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

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INTRODUCTION

It has been estimated that 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 First study; Mazan et al., 2009). A problem with the Quebec data was that parish clergy did not record the cause of death at the time, so there was no know exact method to determine who died from measles during the epidemic. However, we utilized a set of methods to follow 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 trace the origin, spread, duration and severity of the epidemic.

It was found that the epidemic originated in Western New France during the 2nd quarter of 1714 (in late March). By the 3rd quarter (around September), the epidemic had spread to all parts of the colony and had run its course by the 2nd quarter of 1715. The epidemic was quite severe among children under 15 years of age, but severity declined with age and varied by sex and region. Children in the East 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 risk factors associated with measles mortality at the individual level.

In the second study of this series, I examined the risk factors of measles mortality among children under 5 years of age during the acute episode of the epidemic (mid-August to mid-November of 1714). To alleviate the problem of not having cause of death data, to some extent, I applied stringent selection criteria and a crude method that consisted of comparing a risk model applied to the epidemic data with the same model applied to control groups living under normal mortality conditions (i.e. a form of validation). Although there was no way to distinguish between measles and non-measles deaths, these methods helped to identify the possible role that demographic and familial risk factors played during the measles epidemic. Many interesting ideas about the disease process were generated and I was able to find some general similarities and differences with historical and modern studies conducted in other populations. Important risk factors included the age at the time of the epidemic, death of a sibling(s) in the family, immigration status of the parents, age difference from siblings, sibship size and the region of residence.

These 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. Measles has been associated with delayed mortality after the acute phase of infection (Aaby et. al, 1996). Several studies from West Africa have found that there was an increased risk of death after exposure to the virus. The period of susceptibility is believed to last for several weeks to months after the onset of rash and is attributed to a prolonged state of immune suppression. This is characterized by a failure to thrive (i.e. underweight), recurrent infections, persistent pneumonia and diarrhoea. Vitamin A deficiency tends to aggravate these problems (Aaby and Clements 1989; Hull et al., 1983; 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 infants than for older children. 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 follow-up period (Aaby et al., 1990; 1993; Aaby, 1995). They found that this effect occurred to both infants with and without clinical measles. In addition, the delayed impact lasted for up to 3 years past initial measles exposure.

Children under 6 months of age tend to be protected against measles infection due to maternal antibodies if their mothers have acquired immunity to the virus. It was assumed that if infants contract measles after intensive exposure from an older sibling, acute infection is usually less severe. In turn, these exposed infants would have a relatively high recovery rate after the initial infection (Aaby et. al, 1996). However, the studies from Guinea-Bissau suggest that exposure to measles before 6 months may be an important risk factor for mortality after 6 months of age. Aaby et al. (1995) indicate that little is known about delayed mortality after acute measles infection, the possible confounding factors, its determinants and underlying mechanisms. Intensive exposure and high dose of infection may be important to the disease process. Children who were exposed to measles before 6 months of age are most likely to have been exposed intensively at home through an older sibling (Garenne and Aaby, 1989). It was assumed that secondary cases probably receive a high dose of the measles virus, which may induce latent infection and growth faltering (i.e. the failure to thrive).

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. In the above studies, the difference in mortality between exposed children and controls remained equally strong when socio-economic, demographic and cultural background factors were taken into consideration.

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). Aaby (1995) indicated, that previous studies might have ‘exaggerated’ the delayed effect of measles, as some of those studies compared post-measles cases with immunized children, rather than with unimmunized and unexposed children. Contrary to the negative impact, they believed that children who survived the acute phase of infection might incur a survival advantage compared with unimmunized, unexposed children. As such, they postulated that both natural measles and immunization may be associated with ‘non-specific beneficial effects’, presumably due to immunological stimulation. 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 earlier studies, they found 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 indicated that the results of those studies are not conclusive (Perry and Halsey, 2004).

The historical data from Quebec provides a suitable context to examine the above assumptions on the delayed mortality effect of measles infection. At the time of the study, social and environmental conditions were mostly homogeneous and benefited the majority of inhabitants. A typical family had a large number of young children living in the household and thus, a highly susceptible host population. Further, this was possibly only the second known measles epidemic in the colony. Some text discuss a measles epidemic that occurred in Colonial America in 1687 or 27 years earlier (Duffy, 1953). There was an epidemic in New France at the same time, but that one was originally assumed to be typhus. Further analysis is needed to confirm the type of epidemic in the future.

The limited prior exposure would put the colony at a great disadvantage, as the Canadian born children probably had no acquired immunity to the virus. This also means that there were enough deaths to generate a large number of exposed children. Most of those studies were based on a small number of subjects, making the reliability of their parameter estimates uncertain at times. More importantly, measles immunization was a long way off and modern public health knowledge did not exist. As such, the measles virus could be considered to have occurred in a natural habitat with no interference from modern medicine and public health knowledge. As such, historical Quebec provides an ideal setting to study the delayed effects of mortality, as Aaby et al. (1995) indicated - 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.

