RELATIVE RISK ESTIMATION OF TUBERCULOSIS DISEASE MAPPING WITH STOCHASTIC SLIR MODELS

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Abstrak

Tuberkulosis (TB) adalah salah satu sebab utama kematian di negara membangun. Pemantauan penyakit ini pada masa kini hanya berdasarkan kepada jumlah kes yang dilaporkan. Sebagai alternatif, terdapat satu pendekatan yang lebih baik iaitu pemetaan penyakit yang menawarkan risiko relatif taburan geografi penyakit. Kajian terdahulu menggunakan Nisbah Kematian Piawai (SMR) dan model Poisson-gamma untuk menganggarkan risiko relatif tetapi model ini mempunyai beberapa kelemahan. Model SMR tidak dapat mengesan risiko relatif pada kawasan kecil manakala model Poisson-gamma tidak membenarkan penyesuaian kovariat. Oleh itu, matlamat kajian ini adalah untuk membangunkan model statistik alternatif bagi menganggar risiko relatif yang dinamakan model stokastik *Susceptible-Latently infected-Infectious-Recovered* (SLIR). Terdapat empat fasa dalam kajian ini. Pertama, model deterministik SLIR untuk penyebaran penyakit TB dibangunkan. Kemudian, model stokastik SLIR dibentuk. Seterusnya, model stokastik SLIR digunakan untuk menganggarkan risiko relatif bagi penyakit tersebut. Kemudian, prestasi model stokastik SLIR dibandingkan dengan model sedia ada berdasarkan nilai risiko relatif. Akhir sekali, peta risiko TB dibina. Untuk analisis berangka, kajian ini menggunakan satu set data kes TB yang dilaporkan di Malaysia dari 2008 hingga 2015. Penemuan menunjukkan bahawa terdapat perbezaan yang besar pada nilai anggaran risiko relatif apabila menggunakan model stokastik SLIR berbanding dengan model sedia ada. Ini dapat digambarkan dengan jelas melalui pemetaan penyakit di mana beberapa lokasi berubah warna daripada tona rendah (risiko rendah) kepada tona gelap (risiko lebih tinggi). Ini berlaku kerana mengambilkira komponen laten dalam model stokastik SLIR. Sebagai kesimpulan, kajian ini menawarkan model yang lebih baik dalam menganggarkan risiko relatif bagi penyakit TB. Penemuan ini juga dapat membantu kerajaan dalam mengutamakan lokasi yang memerlukan perhatian lanjut terutamanya dari aspek polisi kesihatan dan sokongan kewangan.
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Kata kunci: Pemetaan penyakit, Risiko relatif, Model SLIR, Model stokastik, Tuberkulosis

Abstract

Tuberculosis (TB) is one of the death leading causes in developing countries. The current monitoring of the disease is based only on the total cases reported. Alternatively, a better approach called disease mapping offers geographic distribution of the disease relative risk. Previous studies used Standard Mortality Ratio (SMR) and Poisson-gamma models to estimate relative risk but these models have several drawbacks. SMR model cannot detect relative risk for small areas while Poisson-gamma model cannot allow for covariate adjustments. Hence, the objective of this study is to develop an alternative statistical model in estimating the relative risk called stochastic Susceptible-Latently infected-Infectious-Recovered (SLIR). There are four phases in this study. Firstly, the deterministic SLIR model for TB disease transmission is developed. Then, the stochastic SLIR model is constructed. Next, the stochastic SLIR model is used to estimate the relative risk for the disease. Later, the performance of the stochastic SLIR model is compared with other existing models based on relative risk values. Finally, the TB risk maps are constructed. For numerical analysis, this study used a data set of Malaysia TB cases reported from 2008 to 2015. Findings show that there is a large difference of relative risk estimation values when using stochastic SLIR model compared to existing models. This is clearly visible through disease mapping as some locations change colour from low tone (low risk) to darker tone (higher risk). This is due to the inclusion of latent component in the stochastic SLIR model. As a conclusion, this study offers a better model in estimating relative risk for TB disease. The findings may assist the government in prioritizing locations which need further attention especially in terms of health policy and financial support.

