# Increased risk of severe infections and mortality in patients with newly diagnosed systemic lupus erythematosus: A population-based study

by

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## Declaration of Committee

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# Ethics Statement

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or

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## Abstract

Systemic lupus erythematosus (SLE) is a chronic disease with a broad spectrum of clinical manifestations and infections are a leading cause of morbidity and premature mortality in patients with SLE. Findings from previous studies may be limited because of small sample sizes and using prevalent cohorts. To evaluate the risk of severe infection and infection-related mortality among patients with newly diagnosed SLE. We conducted an age- and gender- matched cohort study of all patients with incident SLE using administrative health data from British Columbia, Canada. Primary outcome was the first severe infection after SLE onset. Secondary outcomes were total number of severe infections and infection-related mortality. Multivariable Cox proportional hazard and Poisson models were used to evaluate the association of SLE with the outcomes, adjusting for confounders. The findings suggest SLE is associated with increased risks of first severe infection, a greater total number of severe infections and infection-related mortality.



**Keywords**: systemic lupus erythematosus, severe infection, mortality, risk, cohort.

## Dedication

The thesis is dedicated to my parents: Xinhua and Hongyan.

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# Chapter 1.

# Introduction

## 1.1. Background

Systemic lupus erythematosus (SLE) is a chronic disease with a broad spectrum of autoantibodies and clinical manifestations. It is a complex disease in which the body's immune system mistakenly attacks healthy tissues in many parts of the body. Although SLE is a relatively rare disease, its burden, in terms of incidence, prevalence and economic loss remains underappreciated and poorly understood[1]. Patients with SLE are, not surprisingly, likely to endure considerably reduced health-related quality of life. Common symptoms include painful and swollen joints, fever, hair loss and red rash[2]. The cause of SLE is not clear but presumably caused by a genetic susceptibility coupled with environment factor to trigger defects in the immune system. SLE is much more common in women than men: women aged 15-45 can be affected about 9 times more often than men[3]. Both men and women with SLE have a higher risk of developing cardiovascular and cerebrovascular disease and malignancy than individuals without SLE, as a consequence of both the disease and its treatments[4, 5]. There have been clinical improvements in controlling inflammatory manifestations of SLE, but a recent study suggested that survival rates of SLE patients have not improved in recent years[6] and are still at least 2-3 fold greater than the general population[7, 8].

Infections are a leading cause of morbidity and premature mortality in patients with SLE. Previous studies reported that 14-45% of SLE patients had severe infections requiring hospitalization and up to 50% of deaths were due to infections[9-12]. In an European multicenter lupus cohort of 1000 patients from seven countries, 36% of the patients had an infection during follow-up and 25% of all deaths were caused by infection[13], similar to reports from British[14] and Spanish cohorts[15]. Furthermore, the largest European SLE study on 3658 patients observed that 19% suffered from a severe infection[12]. Several factors are associated with infection in SLE: these include advanced age, longer disease duration, positive anti-ds DNA antibodies, number of disease manifestations, prednisone dose, use of immunosuppressive drugs, disease activity, and decreased renal function[16-19].

## 1.2. Motivation

Although studies using prevalent and clinic-based lupus cohorts have examined the association between SLE and infection, they were subject to an inherent survivorship bias as only healthier survivors were included and previous infections and deaths could not be included. Other studies used selected samples (e.g., children and women) so their conclusions lack generalizability to all SLE patients[20, 21]. The limitations from existing studies including selected samples, small sizes and prevalent cohorts can negatively affect the accuracy of both the absolute and relative risk estimates of infections in SLE at the population level. Consequently, we still do not have a holistic picture of the SLE-infection association.

Population data which encompass all provincially funded healthcare service data shows promising opportunities to advance the knowledge and management of the SLE patients which cannot be evaluated by the conventional clinical setting with small sample size and selective samples.

To address these knowledge gaps, we conducted a large population-based study of all patients with incident SLE between January 1, 1997 and March 31, 2015 in British Columbia (BC), Canada.

## 1.3. Objective

The objective of this study is twofold: first, to determine whether SLE is an independent risk factor for severe infections and infection-related mortality compared to the general population, second, to identify risk factors of severe infections in SLE patients.

## 1.4. Outline

The project is organized as follows: Chapter 2 introduces the study design, statistical methods used in survival analysis, the concept of competing risks and the technical details of the regression models used to account for competing risks. Chapter 3 describes the descriptive results of the SLE and non-SLE cohort, increased risks of infection and the sensitivity analyses. Chapter 4 provides a brief discussion on findings, limitations, and a discussion of future research.

# Chapter 2.

# Methods

Universal healthcare coverage is available for all residents of the province of British Columbia, Canada (4.7 M in 2015)[22]. Population Data BC, stripped of identifying information, includes data on all provincially funded healthcare service data from January 1, 1990 to March 31, 2015, including all registration information on healthcare professional visits[23], hospitalizations[24], cancer registry[25], vital statistics[26] and all dispensed medications in outpatient settings for all BC residents since January 1, 1996[27]. Several population-based studies have been successfully conducted using Population Data BC[28-31].

Population data are generated for administrative or billing purposes and collected at every healthcare encounter. Although not intended for research purposes because of the lack of clinical details, Population data have been used worldwide in research for the purpose of understanding health trends, monitoring patient outcomes and determining the efficacy of various treatments and medical interventions. The main linkable databases include the following:

The Medical Services Plan includes data on all provincially-funded healthcare services, such as physician visits, procedures performed, investigations ordered, dates of service, types of practitioners (i.e., general practitioners, specialist types), laboratory tests ordered, and the diagnosis for which a service was rendered as determined through an ICD-9-CM diagnostic code.

The Hospital Separation File includes information on all hospital admission and separation dates, up to 16 diagnostic fields representing the reason for admission (primary position) or complications during hospitalization (secondary positions) using ICD-9-CM and ICD-10-CM codes, as well as procedures, interventions and surgeries performed.

PharmaNet data includes information on all prescription medications dispensed for all residents of BC since 1995, regardless of funding source. This data file includes the date

that each prescription was dispensed, its generic drug name, dose, quantity, and days supplied.

The Vital Statistics Files provide information on death, including date of death and underlying cause of death (based on ICD-10-CM codes).

The Registration File provides basic demographic information such as sex, year of birth and geographic information.

The Cancer Registry ascertains and verifies all newly diagnosed cancer cases among residents of the province of BC through multiple sources, including pathology and haematology laboratories, cancer treatment centres, other provincial registries, and death records.

