「減少結核病的傳播，通風換氣的重要性」

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Disclaimer

- The views expressed in this talk are independent from my employer, TCDC and based on my personal experience as a public health official, epidemiologist, infectious specialist and pediatrician
- The piece of manuscript is a collaborative project of MPH program in the affiliated Institute of Epidemiology and Preventive Medicine led by Pro. Fang CT

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The End TB Strategy: Vision, goal, targets 2035

Vision: A world free of TB

Zero TB deaths, Zero TB disease, and Zero TB suffering

Goal: End the Global TB epidemic (<10 cases per 100,000)

Target 1	Target 2	Target 3
95% reduction in deaths due to TB (compared with 2015)	90% reduction in TB incidence rate (compared with 2015)	No affected families face catastrophic costs due to TB

GLOBAL TB PROGRAMME

World Health Organization

INSIGHTS

PERSPECTIVES

Correctly fitted masks are an important tool to reduce airborne transmission of SARS-CoV-2, particularly in enclosed spaces, such as on this Moscow Metro train in Russia.

VIEWPOINT: COVID-19

Reducing transmission of SARS-CoV-2

Masks and testing are necessary to combat asymptomatic spread in aerosols and droplets

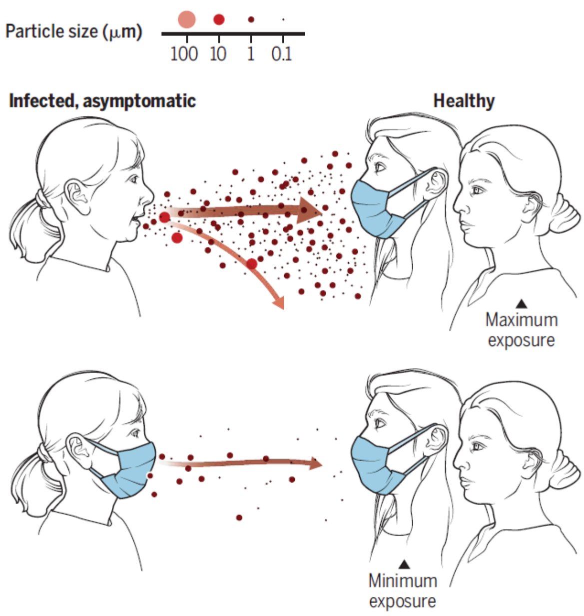
By Kimberly A. Prather[1], Chia C. Wang[2,3], Robert T. Schooley[4]

Respiratory infections occur through the transmission of virus-containing droplets (>5 to 10 μm) and aerosols (≤5 μm) exhaled from infected individuals during breathing, speaking, coughing, and sneezing. Traditional respiratory disease control measures are designed to reduce transmission by droplets produced in the sneezes and coughs of infected individuals. However, a large portion of the spread of coronavirus disease 2019 (COVID-19) appears to be occurring through airborne transmission of aerosols produced by asymptomatic individuals during breathing and speaking (1–3). Aerosols can accumulate, remain infectious in indoor air for hours, and be easily inhaled deep into the lungs. For society to resume, measures designed to reduce aerosol transmission must be implemented, including universal masking and regular, widespread testing to identify and isolate infected asymptomatic individuals.

Humans produce respiratory droplets ranging from 0.1 to 1000 μm. A competition between droplet size, inertia, gravity, and evaporation determines how far emitted droplets and aerosols will travel in air (4, 5). Larger respiratory droplets will undergo gravitational settling faster than they evaporate, contaminating surfaces and leading to contact transmission. Smaller droplets and aerosols will evaporate faster than they can settle, are buoyant, and thus can be affected by air currents, which can transport them over longer distances. Thus, there are two

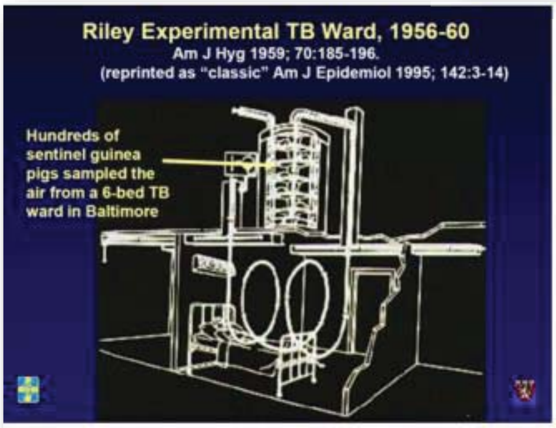
Masks reduce airborne transmission

Infectious aerosol particles can be released during breathing and speaking by asymptomatic infected individuals. No masking maximizes exposure, whereas universal masking results in the least exposure.



