April 2011

Analyzing Epidemics in New France: The Measles Epidemic of 1714-15

Ryan M. Mazan
The University of Western Ontario

Supervisor
Dr. Alain Gagnon
The University of Western Ontario

Graduate Program in Sociology

A thesis submitted in partial fulfillment of the requirements for the degree in Doctor of Philosophy

ANALYZING EPIDEMICS IN NEW FRANCE: THE MEASLES EPIDEMIC OF 1714-15

(Thesis Format: Integrated Article)

By

Ryan Michael Mazan

Graduate Program in
Sociology

A Thesis submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy

School of Graduate and Postdoctoral Studies
The University of Western Ontario
London, Ontario, Canada
April 2011

THE UNIVERSITY OF WESTERN ONTARIO
SCHOOL OF GRADUATE AND POSTDOCTORAL STUDIES

CERTIFICATE OF EXAMINATION

Supervisor	Examiners
_____	_____
Dr. Alain Gagnon	Dr. Roderic Beaujot
	_____
	Dr. Kim Shuey
	_____
	Dr. Eldon Molto
	_____
	Dr. Ken Robert Smith

The thesis by

Ryan Mazan

entitled:

Analyzing Epidemics in New France: The Measles Epidemic of 1714-15

is accepted in partial fulfillment of the
requirements for the degree of
Doctor of Philosophy

Date_____ _____
Chair of the Thesis Examination Board

ABSTRACT

Few epidemics have been documented in the context of historical Quebec. The rich epidemiological and demographic data contained in the *Registre de population du Québec ancien* makes it possible to conduct detailed analyses of historical epidemics and can be beneficial to filling in gaps in modern knowledge. The historical studies of measles have a distinct advantage over modern ones, in that epidemics can be analyzed in a natural state unhindered by modern medical treatment and vaccine campaigns. This dissertation attempts to fill this knowledge gap of infectious diseases through the development of methods to analyze epidemics in the absence of cause of death records. The results show the suitability of these methods to investigate the 1714-15 measles epidemic and its impact on the children in the population.

The first study examined the general dynamics of the epidemic that provisioned the baseline for the subsequent studies. Measles entry to the Montreal area was from Colonial America circa late-March of 1714. The epidemic spread eastwards to most other parts of the colony by late-August of the same year and disappeared early in 1715. Measles was virulent with an estimated death rate of 52.8 per thousand for children under age 15. Infants and toddlers were the main victims, while females were slightly more likely than males to have died from the virus. Although the epidemic originated in the Western parishes, severity finally turned out to be higher in the Eastern parishes of the colony.

The second study identified several measles-specific risk factors among children under age 5 were identified with case/control comparisons, which revealed that the effects of these factors were only significant and intensified during the acute phase of the epidemic.

Contrary to what was reported in modern studies, singletons or children with fewer siblings had higher odds of dying than children in larger sibships. The age difference between siblings appeared to be a more important predictor of death than the size of the sibship, as a larger average difference led to an increased likelihood of death. As well, children with a sibling who died during the epidemic and children with immigrant parents were at higher risk.

In the third study, exposed children who survived the acute episode of the epidemic were followed for 25 months past the estimated date of infection. It was found that children exposed before age 3 had higher long-term mortality than the unexposed children. The difference remained significant while assessing the effects of the demographic and sibship risk factors. For the exposed cohort, the risk of death also varied by age and sex. Only females exposed during infancy had a significantly higher risk of dying, while both exposed male and female toddlers had higher mortality during the follow-up period. In this case, the effect was slightly stronger for males. No significant long-term mortality difference was found among children exposed between 36 and 59 months of age.

Key Words: New France, measles mortality, epidemics, smoothing splines, indirect estimation, life tables, parish data, historical demography, measles risk factors, measles exposure.

DEDICATION

To Maki, Marton, Ma and especially to my late Pa who taught me to never give up.

ACKNOWLEDGEMENTS

I would like to start by thanking my dissertation advisor, Professor Alain Gagnon, for introducing me to the parish data and for all of his support throughout my endeavor. You are a great mentor and friend and I greatly appreciate all of the constructive criticism you provided on the numerous drafts of this study. I also thank Professor Bertrand Desjardins from the University of Montreal for providing continued access to the rich parish data over the years. I also want to acknowledge all of my committee members: Professors – Roderic Beaujot, Kim Shuey, Eldon Molto and Ken Smith for their insightful feedback and helpful comments about my dissertation.

Finally, I would like to thank my family and friends. I am very lucky to have such supportive parents and siblings. Thanks also to my friends for all the laughs and good times you provided along the way. I especially want to thank my wife Maki for your patience and understanding over the years. You are my main inspiration and I can never thank you enough for all of your love and support. A special thanks also goes to my son Marton for coming into this world and giving me the final motivation that I needed to finish this chapter in my life.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Chapter 1

Introduction

In 1608, Samuel De Champlain founded the colony of New France. The colony was originally established as a hunting and fishing outpost and it took many years before it became a permanent settlement (Charbonneau et al., 1993; Charbonneau et al., 2000). The Canadian climate was harsher than in France, but environmental conditions were more favourable for survival. Abundant stocks of wild game and fish provided an ample food supply for the inhabitants of the colony. The Saint Lawrence River Valley also had good agricultural potential. However, this potential was not utilized until later, as population growth was slow from the onset of settlement. At the time, the French had more of an interest in securing dominance over the burgeoning fur trade. In addition, there was little need for European labour, as First Nations allies (i.e., Huron) were directly involved in the collection and transportation of furs. Fur trade merchants did not have a need to populate the colony to any great extent.

As a new settlement, Quebec had a low population density and was relatively isolated from outside contact. These factors helped limit the formation and spread of communicable diseases that usually need large host populations to survive. Historical Quebec was unique for the time because it was not severely impacted by epidemics, as compared with France or Colonial America. This also meant that most early French Canadians were born into quite 'favourable' environmental conditions, as the weight of exogenous deaths over endogenous deaths was relatively low in early times (Nault et al., 1990). That is, the ratio of deaths to infant mortality as a whole was higher during the

neonatal stage as a result of biological causes, rather than in the postnatal stage, which are mostly due to environmental causes.

1.2. Infant and Childhood Mortality in New France

For a general overview of mortality among the children in New France, I have tabulated a series of childhood period mortality rates, which are compared to available rates among English parishes at the time. These general tabulations will serve as the background for more specific studies on measles mortality during the 1714 outbreak that will be presented in the following chapters.

Table 1.1 shows the decennial mortality rates (${}_nm_x$) of French Canadian children from 1660 to 1749. Infant mortality rates were adjusted using Henry's birth interval method for the underregistration of deaths. The underreporting of deaths consisted mostly of infants who died before baptism and was higher during the early period of colonization (see Gagnon and Mazan (2009), for a detailed description of the method). The period rates for the Canadian born children aged 1 to 9 years were not adjusted. They were calculated based on the number of deaths in a given year divided by the estimated population alive at some point during the year. Children without a date of death were also included in the denominator if they had a date and a parish of marriage; it was assumed that they were living in the colony during childhood.

Table 1.1. Decennial childhood mortality rates per 1,000 French Canadian children, New France 1660-1749.

	${}_1m_0$	${}_4m_1$	${}_5m_5$	${}_5m_0$	${}_{10}m_0$
New France[a]					
1660-69	163	6	5	49	33
1670-79	175	7	2	51	33
1680-89	216	20	6	69	40
1690-99	192	12	3	60	36
1700-09	225	20	7	72	44
1710-19	240	22	6	79	46
1720-29	231	17	5	74	44
1730-39	254	30	9	93	58
1740-49	309	27	7	108	63
1660-99	187	11	4	58	35
1700-49	252	23	7	85	51
13 English Parishes[b]					
1650-99	170	27	10	54	33
1700-49	197	28	10	58	37

[a] Corrected infant mortality rates are derived from Gagnon and Mazan (2009).
[b] Childhood mortality rates are derived from Wrigley and Schofield (1983).

It is generally believed that prior to 1700, infant mortality was lower in Quebec than in France (Nault et al., 1990; Charbonneau et al., 2000), although there are no available estimates of French mortality prior to 1740 to provide a basis of comparison. In general, it is difficult to obtain detailed death rates for most populations before 1750, with the exception of Britain and, to a lesser extent, the American Colonies. To provide a comparison for Quebec, rates are thus also shown for 13 parishes in England with relatively low mortality for the time (Wrigley and Schofield, 1983). These 13 parishes provide a reasonable contextual comparison, as they consisted of rural and moderate size towns, which was similar to the situation in Quebec[1].

[1] Note, however, that the adjusted English estimates are suspected to be too low for the time. The reverse projection method used to adjust the English rates may not be as accurate as Henry's method based on birth interval analysis. In the future, a comparison of the two methods using the Quebec data needs be conducted to evaluate this assumption. Nevertheless, the English rates help give a general sense of what was happening in Quebec at the time.

If the rates in the 13 English parishes are assumed to be reliable, then infant mortality was slightly higher in Quebec between 1650 and 1699 (187 vs. 170 per thousand). Some parts of the American colonies had lower while others had higher levels in those times. In New England, for instance, infant mortality was estimated at 150 per thousand before 1700 (Dobson, 1989)[2]. However, the southern colonies of Chesapeake and South Carolina were estimated to have very high levels of infant mortality that ranged from 250 to 300 per thousand births, as Malaria and Yellow Fever were prevalent in those areas. These rates were similar or higher than those recorded in London and other major British cities during the latter half of the seventeenth century. For instance, the London Quakers and the general population of London had an infant mortality rate of around 263 per thousand between 1675 and 1699 (Landers, 1987).

Despite having a higher proportion of infant deaths, mortality was comparatively much lower among 1 to 4 year olds in Quebec. The English parishes had rates that were almost two and a half times higher than those recorded among French Canadian children prior to 1700 (27 vs. 11 per thousand). The same pattern is also observed with children aged 5 to 9 years. The lower child mortality rates in Quebec during those times support the viewpoint of positive environmental conditions. If infants survived past their first birthday, adequate conditions and an abundant food supply would have helped them to thrive during childhood and provide protection against infections. For these reasons, it may be safely assumed that levels of child mortality in New France were lower than the levels prevailing in Europe at the time (Charbonneau et al., 1993).

[2] The rate for New England may also be underestimated because the rates are based fragmented pieces of data and adjusted with the reverse projection method. Unlike New France, the American colonies did not have widely available parish registers during the seventeenth century.

1.3. A Changing Epidemiological Profile

Although mortality was generally low prior to 1700, circumstances began to change by the mid-seventeenth century. At that time, warfare with the Iroquois led to the displacement of their Huron allies and other trading partners from their traditional lands. In the aftermath, French merchants were left to handle most aspects of the fur trade. This new situation created the need to increase the population and agricultural production, as the *courreurs des bois* (the epic "voyageurs") required supplies and a means of trade with the Aboriginal tribes to the West of New France. In 1663, Louis XIV took administrative control over the colony and following the advice of his Minister of Finance Jean Baptiste Colbert, drafted a migration policy for Quebec. The policy was centred on population growth through natural increase rather than by immigration (Charbonneau et al., 1993; Greer, 1997). As such, population growth was slower, compared to their Colonial American neighbours, who had a regular sustained immigration policy.

Louis XIV's policy on natural increase went into effect between 1663 and 1681 and had an immediate impact on population size, as an influx of French immigrants helped shift Quebec into a phase of rapid and sustainable natural growth (excess number of births over deaths). A very high level of completed fertility of 9.2 children on average, coupled with fairly low mortality, led to a population increase of 2.5% per annum (Charbonneau et al., 2000). On the downside, the increasing population density and the intensification of contacts through the widespread fur trade probably contributed to deteriorating epidemiologic conditions. After 1660, childhood mortality began to increase sharply (refer to Table 1.1.). It is clear that the situation worsened in Quebec, as the average

infant mortality rate between 1700 and 1749 became higher than the rate in the 13 English parishes (252 vs. 196 per thousand births).

By 1740, infant mortality was also higher than the rate recorded in France around the same time (309 vs. 287 per thousand births) (Charbonneau et al., 2000). The average childhood death rates among those aged 1 to 9 years remained slightly lower between 1700 and 1749. By 1730, however, the death rate among 1 to 4 year olds was at similar levels to the English parishes. On average, the death rate for children under 5 years of age was 85 per thousand, while the rate was around 58 per thousand in the English parishes between 1700 and 1749 (Wrigley and Schofield, 1983). By comparison, around 35% or over one third of French Canadian children would die before 5 years of age, while a quarter of children in the 13 English parishes were estimated to have died by that age.

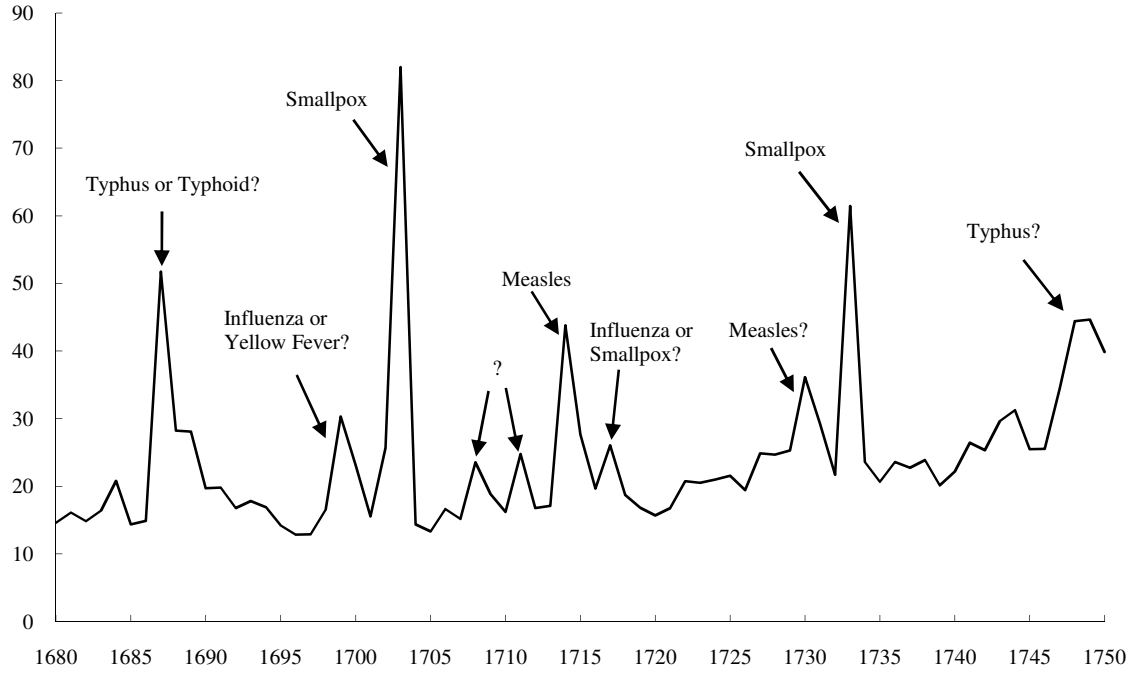
Hence, it may be safely assumed that the increasing density and contact with the outside world created suitable conditions for the introduction and the diffusion of epidemics into colony, and this is precisely the story told by the above figures. As alluded to above, the spread of epidemic diseases was facilitated either through the arrival of ships into the port cities of Quebec and Montreal or from trade routes with their origins scattered throughout North America. The lack of prior exposure to any of the prevalent infectious diseases such as smallpox and measles among others, made the entire Canadian born population highly susceptible to these virulent infections. When these diseases were introduced to the Canadian born for the first time, they would probably spread through the more populated areas of the colony quickly and sometimes virulently among all ages (Black, 1982; Gagnon and Mazan, 2009).

1.4. Epidemics in New France

Figure 1.1. shows the crude annual deaths rates of the French Canadian population over a seventy-year period. The graph clearly shows the sharp mortality peaks caused by periodic crises, which are characteristic of a pre-industrial population (Omran, 2005). Several of the peaks have been identified as epidemics entering the colony at various times. Epidemics that were consistently mentioned throughout the literature on Colonial New France were typhus in 1687, smallpox in 1702-03, measles in 1714-15 and smallpox again in 1732-33 (Charbonneau et al., 1993; Desjardins, 1996; Gagnon and Mazan, 2009; Amorevieta-Gentil, 2010). The arrows with the question marks indicate that an epidemic has not been confirmed and requires further demographic analysis to identify the disease that wreaked havoc on the population. It is clear that not much is known about many of the epidemics that were present in the colony during the late seventeenth and the first half of the eighteenth century, with the exception of the smallpox epidemic of 1702-03 (Desjardins, 1996).

There are very few demographic and statistical analyses of epidemics in the context of historical Canada. Although a more recent study by Gagnon and Mazan (2009) devoted some length to the historical prevalence of epidemics in New France, this study primarily focused on the long-term consequences of exposure to infectious diseases during infancy than the more immediate population impacts. Two notable studies directly related to specific epidemics in New France were conducted by Desjardins (1996) and Dechene and Robert (1993), where the former examined the spread and impact of the *smallpox* epidemic of 1702-03, while the latter analyzed the effects of the 1832 *cholera* epidemic.

Figure 1.1. Crude death rates of French Canadians per thousand population, New France 1680-1750



The smallpox epidemic began in Quebec City in December of 1702 and then spread westward (bypassing Trois Rivières) to Montreal by January of 1703. Smallpox was believed to have been introduced into the colony by an 'Indian Chief from Albany New York'. Desjardins (1996) estimated that 6% of the population died from smallpox during the epidemic. In the East, the epidemic was more virulent, where deaths peaked quickly by January and subsided by April. In contrast, mortality was lower in the West, but the epidemic lingered in the area for a longer duration, where deaths peaked between April and May and subsided by July. Smallpox mortality also varied by age and sex, where infants and females in the reproductive ages had the highest death rates. It was estimated that 25% of infants born during that time and 10% of reproductive females died from the virus.

More than a century later, Asiatic cholera was introduced into Quebec by immigrant ships originating from England in late May of 1832. Cholera was ravaging most of Europe and Russia at the time. Shortly after, in early June, the virulent epidemic began in Quebec City and Montreal simultaneously, while the rural areas were largely spared from the outbreak. Cholera death rates rapidly reached their peak during the same month and remained in the two cities at relatively high levels until September. Overall, death rates were around 11% higher in Quebec City than in Montreal (83 vs. 75 per thousand). Dechene and Robert (1979) found that there was no apparent sex difference in mortality, but deaths varied by age. Adults between the ages of 21 and 60 were the most likely to die during the epidemic and accounted for the majority of cholera deaths. It was estimated that out of the 1 in 13 people who perished during the cholera scourge, most were adults.

The smallpox and cholera epidemics had two very different origins, but the available literature on French Canadian history tends to oversimplify by implying that 'epidemics were introduced into the colony by the arrival of ships from overseas' (Greer, 1997). Many of the epidemics were probably introduced into Québec by maritime vessels carrying infected crewmembers and passengers. However, there is no mention that epidemics could have also spread from the American colonies into New France or vice versa. As noted, Desjardins indicated that the smallpox epidemic entered Quebec from New York State.

By the eighteenth century, the Quebec colonists were clearly in constant contact with the rest of North America. Recurring warfare with Britain and First Nations tribes involved frequent encounters with the outside world. Additionally, the fur trade opened up vast

trade routes with the local Aboriginals, as well as those from the American Colonies and as far west as the prairies (Moore, 1997). As a consequence, the increasing population density of North America, frequent conflicts and continual contact with trading partners created increased contact patterns through which microbial diseases could spread broadly. The larger and denser American population would provide an easy route for the transmission and spread of microbial diseases. In turn, many of the epidemics that originated in Colonial America may have spread from those areas into New France and vice versa.

1.5. A Salutary Source: Duffy's Account of Epidemics in Colonial America

There are a few reliable sources of information about the types of infectious diseases that were prevalent in the French colony. One reliable source, however, is an historical account entitled; "Epidemics in Colonial America" (Duffy, 1953). Duffy documented all known epidemics by type (e.g. smallpox, yellow fever, measles etc.) in Colonial America through various historical sources and documents from the early 17th to late 18th century. Some of Duffy's accounts were criticized by other historians. The reliability of some of the historical sources was put into question, some dates were incorrect and errors were made in terms of the historical figures who described a particular epidemic (Blake, 1954).

However, despite these inconsistencies, the book is still a useful guide for the study of epidemics in historical Quebec. In particular, the dates of epidemics documented in Colonial America coincide with the dates of those occurring in New France (see Figure 1.1.). For instance, Duffy gives a description of smallpox and measles epidemics occurring in Colonial America just prior to the time they began in New France. There is

even a direct reference to Quebec in his description of the 1702 smallpox epidemic. Although, the number of deaths he reported was exaggerated (Desjardins (1996), also noted that deaths were exaggerated in historical accounts), the type of epidemic matches the one observed in New York State around the same time. Thus, the historical accounts in Colonial America, in my opinion, serves as a useful guide to help confirm some of the major epidemics in historical Quebec in conjunction with demographic methods. If the high peaks observed in the French Canadian data coincide with dates of the outbreaks in Colonial America, then it is not unreasonable to assume that the same diseases impacted the population of New France.

1.6. Rationale

The smallpox and cholera studies are very informative in that they give insight into the origin, severity and diffusion (regional variations) of the specified epidemics. They provide part of the framework for the research design of this dissertation. However, those studies only cover a single episode of an epidemic, leaving the historical significance and outcome of other important outbreaks undocumented. The latter offer considerable potential for detailed demographic and statistical analyses of other little known epidemics in historical Quebec. The vital records from the parish registers contain detailed dates on births and deaths by sex and parish. This type of information makes it possible to reconstruct the origin, spread, duration and intensity of any given epidemic at the population level.

The historical data also contain the potential for the analysis of the consequences of a given epidemic at the individual or familial levels. Entire families have been reconstituted

by linking baptismal, marriage and burial records. Reconstitution allows one to utilize multivariate models with the inclusion of risk factors such as demographic and familial composition. In turn, it becomes possible to examine whether these factors have contributed to increased mortality during the epidemic and to follow the survival outcome of a cohort for many years after initial exposure. There is a need to expand on the studies mentioned above to determine the intensity and effects of the varying infections on the population living through those times. A detailed examination of these periodic disturbances at varying units of analysis will help fill in large historical gaps of the effects of infectious diseases in pre-industrial Canada and perhaps shed some new light on risk factors associated with recurrent infectious diseases in developing countries.

1.7. Research Questions

The goals of my dissertation are to develop suitable methods for analyzing mortality data when cause of death records are lacking and to apply statistical models to help answer modern dilemmas facing measles studies. In particular, I am writing a three-paper manuscript thesis to analyze the survival outcome of children exposed to measles during the epidemic of 1714-15 at the population level and eventually leading into analyses at the individual level. My research is primarily focused on the following:

(i) the use of life table methods to explore the general dynamics of the measles epidemic – origin, spread, duration and severity;
(ii) identifying exposed individuals and assessing risk factors of measles death at the individual level;

(iii) follow-up of the exposed cohort to analyze post-measles mortality after initial exposure to the virus.

For this research, the focus is on the measles epidemic of 1714-15 in New France. Little is known about the effect that the epidemic had on the population of Canadian born children. The choice of this epidemic appears arbitrary, as the methods developed in this series are suitable for future analyses on other types of infectious diseases. In addition, plenty of research on measles has been conducted on modern populations, which serves as a useful aid for the research designs and as a basis of comparison. Children are the main focus in all of the studies, as they made up over three quarters of the deaths during the epidemic. Although adult mortality was also elevated, the smaller proportion of adult deaths makes it more difficult to obtain reliable mortality estimates for the older inhabitants of the colony.

A main issue to overcome in this dissertation is that there is no direct method to identify exposed children or deaths from the measles virus. Nevertheless, it does preclude a meaningful analysis. Much of this dissertation is centered on the development of methods to overcome this shortcoming in the historical data. There is, however, a trade-off in this type of study. Although we have to rely on estimation techniques and will never know the exact proportion of deaths or all of the circumstances related to the measles virus, the conditions during that time were pristine or untouched by the influences of modern medicine such as, vaccines and effective treatments (e.g., antibiotic and Vitamin A therapy) based on scientifically derived knowledge. In historical Quebec and the rest of the world during those times, modern medical knowledge did not exist or was primitive.

The perceptions of birth and death were driven by religion and were independent of medical intervention. That is, people relied more on religious conviction and traditional knowledge to deal with crisis situations (Stub, 1982).

In contrast, modern beliefs of death and disease are viewed as a public health problem. The diffusion of basic health knowledge into the general population and the development of effective treatments for infected persons improve the chances of recovery and the survival of children. These factors can be difficult to control adequately and may distort findings, if they are not taken into consideration. In pre-industrial Quebec, these issues did not exist. Therefore, the historical data will allow us to gain an understanding of how an infectious disease operates in a natural state, unhindered by modern advancements in medical technology. Having the rich Quebec data from a 'natural' setting and being able to estimate the course and consequences of the measles epidemic, warrants an investigation into the impact that it had on the population. Furthermore, the replication of modern measles studies with the historical data may help shed some light on many of the issues that have not been clarified in those studies.

1.8. A General Background on Measles

Measles can be traced as far back as 5,000 years ago in the civilizations of the Tigris and Euphrates River Valleys (Drutz, 2001). It is an acute viral illness caused by a virus in the *paramyxovirus* family and is one of the most contagious diseases known to man. Measles has been called the 'largest child killer in history' (Clements and Hussey, 2004). If exposed, almost all non-immune children contract measles with up to 99% of susceptibles contracting the virus after first contact with an infected person. Generally, the virus is

spread through airborne droplets via sneezing and/or coughing. The early latent phase ranges from 5 to 10 days, while the infectious period lasts another 7 days (Murray and Cliff, 1977).

Individuals usually do not die directly from measles, but from complications associated with the virus. Measles attacks epithelial cells and suppresses the immune system, which makes the infected individual highly susceptible to serious complications such as severe diarrhoea and pneumonia. For children, pneumonia is the most common cause of measles related death (Clements and Hussey, 2004; Moss and Ota, 2007). Risk factors for severe complicated measles generally include a young age, malnutrition, Vitamin A deficiency, overcrowding and immune deficiency (Perry and Halsey, 2004). The contribution of many of these factors are not fully understood and there is a general debate on which of these has the most influential effect on mortality outcomes.

Individuals who recover from the virus are immune for the rest of their lives. This means that epidemics are 'self-limiting' and due to the attrition of susceptibles (either through death or immunity), subsequent epidemics can occur (in the absence of migration) only after a new group of susceptibles are born into the population (Giesecke, 2002; Finkenstadt et al., 1998). As such, measles requires a large host population (at least 250,000 people) to become endemic or occur at regular intervals (Bartlett, 1960; Rhodes and Anderson, 1996). In other words, the high infectivity of measles means that a small percentage of susceptible individuals are sufficient to maintain viral circulation in populations of a few hundred thousand. Despite a high rate of natural increase, Quebec had a small population at the time, numbering 24,564 in 1714. Thus, epidemics would

occur at intermittent or more irregular intervals and would not become endemic in Canada until much later. In contrast, measles was endemic in many parts of Europe, as the populations were large enough to sustain the circulation of the virus.

Before the widespread use of the measles vaccine, almost every person in non-isolated parts of the world would have been infected before the age of 18. Historically, measles case fatality rates have ranged between .05% and 30% (Wolfson et al., 2009). The highest rates have been recorded in areas with low natural immunity or vaccination. During the first half of the 20th century, it was estimated that there were 135 million measles cases and around 7 to 8 million deaths per year. In general, measles mortality fell when socioeconomic conditions improved in industrial countries and further reductions were made when the measles vaccine was developed in the 1960s (Clements and Hussey, 2004). By 2000, vaccine coverage reached about 72% of the children in the world through national immunization programs. In most industrialized countries, measles is now well controlled or has even been eliminated. In these areas, the number of confirmed measles cases fell by more than 99% since 1990, with the number of annual measles deaths approaching zero.

In many developing nations, including several African and Asian countries, national childhood immunization coverage remained low until recently. The World Health Organization indicates the poor coverage is reflected in that more than 95% of measles deaths occur in low-income countries with ‘weak health infrastructures’. In 2000, it was estimated that there were over 700,000 measles deaths, with infants and young children

making up most of the casualties (Goldhaber-Fiebert et al., 2010). As such, measles remains a major preventable cause of childhood death in developing countries.