## 2.1. Study design and cohort definitions

Using data from Population Data BC, we assembled a 1:5 matched cohort study with incident SLE patients (SLE cohort) compared with age-, gender- and index year-matched individuals who were randomly selected from the general population (non-SLE cohort).

### 2.1.1. SLE cohort

The case definition of incident SLE included the following: 1) age ≥ 18 years; 2) two principal International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM 710.0) or ICD tenth Revision, Clinical Modification (ICD-10-CM M32.1, M32.8, M32.9) codes for SLE at least two months apart within two years from any type of physician or hospital visit; and 3) no SLE diagnosis in a seven-year run-in period prior to the first ICD code for SLE to ensure incident SLE cases. 99.4% of the SLE patients had at least one of the two ICD codes diagnosed by rheumatologists or from the hospitalization dataset[32]. This definition has 97.6% sensitivity and 97.5% positive predictive value in the Swedish registry data[33]. The date of the second ICD date in the pair of ICD codes to confirm SLE was defined as the SLE diagnosis date. Once a patient was confirmed to have incident SLE, a look back algorithm was applied to search for SLE-related resource use in the patient's history. The date of the first ever ICD code for

SLE was defined as the index date (i.e., SLE onset date), which was the start of the study follow-up for a SLE patient.

### 2.1.2. Non-SLE Cohort

2,000,000 randomly selected BC residents registered with the provincial medical services plan during the study period were used to establish the comparison non-SLE cohort. The randomly selected individuals without any history of SLE were matched to SLE patients (1:5) on age, gender, and the assigned SLE index date (i.e., first-ever SLE visit) of the matched SLE patient. Because by design the SLE patient was alive between the patient's index date and diagnosis date, to avoid immortal time bias, the corresponding selected non-SLE individuals had to remain alive between the assigned SLE index date and diagnosis date.

### 2.1.3. Ascertainment of Outcomes

The primary outcome was the first severe infection during follow-up. Severe infections were defined as infections necessitating admission to hospital or occurring during a hospitalization[34]. Fifty-eight different types of infections (supplementary table S1) were selected *a priori* by a panel of experts and identified using ICD-9 and ICD-10 codes[34]. We chose infections necessitating hospitalization as this case definition has a 95.4% positive predictive value to identify severe infections[35]. Secondary outcomes were the total number of severe infections and infection-related mortality during follow-up. We defined the latter secondary outcome as a death with at least one of the above 58 types of infections listed as the primary cause of death or as other contributing causes of death in the death axis coding as recorded in the individual's vital statistics record[26].

### 2.1.4. Covariate assessment

Baseline covariates were assessed within 12 months prior to the index date (first ever ICD code for SLE). Covariates included prior hospitalized infections before the index date, gender, age, the modified Romano Charlson comorbidity index for administrative data [36], baseline medication use categorized as ever use or never use (glucocorticoids, fibrates, statins, anti-diabetic medications, anticoagulant therapy, other cardiovascular (CVD) drugs, non-steroid anti-inflammatory drugs [NSAIDs], hormone

replacement therapy [HRT], cyclooxygenase-2 [Cox-2] inhibitors, and oral contraceptives), comorbidities (hypertension, cerebrovascular disease, alcoholism, ischemic heart disease, myocardial infarction, congestive heart failure, depression, malignancy and chronic obstructive pulmonary disease [COPD] related diseases), and health resource utilization (number of outpatient visits and hospitalizations).

## 2.2. Statistical analyses

Survival analysis methods are often used to analyze the time until an event has occurred. One way that survival data differs from other types of data is through censoring. The most common type of censoring is right censoring where study ends before the subject experiences the event or drops out of the study prematurely before the event occurs. In this case, the event time is not known but the event is assumed to take place following the censoring time.

One concept to understand survival data is the survival function that gives the probability that a patient will survive beyond any specified time t. That is,

$$S(t) = P(T > t) = 1 - F(t)$$

where F(t) is the cumulative distribution function of the lifetime, T. Estimation of the survival function may be carried out parametrically semi-parametrically or non-parametrically, depending on the model assumption.

A simple and widely used non-parametric estimator of the survival function is the Kaplan-Meier estimator where the number of events that have occurred for each time interval. The survival curves using Kaplan-Meier estimates, are of a stepwise form such that the survival probability only changes at times when an event is observed, or censoring occurs. One limitation with the Kaplan-Meier estimator is that we cannot adjust for predictors or make predictions about a right censored event time without making additional assumptions.

Another key concept is the hazard function which is defined as

$$h(t) = \lim_{\Delta t \to 0} \left( \frac{\text{Prob}\,(t \leq T < t + \Delta t) | \, T \geq t}{\Delta t} \right)$$

The hazard function, which is a function of time, describes the instantaneous rate of occurrence of the event of interest in subjects who are still at risk of the event. Cox Proportional Hazards Model is often used to relate the hazard function to covariates, including age, gender, social economic status, and other characteristics. The Cox Proportional Hazards Model is usually written in terms of the hazard function as follows

$$h(t)=h0(t)\exp(X\beta)$$

where h0(t), baseline hazard function or the hazard for a reference individual with covariate values 0 and X denotes a set of explanatory variables, and β denotes the associated regression parameters. The coefficients are log-hazard ratios. It is semi-parametric because it makes a parametric assumption concerning the effect of the predictors(β) on the hazard function but makes no assumption regarding the nature of the hazard function itself. This method uses the partial likelihood to estimate the parameters, and parameter estimates in the method are obtained by maximizing partial likelihood function. The partial likelihood is motivated by conditioning on the observed failure time $t_i$ and given by:

$$L(\beta) = \prod_{i=1}^{k} \frac{\exp(\beta' x_i)}{\sum_{l \in R(t_i)} \exp(\beta' x_l)}$$

In parametric estimation, because event time is non-negative and rarely normally distributed, distributions such as gamma, Weibull and exponential with non-negative and extreme values are more commonly used. These distributions proved to be good fit for censored or uncensored data.

With the hazard function, the survival function is specified as

$$S(t) = \exp[-H(t)]$$

Where

$$H(t) = \int_0^t h(u)\mathrm{du}$$

We calculated the incidence rates (IRs) of outcomes per 1,000 person-years. For the primary outcome (first severe infection during follow-up), individuals were followed from

the index date until they either experienced the first severe infection, died, left BC or the study period ended, whichever happened first. To compute IRs for the secondary outcomes (total number of severe infections and infection-related death), follow-up ended at death, migration out of BC or the end of study, whichever occurred first, but continued beyond first severe infection.

