ABSTRACT

Tuberculosis (TB), one of the most important infectious diseases worldwide, is a notifiable communicable disease with the highest morbidity and mortality. Recently, multidrug-resistant tuberculosis (MDR TB) and particularly high TB incidence observed in the senior care facilities make TB more difficult to control. TB patients do not stick (non-adherence) to the treatment regimen that is thought to be the main cause for the emergence of MDR TB. Moreover, statistical data on TB cases shows seasonal fluctuations in many countries, however, the seasonal transmission and population dynamics of TB/MDR TB in Taiwan are still poorly understood. Thus, the purpose of this dissertation was threefold: (*i*) to characterize the seasonal population transmission dynamics of TB/MDR TB and to assess the potential infection risks among Taiwan regions, (*ii*) to evaluate indoor TB population transmission dynamics and the efficacy of control measures in the senior care facilities, and (*iii*) to quantify the impact of different multidrug combination regimens with non-adherence on treatment efficacy and drug resistance probability.

This dissertation developed an integrated seasonal transmission dynamic model by linking the population transmission dynamic models and seasonal regression model to understand how seasonality influences the transmission dynamics of TB/MDRTB in Taiwan. The integrated seasonal transmission dynamic model was also used to predict TB/MDR TB incidence trends in the future. A probabilistic risk model was developed to estimate TB/MDR TB infection risks. This study conducted investigations for the senior care facilities to obtain the underlying characteristics including total population size, volume of airspace, ventilation condition, and elderly daily life behavior. A mathematical multiple control model combined with the population transmission dynamic model was used to evaluate the efficacy of various

control strategies for reducing indoor TB transmission in senior care facilities. A pharmacokinetic/pharmacodynamic (PK/PD) based drug treatment model was constructed to explore the population and resistance evolution dynamics of TB bacilli during multidrug combination treatment taking into account non-adherence. This study further used a simple time-dependent bacterial population size based probabilistic function to quantify the probability of resistance to multiple drugs.

The results of model validation demonstrated that the proposed integrated seasonal transmission dynamic model was capable of describing the patterns of TB/MDR TB incidences in Taiwan. Simulation results showed that the TB epidemic in the future will finally be dominated by latently infected TB cases as a result of reactivation and reinfection. This study also found that, in the highest disease burden area, the incidences of TB/MDR TB had a gradually decreasing trend that might be attributable to the effective control TB programmes. The risk assessment indicated that high TB incidence areas had nearly 52 – 65% probabilities exceeding 50% of the total proportion of infected population. The results also indicated that latently infected TB cases were likely to pose the relatively high TB infection risk among populations. Additionally, there was only ~4% probability of having exceeded 10% of the population infected attributable to MDR TB for selected study sites of Taiwan. Although MDR TB seems unlikely to result an emergency, MDR TB remains alarming from a conservative point of view.

Given the analytical results from the integrated mathematical control model, the investigated senior care facilities had a potentially higher risk of TB exposure. Nevertheless, the proposed combinations of engineering control measures along with personal protection could effectively reduce indoor transmission of TB bacilli in the senior care facilities in that the efficacies ranged from 65 – 97%. On the other hand,

results from the drug treatment model showed that the duration of treatment would be increased 1.6 – 3.4 times for patients who were non-adherent to the therapeutic regimen relative to compliance. Non-adherence also led to treatment failure and accelerated the resistant mutants to grow and evolve, resulting in a much higher probability of resistance to multiple drugs. Overall, the determination of optimal treatment regimens depended on the different types of medication adherence.

This dissertation provided an integrated seasonal transmission dynamic model not only to examine the underlying mechanisms of TB seasonal transmission but also to predict the incidence patterns of TB/MDR TB and associated potential infection risks. A better understanding of the mechanisms of TB seasonality is helpful for establishing an early warning system and designing more effective public control programmes. The developed mathematical multiple control model can be applied to determine the optimal control strategies indoors for any infectious diseases. This dissertation hopes that the proposed drug treatment model can be used to improve the treatment protocols for TB or certain of disease that are needed to be treated with multiple drugs.