END TB

Tuberculosis transmission reduced by anti-TB Treatment




Identifying airborne transmission as the dominant route for the spread of COVID-19

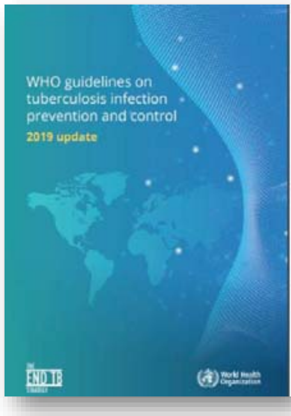
Three principles for infection control

- Administrative measures
- **Environmental controls**
- Use of respiratory protective equipment

WHO Guidelines on TB Infection Prevention and Control , 2019 update

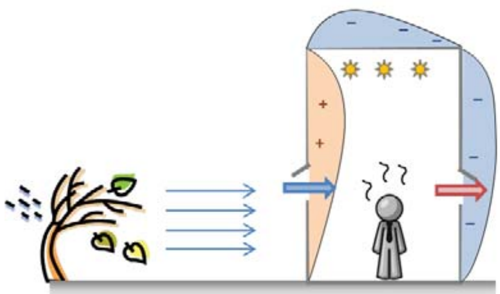
Recommendation 6:

Ventilation systems (including natural, mixed-mode, mechanical ventilation and recirculated air through high-efficiency particulate air [HEPA] filters) are recommended to reduce *M. tuberculosis* transmission to health workers, persons attending health care facilities or other persons in settings with a high risk of transmission



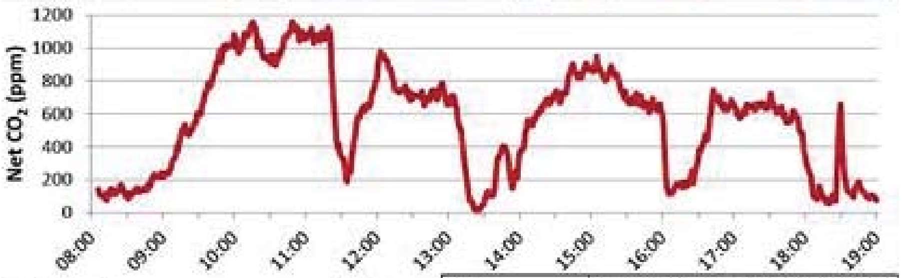
Natural *vs*. mechanical ventilation

- Stabilize
  - Criteria
- Environmental
  - Urban *vs* rural
  - Temperature
- Energy consumption



http://coolvent.mit.edu/intro-to-natural-ventilation/basics-of-natural-ventilation/