Despite the high occurrence of measles epidemics in parts of Africa and Asia, there have been some great strides in the past decade to increase vaccine coverage in those areas. By 2008, 83% of children in the world received one dose of the measles vaccine by their first birthday through routine health services. The increased vaccine coverage resulted in a mortality decline of around 78% between 2000 and 2008 or to 164,000 deaths worldwide by 2008 (Goldhaber-Fiebert et al., 2010). However, it is not known if the recent progress is permanent. As mentioned above, even with a high level of population immunity, the highly infectious nature of measles means that a small percentage of susceptible are enough to maintain viral circulation. Although relatively minor in terms of severity, there has been a resurgence of measles outbreaks in Canada and other developed nations in recent times.

1.9. Data Source

The data used in all of the studies originates from the *Registre de population du Québec ancien*, compiled by the *Programme de recherche en démographie historique* (PRDH) at the University of Montreal (Légaré, 1988). This electronic database contains the date and place of birth, death, marriage(s), places of residence and of origin, names of parents and spouse(s) and secondary information on occupation (if available) for all individuals who lived in the Saint-Lawrence Valley from the 17th to 18th century. Around 700,000 baptismal, marriage and burial certificates were gathered from the parish registers of historical Quebec and were linked together on the basis of names and family ties. The registers were highly reliable and mostly complete, as parish clergy made duplicate

records of each event. As such, very little data were lost and thus, the reconstituted data are considered 'quasi-perfect' (Charbonneau et al., 2000). Further, the population remained quasi-closed until the 19th century because of particular historical and geographical circumstances, the usual problem of missing observations due to migration is greatly reduced (Légaré, 1988; Charbonneau, 1993).

As the development of the database is still in progress, the available information varies in time according to the date of the events and the period of birth and marriage of the individuals. Births are matched with individuals and their parents up to the year 1800, and deaths up to around 1850 (relating to people born before 1750). All ancestors of every individual who married before 1800 can be traced back to the founders of the population. As mentioned above, the process of familial reconstitution is very beneficial to the objectives of this dissertation, as linkages are conducted at the individual and familial levels. Reconstitution not only makes it possible to estimate demographic rates, but also allows for the use multivariate models to analyze specific characteristics of the persons who inhabited the colony from birth until death. This time to event aspect contained in the data allows for detailed analyses of the risk of death before, during and after an epidemic struck the colony.

1.10. Thesis Outline

This dissertation is comprised of three distinct but mutually related studies. The relevant literature and rationale for doing each of the studies are discussed in the following chapters. The various selection methods and statistical models used throughout the studies are discussed in the Data and Methods sections of each chapter. In turn, viewpoints based

on modern knowledge about measles are used to help to explain the possible circumstances of pre-industrial children in the Discussion section of each study. Chapter 2, entitled "The measles epidemic of 1714-15 in New France" examines the general dynamics of the measles epidemic at the population level and builds upon the small existing body of literature on the demographic history of epidemics in New France. This study utilizes spline and life table methods to follow an epidemic when cause of death information is absent. The first part of the study examines the origin, spread and duration of the epidemic. In order to determine these dynamics, a spline was fit through a times series of observed rates to estimate normal mortality conditions. The predicted rates serve as a baseline estimate of normal morality in the absence of period disturbances (i.e., the spline smoothes out the sharp peaks caused by an epidemic). To identify the origin, spread and duration, risk ratios between the normal and epidemic periods are derived to give an indication of where the epidemic began, what regions were affected and the length of time the epidemic remained in the colony (see also Chapter 3, Data and Methods section for a more detailed description of the methods).

To estimate excess measles deaths, splines were fit to the times series data by age, sex and region. Excess mortality is defined as death rates that are significantly higher than what would be expected during a normal period (in the absence of a periodic disturbance caused by crisis mortality). These are generally the sharp peaks that occur periodically when death rates are plotted against time (see Figure 1.1.). Since multiple decrement life table theory assumes that causes of death are mutually exclusive and exhaustive, the measles and the expected death rates in normal conditions are additive and their sum equals the overall observed death rate (Preston et al., 2000). Then, the measles rate equals

the residual difference between the observed and expected death rates. In sum, this study is exploratory in nature and will help determine appropriate areas of study for the subsequent chapters on the consequences of the measles epidemic at the individual level.

Chapter 3, entitled “Risk Factors of mortality among French Canadian children during the measles epidemic of 1714-15” identifies the risk factors associated with higher mortality among children under 5 years of age during the acute episode of the epidemic, as identified in Chapter 2 (i.e., late-August to mid-November of 1714). This study shifts from the population to the individual level of analysis, which is more suitable to answer this type of question.

In modern community studies, several risk factors have been found to increase the risk of death among children exposed to measles. Pre-existing malnutrition prior to an epidemic and Vitamin A deficiency are regarded as major risk factors of measles death (Clements and Hussey, 2004; Moss and Ota, 2007). Measles also exasperates malnutrition because of abnormal protein loss, increased metabolic demands and decreased food intake. As with other infectious diseases, a young age at infection has consistently been found to be an important risk factor (Burstrom et al., 1999). Pison et al., (1992) also found that a larger age difference between sib-pairs and children who were infected by a sibling of the opposite-sex both had a higher odds of death.

In addition, the findings of several community studies in Guinea-Bissau, Senegal, Gambia, Bangladesh, United Kingdom and Denmark suggested that mortality was higher in families with several cases and among secondary cases (i.e., children exposed in the

home) (Garenne and Aaby, 1990 Aaby et al., 1984; 1988, Pison et al., 1992). Older children or the parents (index cases) are probably more likely to introduce measles into the household through outside contacts and infect the younger children in the household (Hull, 1988; Koster, 1988; Pison et al., 1992; Burstrom et al., 1999). The increased risk from crowding or close contact of family members is believed to be mediated through intensive and prolonged exposure to the virus among the secondary cases. Close contact implies 'the absorption of a larger and more lethal dose of measles (i.e., dose response effect) (Aaby, 1988).

Most of the above findings can be replicated with the Quebec data. Although there is no direct method to identify who was exposed or died from measles, we can still maximize the chance identifying and selecting individuals who may have been exposed to the virus. To achieve this, several criteria were imposed to select the study group based on findings from the previous demographic study (Chapter 2) and a method that consisted of comparing a risk model during the epidemic with the same model applied to control groups living under normal mortality conditions.

Using Generalized Estimating Equations with logistic regression to account for correlated nature of the data (i.e. sibling data) and bootstrap binary logistic regression as a check for reliability, I examine the odds of death among an exposed group and unexposed control groups according to the age at infection, cross-sex transmission, sibship size, sex composition and the age differences between children in the household. Other potential risk factors that require further examination and may be unique within the context of New France are the death of a sibling(s) during the epidemic, immigrant status of the parents

and the region of residence. Although there was no way to distinguish between measles and non-measles deaths, this analysis will help identify the possible role that the above demographic and familial risk factors played during the epidemic. Finally, the findings about the disease process generated from this study are compared with studies conducted in modern populations.

Chapter 4, entitled "Delayed measles mortality among exposed children who survived the epidemic of 1714-15 in New France" follows an exposed cohort of children for up to 25 months past the acute phase of the epidemic. Specifically, the study examines whether an exposed cohort of children were subjected to delayed measles mortality (i.e., a death occurring more than 43 days past infection) after initial exposure to the virus, as compared to an unexposed cohort subjected to normal mortality conditions (i.e. the general mortality level in the absence of an epidemic).

Several studies from West Africa have found that there was an increased risk of delayed mortality after exposure to the virus. The period of susceptibility can last for several weeks to years after the onset of rash and is attributed to a prolonged state of immune suppression (Aaby and Clements, 1989; Hull et al., 1983; Aaby et al., 1990; 1993; Aaby, 1995). On the other hand, some community studies have found that exposed children had the same or lower long-term mortality risks than unexposed controls (Aaby et al. 1995; Dollimore et al. 1997, Chen at al. 1994). Aaby et al. (1995; 1996) indicated, that previous studies might have 'exaggerated' the delayed effect of measles, as some compared post-measles cases with immunized (i.e., vaccinated) children, rather than with unimmunized and unexposed children. They concluded that measles vaccination and even natural

infection could be beneficial to children, as it may provide a boost to the immune system and in turn, provide protection against subsequent infections.

The parish data is well suited to help shed some light on these modern dilemmas in measles studies, as the measles epidemic could be considered to have occurred in a natural habitat with no interference from modern medicine (e.g., vaccines and immunization campaigns) and public health knowledge (e.g., effective treatment). In addition, the data contains detailed information on the timing of events, which allows for the replication of the follow-up studies conducted in West Africa from the late 1970s onwards.

This study builds upon the previous two studies on measles in New France and extends the selection and estimation methods to help identify delayed mortality among children who survived past the acute phase of infection. Based on methods described in Chapter 3, exposed children who survived past the acute phase of the epidemic were selected for the follow-up study on the delayed impact of the virus. Since there is no direct procedure to identify when exposure occurred, the timeline for the date of infection was derived from an average scenario based on the natural course of measles. The date of infection for the survivors was estimated using children who died during the acute episode from late-August to mid-November of 1714 (as determined in the previous study, Chapter 3).

As not all children died before the end of the follow-up period (i.e. the study contains censored observations), life tables and Cox proportional hazards models were used to analyze the survival outcome of the exposed children for up to 25 months past the

estimated date of infection. In general, I examine whether exposed children had a different survival outcome, as compared to an unexposed cohort, while assessing for the influence of other effects such as, age at infection, sex, urban/rural residence and sibship composition. The findings are explained in terms of modern viewpoints on delayed measles mortality. Chapter 5 entitled "Conclusions" discusses the general findings in relation to the risk factors, the study designs and outlines future areas of interest on the subject.

1.11. References

Aaby P., Anderson M., Knudsen K. 1996. "Nutritional status and delayed mortality following early exposure to measles". *Epidemiology and Infection* 117: 525-531.

Aaby P. 1995. "Assumptions and contradictions in measles and measles immunization research: Is measles good for something?". *Social Science and Medicine* 5: 673-686.

Aaby P., Samb B., Simondon F., Seck A.M., Knudsen K., Whittle H. 1995. "Non-specific beneficial effect of measles immunisation: analysis of mortality studies from developing countries". *British Medical Journal* 311:481-485.

Aaby P., Anderson M., Knudsen K. 1993. "Excess mortality after early exposure to measles". *International Journal of Epidemiology* 22: 156-162.

Aaby P., Bukh J., Lisse I. M., Da Silva M. C. 1990. "Delayed excess mortality after exposure to measles during the first six months of life". *American Journal of Epidemiology* 132: 49-63.

Aaby P., Clements C. J. 1989. "Measles immunization research: a review". *Bulletin of the World Health Organization* 67: 443-448.

Aaby P. 1988. "Malnutrition and overcrowding/intensive exposure in severe measles infection: Review of community studies". *Review of Infectious Diseases* 10: 478-491.

Aaby P., Bukh J., Lisse I. M., Smits A. J. 1984. "Overcrowding and intensive exposure as determinants of measles mortality". *American Journal of Epidemiology* 120: 49 63.

Amorevieta-Gentil M. 2010. *Les niveaux et les facteurs déterminants de la mortalité infantile en Nouvelle-France et au début du Régime Anglais (1621-1779)*. PhD Thesis. Département de Démographie, Université de Montréal.

Bartlett M. S. 1960. "The critical community size for measles in the United States". *Royal Statistical Society, Series A* 123: 37-44.

Black F. L. 1982. "The role of herd immunity in control of measles". *The Yale Journal of Biology and Medicine* 55: 351-360.

Blake B. J. 1954. "Book Review: John Duffy. Epidemics in Colonial America. Baton Rouge, Louisiana University Press". *Journal of the History of Medicine* 9: 257-259.

Burstrom B., Diederichsen F., Smedman L. 1999. "Child mortality in Stockholm during 1885- 1910: The impact of household size and number of children in the family on the risk of death from measles". *American Journal of Epidemiology* 149: 1134-1141.

Charbonneau H., Desjardins B., Guillemette A., Lardry Y., Légaré J., Nault F. 1993. *The First French Canadians: Pioneers in the St. Lawrence Valley*. Newark: University of Delaware Press.

Charbonneau H., Desjardins B., Légaré J., Denis H. 2000. "The population of the St. Lawrence Valley, 1608-1760" in *A Population History of North America.* Haines M. R., Steckel R .H. (ed.). Cambridge, Cambridge University Press, pp. 99-142.

Chen R.T., Weierbach R., Bisoffi Z., Cutts F., Rhodes P., Ramaroson S., ET AL. 1994. A "post-honeymoon period" measles outbreak in Muyinga Sector, Burundi. *International Journal of Epidemiology* 23:185-93.

Clements C. J., Hussey G. D. 2004. "Measles" in *The Global Epidemiology of Infectious Diseases*. Murray C. J. L., Lopez A. D., Mathers C.D. (ed.). Geneva: WHO.

Dechene L., Robert J-C. 1993. "Le cholera de 1832 dans le Bas-Canada: mesure des inegalites devant la mort" in *The Great Mortalities: Methodological Studies of Demographic Crises in the Past.* Charbonneau H., Larose A. (ed.). Belgium: Oridona Editions (IUSSP), pp. 229-256.

Desjardins B. 1996. "Demographic aspects of the 1702-1703 smallpox epidemic in the St-Lawrence valley". *Canadian Studies in Population* 270: 49-67.

Dobson J. M. 1989. "Mortality gradients and disease exchanges: Comparisons from Old England and Colonial America". *The Society for the Social History of Medicine* 2: 259-297.

Dollimore N., Cutts F., Binka F. N., Ross D. A., Morris S. S., Smith P. G. 1997. "Measles incidence, case fatality, and delayed mortality in children with or without vitamin A supplementation in rural Ghana". *American Journal of Epidemiology* 146: 646-654.

Drutz B. J. 2001. " Measles: Its history and its eventual eradication". *Seminars in Pediatric Infectious Diseases* 12: 315-322.

Duffy J. 1953. *Epidemics in Colonial America*. Baton Rouge: Louisiana State University Press.

Finkenstadt B., Keeling M., Grenfell B. 1997. "Patterns of density dependence in measles dynamics". *Proceedings of the Royal Society B* 265: 753-762.

Gagnon A., Mazan R. 2009. "Does exposure to infectious diseases in infancy affect old age mortality? Evidence from a pre-industrial population". *Social Science and Medicine* 68: 1609-1616.

Garenne M., Aaby P. 1990. "Patterns of exposure and measles mortality in Senegal". *Journal of Infectious Diseases* 16: 1088-1094.

Giesecke J. 2002. *Modern Infectious Disease Epidemiology*. London: Arnold.

Goldhaber-Fiebert J. D., Lipsitch M., Mahal A., Zaslavsky A. M., Salomon J. A. 2010. "Quantifying child mortality reductions related to measles vaccination". *PLoS ONE* 5: 1 - 6 doi:10.1371/journal.pone.0013842.

Greer A. 1997. *The People of New France*. Toronto: University of Toronto Press.

Hull F. 1988. "Increased measles mortality in households with multiple cases in the Gambia, 1981". *Review of Infectious Diseases* 10: 463-467.

Hull F., Williams P. J., Oldfield F. 1983. "Measles mortality and vaccine efficacy in rural West Africa". *Lancet* i: 972-975.

Koster F. 1988. "Mortality among primary and secondary cases of measles in Bangladesh". *Review of Infectious Diseases* 10: 471-473.

Landers J. 1987. "Mortality and metropolis: the case of London 1675-1825". *Population Studies* 41: 59-76.

Légaré J. 1988. "A population register for Canada under the French regime: Context, scope, content, and applications". *Canadian Studies in Population* 15: 1-16.

Moore C. 1997. "Colonization and conflict: New France and its rivals 1600-1760" in *The Illustrated History of Canada*. Brown C. (ed.). Toronto: Key Porter Books Limited, pp. 105-188.

Moss W. J., Ota M. O. 2007. "Measles" in *Infectious Disease Epidemiology: Theory and Practice,* Nelson K. E., Williams C. M. (ed.). Boston: Jones and Bartlett Publishers, pp. 601-621.

Murray G. D., Cliff A. D. 1977. "A stochastic model for measles epidemics in a multi-region setting". *Transactions of the Institute of British Geographers* 2: 158-174.

Nault F., Desjardin B., Légaré J. 1990. "Effects of reproductive behaviour of French Canadians during the seventeenth and eighteenth centuries". *Population Studies* 44: 273-285.

Omran A. R. 2005. "The epidemiologic transition: a theory of the epidemiology of population change". *The Milbank Quarterly* 83: 731-757.

Pison G., Aaby P., Knudsen K. 1992. "Increased risk of death from measles in children with a sibling of opposite sex in Senegal". *British Medical Journal* 304: 284 – 287.

Perry R. T., Halsey N. A. 2004. "The clinical significance of measles: A review". *The Journal of Infectious Diseases* 189(Suppl 1): S4-S16.

Preston S. H., Heuveline P., Guillot M. 2001. *Demography: measuring and modeling population processes*. Oxford: Blackwell Publishers.

Rhodes C. J., Anderson R. M. 1996. "A scaling analysis of measles in epidemics in a small population". *Philosophical Transactions of the Royal Society B* 351: 1679-1688.

Stub H. R., 1982, *The Social Consequences of Long Life*. Springfield Illinois, Charles C Thomas.

Wrigley E.A., Schofield S. R. 1983. *The Population History of England, 1541-1871*. Cambridge: Harvard University Pres

Wolfson J. L., Grais F. R., Francisco J. L., Birmingham E. M., Strebel M. P. 2009. Estimates of measles case fatality ratios: A comprehensive review of community studies. *International Journal of Epidemiology* 38: 192 – 205. doi:10.1371/journal.pone.0013842.

Chapter 2

The Measles Epidemic of 1714-15 in New France*

2.1. Introduction

Spread along the Saint Lawrence Valley, the first French Canadians had a unique epidemiologic profile for the time. The ready access to subsistence resources made the colonists a healthy and robust group of individuals. Indeed the colonists were healthier than their European counterparts, as is evident by their higher life expectancy (Charbonneau et al., 2000). Early on, the population was small and sparsely dispersed over a large area making it harder and slower for viruses to penetrate the vast frontier. A low density probably protected the colony from becoming a perpetual host population of infectious diseases. However, their circumstances began to change by the 18th century. The population was going through a stage of rapid growth due almost exclusively to natural increase (i.e. excess births over deaths). Quebec was a high fertility population (9.2 children per woman married until age 45) and had a natural rate of increase of about 2.5% or a doubling time of approximately 30 years (Charbonneau et al., 2000).

The colonists were also no longer isolated from outside contact with the rest of North America. Colonial America was increasing in size and due to a long sustained immigration, had a much larger population than New France. Recurring warfare with Britain and Aboriginal tribes also led to more frequent encounters with the outside world. Additionally, the fur trade opened up vast trade routes with local Aboriginal tribes, as

* Published: Mazan R., Gagnon A., Desjardins B. 2009. "The measles epidemic of 1714-1715 in New France". *Canadian Studies in Population* 36: 295-323.

well as those from the American Colonies and as far west as the prairies (Moore, 1997). As such, the increasing population density of North America, frequent conflicts and continual contact with trading partners probably led to a greater number of contact patterns through which a virus could be transmitted more efficiently than before. Epidemics began to appear with greater frequency and severity throughout the colony during the first half of the 18th century (Gagnon and Mazan, 2009). These disturbances led to many fatalities, as the lack of exposure in previous times meant that the Canadian born had no acquired immunity to infectious diseases that entered the colony.

Unlike historical Europe, mortality crises resulting from epidemics have not been extensively documented in the Canadian context. Fortunately, detailed Parish registers containing baptisms and burials are available for Québec from the outset of the European population. Because of this information, we have the potential to conduct detailed analyses on the periodic outbreaks in pre-industrial Quebec. So far, only a couple of studies have undertaken such a task (Desjardins, 1996; Dechene and Robert, 1993). The former analyzed the spread and impact of the smallpox epidemic of 1702-03 while the latter was a study on the impact of the 1832 cholera epidemic. These studies are very informative and provide insight into the origin, severity and diffusion (regional variations) of the specified epidemics. Yet, there are many undocumented epidemics such as, a largely unknown measles epidemic in 1714-15.

There is limited historical evidence of a measles epidemic in 1714 in Canada. Additionally, we do not have cause of death records for that period, which would enable us to directly identify the event as a measles epidemic. However, historical accounts from

Colonial America indicate that a 'serious' measles epidemic took place between 1713 and 1715 (Duffy, 1953). The exact origin is not given, but residents of Boston, Massachusetts suffered many fatalities during the outbreak, which began in the late summer of 1713 and had run its course by the end of January 1714. By February of that year, the virus had spread to New York, New Jersey, Connecticut and Pennsylvania (Duffy, 1953). The virus probably arrived in New France a couple months later via Aboriginal traders traveling from Colonial America.

Measles is one of the most contagious diseases and has been called the 'largest child killer in history' (Clements and Hussey, 2004). It is an acute viral illness caused by a virus in the *paramyxovirus* family. If exposed, almost all non-immune children contract measles with approximately 99% of susceptibles contracting the virus after first contact with an infected person. Generally, the virus is spread through airborne droplets via sneezing and/or coughing. The development of an infection (the latent period) ranges from 5 to 10 days, while the infectious period lasts another 7 days (Murray and Cliff, 1977). Individuals usually do not die directly from measles, but from complications associated with the virus. Measles attacks epithelial cells and suppresses the immune system, which makes the infected individual highly susceptible to serious complications such as, severe diarrhoea and pneumonia. For children, pneumonia is the most common cause of measles related death (Clements and Hussey, 2004; Moss and Ota, 2007).

Individuals who recover from the virus are immune for the rest of their lives. This means that epidemics are 'self-limiting' and due to the attrition of susceptibles (either through death or immunity), subsequent epidemics can occur (in the absence of migration) only

after a new group of susceptibles are born into the population (Giesecke, 2002; Finkenstadt et al., 1998). As such, measles requires a large host population (at least 250,000 people) to become endemic or occur at regular intervals (Bartlett, 1960; Rhodes and Anderson, 1996). Despite a high rate of natural increase, Quebec had a small population compared to France, numbering around 24,564 in 1714. Thus, epidemics occurred at intermittent or more irregular intervals and did not become endemic until much later. Nevertheless, these periodic disturbances probably had a large health, social and economic impact on the population living through that particular time.

The objective of the current study is to analyze the general mortality patterns of the measles epidemic of 1714-15 and to build on the small existing body of literature on epidemics in New France. Particularly, we focus on the origin, spread, duration and severity of the measles epidemic. Additionally, we introduce a set of methods suitable for use with parish data to estimate measles mortality when cause of death information is lacking. In sum, this study is exploratory in nature and serves to identify mortality conditions during the epidemic and will help determine appropriate areas of study for future analyses on the consequences of epidemics at the familial and individual levels.

2.2. Data and Methods

The data used in this study originates from the *Registre de population du Québec ancien*, compiled by the *Programme de recherche en démographie historique* (PRDH) at the Université de Montréal (Légaré, 1988; Charbonneau et al., 1993). The database contains, the date and place of birth, death and marriage(s), names of parents and spouse(s) and secondary information on places of residence and of origin for individuals that lived in

the Saint-Lawrence Valley during the 17th and 18th centuries. As the development of the database is still in progress, the availability of information varies by time. Currently, births and deaths are matched with individuals and their parents up to the year 1779 and marriages up to 1799; also, deaths up to 1850 relating to individuals born before 1750 were also added, to allow for mortality measures. All ancestors of every individual who married before 1800 can be traced back to the founders of the population.

2.2.1. Data Quality

The Quebec data are highly reliable and accurate. Records were well organized, duplicates of vital events were kept and relatively few parish records were lost (Charbonneau et al., 2000). However, some information is missing and this could potentially lead to biased estimates. Missing information mostly includes the under-registration of infants dying before baptism, as well as, young children and people who died outside of the parish areas (e.g., voyagers). These losses were evaluated at approximately 10% of the parish records (Desjardins, 1996). The problem of under-registration could be greater because of the possibility of administrative disorganization during an epidemic. However, Desjardins (1996) examined the data and found that the number of unbaptized infants born during epidemics were no different than unrecorded births during 'normal' years. Thus, it was concluded that the clergies kept good records at all times.

The above patterns were confirmed in a study by Gagnon and Mazan (2009) using methods involving birth intervals and intervals between birth and baptism (Blum & Henry, 1988; Charbonneau, 1975; Henry, 1968). For the present study, we use instead

"apparent" infant mortality rates, as the data are not corrected for underreporting. As such, our estimates of infant mortality may be lower than those reported using the correction factors (see Nault et al., 1990). However, the correction factors assume that deaths are constant over the year and are more suitable to examine annual rates over a long period of time. In our case, it is crucial to know the precise date of a person's death because measles is seasonal (i.e., death rates are not constant) and if we know the date of death, we can use the seasonal pattern of the virus to estimate whether a child died from measles or not. We assume that the proportional distribution of deaths by cause would be the same for unrecorded individuals.

2.2.2. Regions

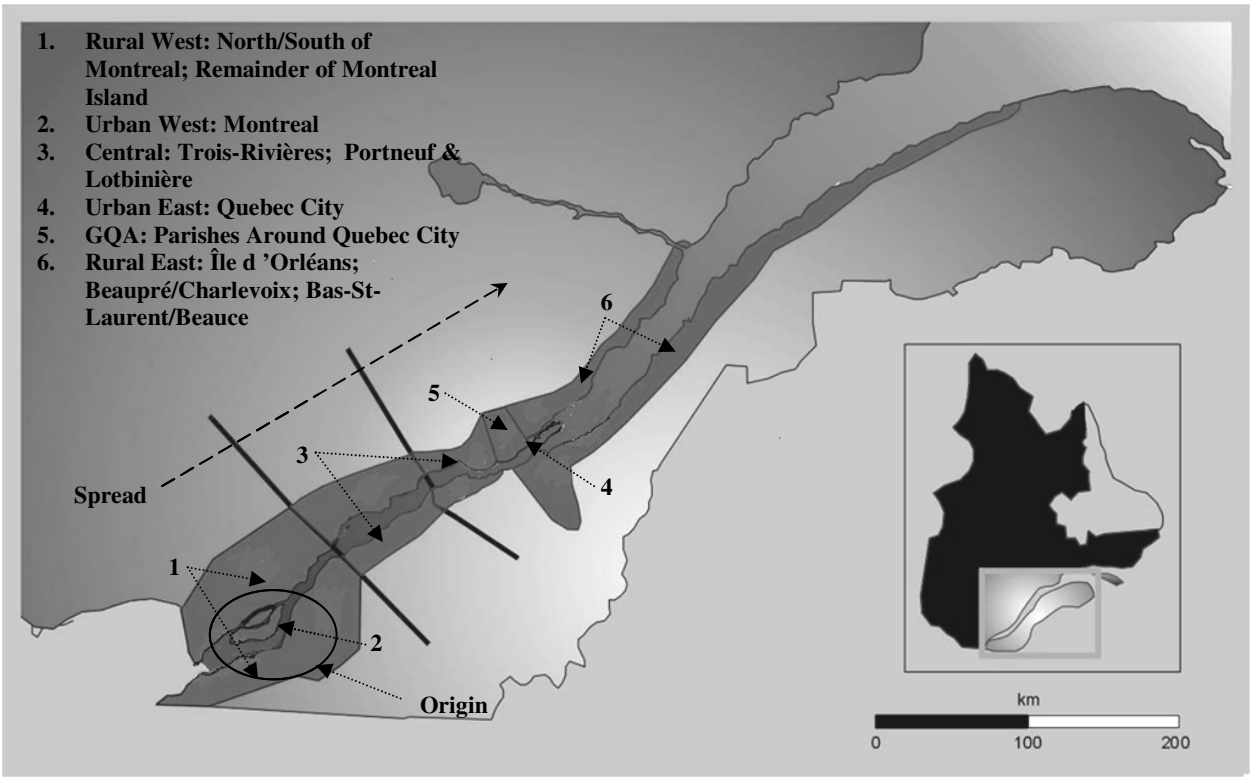
Charbonneau et al. (2000) indicate that records of well-established parishes were globally more complete than those from only recently founded parishes, where the absence of a resident priest, for example, may have caused a greater proportion of underreporting. Including population counts from those parishes would bias mortality estimates downwards because the denominator would be inflated. To alleviate the problem, we only considered 63 well-established parishes (excluding missions).