Keywords: Disease mapping, Relative risk, SLIR model, Stochastic model, Tuberculosis

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$_{i,j}$

List of Abbreviations and Mathematical Symbols

TB	Tuberculosis
EPT	Extrapulmonary tuberculosis
MOH	Ministry of Health
WHO	World Health Organization
RR	Relative Risk
SIR	Susceptible-Infected-Recovered
SLIR	Susceptible-Latently infected- Infected- Recovered
SMR	Standard Mortality/Morbidity Ratio
CI	Confidence Interval
$S_{i,j}$	Total number of susceptible persons for area *i,* at time *j*
$L_{i,j}$	Total number of latently infected persons for area *i,* at time *j*
$I_{i,j}$	Total number of infectious persons for area *i,* at time *j*
$R_{i,j}$	Total number of recovered persons for area *i,* at time *j*
$\bar{I}_{i,j}$	The number of new infectious persons for area *i,* at time *j*
$\Re_{i,j}$	The number of newly recovered persons for area *i,* at time *j*

π	Recruitment rate people per year
r	Per year human birth rate
μ	Natural mortality rate (per year)
μ_T	TB caused mortality rate (per person per year)
λ	Force of infection (per year)
v	Progression rate from latent to active TB (per person per year)
p	Probability of new infections that develop progressive primary active TB
c	TB cure rate (per person per year)
β_0	Overall rate of the process
b_i	Random effect that absorbs residual spatial variation
t	Time

CHAPTER ONE
INTRODUCTION

1.1 What is Tuberculosis?

Tuberculosis or TB (abbreviation for tubercle bacillus) is a bacterial disease caused by *Mycobacterium tuberculosis* (*M. tuberculosis*) organism which these slow-growing bacteria grow well in the area of the body that has a lot of blood and oxygen (Bhowmik, Chandira, & Pradesh, 2009). In the past, according to Kumar, Abbas, Fausto, and Mitchell (2007) TB was also called as consumption, phthisis or phthisis pulmonalis. Tuberculosis usually affects the lung (pulmonary TB or PTB), but also can affect any other part of the body, for example bones, kidneys, lymph nodes and brain as the infection can spread via blood from the lung which is called as extrapulmonary tuberculosis (EPT) (New York State Department of Health Tuberculosis (TB), 2007).

Konstantinos (2010) and Kethireddy (2010) stated that TB can be transmitted from a person to another through air. Tiny droplets released into the air when people with active TB infection sneeze, cough or spit. Even though the droplets dry out quickly, the bacteria can still remain airborne in the air for hours especially in small area with no fresh air.

The infection of TB can either be latent or active TB. When someone inhales air that containing *M. tuberculosis* that are expelled into the air by other person with infectious TB, that person will become infected. However, someone who had been infected with the bacteria, he or she does not necessarily become sick. This is

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Appendix A
Knowledge Dissemination

1) Ijlal Mohd Diah (2016). Relative Risk Estimation of Tuberculosis with Standardized Morbidity Ratio in Malaysia, *Global Journal of Pure and Applied Mathematics*. ISSN 0973-1768, 12(5), 4011–4019.

2) Ijlal Mohd Diah, Nazrina Aziz and Nazihah Ahmad (2016). Tuberculosis Disease Mapping with Poisson-Gamma Model in Malaysia. *Research Journal of Applied Sciences, 11, 822-825.* doi:10.3923/rjasci.2016.822.825

3) Ijlal Mohd Diah, Nazrina Aziz, Nazihah Ahmad, & Maznah Mat Kasim (2016). Tuberculosis disease mapping with stochastic equation. *IACE' 2016- Proceeding of the 3rd Innovation and Analytics Conference & Exhibition, 77-82*.