Considering the above issues, this study explores the assumptions made about the delayed mortality associated with measles infection for children exposed before 5 years of age. This study also builds upon the previous two studies on measles in New France and extends the selection and estimation methods to help determine the exposed cohort and to estimate the time of infection. 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, I examine whether exposed children had a different survival outcome, as compared to an unexposed cohort, while controlling potential confounding effects such as, age at infection, sex, urban/rural residence and sibship composition.

DATA AND METHODS

The data used in this follow-up study is taken 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 elsewhere, 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 that lived in the Saint-Lawrence Valley during 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.

Study Population

As mentioned above, the study of epidemics in New France poses a challenge because parish clergy did not record measles cases/deaths during those times. Not knowing who was infected makes it difficult to distinguish between the effects of measles and other causes of death. As such, I had to develop a suitable selection method when exposure data is lacking. Based on the previous study, a method to estimate exposure during the epidemic is to maximize the chance of selecting individuals who were exposed to the virus. Generally, the first part of the selection process is a continuation from the preceding study. Based on several selection criteria developed in that study, I selected Canadian born children under 5 years of age at the time of the epidemic who were likely exposed between late-August and mid- November of 1714 in the most severely affected parishes (see the preceding article for a full description of the selection methods).

The sharp autumn peak of the epidemic was used to approximate the individuals who were believed to have died during the acute phase of infection. It was assumed that the majority of acute deaths probably took place during that time, as death rates were at their peak. This was achieved by selecting parishes with the largest residual difference between the observed and expected values of a smoothing spline fit through a time-series of mortality rates (see the First study for a description of the method). A larger than normal level of mortality probably indicates that a large proportion of excess deaths may have been due to the measles virus. There were 24 parishes that fit this criterion and selected for the study. As measles is highly infectious, up to 99% of susceptibles would contract the virus after first contact with an infected person (Murray and Cliff, 1977). Given the highly infectious nature of the virus and that none of the children had any known prior exposure, it is possible that the vast majority of children were infected within a given family or parish. For simplicity, it was assumed that all children were infected in the selected parishes.

The next step in selecting children for this study 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). As such, delayed mortality is defined as a death that takes place at least 30 days after the appearance of the measles rash. The problem is that we do not know the precise time when these children were infected. However, based on the following observations, we can still approximate the general time when the infection began on region by region basis.

Since we don’t know exactly when exposure occurred, the timeline for the date of infection was derived from an average scenario based on the natural course of measles. The incubation period for measles lasts from 8 to 12 days before the onset of signs and symptoms and the measles rash the rash appears from 12 to 14 days after initial exposure to measles. 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 estimated time at infection in this study 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.

The date of infection was estimated using children who died during the acute episode from late-August to mid-November of 1714 (as determined by the previous study). Not much literature exists on the time from infection until death, but one study found that most acute deaths occurred within 1 to 2 weeks from onset of the measles rash (Joshi et al., 2009). As such, a two-week lag period was applied when estimating the time from infection until death. For example, if an individual died in the 38th week of 1714, they were assumed to have developed the rash 2 weeks prior to the time of death. In this case, the time at infection (measles rash) was estimated to have occurred during the 36th week of 1714.

The surviving family members were assumed to have been infected around the same time, so they were also assigned the same time of infection as their dead sibling. It was assumed that a death in the family was a good indication that all family members were exposed. Neonatal deaths were excluded from this process. They appeared more resistant to death from measles in the population based study (see the First study; Mazan et al., 2009). To estimate the age at infection for families with no deaths during the acute episode, the average time of infection was estimated for each region based on the individuals who died during the acute phase. These children were assigned a regional age at infection, as they were assumed to be infected around the same time as families with a dead sibling in a given region.

As such, a child had to survive at least 30 days past the familial date of onset and the death of the sibling to be considered to have died from delayed measles mortality. Upon further analysis, an additional 2 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 classification of a delayed death to 43 days past the estimated date of infection. The penalty was applied to reduce the likelihood of a false positive classification, as estimation is based on an average scenario. There may be large error for some cases, if they were actually infected at a much earlier or later time than what was estimated.

Based on the above selection criteria, the cohort of children exposed before 5 years of age could have entered the study between early-August and the end of October of 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. 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. The 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 (see the Results section for a more detailed discussion of the subsequent epidemic).

I also used the same criteria to select unexposed cohorts (1708 and 1721) living through periods with no known epidemic, as a basis of comparison. In order to facilitate comparisons and stabilize estimates, the 1708 and 1721 cohorts were combined. 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 the previous study. This is a common problem in this type of study (variance increases with age). Although the number of events was small and it created

limits on the number of controls used or parameters estimated, the estimates were stable in most circumstances.

In addition, the two unexposed cohorts had a similar survival outcome over the course of the follow- up period. There were no significant differences in survival by age and sex. The 1721 cohort had a higher level of infant mortality than the 1708 cohort, as the level began increasing in Montreal after the measles epidemic (see the First study). However, the difference was not significant. Otherwise, mortality was generally stable during that time in history. As such, selecting the cohorts before and after the epidemic provides a more conservative comparison, as it accounts for the increasing level of infant mortality. The exposed cohort was also tested against other cohorts besides the one used in the study (not shown here). In those instances, the effects were the same or even became stronger. The unexposed cohorts selected for the study represented typical mortality conditions for that time – they had the smallest residual difference between the observed and expected values of a spline fit through mortality times-series data by age, sex and region. The unexposed cohort was assigned the same regional age at infection as the exposed cohort and was also followed over a 25 month period (N = 3,999).