Table 2.1. The Designated Urban Towns and Rural Regions, New France 1710-1719

Region	**Name**
Rural West	*North of Montreal, South of Montreal & Remainder of Montreal Island*
Urban West	*Montreal*
Central	*Trois-Rivières, Portneuf & Lotbinière*
Urban East	*Quebec City*
Greater Quebec Area (GQA)	*Parishes surrounding Quebec City*
Rural East	*Orleans Island, Beaupré/Charlevoix, Bas-St-Laurent/Beauce*

Additionally, we divided the parishes into broad regions to increase the population size and number of events (deaths) so that rates could be estimated (or to reduce the high random variation due to the small number of events). Quebec City and Montreal are presented as their own separate regions or as the administrative urban centres, while the remaining 61 parishes are divided into 4 broad regions or rural areas. The division of the 63 parishes into six broad regions is depicted in Table 2.1 and Figure 2.1.

Figure 2.1. Regional map depicting the origin and spread of measles, New France 1714-15



2.2.3. Study Population

The study population consists of inhabitants residing in the 63 established parishes (6 regions) between 1710 and 1719. We selected Canadian born individuals less than 15 years of age with a registered date of birth and a known parish of death within the colony.

We only focus on infants and children up to age 15 because 79% of the recorded deaths occurred in those age groups during the epidemic. Further selection criteria were implemented in order to derive an estimate of the population size for each of the regions. Internal migration was quite common in the colony and if the transient population was not taken into consideration, estimates could be significantly biased.

A simple method to lessen the potential bias introduced by internal migration is to estimate the region of residence for each individual by using information about other family members. We used the following criteria: 1) If all family members were born and died in the same parish, this was used as the place of residence for each year; 2) When the parish of birth and death were different for some members and there was a birth or death in the family during the year of interest, we used the recorded parish of the event as the place of residence for the entire family and; 3) Otherwise, the parish with the most recent birth or death prior the year of interest was designated as the current residence of that particular family. Table 2.2 shows the population estimates and vital events of the six regions between 1710 and 1719.

Table 2.2. Regional population estimates and vital events, New France 1710-1719

Region	1710	1711	1712	1713	1714	1715	1716	1717	1718	1719
Rural West	3,344	3,425	3,541	3,673	3,794	3,874	3,979	4,073	4,152	4,257
Urban West	2,859	2,932	2,990	3,075	3,119	3,115	3,129	3,170	3,195	3,241
Central	2,684	2,739	2,805	2,853	2,954	2,985	3,027	3,114	3,178	3,250
Urban East	2,386	2,459	2,506	2,581	2,636	2,627	2,630	2,679	2,650	2,685
Greater Quebec Area (GQA)	2,513	2,536	2,503	2,558	2,651	2,661	2,606	2,662	2,674	2,721
Rural East	3,460	3,577	3,701	3,761	3,887	3,913	3,934	4,008	4,092	4,175
Colony	17,245	17,668	18,044	18,501	19,041	19,175	19,305	19,704	19,940	20,327
Births	862	801	855	861	949	837	884	972	922	948
Deaths	334	539	378	391	918	669	464	609	476	440

2.2.4. Estimation of Mortality from Measles

Since parish priests did not record the cause of death, we cannot get a direct estimate of measles mortality rates. Thus, we indirectly estimated the expected or normal quarterly death rate, ${}_n\hat{m}_x$ to derive risk ratios and a set measles death rates or ${}_n m_x^{measles}$. The choice of a functional form to identify large deviations from the normal rate is not without problems. For instance, a single functional form fit with ordinary least squares is sensitive to outliers (or the peaks and troughs of a time series) and these tend to pull the fitted line in their direction (Palloni, 1990). This influence may distort any 'real' difference between normal and non-normal conditions.

When a single functional form cannot produce a satisfactory fit to the data, one alternative would be to fit a spline over sub ranges of the data (London, 1985). A cubic spline is a piecewise polynomial that is twice continuously differentiable (Prenter, 1975). The data range is divided into *n* piecewise curves, which are joined together smoothly by *n* - 1 internal knots (k_i). In the present study, we fit a series a smoothing splines through all data points between the 1st quarter of 1710 and the 4th quarter of 1719 to estimate the expected death rate or ${}_n\hat{m}_x$. We found that a good approximation of normal mortality was obtained by dividing the data range (*y, z*) into three segments, joined together by two internal knots, at $x = k_1$ and $x = k_2$. Parameters of the cubic splines were estimated by weighted least squares, where the sum of squares minimizing equation is (London, 1985: 103):

$$SS = \sum_{a}^{h_1} {}_n w_x [{}_n m_x - {}_x \hat{m}_{x(0)}]^2 + \sum_{h_{1+1}}^{h_2} {}_n w_x [{}_n m_x - {}_n \hat{m}_{x(1)}]^2 + \sum_{h_{2+1}}^{b} {}_n w_x [{}_n m_x - {}_n \hat{m}_{x(2)}]^2 \qquad \textbf{[1]}$$

where h_1 is the closest value of x less than or equal to k_1, h_2 is defined the same with respect to k_2, and ${}_n w_x$ are the weights (for a more formal treatment of the subject see London, 1985: 102-107; Benjamin & Pollard, 1980: 345-355). The weights or ${}_n w_x$ are the reciprocal of the variance. For infants, VAR (${}_n m_x$) was assumed to be binomially distributed (see Chiang, 1984: 84), while for 1 to 4 and 5 to 14 year olds, we used the Poisson approximation to the binomial distribution ($1/({}_n m_x^2 / {}_n D_x)$). The Poisson approximation is computationally easier and when the number of events (${}_n D_x$) is small and the population at risk is large (${}_n P_x > 100$), both methods produce similar variance estimates. The following prediction equations for each of the 3 segments can be substituted into formula [1]:

$$\left.\begin{aligned} {}_n\hat{m}_{x(0)} &= a + b_x + c_x^2 + d_x^3; \text{for } y \le x \le k_1 \\ {}_n\hat{m}_{x(1)} &= a + b_x + c_x^2 + d_x^3 + e(x-k_1)^3; \text{for } k_1 \le x \le k_2 \\ {}_n\hat{m}_{x(2)} &= a + b_x + c_x^2 + d_x^3 + e(x-k_1)^3 + f(x-k_2)^3; \text{for } k_2 \le x \le z \end{aligned}\right] \qquad \textbf{[2]}$$

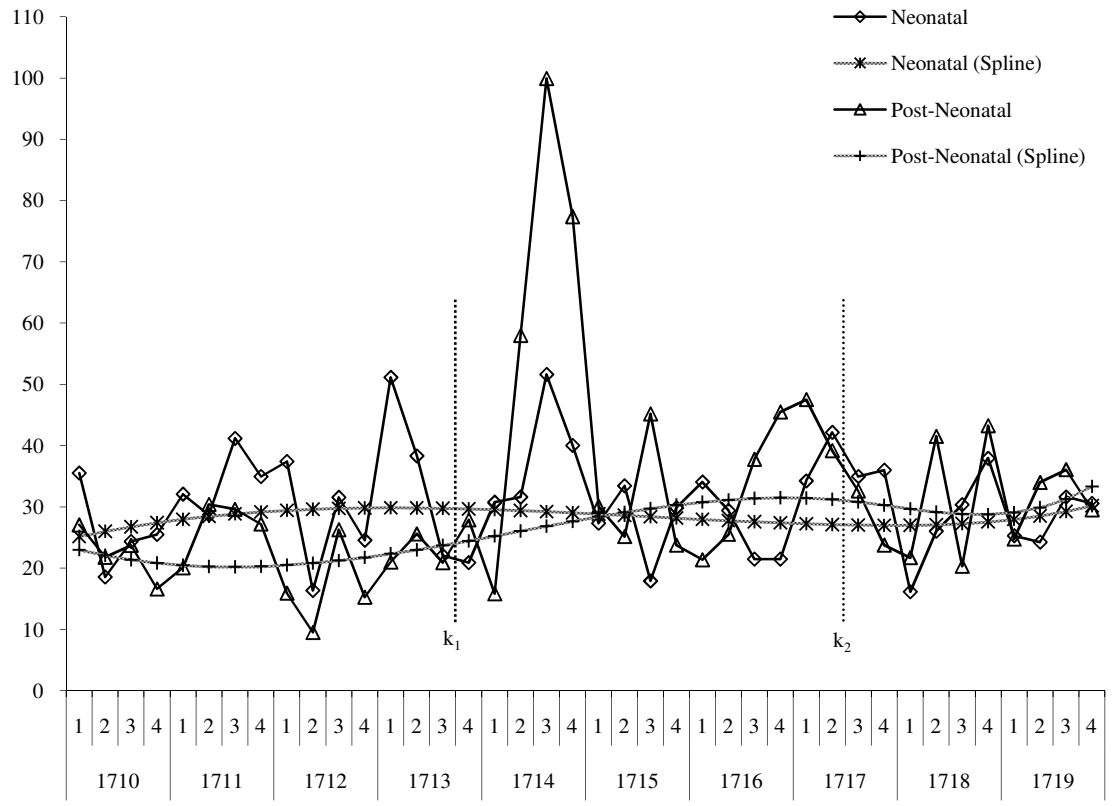
where $y = 1$ (1st quarter of 1710), $z = 40$ (4th quarter of 1719), $k_1 = 15.5$ and $k_2 = 30.5$. The locations of the knots were determined by a visual examination of line graphs for each of the age groups and regions (e.g., see figures 2.1 and 2.2). It was found manually that the knots could be placed in the same location for each of the groups. Predicted quarterly rates (${}_n\hat{m}_x$) serve as an estimate of the normal quarterly death rate for ages x to $x + n$. These are the expected morality conditions in the absence of period disturbances such as, epidemics.

To examine the origin, spread and duration of the epidemic, we estimated ${}_n\hat{m}_x$ for the colony by age (i.e. neonatal (<28 days), post neonatal (28 to 365 days), infants (< 365

days), 1 to 4 year olds and 5 to 14 year olds). The age-specific quarterly death rates were annualized to adjust for differences in the number of days in each quarter and to facilitate comparability between the quarters and regions. These rates were then divided by the expected annual rate of the colony to produce age-specific risk ratios for each of the regions (${}_nRR_x = {}_nm_x / {}_n\hat{m}_x$)[3]. Figure 2.2 shows an example of smoothing splines fit through a series of neonatal and post-neonatal mortality rates (or $m_{<28}$, m_{28-365}) to estimate the expected rates, $\hat{m}_{<28}$ and $\hat{m}_{28-365}$ for the colony. The trends in the graph may reflect a general worsening of the environment in the colony, as post neonatal mortality (exogenous) became higher than neonatal mortality (endogenous; see Lalou, 1990).

[3] One should exercise caution when interpreting the ratios, as some of the observed rates are based on a small number of events. For instance, a small increase in the number of deaths can produce larger than normal level of risk in the population. As such, large fluctuations may be a combination of random variation and excess mortality from the epidemic. However, the risk table should allow one to gauge an approximate level of risk relative to 'normal' mortality conditions in the colony.

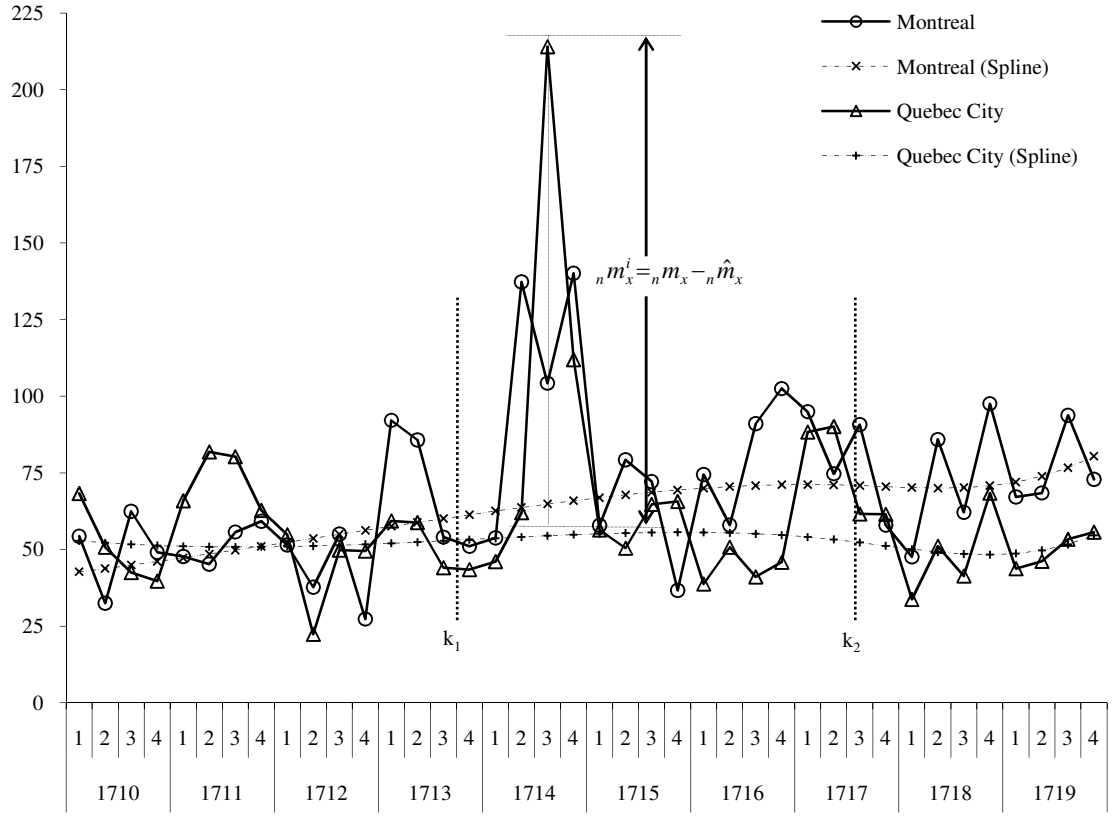
Figure 2.2. Cubic spline function to estimate the expected death rate of the colony, Neonatal and Post-neonatal mortality



The above scenario could mean that cause of death boundaries are overlapping and the difference between the true and estimated parameters are distorted. In the absence of cause of death records, there is never an exact way to know how someone died. However, we still can derive an acceptable estimation of measles deaths by fitting a series of smoothing splines through the data points. For simplicity, the assumption allows ${}_n m_x^{measles}$ to equal the residual difference between the observed and predicted rates or ${}_n m_x^{measles} = {}_n m_x - {}_n \hat{m}_x$. Figure 2.3 shows the general procedure of obtaining an estimate of ${}_1 \hat{m}_0$ and ${}_1 m_0^{measles}$ in Montreal and Quebec City from the observed data. The trends of the

splines show a clear worsening of general morality conditions in Montreal, as compared to Quebec City.

Figure 2.3. Cubic spline function to estimate the expected and measles death rates among infants, Montreal and Quebec City



2.3. Results

In this section, the general dynamics of the measles epidemic are examined through a regional analysis of the origin, spread and duration of the epidemic by age and sex. In addition, the severity of the epidemic is examined with estimates of death rates from measles based on the spline and life table methods discussed in the Data and Methods section by age, sex and region.

2.3.1. Origin, Spread and Duration

The origin, spread and duration of the measles epidemic can be found through an examination of the risk ratios of infant and childhood mortality. Figures 2.4 a) through e) show the observed quarterly mortality rates of the six regions. Table 2.3 shows the annualized quarterly age-specific risk ratios by region and quarter. The range of shades in the table portrays the hot and cold spots during the epidemic. For example, no shade indicates lower than expected mortality, while darker shades indicate a much higher than expected rate. The graphs and risk table should be used in conjunction with one another to give a clear picture of the events in 1714 and 1715.

As mentioned above, we do not have detailed cause of death records, which would help us identify the event as a measles epidemic. However, historical accounts in colonial America report a 'serious' measles epidemic between 1713 and 1715 (see Section 2.1). The origin of the virus is unknown, but many fatalities were reported in Boston, Massachusetts. The epidemic began in the late summer of 1713 and had run its course by the end of January 1714. By February of that year, the virus had spread to New York, New Jersey, Connecticut and Pennsylvania (Duffy, 1953).

Figure 2.4. Quarterly neonatal mortality rates by region for: a) neonatal; b) post-neonatal; c) infants; d) 1 to 4 year olds and; e) 5 to 14 year olds, New France 1713-15

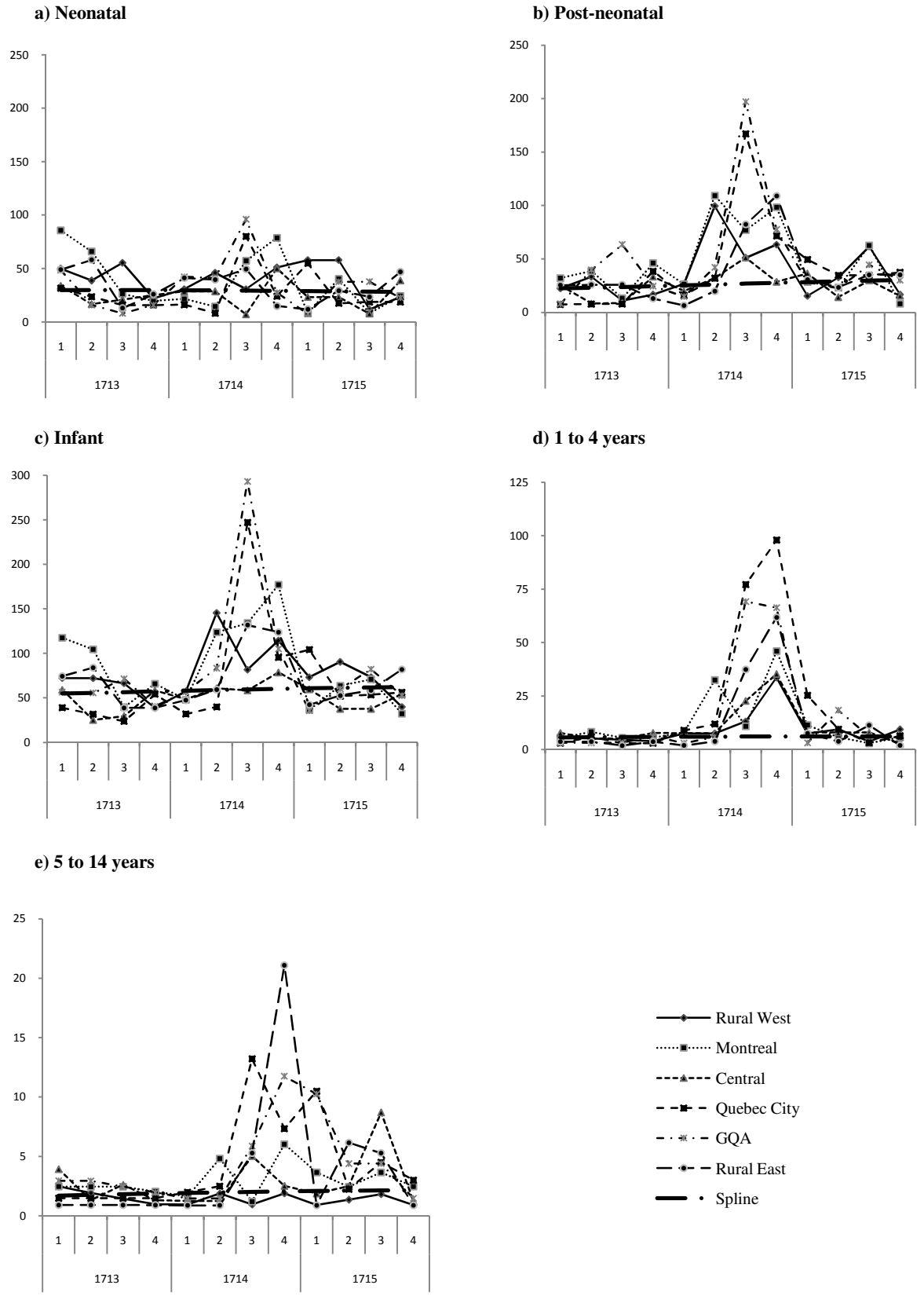


Table 2.3. Mortality Ratios comparing the 'Annualized' Quarterly Rates to the Normalized Annual Rate by Age and Region, New France: 1714-15

Age	Year	Quarter	Colony	Rural West	Montreal	Central	Quebec City	GQA	Rural East
<28 days	**1714**	**1**	0.86	0.85	0.60	0.80	0.45	1.17	1.14
		2	0.87	1.26	0.39	0.79	0.22	1.13	1.09
		3	1.41	0.83	1.56	0.19	2.18	2.61	1.35
		4	1.09	1.39	2.14	1.36	0.65	0.75	0.40
	1715	**1**	0.74	1.57	0.22	0.63	1.49	0.20	0.32
		2	0.91	1.57	1.10	0.63	0.47	1.02	0.80
28-365 days	**1714**	**1**	0.48	0.86	0.54	0.42	0.40	0.48	0.21
		2	1.74	2.98	3.27	0.96	0.95	1.26	0.59
		3	2.96	1.51	2.27	1.51	4.95	5.84	2.43
		4	2.29	1.87	2.91	0.85	2.12	2.29	3.22
	1715	**1**	0.91	0.46	0.86	1.10	1.49	0.85	0.93
		2	0.75	0.98	0.70	0.43	1.04	0.67	0.70
0 to 1	**1714**	**1**	0.48	0.83	0.69	0.41	0.46	0.83	0.69
		2	1.74	2.08	1.77	0.87	0.57	1.19	0.85
		3	2.96	1.16	1.90	0.83	3.50	4.16	1.87
		4	2.29	1.62	2.51	1.11	1.35	1.49	1.76
	1715	**1**	0.81	1.04	0.52	0.84	1.48	0.50	0.60
		2	0.83	1.28	0.90	0.53	0.74	0.85	0.75
1 to 4	**1714**	**1**	0.99	1.01	1.15	1.12	1.19	0.39	0.25
		2	1.75	1.00	4.54	1.10	1.57	0.78	0.50
		3	5.78	1.73	1.50	3.25	10.12	9.24	4.96
		4	8.87	4.45	6.37	5.06	12.85	8.86	8.18
	1715	**1**	1.62	1.03	1.56	1.08	3.46	0.42	1.03
		2	1.41	1.28	0.78	1.08	1.30	2.51	0.51
5 to 14	**1714**	**1**	0.64	0.39	0.67	0.52	0.82	0.60	0.36
		2	1.01	0.77	1.96	0.51	1.01	0.60	0.36
		3	2.33	0.38	0.48	2.02	5.32	2.36	2.12
		4	4.28	0.76	2.42	1.01	2.95	4.73	8.48
	1715	**1**	1.90	0.37	1.47	0.76	4.22	4.12	0.35
		2	1.57	0.55	0.98	1.00	0.90	1.77	2.48

Legend:

<1.50	1.50 - 1.99	2.00 - 4.99	>5.00

There is no indication that the epidemic had spread into New France at that time. Mortality levels in the 1st quarter of 1714 were at or below normal throughout colony. However, by the spring of 1714, a sudden increase in mortality appeared in the Western parishes. As seen in Figures 2.4 a) through e) and Table 2.3, all age groups in Montreal had higher than normal death rates. For instance, post-neonatal risk ratios reached 3.27 times the normal rate in Montreal. The patterns observed in the risk table give a good indication that the virus originated in the Western area of the colony. Another factor is that Aboriginals usually traveled from the American territory to the French colony via a canoe route consisting of the Hudson River, Lake Champlain and the Richelieu River. As such, we believe that the Canadian origin of the epidemic was somewhere around Montreal and the surrounding Rural parishes during the 2nd quarter of 1714 (late March). It then spread eastward and reached the Central and Eastern parishes near the end of the 3rd quarter (around September) (see also Figure 2.1).

By the late 3rd quarter of 1714, the risk of death was elevated in all areas, particularly in the Eastern parishes. Notice that neonatal risk is not as pronounced as in the other age groups. Neonates may have incurred some advantage, as maternally acquired antibodies and the general benefits of breast milk tend to provide protection against measles infection during the first months of life (Moss and Ota, 2007; Mandomando et al., 2008). Interestingly, post-neonatal and early childhood death ratios declined in Montreal between the 2nd and 3rd quarters, but increased again by the 4th quarter. These distinct crown shaped (or bimodal) mortality peaks are evident in figures 2.4 b) and 3 d). During that time, mortality levels peaked in the Central parishes, Quebec City and the Rural East.

For 1 to 4 year olds, mortality peaked during the fourth quarter of 1714 in all areas, with Quebec City having the highest risk ratio at 12.85 times the normal rate. Mortality began approaching expected levels by the first quarter of 1715, except in Quebec City, where the risk remained 3.46 times higher than normal.

In most regions, mortality rates among 5 to 14 year olds (later childhood) were also elevated during the epidemic. Risk ratios ranged from a low of .76 in the Rural West to a high of 8.48 times the normal rate in the Rural East. The elevated risk of death in the East continued well into 1715 and began to return to normal levels by the 2nd quarter of that year. Curiously, the rates in the Rural West remained well below the expected rate for the entire duration of the epidemic. This pattern suggests that residents had a better chance of recovery or were previously exposed to measles and had acquired immunity. At this point, however, we are not aware of any other serious measles epidemics taking place before this one. These patterns may be more of an indication of a higher chance of recovery from the virus (possibly, better nutrition). Additionally, infants in the Central region had a much lower risk ratio than infants in the other regions. This trend could be the result of greater isolation and lower contact density. Colonists usually travelled from Montreal to Quebec City or vice versa without stopping in Trois-Rivières.

Notice that post-neonatal and 5 to 14 year old mortality rates were also elevated during the 3rd quarter of 1715 (refer to Figures 2.4 b) and e)). We believe this surge may be the result of another epidemic or delayed measles complications. This may also be the case with the elevated ratios during the 2nd quarter of 1715. After a measles epidemic,

recovering individuals tend to be immunocompromised and are more susceptible to other infections. It is believed that morbidity and mortality can be increased for up to a year after the initial epidemic (Clements and Hussey, 2004). In our case, the excess deaths in the 3rd quarter occurred in July and tend not to follow the typical seasonal pattern of measles in North America (i.e., autumn to later winter/spring). In addition, a smallpox epidemic was reported in New York and other parts of the American colonies during the summer of 1715 (Duffy, 1953). This epidemic may have also reached New France, as well. As such, we do not consider the increased rates as a direct result of the 1714 measles epidemic. Taking these factors into consideration, we believe that the epidemic may have lasted somewhere around 15 months or between the 2nd quarter of 1714 and the 2nd quarter of 1715.

2.3.2. Estimated Deaths from Measles

Now that we have an idea on the origin, spread and duration of the measles epidemic, we turn to its severity. This was accomplished by estimating the measles death rates by age, sex and region (Table 2.4). Annual rates are shown, but estimates for 1 to 4 and 5 to 14 year olds do not follow the normal calendar year. These estimates coincide with the duration of the epidemic. For 1 to 4 year olds, we examine deaths between the 2nd quarter of 1714 and the 1st quarter of 1715, while for 5 to 14 year olds we examine deaths occurring between the 3rd quarter of 1714 and the 2nd quarter of 1715. Although the epidemic may have had a longer duration, we only show the 12 months when most of the regions were infected.

2.3.3. Normal Mortality Conditions

Before we examine the severity of the epidemic, we first give a brief description of the expected level of mortality under normal conditions (based on rates estimated with the splines). For infants, the probability of death under normal conditions was estimated at 230 deaths per thousand live births, with males at a slightly higher risk of death. As we mentioned above, our estimates of infant mortality will be lower than those of others because we did not correct for underreporting (see Section 2.2.1). For instance, other estimates of infant mortality range from 240 to 246 deaths per thousand live births roughly during this time period (Henripin, 1954; Charbonneau, 1975; Lalou, 1990; Gagnon and Mazan, forthcoming). Mortality also varied by region with the West having the highest rate (261.5 per thousand) followed by the East (219.9 per thousand) and Central Regions (177.7 per thousand). Montreal had the highest level of infant mortality in the colony, where 28.4% of infants would die before their first birthday. Generally, early childhood mortality (1 to 4 year olds) was slightly higher among females throughout the entire decade. For older children (5 to 14 year olds), the expected death rate was around 7 per thousand for both males and females. Mortality in the Central region appeared to be the highest (9.3 per thousand), while rates in the West and East were about the same[4].

[4] Estimates of mortality at this age in the Central region are based on a smaller number of events. As such, these estimates are subject to a higher degree of random variation than the other regions.