4) Ijlal Mohd Diah, Nazrina Aziz, Nazihah Ahmad, & Maznah Mat Kasim (2016). Tuberculosis disease mapping with stochastic equation. Presentation Session in *IACE' 2016- 3rd Innovation and Analytics Conference & Exhibition,* 30th October – 1st November 2016.

5) Ijlal Mohd Diah, Nazrina Aziz, & Maznah Mat Kasim (2017). Tuberculosis disease mapping in Kedah using standardized morbidity rato. *ICAST' 2017- Proceeding of the 2nd International Conference on Applied Science and Technology, 1891*(1). https://doi.org/10.1063/1.5005429

6) Ijlal Mohd Diah, Nazrina Aziz, & Maznah Mat Kasim (2017). Tuberculosis disease mapping in Kedah using standardized morbidity rato. Presentation

Session in *ICAST' 2017- Proceeding of the 2nd International Conference on Applied Science and Technology,* 10th April – 12th 2017.

7) Ijlal Mohd Diah, Nazrina Aziz & Maznah Mat Kasim, (2017). A Comparison of Four Disease Mapping Techniques as Applied to TB Diseases in Malaysia. *Journal of Telecommunication, Electronic and Computer Engineering. 9* (2-11), 133–137.

Appendix B

WinBUGS Output of Summary Statistics for Relative Risk Estimation based on Stochastic SLIR Model

AB-1: Summary Statistics for the State of Perlis

node	mean	sd	MC error	2.5%	median	97.5%
RRH[1,2]	0.0487	0.00152	1.9E-5	0.04583	0.0487	0.05158
RRH[1,3]	0.831	0.02594	3.243E-4	0.7824	0.831	0.8807
RRH[1,4]	0.8337	0.02602	3.254E-4	0.7849	0.8337	0.8835
RRH[1,5]	0.863	0.02693	3.36E-4	0.8124	0.863	0.9145
RRH[1,6]	1.045	0.0361	4.078E-4	0.9836	1.045	1.107
RRH[1,7]	0.9028	0.02818	3.523E-4	0.85	0.9028	0.9567
RRH[1,8]	0.7148	0.02231	2.79E-4	0.673	0.7148	0.7575

AB-2: Summary Statistics for the State of Kedah

node	mean	sd	MC error	2.5%	median	97.5%
RRH[2,2]	0.05011	6.724E-4	7.2E-6	0.04898	0.05011	0.05128
RRH[2,3]	0.7865	0.01055	1.148E-4	0.7688	0.7865	0.8048
RRH[2,4]	0.8452	0.01134	1.215E-4	0.8262	0.8452	0.8649
RRH[2,5]	0.8293	0.01113	1.192E-4	0.8106	0.8293	0.8486
RRH[2,6]	0.8401	0.01127	1.207E-4	0.8212	0.8401	0.8597
RRH[2,7]	0.8203	0.01101	1.179E-4	0.8018	0.8203	0.8394
RRH[2,8]	0.9157	0.01229	1.316E-4	0.8951	0.9157	0.937

AB-3: Summary Statistics for the State of Pulau Pinang

node	Mean	sd	MC error	2.5%	median	97.5%
RRH[3,2]	0.05117	6.701E-4	8.222E-6	0.05005	0.05117	0.05233

RRH[3,3]	1.103	0.01444	1.772E-4	1.079	1.103	1.128
RRH[3,4]	1.113	0.01458	1.789E-4	1.089	1.113	1.139
RRH[3,5]	1.071	0.01402	1.72E-4	1.047	1.071	1.095
RRH[3,6]	1.105	0.01447	1.775E-4	1.081	1.105	1.13
RRH[3,7]	1.102	0.01443	1.771E-4	1.078	1.102	1.127
RRH[3,8]	1.112	0.01456	1.786E-4	1.087	1.112	1.137