Risk Factors

For this study, the same controls were used from the previous study on the risk factors associated with acute measles mortality (see the Second article 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 in the normal periods. In this case, there were fewer events (deaths) during the follow-up than in the acute episode. As such, the categories of the controls were collapsed to lessen the number of parameters to be estimated in the multivariate models. Although there is some loss of information by collapsing categories, the trade-off is the model estimates are more stable by having fewer parameters.

The region of residence at the time of the epidemic was included to capture urban/rural differences in mortality. Children residing in the rural areas served as the reference category. 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 (<11 months). Models were also run using each age group individually to find whether exposed children at different ages had higher or the same mortality as the unexposed cohort.

To account for sex differences in mortality, the sex of the child was also included as a risk factor in the models. Females served as the reference category. In this case, as well, some models were run individually for each of the sexes to see if the cohort effect was different for the exposed males 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 to the post-measles period. Immigrant status of parents was divided into 2 groups: Canadian born and either/both parent(s). Canadian born parents served as the reference category.

The sibling composition controls include the age difference from 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 the virus into the household. 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 may reflect the incidence of multiple and secondary cases in a given family. As mentioned elsewhere, this measure may be a good alternative when that type of information is lacking, as in this study. 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. If there is a death in the family, then it could be an indication of multiple cases in the household. No dead siblings during the given period served as the reference group. Table 1 summarizes the coding of the controls and gives the number of families in each category for the Cox proportional hazards models.

Table 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)
	N	N	N
Total	3,552	1,071	2,468
Cohort			
Exposed	1,071	-	-
Unexposed†	2,481		
Residence			
Urban	1,081	309	772
Rural†	2,438	742	1,696
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
None[†]	3,335	959	2,376

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

Life Tables and Cox proportional hazards models

The statistical models used in this study are the same as the ones used in the 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 life tables. The life table takes on the general form:

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

where q_x is the probability of dying in the interval x to x + n, d_x is the number dying in the interval x to x + n, N_x is the size of the cohort and the conditional probability of surviving in the interval x to x + n (p_x) is the reciprocal of q_x. Mantel-Haenszel (M-H) hazards ratios and significance tests were used to compare the life table survival curves of the exposed and unexposed cohorts (see Breslow and Day, 1987; Esteve and Raymond, 1994 for a formal treatment of the M-H procedure).

For the multivariate models, a series of Cox regression models were fit, 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):

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

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[1]. Since the data contains correlated observations or the possibility of temporal dependence among groups of individuals (e.g. siblings), we also ran the same models with robust variance estimation. This procedure

[1] 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.

involves relaxing the temporal independence assumption by accounting for the clustering of observations. Cases were clustered by the mother.

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 from the exposed and unexposed cohorts survived the follow-up period. However, the risk of death for the exposed cohort was higher during that time.

Life Tables

Table 2 gives the summary statistics for the 2-year follow-up life tables of 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 probability of dying within the 2-year follow-up period declined with age for both cohorts. This pattern is expected, as the pattern follows the empirical age pattern of mortality at the younger ages. For instance, 13.5% (.135 x 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 the older children who were exposed between 36 and 59 months of age.

Table 2 – Summary statistics of the 2-year follow-up life tables for children exposed to the measles epidemic of 1714 and the unexposed comparison cohorts of 1708 and 1721, New France

	All Children			Males			Females		
Age at Exposure	Probability of dying within the 2-year follow-up period		Mantel-Haenszel Hazard Ratio	Probability of dying within the 2-year follow-up period		Mantel-Haenszel Hazard Ratio	Probability of dying within the 2-year follow-up period		Mantel-Haenszel Hazard Ratio
months	${}_nq_{x(Exposed)}$	${}_nq_{x(Unexposed)}$	HR_{M-H}	${}_nq_{x(Exposed)}$	${}_nq_{x(Unexposed)}$	HR_{M-H}	${}_nq_{x(Exposed)}$	${}_nq_{x(Unexposed)}$	HR_{M-H}
< 11	0.135	0.113	1.29	0.137	0.137	1.01	0.133	0.078	1.76*
12 to 35	0.077	0.036	2.16***	0.089	0.038	2.41***	0.064	0.034	1.91*
36 to 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*