To further adjust for potential confounders, multivariable Cox proportional hazard (PH) models [37] were used to compute the adjusted hazard ratios (aHR) of infections and infection-related mortality for the SLE cohort compared to the non-SLE cohort, adjusting for baseline variables. The variables adjusted in the model were demographic, health care resource utilization, medication use, comorbidities and prior hospitalized infection. The effects of risk factors on infections were estimated in the SLE cohort and were expressed in hazard ratios with 95% confidence intervals. Additionally, we used Poisson regression with over-dispersion [38] to determine the adjusted rate ratios (aRR) of total number of severe infections that occurred during follow-up for SLE compared with the non-SLE cohort controls and to identify risk factors of recurrent severe infections for the SLE patients.

## 2.3. Sensitivity analyses

The survival analyses we conducted above rely on the important assumption of independent or noinformative censoring [39] which suggests that at a given time, the subjects being followed have the same risk for the occurrence of the event as those who remained under follow-up. However, this assumption may not hold true in the presence of competing risk. A competing risk is an event which precludes the occurrence of the event of interest. For instance, when the primary outcome was time to infection, death serves as a competing risk. A subject who died is no longer at risk of infection. Competing risks are common in studies where different events can occur and one is interested in which event occurred first.

When analyzing survival data in the presence of competing risks, censoring subjects when a competing event occurs is problematic because it is not realistic to assume the subjects who had competing events can be represented by those who remain alive thus violating the assumption of noninformative censoring. In many practical applications,

censoring subjects when competing event occurs generally lead to overestimation of the cumulative incidence of an event in the presence of the competing events [40].

The Cumulative Incidence Function (CIF), defined as 1 – S(t), allows for estimation of the incidence of the occurrence of an event while taking competing risk into account. Estimating the incidence of an event as a function of follow-up time provides important information on the absolute risk of an event. The cumulative incidence function for the kth cause is defined as: $CIF_k(t) = P(T \leq t, D = k)$, where D is a variable denoting the type of event that occurred. The difference resides in the fact that in the presence of competing risks, only 1 event can occur which precludes the occurrences of other events. $CIF_k(t)$ is therefore the probability of kth event at or before time t and before other events occur.

When analyzing data with competing events, two different types of hazard functions are of interest: the cause-specific hazard function and the subdistribution hazard function. The cause-specific hazard function is defined as

$$h_k^{cs}(t) = \lim_{\Delta t \to 0} \left( \frac{\text{Prob}\,(t \leq T < t + \Delta t, K = k) |\, T \geq t}{\Delta t} \right)$$

The cause-specific hazard function denotes the instantaneous rate of occurrence of the kth event in subjects who have never experienced any of the different types of events. On the other hand, the subdistribution hazard function is defined as

$$h_k^{sd}(t) = \lim_{\Delta t \to 0} \left( \frac{\text{Prob}\,(t \leq T < t + \Delta t, K = k | T > t \ \cup (T < t \cap \ K \neq k)}{\Delta t} \right)$$

The subdistribution hazard function denotes the risk of failure from the kth event in subjects who have not yet experienced an event of type k. Note that the risk set for the subdistribution hazard function differs from that for the cause specific hazard function, which only includes those who are currently event free.

There are 2 different hazard regression models accounting for the competing risks: modeling the cause-specific hazard and modeling the subdistribution hazard function. The subdistribution hazard model has also been described as a CIF regression model because one may directly predict the cumulative incidence for an event of interest using the usual relationship between the hazard and the incidence function under the

proportional hazards model. Thus, the subdistribution hazard model allows one to directly estimate the effect of covariates on the cumulative incidence function for the event of interest.

As a result of modelling different hazard function, each model has its unique interpretation. The subdistribution hazard model is preferable when the focus is on estimating incidence or predicting prognosis in the presence of competing risks whereas cause-specific hazard models may be more appropriate for addressing epidemiological questions of etiology. The rationale is a regression coefficient from a cause-specific hazard model can be interpreted as the relative effect of the corresponding covariate on the relative increase in the rate of the occurrence of the primary event in subjects who are currently event free. In comparison, prediction models are often interested in estimating the absolute incidence where one may link the effect of covariates to the cumulative incidence for an event of interest in the subdistribution regression model.

To examine the robustness of our results, we performed three sensitivity analyses. First, to assess the effect of an unmeasured confounder (i.e. smoking), we calculated the aHR and aRR by adding the simulated unmeasured confounder in the multivariable Cox and Poisson models, respectively. To simulate the smoking distribution for individuals, we used a smoking prevalence ranging from 42% to 46% in the SLE cohort[41], a prevalence of 31% for the non-SLE cohort (corresponding to the estimated prevalence of smoking for the general population of Canada aged 15 and older)[42] and odds ratios (OR) for the association between smoking and infection ranging from 2.20-2.60[43]. Second, we used the Fine-Gray method[44] to compute the crude CIF of first severe infections and infection-related mortality, while accounting for competing risks of death due to causes unrelated to infection. Gray's Test [45] was used for comparing the crude CIFs between the two cohorts. To further adjust for potential confounders, multivariable subdistribution proportional hazard models were used[46]. Last, because the medication data were fully captured for all BC residents only after January 1,1996 [27], there existed uncertainty about the baseline medication data (12 months prior to the index date) for 611 SLE cases whose index date was before January 1, 1997. We therefore conducted sensitivity analyses that excluded these 611 SLE cases.

All statistical analyses used SAS V.9.4 (SAS Institute, Cary, North Carolina, USA).

## 2.4. Ethical approval

No personal identifying information was made available as part of this study. Procedures used were in compliance with British Columbia's Freedom of Information and Privacy Protection Act. Ethical approval was obtained from the University of British Columbia's Behavioral Research Ethics Board (H15-00887).

## 2.5. Data availability

All the data are made available via Population Data BC (https://www.popdata.bc.ca/).

# Chapter 3.

# Results

## 3.1. Baseline Characteristics

Table 1 summarizes the baseline characteristics for SLE and non-SLE cohorts. During the study period, we identified 5,169 newly diagnosed SLE patients (86% female) with mean age of 46.9 years at the index date (first ever ICD code for SLE). The mean and median time between the index date (first ever ICD SLE code) and the SLE diagnosis date (the second ICD code in the pair of ICD codes to confirm SLE) was 3.1 and 0.9 years, respectively.

Compared to the non-SLE cohort, the SLE cohort had significantly higher numbers of all outpatient visits and hospitalizations, greater Charlson comorbidity index scores and a higher prevalence of all selected comorbidities and prior hospitalized infection. In the SLE cohort, the most used prescriptions during 12 months prior to the index date were NSAIDs and Cox-2 inhibitors (39%), glucocorticoids (25%), followed by CVD drugs excluding anticoagulant therapy (20%).