AB-4: Summary Statistics for the State of Perak

node	**Mean**	**sd**	**MC error**	**2.5%**	**median**	**97.5%**
RRH[4,2]	0.05044	6.184E-4	6.015E-6	0.04944	0.05046	0.05147
RRH[4,3]	0.8932	0.01095	1.065E-4	0.8754	0.8935	0.9114
RRH[4,4]	0.9651	0.01183	1.151E-4	0.9458	0.9653	0.9846
RRH[4,5]	0.8438	0.01034	1.006E-4	0.827	0.844	0.8609
RRH[4,6]	0.918	0.01125	1.095E-4	0.8997	0.9182	0.9366
RRH[4,7]	0.912	0.01118	1.087E-4	0.8938	0.9122	0.9304
RRH[4,8]	0.9516	0.01166	1.135E-4	0.9326	0.9518	0.9709

AB-5: Summary Statistics for the State of Kuala Lumpur & Putrajaya

node	**mean**	**Sd**	**MC error**	**2.5%**	**median**	**97.5%**
RRH[5,2]	0.05207	6.128E-4	6.761E-6	0.05108	0.05207	0.05311
RRH[5,3]	1.362	0.01603	1.768E-4	1.336	1.362	1.389
RRH[5,4]	1.371	0.01614	1.781E-4	1.345	1.371	1.399
RRH[5,5]	1.59	0.01871	2,064E-4	1.56	1.59	1.622
RRH[5,6]	1.52	0.01789	1.974E-4	1.491	1.52	1.55
RRH[5,7]	1.524	0.01794	1.979-4	1.495	1.524	1.555
RRH[5,8]	1.429	0.01682	1.856E-4	1.402	1.429	1.458

AB-6: Summary Statistics for the State of Selangor

node	mean	sd	MC error	2.5%	median	97.5%
RRH[6,2]	0.05156	5.249E-4	5.389E-6	0.05079	0.05156	0.05235
RRH[6,3]	0.7675	0.007814	8.022E-5	0.756	0.7675	0.7793
RRH[6,4]	0.8851	0.009011	9.252E-5	0.8719	0.8851	0.8987
RRH[6,5]	0.9156	0.009321	9.57E-5	0.9019	0.9156	0.9296
RRH[6,6]	0.945	0.00962	9.877E-5	0.9308	0.945	0.9595
RRH[6,7]	1.057	0.01076	1.105E-4	1.041	1.057	1.073
RRH[6,8]	1.139	0.0116	1.191E-4	1.112	1.139	1.157

AB-7: Summary Statistics for the State of Negeri Sembilan

node	mean	sd	MC error	2.5%	median	97.5%
RRH[7,2]	0.05046	8.727E-4	9.799E-6	0.0489	0.05046	0.0521
RRH[7,3]	0.6989	0.01209	1.357E-4	0.6773	0.6989	0.7215
RRH[7,4]	0.7149	0.01236	1.388E-4	0.6929	0.7149	0.7381
RRH[7,5]	0.682	0.0118	1.324E-4	0.661	0.682	0.7041
RRH[7,6]	0.6101	0.01055	1.185E-4	0.5912	0.6101	0.6298
RRH[7,7]	0.834	0.01442	1.691E-4	0.8083	0.834	0.861
RRH[7,8]	0.918	0.01588	1.783E-4	0.8896	0.918	0.9477

AB-8: Summary Statistics for the State of Melaka

node	mean	sd	MC error	2.5%	median	97.5%
RRH[8,2]	0.04988	8.843E-4	1.001E-5	0.04827	0.04988	0.0515
RRH[8,3]	0.7227	0.01281	1.45E-4	0.6993	0.7227	0.7461
RRH[8,4]	0.8084	0.01433	1.622E-4	0.7822	0.8084	0.8346
RRH[8,5]	0.9199	0.01631	1.846E-4	0.8901	0.9199	0.9497

RRH[8,6]	0.9283	0.01646	1.863E-4	0.8982	0.9283	0.9583
RRH[8,7]	0.9163	0.01624	1.839E-4	0.8866	0.9163	0.946
RRH[8,8]	1.089	0.0193	2.185E-4	1.054	1.089	1.124

