THE AGE-STRUCTURED STOCHASTICS-($I^{(C)}$ $I^{(A)}$)-R MODEL FOR ACUTE AND CHRONIC HEPATITIS B DISEASE MAPPING IN MALAYSIA

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ABSTRACT

The main objective of this study is to introduce an alternative method to estimate the relative risk for acute and chronic hepatitis B based on the age group. This study considers the transmission of the disease in the S-($I^{(C)}$ $I^{(A)}$)-R stochastic model and used it as the equation for relative risk. In this study, the SIIR model related with hepatitis B have been revised and expanded to formed an the alternative S-($I^{(C)}$ $I^{(A)}$)-R model according to the age structure. Model S-($I^{(C)}$ $I^{(A)}$)-R are based on the age structure proposed used to estimate the relative risk for acute and chronic hepatitis B in Malaysia. Results are compared with the general method used to estimate the relative risk by using SMR and Poisson-gamma model. Results of the analysis of data from Malaysia showed that, for acute hepatitis B, children identified as having a higher risk compared to adults. While for chronic hepatitis B, adults identified as having a higher risk compared to children. This decision is based on the disease risk map produced using age-structured S-($I^{(C)}$ $I^{(A)}$)-R stochastic model. In conclusion, the alternative method to estimate the relative risk of acute and chronic hepatitis B provide are a better estimated than the SMR and Poisson-Gamma, which did not have a zero relative risk for a specific area and each state has a relative risk that are more accurately summarized in the age-structured S-($I^{(C)}$ $I^{(A)}$)-R model. As implication, the alternative methods of disease risk map proposed in this study can be used as reference by the authorities or a medical officer in the control of hepatitis B acute and chronic in Malaysia.

Model Stokastik S-($I^{(C)}I^{(A)}$)-R Berstruktur-Umur bagi Pemetaan Penyakit Hepatitis B Akut dan Kronik Hepatitis B di Malaysia

ABSTRAK

Objektif utama kajian ini adalah untuk memperkenalkan satu kaedah alternatif anggaran risiko relatif bagi hepatitis B akut dan kronik berdasarkan kumpulan umur. Kajian ini mengambilkira transmisi penyakit dalam model stokastik S-($I^{(C)}$ $I^{(A)}$)-R dan menggunakannya dalam persamaan risiko relatif. Dalam kajian ini, model SIIR yang berkaitan dengan hepatitis B telah dikaji semula dan diperluaskan untuk membentuk satu model alternatif S-($I^{(C)}$ $I^{(A)}$)-R mengikut struktur umur. Model S-($I^{(C)}$ $I^{(A)}$)-R adalah berdasarkan struktur umur yang dicadangkan digunakan untuk menganggarkan risiko relatif bagi penyakit hepatitis B akut dan kronik di Malaysia. Hasil analisis dibandingkan dengan kaedah umum yang digunakan untuk menganggar risiko relatif dengan menggunakan kaedah SMR dan model Poisson-gamma. Keputusan analisis ke atas data hepatitis B dari Malaysia menunjukkan bahawa, bagi hepatitis B akut, kanak-kanak dikenalpasti mempunyai risiko yang tinggi berbanding dengan orang dewasa. Manakala bagi hepatitis B kronik, orang dewasa dikenalpasti mempunyai risiko yang tinggi berbanding kanak-kanak. Keputusan ini adalah berdasarkan kepada peta risiko penyakit yang dihasilkan dengan menggunakan model stokastik berstruktur umur S-($I^{(C)}$ $I^{(A)}$)-R . Kesimpulannya, kaedah alternatif yang diperkenalkan bagi menganggar risiko relatif hepatitis B akut dan kronik memberikan anggaran yang lebih baik berbanding kaedah SMR dan model Poisson-Gamma, yang mana tidak ada risiko relatif sifar bagi kawasan tertentu dan setiap negeri mempunyai risiko relatif yang lebih tepat yang terangkum dalam model berstruktur umur S-($I^{(C)}$ $I^{(A)}$)-R. Implikasinya, kaedah altenatif dan peta risiko penyakit yang dicadangkan dalam kajian ini boleh digunakan sebagai rujukan oleh pihak berkuasa atau pegawai perubatan dalam mengawal penyakit hepatitis B akut dan kronik di Malaysia.