## 3.2. Time to the first severe infection

During follow-up we observed 955 first severe infections (mean follow-up time of 9.4 years) in the SLE cohort compared with 1,988 (mean follow-up time of 10.1 years) in the non-SLE cohort. The IR for severe infections in the SLE cohort was 19.7 events per 1,000 person-years, while the IR in the non-SLE cohort was 7.6 events per 1,000 person-years. Among the patients who had infections, the mean time to first infection was 7.4 and 7.9 years from the index date for the SLE and non-SLE cohorts, respectively.

Multivariable Cox PH models were used to estimate the association of SLE with the first post-SLE-onset infection. The age- and gender-adjusted HR for first severe infection for SLE was 2.67 (95% CI, 2.47-2.88) compared to the non-SLE cohort. The fully aHR adjusting for all baseline covariates was 1.82 (95% CI, 1.66-1.99, Table 2).

The risk factor analysis using the SLE cohort (Table 3) revealed that the use of glucocorticoids (aHR= 1.34, 95% CI; 1.16-1.55) and CVD medications excluding anticoagulant therapy (aHR=1.43, 95% CI; 1.23-1.68) were statistically significant risk factors for new severe infections. Other independent risk factors identified by the multivariable analysis showed having a hospitalized infection, congestive heart failure, malignancy or a higher number of visits to physicians and hospitals within 12 months prior to the index date, greater Charlson comorbidity index and older age at the index date, male sex were also positively associated with first severe infections. Higher income, on the other hand, was negatively associated the first severe infections.

## 3.3. Total number of severe infections

The SLE cohort had a total of 1,898 severe infections, and 363 SLE patients (7%) had recurring severe infections with a range of 2-20 episodes, while the non-SLE cohort had 3,114 severe infections of which 579 individuals (2%) had recurring severe infections with a range of 2-15 episodes. In the multivariable over-dispersed Poisson regression analysis for rate of severe infection, SLE was also associated with an increased risk of a greater total number of severe infections after adjusting for baseline covariates (age- and gender- adjusted RR=3.28 (95% CI, 2.90-3.72)). The fully aRR was 2.07 (95% CI, 1.82-2.36, Table 2).

In risk factor analysis (Table 3) for recurrences of severe infections in SLE patients, NSAIDs and Cox-2 inhibitors, glucocorticoids, anticoagulant therapy and CVD drugs excluding anticoagulant therapy were risk factors for recurring severe infections. Other risk factors (older age, male sex, prior hospitalized infection, hypertension, congestive heart failure, COPD-related diseases, depression, malignancy and greater Charlson comorbidity index) were also associated with a higher frequency of severe infections while higher income was associated with a lower rate of severe infections.

## 3.4. Mortality related to infection

During follow-up, there were 539 deaths in SLE patients of which 114 (21%) were related to severe infection (Table 2). In comparison, in the non-SLE cohort, we observed 1,495 deaths in total and 269 (18%) deaths were related to severe infection (Table 2).

The incidence rate ratio for infection-related mortality between SLE and non-SLE cohort was 2.17 (95% CI, 1.76-2.73, Table 2). The age- and gender- adjusted HR was 2.34 (95% CI, 1.88-2.91, Table 2). After further adjustment for baseline covariates, the aHR of infection-related mortality for SLE compared to non-SLE cohort was 1.61 (95% CI, 1.24-2.08, Table 2).

Older age, male sex and the number of hospitalizations were associated with higher risk of deaths caused by infection in SLE patients while glucocorticoids and immunosuppressive drugs were not found to be significant risk factors (Table 3). Higher income was a protective factor (HR ranging from 0.04-0.49 for different levels of income) for infection-caused mortality.

## 3.5. Sensitivity analyses

We performed three sensitivity analyses. First, multivariable Cox PH models were used to estimate the association of SLE with the first post-SLE-onset infection and infection-related mortality adjusting for baseline covariates and the unmeasured confounder, smoking history. Similarly adjusting for baseline covariates and smoking history, a Poisson count model was used to estimate the association of SLE with the total number of severe infections. Table 4 reports the comparison of the results from the primary analysis with sensitivity analyses. The aHR of first severe infection and infection-related mortality for SLE and aRR of total number of infections for SLE remained significant, but attenuated at values of 46% smoking prevalence in the SLE cohort and OR of 2.60 for the association between smoking and infection (Table 4). Secondly, after accounting for the competing risk of death due to causes unrelated to infection, CIFs (Figure 1 and 2) and Gray's tests show patients in the SLE cohort had a statistically significant faster rate to their first severe infection and infection-related death than individuals in the non-SLE cohort (P-value < 0.001). Using subdistribution models, the aHR also remained significant, but the effect sizes were slightly attenuated for infection-related mortality (Table 4). Last, the aHR and aRR remained statistically significant for severe infection and infection-related mortality when using individuals with index date after January 1, 1997 only (Table 4).

# Chapter 4.

# Discussion

## 4.1. Summary

To our knowledge, this is the first study to evaluate the risk of severe infections in a large population-based and incident SLE cohort. We observed that almost one in five SLE patients developed severe infection. Compared to the general population, SLE patients demonstrated significantly increased risks for first severe infection (1.8-fold), total number of severe infections (2.1-fold) and infection-related mortality (1.6-fold). These risks were independent of traditional risk factors for infection and the results remain robust in the presence of an unmeasured confounder (smoking) and competing risk of death. The assumption of proportional Hazards was met by the global *Schoenfeld residuals* test for the model. Compared to the studies with selected samples, our findings are generalizable to all BC residents.

The observed cumulative incidence of infection in 19% of all 5,169 SLE patients is consistent with previous studies using prevalent cohorts [9-12]. We also observed that 21% of overall mortality was related to severe infection, a percentage which is very close to a US study conducted in 1995 using a prevalent cohort over a study period of 11 years[47]. In terms of risk difference, compared to the general population, there was an increased risk for infections among patients with SLE. These findings are in agreement with previous studies of severe infections in SLE patients[14, 15]. We deem that our findings are generalizable to the general SLE population due to the large population-based incident SLE cohort, as compared with previous studies that had a small sample size from selected samples (< 150 hospitalized patients, for example[7,8]) Our study also has the advantage of being able to adjust for important infection risk factors such as comorbidities, income level, medications, prior hospitalized infection, unmeasured confounders and competing risks.