AB-9: Summary Statistics for the State of Johor

node	mean	sd	MC error	2.5%	median	97.5%
RRH[9,2]	0.0505	5.696E-4	5.818E-6	0.0496	0.0505	0.05141
RRH[9,3]	0.9279	0.01047	1.069E-4	0.9114	0.9279	0.9446
RRH[9,4]	1.001	0.01129	1.154E-4	0.9835	1.001	1.019
RRH[9,5]	0.9137	0.01031	1.053E-4	0.8974	0.9137	0.9301
RRH[9,6]	0.8675	0.009784	9.994E-5	0.8521	0.8675	0.8831
RRH[9,7]	0.8537	0.009628	9.835E-5	0.8385	0.8537	0.869
RRH[9,8]	0.9527	0.01075	1.098E-4	0.9358	0.9527	0.9699

AB-10: Summary Statistics for the State of Pahang

node	Mean	sd	MC error	2.5%	median	97.5%
RRH[10,2]	0.04961	7.182E-4	7.493E-6	0.04838	0.04961	0.05089
RRH[10,3]	0.9093	0.01316	1.373E-4	0.8867	0.9093	0.9327
RRH[10,4]	0.8717	0.01262	1.317E-4	0.8501	0.8717	0.8942
RRH[10,5]	0.7801	0.01129	1.178E-4	0.7607	0.7801	0.8002
RRH[10,6]	0.813	0.01177	1.228E-4	0.7928	0.813	0.8339
RRH[10,7]	0.7925	0.01147	1.197E-4	0.7728	0.7925	0.8129
RRH[10,8]	0.8338	0.01207	1.259E-4	0.8131	0.8338	0.8553

AB-11: Summary Statistics for the State of Terengganu

node	Mean	sd	MC error	2.5%	median	97.5%

RRH[11,2]	0.04983	7.79E-4	8.561E-6	0.04848	0.04983	0.05126
RRH[11,3]	1.138	0.01779	1.955E-4	1.107	1.138	1.171
RRH[11,4]	1.005	0.01571	1.727E-4	0.9777	1.005	1.034
RRH[11,5]	0.9149	0.0143	1.572E-4	0.8901	0.9149	0.9412
RRH[11,6]	0.9339	0.0146	1.605E-4	0.9086	0.9339	0.9608
RRH[11,7]	0.9532	0.0149	1.638E-4	0.9273	0.9532	0.9806
RRH[11,8]	0.9307	0.01455	1.599E-4	0.9055	0.9307	0.9575

AB-12: Summary Statistics for the State of Kelantan

node	**mean**	**sd**	**MC error**	**2.5%**	**median**	**97.5%**
RRH[12,2]	0.0503	6.347E-4	6.992E-6	0.04927	0.0503	0.05138
RRH[12,3]	1.325	0.01672	1.842E-4	1.298	1.325	1.353
RRH[12,4]	1.321	0.01667	1.836E-4	1.294	1.321	1.349
RRH[12,5]	1.297	0.01636	1.803E-4	1.27	1.297	1.325
RRH[12,6]	1.221	0.01541	1.697E-4	1.196	1.221	1.247
RRH[12,7]	1.166	0.01471	1.621E-4	1.142	1.166	1.191
RRH[12,8]	1.163	0.01468	1.617E-4	1.14	1.163	1.188

AB-13: Summary Statistics for the State of Sabah

node	**mean**	**sd**	**MC error**	**2.5%**	**median**	**97.5%**
RRH[13,2]	0.05318	5.307E-4	5.272E-6	0.0524	0.05318	0.05397
RRH[13,3]	1.775	0.01771	1.759E-4	1.749	1.775	1.801
RRH[13,4]	1.856	0.01852	1.84E-4	1.829	1.856	1.884
RRH[13,5]	1.741	0.01737	1.726E-4	1.715	1.741	1.767
RRH[13,6]	1.881	0.01877	1.864E-4	1.853	1.881	1.909
RRH[13,7]	1.885	0.01881	1.869E-4	1.858	1.885	1.913
RRH[13,8]	2.015	0.0201	1.997E-4	1.985	2.015	2.044