High pressure *Low pressure*

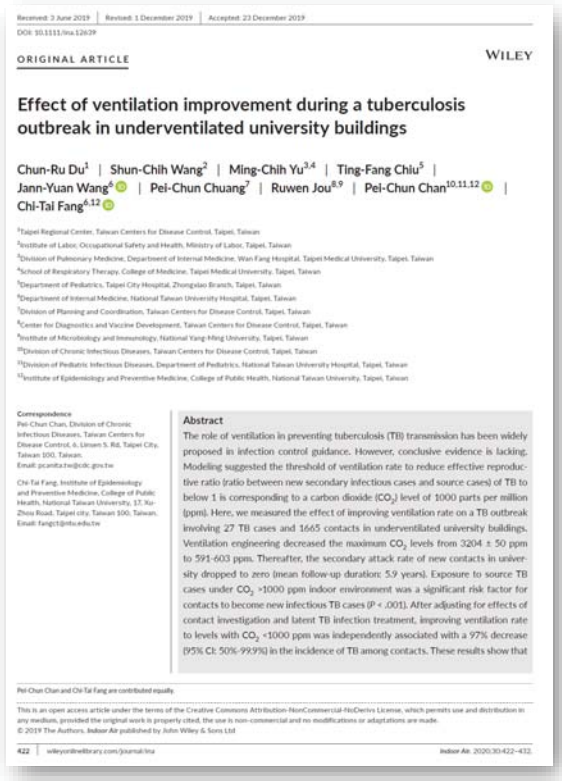


OP-144-01

DESMOND TUTU HIV CENTRE

Place	Number of Minutes	Litres of Rebreathed Air
Amphithéâtre bleu	476	69.99
Palais Passages	100	5.37
Hotel	316	1.04
Pavement Cafe	35	0.65
Outdoors	78	0.00
Sleeping	434	0.00
Total	1439	77.06

Curtesy from Carl Morrow, Paris, IUATLD 2013



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ORIGINAL ARTICLE

WILEY

Effect of ventilation improvement during a tuberculosis outbreak in underventilated university buildings

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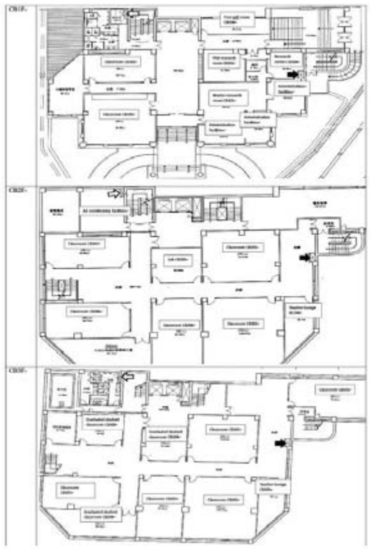
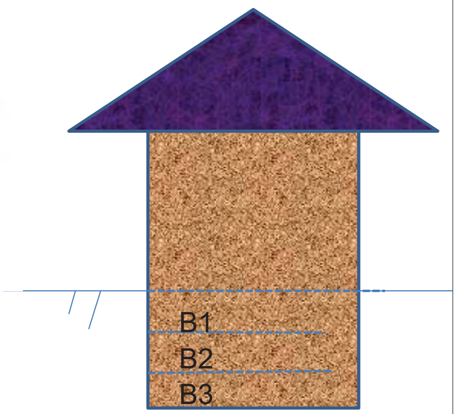
Abstract
The role of ventilation in preventing tuberculosis (TB) transmission has been widely proposed in infection control guidance. However, conclusive evidence is lacking. Modeling suggested the threshold of ventilation rate to reduce effective reproductive ratio (ratio between new secondary infectious cases and source cases) of TB to below 1 is corresponding to a carbon dioxide (CO_2) level of 1000 parts per million (ppm). Here, we measured the effect of improving ventilation rate on a TB outbreak involving 27 TB cases and 1665 contacts in underventilated university buildings. Ventilation engineering decreased the maximum CO_2 levels from 3204 ± 50 ppm to 591-603 ppm. Thereafter, the secondary attack rate of new contacts in university dropped to zero (mean follow-up duration: 5.9 years). Exposure to source TB cases under CO_2 >1000 ppm indoor environment was a significant risk factor for contacts to become new infectious TB cases (P < .001). After adjusting for effects of contact investigation and latent TB infection treatment, improving ventilation rate to levels with CO_2 <1000 ppm was independently associated with a 97% decrease (95% CI: 50%-99.9%) in the incidence of TB among contacts. These results show that