The observed increased risk of infection in SLE patients may be a result of both intrinsic and extrinsic factors. Intrinsic factors include the immune system dysfunctions, with more active SLE with impaired chemotaxis and phagocytosis of macrophages and polymorphonuclear cells diminishing the body’s immune complexes and abnormal T cell

production[48]. On the extrinsic side, the use of immunosuppressive medications and glucocorticoids has been studied in previous studies[49-51]. These medications inhibit the immunologic network and therefore decrease the resistance to a wide variety of bacterial, viral, protozoal, and fungal agents[50]. Conversely the elevated risk for infection due to the immunosuppressive actions may be counterbalanced by the benefit of these medications in controlling inflammation[34]. This work examines the total effect of these intrinsic and extrinsic factors on infections. As such, we did not adjust for the medication uses (e.g., glucocorticoids use) during follow up because this would mean adjusting for mediators which is inappropriate for studying the total risk of having SLE on infections. Future research can focus on quantifying the relative contributions of these intrinsic and extrinsic factors on the increased infection risk in SLE patients. We note that in such analysis, simply entering the use of medications during follow-up as time-varying covariates in a traditional time-dependent multivariable Cox model can yield biased effect estimates because medication use is both a time-dependent confounder and a mediator.

## 4.2. Limitations

Our study has limitations common to observational studies that use administrative data. First, uncertainty around the diagnostic accuracy of SLE cannot be completely ruled out. However, we used a strict algorithm with high positive predictive value (97.5%) for SLE diagnostic accuracy. Nevertheless, misclassification would be a conservative bias where the observed effect would bias the estimates towards the null. Second, due to inaccuracy in prescription data (including glucocorticoid use at baseline) before 1996, we conducted a sensitivity analyses on individuals with index date on or later than January 1, 1997 only. The corresponding results remained robust. Although we adjusted for all known risk factors for infections available in our data, there are other risk factors such as smoking for which data is currently unavailable. Administrative data typically do not contain physician assessments or related assessments (e.g., disease activity, weight and race). The lack of clinical information causes confounding by unobservables. Nonetheless, in our sensitivity analyses adjusting for plausible unmeasured confounders, the results remained statistically significant for each of the outcomes using values of 46% prevalence of smoking in the SLE cohort and an odds ratio of 2.60 for the association between smoking and the infection. Events such as leaving BC were

censored because such information is also not available. Information about the health service renewal status for individuals is helpful to determine whether and when individuals leave the province. Last, since there is a lack of details for non-hospitalized infection in administrative data, there may have been severe infections (e.g., endemic mycoses) that didn't result in hospitalization[52]. As a result, our results may have underestimated the risk of infections.

Despite the limitations, our study has some strengths. First, we used a large Canadian administrative dataset with a substantial timespan from 1997-2015 based on the entire SLE population in BC, which makes our results more generalizable. To the best of our knowledge, this is the largest SLE cohort assembled to date to study the relationship between SLE and infection. Second, using an incident cohort can avoid the survival bias associated with prevalent cohorts[53]. Finally, unlike previous studies, we performed sensitivity analyses to account for the effect of unmeasured confounders, competing risk of death and inaccuracy of the prescription data before 1996 which make our results robust and less biased.

Our findings highlight the risk for severe infection and shed light on important implications for SLE patients and their treating physicians. Increased awareness of the risk of infections can identify their early signs and potentially prevent hospitalizations. We suggest that in the clinical setting, physician visits provide an opportunity to promote infection prevention behavior for SLE patients. For instance, in some cases, infections may be prevented with vaccinations[54], and regular physician consultations could be valuable for awareness and promotion of appropriate vaccination strategies.

## 4.3. Future work

There is a need for additional research on the risk of infection in SLE patients given the large burden and possibility for prevention. Future studies should aim to comprehensively examine risk factors for severe infection in SLE patients in order to develop and implement strategies for the prevention of severe infection and infection-related mortality. One plausible reason for the increased risk of infection in SLE patients is the inflammation that may lead to the use of glucocorticoids for disease management[34]. Appropriate and opportune management of disease activity in SLE can decrease inflammation and potentially mitigate the risk of severe infections while

minimizing the use of glucocorticoids. In order to reduce the infection-related morbidity and mortality in SLE, evidence on the risk factors for and burden of inflammation in SLE is required.

When the straightforward rule-based treatment guidelines are difficult to be established, how to optimize the sequence of specific treatments for the patients with SLE becomes a central problem for the treating doctors to make clinical recommendations. The statistical learning methods provides a promising data-driven technique to explore and examine the best strategies[55]. Further studies are warranted to leverage on the administrative data and modern statistical methods to learn about the effect of drug combinations in the long run.

In summary, this is the first comprehensive population-based study assessing the SLE-infection association. Our study demonstrates that one in five SLE patients developed severe infections and 21% of overall mortality was related to severe infection. SLE patients have 82%, 107% and 61% increased risks of developing the first severe infection, a greater total number of severe infections and infection-related mortality compared to the general population, demonstrating that SLE is an independent risk factor for severe infection and infection-related mortality. This result expands on the findings of previous studies and has important implications for the prevention, screening and treatment of infections. We recommend a closer surveillance for severe infections in SLE patients and risk assessment for severe infections for SLE patients after diagnosis. Further studies are warranted to further identify risk factors for infections in SLE patients to develop personalized treatment regimens and to select treatment in practice by synthesizing patient information.

# Tables

**Table 1 Baseline characteristics of individuals with SLE and without SLE**

| Variable * | SLE cohort N=5,169 | Non-SLE cohort N=25,845 |
|---|---|---|
| Demographics | | |
| Age, mean (median) | 46.9 (47) | 46.9 (47) |
| Female, n (%) | 4,384 (86.2%) | 22,270 (86.2%) |
| Rural, n (%) | 785 (15.2%) | 3,334 (12.9%) |
| Neighborhood income quintile, n (%) | | |
| 1 (Lowest) | 1,014 (19.6%) | 4,380 (17.0%) |
| 2 | 950 (18.4%) | 4,558 (17.6%) |
| 3 | 978 (18.9%) | 4,577 (17.7%) |
| 4 | 922 (17.8%) | 4,841 (18.7%) |
| 5 (Highest) | 858 (16.6%) | 4,762 (18.4%) |
| Unknown | 447 (8.7%) | 2,727 (10.6%) |
| Health Resource Utilization *, mean (median) | | |
| Number of outpatient visits | 22.9 (19.0) | 7.0 (10.6) |
| Number of hospitalizations | 0.1 (0.0) | 0.0 (0.0) |
| Comorbidities *, n (%) | | |
| Alcoholism | 48 (0.9%) | 133 (0.5%) |
| Hypertension | 781 (15.1%) | 3,253 (12.6%) |
| Cerebrovascular accidents | 64 (1.2%) | 90 (0.4%) |
| Ischemic heart disease | 345 (6.7%) | 697 (2.7%) |
| Myocardial infarction | 31 (0.6%) | 77 (0.3%) |
| Congestive heart failure | 82 (1.6%) | 161 (0.6%) |
| COPD-related diseases | 131 (2.5%) | 329 (1.3%) |
| Depression | 722 (14.0%) | 2,284 (8.8%) |
| Malignancy | 261 (5.1%) | 856 (3.3%) |
| Charlson comorbidity index, mean (median) | 0.6 (0.0) | 0.2 (0.0) |
| Medications *, n (%) | | |
| NSAIDs | 2,030 (39.3%) | 3,697 (14.3%) |
| HRT | 492 (9.5%) | 1,434 (5.6%) |
| Glucocorticoids | 1,281 (24.8%) | 737 (2.9%) |
| Anticoagulant therapy | 166 (3.2%) | 220 (0.9%) |
| CVD drugs excluding anticoagulant therapy | 1,049 (20.3%) | 3,446 (13.3%) |