Table 2.4. Estimated annual death rates from measles and all other causes by age, sex and region, New France: 1714-15

0 to 14				0 to 1					1 to 4					5 to 14				
				1st quarter of 1714 to 4th quarter of 1714					2nd quarter of 1714 to 1st quarter of 1715					3rd quarter of 1714 to 2nd quarter of 1715				
	${}_{15}m_0$ measles	C.I	Measles deaths (%)	q_0	q_0 other	q_0 measles	C.I	Measles deaths (%)	${}_4m_1$	${}_4m_1$ other	${}_4m_1$ measles	C.I	Measles deaths (%)	${}_{10}m_5$	${}_{10}m_5$ other	${}_{10}m_5$ measles	C.I	Measles deaths (%)
Colony	52.8	47.6-57.2	59.6	405.2	230.0	175.3	150.9-199.7	43.2	111.0	24.0	87.0	76.2-99.3	78.4	20.6	7.2	13.3	11.5-18.1	64.8
Sex																		
Males	49.4	43.3-56.4	57.2	395.6	233.4	162.2	129.8-194.6	41.0	112.1	22.7	89.4	74.4-107.4	79.8	16.4	7.3	9.1	6.1-13.6	55.7
Females	55.1	48.4-62.7	60.8	416.4	226.0	190.4	153.5-227.3	45.7	109.9	26.3	83.5	68.9-101.3	76.0	25.0	7.2	17.8	13.3-23.8	71.1
Region																		
West	35.4	29.4-42.6	47.8	433.6	261.5	172.1	131.8-212.4	39.7	77.5	22.9	54.6	41.3-72.2	70.5	8.7	6.6	2.1	0.8-5.6	24.4
Central	22.4	15.7-32.1	42.6	226.2	177.7	48.5	12.6-84.5	21.5	73.4	25.0	48.4	30.9-75.7	65.9	21.2	9.3	12.0	6.4-22.6	56.4
East	75.7	67.8-84.5	68.0	431.5	219.9	211.5	174.4-248.6	49.0	148.1	24.5	123.6	105.3-145.0	83.4	33.3	6.5	26.7	21.0-34.0	80.4
Urban																		
Montreal	45.4	35.3-58.4	51.7	482.1	284.2	197.9	132.6-263.2	41.0	100.6	23.8	76.8	53.1-111.0	76.4	13.3	8.5	4.8	1.8-12.9	36.4
Quebec City	90.8	74.8-110.1	70.3	414.4	220.1	194.3	125.0-263.5	46.9	212.2	30.4	181.8	141.4-233.7	85.7	34.0	8.3	25.7	16.1-41.2	75.6
Rural																		
Rural West	28.1	21.3-37.0	43.9	398.8	244.7	154.1	103.2-205.0	38.6	61.7	22.3	39.4	25.7-60.4	63.9	5.1	5.1	-	-	-
Rural East	70.1	61.3-80.2	67.0	437.8	219.9	217.8	174.0-261.7	49.8	123.8	22.3	101.5	82.5-124.9	82.0	33.0	5.9	27.1	20.5-35.8	82.2

2.3.4. Epidemic Conditions

Survival prospects worsened for children under the age of 15 when the measles epidemic appeared in the colony during the early spring of 1714 (see Table 2.4). Based on our spline functions described in the methods section, we estimated an overall measles death rate of 52.8 per thousand for children under age 15, which accounted for approximately 59.6% of all deaths. We also estimated that 43.2% of all deaths among infants, 78.4% for 1 to 4 year olds and 64.8% for 5 to 14 year olds could have been from the measles virus. Children in the East had the highest measles death rate, as they were 2.1 and 3.4 times more likely than children in the West and Central regions to have died from measles (i.e. 75.7 vs. 35.4 and 22.4 per thousand).

Overall, infant measles death rates in the East and West were quite similar: 21.2% of infants were estimated to have died from measles in the East, while 17.2% died in the West. Only 4.9% infants died from measles in the Central region. Among young children, however, measles death rates varied considerably by region. The measles death rate for this age group was estimated to be highest in Quebec City (181.8 per thousand), followed by the Rural East (101.5), Montreal (76.8), Central (48.4) and Rural West (39.4). On average, young children in the East were 2.3 times as likely as those in the West and Central regions to have died from the virus.

In Quebec City, the epidemic must have been quite severe among young children, as infants only had a 6.9% higher risk of measles death than 1 to 4 year olds (i.e. 194.3 vs. 181.8 per thousand). In comparison, infants in Montreal were 2.6 times more likely to die from measles than young children. Similarly, older children in the West had had a much

lower risk of death than children in the East and Central Regions. In the Rural West, there is no clear evidence that any child aged 5 to 14 years died from measles. On the other hand, high measles death rates were evident in the Eastern parishes. Children in the East were 2.2 and 5.6 times more likely to die from measles than those residing in the Central region and Montreal, respectively.

Generally, females under 15 years of age were slightly more likely than males to die from measles (55.1 vs. 49.4 per thousand). Lower survival among females is consistent with a study of measles mortality in 78 countries between 1950 and 1989 (Garenne, 1994). Sex differences become even clearer when ages are broken down into their standard groupings. Female infants had 17% higher mortality from measles than males, while for 1 to 4 year old males had a slightly higher risk of death. The latter pattern is not unusual because some studies have found no clear sex difference (Moss and Ota, 2007). For 5 to 14 year olds, we estimated that females were almost twice as likely as males to have died from measles (17.8 vs. 9.1 per thousand). Garenne (1994) also found a similar pattern in this age group (though not as large of a difference). The factors that contribute to the differences are largely unexplained. It is not clear whether the sex difference is biologically or socially based (Clements and Hussey, 2004). More than likely, it is a combination of social and biological differences. Although females generally had a higher risk of death from measles, the epidemic had severe consequences on male children as well.

2.4. Discussion and Conclusion

A severe measles epidemic entered the Western part of New France during the 2nd quarter of 1714 (in late March). By the 3rd quarter (around September), the epidemic had spread to most parts of the colony and had run its course by the 2nd quarter of 1715. Although we do not have detailed cause of death data for that time, we were able to estimate measles death rates by fitting a series of smoothing splines through the data by age, sex and region. We found that the epidemic was quite severe among all age groups, but the severity declined with age and varied by region. However, risks ratios comparing epidemic with normal mortality conditions were generally higher for children than for infants. Children in the East had the highest risk of death in the colony, while females were more likely than males to have died from measles. This sex differential continues to be observed in modern populations (Garenne, 1994).

A further issue that needs to be addressed are the possible reasons for the high number of measles fatalities in the colony. Measles epidemics can be of mild to severe forms, but this epidemic proved to be often fatal for children less than 15 years of age. Practitioners in 18th century England reported that most healthy children 'rarely' died from measles (Duncan et al., 1997). Rather, death was more common in infants of 'weak constitution', particularly among the working class in the large cities. If healthy children have a higher chance of recovery from measles infection, then there must have been an event in the colony that would have acted as a 'trigger' for the mortality crisis. According to Palloni (1990), there is usually a 'triggering event' preceding any crisis.

In the case of New France, the triggering event could have been poor climatic conditions. Duncan et al. (1997) found that, low spring and autumn temperatures were associated with measles epidemics and mortality in 17th and 18th century England. Further, Canada has always been well known for its frequent cold snaps and, generally, as a nation with a 'cold climate'. These trends coincide with the seasonal patterns of the measles virus. In the Northern Hemisphere, measles epidemics usually peak during the spring, autumn and early winter months (when contact density increases) (Cliff et al., 1998).

In turn, a poor climate could have led to poor harvests, food shortages containing essential vitamins and even malnutrition. In fact, "poor to disastrous harvests" were reported in New France between 1714 and 1717 (Crowley, 1991). There was no indication of the exact regions affected or whether the entire colony experienced poor harvests. Judging by the severity of the epidemic, the children in the East would be in the disadvantaged situation. The farming season in the Eastern (northern) regions are shorter than in the West. Also, the soils were very fertile in the plains around Montreal and the land was easier to cultivate than in the Eastern region of Charlevoix. Poor harvests may have led to nutritional deficiencies and left the colonists in a vulnerable state.

Pre-existing malnutrition is regarded as a major predictor of measles mortality. In 17th and 18th century England, for instance, measles mortality was found to be positively associated with wheat prices (a proxy for malnutrition) (Duncan et al., 1997). It is believed that the influence of malnutrition is mediated through immune suppression (Clements and Hussey, 2004). In particular, vitamin A deficiency and protein energy malnutrition are the common nutritional risk factors associated with an increased risk of

death. Vitamin A is essential because it replenishes epithelial cells (the first line of defense) and helps regulate the immune system, which prevents or fights off infections by producing white blood cells to destroy harmful bacteria or viruses. An infected person with a vitamin A deficiency tends to have an increased risk of developing complications associated with measles immune suppression such as, severe diarrhoea and pneumonia (Moss and Ota, 2007). As such, the WHO recommends giving high doses of vitamin A supplements to infected children in areas where vitamin A deficiency is widespread or the measles case fatality rate is 1%. Arguably then, an improved diet and Vitamin A supplementation during an epidemic leads to a 'marked fall' in measles mortality (Barclay et al., 1987; Berman, 1991; Clements and Hussy, 2004).

Another possibility for the high death rates is overcrowding in households. Several community studies on West Africa, Asia and Europe found that mortality was higher in families with several cases and among secondary cases (i.e. children infected at home) (Garenne and Aaby, 1990). A couple of the studies in Senegal even concluded that the 'effect of malnutrition was less important than overcrowding and intensive exposure to the virus' (Aaby et al., 1984; 1988). Generally, it is suggested that close contact with other family members serves to increase the generational intensity of the virus. The increased mortality risk associated with close family contact is explained as a 'dose-response effect': the closer the contact between family members, the higher the dose of infective particles transmitted and the higher the mortality of the other family members (Garenne and Aaby, 1990). As such, this implies that the effect of crowding on the risk of death may be mediated through intensive exposure to the virus.

In other community studies, the age at infection and family size have also been found to be important risk factors of measles mortality (Reves, 1985; Pison et al., 1992; Burstrom et al., 1999). Pison et al., (1992) found that a larger age difference between sibling pairs resulted in a higher odds of death from measles. In the case of Quebec, older children may have been more likely to be infected outside of the home (index child) and then infect the younger children in the household (secondary cases). Older children would have a better chance of fighting off the infection because of a fully developed immune system. Younger children, on the other hand, would be at a dual disadvantage because of an underdeveloped immune system and further suppression due to widespread malnutrition. In turn, younger children who contract the virus, given the age-associated differences in risk and the intensity hypothesis, would have a greater likelihood of dying (Pison et al., 1992; Burstrom et al., 1999). These issues are addressed in some detail in the subsequent chapters.

As New France was considered a 'natural fertility' population, a typical family would usually have a large number of young children in the household. If crowding or sibling transmission were the more important determinants, then we would expect mortality rates to be similar in each region, as family size was equally large in all parts of the colony. This is clearly not the case, as overall measles mortality was estimated to be higher in the East. Thus, we suspect that the severity of the epidemic was largely a result of widespread malnutrition or vitamin A deficiency in the East. These circumstances probably made the inhabitants highly vulnerable and contributed to the higher number measles deaths in that particular region.

2.5. References

Aaby P. 1988. “Malnutrition and overcrowding/intensive exposure in severe measles infection: Review of community studies”. *Review of Infectious Diseases* 10: 478-491.

Aaby P., Bukh J., Lisse I. M., Smits A. J. 1984. “Overcrowding and intensive exposure as determinants of measles mortality”. *American Journal of Epidemiology* 120: 49 63.

Barclay A. J. G., Foster A., Sommer A. 1987. “Vitamin A supplements and mortality related to measles”. *British Medical Journal* 294: 294-296.

Bartlett M. S. 1960. “The critical community size for measles in the United States”. *Royal Statistical Society, Series A* 123: 37-44.

Benjamin B., Pollard J. H. 1980. *The Analysis of Mortality and Other Actuarial Statistics.* London: Heinemann.

Berman S. 1991. “Epidemiology of acute respiratory infections of children in developing countries”. *Review of Infectious Diseases* 13: S454-S462.

Blum, A., Henry, L. 1988. *Techniques d'analyse en démographie historique*. Paris: INED.

Burstrom B., Diederichsen F., Smedman L. 1999. Child mortality in Stockholm during 1885- 1910: The impact of household size and number of children in the family on the risk of death from measles. *American Journal of Epidemiology* 149: 1134-1141.

Charbonneau H., Desjardins B., Guillemette A., Lardry Y., Légaré J., Nault F. 1993. *The First French Canadians: Pioneers in the St. Lawrence Valley*. Newark: University of Delaware Press.

Charbonneau H., Desjardins B., Légaré J., Denis H. 2000. “The population of the St. Lawrence Valley, 1608-1760” in *A population History of North America.* Haines M. R., Steckel R .H. (ed.). Cambridge, Cambridge University Press, pp. 99-142.

Charbonneau H. 1975. *Vie et Mort de nos Ancêtres Montréa*l. Montréal: Les Presses de l'Université de Montréal.

Chiang C. L. 1984. *The Life Table and its applications*. Florida: Robert E. Krieger Publishing.

Clements C. J., Hussey G. D. 2004. “Measles” in *The Global Epidemiology of Infectious Diseases.* Murray C. J. L., Lopez A. D., Mathers C.D. (ed.). Geneva: WHO.

Crowley T., 1991, “Violence and protest”, in *Economy and society during the French regime, to 1759,* Cross M. S., Kealey G. S., (ed.). Toronto, McClelland and Stewart, pp. 120-151.

Dechene L., Robert J-C. 1993. “Le cholera de 1832 dans le Bas-Canada: mesure des inegalites devant la mort” in *The Great Mortalities: Methodological Studies of Demographic Crises in the Past.* Charbonneau H., Larose A. (ed.). Belgium: Oridona Editions (IUSSP), pp. 229-256.

Desjardins B. 1996. “Demographic aspects of the 1702-1703 smallpox epidemic in the St-Lawrence valley”. *Canadian Studies in Population* 270: 49-67.

Duffy J. 1953. *Epidemics in Colonial America*. Baton Rouge: Louisiana State University Press.

Duncan C. J., Duncan S. R., Scott S. 1997. “The dynamics of measles epidemics”. *Theoretical Population Biology*, 52, pp. 155-163.

Finkenstadt B., Keeling M., Grenfell B. 1997. “Patterns of density dependence in measles dynamics”. *Proceedings of the Royal Society B* 265: 753-762.

Gagnon A., Mazan R. 2009. “Does exposure to infectious diseases in infancy affect old age mortality? Evidence from a pre-industrial population”. *Social Science and Medicine* 68: 1609-1616.

Garenne M. 1994. “Sex differences in measles mortality: A world review”. *International Journal of Epidemiology* 23: 632-642.

Garenne M., Aaby P. 1989. “Patterns of exposure and measles mortality in Senegal”. *Journal of Infectious Diseases* 16: 1088-1094.

Giesecke J. 2002. *Modern Infectious Disease Epidemiology*. London: Arnold.

Henripin J. 1954. *La Population Canadienne au Début du XVIIIe Siècle: Nuptialité, Fécondité, Mortalité Infantile*. Paris: Presses universitaires de France.

Henry L. 1968. “The verification of data in historical demography”. *Population Studies* 22: 61-81.

Lalou, R. 1990. *Des Enfants pour le Paradis. La Mortalité des Nouveau-nés en Nouvelle-France*. Thèse présentée à la Faculté des études supérieures en vue de l'obtention du grade de philosophiae doctor (démographie). Université de Montréal.

Légaré J. 1988. “A population register for Canada under the French regime: Context, scope, content, and applications”. *Canadian Studies in Population* 15: 1-16.

London D. 1985. *Graduation: The Revision of Estimates*. Winsted and Abington, Connecticut: ACTEX Publications.

Mandomando I. M., Naniche D., Pasetti M. F., Valles X., Cuberos L., Nhacolo A., Kotloff K. L., Levine M. M., Alonso P. 2008. "Measles-specific neutralizing antibodies in rural Mozambique: Seroprevalence and presence in breast milk". American Journal of Tropical Medicine and Hygiene 79: 787-792.

Moore C. 1997. "Colonization and conflict: New France and its rivals 1600-1760" in *The Illustrated History of Canada*. Brown C. (ed.). Toronto: Key Porter Books Limited, pp. 105-188.

Moss W. J., Ota M. O. 2007. "Measles" in *Infectious Disease Epidemiology: Theory and Practice,* Nelson K. E., Williams C. M. (ed.). Boston: Jones and Bartlett Publishers, pp. 601-621.

Murray G. D., Cliff A. D. 1977. "A stochastic model for measles epidemics in a multi-region setting". *Transactions of the Institute of British Geographers* 2: 158-174.

Nault F., Desjardin B., Légaré J. 1990. "Effects of reproductive behaviour of French Canadians during the seventeenth and eighteenth centuries". *Population Studies* 44: 273-285.

Palloni A. 1990. "Assessing the levels and impact of mortality in crisis situations" in *Measurement and Analysis of Mortality: New Approaches*. Vallin J., D'Souza S., Palloni A. (ed.). Oxford: Clarendon Press, pp. 195-228.

Pison G., Aaby p., Knudsen K. 1992. "Increased risk of death from measles in children with a sibling of opposite sex in Senegal". *British Medical Journal* 304: 284 – 287.

Prenter P. M. 1975. *Splines and Variational Methods*. New York: John Wiley & Sons.

Reves R. 1985. "Declining fertility in England and Wales as a major cause of the twentieth century decline in mortality: The role of changing family size and age structure in infectious disease mortality in infancy". *American Journal of Epidemiology* 122: 112 – 126.

Rhodes C. J., Anderson R. M. 1996. "A scaling analysis of measles in epidemics in a small population". *Philosophical Transactions of the Royal Society B* 351: 1679 – 1688.

Chapter 3

Risk factors of mortality among French Canadian children during the measles epidemic of 1714-15[*]

3.1. Introduction

In past populations, measles epidemics were responsible for many deaths, especially among young children (Duffy, 1953). An example of one such epidemic was in New France. The epidemic began in the Western part of the colony during the second quarter of 1714 (late March). By the third quarter (around September), measles had spread to most parts of the colony and vanished by the second quarter of 1715 (see Chapter 2). The epidemic was highly virulent among children under 15 years of age, but severity declined with age and varied by sex and region. It was estimated that children living in the Eastern parishes had the highest risk of death in the colony and females were more likely than males to have died from the virus. The severity of the epidemic was believed to have been modulated by a combination of factors such as, lack of prior exposure, malnutrition (more severe in the East) and sibling transmission in the household. Together, these factors acted synergistically increasing the vulnerability of the inhabitants and probably contributed to the high severity of the measles epidemic in general.

Several risk factors have been linked with higher measles mortality. Pre-existing malnutrition is regarded as one of the major risk factors of measles mortality (Clements and Hussey, 2004; Moss and Ota, 2007). Measles also contributes to malnutrition because

[*] In Submission: Mazan R. 2010. "Risk factors of mortality among French Canadian children during the measles epidemic of 1714-15". *Genus,* Revised and Resubmitted.

of protein-losing enertopathy (i.e., abnormal loss of protein), increased metabolic demands and decreased food intake. Increased measles mortality has been associated with increases in wheat prices (a proxy for malnutrition) during the seventeenth and eighteenth centuries in England (Duncan et al. 1997). It is believed that the influence of malnutrition is probably mediated through immune suppression (Clements and Hussey, 2004). In particular, protein energy malnutrition and Vitamin A deficiency have been linked to an increased risk of death from measles. Arguably, an improved diet and Vitamin A supplementation during an epidemic leads to a 'marked fall' in measles mortality. Vitamin A therapy, for instance, has been proven to be an effective treatment for infected cases in developing countries and can reduce the risk of death by up to 50% (Barclay et al., 1987; Berman, 1991; Clements and Hussy, 2004).

Community studies conducted in Guinea-Bissau, Senegal, Bangladesh, Gambia and Denmark among others found that mortality was higher in families with several cases and among children exposed inside the home (i.e., secondary cases) (Aaby et al., 1984; 1988; Hull, 1988; Koster, 1988; Pison and Bonneuil, 1988). Two of those studies concluded that crowding (i.e., number of persons in the household) and intensive exposure were more important risk factors than pre-existing malnutrition (Aaby et al., 1984; 1988).

Overcrowding or close contact with other family members intensifies exposure to the virus among secondary cases in the household and in turn, increases the risk of acute measles death. These findings suggest that the influence of crowding and clustering of cases on the risk of death may be mediated through intensive exposure. The risk associated with close familial contact is usually explained as a 'dose-response effect': the

closer the contact between family members, a higher dose of infective particles transmitted to the other family members (Garenne and Aaby, 1990). Close physical contact between family members implies 'the absorption of a larger and more lethal dose of the virus' (Aaby, 1988).

As with many other infectious and parasitic diseases, the age at infection is an important risk factor of measles mortality (Hull, 1988). The risk of death from measles tends to peak between 6 and 24 months of age and then declines with increasing age (Burstrom et al., 1999). Infants below 9 months of age tend to have a lower risk than toddlers, as they benefit from passive immunity in terms of placental transferred measles antibodies and from Immunoglobulin A contained in breast milk (Mandomando et al., 2008). Typically, younger unexposed children are at a high risk of death because they have an underdeveloped immune system and lack general protection from maternal antibodies. In addition, crowding or large families with many young children in the household are believed to be at an increased risk of death because of the higher probability of infection at the younger ages (Reves, 1985). However, Burstrom et al., (1999) did not find support that the risk of death in crowded households was mediated through a low age at infection. Rather, they concluded that crowding had an independent effect on the risk of death from measles.

In other studies, it was found that a larger age difference between sibling pairs resulted in a higher odds of death from measles (Pison et al., 1992). Older children or the parents (more likely the index cases in households) are probably more likely to introduce measles into the household through outside contacts. In turn, younger children who are infected as

secondary cases are at an increased risk of death, as they are believed to receive a more 'lethal' and prolonged dose of the measles virus (Hull, 1988; Aaby, 1988; Koster, 1988; Pison et al., 1992; Burstrom et al., 1999). Measles mortality has consistently been found to be higher among secondary cases exposed in the home than index cases with more 'casual' exposure outside of the home (Aaby, 1995; Perry and Halsey, 2004).

Modern studies have also found that cross-sex transmission of the virus increased the risk of death, as households with opposite sex sib-pairs had higher mortality than ones with same sex sib-pairs (Aaby, 1992; 1995; Pison et al., 1992). There is no clear explanation for the differences, but it is likely a combination of biological and social factors. One possible cultural explanation is that one of the sexes is more likely to be an index case due to specific behavioural patterns. In European-American culture, for instance, there is evidence that females are more likely to be the index case. This would account for higher male deaths. In Muslim societies, it would be the other way around, as boys are more likely to be infected outside of the home (Pison et al., 1992).

Historical data from Quebec provides a suitable context to test some of the above assumptions on the risk factors of death during a measles epidemic. Modern medicine and public health knowledge were non-existent at the time. As such, the measles virus could be considered to have occurred in a natural habitat with no interference from the vast improvements in health and medical knowledge. In general, social and environmental conditions were also better than in France at the time and these circumstances probably benefited the majority of inhabitants (Charbonneau et al., 2000; Greer, 1997). The early French settlers were mostly farmers who had good access to an adequate source of

subsistence resources. As a new settlement and an expanding frontier, land and resources were plentiful, where motivation to clear the land was the key factor in accumulating resources for subsistence living rather than a reliance on the intergenerational transfer of land through inheritance. Further, as this was the first confirmed measles epidemic in the colony, the entire population was at a great risk, as the Canadian born probably had no acquired immunity to the virus. This epidemic can probably be considered as a 'virgin soil epidemic'- the introduction of a disease for the first time or one that has been absent in a population for many generations. If this were the case, most if not all of the Canadian born population would be susceptible to infection (Haggett and Smallman-Raynor, 2000).

This study utilizes the rich information contained in the Registre de population du Québec ancien (PRDH) to analyze risk factors of measles mortality among children under 5 years of age. A problem with the Quebec data is that parish clergy did not record the cause of death at the time, so there is no direct method to identify who was exposed or died from measles. However, we have a good estimate of the general dynamics of the epidemic and as indicated by the consistent patterns found in the above studies, measles tends to have a predictable outcome. Based on findings from the previous demographic study (Chapter 2), this study imposes several selection criteria to maximize the chance of identifying and selecting individuals who were likely exposed and died from the virus.

In addition, this study assesses the effect of risk factors in the absence of cause of death and exposure records by comparing models applied during the epidemic period with the same models applied to control groups subjected to normal mortality conditions. Using standard logistic regression and GEE binary logistic regression to account for correlated

nature of the data (i.e., sibling data), this study explores the survival outcome of children likely exposed to measles by such risk factors as the approximate age at infection, cross-sex transmission, sibship size, sex and age differences of the children in the household. Other potential risk factors that require further examination and are unique within the context of New France are the immigrant status of the parents and region of residence.

3.2. Data and Methods

The data used in this study originates from the highly reliable and accurate *Registre de la population du Québec ancien*, compiled by the *Programme de recherche en démographie historique* (PRDH) at the Université de Montréal (Légaré 1988; Charbonneau et al. 1993). The database contains the date and place of birth, death and marriage(s), names of parents and spouse(s) and secondary information on places of residence and of origin for individuals that lived in the Saint-Lawrence Valley in the 17th and 18th centuries. The population remained quasi-closed until the 19th century because of particular historical and geographical circumstances, and thus the usual problem of missing observations due to migration is greatly reduced (Charbonneau et al. 1993; Desjardins 1996). As the development of the database is still in progress, the available information varies in time according to the date of the events and the period of birth and marriage of the individuals. Births are matched with individuals and their parents up to 1776, and deaths up to around 1850 (relating to individuals born before 1750). All ancestors of every individual who married before 1800 can be traced back to the founders of the population.

3.2.1. Study Population

A sound method to analyze risk factors during the epidemic when the cause of death is unknown is to maximize the chance of selecting individuals who were exposed to the virus. In order to achieve this, several criteria were applied. Most of the criteria are based on the findings from the previous demographic study (Chapter 2). This study only considered children under the age of 5 because most deaths occurred at these ages during the epidemic. Neonatal deaths were excluded, as those are subject to endogenous causes of death (e.g., congenital anomalies) and were likely unrelated to measles infection. Further, only families with Canadian born children were selected, as many immigrant sibships could not be linked together. Many of these mothers did not have an identification number to allow for the linkage to other family members.

Although the epidemic was of a longer duration, this study only considers children who were likely exposed between late-August and mid-November of 1714. The epidemic peaked during this time and it is more likely that many of the deaths were acute measles fatalities (i.e., a death taking place within 30 to 43 days from the onset of the measles rash). In the previous study, we examined 63 well-established parishes over the course of the epidemic. In this study, the focus was narrowed to fewer parishes or the ones with the highest level of mortality between late-August and mid-November. As the epidemic entered some parishes at different times, not all would have had elevated mortality during the period of interest.

Similar to Chapter 2, parishes with higher than normal mortality were identified by examining risk ratios comparing the observed death rates of each of the parishes to the

expected death rates of their respective regions (i.e., Rural East, Quebec City, GQA, Rural West and Montreal). The expected rates were estimated by fitting splines through the regional time-series data for children under age 5 (see Chapter 2 for a detailed description of the method and Figure 2.3). The expected death rates were estimated for the broader regions to stabilize estimates, as many of the individual parishes had small number of inhabitants. Larger than normal mortality levels probably indicate that a significant proportion of excess deaths may have been from measles (e.g., for Quebec City: *RR* = .254/.020 = 12.7).

All together, 25 parishes with higher than normal mortality between late-August and mid-November were selected for the study[5]. In general, the observed rates ranged from 3.5 to 14.5 times higher than the expected mortality rates between late-August and mid-November with the parish of L'Ancienne Lorette in the Greater Quebec Area (GQA) having the highest ratio. For simplicity, and given that there was no prior exposure to measles among the French Canadian born in the colony, it was assumed that all children were exposed to the virus in the selected parishes. In sum, the study population consists of Canadian born children between the ages of 1 and 60 months who were alive at some point in the established parishes between late-August and mid-November of 1714 (n = 2,651) [6].

[5] The parishes selected for the analysis were: *Notre-Dame-de-Montréal*; *Rural West* (Boucherville, Pointe-aux-Trembles, Laprairie, St.-François de Sales, Varenne and St-François-du-Lac); *Notre-Dame-de-Québec*; *Greater Quebec Area* (Beauport, L'Ancienne Lorette, Charlesbourg and Ste-Foy); *Rural East* (Beaumont, Rivière-Ouelle, L'Islet, St-Thomas, Ste-Anne-deBeaupré, Château-Richer, Cap-Santé, Neuville, Ste-Famille, St-Laurent, St-Pierre, St-François, and St-Jean).