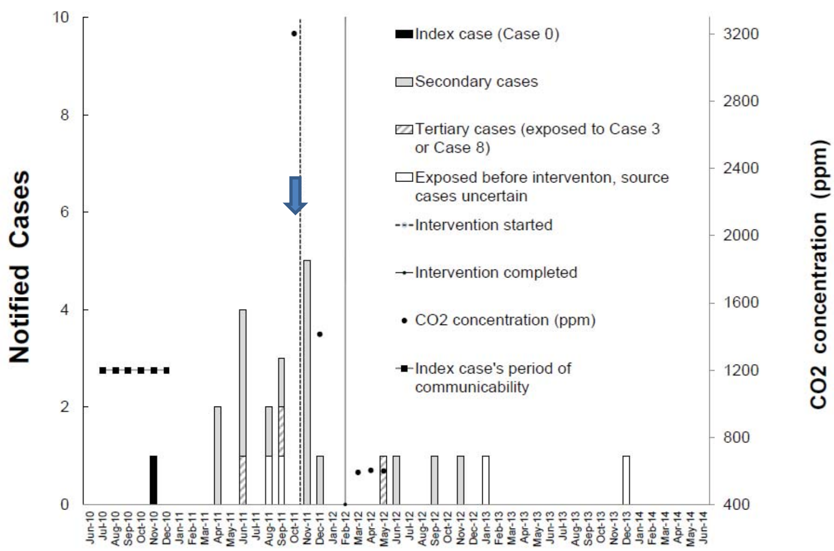
Pei-Chun Chan and Chi-Tai Fang are contributed equally.

422 | wileyonlinelibrary.com/journal/ina Indoor Air. 2020;30:422–432.





Epidemic curve by notification data of active TB cases and CO2 concentration (the max. values of daily average) in the underground floors of Building C before and after ventilation engineering intervention



The National Reference Laboratory of Mycobacteriology performed DNA fingerprinting with standard IS*6110* restriction fragment length polymorphism, which showed an identical genotype for all collected strains isolated from the index case and the subsequent 22 cases.

Measurement of Indoor CO2 Levels

- Standard portable CO2 meters, TSI-8760
- The CO2 meters were calibrated using the National Institute of Standards and Technology standard gases (0/910/3010 ppm).
- To measure the steady state, CO2 was measured during peak hours (10AM to noon or 1PM to 5PM) and after the classrooms had been occupied for at least 30 minutes.

Air Change Per Hour (ACH)

- 每小時換氣次數(ACH)
- 某房間(容積V)內的空氣，每小時被換氣系統提供新鮮空氣所置換次數，一般使用之單位為1/hr或次/hr。
- 每分鐘空氣被置換次數
  - 1/min或次/min
  - Q (m^3/min)/V(m^3) * 60
  - ACH

Estimation of ventilation rate

- The relationship between the steady state CO2 level (which represents the per person ventilation level) and room ventilation rate *Q* is given by Issarow et al:

$$CO2\ (steady\ state) = C_E + npC_a/Q$$

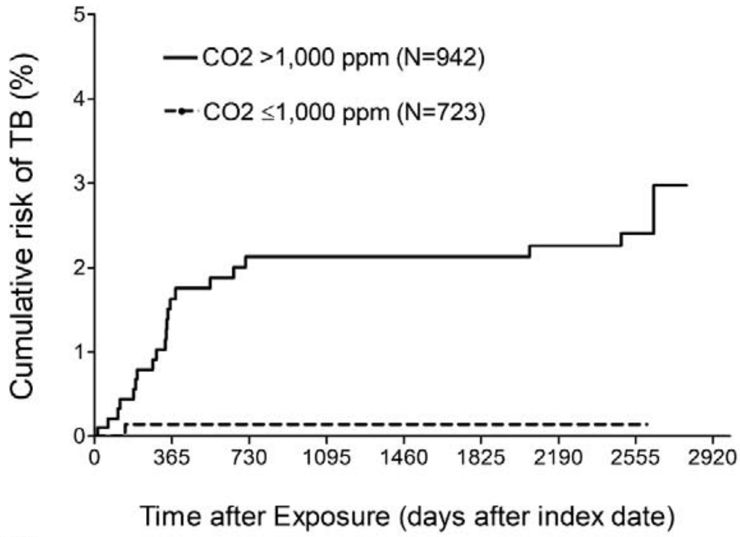
- Here C_E is the CO2 level of outdoor ambient air (400 ppm), *n* is the number of room occupants, *p* is the breathing rate (6 liter/min), ***Q* is ventilation rate (L/s),** and C_a is the CO2 fraction in exhaled breath (38,000 ppm).
- For a standard classroom (180 m^3) with 30 students, substituting *p*Ca by average CO2 generation rate (0.0048 L/s per person), a CO2 level of 3,204 ppm (before the interventions) is equivalent to 1.7 L/s per person. After ventilation engineering, the CO2 levels decreased to 591–603 ppm, equivalent to 23.6 -25.1 L/s per person.