| Variable * | SLE cohort N=5,169 | Non-SLE cohort N=25,845 |
|---|---|---|
| Fibrates/statins | 297 (5.5%) | 1,372 (5.3%) |
| Anti-diabetic medications | 169 (3.3%) | 854 (3.3%) |
| History of Infection * | | |
| Prior hospitalized infection | 1,105 (21.4%) | 3,095 (12.0%) |

Abbreviations: SLE, systemic lupus erythematosus; SD, standard deviation; COPD, chronic obstructive pulmonary disease; NSAIDs, non-steroidal anti-inflammatory drugs including cyclooxygenase-2 inhibitors; HRT, hormone replacement therapy; CVD, cardiovascular diseases.

*All baseline characteristics were measured over one year prior to the start of follow-up except that age was measured at the start date of the follow-up.

**Table 2 Risk of severe infection in SLE relative to non-SLE during follow-up**

| Post-SLE diagnosis first severe infection | | |
|---|---|---|
| | SLE cohort N=5,169 | Non-SLE cohort N=25,845 |
| No. of events | 955 | 1, 988 |
| IR per 1,000 person-years | 19.74 | 7.61 |
| IRR (95% CI) | 2.59 (2.39-2.80) | 1.00 |
| Age and gender adjusted HR (95% CI) | 2.67 (2.47-2.88) | 1.00 |
| Fully adjusted HR* (95% CI) | 1.82 (1.66-1.99) | 1.00 |
| Post-SLE total number of severe infections | | |
| Infection episodes | 1,898 | 3,114 |
| IR per 1,000 person-years | 38.4 | 11.87 |
| IRR (95% CI) | 3.24 (3.06-3.43) | 1.00 |
| Age and gender adjusted rate ratio (95% CI) | 3.28 (2.90-3.72) | 1.00 |
| Fully adjusted rate ratio* (95% CI) | 2.07 (1.82-2.36) | 1.00 |
| Infection-related mortality | | |
| No. of infection-related death events | 114 | 269 |
| IR per 1,000 person-years | 2.17 | 1.00 |
| IRR (95% CI) | 2.20 (1.76-2.73) | 1.00 |
| Age and gender adjusted HR (95% CI) | 2.34 (1.88-2.91) | 1.00 |
| Fully adjusted HR* (95% CI) | 1.61 (1.24-2.08) | 1.00 |

Abbreviations: SLE, systemic lupus erythematosus; IR, incidence rate; IRR, incidence rate ratio; HR, hazard ratio; CI, confidence interval.

*Adjusted for covariates listed in Table 1.

**Table 3 Risk factors for severe infection outcomes in SLE***

| | Post-SLE first severe infection | Recurring severe infections | Infection-caused death |
|---|---|---|---|
| Risk factors | HR (95% CI)<br>P-value | RR (95% CI)<br>P-value | HR (95% CI)<br>P-value |
| Demographics | | | |
| Age (reference:47-) | 1.51 (1.32-1.74)<br><.0001 | 1.36 (1.23-1.50)<br><.0001 | 5.47 (1.81- 16.7)<br>0.0025 |
| Sex (reference: female) | 1.24 (1.04-1.47)<br>0.0173 | 1.25 (1.11-1.42)<br>0.0004 | 2.68 (1.08-6.64)<br>0.0338 |
| Neighborhood Income Quintile | | | |
| (reference: 1 being Lowest) | | | |
| 2 | 0.92 (0.75-1.12)<br>0.4130 | 0.85 (0.73-0.98)<br>0.0216 | 0.28 (0.08-1.11)<br>0.0712 |
| 3 | 0.78 (0.63-0.96)<br>0.0187 | 0.80 (0.69-0.93)<br>0.0028 | 0.49 (0.67-0.90)<br>0.2103 |
| *4* | 0.77 (0.62-0.95)<br>0.0149 | 0.68 (0.58-0.80)<br><.0001 | 0.11 (0.01-0.84)<br>0.0336 |
| *5 (Highest)* | 0.67 (0.54-0.84)<br>0.0004 | 0.69 (0.59-0.81)<br><.0001 | 0.04 (0.12-0.91)<br>0.0404 |
| Unknown | 0.56 (0.44-0.72)<br><.0001 | 0.93 (0.81-1.09)<br>0.4912 | 0.28 (0.06-1.24)<br>0.0936 |
| Health Resource Utilization | | | |
| Number of outpatient visits (Reference: 23-) | 1.29 (1.12-1.48)<br>0.004 | 1.28 (1.16-1.42)<br><.0001 | |
| Number of hospitalization (Reference: 1-) | 2.98 (2.26-3.95)<br><.0001 | 2.78 (2.33-3.31)<br><.0001 | 11.08 (3.61-34.00)<br><.0001 |
| Number of rheumatologist visits (Reference: 1-) | | 0.78 (0.67-0.91)<br>0.0013 | |
| Comorbidities | | | |
| Ischemic heart disease | | 0.79 (0.66-0.93)<br>0.0046 | |
| Congestive heart failure | 1.53 (1.07-2.20)<br>0.0194 | 1.95 (1.58-2.40)<br><.0001 | |

| | Post-SLE first severe infection | Recurring severe infections | Infection-caused death |
|---|---|---|---|
| Risk factors | HR (95% CI)<br>P-value | RR (95% CI)<br>P-value | HR (95% CI)<br>P-value |
| Depression | | 1.21 (1.07-1.37)<br>0.0019 | |
| Malignancy | 1.41 (1.09-1.82)<br>0.0084 | 1.25 (1.05-1.49)<br>0.0137 | |
| Charlson comorbidity index (Reference: 0.6-) | 1.29 (1.12-1.49)<br>0.0006 | 1.43 (1.29-1.59)<br><.0001 | |
| Medications | | | |
| NSAIDs & Cox-2 inhibitors | 1.34 (1.16-1.55)<br><.0001 | 1.16 (1.05-1.27)<br>0.0025 | |
| Glucocorticoids | 1.43 (1.23-1.68)<br><.0001 | 1.37 (1.24-1.52)<br><.0001 | |
| Anticoagulant therapy | | 1.33 (1.10-1.61)<br>0.0034 | |
| CVD drugs excluding anticoagulant therapy | | 1.33 (1.18-1.49)<br><.0001 | |
| Infection History | | | |
| Prior hospitalized infection (reference: No) | 1.71 (1.49-1.97)<br><.0001 | 1.95 (1.77-2.15)<br><.0001 | |