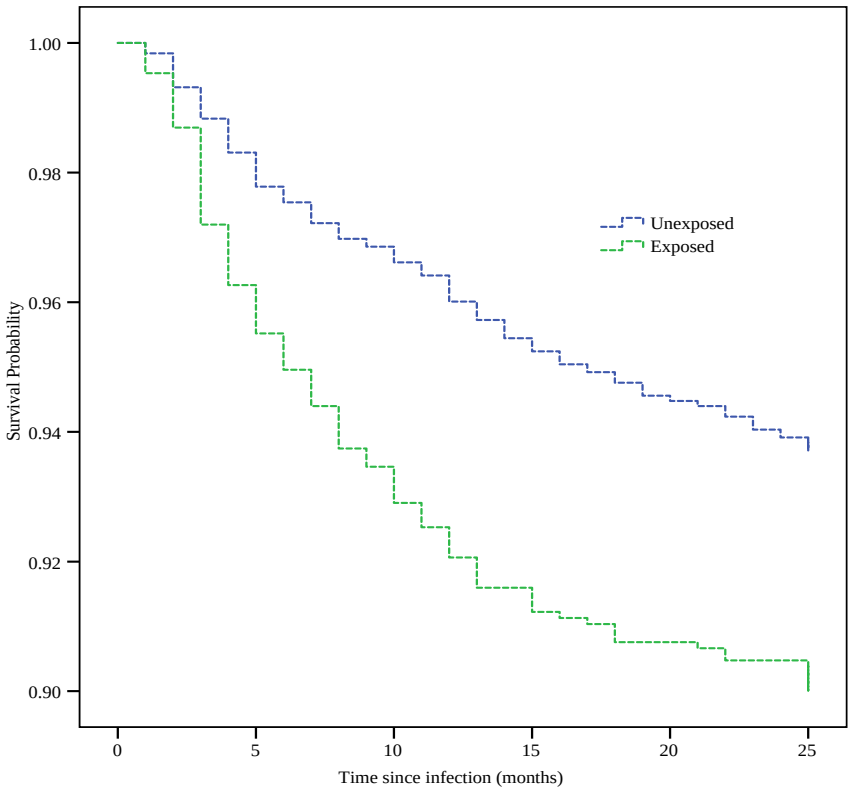
p <.001***, p <.01**, p <.05*
[F] High sampling variability - Number of events was too small to produce reliable estimates.
[a] Adjusted for age at infection/observation.

In terms of statistical tests for cohort differences, children exposed during infancy had a slightly higher probability of dying, but the difference was not significant ($HR_{M-H} = 1.29$, $p > .05$). When looking at the sex-specific risk, the reason for the non-significant effect becomes apparent, as exposed males had the same survival chances as unexposed males (1.01 $p > .05$). Exposed female infants, on the other hand, had significantly higher risk of dying than unexposed females ($HR_{M-H} = 1.76$, $p < .05$). Similarly, females exposed before 6 months of age had a higher risk of dying, where they were 1.77 more likely to die ($p< .05$), as compared to infants born into normal

conditions. Almost a fifth (19.1%) of exposed females died within the 2- year follow-up period, while 11.3% of unexposed females died. These females even had a slightly higher probability of dying than exposed and unexposed males (16.9%; 14.9%). For children exposed as toddlers, the risk of dying was twofold (HR_{MH} = 2.16, p > .001). Both exposed male and female toddlers had a significantly higher risk of death, but the effect was stronger for the males (HR_{MH} = 2.41, p > .001; 1.91, p > .05). 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 younger ages. As such, it was not possible to obtain a reliable estimate for each of the sexes at that age. Given that reliability is a problem with the older children and they had the same mortality as unexposed children, only children exposed before 3 years of age were considered for the overall hazard ratio and later in the multivariate models.

Figure 1 shows the life table survival curves of children exposed before 3 years of age and the comparison cohort. The survival curves clearly demonstrate that exposed children had a poorer survival outcome during the 2-year follow-up period. The sharp decline in survival is most apparent within the first six months after exposure – the pattern looks the same as studies in West Africa (see Aaby et al., 1993). By the second year mortality was approaching normal levels (not visible here because the plot shows cumulative survival). The effect seemed to last slightly longer for exposed infants. After adjusting for age at infection/observation, children exposed before 3 years of age were 1.62 times more likely to die within the 2-year follow-up period than the unexposed cohort (p <.001) .

Figure 1 – Survival curves of exposed and unexposed children before 3 years of age, New France



Proportional hazards Models

Table 3 gives the Hazard ratios (HR) and the robust standard errors (RSE) of the multivariate proportional hazards models (A through C) for the 25 month follow-up data of the exposed (1714) and unexposed cohorts (1708, 1721). Bootstrap hazard ratios (HR_{BS}) are also provided to demonstrate the stability of the parameter estimates and check for bias in the models. To obtain the bootstrap coefficients, I randomly selected 1 child from each family with replacement. The random selection procedure was repeated 100 times. Models A through C include all of the risk factors entered simultaneously. The multivariate models only include children less than 3 years of age as it was shown with the life tables that post measles mortality of older children was not significantly different from mortality levels of the unexposed cohorts. 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 ratios (HR).