Reconstruction

Before intervention

After removal of upper 2/3 glass

P < .001, median time from exposure to TB notification: 11 months, interquartile range: 6-18 months



Number at risk

CO2 >1,000 ppm	942	805	776	776	776	776	775	276
CO2 ≤1,000 ppm	723	697	695	695	694	670	323	77

Kaplan-Meier estimates for the risk of contacts to become new infectious TB cases, by ventilation status at the time of exposure to source cases **(person-time after the start of IPT was censored)**

Risk factors for 1035 smear-positive contacts to acquire active TB

Variates	No. of TB cases[a] in each category of the contact (%)	Univariable HR	95% CI	P value	Multivariable Adjusted HR	95% CI	P value
Contacts of index case							
No	3/895 (0.3)	1.0			1.0		
Yes	19/140 (13.6)	46.5	38.7-157.7	<.0001	27.9	8.1-96.9	<.0001
Household contacts							
No	20/995 (2.0)	1.0			1.0		
Yes	2/40 (5.0)	2.7	0.6-11.7	.1796	57.5	6.8-487.1	.0002
Contact under CO_2 level >1000 ppm							
No	1/449 (0.2)	1.0					
Yes	21/586 (3.6)	14.3	1.9-107.0	.0095	32.8	2.0-540.3	.0145

Relative effect = 1−(1∕adjustedhazardratio for exposure under low ventilation)

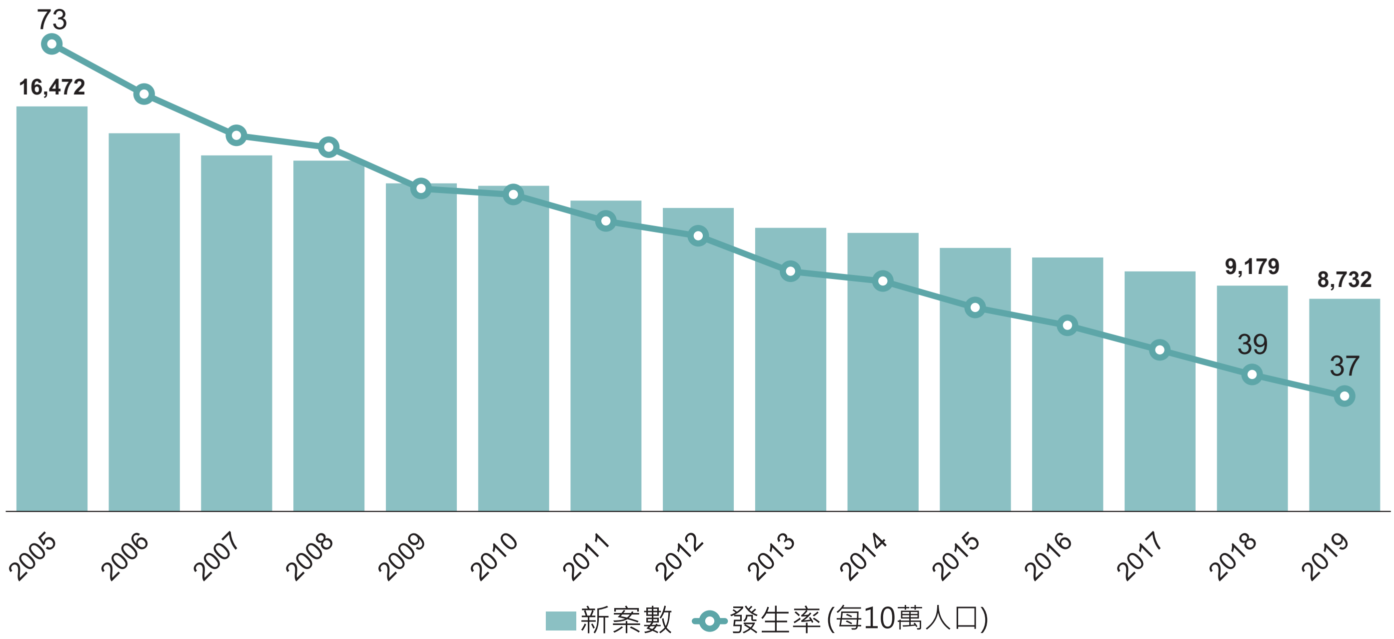
Ventilation improvement to levels with CO2 <1000 ppm was associated with a **97% decrease** in incidence of infectious TB cases among contacts (95% CI:50%-99.9%).