* All variables listed in Table 1 were selected for Cox and Poisson models using stepwise selection (P<0.15 for entry, P>0.05 for exit). Only variables selected in at least one of the above three models are reported in this table. 95% CI, 95% confidence interval; HR, hazard ratio; RR, rate ratio; COPD, chronic obstructive pulmonary disease; NSAIDs, non-steroidal anti-inflammatory drugs; Cox-2, cyclooxygenase-2; HRT, hormone replacement therapy.

**Table 4 Sensitivity analyses for the risk of severe infection and infection-related mortality in SLE**

| Analyses | Post-SLE first severe infection | Post-SLE Total number of severe infections | Infection-related death |
|---|---|---|---|
| | aHR (95% CI)* | aRR (95% CI)* | aHR (95% CI)* |
| Primary analyses | 1.82 (1.66-1.99) | 2.07 (1.82-2.36) | 1.61 (1.24-2.08) |
| Sensitivity analyses modeling smoking with prevalence = 42% and OR = 2.2 | 1.68 (1.54-1.84) | 1.93 (1.81, 2.07) | 1.56 (1.20-2.01) |
| Sensitivity analyses modeling smoking with prevalence = 42% and OR = 2.6 | 1.64 (1.50−1.80) | 1.89 (1.77-2.02) | 1.53 (1.19-1.99) |
| Sensitivity analyses modeling smoking with prevalence = 46% and OR = 2.2 | 1.65 (1.51-1.81) | 1.90 (1.78-2.04) | 1.54 (1.19-2.00) |
| Sensitivity analyses modeling smoking with prevalence = 46% and OR = 2.6 | 1.60 (1.47-1.76) | 1.85 (1.73-1.98) | 1.52 (1.18-1.97) |
| Sensitivity analyses accounting for competing risk of death due to causes unrelated to infection | 1.85 (1.68-2.03) | NA | 1.51 (1.16-1.96) |
| Sensitivity analyses excluding cases with index date earlier than 1997, January 1 | 1.76 (1.59-1.94) | 1.95 (1.81-2.10) | 1.57 (1.19-2.08) |

*Adjusted for covariates listed in Table 1.

NA= not applicable

# Figures

**Figure 1** **Cumulative incidence functions of first severe infection among SLE and non-SLE. Cumulative incidence was estimated adjusting for other-causes of death as competing events.**

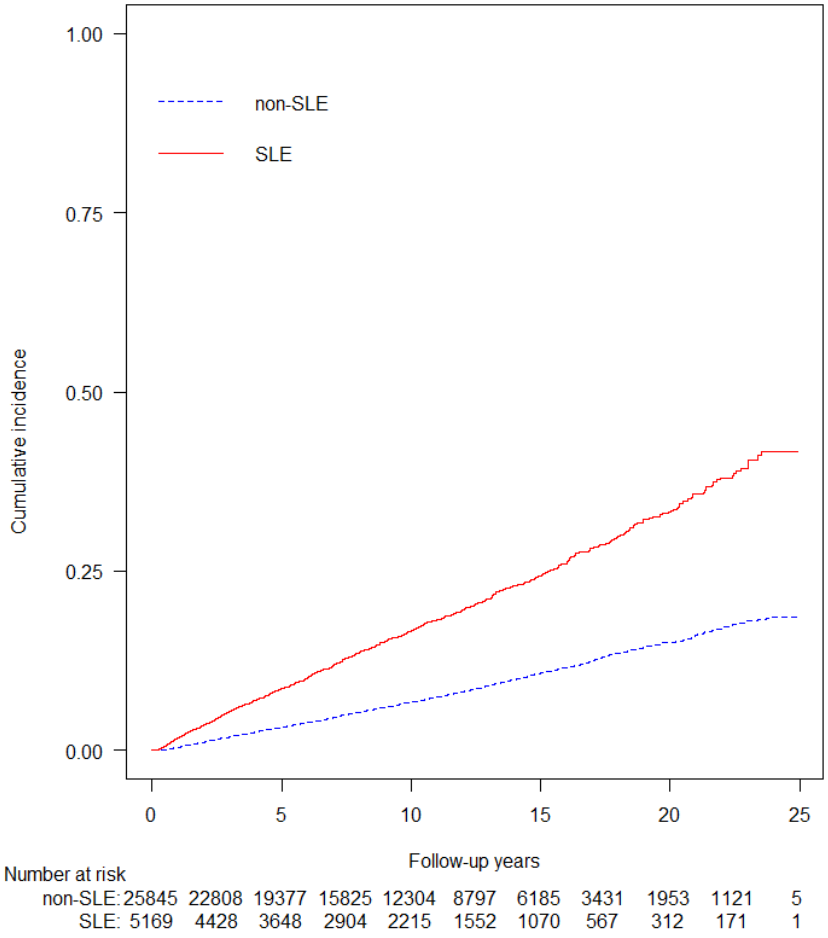
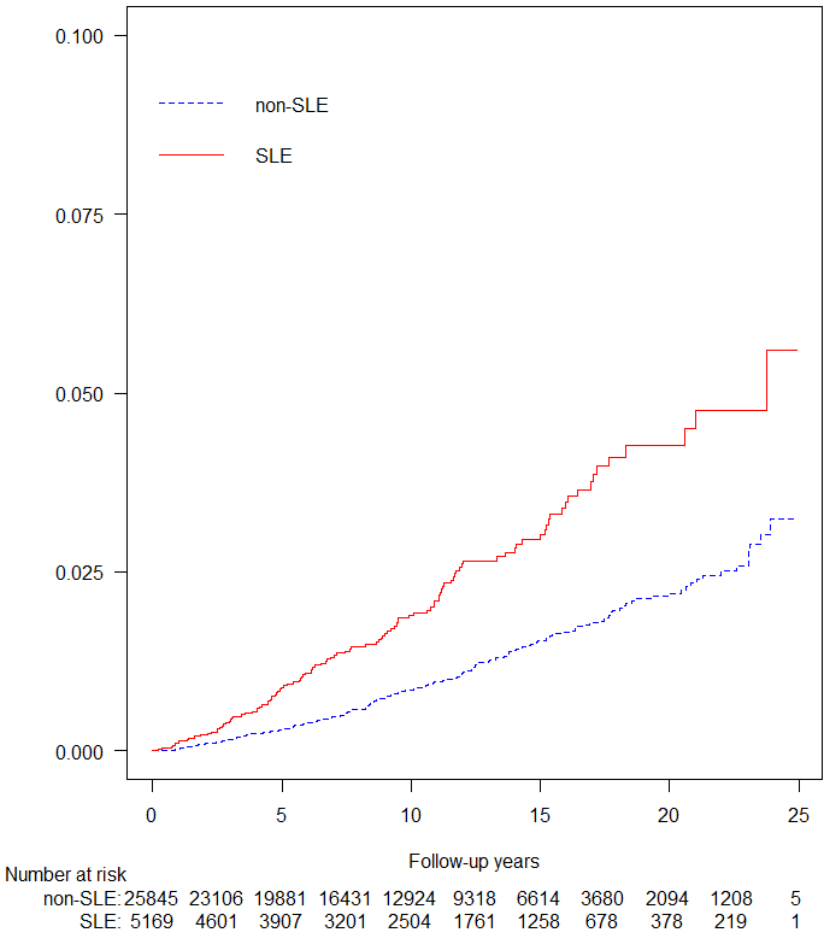