Table 3 – Multivariate Cox proportional hazard analysis of the risk of death for the exposed and unexposed cohorts during the 25 month follow-up period, New France

	Model A			Model B			Model C		
	Exposed vs. Unexposed			Exposed (1714)			Unexposed (1708, 1721)		
Risk Factor	N = 3,552			N = 1,071			N = 2,481		
	n_{BS} = 2,591			n_{BS} = 819			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 Exposure									
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
None†												

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

Overall, children who were exposed to measles before 3 years of age had a significantly higher risk of dying within the 2 year follow-up period than the unexposed cohort, while controlling for potential confounding effects (HR = 1.68, p < .001). The hazard ratio for the exposed cohort was slightly attenuated with the introduction of controls. The other covariates in the model are all significant with the exception of the immigrant status of the parents. Although exposed males had a higher risk of death than exposed females, the difference was not significant. As indicated previously, this pattern probably reflects the higher than normal female mortality of the exposed cohort over the 2-year follow-up period. The effect, however, resembled the unexposed cohort, as males were showing a higher risk of death (HR = 1.36, p > .05; 1.59, p < .01).

For the unexposed cohort, the sex differential follows an expected pattern - male children were at a significantly higher risk of dying than female children. the age pattern for the estimated age at infection also resembled the unexposed cohort. Mortality continued to be high for the 12 to 23 month old group, as the risk of death was not significantly different from infants (HR = 0.83, p > .05). This reflects the high risk of death among children exposed between 12 and 23 months of age during the follow-up period. In contrast, the unexposed cohort follows a typical mortality pattern, where risk declined steadily with age. The urban/rural differential had a strong effect on mortality in all of the models. In both models, exposed and unexposed children residing in the urban towns (Montréal and Quebec City) had double the risk of dying within the 2 year follow-up period (HR = 2.19, p < .001; 2.60, p < .001, respectively)[2].

The death of a sibling during the acute phase of the epidemic remained a significant risk factor during the follow-up period, For the exposed cohort, children who had a sibling that died were almost three times more likely to die than children without a death in the family. The difference was not significant for the unexposed group (HR = 2.86, p < .001; 0.92, p >.05). Interestingly, the average age difference from other siblings in the household had the opposite effect from the previous study. To recap, children with older siblings had a higher risk of dying during the acute episode (i.e. the effect possibly reflects the transmission of the virus between index and secondary cases). In this analysis, exposed children with siblings closer in age or less than 4 years apart had almost double the risk of dying in the follow-up period (possibly reflects the intensity of exposure when having multiple secondary cases in the household). The effect follows the same direction for the unexposed cohort, but it was not significant (HR = 1.92, p < .01; 1.10, p >.05).

[2] It should be noted that the regional variation in mortality (i.e. Rural West, Montreal, Quebec City, GQA and Rural East, see the preceding article) disappear during the post-measles period (not shown here). Keep in mind that in the follow-up period there are fewer events, so that in itself, could lead to the diminished significance by spreading the data thin through the use of too many categories. Although regional mortality was not significantly different for the cohort (except for the urban/rural differential), 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).

Table 4 – Multivariate Cox proportional hazard analysis of the risk of death for the exposed and unexposed cohorts during the 25-month follow-up period by age and sex, New France

Age at Infection	Cohort	Model D All Children		Model E Males		Model F Females	
		HR	ASE	HR	ASE	HR	ASE
< 11 months[a]							
	Exposed	1.37	0.173	1.04	0.229	1.84*	0.270
	Unexposed[†]						
12 to 35 months[a]							
	Exposed	2.12***	0.194	2.34**	0.265	1.91*	0.289
	Unexposed[†]						
< 36 months							
	Exposed	1.68***	0.128	1.53*	0.169	1.91**	0.197
	Unexposed[†]						
< 6 months[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, immigration status, age difference between siblings and dead sibling.

Table 4 shows the Hazard ratios (HR) and asymptotic standard errors (ASE) of the multivariate proportional hazards models (D through F) of the 25 month follow-up period for the exposed (1714) and unexposed cohorts (1708, 1721) by the estimated age at infection and sex with the addition of controls. When controlling for potential confounding effects, age and sex specific mortality differences remain similar to the life table models. Overall, both males and females exposed to measles before 3 years of age had a higher risk of dying within the 2 year 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, $p < .01$, HR = 1.53, $p < .05$, respectively).

Children exposed before 1 year of age had an increased risk of death, but the difference was not significant (HR = 1.37, $p > .05$). Females exposed before 1 year of age had a significantly higher risk of dying, while exposed males had the same risk as unexposed children (HR = 1.84, $p < .05$, HR = 1.04, $p > .05$, respectively). Infants exposed prior to 6 months of age were also more likely to die within the 2- year follow-up period. These infants had a 52% higher risk of dying than unexposed infants (HR = 1.52, $p < .05$). Once again, the mortality hazard was only significant for female infants, where they had 1.79 times the risk of dying ($p < .05$). Children exposed between 12 and 35 months of age continued to be at a much higher risk of dying than unexposed children (HR = 2.12, $p < .001$). Similar to the life tables, both exposed male and female children had a higher risk of dying. The cohort effect was stronger for males, where they had 2.34 times the risk, while females had 1.91 times the risk of dying within the 2 year follow-up period ($p < .01$; $p < .05$, respectively).