Risk factors for 667 contracts to have latent TB infection

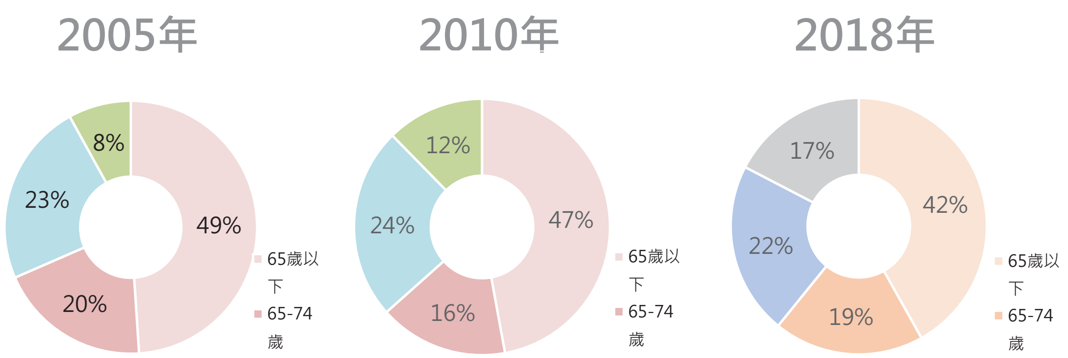
Variates	No. of LTBI cases[a] in each category of the contact (%)	Univariable			Multivariable		
		OR	95% CI	P value	Adjusted OR	95%CI	P value
Contacts of index case[b]							
No	222/565 (39.3)	1.0			1.0		
Yes	80/102 (78.4)	5.6	3.4-9.3	<.0001	4.9	2.9-8.1	<.0001
Contact under CO_2 level >1000 ppm							
No	57/179 (31.8)	1.0			1.0		
Yes	45/488 (50.2)	2.2	1.5-3.1	<.0001	1.6	1.1-2.3	.014

Ventilation improvement to levels with indoor CO2 <1000 ppm was associated with a **38%** decrease in likelihood of LTBI among the contacts (95% CI: 9%-57%).

全國結核病發生率



TB 年齡趨勢 2005-2018年



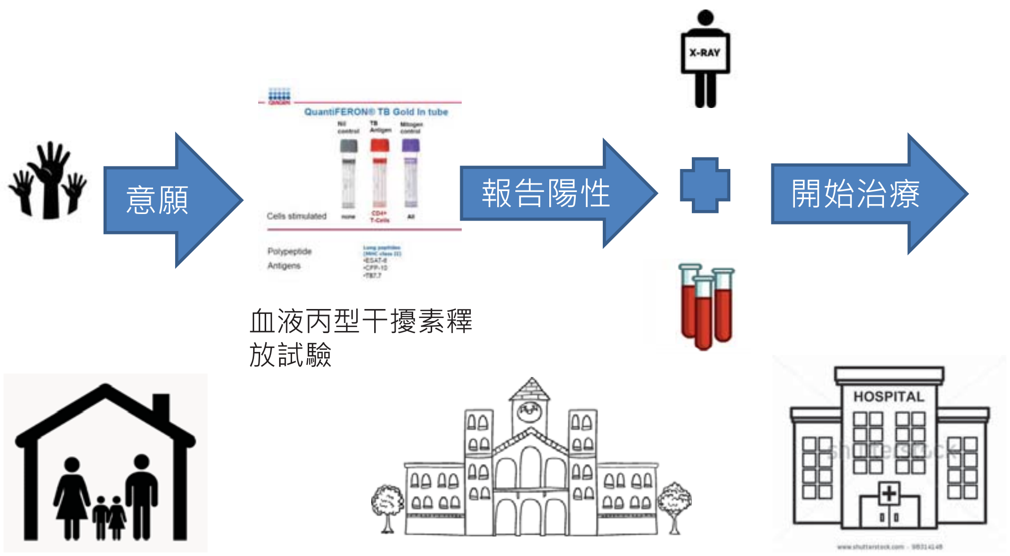
65歲及以上占比58%，由於人口老化影響，高齡個案比重逐年上升
75歲及以上更高達39%