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DIC	Deviance Information Criterion
HCC	Hepatocellular carcinoma
MOH	Ministry of Health
RR	Relative Risk
SIR	Susceptible - Infected -Recovered
S-($I^{(C)}I^{(A)}$)-R	Susceptible -Infected Chronic - Infected Acute - Recovered
SMR	Standardized Morbidity Ratio

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CHAPTER 1

INTRODUCTION

1.1 Research Background and Motivation

This research is about a study of the geographical distributions of an infectious disease. There are three main areas of application in this study, which are disease mapping and clustering, and ecological analysis (Lawson, 2001). The application that will be the focus of this research is the disease mapping. In the disease mapping, a quick overview of the information about the infectious disease can be visually presented by taking the geographical data into account. The purpose of the analysis is to estimate the relative risk of a disease of interest across a geographical study area, where the main aim is to reduce the noise in the disease mapping (Samat & Percy, 2012). Scientists and public health officials have observed and mapped the

geographical incidence of the infectious disease in relation to weather and climate for hundreds of years, and formally for at least a half century (Reisen, 2010).

An epidemiology is influenced by a mathematical theory, where most of the phenomena observed in a population are complex with their own characteristics. The mathematical models are formed by summarizing the relationship between the influencing factors and geographical distribution of the disease. It has also helped in understanding the spread of the disease in a population in time and space (Choisy, Guegan & Rohani, 2007). Issues such as the geographical data, map interpretation and production, analysis and modelling must be taken into consideration within this research. The production of a good map can help to predict the transmission of the infectious disease and make a big impact on public health. It also can be an indicator to predict the high and low risk areas for the transmission of the disease. A public awareness program, vaccination or more attention from the health sector can be carried out as a precaution.

According to the Environmental Health Perspective, the concern is more on the methods for describing the overall spatial pattern of cases aggregated over small areas. Lawson & Leiminch (2000) compared a number of models that could be used for the disease mapping by goodness of fit, where the criteria include the correlation between the simulated and smoothed maps and a Bayesian information criterion. Therefore, the main aim of this research is to review, extend and improve the existing model, practically a model proposed by Kalajdzievska and Li (2007). From the existing model proposed by Kalajdzievska and Li (2007), a new alternative model

will be introduced. The new alternative model are based on stochastic S-($I^{(C)}$ $I^{(A)}$)-R model that focused on age group for the transmission of hepatitis B.

1.2 Problem Statement

The focus of the disease mapping study is to display on the map the disease risks which are estimated based on a better relative risk estimation method that considers the disease transmission model. Usually, the disease transmission will be written in the form of a mathematical model to explain the routes of the disease transmission.

Many studies show that a lot of factors can influence the risk of becoming infected with hepatitis B such as the transmission of hepatitis B, early vaccination, genotype, age structure, immigrant effect and ethnic groups (see, for example, Edmunds et. al, 2000; Wilson, Nokes & Carman, 2000; Wong et al., 2013; Yap et.al , 2010; Ross et al., 2000; Panessa et al., 2009).

In Malaysia, the current methods used to estimate the high-low area areas are based on the total number of the hepatitis B cases in each region that have been reported (Health Facts, 2014). The areas spotted to have a high number of hepatitis B cases are said to have a high risk of contracting with the acute and chronic hepatitis B, whereas the areas spotted to have a low number of hepatitis B cases are said to have a low risk of contracting with the acute and chronic hepatitis B. The method used

showed only the number of cases reported with hepatitis B without considering important features such as the geographical area, number of people in a population, age and gender, which are important to be considered before the areas are identified as a high or low-risk areas for the disease occurrences.

To spot the high or low-risk area, the relative risk for each region needs to be determined. The relative risk estimation usually begins with the Standardized Morbidity Ratio (SMR) that is a traditional method to estimate the relative risk. SMR is a mortality or morbidity ratio, where mortality represents death and morbidity represents incidence. In this study, the SMR refers to the ratio of the observed incidence with the expected incidence. Since the SMR is originally used to compare the mortality risk of the study population to that of a standard population. The SMR are calculated by the ratio of observed/expected. Here, the SMR will be zero when there is no observed data count in the areas (Jonas 2002). This indicates that zero SMR represent no risk of getting infected with the disease. This zero result cannot be used because each individual will have a risk of getting infected with the disease.

In Malaysia, most cases of hepatitis B were registered either by the screening program of rehabilitation, jails, prisons, blood banks, and others. Most hepatitis B positive cases are coming from drug pushers and lock prison rehabilitation. Each registration procedure is based on a case detected or diagnosed. In addition, the Ministry of Health Malaysia does not register for the follow-up cases on the recovery rate, but for the positive acute hepatitis B patients, they will be fully recovered depending on the treatment and time constraint. Another problem is the acute

and chronic hepatitis B cases are difficult to distinguish unless further tests are done such as the liver function tests and liver scan, where most cases reported are patient are already infected with chronic Hepatitis B.