[6] To determine where a child was living during the epidemic is not straightforward because only information on the parish of birth, marriage and death is available. Internal migration was quite common in the colony and if the transient population was not taken into consideration, estimates could be significantly biased. One method to lessen the potential bias introduced by internal migration is to estimate the region of residence for each individual at any given time by

To assess whether the effects of the risk factors were specific to the measles epidemic, the same criteria was used to select individuals subjected to normal mortality conditions as a basis of comparison (i.e. 1708-10 and 1721-23). One control group was selected prior to the epidemic and the other was selected some time after the epidemic to account for the increasing level of infant mortality in Western Quebec. A normal period for that time is defined as the most typical rates children were subjected to in the absence of a periodic disturbance such as, an epidemic (see Chapter 2, Mazan et al., 2009). To identify the normal periods, the same spline method was used to compare ratios of observed and expected rates for each of the broad regions. The particular periods (i.e., 1708-10 and 1721-23) were chosen because the observed mortality rates for children under age 5 were virtually the same as the expected rates based on the fitted splines. The risk ratios of the observed to expected rates ranged between +11% and -9% for each of the periods by the regions. In addition, there were no known epidemics or poor harvests reported during those times.

The exposed group was also tested against other control groups besides the one used in the study (not shown here). In those instances, the effects were the same. Note that the control groups were observed from late-August until mid-November on 6 separate occasions (i.e. 1708-10, n = 2,870 and 1721-23, n = 3,402) rather than on a single occasion, as with the exposed group. More observation periods were necessary to provide

---

using information about other family members. I used the following criteria: 1) If all family members were born and died in the same parish, this was used as the place of residence for each member; 2) When the parish of birth and death were different for some members and there was a birth or death in the family during the year of interest, the recorded parish of the event was designated as the place of residence for the entire family and; 3) Otherwise, the parish with the most recent birth or death prior to the year of interest was designated as the current residence of that particular family.

a reliable comparison, as fewer unexposed children died between late-August and mid-November on any single normal period. In addition, selecting deaths during the same months controls for seasonal variations in mortality.

The control groups were created using a staggered approach, so that each family was counted in only one of the observation periods. If a family had no deaths or a death in more than one of these periods (a rare occurrence), they were counted at the last period (e.g. 1710 or 1723). Those with a death in any one of the periods were counted at the time of the child's death. This method was preferred over selecting and combining a single period before and after the epidemic. In that situation, there would be fewer deaths and estimates would be less reliable given the number of parameters to be estimated in the models. As the focus of this study was to identify risk factors during the epidemic, it was more important not to lose information by having to collapse categories or to reduce the number of parameters estimated.

3.2.2. Risk Factors

This study incorporates a model with two main components. The first component consists of demographic risk factors. As mentioned above, the risk of death from measles is strongly influenced by the age at infection. Before estimating the age at infection, an estimate of the date of infection had to be obtained. Since the date of infection is not directly known, a timeline was derived from an average scenario based on the natural course of measles. In general, the measles incubation period lasts from 8 to 12 days and the measles rash appears 12 to 14 days after exposure. Complications typically occur within the first week of the onset of signs and symptoms. If there are no complications,

recovery begins soon after the appearance of the rash (Halsey and Perry, 2004). The date of infection starts at the appearance of the measles rash, as it is usually the starting point to measure the time until death (Aaby, 1995). There is limited literature on the time from infection until death, but one study found that most acute deaths occurred within 1 to 2 weeks from the onset of the measles rash (Joshi et al., 2009).

The date of infection was estimated using the date of death distribution among children who died during the acute phase between late-August and mid-November. The measles timeline was then used to adjust the date of death into the date of infection. For children who died during the acute phase, a two-week lag period was applied when estimating the time from infection until death. For example, individuals who died in the 38th week of 1714 were assumed to have developed the rash during the 36th week of 1714. Neonatal deaths were excluded from this process. For surviving family members, it was assumed that the date of infection occurred around the same time and thus, they were also assigned the same date of infection as the dead child. An average date of infection was estimated for the remainder of the families with no deaths. These dates were estimated based on the date of death distributions for each of the regions, as the epidemic entered the regions at slightly different times (see Chapter 2). Infection dates among these children were assumed to follow the regional distribution where they resided.

In turn, the approximate age at infection was obtained by subtracting the date of infection from the date of birth of each child. The age of the child at the estimated time of infection was divided into 4 groups to reflect the age pattern of measles deaths: <6 months, 6 to 11 months, 12 to 23 months and 24+ months. Individuals who were 24

months and older served as the reference category. Note that this study is cross-sectional and the following risk factors were measured at the estimated date of infection.

The region of residence at the time of the epidemic was included to capture the regional (urban/rural) differences in mortality. During the epidemic period, this measure also serves as a proxy for malnutrition, as Eastern Quebec was believed to be disadvantaged in terms of this attribute and suffered a greater number of losses than the West (Chapter 2, Mazan et al., 2009). Quebec City and Montreal are presented as their own separate regions or as the major urban towns. Otherwise, the remaining 23 rural parishes were divided into 3 broad regions - Rural West, Greater Quebec Area (GQA) and Rural East. The Rural West serves as the reference category. The sex of the child was also included as a risk factor of childhood mortality. Generally, it was estimated that female children were slightly more likely to have died from measles in the demographic study (see Chapter 2; Mazan et al, 2009). In addition, females have been found to have a lower probability of survival during measles epidemics in some modern populations (Garenne, 1994). Females serve as the reference category.

The immigrant status of the parents has not been included as a risk factor in any of the above studies. Immigration may not be an important issue in those countries where the modern studies took place. However, in New France there were a considerable number of immigrants in the colony. Immigrant status of the parents was included because it is possible that children with immigrant parents may have lacked support from extended kinship during crises such as, 'poor harvests' or the patterns could reflect differences in social status. Large well established Canadian families may have acted as a buffer against

food shortages by helping one another, while immigrant parents may have had little aid in a time of crisis. Immigrant status of parents was categorized into 4 groups to explore this assumption: Canadian born parents, immigrant mother, immigrant father and both immigrant parents. Canadian born parents serve as the reference category.

The second component of the model consists of characteristics of the children and their siblings. The number of children in the household is considered to be an important risk factor of measles death. This factor usually serves as a proxy for overcrowding and the intensity of exposure to the virus. Generally, one would expect that individuals from families with numerous younger children would be at higher probability of death. A larger number of siblings can increase the transmission rate and intensity or it could increase material deprivation in contemporary populations (Burstrom et al., 1999). The number of siblings in the household includes all unmarried siblings at the estimated date of infection in a given period, with the exception of neonates[7]. For the models examining sibship composition, the number of siblings was coded as: 1 or 2 siblings and 3 or more siblings, with 3 or more siblings serving as the reference group. In models that compare for the effects of singletons to children with siblings, it is coded as: No siblings, 1 or 2 siblings and 3 or more siblings.

Another factor not taken into consideration in modern community studies is the death of a sibling during an epidemic. This may be due to the lack of data and/or the small number of deaths on which most of those studies are based. This measure may serve as a proxy

[7]In this study, the term household means that children are expected to live in the same house based on maternal ties, until marriage. It is not the actual number of children in the household, as in census data.

for the incidence of multiple secondary cases and severity of infection in a given family and may be a good alternative measure when more direct information on secondary cases is lacking. In this study, it would be assumed that if measles entered the household, all members would be infected, as there was no prior exposure in the colony. As such, the death of a child may reflect a higher severity of infection through intensive exposure to the virus and in turn, increased the risk of death for the other siblings (i.e., the dose response effect). It could also reflect unobserved heterogeneity (e.g., some families were more robust, better established or varied in the degree of malnutrition). Children without a dead sibling during the acute phase served as the reference group.

The age difference between siblings in the household is also included in the analysis. As mentioned above, it has been found that older siblings (index cases) may increase the risk of measles death among their younger siblings (secondary cases) by introducing the virus into the household. This factor was estimated by subtracting each child's age at time *x* from the average age of the sibship at time *x*. The average age difference was then coded as < 2 years, 2 to 5 years and 6+ years; with < 2 years serving as the reference group. Modern studies found that children infected by a sibling of the opposite sex were at a higher risk of dying (Pison et al., 1992; Aaby, 1992). As such, this study also compares mortality differences of same and opposite sex sibling pairs to assess whether cross-sex transmission may have increased the risk of death during the epidemic. In those models, same sex sibling pairs serve as the reference group.

Table 3.1. Description of the study population and risk factors included in the GEE logistic regression models

Demographics	Model A Normal 1708-10	Model B Epidemic 1714	Model C Normal 1721-23
Children under 5 years of Age	2,870	2,651	3,402
Families by Mother	1,387	1,414	1,645
Deaths	267	292	332
Region			
Rural East	768	772	774
Quebec City	368	300	489
GQA	722	632	772
Montreal	482	423	562
Rural West†	530	524	805
Age at Infection			
1 to 5 months	599	398	709
6 to 11 months	248	221	344
12 to 23 months	557	511	605
24+ months†	1,466	1,521	1,744
Immigrant Status			
Both Parents	195	123	115
Mother	202	205	271
Father	879	731	770
French Canadian†	1,594	1,592	2,246
Sex			
Male	1,361	1,323	1,607
Female†	1,509	1,328	1,795
No. of Siblings			
1 or 2 Sibs	1,001	929	1,328
3+ Sibs†	1,869	1,722	2,074
Sibling Survival			
Sibling died	472	396	527
No Death†	2,398	2,255	2,875
Age Difference			
6+ years	881	887	962
2 to 5 years	1,213	1,130	1,462
< 2 years†	776	634	978

†Reference category - basis of comparison for the other categories.

Table 3.1 summarizes the coding of the covariates and gives the number of families in each category for the logistic regression models. Generally, each of the risk factors follow the same distributional patterns for the exposed and control groups. Note that the number of deaths are not directly comparable between the controls and exposed children. The deaths for the control groups are the total number of deaths over three consecutive years (1708-10 and 1721-23) from late-August to mid-November. To make the death rates of the control groups comparable to the exposed group, the rates should be averaged over three years (i.e., 1/3[267/2,870]; 1/3[332/3,402] vs. [292/2,651]) (see also Table 3.2). Note that there were many more immigrant fathers than mothers in the population at the time. The reason is that very few females migrated into the colony after 1680.

3.2.3. Binary logistic regression models for correlated responses (GEE)

As there can be more than one family member in the study group, the responses can be highly correlated. If the correlated responses are not taken into consideration, then incorrect inferences may result. To account for correlated responses, GEE binary logistic regression was used to assess the effects of the regional and sibling risk factors on the odds of a child dying during the measles epidemic and the normal periods.

Generally, the interpretation of GEE coefficients and significant tests are the same as the standard logistic regression. However, the underlying assumptions and the method of estimating the coefficients are different (Kleinbaum and Klein, 2002). The GEE model uses a quasi-likelihood method to estimate the regression coefficients and robust variance estimation to estimate standard errors, which account for the correlated responses. The

GEE binary logistic regression takes on the same form as standard logistic regression when given as the logit transformation:

$$\text{logit}(\pi) = \beta_0 + \beta_i X_i + \ldots + \beta_j X_j ; \qquad \textbf{[1]}$$

where β_0 is the intercept of the model, β_i is the slope of risk factor i and X_i is any given value of factor i. As π increases from 0 to 1, the odds increase from 0 to ∞ and the logit increases from $-\infty$ to ∞. For $\beta > 0$, π increases as X increases, while for $\beta < 0$, π decreases as X increases. The main assumption of the model is that family members may be correlated within clusters, but are independent between clusters. In this analysis, the mother is used to identify clusters (i.e., siblings). The GEE model requires that a correlation structure be specified for the estimation of the correlation parameters, coefficients and standard errors. For simplicity, it was assumed that the correlation structure was independent (i.e. responses were uncorrelated within clusters). This assumption makes the model similar to standard logistic regression, but includes robust standard errors to account for correlated observations. For regression diagnostics, cross tabulations were examined for zero cell counts and complete separation (i.e., when a logistic model perfectly or nearly perfectly predicts the response). In addition, deviance and studentized residuals were examined for outlying cases and Cook's distance was used to check for influential cases. No serious problems were found with the data.

3.3. Results

Table 3.2 gives the descriptive statistics and mortality rates of the exposed and unexposed children under 5 years of age (1708-10 and 1721-23). Generally, the means and standard deviations of the study periods are similar to one another. During the epidemic period, there was an average of 4.7 unmarried children (SD = 2.1) presumably living in the

household (2.4 girls and 2.3 boys). The average age of the siblings was 6.7 years (SD = 3.7) and the average age difference between siblings in the household was 4.8 years (SD = 3.2). Before turning the focus to the analysis of the risk factors, it is a good idea to get a general idea about the impact of the epidemic during the acute episode.

Table 3.2. Descriptive statistics and death rates[*] during the measles epidemic of 1714 and the comparison groups of 1708-10 and 1721-23, New France

Descriptives	Normal[*] 1708-10	Epidemic 1714	Normal[*] 1721-23
	MEAN ± SD	**MEAN ± SD**	**MEAN ± SD**
No. of children in the household	4.7 ± 2.2	4.7 ± 2.1	4.6 ± 2.3
No. of boys in the household	2.3 ± 1.5	2.3 ± 1.5	2.2 ± 1.5
No. of girls in the household	2.5 ± 1.6	2.4 ± 1.5	2.4 ± 1.5
Age of children in the household	6.1 ± 3.7	6.7 ± 3.7	5.9 ± 3.9
Age difference between children in the household	4.5 ± 3.3	4.8 ± 3.2	4.4 ± 3.3
Age at Infection (months)	Deaths per 1,000 late-August until mid-November in year *i*		
1 to 11 months	53.5	176.1	68.0
12 to 59 months	21.6	90.1	16.8
1 to 59 months	31.0	110.1	32.6

[*]To make the control groups comparable to the epidemic period, the death rates are based on the average number of deaths from late-August until mid-November over the 3 observation periods.

Overall, the epidemic was quite severe during the acute phase from late-August to mid-November (see Chapter 2, Mazan et al., 2009 for a detailed analysis on the severity of the epidemic). Note that the rates for the two control groups were averaged over the three observation periods to make them comparable to the acute episode of the epidemic. On average, children exposed between 1 and 59 months of age were 3.5 times more likely to

have died between late-August and mid-November than the control groups (110.1 per 1000 vs., 31.0 and 32.6 per 1000). Exposed infants were 2.9 times more likely (176.1 per 1000 vs. 53.5 and 68.0 per 1000), while children exposed between 12 and 59 months of age were 4.8 times more likely to die than the control groups subjected to normal mortality conditions (90.1 per 1000 vs. 21.6 and 16.8 per 1000).

Table 3.3 gives the odd ratios (OR) and the robust standard errors (RSE) of the GEE logistic regression models (A through C) fit to the data from late-August to mid-November of 1714 and the comparison models representing normal mortality conditions (1708-10 and 1721-23). In addition, the bootstrap odds ratios (OR_{BS}) are also provided to demonstrate the stability of the parameter estimates and as a check for bias in the models. To obtain the bootstrap coefficients, one child from each family was randomly selected 100 times with replacement. Models A through C show the full models with the risk factors entered simultaneously. For clarity, bivariate and nested models are not shown here. The risk factors remain stable under all those circumstances meaning that they are largely orthogonal. All models and especially the epidemic model appear to fit the data reasonably well and the bootstrap odds ratios were in general agreement with the GEE estimated ratios.

The region of residence was an important childhood risk factor, especially in Models B and C. However, the likelihood of death varied by the time period under consideration. During the epidemic, children residing in the Eastern regions, particularly in Quebec City and the Greater Quebec Area were more likely to die than ones residing in the Rural West. Young children in Quebec City had the highest odds of dying compared to children

in the Rural West (OR = 2.66, $p < .001$), followed by the GQA (OR = 1.91, $p < .001$) and then the Rural East (OR = 1.50, $p < .05$). The difference between children in Montreal and the Rural West was not significant.

The risk of death during the normal periods was quite different from the risk during the epidemic period. These patterns probably also reflect changing mortality conditions over time. In model A, the region of residence was not much of a factor in the risk of death of a child. These patterns are expected because prior to the epidemic mortality conditions did not vary greatly from one region to another. Only Quebec City had a significant odds of losing a child than the Rural West (OR = 1.79, $p < .01$). After the epidemic, conditions probably worsened in the Western parishes (mostly in Montreal), as childhood mortality rates in the West exceeded those in the East, especially in regards to infant mortality (see Chapter 2).

In addition, the urban/rural mortality differential was now much more apparent throughout the colony. The high level of urban mortality is reflected in Model C, where children in both of the urban towns (Montreal and Quebec City) had a higher odds of dying than ones in the Rural West (OR = 1.61, $p < .01$, OR = 2.12, $p < .001$, respectively). In contrast to the epidemic model, children in the Rural East had a significantly lower odds of dying (OR = 0.50, $p < .01$), while mortality among children in the GQA did not differ significantly from the Rural West.

Table 3.3. GEE and bootstrap logistic regression models of childhood risk factors applied to the exposed group of 1714 and the unexposed comparison groups of 1708-10 and 1721-23

Risk Factor	Model A Normal (1708-10) n_{GEE} = 2,870 n_{BS} = 1,387			Model B Epidemic (1714) n_{GEE} = 2,651 n_{BS} = 1,414			Model C Normal (1721-23) n_{GEE} = 3,402 n_{BS} = 1,645		
	OR	RSE	OR_{BS}	OR	RSE	OR_{BS}	OR	RSE	OR_{BS}
Region									
Rural East	0.71	0.225	0.76	1.50*	0.203	1.79	0.50**	0.241	0.49
Quebec City	1.79*	0.231	1.93	2.66***	0.224	2.62	1.61*	0.190	1.72
GQA	1.01	0.215	1.03	1.91***	0.199	1.97	0.95	0.180	0.87
Montreal	1.40	0.223	1.50	1.10	0.233	1.20	2.12***	0.168	2.26
Rural West†									
Age									
<6 months	5.66***	0.190	6.49	4.21***	0.192	3.91	10.17***	0.175	8.78
6 to 11 months	4.71***	0.238	5.29	3.63***	0.226	3.48	5.25***	0.219	4.61
12 to 23 months	4.01***	0.188	4.74	4.87***	0.167	5.26	3.93***	0.190	3.88
24+ months†									
Immigrant Status									
Both Parents	1.04	0.260	1.16	2.26***	0.254	2.70	0.92	0.320	0.74
Mother	1.36	0.232	1.64	0.75	0.268	0.83	0.99	0.239	0.98
Father	1.07	0.157	1.16	1.36*	0.146	1.38	1.17	0.129	1.14
French Canadian†									
Sex									
Male	1.43**	0.131	1.33	1.32*	0.127	1.27	1.46**	0.121	1.46
Female†									
No. of Siblings									
1 or 2 Sibs	0.75	0.158	0.76	1.80***	0.149	1.79	1.01	0.149	1.24
3+ Sibs†									
Sibling Survival									
Sibling died	1.26	0.232	1.34	4.00***	0.211	4.07	1.53*	0.217	1.65
No Death†									
Age Difference									
6+ years	0.63*	0.216	0.60	1.92**	0.222	1.83	0.70	0.211	0.81
2 to 5 years	0.74	0.169	0.72	1.48*	0.185	1.53	0.75	0.153	0.81
< 2 years†									

†Reference category - basis of comparison for the other categories.
p <.001***, p <.01**, p <.05*

The age of a child during the epidemic and normal periods was the strongest predictor of death in all of the models. In most populations, we would expect to find a rapid decline in the age pattern of mortality between infancy and childhood (i.e., exponential decline). This seems to be the case in the normal models, as they follow the typical mortality curve, where the odds of dying declined rapidly from infancy onward (OR = 5.66, 4.71, 4.01 $p < .001$ and OR = 10.17, 5.25, 3.93 $p < .001$ for Models A and C, respectively).

In contrast, the age pattern in the epidemic model was altered to some degree, where the likelihood of dying was highest among toddlers aged 12 to 23 months. Infants aged 1 to 6 months had a 4.21 higher odds ($p < .001$), those aged 6 to 11 months had a 3.63 odds ($p < .001$), while toddlers had a 4.87 higher the odds of dying than children aged 24+ months ($p < .001$). The intensification of the odds ratio at ages 12 to 23 months reflects the increased mortality as a result of the measles epidemic. As mentioned above, measles mortality tends to peak between the ages of 6 and 24 months and declines thereafter (Burstrom et al., 1999). This pattern is clearly evident in Model B.

Immigrant status of the parents also shows large differences between the epidemic and normal periods. During the epidemic, children with fathers and both parents who were immigrants had a higher odds of dying (OR = 1.36, $p < .05$, OR = 2.26, $p < .001$, respectively). Children with immigrant mothers did not a have significantly different mortality than children of Canadian born parents. This could be due to the small number of cases, as very few mothers migrated to New France after 1680. In contrast, the immigrant status of parents does not significantly differ from one group to the next during the normal periods. These patterns are consistent in both Models A and C.

The sex differential in mortality follows the same pattern for the full models fit to the epidemic data and those fit to the normal data. In all models, male children had a higher odds of dying than female children (OR = 1.32, $p < .05$ vs. OR = 1.43, $p < .01$ and OR = 1.46, $p < .01$ for models A, B and C, respectively). Note that models run separately for each sex are not shown here. Generally, the risk factors behaved similarly for males and female children during the epidemic and normal periods. In addition, parameter estimates become less reliable when analyzing risk factors by sex, as the parameters were based on a smaller number of events.

Table 3.4. Logistic regression models comparing mortality of male and female infants (1 to 11 months) during the measles epidemic of 1714 and the comparison groups of 1708-10 and 1721-23

Risk Factor[a]	Model D Normal (1708-10) N = 847		Model E Epidemic (1714) N = 619		Model F Normal (1721-23) N = 1,053	
	OR	SE	OR	SE	OR	SE
Sex						
Male	1.49*	0.195	1.11	0.226	1.51**	0.158
Female†						

†Reference category - basis of comparison for the other categories.
p <.001***, p <.01**, p <.05*
[a]Controls include: sibship size, dead sibling, age difference and immigrant status of parents.

There is an interesting trend when comparing the sex differences in mortality within each of the exposed and unexposed groups (see Table 3.4). For the normal models D and F, male infants had a significantly higher odds of dying (OR = 1.49, $p < .05$ and OR = 1.51, $p < .01$), while there was no significant difference between males and female infants during the epidemic period (OR = 1.11, $p > .05$). This pattern probably reflects the results from the previous study, where it was found that female infants were slightly more likely to have died from measles (see Chapter 2; Mazan et al., 2009). However, the odds ratio

does not directly show that measles mortality was higher among females because there are other causes of death in operation that could not separated from measles deaths.

The number of siblings in the household did not follow the pattern that one would expect, based on other studies. Instead, smaller families or children with 1 or 2 siblings had a higher odds of dying than children with 3 or more siblings (OR = 1.80, $p < .001$). Interestingly, this effect was not present in the normal models. In addition, Model E in Table 3.5 shows that children with no siblings also had higher odds of dying than children with 3 or more siblings. The effect for singletons was even stronger than among children with 1 or 2 siblings (OR = 1.91, $p < .001$ and OR = 1.37, $p < .05$). Possibly, it was the age of the children in the household that was the more important risk factor than the size of the sibship.

Table 3.5. GEE and bootstrap logistic regression models comparing mortality of children with and without siblings during the measles epidemic of 1714 and the comparison groups of 1708-10 and 1721-23

	Model A			Model B			Model C		
	Normal (1708-10)			Epidemic (1714)			Normal (1721-23)		
Risk Factor[a]	n_{GEE} = 3,083			n_{GEE} = 2,954			n_{GEE} = 3,726		
	n_{BS} = 1,600			n_{BS} = 1,717			n_{BS} = 1,969		
	OR	RSE	OR_{BS}	OR	RSE	OR_{BS}	OR	RSE	OR_{BS}
<u>No. of Siblings</u>									
No Sibs	0.66	0.253	0.58	1.91***	0.175	1.97	0.90	0.193	0.89
1 or 2 Sibs	0.89	0.139	0.93	1.37*	0.142	1.36	1.13	0.124	1.29
3+ Sibs[†]									

[†]Reference category - basis of comparison for the other categories.
p <.001***, p <.01**, p <.05*
[a]Controls include: region of residence, age at infection, sex and immigrant status of parents.

The average age difference between siblings in the household indeed shows an interesting pattern between the normal and epidemic periods (Tables 3.3 and 3.6). In the normal models, siblings who were 2 to 5 and 6 or more years apart appear to have had a lower odds of dying, although the difference only reached significance in model A for siblings 6+ years apart (OR = 0.63, $p < .05$). During the epidemic, the effect was reversed, where children who were on average 2 to 5 and 6 or more years apart had a higher odds of death than children with siblings closer in age (OR = 1.92, $p < .01$ and OR = 1.48, $p < .05$).

Generally, a child's likelihood of dying increased when one of their siblings died, as compared to children who did not have a sibling that died. Although the death of a sibling increases the odds of death in the control groups, this effect only reached significance in model C (OR = 1.53, $p < .05$). In the epidemic model, however, the death of a sibling was highly significant, where the odds of death for a child with a sibling who died was 4 times higher than a child without a sibling who died ($p < .001$). Despite the similar patterns between Models A and C, the highly intensified effect in Model B may be largely a consequence of the measles epidemic.

With the historical data, the Pison et al. (1992) study on cross-sex transmission could be replicated to some extent. To examine whether cross-sex transmission was a significant risk factor during the measles epidemic, two children less than 10 years of age were randomly selected from each family and then one of the those pairs was randomly selected for the analysis. This random selection procedure was repeated 100 times with replacement. The models were run with the same controls used in the previous models to

test for the effects of cross-sex transmission during the epidemic and normal periods (see Table 3.6).

Models D through F show the bootstrapped odds ratios and standard errors of the coefficients for the sib-pair analysis. There appears to be no evidence of cross-sex transmission during the epidemic. The odd ratios show that the risk of death was similar for opposite and same sex siblings. In addition, the models were also run using households with two children at the time of the epidemic and normal periods (similar to what was done in Pison et al., 1992) (not shown here). No significant differences were found in those models, as well. However, consistent with Model B, the age difference between the sibling-pairs was significant. In this model, however, only cases in which children were 6 or more years apart from their designated sibling-pair reached statistical significance (OR = 1.90, $p < .05$).

Table 3.6. Bootstrap logistic regression models comparing mortality of opposite and same sex sib-pairs during the measles epidemic of 1714 and the comparison groups of 1708-10 and 1721-23

Risk Factor[a]	Model D Normal (1708-10) n_{BS} = 1,423		Model E Epidemic (1714) n_{BS} = 1,497		Model F Normal (1721-23) n_{BS} = 1,708	
	OR_{BS}	SE_{BS}	OR_{BS}	SE_{BS}	OR_{BS}	SE_{BS}
Sib-pair						
Opposite Sex	1.02	0.220	0.90	0.216	0.93	0.205
Same Sex[†]						
Age Difference						
6+ years	0.85	0.266	1.90[*]	0.276	0.82	0.243
2 to 5 years	0.89	0.345	1.36	0.342	0.85	0.336
< 2 years[†]						

[†]Reference category - basis of comparison for the other categories.
p <.001***, p <.01**, p <.05*
[a]Controls include: region of residence, age at infection, sibling died and immigrant status of parents.

3.4. Discussion and Conclusions

This study was the first step in exploring whether one can identify risk factors of measles mortality in historical data and in turn, find similar patterns of disease processes between historical and modern populations. The use of this historical data has one distinct advantage over modern studies on measles epidemics. In historical Quebec, there was no potential confounding influence from the effects of modern medicine, public health knowledge and other technological improvements that are difficult to control and may distort findings. For instance, vaccination, effective treatments and the diffusion of modern health knowledge (i.e., proper care techniques for mothers) into the general population can influence the survival outcome of infected children. In essence, the situation in Québec can be thought of as a natural setting for the study of epidemics unhindered by these modern advancements in medicine and knowledge.

The main limitation of this study was that parish clergy did not record the cause of death at the time. To alleviate the problem, stringent selection criteria were applied to select the parishes most likely to be exposed to measles on the one hand and by conducting an analysis that consisted of comparing risk factors applied to the epidemic data with the same model applied to control groups subjected to normal mortality conditions on the other. In addition, it is also difficult to distinguish between acute and delayed measles deaths, as the models were based on an approximation of the date of infection. An attempt to control for this aspect was done by only selecting deaths that occurred in parishes when mortality rates were reaching their peak levels between late-August and mid-November of 1714. It was assumed that these deaths were more likely to be acute, as they occurred

within such a short time from one another (i.e., less than 43 days from the estimated date of infection).