As mentioned in the previous 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. The outbreak began in Western Quebec in late fall and spread to the East by early winter. The epidemic was relatively short-lived, where deaths peaked for a few weeks in each area and then dissipated. There were a couple accounts of epidemics in other locations around the same time. Duffy (1953) indicated through historical accounts that there was an influenza type epidemic in the area of Charleston Virginia in late December of 1716. In addition, smallpox was reported by the colonists to have been prevalent among the Aboriginal populations in New York State. Further analysis needs to be done on this particular epidemic to find out what happened during that time.

Table 5 – Multivariate Cox proportional hazard analysis of the risk of death for the exposed and unexposed cohorts with the extended follow-up period by age and sex, New France

Age at Infection	Cohort	Model G Males HR	Model G Males HR_{ext}	Model H Females HR	Model H Females HR_{ext}
< 11 months[a]					
	Exposed	1.04	1.15	1.84*	2.23**
	Unexposed†				
12 to 35 months[a]					
	Exposed	2.34**	2.14**	1.91*	2.21**
	Unexposed†				
< 36 months					
	Exposed	1.53*	1.56*	1.91**	2.29***
	Unexposed†				
< 6 months[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.

Table 5 shows exposed children during the follow-up period and the extended follow-up period that includes exposed children who died during the epidemic. Although exposure to measles may be unrelated to the survival outcome of the subsequent epidemic, some interesting patterns emerge with the exposed cohort. When the epidemic hit the colony, the cohorts would have ranged from 2 to 5 years of age. Mortality was generally at normal levels for the exposed cohort by that time. Exposed females had a higher probability of dying during the extended time than exposed females and both exposed and unexposed males (.034 vs. .006, .022 and .010, respectively).

Male deaths were elevated above normal, but not to any great extent, as compared to mortality of exposed females. For males exposed before 1 year of age, the hazard ratio increased slightly during the epidemic, but the difference still did not reach significance ($HR_{ext} = 1.15$, $p > .05$). It appears not to have affected older males much either, as most male deaths were from those exposed before 1 year of age. Although the cohort effect was still modest, the hazard was on the decline for males exposed between 1 and 3 years of age ($HR_{ext} = 2.14$, $p < .01$). In contrast, the

hazard ratios increased for females exposed before 3 years of age. In both cases, the hazard ratios increased for females exposed when they were infants and toddlers (HR_{ext} = 2.23, $p < .01$; 2.21, $p < .01$). This trend reflects the higher exposed female probability of death during that short time, as compared to the other cohorts. All controls remained the same during the extended follow-up period with the exception of the immigrant status of the parents. It became significant during the subsequent epidemic, as it was found that the majority of deaths were among exposed children who had an immigrant parent (particularly, fathers).

DISCUSSION

This study compared the survival of a group of children after exposure to measles with the survival of an unexposed cohort for the same length to time. The length of follow-up time was up to 25 months past the estimated date of infection or observation period for the unexposed cohort. Overall, children who were likely exposed to measles before 3 years of age 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 even when controlling for potential confounding effects. The probability of death was higher for both male and female children, as compared to children living under normal mortality conditions.

Similar to the previous studies on measles in New France, the main limitation of this study was that there is no way to be certain whether all deaths were related to measles. The parish clergy did not record the cause of death at the time. A partial solution to this issue was to maximize the chance of finding measles cases by selecting parishes with the higher than normal mortality during the epidemic (see Methods section). In addition, some deaths at the beginning of the follow-up period may have occurred during the acute episode of the epidemic, as the models are based on an approximation of the date of infection. I attempted to control for this aspect by only selecting deaths that occurred at least 6 weeks past the estimated date of infection. The deaths that ended up being selected for the study occurred after the death rates reached their peak during the acute episode. Further, the survival curve highly resembled the survival curves of post-measles studies done in West Africa (see Aaby et al. 1993).

Another limitation of the study was the assumption that all children in the selected parishes were exposed to measles. There is no exact way to know, if in reality, every child had an equal probability of infection. In terms of compensating for the lack of cause of death and infection, data, I selected an unexposed cohort from another time period to serve as the basis of comparison for the exposed cohort. Although there was no way to distinguish between measles and non-measles deaths, these methods helped to identify the possible impact of measles well after exposure.

The small number of events on which the comparisons were based also posed a problem for the study. Although the number of events was small and it created limits on the number of controls used or parameters estimated, estimates were stable in most circumstances (variance increased with age). The exposed cohorts were tested against other cohorts besides the one used in the study (not shown here). In those instances, the effects were the same or even became stronger. The unexposed cohorts that were selected for the study represented the mortality conditions typical for that time (see Methods section). In light of the limitations, the reader is advised that

the findings be viewed with some caution until this study is replicated with data on subsequent measles epidemics in New France.

Despite the above-mentioned limitations, there are some similarities with these findings and the series of community studies on exposure in early life (Aaby et al. 1990, 1993, 1996). In those studies, it was found that children exposed before 6 months of age were more likely to die than unexposed children during the 5-year follow-up period. Mortality was increased for up to 3 years past initial exposure and excess mortality was higher for exposed infants with and without clinical measles (some did have sub-clinical measles). However, they found no sex differences in mortality In the historical study, the mortality differential was only significant for female children exposed during infancy and mortality was returning to normal levels by the second year of follow-up.