Since it was hard to detect the disease in the early stages, a specific method need to be used to estimates the relative risk of hepatitis B so that an early prevention can be made to control the disease. The common methods that have been used to estimate the relative risk are by using the SMR and Poisson-gamma method. Standardized Morbidity Method (SMR) is the ratio of observed over expected number of cases. Since the SMR is the ratio, if the observed number of cases are zero then the SMR will also be zero. This shows that the region will have zero risk of getting infected with the disease which are not acceptable because each region should have a risk of getting infected with the disease. Whereas, the Poisson-gamma model are used to indicate the unkwon random variable with positive parameters α and β. The drawback of Poisson-gamma model are it do not allow addition of new parameter into the model. Since SMR and Poisson-gamma model have some drawbacks, a new alternative method will be introduced to estimates the relative risk. So, this study will estimate the relative risk for the acute and chronic hepatitis B based on the SMR method and Poisson-gamma model and then compare it with the new alternative method using the S-($I^{(C)}I^{(A)}$)-R model to give a better relative risk estimation model of the acute and chronic hepatitis B in Malaysia. The model that will be used in this study is a general epidemic model with the asymptomatic carriers that have been proposed by Kalajdzievska and Li (2007) that will be further discussed in Chapter 3.

1.3 Objectives of the Research

The objectives of this research are:

1. To review, extend and propose a discrete time and space stochastic model based on different equations in the form of the age-structured S-($I^{(C)}I^{(A)}$)-R acute and chronic hepatitis B transmission.

2. To propose an alternative method of the relative risk estimation for the hepatitis B disease mapping based on age-structured S-($I^{(C)}I^{(A)}$)-R model.

3. To estimate the relative risk for the hepatitis B disease mapping based on the discrete time and space using the stochastic age-structured S-($I^{(C)}I^{(A)}$)-R model for the acute and chronic hepatitis B transmission in Malaysia.

4. To compare the result of the relative risk estimation based on the SMR method, Poisson-gamma Model and stochastic age-structured S-($I^{(C)}I^{(A)}$)-R Model for the hepatitis B data from Malaysia by using risk map.

1.4 Significance of the Research

This research is carried out to propose a new alternative method in estimating the relative risk for the acute and chronic hepatitis B in Malaysia. This research used the stochastic disease transmission that is suitable in representing the real life situation. Here, the stochastic transmission of hepatitis B is split into two stages: acute and

chronic. Due to the availability of the data, the stochastic model can fit the real data by understanding the distribution assigned to the characteristics of the process involved.

Furthermore, this study would also become a review of the transmission of the acute and chronic hepatitis B in Malaysia in the year 2013. From this research, the comparison of the estimated relative risk based on the SMR method, Poisson-gamma and stochastic S-($I^{(C)}I^{(A)}$)-R models will show that the stochastic S-($I^{(C)}I^{(A)}$)-R model is best for estimating the risk. This is where the result of the relative risk can be used by the authorities for the health awareness programs, especially for areas spotted with the high-risk of acute hepatitis B.

In addition, the maps produced with colour contours can give general information to the medical authority and for the public awareness that people are in a high or low-risk area of getting infected with hepatitis B. People in a high-risk area should do the blood test early so that an early vaccination can be provided before the person gets into the chronic stages. In the future, this research can provide the baseline information in estimating the relative risk of the acute and chronic hepatitis B in Malaysia.

1.5 Organization of the Thesis

This thesis is organized into five chapters. Chapter 1 introduces the research background, and the motivation, objectives and significance of the research.

In Chapter 2, a brief explanation on hepatitis B based on the basic fact and medical background of the disease is presented. This includes the symptoms, causes, transmission, prevention, treatment and vaccine development for hepatitis B. The disease transmission model and disease mapping related to hepatitis B are also discussed in this chapter.

Then, Chapter 3 explains and describes the compartmental and stochastic terms in the S-($I^{(C)}I^{(A)}$)-R model. The main references in building the model are based on the SIR model introduced by Lawson (2000) and general epidemic model with asymptomatic carriers known as the S-($I^{(C)}$ $I^{(A)}$)-R model (Kalajdzievska & Li, 2007). From the basic SIR Model, new models are developed to be implemented directly on the hepatitis B disease. There are four types of the S-($I^{(C)}I^{(A)}$)-R model introduced in this study. The basic S-($I^{(C)}I^{(A)}$)-R model for hepatitis B, the S-($I^{(C)}I^{(A)}$)-R model based on age group (Type I), the S-($I^{(C)}I^{(A)}$)-R model based on age group (Type II), and the S-($I^{(C)}$-$I^{-(A)}$)-R model based on age group (Type III). This study used the stochastic S-($I^{(C)}$-$I^{-(A)}$)-R model based on age group Type III to estimate the relative risk of acute and chronic hepatitis B in Malaysia. The other models can be used for different focuses of research in the future.