Another limitation of the study was the assumption that all children in the selected parishes were exposed to measles. There is no direct method to check whether every child had an equal probability of infection. However, since there was no prior exposure to measles, it can be assumed that if a given parish was exposed to measles, most if not all of the population would have been susceptible to infection. As a result of the above limitations, the reader is advised that the findings should be viewed with some caution until the findings of this study can be replicated with other studies on subsequent measles epidemics in New France. Although there are several limitations with the study, these methods helped to identify the possible role that demographic and familial risk factors played during the measles epidemic.

Regional differences in mortality were similar to the results obtained from the previous study on the general dynamics of the epidemic (Chapter 2; Mazan et al., 2009). Children in the Eastern parishes had higher odds of dying than children in Western Quebec. This was particularly true in Quebec City and the rural parishes surrounding the urban town (GQA). We suspected that poor harvests reported between 1714 and 1717 may have played a role in the regional variation (Crowley, 1991). Although there was no indication of the exact regions affected by the poor harvests, we suspected that the inadequate harvests were more likely to have occurred in the East and may have contributed to an increased the risk of death among exposed children.

As with many other studies, the odds of dying from measles appeared to vary by the estimated age at infection (Hull, 1988; Reves, 1985; Burstrom et al., 1999). As mentioned above, the risk of death from measles usually peaks between 6 and 24 months and declines thereafter. In this epidemic, the odds of dying followed the same pattern, where toddlers (12 to 23 months) had the highest odds of dying. In contrast, mortality showed a typical pattern during the normal periods, where the likelihood of dying rapidly declined from infancy onward.

Although not directly apparent in the findings from this study, there may be a link between the age pattern of mortality and poor harvests. Palloni (1990) indicates that children over 1 year of age tend to be more sensitive to food shortages because they depend more on solid foods and their immune systems are not fully developed. In the previous demographic study, it was found that older children living in the East were at a higher risk of dying than children in the West. Perhaps, the higher likelihood of death among toddlers in the East reflected some degree of malnutrition, as Eastern Quebec was thought to be more likely to have experienced poor harvests during that time.

Infants, on the other hand, may incur some protection during a crisis because they tend to be nourished with breast milk (Palloni, 1990). Breast milk plays an important role in protecting infants from general infections. Protective antibodies such as Immunoglobulin A (IgA) are secreted through breast milk, which provide some general benefits to the nursing infant (Mandomando et al., 2008). In populations where measles epidemics are relatively frequent, infants less than 9 months of age are usually protected by measles-specific antibodies transferred through the placenta by mothers who were either exposed

to natural measles or immunized against measles (Caceres et al., 2000). Placental transferred antibodies usually provide protection for infants in the early months of life, as these antibodies tend to diminish below protective levels between 4 and 8 months after birth. Breast milk may also contain measles-specific antibodies, which may provide additional protection for the infant against early exposure when placental transferred antibodies have diminished below protective levels (Mandomando et al., 2008).

In Québec, however, this is the first confirmed measles epidemic in the colony. As such, most if not all of the population would have had no prior exposure to measles and thus most of the population would be susceptible to infection. Further, studies on measles epidemics in the Canadian Arctic and Greenland found that maternal antibodies were lacking in infants when measles entered the colony for the first time, as none of the adults had been previously exposed (Black, 1982). In those epidemics, all ages were affected with infants and seniors typically experiencing the highest death rates (Haggett and Smallman-Raynor, 2000). In this epidemic, infants appeared to have incurred little to no protection from the virus, as mortality was very high across the colony (Mazan et al., 2009). For instance, it was estimated that infants in Montreal and Quebec City had close to the same probability of dying from measles during the epidemic (197.9 vs. 194.3 per thousand, respectively).

As mentioned previously, the risk factors behaved in a similar pattern for both male and female children during the epidemic and normal periods (models not shown here). Parameter estimates became less reliable when analyzing the risk factors separately for each sex, as the measures were based on a smaller number of events. Overall, there were

no discernable sex differences between the epidemic and normal periods for children under 5 years of age. In all of the models, males had higher odds of death than females. This pattern resembles the findings from the demographic study, as measles death rates were estimated to be similar among male and female children between 1 and 4 years of age.

Sex differences may yet come into effect, but this depends on the age at infection. When models were estimated for infants, there was no significant sex difference during the epidemic period, while male infants had a higher odds of dying during the normal periods (see Table 3.5). This may be an indication that measles was more severe among female infants during the acute episode (see also Chapter 2). Garenne (1994) also found that female children had higher measles mortality in a comparative study on measles in American and European populations. However, the sex difference may not be apparent at the individual level because measles deaths could not be separated from other causes of death. I suspect that if measles deaths could be partitioned from other causes, then it would show that female infants had a higher odds of dying. Note that sex-differentials appear to be more important during the post-measles episode and are dealt with extensively in the next chapter.

There was no evidence that overcrowding or larger sibships led to an increased risk of death. To the contrary, it was found that children with few or no siblings had higher odds of dying. Perhaps, in a population with no prior exposure, the size of the family or the crowding effect does not matter as much as the age of the children in a given family. Further, if the parents had no prior exposure to measles, they could have introduced

measles into the household and transmitted the virus to their small children making them more likely to become secondary cases. A typical completed family in historical Québec was large with an average of 9.2 children per mother. In the Quebec context, a small family size probably meant that younger married couples were just starting to have children. Therefore, a small family would be an indication that the children were young or at an age, where they were at a high risk of dying from measles.

In modern populations, large families tend to be poorer and less educated than smaller ones. Lower socioeconomic status has been found to be associated with an increased risk of measles death (Burstrom et al., 1999; Perry and Halsey, 2004). In historical Quebec, however, a large family may have indicated greater wealth than smaller young families just starting their reproductive lives. Larger families could imply that there was greater access to resources and probably occupied the more fertile lands, since many had been established for at least two or three generations (Mazan and Gagnon, 2007). If there were poor harvests, these larger families may have been better off because of mutual support from an extended kinship. The Quebec family was considered a 'collective and egalitarian unit' and its members tended to migrate together and establish farms within a close proximity (Bouchard, 1992; 1994). As *pionniers accapareurs* ("monopolizing pioneers"), siblings would cooperate to take over large stretches of land to establish themselves and their descendants (Mathieu et al., 1992; Gagnon, 2001). This characteristic allowed family members to remain close to one another and probably provide support during times of need.

The above assumptions may help explain why children with immigrant fathers and both immigrant parents were at a higher risk of death, while ones with immigrant mothers had no different mortality from children of Canadian born parents. Perhaps, the increased odds of death among these children reflect differences in social class between children with immigrant and non-immigrant parents. It is possible that children with fathers and both parents who were immigrants may have lacked support from an extended kinship during crises such as poor harvests and an impending epidemic. Large well-established Canadian families may have acted as a buffer against crises such as food shortages by helping one another (i.e. access to abundant resources), while immigrant parents may have had little help during a crisis situation. However, it would not matter so much if the mother was an immigrant because their Canadian born husband may have been more likely to belong to a well-established family. These attributes may have helped children remain adequately nourished and in turn, have a better chance of fighting off the infection[8].

There was no evidence that cross-sex transmission of sib-pairs played a role in increasing the likelihood of death during the epidemic. However, the acute death of a sibling was found to significantly increase a child's odds of dying. When a sibling died during the epidemic, the odds of another child dying in the family was greatly intensified. Although there is no direct way to distinguish between index and secondary cases, the death of a sibling may reflect the incidence of multiple secondary cases and intensive exposure in the household. When there are multiple secondary measles cases in a family, the risk of

[8] Note, however, that the non-significant effect could have been due to the small number of immigrant mothers in the sample.

death tends to be greatly increased for those particular cases (Aaby et al., 1984; 1988; Hull, 1988; Koster, 1988; Garenne and Aaby, 1990).

Generally, it is hypothesized that close contact with other family members increases the generational intensity of the virus, where a higher dose of the virus is transmitted to other family members (i.e., dose response effect) (Garenne and Aaby, 1990). The effect of parental deaths on the survival outcome their children were also examined (not shown here). However, there were too few parental deaths to generate any reliable estimates. The small number of parental deaths during the epidemic could be an indication that parents were more likely to be the index cases in the household and/or they had a better chance of recovery or they may have been previously exposed to measles. The latter could especially be true for immigrant parents.

Similar to the findings from the Pison et al. study, children with a larger age difference from their siblings had higher odds of death in both the full and sib-pair models. In the case of Quebec, older children may have been more likely to be infected outside of the home and then infect the younger children in the household (secondary cases). Older children would have a better chance of fighting off the infection because of a weaker or more casual dose contracted outside of the home and a more mature immune response. Younger children, on the other hand, would be at a dual disadvantage because of an underdeveloped immune system and further suppression due to possible malnutrition. In turn, younger children who contracted the virus, given the age-associated differences in risk and the intensity hypothesis, would have a greater likelihood of dying. In a population with no prior measles exposure, it is quite possible that either of the parents

could have been the index case in the household, especially for the smaller and younger families. This same disease process could apply in those situations, as well.

3.5. References

Aaby P. 1995. "Assumptions and contradictions in measles and measles immunization research: Is measles good for something?". *Social Science and Medicine* 5: 673-686.

Aaby P. 1992. "Influence of cross-sex transmission on measles mortality in rural Senegal". *The Lancet* 340: 388-391.

Aaby P. 1988. "Malnutrition and overcrowding/intensive exposure in severe measles infection: Review of community studies". *Review of Infectious Diseases* 10: 478-491.

Aaby P., Bukh J., Lisse I. M., Smits A. J. 1984. "Overcrowding and intensive exposure as determinants of measles mortality". *American Journal of Epidemiology* 120: 49-63.

Barclay A. J. G., Foster A., Sommer A. 1987. "Vitamin A supplements and mortality related to measles". *British Medical Journal* 294: 294-296.

Berman S. 1991. "Epidemiology of acute respiratory infections of children in developing countries". *Review of Infectious Diseases* 13: S454-S462.

Black F. L. 1982. "The role of herd immunity in control of measles". *The Yale Journal of Biology and Medicine* 55: 351-360.

Bouchard G., 1992, "Transmission of family property and the cycle of Quebec rural society from the seventeenth to the twentieth century", in *Canadian Family History: Selected Readings,* Bradley B. (ed.). Toronto, Copp Clark Pitman, pp. 112-134.

Bouchard G., 1994, "Family reproduction in new rural areas: Outline of a North American model", *The Canadian Historical Review*, 75, pp. 475-494.

Burstrom B., Diederichsen F., Smedman L. 1999. "Child mortality in Stockholm during 1885- 1910: The impact of household size and number of children in the family on the risk of death from measles". *American Journal of Epidemiology* 149: 1134-1141.

Caceres V. M., Strebel P. M., Sutter R. W. 2000. "Factors determining

prevalence of maternal antibody to measles virus throughout infancy". *Clinical Infectious Diseases* 31: 110-119.

Charbonneau H., Desjardins B., Guillemette A., Lardry Y., Légaré J., Nault F. 1993. *The First French Canadians: Pioneers in the St. Lawrence Valley*. Newark: University of Delaware Press.

Clements C. J., Hussey G. D. 2004. "Measles" in *The Global Epidemiology of Infectious Diseases*. Murray C. J. L., Lopez A. D., Mathers C.D. (ed.). Geneva: WHO.

Desjardins B. 1996. "Demographic aspects of the 1702-1703 smallpox epidemic in the St-Lawrence valley". *Canadian Studies in Population* 270: 49-67.

Duncan C. J., Duncan S. R., Scott S. 1997. "The dynamics of measles epidemics". *Theoretical Population Biology*, 52, pp. 155-163.

Gagnon A., Heyer E., 2001, "Intergenerational correlation of effective family size in early Québec (Canada)", *American Journal of Human Biology*, 13, pp. 645-659.

Garenne M. 1994. "Sex differences in measles mortality: A world review". *International Journal of Epidemiology* 23: 632-642.

Garenne M., Aaby P. 1990. "Patterns of exposure and measles mortality in Senegal". *Journal of Infectious Diseases* 16: 1088-1094.

Greer A. 1997. *The People of New France*: University of Toronto Press.

Haggett A. D. C., Smallman-Raynor M. R. 2000. *Island Epidemics*: Oxford University Press.

Hull F. 1988. "Increased measles mortality in households with multiple cases in the Gambia, 1981". *Review of Infectious Diseases* 10: 463-467.

Koster F. 1988. "Mortality among primary and secondary cases of measles in Bangladesh". *Review of Infectious Diseases* 10: 471-473.

Kleinbaum D. G., Klein M. 2002. *Logistic Regression: A Self-Learning Tex*t. New York: Springer-Verlag.

Légaré J. 1988. "A population register for Canada under the French regime: Context, scope, content, and applications". *Canadian Studies in Population* 15: 1-16.

Mandomando I. M., Naniche D., Pasetti M. F., Valles X., Cuberos L., Nhacolo A., Kotloff K. L., Levine M. M., Alonso P. 2008. "Measles-specific neutralizing antibodies in rural Mozambique: Seroprevalence and presence in breast milk". American Journal of Tropical Medicine and Hygiene 79: 787-792.

Matthieu J., Laberge A., Goucher L., Postolect G., 1992, “L’accaparement foncier et la reproduction sociale dans la vallée du Saint-Laurent au XVIIIe siècle”, in *Transmettre, hériter, succéder. La reproduction familiale en milieu rural : France-Québec, XVIIIe-XXe siècles*, R. Bonnain, G. Bouchard, J. Goy (eds), Lyon/Paris/Villeurbanne, Presses Universitaires de Lyon, pp.121-133.

Mazan R., Gagnon A., Desjardins B. 2009. “The measles epidemic of 1714-1715 in New France”. *Canadian Studies in Population*. 36: 295-323.

Mazan R., Gagnon A. 2007. Familial and Environmental Influences on Longevity in Historical Quebec. *Population* 62: 271-291.

Moss W. J., Ota M. O. 2007. "Measles" in *Infectious Disease Epidemiology: Theory and Practice*, Nelson K. E., Williams C. M. (ed.). Boston: Jones and Bartlett Publishers, pp. 601-621.

Pison G., Aaby P., Knudsen K. 1992. “Increased risk of death from measles in children with a sibling of opposite sex in Senegal”. *British Medical Journal* 304: 284 – 287.

Perry R. T., Halsey N. A. 2004. “The clinical significance of measles: A review”. *The Journal of Infectious Diseases* 189(Suppl 1): S4-S16.

Reves R. 1985. “Declining fertility in England and Wales as a major cause of the twentieth century decline in mortality: The role of changing family size and age structure in infectious disease mortality in infancy”. *American Journal of Epidemiology* 122: 112 – 126.

Chapter 4

Delayed measles mortality among exposed children who survived the epidemic of 1714-15 in New France

4.1. Introduction

Measles caused a considerable number of fatalities in New France during the 1714-15 epidemic. In the first study of this series, the general origin, spread, duration and intensity of the epidemic were described at the aggregate level (see Chapter 2). A set of methods were developed to analyze an epidemic when cause of death information is lacking. A series of smoothing splines were fit to the time-series data by age, sex and region to estimate measles mortality and to trace the origin, spread, duration and severity of the epidemic. The epidemic originated around the Montreal area in late March of 1714. By September, the epidemic had spread to all parts of the colony and had run its course in early 1715. The epidemic was severe among children under 15 years of age, but severity declined with age and varied by sex and region. Children in the Eastern parishes had the highest risk of death in the colony, while females were more likely than males to have died from the virus. The general overview of the epidemic served as a benchmark for determining the study population of more a detailed analysis on the identification of risk factors associated with measles mortality at the individual level.

The objectives of the second study were twofold. First, methods were developed to identify children who were most likely exposed to measles. The second was to identify risk factors of measles mortality among exposed children during the acute episode of the epidemic by making comparisons with control groups subjected to normal mortality conditions. Although there was no direct method to partition measles and non-measles

deaths, these indirect methods helped clarify the possible role that demographic and familial risk factors played during the measles epidemic. Many interesting findings about the disease process were generated and some general similarities and differences were found with modern studies conducted in other populations. Important risk factors included the estimated age at infection, death of one or more sibling(s) in the family, immigrant status of the parents, age difference between siblings, sibship size, and the region of residence. The first two studies serve as a benchmark for determining the selection criteria to analyze the fate of the exposed children who survived the acute phase of infection, which is the subject of this third study.

Measles has been associated with delayed mortality after the acute phase of infection (Aaby et. al, 1996). Studies conducted in West Africa have found that there was an increased risk of delayed death after exposure to the virus. The period of susceptibility is believed to last from several weeks to several months after the onset of rash and is attributed to a prolonged state of immune suppression and increased susceptibility to secondary infections. This is characterized by a failure to thrive, recurrent infections, persistent pneumonia and diarrhoea. Vitamin A deficiency has also been implicated as a contributing risk factor (Hull et al., 1983; Aaby and Clements, 1989; Clements and Hussey, 2004).

Hull et al. (1983) found that exposed children in the Gambia had a significantly higher risk of dying after the acute phase of infection compared with community controls. Delayed mortality was found to be higher among individuals who were exposed as infants than among those exposed as older children. Another Gambian study found that exposed

toddlers (12 to 35 months) also had higher delayed mortality than unexposed controls (Hull, 1988). Likewise, studies from Guinea-Bissau found that infants who were exposed to measles during the first six months of life were three to four times more likely to die than community controls during the 60-month follow-up period (Aaby et al., 1990; 1993; Aaby, 1995). They found that the delayed effect lasted for up to 3 years past initial exposure and that it occurred even if these infants did not develop clinical measles. In another study, Aaby et al. (1996) examined whether the pre-exposure state of nutrition was associated with delayed mortality. They found that exposed children weighed less before being exposed than controls, but there was no association between pre-exposure weight and the subsequent risk of dying. Further, the difference in mortality between exposed children and controls remained equally strong after controlling for socio-economic, demographic and other cultural background factors.

In populations where measles epidemics are frequent, placental transferred antibodies provide protection from measles infection for infants less than 9 months old if their mothers acquired immunity through natural infection or immunization. Due to the protection afforded by maternal antibodies, acute infection was usually less severe if infants contracted measles after intensive exposure from an older sibling. Moreover, exposed infants would have had a relatively high recovery rate after infection (Aaby et Al., 1996). However, findings from studies in Guinea-Bissau concluded that exposure to measles before 6 months was an important long-term risk factor of mortality. Aaby et al. (1995) indicate that little is known about delayed mortality after acute measles infection, including the possible confounding factors, its determinants and the underlying mechanisms. As in the case for older children, intensive exposure and a high dose of

infection may be important to the disease process. Children who were exposed to measles before the age of 6 months are most likely to have been exposed intensively at home from repeated contact with an older sibling (Garenne and Aaby, 1990). The higher dose of the virus received by secondary cases may induce latent infection, malnutrition and growth faltering (i.e., the failure to thrive) later on in childhood.

Not all studies have found support for the delayed mortality effect after the acute phase of infection. Dollimore et al. (1997) did not find increased post-measles mortality in their study of epidemics in Ghana between 1989 and 1991. Likewise, no support of a delayed effect was found among children in Burundi (Chen at al., 1994). The researchers indicated that previous studies might have 'exaggerated' the delayed effect, as some of those studies compared post-measles cases with immunized children, rather than with unimmunized and unexposed children. It was proposed that both natural measles infection and immunization may have 'non-specific beneficial effects', presumably due to immunological stimulation and an increased resistance to general infections (Aaby et al., 1995).

Contrary to the delayed mortality effect, they argued that children who survived the acute phase of infection actually might incur a survival advantage compared with unimmunized, unexposed children. Aaby et al. (1995) followed further on this assumption by reanalyzing data from several community studies in Senegal, Guinea-Bissau and Bangladesh. Contrary to the findings in the earlier studies, there was no evidence of a delayed effect in any of the regions. In Guinea-Bissau and Bangladesh, post-measles cases had a significantly lower risk of dying, while in Senegal, post-measles cases had a

similar risk of dying compared with unimmunized children in the community. However, others have challenged the results of those studies, as the mean age of infection in those studies was over 40 months (Dollimore et al., 1997; Perry and Halsey, 2004). A higher mean age at infection is usually associated with a lower case fatality rate because older children have a better chance of recovery, due in part, to a more mature immunological response.

The historical data from Quebec provides an ideal research context to examine the above contradictions on delayed mortality after measles exposure. The Registre de population du Québec ancien (PRDH) data contains detailed information that will allow for the analysis of the time to death during a follow-up period. Further, this was the first confirmed measles epidemic in the colony, which means that Canadian born children probably had no acquired immunity to the virus. The lack of previous exposure also means that there were enough exposed and infected children to generate a sufficiently large number of deaths. Most of the community studies conducted in West Africa were indeed based on a small number of subjects, making the reliability of their parameter estimates uncertain at times.

Finally, this study takes advantage of the fact that modern medicine, measles immunization and public health in general, were nonexistent in pre-industrial Québec. Aaby et al. (1995) indicated that if natural measles and immunization have 'non-specific' beneficial effects, the best comparison for determining the extent of post-measles mortality would be against 'unimmunized and unexposed children' and, as such, historical Quebec provides an ideal setting to study the delayed effects of mortality.

This chapter examines the above assumptions relative to delayed measles mortality among a cohort of children exposed before the age of 5 years. It also builds upon the previous two studies on measles in New France and extends the selection and estimation methods to help identify the exposed cohort and the individuals who died during the post-measles phase. Using life tables and multivariate Cox proportional hazards models, the exposed children are followed for up to 25 months past the estimated date of infection. In general, the objective of the study is to assess whether exposed children had a different survival outcome, compared to an unexposed cohort, while assessing the effects of the estimated age at infection, sex, urban/rural residence, immigrant status of parents and sibship composition.

4.2. Data and Methods

The data for this follow-up study derives from the *Registre de population du Québec ancien*, compiled by the *Programme de recherche en démographie historique* (PRDH) at the Université de Montréal (Légaré, 1988; Charbonneau et al., 1993). As mentioned in Chapter 2, the parish register is highly reliable and accurate. The database contains the date and place of birth, death and marriage(s), names of parents and spouse(s) and secondary information on places of residence and of origin for individuals who lived in the Saint-Lawrence Valley during the 17th and 18th centuries. This valuable data has already served to address the familial component of longevity and the long-term consequences of exposure to epidemics, using survival models (Mazan and Gagnon, 2007; Gagnon and Mazan, 2009).

The population remained quasi-closed until the 19th century because of particular historical and geographical circumstances and thus the usual problem of missing observations due to migration is greatly reduced (Charbonneau et al., 1993; Desjardins, 1996). As the development of the database is still in progress, the available information varies in time according to the date of the events and the period of birth and marriage of the individuals. Births are matched with individuals and their parents up to 1799, and deaths up to around 1850 for individuals born before 1750. All ancestors of every individual who married before 1800 can be traced back to the founders of the population.

4.2.1. Study Population

As this is a follow-up study of the exposed children under age 5 who survived past the acute phase of infection, the selection of cases is a continuation from the previous study (see chapter 3). The surviving Canadian born children were selected from the same parishes, where children were likely exposed to measles between late-August and mid-November of 1714. Children without a sibling during the epidemic were not included since one of the main focuses of this study is on relations between siblings. The approximate age and date of infection for those exposed during the acute phase was already determined in the previous study (see Chapter 3 for a full description of how the date of infection was estimated). This section expands upon the estimated date of infection to help identify cases of delayed deaths.

The next step in the study design is to define what constitutes delayed mortality. Acute measles mortality is defined as a death taking place within 30 to 43 days from the onset of the measles rash (12 to 14 days after exposure), depending on the study (Wolfson et al.,

2009). Delayed mortality is defined as a death that takes place at least 30 days after the appearance of the rash (i.e., the date of infection in this study). The time when the infection began can be approximated on a region by region basis from an average scenario based on the natural course of measles, as described in Chapter 3. For the purpose of the present study, the estimated time at infection starts after the incubation period, as the appearance the measles rash is the starting point to estimating whether a death should be classified as acute or delayed (Aaby, 1995).

Initially, a child had to survive at least 30 days past the familial date of onset and/or the death of the sibling to be considered to have died from delayed measles mortality. Upon further analysis, an additional two week lag period was added to account for deaths occurring too soon after the initial 30 day cut-off. The additional lag period increases the time of a delayed death to 43 days past the estimated date of infection. This time period of six weeks is also commonly used as the cut-off point between acute and delayed deaths (Wolfson et al., 2009). The penalty was applied to reduce the likelihood of a false positive classification, as estimation is based on an average scenario of the natural course of measles. If some cases were actually infected at a later time than was estimated (i.e., closer to the tail of the distribution), there is a likelihood that some may have been acute deaths. The extra time was added to reduce the chances of that occurring.

Based on the above selection criteria, the cohort of children exposed before 5 years of age could have entered the study between mid-August and the end of October 1714, given that they survived at least 43 days past the estimated date of infection (N = 1,805). The earliest time for a death to be considered as a delayed death occurred during October of

that year – after the mortality peak characterizing the acute phase, was on the decline (see Chapter 2). The exposed cohort was followed until death or up to 25 months (mid-November of 1716) past the estimated date of infection, where survivors were censored at that time. The follow-up period was stopped at that date because an epidemic occurred between the end of November 1716 and early February of 1717. This epidemic was not included in the follow-up period because any deaths that occurred during that time may have been unrelated to the prior measles epidemic[9].

The same criteria were used to select unexposed cohorts (1708 and 1721) living through periods with no known epidemic, as a basis of comparison. Selecting the cohorts before and after the epidemic provides a more conservative comparison, as it accounts for the secular increasing level of child mortality that took place during the 18th century (see Gagnon and Mazan 2009; Amorevieta-Gentil, 2010). The 1721 cohort had a higher level of child mortality than the 1708 cohort, as the level began increasing in Montreal after the measles epidemic (see Chapter 2). Despite the increasing child mortality, the two unexposed cohorts had similar survival outcomes over the course of the follow-up period. There were no significant differences in survival by age and sex. Therefore, in order to facilitate comparisons and stabilize estimates, the 1708 and 1721 cohorts were combined (N = 3,999).

[9] Based on historical accounts, Duffy (1953) indicated that there was an influenza type epidemic in the area of Charleston Virginia in late December of 1716. Further analysis needs to be done on this particular epidemic to find out what really happened, but I will assume that the epidemic in Quebec was also influenza. When the flu epidemic hit the colony, the exposed cohort ranged from 2 to 5 years of age and mortality was generally at normal levels by that time. The outbreak started in Western Quebec in late fall and spread eastward by early winter. The epidemic was relatively short-lived, where deaths peaked for a few weeks in each area and then dissipated.

The pooled unexposed cohort served to increase the reliability of the estimates, as the measures were based on a smaller number of events (deaths) than in the previous study. This is a common problem in this type of study (i.e., higher variability in some parameter estimates due to the small number of events). Although the number of events was small and created limits on the number of controls that could be included, the parameter estimates were stable in most circumstances. The exposed cohort was also tested against other cohorts (e.g., 1707, 1709, 1722 and 1723) besides the one used in the study, with no appreciable differences (not shown here). The unexposed cohorts selected for the study represented typical mortality conditions for that time, in as much as "typical" meant "years without notable epidemics". As determined in the previous chapter, there was little difference between the observed and expected death rates when a spline was fit through the mortality times-series data.

4.2.2. Risk Factors

For this study, the same controls were used from the previous study on the risk factors associated with measles mortality during the acute episode (see the Chapter 3 for a full description of the risk factors). The following controls were found to be important predictors of mortality during the acute episode of the epidemic and some also during the normal periods. Since there were fewer events (deaths) during the follow-up than in the acute episode, the categories of the control variables were collapsed to lessen the number of parameters to be estimated in the multivariate models. As the objective of the study was to examine the impact of the epidemic after it ended, it was more important to retain a reliable estimate of mortality.

The region of residence at the time of the epidemic was included to capture urban/rural differences in mortality, with children residing in the rural areas as the reference category. As with many infectious and parasitic diseases, the risk of death from measles has a largely predictable age pattern. The age at the estimated time of infection was divided into 4 age groups to reflect this pattern: <6 months, < 12 months, 12 to 35 months and 36 to 59 months. Individuals who were exposed during infancy served as the reference category in the overall model. Two variations of infancy are explored to provide a comparison to the Aaby et al. studies of early life exposure (< 6 months) and the Hull study of exposure during infancy (<12 months). Models were also examined with each age group analyzed separately to find whether exposed children at different ages had higher or the same mortality as the unexposed cohort.

The sex of the child was included as a risk factor in the models, with females as the reference category. Some models were run separately for each of the sexes in order to check if age-specific exposure was different among the male and female cohorts. The immigrant status of the parents was also included to measure whether the apparent lower survival outcome of children with immigrant parents extended into the post-measles phase. Immigrant status of parents was divided into 2 groups: Canadian born and either/both parent(s). Children with Canadian born parents served as the reference category.