Aaby et al. (1990, 1993, 1996) indicated that 'socio cultural confounding could not explain the difference'. In one of the studies, they also found that increased mortality was not related to the preexisting state of nutrition. Although exposed children weighed less before exposure than controls, there was 'no association between pre-exposure weight and the subsequent risk of dying' (Aaby et al. 1996). Since controlling for potential confounding effects did not diminish the exposure effect, they suggested that higher delayed mortality among exposed infants was probably related to 'biological processes'. In light of those findings, the authors concluded that 'exposure to the virus itself is a critical factor in explaining delayed measles mortality (Aaby et al. 1990). The reasons for the increased mortality are not conclusive, but increased delayed mortality has been attributed to viral persistence (never demonstrated), prolonged immune suppression or Vitamin A deficiency. It is more likely a combination of these factors (Clements and Hussey, 2004).

Interestingly, the strong regional differences apparent in the first two studies of this series (i.e. the Eastern regions had higher mortality, see the preceding articles) disappeared during the post-measles period (not shown here). This pattern is worthy of note because the regional differences were also a proxy for the location of the areas that may have been affected more by the poor harvests reported between 1714 and 1717 (i.e. Eastern Quebec). However, the diminished regional significance could have been due to a smaller number of events by spreading the data thin through the use of too many categories. Perhaps, the poor harvests reported between 1714 and 1717 did not have much of an influence on exposed children past the acute episode of the epidemic and the children were subjected more to the shortcomings of their own biology.

On the other hand, complications from measles are more severe in malnourished children, particularly those with a Vitamin A deficiency (even mild deficiency) (Perry and Halsey, 2004). Further, as malnutrition tends to coexist with an epidemic, the relative contribution to acute and delayed mortality is unclear. One has to ask the question: would these children have had higher mortality after the acute episode, if harvests were producing their usual yields? In addition, older children (exposed between 12 to 35 months of age) had higher mortality in this study. Palloni (1990) indicates, that young children are especially sensitive to crises triggered by food shortages because they depend more on solid foods and their immune systems are not completely developed. Infants, on the other hand, may incur some protection from breastfeeding. The combination of food scarcity and infectious diseases may have a strong influence on the survival

outcome of children over 1 year of age. As such, the influence of nutrition on measles outcomes should not be dismissed until improvements in measurement can disentangle the often-coexistent effects.

Several studies from West Africa and Europe found that children exposed in the household had higher mortality than those exposed outside of the home (Garenne and Aaby, 1990). Crowding in the household and intensive exposure are the common explanations for the increased mortality of secondary cases. The crowding phenomenon is likely secondary to a higher inoculation from more intensive and prolonged exposure compared with more 'casual' exposure outside of the home (Perry and Halsey, 2004). This was evident in the previous study, where it was shown that children with older siblings (larger age difference) had a higher risk of dying during the acute episode. It was suggested that the effect may have reflected the transmission of measles to young children (secondary cases) via older children (index cases) who were probably more likely to introduce the virus into the home (Mazan, in submission; see the Second study).

It was also found that post-measles mortality was significantly related to the intensity of exposure in Senegal (Garenne and Aaby, 1990). In this study, the expected proxies of intensive exposure in the household (i.e. death of a sibling during the acute episode and the age difference between siblings) were highly significant in all models, regardless of the sex of a child. In contrast to the acute phase, the direction of the relative 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, as compared to the unexposed cohort. Further, the death of a sibling during the acute phase of the epidemic continued to be a strong risk of death for the exposed children. These patterns may reflect the increased risk of death from intensive exposure when having multiple secondary cases in the household. As such, a household with a sibling who died and/ or other younger children in the household may reflect severe measles in the family. Perhaps, the age composition of a sibship may be more important than size of the sibship (number of siblings in the household was not significant in this study).

One of the more interesting findings was the sex-differential in mortality for the exposed children. In contrast, no sex differences were found in the studies conducted in West Africa (Aaby, 1995). This may have been due to the small number of events on which their studies were based. In this study, the overall exposure effect appeared stronger among female children. For children exposed before 1 year of age, only females had a significantly higher risk of death. Males had to the same risk as the unexposed cohort. A similar pattern was observed for children exposed before 6 months of age. For children exposed between 12 and 35 months of age (especially 12 to 23 months), both males and females had a significantly higher risk of dying during the follow-up period, but the effect was stronger for males who were exposed as toddlers.

The sex differential appeared to extend beyond the follow-up period, as exposed female children also had higher mortality during the subsequent epidemic. When the epidemic hit the colony, the cohorts would have ranged from 2 to 5 years of age. At this point, further analysis is required to identify the type of outbreak, but it could have been influenza or smallpox. These were prevalent at the same time in Colonial America (Duffy, 1953). Mortality was generally at normal levels for the exposed cohort by that time. The risk of death was more apparent among exposed female children, as they had a higher probability of dying than exposed females and both exposed and

unexposed males. Male deaths were elevated above normal, but not to as much of an extent, as compared to exposed females and the unexposed cohort.

