born with gestational age above 36 weeks developed more number of RSV (62 cases) than those who born prematurely <36 weeks (34 cases), Same with Birthweight that more number of cases who born with normal birthweight i.e. above 2500g (102 cases) than those who born underweight <2500g (20 cases). The reason might be there were not enough data which could decide either there would be reason of RSV in Nunavut or not, it is found in previous research that there is significant relation between premature birth and lower birthweight with developing RSV. The complete data could be open window for real reason of RSV.

Limitation of the study

There are few limitations of this study: (a) The cases considered in this study were lab-confirmed RSV cases which could have possibility of underestimation the actual number of RSV cases. (b) Not everyone swabbed for RSV in the Kivalliq and Kitikmeot region because of absence of certain facilities, so that it could have also underestimated the actual number of RSV cases in those two regions or over estimation of number of cases in Qikiqtaaluk region. (c) Qikiqtani General Hospital situated in Qikiqtaaluk region, which could possibility to have a greater number of cases of Qikiqtaaluk region hospitalized and more number of medium level of cases because of hospitalization even they might have had mild RSV.

Recommendations

(a) Compared estimated cost of universal Synagis® program, including medical cost for estimated no. of cases assuming effectiveness is similar in general population.

Estimated cost for universal Synagis® program = [% of cases among Synagis® participants (mild, medium, severe) x total population 0-23 months x average cost incurred per case (mild, medium, severe)].

(b) According to analysis the more number of severe cases or higher incidence rate observed in age group under one so requiring the most care which may lead to long term health consequences in addition to higher cost. So more focused in this age group which could ultimately reduce the incident rate. (c) Try to more focus on reducing risk factors of RSV, should gather all the other data which could finally evaluate the risk factor complete picture, in that light documented some policies regarding avoiding smoking inside the house or in front of young children who are more susceptible to Infection. (d) Continue efforts to address risk factors, preliminary risk factor association show high exposure to tobacco smoke among RSV cases and milder infections among cases exclusively breastfed for at least 2 months

Future activities of this program

It is recommended for future to gather all the risk/protective factors other than Meditech database which are in the form of paper charts etc. and then analyses the association between the risk/protective factors with RSV infection. Also, recommended to see how the factors may influence level of infection with hospitalization (with/without intubation) and non-hospitalized patients as group to compare against each other on a bigger scale.

Citation: Sharif S, Sharif H, Sharif N, et al. RSV Infection in Nunavut - cost analysis and associated risk factors: implication of vaccination program and public health planning. *Vaccine Immunol Open Access J.* (2018);1(1):26–36.
DOI: 10.30881/vioaj.00007

Acknowledgements

The authors thank to Dr. Kim Barker (CMOH-GN) and team of Department of Health Information, Government of Nunavut.

Disclaimer

This project is being funded my Public Health Agency of Canada (PHAC).

Conflicts of Interest

The authors declare no conflict of interest.

Author Contributions

Sana Sharif involved in study design, data cleaning, data collection, data analysis, interpretation of results, evidence based recommendations and development of the manuscript. Hina Sharif contributed in supportive literature search, cost-effective benefits evidence of immunization. Nadia Sharif and Rafay Sharif involved in RSV alternative medical services suggestion and contributed in revising it critically for substantial intellectual content. Yinying Su involved in research approved suggestions. All authors read and approved the final manuscript.