The sibling composition controls include the age difference between siblings and the death of a sibling during the acute phase. As mentioned above, it has been found that older siblings (index cases) may increase the risk of measles death among their younger

siblings (secondary cases) by introducing and secreting a higher dose of the virus to those children. However, there is no information on the behaviour of this measure during the post-measles period. This factor was estimated by subtracting each child's age at time x from the average age of the sibship at time *x*. The average age difference was then coded as < 4 years and 4+ years, with 4+ years serving as the reference group.

The death of a sibling during the acute phase serves as a proxy for the incidence of multiple and secondary cases in a given family. As mentioned in Chapter 3, this measure may be a good alternative when information on secondary cases are lacking. It is important to know about secondary cases because they have been found to be at the highest risk of death during an epidemic (i.e., the dose response effect) and afterwards (Aaby, 1995). If there is a death in the family, then it could be an indication of severe infection in the household. Individuals without a dead sibling during the given period formed the reference group. Table 4.1 summarizes the coding of the controls and gives the number of families in each category for the Cox proportional hazards models.

Table 4.1. Description of the categorical variables included in the multivariate Cox proportional hazards models for children exposed before 3 years of age and the unexposed comparison cohort, New France

Risk Factor	Exposed vs. Unexposed	Exposed (1714)	Unexposed (1708, 1721)
Total	3,552	1,071	2,481
Cohort			
Exposed	1,071	-	-
Unexposed†	2,481		
Residence			
Urban	1,081	309	772
Rural†	2,471	762	1,709
Sex			
Male	1,728	560	1,168
Female†	1,824	511	1,313
Age at Exposure			
<12 months†	1,300	392	908
12 to 23 months	1,109	317	792
24 to 35 months	1,143	362	781
Immigrant Status			
Immigrant Parent(s)	1,114	329	785
French Canadian†	2,438	742	1,696
Age Difference			
< 4 years	1,955	636	1,319
4+ years†	1,597	435	1,162
Sibling Survival			
Sibling Died	217	112	105
No Death†	3,335	959	2,376

† Reference category- basis of comparison for the other categories.

4.2.3. Life Tables and Proportional Hazards Models

To improve comparability, I used statistical models that were similar to the ones used in the series of studies conducted by Aaby and colleagues – life tables and Cox proportional hazards models. Preliminary comparisons of survival between the exposed and unexposed cohorts were done using discrete or clinical life tables. The survival times of the each of

the children were subdivided into 24 discrete monthly intervals (e.g., 0-1, 1-2 … 24-25) by exposure status, age and sex. The life table takes on the general actuarial form:

$$q_x = d_x / N_x \text{ and } p_x = (1 - q_x); \qquad \textbf{[1]}$$

where q_x is the probability of dying in the monthly interval x to x + n, d_x is the number dying in the monthly interval x to x + n, N_x is the size of the cohort and p_x is the conditional probability of surviving or the complement of q_x. In this study, I only present the summary probabilities of dying for each of the groups based on the entire follow-up period (i.e., probability of dying between 0 to 25 months) to facilitate comparisons (see Table 4.2). Mantel-Haenszel (M-H) hazards ratios and significance tests were used to compare the life table survival of the exposed and unexposed cohorts (see Breslow and Day, 1987; Esteve and Raymond, 1994 for a formal treatment of the M-H procedure). Note that the M-H hazard ratios estimated from the discrete life tables are identical to the Cox hazard ratios without the addition of controls.

For the multivariate models, a series of Cox regression models were fitted in order to assess whether the predictors had any influence on the individual's survival time. The Cox regression model expresses a transformation of the hazard as a linear function of the predictors. A continuous hazard function is a rate with no upper bound (∞) and thus, the logarithm of the hazard is treated as the outcome variable (Singer and Willet, 2003: 514):

$$\log h(t_i) = \log h_o(t) + [\beta_1 X_1 + \beta_2 X_2 + ... + \beta_i X_i]. \qquad \textbf{[2]}$$

The log hazard ($\log h(t_i)$) equals the baseline function ($\log h_0(t)$) or when the covariates equal 0 plus a weighted linear combination of predictors (β) that measure the effect of

the covariates on $\log h(t_i)$. The main assumptions of the Cox proportional hazards model are: 1) a log-linear relationship between the covariates and the underlying hazard function and; 2) a multiplicative relationship between the underlying hazard function and the log-linear function of the covariates (Blossfeld et al., 1989). It is assumed that the hazard function of any two individuals have parallel age (time) patterns (Namboodiri and Suchindran, 1987; Elandt-Johnson and Johnson, 1980). All of the covariates included in the models appeared to meet the proportionality assumption[10]. Since the data contain correlated observations or the possibility of temporal dependence among groups of individuals (i.e., siblings), the standard errors of the coefficients were adjusted using robust variance estimation. This procedure involves relaxing the temporal independence assumption by accounting for the clustering of observations, here by sibships (siblings were identified as individuals having the same mother).

4.3. Results

In this section, the results of the life tables and Multivariate Cox Proportional Hazards models are presented for the 25-month follow-up period comparing the survival outcome of the exposed and unexposed cohorts. In general, most children in both the exposed and unexposed cohorts survived the follow-up period. However, the risk of death for the exposed cohort was higher during that time.

[10] Any potential violations of the proportionality assumption were checked with log[S(*t*)] plots of the categorical variables and Schoenfeld residual plots of all covariates. The covariates showed no deviation from time invariance. Additionally, there were no significant correlations between the Schoenfeld residuals and time (age at death) for each of the covariates.

4.3.1. Life Tables

Table 4.2 gives the summary statistics of 30 clinical life tables for the 25-month follow-up period for the exposed and unexposed cohorts by the estimated age at infection or observation period for the unexposed cohort and by sex of the child. The Mantel-Haenszel hazard ratios are also provided to give a comparison of the overall difference in mortality between the exposed and unexposed cohorts over the follow-up period. Overall, the probability of dying within the follow-up period declined with age for both cohorts. This pattern is expected, as it follows the empirical age pattern of mortality at the younger ages (i.e., exponential decline). For instance, 13.5% (.135 × 100) of children exposed to measles during infancy died within 2 years after exposure, 7.7% of exposed toddlers (12 to 35 months) died within 2 years and so forth. In general, survival among the exposed cohort was lower for all age groups with the exception of older children who were exposed between 36 and 59 months of age[11].

After adjusting for the estimated age at infection/observation, children exposed before 3 years of age were 1.62 times more likely to die within the 25 month follow-up period than the unexposed cohort ($p < .001$). In total, 9.8% (.098 × 100) of children exposed before 3 years of age died, as compared to 6.2% of unexposed children during the follow-up period. The overall delayed effect was stronger for females exposed before age 3 than exposed male children ($HR_{M-H} = 1.79$, $p > .01$ vs. 1.49, $p > .05$, respectively).

[11] Given that reliability is a problem with the older children and that they had the same mortality as unexposed children, only children exposed before the age of 3 were considered for the overall hazard ratio and later in the multivariate models.

Table 4.2. Summary statistics of the 25-month follow-up life tables for children exposed to measles and the unexposed cohort by age and sex, New France

	Total			Males			Females		
Age at Infection	Probability of dying in follow-up ($_nq_x$)		Mantel-Haenszel Hazard Ratio	Probability of dying in follow-up ($_nq_x$)		Mantel-Haenszel Hazard Ratio	Probability of dying in follow-up ($_nq_x$)		Mantel-Haenszel Hazard Ratio
Months	Exposed	Unexposed	HR_{M-H}	Exposed	Unexposed	HR_{M-H}	Exposed	Unexposed	HR_{M-H}
< 11	0.135	0.113	1.29	0.137	0.137	1.01	0.133	0.078	1.76*
12-35	0.077	0.036	2.16***	0.089	0.038	2.41***	0.064	0.034	1.91*
36-59	0.022	0.026	0.85	F	F	F	F	F	F
< 36	0.098	0.062	[a]1.62***	0.107	0.076	[a]1.49*	0.088	0.050	[a]1.79**
< 6	0.180	0.132	1.41*	0.169	0.149	1.15	0.191	0.113	1.77*

p <.001***, p <.01**, p <.05*
[F]High sampling variability-Number of events was too small to produce reliable estimates.
[a]Adjusted for age at infection/observation.

Exposed infants (less than 12 months) had a slightly higher probability of dying than unexposed children, but the difference did not reach statistical significance (HR_{M-H} = 1.29, p > .05). When testing the sex-specific risk, the reason for the non-significant effect becomes apparent. Exposed and unexposed male infants had the same risk of dying during the follow-up period (HR_{M-H} = 1.01, p > .05). Exposed female infants, on the other hand, had a significantly higher risk of dying than unexposed females (HR_{M-H} = 1.76, p < .05). Similarly, females exposed before 6 months were 1.77 more likely to die than unexposed infants (p < .05), as compared to infants subjected to normal conditions. Almost one fifth (19.1%) of females exposed before 6 months of age died within the 25 month follow-up period, while 11.3% of unexposed female infants died. These female infants even had a slightly higher probability of dying than both exposed and unexposed males (16.9% and 14.9%, respectively).

For exposed toddlers, the risk of dying was twofold (HR_{M-H} = 2.16, p > .001). Both exposed male and female toddlers had a significantly higher risk of death, but the

magnitude of the effect was stronger for males ($HR_{M-H} = 2.41$, $p > .001$ and 1.91, $p > .05$, respectively). Around 8.9% (.089 × 100) of exposed male toddlers died and 6.4% of exposed females died during follow-up, as compared to 3.8% and 3.4% of unexposed male and female toddlers, respectively. The survival of children exposed past 3 years of age was not significantly different from the survival of unexposed children. These probabilities are based on fewer events than the corresponding figures at younger ages and it was not possible to obtain a reliable estimate for each of the sexes.

4.3.2. Proportional Hazards Models

Although Table 4.2 shows that exposed children had a higher risk of dying than unexposed children during the follow-up period, the analysis was conducted without an assessment of the other risk factors. To further test the delayed measles effect, Table 4.3 shows the Hazard ratios (HR) and asymptotic standard errors (ASE) of the multivariate proportional hazards models (A through C) for each age at infection/observation and sex, while assessing the effects of the other demographic and sibship factors. Even when controlling for the other effects, the age and sex-specific hazard ratios remain similar to the life table ratios in Table 4.2. The hazard ratios between the exposed and unexposed cohorts actually increase slightly with the inclusion of the other factors in the models.

Overall, children who were exposed to measles before 3 years of age had a significantly higher risk of dying during the 25 month follow-up period than the unexposed cohort, while assessing the effects of the demographic and sibship factors ($HR = 1.68$, $p < .001$). Both males and females exposed to measles before 3 years of age also had a significantly higher risk of dying within the follow-up period than unexposed children. The post-

measles effect remained stronger for females, as they had close to double the risk, while males had a 53% higher risk of dying (HR = 1.91, $p < .01$ and HR = 1.53, $p < .05$, respectively). The rest of ratios in Table 4.3 are not interpreted since the patterns are identical to the ratios derived from the life table models presented in Table 4.2.

Table 4.3. Multivariate Cox proportional hazard models for the exposed and unexposed cohorts during the 25-month follow-up period by age and sex, New France

Age at Infection (months)	Cohort	Model A All Children		Model B Males		Model C Females	
		HR	ASE	HR	ASE	HR	ASE
< 12[a]							
	Exposed	1.37	0.173	1.04	0.229	1.84*	0.270
	Unexposed[†]						
12 to 35[a]							
	Exposed	2.12***	0.194	2.34**	0.265	1.91*	0.289
	Unexposed[†]						
< 36[b]							
	Exposed	1.68***	0.128	1.53*	0.169	1.91**	0.197
	Unexposed[†]						
< 6[a]							
	Exposed	1.52*	0.193	1.28	0.265	1.79*	0.288
	Unexposed[†]						

[†]Reference category- basis of comparison for the other categories.
$p < .001^{***}$, $p < .01^{**}$, $p < .05^{*}$
[a]Controls include: residence, immigrant status, age difference between siblings and dead sibling.
[b]Controls are the same as in Table 4.4.

Table 4.4 gives the Hazard ratios (HR) and the robust standard errors (RSE) of the multivariate proportional hazards models (D through F) for the 25-month follow-up period of the exposed (1714) and unexposed cohorts (1708, 1721). Model D includes both the exposed and unexposed cohort with all of the risk factors entered simultaneously. Models E and F show the exposed and unexposed cohorts individually to assess the impact that the demographic and sibship factors had on each of the groups. Bootstrap hazard ratios (HR_{BS}) are also provided to demonstrate the stability of the parameter

estimates and as a check for bias in the models. Bootstrap coefficients were obtained by randomly selecting one child from each family 100 times with replacement.

Table 4.4. Multivariate Cox proportional hazard models for the exposed and unexposed cohorts under the age of 3 during the 25-month follow-up period, New France

Risk Factor	Model A Exposed and Unexposed N = 3,552 n_{BS} = 2,591			Model B Exposed (1714) N = 1,071 n_{BS} = 819			Model C Unexposed (1708, 1721) N = 2,481 n_{BS} = 1,772		
	HR	RSE	HR_{BS}	HR	RSE	HR_{BS}	HR	RSE	HR_{BS}
Cohort									
Exposed	1.68***	0.128	1.90	-	-	-	-	-	-
Unexposed†									
Residence									
Urban	2.28***	0.132	2.14	2.19***	0.211	2.20	2.60***	0.171	2.43
Rural†									
Sex									
Male	1.50**	0.126	1.50	1.36	0.199	1.36	1.59**	0.164	1.67
Female†									
Age at Infection									
0 to 11 months†									
12 to 23 months	0.57***	0.144	0.52	0.83	0.220	0.73	0.44***	0.194	0.40
24 to 35 months	0.25***	0.186	0.23	0.25***	0.285	0.23	0.25***	0.247	0.21
Immigrant Status									
Immigrant Parent(s)	1.07	0.136	1.11	1.32	0.213	1.34	0.92	0.177	0.93
French Canadian†									
Age Difference									
4+ years	1.38*	0.127	1.54	1.92**	0.202	2.21	1.10	0.164	1.17
< 4 years†									
Sibling Survival									
Sibling Died	1.87**	0.202	1.84	2.86***	0.247	2.58	0.82	0.418	0.82
No Death†									

†Reference category- basis of comparison for the other categories.
p <.001***, p <.01**, p <.05*

All models and especially the exposed cohort appear to fit the data reasonably well and the bootstrap hazard ratios (HR_{BS}) are in general agreement with the Cox estimated hazard ratios (HR). The risk factors in the model were all significant with the exception of

the immigrant status of the parents. Generally, the demographic risk factors behaved similarly in the models run separately for the exposed and unexposed cohorts (Models D and F). However, the magnitude of the demographic factors are more pronounced for the unexposed cohort, suggesting that measles was less discriminating than the usual risk factors prevalent in "normal" conditions, buffering out differences in its long-term sequeala. The urban/rural differential was important in all models. In models D and F, exposed and unexposed children residing in the urban towns (Montréal and Quebec City) had over twice the risk of dying during follow-up period (HR = 2.19, $p < .001$; 2.60, $p < .001$, respectively)[12].

The sex differential in mortality also behaved similarly for exposed and unexposed children, as males had a higher risk of dying in both models. However, the sex difference was only significant among the unexposed cohort (HR = 1.59, $p < .01$ and 1.36, $p > .05$, respectively). As would be expected, the risk of death declines with an increasing age at infection/observation in both models during the follow-up period. However, mortality continued to be high for children exposed between 12 and 23 months of age, as the risk of death was not significantly different from infants (HR = 0.83, $p > .05$). This indicates that toddlers were slow to recover after the acute episode of the epidemic. In contrast, the unexposed cohort follows a typical mortality pattern, as risk was significantly lower at each proceeding age after infancy (HR = 0.44 and 0.25, $p > .001$)

[12] It should be noted that the regional variation in mortality (i.e. Rural West, Montreal, Quebec City, GQA and Rural East, see Chapters 2 and 3) disappeared during the post-measles phase (not shown here). Note that in the follow-up period there are fewer events. A fewer number of events could lead to the diminished significance when the data is spread thin through the use of too many categories or parameters to be estimated. Although regional mortality was not significantly different for the exposed cohort (except for the urban/rural difference), exposed children in each of the Rural and Urban regions had higher mortality than the unexposed cohorts residing in those same regions (not shown here).

The familial risk factors show some interesting patterns during the post-measles phase. As with the acute phase of the epidemic, the death of a sibling remained highly significant during the follow-up period. For the exposed cohort, children who had a sibling that died during the acute phase were almost three times more likely to have died during the post-measles phase than exposed children without a death in the family (HR = 2.86, $p < .001$). The difference was not significant for the unexposed group (HR = 0.92, $p > .05$). Interestingly, the age difference between siblings in the household had the opposite effect from the previous study (see Chapter 3). In the present case, exposed children with siblings closer in age (or less than 4 years apart) had almost twice the risk of dying over the follow-up period (HR = 1.92, $p < .01$). The effect follows the same direction for the unexposed cohort, but was not significant (HR = 1.10, $p > .05$).

As mentioned in the Data and Methods section, the follow-up period was stopped at 25 months past the estimated date of infection because an epidemic occurred between the end of November 1716 and early February of 1717. Table 4.5 shows the hazard ratios between the exposed and unexposed cohorts during the 25-month and extended follow-up period, which includes the subsequent flu epidemic. Although exposure to measles may be unrelated to the survival outcome of the epidemic, some interesting patterns emerge with the exposed cohort.

Table 4.5. Multivariate Cox proportional hazard models for the exposed and unexposed cohorts with the extended follow-up period by age and sex, New France

Age at Infection (months)	Cohort	Model G Males		Model H Females	
		HR	HR_{flu}	HR	HR_{flu}
< 12[a]					
	Exposed	1.04	1.15	1.84*	2.23**
	Unexposed†				
12 to 35[a]					
	Exposed	2.34**	2.14**	1.91*	2.21**
	Unexposed†				
< 36[b]					
	Exposed	1.53*	1.56*	1.91**	2.29***
	Unexposed†				
< 6[a]					
	Exposed	1.28	1.38	1.79*	2.16**
	Unexposed†				

†Reference category- basis of comparison for the other categories.
p <.001***, p <.01**, p <.05*
[a]Controls include: residence, immigrant status, age difference between siblings and dead sibling.
[b]Controls are the same as in Table 4.4.

The magnitude of the hazard ratios among females exposed during infancy and toddlerhood increased when extending the follow-up period to include the subsequent epidemic (HR_{flu} = 2.23, p < .01; 2.21, p < .01). This trend reflects the higher probability of death among exposed females during that short time period, as compared to the other cohorts. In terms of the probabilities derived from life tables, females exposed before age 3 had a higher probability of dying between late-November and early-February than unexposed females and both exposed and unexposed males (3.4% vs. 0.6%, 2.2% and 1.0%, respectively). Exposed males also had an elevated risk compared to the unexposed group, but not to the extent of exposed females. All effects remained the same during the extended follow-up period with the notable exception of the immigrant status of the parents. Interestingly, the effect became significant when including the subsequent

epidemic, as it was found that a large portion of deaths were among exposed children who had at least one immigrant parent (particularly, an immigrant father). Although not reported in Table 4.5, exposed children with at least one immigrant parent had a 52% higher risk of death than exposed children with Canadian born parents ($HR_{flu} = 1.52$, $p < .05$).

4.4. Discussion and Conclusions

This study compared the survival of a group of children after exposure to measles with the survival of an unexposed cohort. Overall, children who were exposed to measles before age 3 had a higher probability of death than the unexposed cohort for up to 2-years past the estimated date of infection. The effect remained highly significant when controlling for potential confounding effects. The probability of death was higher for both boys and girls, as compared to their counterparts living under normal mortality conditions. Breaking down the results by age at infection, it was found that girls exposed during infancy had a significantly higher risk of dying than unexposed girls, while the corresponding figures were not significantly different for boys. On the other hand, both males and female children exposed between 12 and 35 months of age had a higher risk of dying than unexposed children. In this case, the effect was slightly stronger for boys. No significant mortality difference was found among children exposed between 36 and 59 months of age.

There were some general similarities found between this study and several modern studies conducted on early life exposure (Hull et al., 1983; Aaby et al. 1990, 1993, 1996). Those studies found that children exposed during infancy (before 6 months in the Aaby et

al. studies and 12 months in the Hull et al. study) were more likely to die following measles infection than unexposed controls. Mortality was increased for up to 36 months past infection and was higher for exposed infants with and without clinical measles. By comparison, this study found that post-measles mortality for infection during infancy was only significant among females and that mortality was returning to normal levels before the second year of follow-up. Note also that the above studies did not examine for sex differences in mortality, probably because of the small number of events involved.

This study is also concordant with the modern studies showing that measles exposure had long-term consequences. In all cases, exposure remained significant when assessing the effects of the demographic and sibship factors. Aaby et al. (1990) also found that 'socio cultural confounding' could not account for the long-term difference between the exposed and unexposed cohorts. In one of their early life studies, they even found no relation between delayed mortality and pre-existing nutrition (Aaby et al. 1996). They suggested that higher delayed mortality was probably related to 'biological processes' and concluded that 'exposure to the virus itself is a critical factor of delayed mortality'. The physiological reasons for the long-term risk are not conclusive, but delayed mortality is likely a combination of viral persistence (never demonstrated), prolonged immune suppression and Vitamin A deficiency (Clements and Hussey, 2004). These adverse effects would make sense in the absence of modern and effective measles treatment such as Vitamin A and antibiotic therapies and vaccination of infected cases.

Interestingly, the strong regional differences that were apparent during the acute phase (i.e., the Eastern region had higher mortality, see Chapters 2 and 3) disappeared during

the post-measles period (not shown here). This change is worth noting because the regional differences provided a means to identify children who were likely affected by the poor harvests that were reported between 1714 and 1717 (i.e., Eastern Quebec). One possible reason for the diminished regional differences could be the presence of too many regional categories with too few events. Another possibility is that malnutrition did not have much of an influence on exposed children past the acute episode.

It would be presumptuous, however, to suggest that nutritional deficiencies have a limited influence on long-term measles mortality. It is now well recognized that measles complications tend to be more severe in malnourished children, particularly those with Vitamin A deficiency (even mild deficiency) (Perry and Halsey, 2004). As there is a synergistic effect between malnutrition and infectious diseases, the relative contribution to acute and delayed mortality can be difficult to delineate (Belamarich and Adam, 1998). Further, measles infection can intensify or lead to the onset of malnutrition after infection because of the abnormal loss of protein, increased metabolic demands and decreased food intake (Moss and Ota, 2007).

If both malnutrition and measles compromise the immune system, it is expected that toddlers have higher long-term sequeala from the infection. In this study, both boys and girls infected during this critical period of childhood had higher mortality (see also Chapter 3). As mentioned in the previous chapters, children of that age may be at a higher risk than infants during crises related to food shortages because they depend more on solid foods and their immune systems are not completely developed, while infants may at least incur some general protection from breastfeeding (Palloni, 1990). In many historical

populations, the combination of food scarcity and infectious diseases had a strong influence on the long-term survival outcome of children over age 1, but not so much for infants (Bengtsson, 2004).

The role of nutrition was also revealed, albeit indirectly, through the use of the immigration status of the parents. Although the risk was still higher, the effect did not reach significance during the follow-up period. If measles exposure is an important risk factor of delayed mortality, then the difference between exposed children with and without immigrant parents should diminish, as in the normal periods. The difference disappeared during the post-measles phase because the most socially disadvantaged (i.e., less resources) were eliminated quickly during the acute phase. Therefore, the age at infection and underlying physiological factors were playing a larger role in influencing higher post-measles mortality among exposed children, regardless of parental origin.

During the subsequent flu epidemic, however, the immigrant status of parents became a significant factor. The majority of flu deaths were among exposed children who had at least one immigrant parent (particularly, fathers). The return of a significant difference may reflect the renewed importance of varying levels of socio-economic status, mutual support and access to resources during crisis situations (see Chapter 3). These social and environmental factors may come into effect with more intensity when the population is compromised by further insults (i.e., another epidemic). Modern studies also show that maternal education and socio-economic status were inversely related to measles mortality (Aaby et al., 1990; Koenig et al., 2001).

As in the second study (Chapter 3), the indirect proxies of intensive exposure in the household (death of a sibling during the acute episode and age difference between siblings) were highly significant in the post-measles models, regardless of age and sex. In contrast to the acute phase, however, the direction of the effect of the age difference between siblings became reversed. Exposed children who had siblings closer in age (< 4 years) had a higher risk of dying during the follow-up period. The higher delayed mortality among children who are closer in age could be due to increased sibling competition for limited resources, which may be particularly intense when birth intervals are short.

The apparent sex-difference in long-term mortality among exposed infants was unexpected because modern studies did not explore this possibility. The sex differential also extended beyond the follow-up period, as exposed girls had higher mortality during the subsequent influenza epidemic. Exposed boys also had an elevated risk above normal, but not to the extent that it was for females. This trend indicates that exposed girls were at a higher susceptibility of dying from secondary infections than boys following measles exposure.

In the mid-1980s, a higher proportion of children were becoming infected with measles before 9 months of age in some developing countries (Aaby, 1995). In 1989, the World Health Organization (WHO) introduced a new high-titre Edmonston-Zagreb measles vaccine (i.e., a strain with a higher dosage of the virus) to induce protective immunity in early life. As it turned out, a series of community studies found that long-term mortality was higher among female recipients of the high-titre vaccine in comparison with females

given the Standard Schwarz Medium-Titre vaccine (Aaby et al., 1995). Some hypothesized a sex-specific difference in the immune response to the vaccine that would have been beneficial for boys, but detrimental to girls (Aaby, 1995; Clements and Hussey, 2004).

Hence, the adverse effect of a higher dose vaccine in modern populations appears similar to the effects of intensive exposure of natural measles in early life in historical Québec. In that sense, I hypothesize that it was intensive exposure in early life that made girls more susceptible to general infections than boys in the long-term. Another possible explanation for the difference is selection. Infant mortality is in general higher among males and were perhaps more selected than girls and thus less likely to die from measles. But more direct causes could also explain the higher mortality among girls, such as the preferential treatment of boys, although there is no evidence of such a sex-differential in early French Canadian society.

In opposition to their earlier claims, Aaby and colleagues (1995; 1996) suggested that measles immunization and natural infection might have 'beneficial' long-term effects on children. The researchers explained that their previous studies might have 'exaggerated' the delayed effect because they compared exposed cases with immunized children (see Introduction). Generally, the reasoning behind their paradigm shift is unclear. Only a few of the previous studies compared post-measles cases to immunized children. For instance, the studies on early life exposure were not contested, as these studies consisted of comparisons between exposed and unexposed and unimmunized controls (Hull, 1988; Aaby et. al., 1990; 1993; 1996).

In closing, there are a few issues that need to be addressed regarding the aforementioned studies. In those studies, the age at infection was relatively high, where the mean age was over 40 months. In this study, as well, the risk of death among older children exposed past the age of 3 was no different than for the unexposed cohort. A higher mean age at infection is generally the result of vaccination at a younger age and tends to be associated with a lower case fatality rate (Perry and Halsey, 2004; Clement and Hussey, 2004). A lower case fatality would be expected, as older children are probably more likely to recover from measles, due to a more mature immunological response. The researchers even indicated that the high mean age could explain why no significant post-measles effect was found (Aaby et al. 1996; Dollimore et al. 1997). However, neither of the research teams followed-up on their suggestion.

Another weakness of the post-measles studies done in West Africa is that they did not control for the potential effects of modern public health knowledge, medical care and differences in socio-economic status. These factors were probably improving over time when the studies took place from the late 1970s onwards and should have been given further consideration. In addition, effective treatment for measles cases such as, Vitamin A therapy, prompt antibiotic treatment for pneumonia, widespread immunization campaigns and promotion and prevention measures used by health workers have also contributed to a lower case fatality rate in the past 25 years (Perry and Halsey, 2004).

In summary, public health interventions could have contributed to a better survival outcome for the children in those studies. In historical Quebec, on the other hand, modern medical knowledge, treatments and immunization campaigns did not exist. The

conditions during that time were pristine or untouched by the influences these modern advancements in the prevention and treatment of disease. Therefore, the study of measles in pre-industrial Quebec helps provide some closure on the debate of the alleged exaggeration of post-measles mortality. This study has clearly shown that there was an increased risk in long-term mortality among children exposed to measles.