AB-14: Summary Statistics for the State of Sarawak

node	mean	sd	MC error	2.5%	median	97.5%
RRH[14,2]	0.05232	5.733E-4	5.868E-6	0.051	0.05232	0.05323
RRH[14,3]	1.293	0.01416	1.45E-4	1.27	1.293	1.315
RRH[14,4]	1.326	0.01452	1.487E-4	1.302	1.326	1.349
RRH[14,5]	1.248	0.01367	1.399E-4	1.226	1.248	1.269
RRH[14,6]	1.367	0.01497	1.533E-4	1.343	1.367	1.39
RRH[14,7]	1.46	0.016	1.638E-4	1.435	1.46	1.486
RRH[14,8]	1.56	0.01709	1.749E-4	1.532	1.56	1.587

Appendix C

WinBUGS Code for Relative Risk Estimation based on SMR Method, Poisson-gamma Model, Stochastic SIR Model and Stochastic SLIR Model

AC-1: WinBUGS Code for Estimation of Relative Risk based on SMR Method and Poisson-gamma Model

```
model{
for (i in 1:M){
for (j in 1:T){

        #Relative Risk
        theta[i,j]<-y[i,j]/e[i,j]
}}}
```

Figure AC.1. SMR method in WinBUGS


```
model{
for (i in 1:M){
for (j in 1:T){
        #Poisson likelihood for observed counts
        y[i,j]~dpois(mu[i,j])
        mu[i,j]<-e[i,j]*theta[i,j]
        #Relative Risk
        theta[i,j]~dgamma(a,b)
}
}
#Prior distribution for "population" parameters
a~dexp(0.1)
b~dexp(0.1)
#Population Mean and Population variance
mean<-a/b
var<-a/pow(b,2)
}
```

Figure AC.2. Poisson-gamma model in WinBUGS

The code for SMR method and Poisson-gamma model were adapted from Nor Azah and Syafiqah Husna (2013) which was used to analyze dengue disease occurrence for districts in Perak, Malaysia. Moreover, this Poisson-gamma model's code was written by Lawson et al. (2003) in their study which was applied to analyze influenza data from South Carolina.

AC-2: WinBUGS Code for Estimation of Relative Risk based on the Stochastic SIR Model

This code has been written by Lawson (2006) to analyze influenza seasons in 13 consecutive time periods in South Carolina for the year 2004-2005. Nevertheless, in order to suit the particular requirement of this study, we modified the notations and formulations used in that WinBUGS code.

```
Model{
for (i in 1:M){
      Rh[i,1]<-0
      Sh[i,1]<-Nh[i]
      muH[i,1]<-Sh[i,1]
      Ih[i,1]~dpois(muH[i,1])
}
for (i in 1:M){
for (j in 2:T){
         Rh[i,j]<-betaR*Ih[i,j]
         Sh[i,j]<-Sh[i,j-1]-Ih[i,j-1]-Rh[i,j-1]
         Ih[i,j]~dpois(muH[i,j])
         log(muH[i,j])<-beta0+log(Sh[i,j]+0.001)+log(Ih[i,j-1]+0.001)+b1[i]

#Relative Risk
theta[i,j]<-muH[i,j]/eH[i,j]
}
}
#CAR prior distribution for random effects, the sum of b1 is always zero
b1[1:14]~car.normal(adj[],weights[],num[],tau.b1)
for (k in 1:sumNumNeigh){
weights[k]<-1}

#Other priors
beta0~dflat()                    #Flat prior for the intercept
tau.b1~dgamma(0.01,0.01)         # Prior on precision
betaR<-0.001

}
```

Figure 4.6. Stochastic SIR model in WinBUGS