**Figure 2** **Cumulative incidence functions of infection-related death among SLE and non-SLE. Cumulative incidence was estimated adjusting for other-causes of death as competing events.**



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# Appendix

Table S1: ICD-9 and ICD-10 codes for infection

| ICD-9 | ICD-10 |
|---|---|
| 038 041 053 054 460 461 462 463 464 465 466 | A40 A41 J00 J01 J02 J03 J04 J05 J06 |
| 480 481 482 483 484 485 486 487 488 590 | J09 J10 J11 J12 J13 J14 J15 J16 J17 J18 |
| 597 599 601.0 601.1 601.2 601.3 601.4 604 616.1 | J20 J21 J22 L00 L01 L02 L03 L04 L05 L06 |
| 616.2 616.3 616.4 647 670 680 681 682 684 685 | L07 L08 N30 N34 N37 N39 N41.0 N41.3 N45 |
| 686 658.4 670.0 615.0 615.9 646.6 659.2 659.3 | N71.0 N71.9 N76.0 N76.2 N77 O411 O85 O86 |
| 672 760.2 771 999.3 659.3 672 76.02 771 999.3 | O23 O75.2 O75.3 P35 P36 P37 P38 P39 |

ICD-9

038 Septicemia

041 Bacterial infection in conditions classified elsewhere and of unspecified site

053 Herpes zoster

054 Herpes simplex

460 Acute nasopharyngitis

461 Acute sinusitis

462 Acute pharyngitis

463 Acute tonsillitis

464 Acute laryngitis and tracheitis

465 Acute upper respiratory infections of multiple or unspecified sites

466 Acute bronchitis and bronchiolitis

480 Viral pneumonia

481 Pneumococcal pneumonia

482 Other bacterial pneumonia

483 Pneumonia due to other specified organism

484 Pneumonia in infectious diseases classified elsewhere

485 Bronchopneumonia, organism unspecified

486 Pneumonia, organism unspecified

487 Influenza

488 Influenza due to identified avian influenza virus

590 Infections of kidney

597 Urethritis, not sexually transmitted, and urethral syndrome

599 Other disorders of urethra and urinary tract

601.0 Acute prostatitis

601.1 Chronic prostatitis

601.2 Abscess of prostate

601.3 Prostatocystitis

601.4 Prostatitis in diseases classified elsewhere

604 Orchitis and epididymitis

616.1 Vaginitis and vulvovaginitis

616.2 Cyst of Bartholin's gland

616.3 Abscess of Bartholin's gland

616.4 Other abscess of vulva

647 Infectious and parasitic conditions in the mother classifiable elsewhere, but complicating pregnancy, childbirth, or the puerperium

670 Major puerperal infection

680 Carbuncle and furuncle

681 Cellulitis and abscess of finger and toe

682 Other cellulitis and abscess

683 Acute lymphadenitis

684 Impetigo

685 Pilonidal cyst

686 Other local infections of skin and subcutaneous tissue

658.4 Infection of amniotic cavity

670 Major puerperal infection

615 Inflammatory diseases of uterus, except cervix

615.9 Unspecified inflammatory disease of uterus

646.6 Infections of genitourinary tract in pregnancy

659.2 Maternal pyrexia during labor, unspecified

659.3 Generalized infection during labor

672 Pyrexia of unknown origin during the puerperium

760.2 Maternal infections

771 Infections specific to the perinatal period

999.3 Other infection

ICD-10

A40 Streptococcal sepsis

A41 Other sepsis

J00 Acute nasopharyngitis [common cold]

J01 Acute sinusitis

J02 Acute pharyngitis

J03 Acute tonsillitis

J04 Acute laryngitis and tracheitis

J05 Acute obstructive laryngitis [croup] and epiglottitis

J06 Acute upper respiratory infections of multiple and unspecified sites

J09-J18 Influenza and pneumonia

J20-J22 Other acute lower respiratory infections

L00-L08 Infections of the skin and subcutaneous tissue

N30 Cystitis

N34 Urethritis and urethral syndrome

N37 Urethral disorders in diseases classified elsewhere

N39 Other disorders of urinary system

N41.0 Acute prostatitis

N41.3 Prostatocystitis

N45 Orchitis and epididymitis

N71.0 Acute inflammatory disease of uterus

N71.9 Inflammatory disease of uterus, unspecified

N76.0 Acute vaginitis

N76.2 Acute vulvitis

N77 Vulvovaginal ulceration and inflammation in diseases classified elsewhere

O41.1 Infection of amniotic sac and membranes

O85 Puerperal sepsis

O86 Other puerperal infections

O23 Infections of genitourinary tract in pregnancy

O75.2 Pyrexia during labour, not elsewhere classified

O75.3 Other infection during labour

P35 Congenital viral diseases

P36 Bacterial sepsis of newborn

P37 Other congenital infectious and parasitic diseases

P38 Omphalitis of newborn with or without mild haemorrhage

P39 Other infections specific to the perinatal period