4.5. References

Aaby P., Samb B., Anderson M., Simondon F. 1996. "No long-term excess mortality after measles infection: A community study". *American Journal of Epidemiology* 143: 1035-1041.

Aaby P., Samb B., Simondon F., Seck A.M., Knudsen K., Whittle H. 1995. Non-specific beneficial effect of measles immunisation: analysis of mortality studies from developing countries. *British Medical Journal* 311:481-485.

Aaby P. 1995. "Assumptions and contradictions in measles and measles immunization research: Is measles good for something?". *Social Science and Medicine* 5: 673-686.

Aaby P., Bukh J., Lisse I. M., Da Silva M. C. 1990. "Delayed excess mortality after exposure to measles during the first six months of life". *American Journal of Epidemiology* 132: 49-63.

Aaby P., Anderson M., Knudsen K. 1993. "Excess mortality after early exposure to measles". *International Journal of Epidemiology* 22: 156-162.

Aaby P., Anderson M., Knudsen K. 1996. "Nutritional status and delayed mortality following early exposure to measles". *Epidemiology and Infection* 117: 525-531.

Aaby P., Clements C. J. 1989. "Measles immunization research: a review". *Bulletin of the World Health Organization* 67: 443-448.

Amorevieta-Gentil M. 2010. *Les niveaux et les facteurs déterminants de la mortalité infantile en Nouvelle-France et au début du Régime Anglais (1621-1779)*. PhD Thesis. Département de Démographie, Université de Montréal.

Belamarich P. R., Adam H. M. 1996. "Measles and malnutrition". *Pediatrics in Review* 19: 70-71.

Bengtsson T., Campbell C., Lee J. Z. 2004. *Life under pressure: mortality and living standards in Europe and Asia, 1700-1900*. Cambridge: The MIT Press.

Blossfeld H., Hamerle A., Mayer K. U. 1989. *Event History Analysis: Statistical Theory and Application in the Social Sciences*. New Jersey, Lawrence Erlbaum Associates.

Breslow N.E., Day N.E. 1987. *Statistical Methods in Cancer Research. Vol. II, The Design and Analysis of Cohort Studies* (IARC Scientific Publication No. 82). Lyon: IARC Press.

Charbonneau H., Desjardins B., Guillemette A., Lardry Y., Légaré J., Nault F. 1993. *The First French Canadians: Pioneers in the St. Lawrence Valley*. Newark: University of Delaware Press.

Chen R.T., Weierbach R., Bisoffi Z., Cutts F., Rhodes P., Ramaroson S., ET AL. 1994. A "post-honeymoon period" measles outbreak in Muyinga Sector, Burundi. *International Journal of Epidemiology* 23:185-93.

Clements C. J., Hussey G. D. 2004. "Measles" in *The Global Epidemiology of Infectious Diseases*. Murray C. J. L., Lopez A. D., Mathers C.D. (ed.). Geneva: WHO.

Desjardins B. 1996. "Demographic aspects of the 1702-1703 smallpox epidemic in the St-Lawrence valley". *Canadian Studies in Population* 270: 49-67.

Dollimore N., Cutts F., Binka F. N., Ross D. A., Morris S. S., Smith P. G. 1997. "Measles incidence, case fatality, and delayed mortality in children with or without vitamin A supplementation in rural Ghana". *American Journal of Epidemiology* 146: 646-654.

Duffy J. 1953. *Epidemics in Colonial America*. Baton Rouge: Louisiana State University Press.

Elandt-Johnson R. C., Johnson N. L. 1980. *Survival Models and Data Analysis*. New York: John Wiley and Sons.

Esteve J., Benhamou E., Raymond L.1994. *Statistical Methods in Cancer Research. Vol. IV. Descriptive Epidemiology* (IARC Scientific Publication No. 128). Lyon: IARC Press.

Garenne M., Aaby P. 1990. "Patterns of exposure and measles mortality in Senegal". *Journal of Infectious Diseases* 16: 1088-1094.

Hull F. 1988. "Increased measles mortality in households with multiple cases in the Gambia, 1981". *Review of Infectious Diseases* 10: 463-467.

Hull H. F., Williams P. J., Oldfield F. 1983. “Measles mortality and vaccine efficacy in rural West Africa”. *Lancet* i: 972-975.

Joshi A. B., Luman E. T., Nandy R., Subedi B. K., Jayantha B. L., Liyanaga J.B., Wierzbat F. 2009. “Measles deaths in Nepal: estimating the national case-fatality ratio”. *Bulletin of the World Health Organization* 87: 456-465.

Koenig M. A., Bishai D., Khan M. A. 2001. Health interventions and health equity: the example of measles vaccination in Bangladesh. *Population Development Review* 27:283–302.

Légaré J. 1988. “A population register for Canada under the French regime: Context, scope, content, and applications”. *Canadian Studies in Population* 15: 1-16.

Mazan R., Gagnon A., Desjardins B. 2009. “The measles epidemic of 1714-1715 in New France”. *Canadian Studies in Population* 36: 295-323.

Murray G. D., Cliff A. D. 1977. “A stochastic model for measles epidemics in a multi-region setting”. *Transactions of the Institute of British Geographers* 2: 158-174.

Namboodiri K., Suchindran C. M. 1987. *Life Table Techniques and Their Applications*. San Diego, Academic Press.

Perry R. T., Halsey N. A. 2004. “The clinical significance of measles: A review”. *The Journal of Infectious Diseases* 189(Suppl 1): S4-S16.

Singer J. D., Willett J. B., 2003, *Applied Longitudinal Data Analysis: Modeling Change and Event Occurrence*. New York, Oxford University Press.

Chapter 5

Conclusion

5.1. General Findings and Themes

The objectives of the dissertation were to address three research problems: 1) the use of life table methods to explore the general dynamics of the measles epidemic – origin, spread, duration and severity; 2) the identification of exposed individuals and an assessment of risk factors specific to measles at the individual level and; 3) a follow-up of the exposed cohort to analyze post-measles mortality. The first study was conducted at the aggregate level, while the second study shifted the focus to a cross-sectional analysis of the exposed children. The third study dealt with time to event data at the individual level to conduct a follow-up study of the exposed cohort.

Many interesting findings were generated from the three studies. Some agreed with modern studies, while others were unique to pre-industrial Quebec. In this section, I highlight the most important of these findings and discuss the hypotheses regarding the risk factors that impacted the French Canadian children during and after the epidemic.

In Chapter 2, we examined the general dynamics of the measles epidemic to set the stage for the following two studies. A few main results are worth reporting again. Most of the victims were infants and young children and girls were at a slightly higher risk of dying than boys. Infant measles mortality was similar in Montreal and Quebec City (197.9 and 194.3 per thousand, respectively). One of the important aspects generated from the regional analysis was it helped identify Eastern Quebec as the hardest hit region, where,

as it turned out, poor harvests were repeatedly reported between 1714 and 1717 (Crowley, 1991).

We suspected that the regional variation in mortality reflected an interaction between the age at infection and food shortages or Vitamin A deficiency. The higher measles death rate among toddlers and older children in the East may have stemmed at least partly from malnutrition in those areas. Children over age 1 tend to be sensitive to food shortages, as they depend more on solid foods and their immune systems are not completely developed (Palloni, 1990). As both measles and malnutrition suppress the immune system, it is expected that toddlers and older children were at an increased risk of dying during and after the epidemic.

We assumed that infants, on the other hand, were less affected during food shortages because they depend on breast milk and may incur some general protection from infections. However, the 1714 epidemic was the first confirmed measles epidemic in the colony. As such, most if not all of the inhabitants would have had no prior exposure. This would also be an indication that placental transferred measles antibodies were probably lacking in infants, as most if not all of the mothers also had no prior exposure (Black, 1982). Indeed, we found that infants appeared to have incurred little protection from the virus, as mortality was well above normal across the colony. In turn, the high infant mortality level brings further evidence that the 1714 epidemic was the first Measles epidemic.

In Chapter 3, I identified measles specific-risk factors among children under age 5 during the acute episode of the epidemic. Similar to Chapter 2, the age at infection and the region of residence had a strong influence on the odds of death during the acute phase of the epidemic. Exposed toddlers were especially disadvantaged in this regard. These findings helped confirm that nutritional status was playing a large role in influencing the fate of many children during that time. In studies on intensive measles exposure, the importance of malnutrition was underestimated (Aaby, 1984; 1988). However, I would express reservations given the clear regional differences in the first two studies. If malnutrition played a limited role, I would have expected the mortality levels of children over age 1 to be virtually the same throughout the affected parishes.

I now turn to familial factors that also point to the importance of nutritional status. Many modern studies have found that children in crowded households are at an increased risk of dying (Koster, 1988). In contrast, I found that singletons or children with fewer siblings were to the contrary, more likely to die than children belonging to larger sibships during the acute phase. In the context of a natural fertility population, a small family is usually young and recently formed. Larger (older) families were wealthier than smaller (younger) families who were just starting to have children. In pre-industrial Quebec, these larger well-established families would have a greater access to resources and occupy the more fertile lands, as many had been established for at least two or three generations (Mazan and Gagnon, 2007).

Mutual aid among kin in these large and well-established families may have acted as a buffer against food shortages during times of poor harvests (e.g., improved access to

resources). This line of reasoning was further supported when it was found that children with fathers or both parents who were immigrants also had higher odds of death during the acute phase of the epidemic. I believe that the increased odds of death among these children reflects differences in socio-economic status (e.g., access to resources), as well as, the lack of support from an extended kinship, which may be critical during a crisis situation.

In addition to the above assumptions, I also argue that many of the immigrant parents and small (young) families were in the early to mid-stages of developing the land for subsistence farming. It would take at least five years to develop the land to make it suitable for subsistence living (Greer, 1997). As such, many of these families could have been at a stage where the farm was already producing limited quantities of food when the poor harvests began and the epidemic struck the colony. These circumstances alone could have been enough to weaken the children and make them at a higher risk of dying from measles.

Surprisingly, the immigrant status of the parents was not significant after the measles epidemic, but then reached significance again during the subsequent outbreak of influenza in late-1716. The non-significant difference could have been due to the smaller number of events during the follow-up period, but there could be other explanations for this pattern. I hypothesized that the return of the significant difference confirmed the importance of varying levels of socio-economic status, mutual support and access to resources during crisis situations. These social factors may only come into effect when there is a sudden crisis (i.e., an epidemic) that would put this group at a greater disadvantage. This

hypothesis finds support in the fact that there was no mortality difference between children with and without immigrant parents during normal periods. Therefore, social factors acting to affect nutritional status are more likely to come into play when there is a sudden crisis in the population.

During a sudden crisis, the most severely malnourished and immune compromised children were eliminated quickly during the acute phase. The children who survived were probably at least somewhat better-off in terms of social standing. It then makes sense that the significance of the above factors related to social differences disappeared during the post-measles phase. However, the surviving children were probably still frail and highly susceptible to developing secondary infections in the months following infection, regardless of the region of residence, the size of their families or parental background. In that regard, I would have to agree that 'measles exposure itself' is a critical factor of long-term mortality in the absence of modern treatments (Aaby et al., 1996). The age at infection and associated physiological aspects of the disease (e.g., prolonged immune suppression and growth faltering) must have been one of the more dominant factors of long-term mortality.

I now review the impact of sibship composition and its relationship to intensive exposure in the household. The death of a sibling and the age difference between siblings were both significant risk factors of acute and delayed mortality in Chapters 3 and 4, respectively. As both factors had little effect on survival in the normal periods, they reflected the severity of measles in the family through intensive exposure between an index and multiple secondary cases. The main reason for this belief is that the death of a sibling was

significant regardless of the age at infection, the sex of the child or the region of residence. This assumption is also supported by findings from modern studies, which consistently report higher acute and delayed measles mortality among secondary cases (Aaby et al., 1984; Aaby, 1988; Koster, 1988; Garenne and Aaby, 1990). The severity of measles in a family indicates a higher prolonged dosage suppressed immune functioning to a point where these children had a little resistance to secondary infections for up to several months after exposure.

The effect of the age difference between siblings was not so straightforward during the acute and delayed phases. In Chapter 3, children with older siblings (i.e., larger age difference) had higher odds of dying. Based on findings from modern studies, I assumed that older children (index cases) were introducing measles into the home and exposing their younger siblings to secondary, more intensive infection (Pison et al., 1992; Perry and Halsey, 2004). In contrast to what occurred during the acute phase, however, exposed children who had siblings closer in age had a higher risk of dying during the follow-up period. As in the acute phase, this pattern may also reflect severe measles stemming from malnutrition and/or intensive exposure. Alternatively, siblings closer in age may have higher long-term mortality because they had to compete with their sick siblings for care from their parents. Studies in Bangladesh have found that mortality was higher among siblings who received less care (Hull, 1988).

In my opinion, the most interesting finding was the sex-differential in mortality among exposed children. As noted in Chapter 2, we found that females exposed during infancy and at age 5 and over were more likely to have died from the virus. Higher mortality

among older girls may have some relation with the age difference between siblings. This observation is part of a new endeavour and was not specified in the previous chapters. In future research, I will test the hypothesis that older girls were at an increased risk because they were helping their mothers care for their younger infected siblings. Helping with childcare would increase their risk of becoming intensively exposed (if they were secondary cases). At this point, the number of events was too small to assess this effect.

The sex difference in mortality was also apparent in the post-measles study. The most interesting aspect was that only exposed infant girls had higher long-term mortality. The differential also extended to the flu epidemic in late 1716. To help explain the early life difference, I drew an analogy from a series of immunization studies that found long-term mortality was higher among infant girls administered a high-titre vaccine at age 4 to 6 months (i.e., a strain with a higher dosage of the virus) in comparison with females given a standard medium-titre vaccine (Aaby et al., 1995).

The adverse effects of the higher dose vaccine appeared to react similarly to intensive exposure from natural measles in early life (Aaby, 1995). If that was the case, it was intensive exposure in early life that made girls more susceptible to general infections than boys in the long-term. This difference, however, could have also resulted from selection. Males in general have higher infant mortality and perhaps were more selected and less likely to die from measles because the infected ones who survived were more robust than infected girls. Alternatively, higher long-term mortality may reflect preferential treatment of male infants. Perhaps, males were more valued in early French Canadian society and

received better care than females. If any of these situations were the case, male infants had a slight survival advantage over females after measles infection.

5.2. Some Remarks on the Study Designs

There were many challenges faced when working on the research designs. Generally, it was a trial and error process to estimate measles mortality and identify exposed cases. The designs of the studies may seem straightforward and systematic the way they are currently depicted, but this was very difficult to accomplish. I could not find any previous studies to provide much direct help in identifying measles cases or any other type of infectious diseases from parish data. As such, I was left to my own devices to come up with suitable methods to analyze the impact of the measles epidemic.

For the first study, I developed a set of indirect methods to model excess mortality resulting from the epidemic when there was no information on the causes of death. A series of smoothing splines were fit to the time-series data by age, sex and region to estimate normal mortality and life table methods were utilized to partition measles deaths from all other causes. The spline turned out to be a very useful tool because it is non-monotone and could capture the changing slopes in the time-series data. These methods turned out to be very suitable and allowed for a thorough descriptive analysis of the epidemic. The first study provided a benchmark for selecting the study population of the more detailed analyses conducted at the individual level in the following two studies.

The main challenge in the second and third studies was to develop methods to identify exposed children and correctly classify acute and delayed deaths. Identification of

exposed cases was based on the findings from Chapter 2 and included narrowing the focus to the most affected parishes based on spline methods. The date of infection was estimated based on the distribution of deaths during the acute phase (late-August to mid-November) and an average scenario derived from the natural course of measles exposure. The selection methods and findings from the first two studies were expanded to select the follow-up analysis on the exposed cohort who survived the acute phase of infection.

Probably, the most difficult aspect of the study designs in the acute and post-measles studies was to ensure that acute and delayed deaths were classified correctly. I had to switch back and forth between the acute and post-measles designs and apply strict time lines based on the natural course of measles infection to make sure that there was limited false classification of deaths. This was a long process, requiring many graphical analyses of death distributions and generally going through each death in the parish data to determine whether they died during the acute or post-measles phase. The estimated date of infection and average scenario that I developed simplified the process. After much trial and error, I am sure that much of the overlap between them has been removed. In sum, I believe that the study designs are well suited to analyze the general and detailed impacts of an epidemic. However, these methods require further testing on other epidemics to ensure that they are valid. One of my plans for the future will be to apply these methods to other epidemics in order to refine them and make them a standard tool for analyzing epidemics from the parish data.

5.3. Closing Remarks, Policy Implications and Future Directions

This dissertation has shown that the parish data contains valuable information on epidemics in historical Quebec. I conducted three very thorough analyses on the impact that measles had on French Canadian children. Given the results of these studies, I would have to conclude that measles infection in those times surely did not appear 'beneficial' to any child having to face such a crisis. Most did survive the acute phase, but they still had a higher risk of death after the epidemic. The poor crops reported during the same time surely did not help matters either. It appears that these children were dealt a double blow and all they had at their disposal was traditional knowledge to deal with the situation at hand.

The major benefit of the historical data is that I was able to analyze the epidemic in a natural and pure state without interference from modern medical advancements. Most of the modern studies that took place from the late 1970s onwards were conducted when immunization coverage, effective treatments, access to medical care, public health knowledge and socio-economic status were improving in parts of those developing countries. The general improvements in health care over time may be a probable reason for the contradictory results in those studies, especially in regards to nutrition and long-term mortality. The point is, however, that those studies did not control for general improvements in medicine and effective treatment during an outbreak. It can be easily assumed that the children in those studies were given some form of treatment (e.g., Vitamin A or antibiotics) while they were infected with measles. In turn, these treatments could have buffered out the effects of such factors and nutrition and prolonged immune

suppression. Surely, these modern interventions improved the survival outcome of those children during and after infection.

These historical studies even have policy implications in modern times. First, it has been demonstrated that malnutrition played an important role in influencing the levels of measles mortality. Malnutrition has been generally accepted an important risk factor, but the effects are not always apparent (Clements and Hussey, 2004; Perry and Halsey, 2004). The effect of malnutrition on measles mortality in modern studies may be masked by modern methods of treatment. Therefore, the findings generated from my historical studies can be used to inform policy among health workers to make them aware of the potential consequences among malnourished children infected with measles. Second, the findings relating to factors such as sex differences in long-term mortality (particularly, among exposed infant girls) can also add valuable knowledge to complement modern studies, which are often limited by a small numbers of events. If this type of study was conducted before the WHO began administering the high-titre measles vaccine among infants aged 4 to 6 months, many needless females deaths could have been avoided. The findings from these studies clearly show that historical data can be beneficial to filling in gaps in modern knowledge, as well.

There are many potential studies that can be conducted from the parish data. Regardless of the limitations mentioned throughout the chapters, the historical studies generated comparable findings to the modern measles studies. Given that the modern and historical studies show comparable results, further investigations are warranted on the effects of subsequent measles and other epidemics that entered the colony. To validate these studies

further, they need to be replicated by analyzing the parish data on other measles outbreaks. As yet to be confirmed, the next measles epidemic occurred in 1729. If the 1729 epidemic can be confirmed as measles, the next step would be to replicate the three studies by analyzing data on that particular time period.

The methods developed for these studies are general and can be applied to examine other types of infectious diseases such as, smallpox or typhus. These types of studies will allow for comparisons to be drawn between the effects of measles and the other infections that ravaged the colony during 18th century. Comparative studies on different types of infectious diseases may shed some light on whether the risk factors were specific to measles infection or were general risk factors that also applied to other infections. Further replication and comparative studies would allow for more solid conclusions and help to better understand the childhood effects of infectious diseases during the pre-industrial era.

5.4. References

Aaby P., Samb B., Anderson M., Simondon F. 1996. "No long-term excess mortality after measles infection: A community study". *American Journal of Epidemiology* 143: 1035-1041.

Aaby P., Samb B., Simondon F., Seck A.M., Knudsen K., Whittle H. 1995. Non-specific beneficial effect of measles immunisation: analysis of mortality studies from developing countries. *British Medical Journal* 311:481-485.

Aaby P. 1995. "Assumptions and contradictions in measles and measles immunization research: Is measles good for something?". *Social Science and Medicine* 5: 673-686.

Aaby P. 1988. "Malnutrition and overcrowding/intensive exposure in severe measles infection: Review of community studies". *Review of Infectious Diseases* 10: 478-491.

Aaby P., Bukh J., Lisse I. M., Smits A. J. 1984. "Overcrowding and intensive exposure as

determinants of measles mortality". *American Journal of Epidemiology* 120: 49 63.

Black F. L. 1982. "The role of herd immunity in control of measles". *The Yale Journal of Biology and Medicine* 55: 351-360.

Clements C. J., Hussey G. D. 2004. "Measles" in *The Global Epidemiology of Infectious Diseases*. Murray C. J. L., Lopez A. D., Mathers C.D. (ed.). Geneva: WHO.

Crowley T., 1991, "Violence and protest", in *Economy and society during the French regime, to 1759,* Cross M. S., Kealey G. S., (ed.). Toronto, McClelland and Stewart, pp. 120-151.

Garenne M., Aaby P. 1990. "Patterns of exposure and measles mortality in Senegal". *The Journal of Infectious Diseases* 16: 1088-1094.

Hull F. 1988. "Increased measles mortality in households with multiple cases in the Gambia, 1981". *Review of Infectious Diseases* 10: 463-467.

Koster F. 1988. "Mortality among primary and secondary cases of measles in Bangladesh". *Review of Infectious Diseases* 10: 471-473.

Mazan R., Gagnon A. 2007. Familial and Environmental Influences on Longevity in Historical Quebec. *Population* 62: 271-291.

Palloni A. 1990. "Assessing the levels and impact of mortality in crisis situations" in *Measurement and Analysis of Mortality: New Approaches*. Vallin J., D'Souza S., Palloni A. (ed.). Oxford: Clarendon Press, pp. 195-228.

Perry R. T., Halsey N. A. 2004. "The clinical significance of measles: A review". *The Journal of Infectious Diseases* 189(Suppl 1): S4-S16

Curriculum Vitae

Name: Ryan M. Mazan

Education:

PhD (Sociology)	Department of Sociology, University of Western Ontario 2011
MA (Sociology)	Department of Sociology & Anthropology, Carleton University 2003
BA (Sociology)	Department of Sociology, University of Manitoba 2001

Area of Specialization:

Demography with a special interest in epidemics, population health, morbidity, mortality, medical sociology, historical demography, statistical analysis and quantitative methods.

Major Awards:

Ontario Graduate Scholarship (OGS); 2004-2005, 2005-2006

Western Graduate Research Scholarship (WGRS); 2005-2006, 2006-2007

President's Scholarship for Graduate Study (PSGS); 2003-2004

Research/Work Experience:

Social/Demographic Statistician, NWT Bureau of Statistics, Government of the Northwest Territories; 02/2010-Present
(Population Estimates and Projections; Vital Statistics; Census; Health and Social Data)

Senior Health Analyst: Social Demographics, Department of Health & Social Services, Government of the Northwest Territories; 02/2007-01/2010
(Statistical analysis of health related data; writing reports)

Research Assistant, Institute for Circumpolar Health Research; 10/2008-Present
(Arthritis in Northern Canada)

Research Assistant, Department of Sociology, University of Western Ontario; 04/2005-Present

(Longevity, Maternal mortality/Child Survival, Epidemics in Historical Quebec)

Instructor, Department of Sociology, University of Western Ontario; 09/2006-12/2006
(Teaching Social Statistics (SOC 205a-004) During the Fall-Term)

Teaching Assistant, Department of Sociology, University of Western Ontario; 09/2003-04/2006
(Introductory Sociology, Advanced Statistics, Quantitative Research Methods)

Teaching Assistant, Department of Sociology & Anthropology, Carleton University; 2001-2003 (Social Statistics)

Publications:

Articles in Refereed Journals:

MAZAN, Ryan, Alain GAGNON and Bertrand DESJARDINS. 2009. The Measles Epidemic of 1714- 1715 in New France. *Canadian Studies in Population*, 36:295-319.

GAGNON, Alain and Ryan MAZAN. 2009. Does exposure to infectious diseases in infancy affect old-age mortality? Evidence from a pre-industrial population. *Social Science & Medicine*, 68: 1609-1616.

SMITH, Ken R., Alain GAGNON, Richard M CAWTHON, Geri MINEAU, Ryan MAZAN, and Bertrand DESJARDINS. 2009. Familial Aggregation of Survival and Late Female Reproduction. *Journal of Gerontology: Biological Sciences*, 64A: 740–744.

DAVIS, Christopher G., Gerald THOMAS, Rebecca JESSEMAN, Ryan MAZAN. 2009. Drawing the line on risky use of cannabis: Assessing problematic use with the ASSIST. *Addiction Research & Theory*, 17: 322-332.

MAZAN, Ryan & Alain GAGNON. 2007. Familial and Environmental Influences on Longevity in Historical Quebec. *Population*, 62: 271-291.

Chapters in Books:

GAGNON, Alain, Ryan MAZAN, Bertrand DESJARDINS, and Ken R. SMITH. 2008. Post-reproductive longevity in a natural fertility population. In *Kinship and Demographic Behavior in the Past*, Editor(s): Tommy Bengtsson and Geraldine P. Mineau. IUSSP/Springer Press.

Technical Papers:

Ken Smith, Alain Gagnon, Richard Cawthon, Geraldine Mineau, Richard Kerber, Ryan Mazan, Elizabeth O'Brien, and Bertrand Desjardins. 2008. Familial Aggregation

in Longevity and Late Reproduction. Discussion Paper No. 07-03. Population Studies Centre, UWO. http://sociology.uwo.ca/popstudies/dp/dp07-03.pdf.

Alain Gagnon & Ryan Mazan. 2006. Influences of early life conditions on old age mortality in old Québec. Discussion Paper No. 06-05. Population Studies Centre, UWO. http://sociology.uwo.ca/popstudies/dp/dp06-05.pdf.

Ryan Mazan & Alain Gagnon. 2005. Familial and Environmental Influences on Longevity in a Pre-Industrial Population. Discussion Paper No. 05-05. Population Studies Centre, UWO. http://sociology.uwo.ca/popstudies/dp/dp05-05.pdf.

Alain Gagnon, Ryan Mazan & Ken R. Smith. 2005. Post-Reproductive Longevity in a Natural Fertility Population. Discussion Paper No. 05-04. Population Studies Centre, UWO. http://sociology.uwo.ca/popstudies/dp/dp05-04.pdf.

Papers in Submission:

MAZAN, Ryan. 2010. Risk factors of mortality among French Canadian children during the measles epidemic of 1714-15. *Genus*; Revised and Resubmitted.

Papers Presented:

Ryan Mazan. Delayed measles mortality among exposed children who survived the epidemic of 1714-15 in New France. June, 2010. Presented at the Congress of the Humanity and Social Sciences, Concordia University, Montreal QC.

Ryan Mazan. Risk Factors of mortality among French Canadian children during the measles epidemic of 1714-15. October, 2009. Presented at the XXVI IUSSP International Population Conference, Marrakech, Morocco.

Ryan Mazan. Mortality of French Canadian families during the measles epidemic of 1714-15. June, 2008. Presented at the Congress of the Humanity and Social Sciences, UBC, Vancouver BC.

Ryan Mazan, Alain Gagnon & Bertrand Desjardins. The Measles Epidemic of 1714-1715 in New France. May, 2007. Presented at the *XIVème COLLOQUE NATIONAL DE DEMOGRAPHIE* (CUDEP), Bordeaux, France.

Alain Gagnon & Ryan Mazan. Influences of early life conditions on old age mortality in old Québec. June, 2006. Presented at the IUSSP Scientific Committee on Historical Demography: "Early-life conditions, social mobility and other factors that influence survival to old age", Lund University, Lund, Sweden.

Ryan Mazan. Estimating and Explaining Adult Mortality in Colombia: The Post War Years (1954-2001). June, 2006. Presented at the Congress of the Humanity and Social Sciences, York University, Toronto ON.

Alain Gagnon, Ryan Mazan, Bertrand Desjardins & Ken R. Smith. Post-Reproductive Longevity in a Natural Fertility Population. October, 2005. Presented at the International Seminar on Kinship and Demographic Behaviour (IUSSP Scientific Committee on Historical Demography), University of Utah, Salt Lake City.

Ryan Mazan & Alain Gagnon. Sibling Survivorship and Familial Longevity in 17th and 18th Century Quebec. June, 2005. Presented at the Congress of the Humanity and Social Sciences, UWO, London ON.

Membership of Professional Associations:

Canadian Population Society (CPS)
International Union for the Scientific Study of Population (IUSSP)
Population Association of America (PAA)