# 中文摘要

流行性感冒為一室內高傳染性及呼吸性疾病，且每年造成世界性重症及死亡案例。近年研究利用不同研究方法加以探究室內流行性感冒之傳輸過程，然而主要傳輸途徑仍具爭議性。因此，本博士論文之研究目的有三(1)發展一描述流感病毒、宿主及環境三者間交互動態之整合性病毒—宿主—環境廣義模式以更加以量化疾病傳輸過程及潛在傳輸過程及機制、(2)以一機率性風險方式評估病毒—宿主—環境交互動態下呼吸性疾病風險及(3)根據機率風險估計值提出一最佳控制策略以降低呼吸性感染及症狀進展風險以降低流感之疾病負擔。

本研究重新分析流感監測及人體實驗資料以推估特定季節性及大流行性流感流行病學及室內傳輸參數。本研究考量流感飛沫之移除機制(重力沉降、擴散沉積及失活)、釋放機制(咳嗽及打噴嚏)及傳輸機制(吸入及接觸途徑)，藉以量化室內流感之傳輸。此外，本研究藉由一病毒散布模式描述沉積至呼吸道內部之流感飛沫進一步觸發感染，以致流感病毒複製及散布之過程。藉聯結 Wells-Riley 數理模式及易感—暴露—感染—復原(SEIR)族群傳輸動態模式，量化教室及教師辦公室內流感之族群傳輸。本研究發展一非滅絕性分支過程為基礎之流行機率模式，評估室內感染者人數及有效再生數($R_e$)改變之室內流感爆發流行機率。根據流感飛沫驅動之病毒—宿主—環境交互動態模式加以推估呼吸性疾病風險機率。本研究亦提出多重效能之控制策略模式，評估不同控制策略組合對流感爆發控制之潛能。

本研究之研究結果指出 p-H1N1 具有最高之疾病傳輸潛力，其中教室及教師辦公室內之病毒釋出率($q$)及基本再生數($R_0$)其推估值分別為 1,494 (95% 信賴區間：252 – 10,508)與 1,352 (228 – 9,597) quanta $d^{-1}$ 及 2.41 (0.45 – 12.42)與 1.83

(0.34 – 9.65)。教室內飛沫驅動之流感傳輸其流行病學參數 $q$ 及 $R_0$ 之推估值分別介於 26 – 869 quanta $d^{-1}$ 及 0.10 – 3.54。兩種室內設定具有相似之族群傳輸動態，其中 p-H1N1 會較快於 2.55 – 2.60 天達到感染人數高峰值。流感飛沫驅動之族群傳輸動態具有較低之傳輸潛力，於 3.9 天達到感染人數高峰值。隨著室內感染人數及 $R_e$ 之增加，將大幅提高流感爆發之流行機率，尤其是教室內之 p-H1N1 流行機率。藉由流感病毒—宿主—環境交互動態模式推估之特定病毒散布濃度分布，宿主族群有 50%機率其感染分率會超過 50% (95% 信賴區間：34 – 67)及呼吸道症狀分數會超過 0.20 (0.15 - 0.45)，顯示控制策略施行之重要性。結合非工程及工程控制策略之施用可有效控制室內 p-H1N1 之爆發。就季節性流感而論，非工程控制策略之施用即可有效控制疾病爆發。由流感飛沫驅動之教室內傳輸，二項非工程控制策略(配戴手術型口罩及施打疫苗)之組合足以達到流感爆發之完全控制。

本研究建構一整合式流感病毒—宿主—環境之交互動態模式，以檢視潛在之流感傳輸機制及過程以及相關之呼吸性疾病風險。室內環境之宿主須當心預防流感感染，勝過呼吸性症狀分數之發展。具有較高疾病傳輸能力之室內環境須同時施行非工程及工程控制策略以減緩整體之呼吸性疾病風險。