There is no way to be sure whether there is any relation between measles exposure and risk of death during the subsequent epidemic. However, preliminary analysis of period rates suggests that males had higher excess mortality during the epidemic. Interestingly, while the immigrant status of the parents did not quite reach significance during the follow-up period, it became significant during the subsequent epidemic. It was found that the majority of deaths were among exposed children who had an immigrant parent (particularly, fathers). Perhaps, the effect found during the acute phase was not measles-specific, but a more general difference that places these families at an increased risk during other types of disturbances. The pattern may reflect differences in social class or a lack of access to resources during a crisis situation (see the Second study). This factor should be given further consideration for future studies on epidemics in New France.

The sex-differential in mortality was also found in a series measles immunization studies done in West Africa and Haiti. In the mid-1980s, a higher proportion of children were becoming infected with measles before 9 months of age, as children were usually immunized at 9 months of age (Aaby, 1995). Despite the presence of maternal antibodies in infants at this age, the WHO recommended that medium and high-titre measles vaccines be administered from 4 to 6 months of age in areas of 'high incidence and mortality'. The community follow-up studies found that long-term mortality was higher among female recipients of the Edmonston-Zagreb High-Titre vaccine (EX-HT), as compared to females given the standard dose of the Schwarz medium-titre vaccine (Aaby et al., 1995). There was no survival difference observed among male infants. As a result of these studies, the WHO went back to administering the standard Schwarz vaccine at 9 months of age. It was suggested that the high-titre vaccine behaved similar to natural measles, where it lead to immunosuppression and increased susceptibility to general infections in female children. At this point, there is no conclusive explanation for the sex differential during infancy. It may be an underlying genetic or biological difference between males and females that has yet to be indentified (Clements and Hussey, 2004).

As mentioned elsewhere, some community studies have found that exposed children had the same or lower mortality than unexposed controls (see Introduction) (Aaby et al. 1995; Dollimore et al. 1997, Chen at al. 1994). 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, as compared to unexposed children. Aaby et al. (1995; 1996) indicated that previous studies might have 'exaggerated' the delayed effect of measles, as some of those studies compared post-measles cases with immunized children, rather than with unimmunized and unexposed children. It should be noted that the early life exposure studies were not contested, as the delayed mortality effect was found consistently during infancy (Hull, 1988; Aaby et. al., 1990; 1993; 1996).The authors believed that children who survived the acute phase of infection might incur a survival advantage over unimmunized, unexposed children. It was concluded that both natural measles and immunization may be associated with 'non-specific beneficial effects', presumably due to immunological stimulation. In this case, it would appear that males had a slight survival advantage over females. However, others have indicated that the results of those studies are not conclusive (Perry and Halsey, 2004).

Some issues need to be addressed with these studies. In those studies, the age at infection was relatively high. In most of those studies, the mean age at infections was over 40 months. A higher mean age at infection is associated with a lower cases fatality rate (this is the result of vaccination at a young age) (Perry and Halsey, 2004; Clement and Hussey, 2004). In this study, as well, the risk of death among older children exposed past 3 years of age was no different than the unexposed cohort. This should be expected, as older children are probably more likely to recover from a bout with measles. In addition, Vitamin A therapy, prompt antibiotic treatment for pneumonia and widespread immunization campaigns have also contributed to a lower case fatality rate in recent years (Perry and Halsey, 2004).

Most of the studies in West Africa do not control for the potential effects of access to modern public health knowledge, medical care and differences in education and socio-economic status. These factors were probably improving over time when the studies took place from the late 1970s onwards and should be given further consideration. Education and socio-economic status tend to be inversely related to survival after measles exposure and immunization Aaby et al (1990), found an inverse relation between mothers' level of education and post-measles mortality for children exposed before 6 months of age. In addition, Koenig et al. (2001) found that unvaccinated children of low socio-economic status were more likely than better-off children to die from measles. In addition, the WHO (2004) recommends that health workers provide information to mothers of children with measles to help in the prevention of other infections and malnutrition. Generally, they advise mothers on the importance of nutrition/feeding during measles, when to seek medical help and so forth. No conclusive results exist, but one would expect that the diffusion of public health knowledge into the high incidence areas that can be put into practice at home may be an effective method to reduce the chance of developing complications and subsequent morbidity and mortality.

The point is that there are many modern advancements which may have had an effect on the survival outcome of the children in those studies. In historical Quebec, on the other hand, conceptions of death and disease were religiously driven. As modern medical knowledge did not exist at that time, people probably had to rely on traditional knowledge to deal with those crisis situations. There is trade-off in this type of study. Although we have to rely on estimation techniques and will never know the exact proportion of excess deaths related to measles exposure, the conditions during that time were pristine or untouched by the influences of modernization. Having this type of data and generating similar finding to studies in modern populations warrants further investigation into subsequent measles and other types of epidemics that struck the colony. Once these studies are replicated, a clearer picture of what happened during those time will come into full view.