References

1. Morris JA, Blount Jr RE, Savage RE. Recovery of cytopathogenic agent from chimpanzees with goryza. *Proc Soc Exp Biol Med*. 1956;92(3):544–549.
2. Mclntosh K. Respiratory syncytial virus. In: *Viral Infections of Humans*. Springer; 1997:691–711.
3. Nair H, Nokes DJ, Gessner BD, et al. Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. *The Lancet*. 2010;375(9725):1545–1555.
4. McCarthy CA, Hall CB. Respiratory Syncytial Virus. *Pediatr Rev*. 2003;24(9):301.
5. Banerji A, Panzov V, Young M, et al. The real-life effectiveness of palivizumab for reducing hospital admissions for respiratory syncytial virus in infants residing in Nunavut. *Can Respir J*. 2014;21(3):185–189.
6. Sommer C, Resch B, Simões EA. Suppl 2: Risk Factors for Severe Respiratory Syncytial Virus Lower Respiratory Tract Infection. *Open Microbiol J*. 2011;5:144.
7. Walsh EE, Falsey AR, Hennessey PA. Respiratory syncytial and other virus infections in persons with chronic cardiopulmonary disease. *Am J Respir Crit Care Med*. 1999;160(3):791–795.
8. Falsey AR, Walsh EE. Respiratory syncytial virus infection in adults. *Clin Microbiol Rev*. 2000;13(3):371–384.
9. Raboni SM, Nogueira MB, Tsuchiya LR, et al. Respiratory tract viral infections in bone marrow transplant patients. *Transplantation*. 2003;76(1):142–146.
10. Hassan IA, Chopra R, Swindell R, Mutton KJ. Respiratory viral infections after bone marrow/peripheral stem-cell transplantation: the Christie hospital experience. *Bone Marrow Transplant*. 2003;32(1):73.
11. Justice Canada. *Nunavut Act*.; 1993.
12. Figueras-Aloy J, Carbonell-Estrany X, Quero J, Group IS. Case-control study of the risk factors linked to respiratory syncytial virus infection requiring hospitalization in premature infants born at a gestational age of 33–35 weeks in Spain. *Pediatr Infect Dis J*. 2004;23(9):815–820.
13. Nishimura T, Suzue J, Kaji H. Breastfeeding reduces the severity of respiratory syncytial virus infection among young infants: a multi-center prospective study. *Pediatr Int*. 2009;51(6):812–816.
14. Holman RC, Shay DK, Curns AT, Lingappa JR, Anderson LJ. Risk factors for bronchiolitis-associated deaths among infants in the United States. *Pediatr Infect Dis J*. 2003;22(6):483–489.
15. Figueras-Aloy J, Carbonell-Estrany X, Quero J, Group IS. Case-control study of the risk factors linked to respiratory syncytial virus infection requiring hospitalization in premature infants born at a gestational age of 33–35 weeks in Spain. *Pediatr Infect Dis J*. 2004;23(9):815–820.
16. McConnochie KM, Roghmann KJ. Parental smoking, presence of older siblings, and family history of asthma increase risk of bronchiolitis. *Am J Dis Child*. 1986;140(8):806–812.
17. Simoes EA. Environmental and demographic risk factors for respiratory syncytial virus lower respiratory tract disease. *J Pediatr*. 2003;143(5):118–126.
18. Meissner HC. The unresolved issue of risk factors for hospitalization of infants with respiratory syncytial virus infection born after 33–35 weeks gestation. *Pediatr Infect Dis J*. 2004;23(9):821–823.
19. Law BJ, Langley JM, Allen U, et al. 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*. 2004;23(9):806–814.
20. Figueras-Aloy J, Carbonell-Estrany X, Quero-Jiménez J, et al. FLIP-2 Study: risk factors linked to respiratory syncytial virus infection requiring hospitalization in premature infants born in Spain at a gestational age of 32 to 35 weeks. *Pediatr Infect Dis J*. 2008;27(9):788–793.
21. Welliver RC. Review of epidemiology and clinical risk factors for severe respiratory syncytial virus (RSV) infection. *J Pediatr*. 2003;143(5):112–117.
22. Ballow M, Cates KL, Rowe JC, Goetz C, Desbonnet C. Development of the immune system in very low birth weight (less than 1500 g) premature infants: concentrations of plasma immunoglobulins and patterns of infections. *Pediatr Res*. 1986;20(9):899.
23. https://www.drugs.com/synagis.html
24. Fetus A joint statement with the, Committee N. Palivizumab and respiratory syncytial virus immune globulin intravenous for the prophylaxis of respiratory syncytial virus infection in high risk infants. *Paediatr Child Health*. 1999;4(7):474–480.
25. Okiro EA, White LJ, Ngama M, Cane PA, Medley GF, Nokes DJ. Duration of shedding of respiratory syncytial virus in a community study of Kenyan children. *BMC infectious diseases*. 2010;10(1):15.
26. Canadian Institution for Health Information. Patient Cost Estimator Methodological Notes and Glossary. 2013.