關鍵字：流行性感冒；呼吸性疾病；室內空氣品質；交互動態；流行機率；風險評估；控制策略

# ABSTRACT

Influenza is a highly-contagious respiratory disease generally occurring indoors and causes severe illness and death cases worldwide annually. Recent studies have explored the indoor influenza transmission process in various ways, however, the dominant transmission pathways remain debated. Therefore, the purposes of this dissertation were threefolds: (i) to develop an integrated virus-host-environment (V-H-E) general model describing the interaction dynamics among influenza virus, host, and environment to better quantify the underlying disease transmission processes and mechanisms, (ii) to assess probabilistically the respiratory disease risks based on V-H-E interaction dynamics, and (iii) to propose an optimum control strategy based on probabilistic risk estimates to reduce the overall respiratory infection and symptom development risks for mitigating influenza disease burdens.

This dissertation reanalyzed the surveillance and human experimental data to estimate specific epidemiological and indoor transmission parameters for seasonal and pandemic influenza. Influenza droplet removal (gravitational settling, diffusive deposition, and inactivation), generation (coughing and sneezing), and transmission (inhalation and contact) mechanisms were taken into account for indoor influenza transmission. Moreover, the deposited influenza droplets in the respiratory tracts that further triggered the infection and virus replication and shedding could be elucidated by the viral shedding dynamic model. By incorporating the Wells-Riley mathematical model into the susceptible-exposed-infectious-recovery (SEIR) population transmission dynamic model, influenza transmission within hosts could be quantified in both the classroom and teacher office settings.

An epidemic probability model based on a non-extinction branching process was developed to assess the indoor epidemic probability of influenza outbreaks according

to alteration in infected individual introductions and effective reproduction number ($R_e$). Based on the droplet-driven V-H-E interaction dynamics, respiratory disease risks could thus be estimated probabilistically. Multi-efficacy control measure models were also developed to assess the potential of influenza outbreak containment based on different control measure combinations.

The estimated results indicated that pandemic H1N1 2009 (p-H1N1) had the highest disease transmission potential in which the quantum generation rate ($q$) and basic reproduction number ($R_0$) estimates were 1,494 (95% CI: 252 – 10,508) and 1,352 (228 – 9,597) quanta $d^{-1}$ and 2.41 (0.45 – 12.42) and 1.83 (0.34 – 9.65), respectively, in the classroom and teacher office setting. For the droplet-driven transmission in the classroom, $q$ and $R_0$ were estimated to be within the ranges of 26 – 869 quanta $d^{-1}$ and 0.10 – 3.54, respectively. Both indoor settings had similar population transmission dynamics in which the infected number of p-H1N1 peaked faster at day 2.55 – 2.60. Infected individuals in the droplet-driven SEIR transmission dynamics would peak slower at day 3.9 because of its lower transmission potential.

Increments of infector introductions and $R_e$ would greatly increase the epidemic probability of influenza outbreak, especially for p-H1N1 in the classroom. Given certain viral shedding levels estimated from the V-H-E interaction dynamic model, it is likely that over 50% (95% CI: 34 – 67) population would become infected but with mild increments in respiratory symptom scores (RSS) of 0.20 (95% CI: 0.15 – 0.45), indicating the importance in implementing control measures. Combining both engineering and non-engineering interventions could efficiently control p-H1N1 outbreaks indoors, whereas for seasonal influenza, non-engineering interventions were effective in containing outbreaks. For the influenza droplet-driven transmission in the classroom, the control measure combination of two non-engineering

interventions (*i.e.*, surgical mask wearing and vaccination) showed complete influenza outbreak containment.

This study constucted an integrated V-H-E interaction dynamic model for examining the underlying influenza transmission mechanisms and processes as well as associated respiratory disease risks. People in the indoor enclosure should be aware of influenza infection rather than development of the respiratory symptom scores (RSS). An indoor environment with high transmission potentials should implement both non-engineering and engineering control strategies to mitigate the overall respiratory disease risks.

**Keywords:** Influenza; Respiratory disease; Indoor air quality; Interaction dynamics; Epidemic probability; Risk assessment; Control measure