Keywords: Tuberculosis; Multidrug-resistant tuberculosis; Transmission; Population dynamics; Seasonality; Infection risk assessment; Control measure; Drug treatment

中文摘要

結核病(Tuberculosis)是全球重要傳染病之一，亦是台灣發生率及死亡率最高之法定傳染病。近年來，多重抗藥性結核病(Multidrug-resistant tuberculosis)與高結核病發生率之老人安養照護機構，皆使得結核病更加難以控制。結核病患不遵從治療方案被認為是多重抗藥性結核病興起之重要原因。此外，統計資料顯示，許多國家之結核病案例數具季節性擾動，然而，台灣結核病與多重抗藥性結核病之季節性傳輸與族群動態仍缺乏探討。因此，本論文研究目的有三：(1)描述台灣地區結核病與多重抗藥性結核病之季節性族群傳輸動態，並評估其可能之感染風險，(2)評估老人安養照護機構室內結核病族群傳輸動態及控制策略效能，及(3)量化不同多重藥物組合方案與服藥不遵從對於治療成效及抗藥性機率之衝擊。

本研究連結族群傳輸動態模式與季節性迴歸模式建構一整合性季節傳輸動態模式，藉以了解季節性如何影響台灣結核病與多重抗藥性結核病之傳輸動態。此模式亦可用於預測未來結核病與多重抗藥性結核病發生率趨勢。接著以機率風險模式推估結核病與多重抗藥性結核病之感染風險。進一步，本研究針對老人安養照護機構進行調查以獲得相關特性，包含總人口數、空間體積、通風情形及老人日常生活行為。再結合數學多重控制模式與族群動態模式，以評估不同控制策略對於降低老人安養照護機構室內結核病傳輸之成效。本研究另建構以毒理動力及動態(PK/PD)為基礎之藥物治療模式並考量服藥不遵從，以探討於多重藥物混合治療過程中，結核菌之族群與抗藥性演化動態。進而運用一簡易隨時變細菌族群數為基礎之機率方程式，量化對於多重藥物產生抗藥性之機率。

本研究所提出之整合性季節傳輸動態模式能夠描述台灣結核病與多重抗藥性結核病發生率趨勢。模擬結果顯示，由於再活化與再感染之發病機制，未來結

核病疫情終將以潛伏感染結核病患為主。本研究亦發現在高疫情負擔地區，結核病與多重抗藥性結核病發生率呈現逐漸下降趨勢，其可能歸因於有效之結核病控制計劃。再者，風險分析結果指出，在結核病高發生率地區有將近 52–65%機率，其受感染人口之總比例會超過 50%。結果亦指出，潛伏感染結核病患可能對人群造成相對較高之結核病感染風險。此外，於本研究所探討之地區，其多重抗藥性結核病僅有 4%機率會造成至少 10%人口感染。儘管多重抗藥性結核病似乎不太可能導致緊急危機，但從保守觀點來看，多重抗藥性結核病仍應提出警訊。從整合性數學控制模式分析結果，顯示本研究所調查之老人安養照護機構具有潛在較高結核病暴露風險。但藉由結合工程控與個人防護措施則能夠有效地降低結核菌在老人安養照護機構室內之傳輸，其效能介於 65–97%。另一方面，藥物治療模式模擬結果顯示，病患若對於治療處方不遵從，其所需療程時間會比完全服藥遵從之病患高出 1.6–3.4 倍。服藥不遵從性亦可導致治療失敗且促進抗藥性菌株成長與演化，導致有較高之機率對多重藥物產生抗藥性。整體而言，最佳治療方案選定取決於不同服藥遵從性類型。

本論文提供一整合性季節傳輸動態模式，不僅用以檢視潛在之結核病季節傳輸機制，亦可預測結核病與多重抗藥性結核病之發生率趨勢及其潛在感染風險。深入了解結核病季節性機制有助於建立預警系統及制定更有效之公共控制計劃。本研究所發展之數學多重控制模式，可運用於任何傳染性疾病，以決定室內最佳控制策略。並期望所提出之藥物治療模式可用以改善結核病治療方案或需要多重藥物治療之疾病。

關鍵字：結核病；多重抗藥性結核病；傳輸；族群動態；季節性；感染風險評估；控制策略；藥物治療