In Chapter 4, the application of the relative risk estimation based on SMR method, Poisson-gamma model and stochastic S-($I^{(A)}I^{(C)}$)-R model to the acute and chronic hepatitis B data from Malaysia is presented. The WinBUGS software is used in the analysis. The software generated an approximation solution based on the discrete time model. The information will be about the susceptible acute hepatitis B, susceptible chronic hepatitis B, infective acute hepatitis B, and infective chronic hepatitis B that are being used to analyse the relative risk estimation for the hepatitis B mapping. In the end, the disease maps that show the high and low-risk areas for the acute and chronic hepatitis B in Malaysia are produced, and a better method is revealed.

Lastly, Chapter 5 concludes with the overall findings of this research. It summarizes the main contributions and highlights the models introduced by the researcher that offer a better way to approximate the relative risks of hepatitis B in Malaysia. The contribution and recommendations for future work are also included at the end of this chapter.

CHAPTER 2

LITERATURE REVIEW

2.1 Introduction

This chapter describes the hepatitis B virus that commonly causes the liver disease. It discusses the disease transmission, research related to hepatitis B and the disease mapping.

2.2 Hepatitis B Infectious Disease

The viral hepatitis B has been recognized as a common hepatitis in human and it is also responsible for most of the worldwide hepatitis disease burden. The history of hepatitis started in 1883 in Germany. Hepatitis was transmitted by a direct inoculation of blood or blood product that occurred after a smallpox immunization campaign among the shipyard workers in Bremen, Germany (Shepard et al., 2006). Blood product was confirmed as a source of the hepatitis transmission through the investigation of a jaundice outbreak that occurred after the administration of the yellow fever vaccine, measles and mumps convalescent plasma, and transfusion of whole blood (Beeson, 1943).

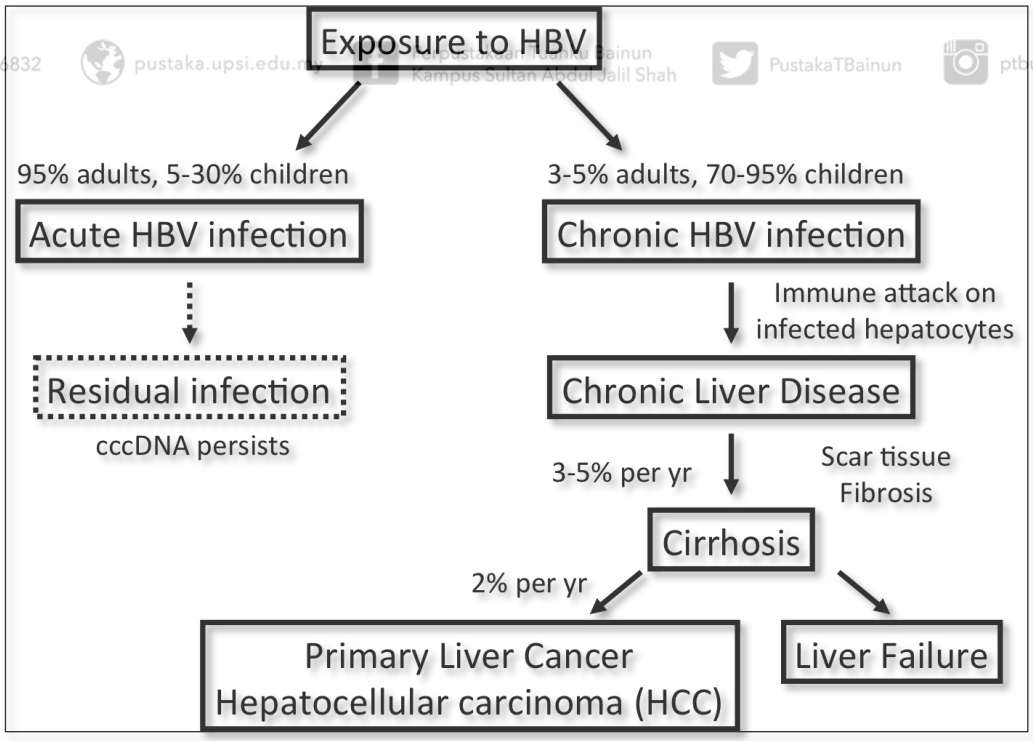

Figure 2.1. The transmission of hepatitis B (Ganem & Pince, 2004)