推動潛伏結核感染診斷與治療

未診斷
潛伏結核感染者

- **2020** HIV感染者及矯正機關收容人
- **2019** 中傳染力個案之共同居住/患有慢性病接觸者納入LTBI診斷及治療
  公衛及醫事人員潛伏結核感染宣導及篩檢治療活動
- **2018** 推動長照機構老人族群TB暨LTBI整合計畫
- **2017** 回溯高傳染性個案接觸者納入診斷/治療、高風險族群LTBI治療試辦計畫、新增4R處方
- **2016** 於全國推動「潛伏結核全都治計畫」，導入「速克伏」短程治療處方
- **2015** 於6縣市推動IGRA及「潛伏結核全都治試辦計畫」
- **2012** 擴大LTBI治療服務對象至1986年以後出生接觸者
- **2008** 推動<13歲接觸者LTBI治療

Test and Treat –
潛伏結核不傳染，篩檢治療不發病!

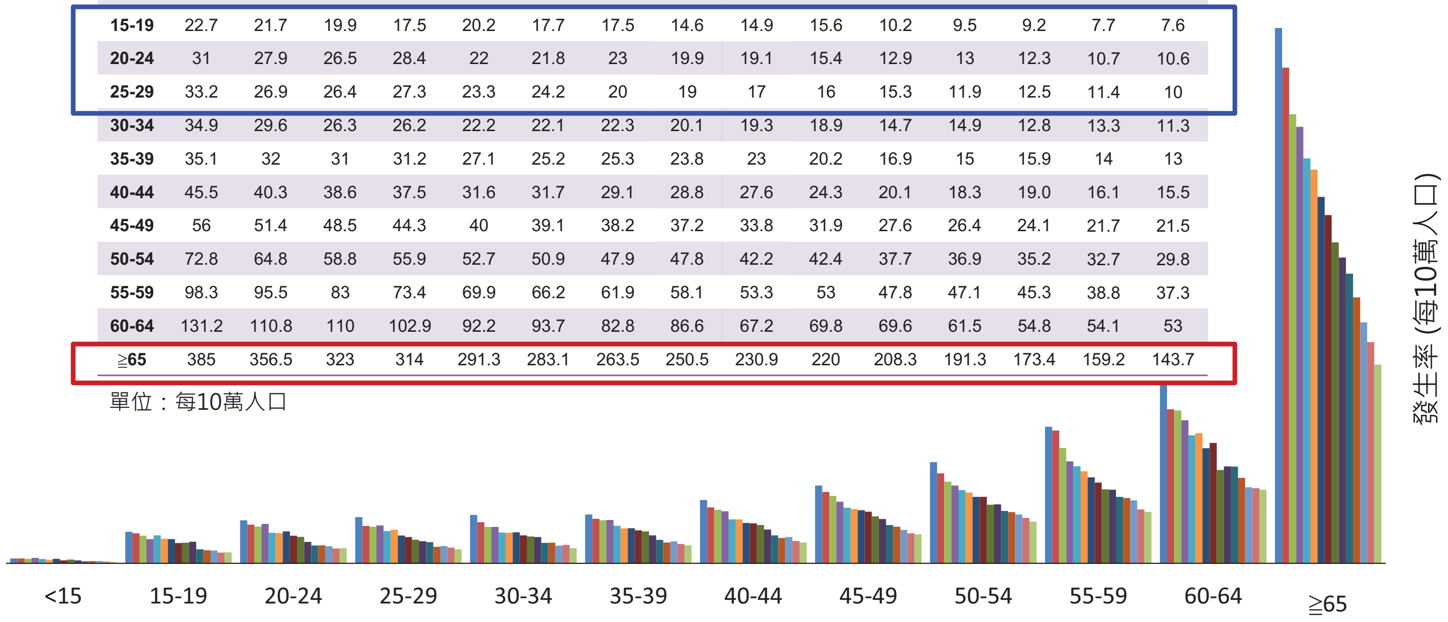


血液丙型干擾素釋放試驗

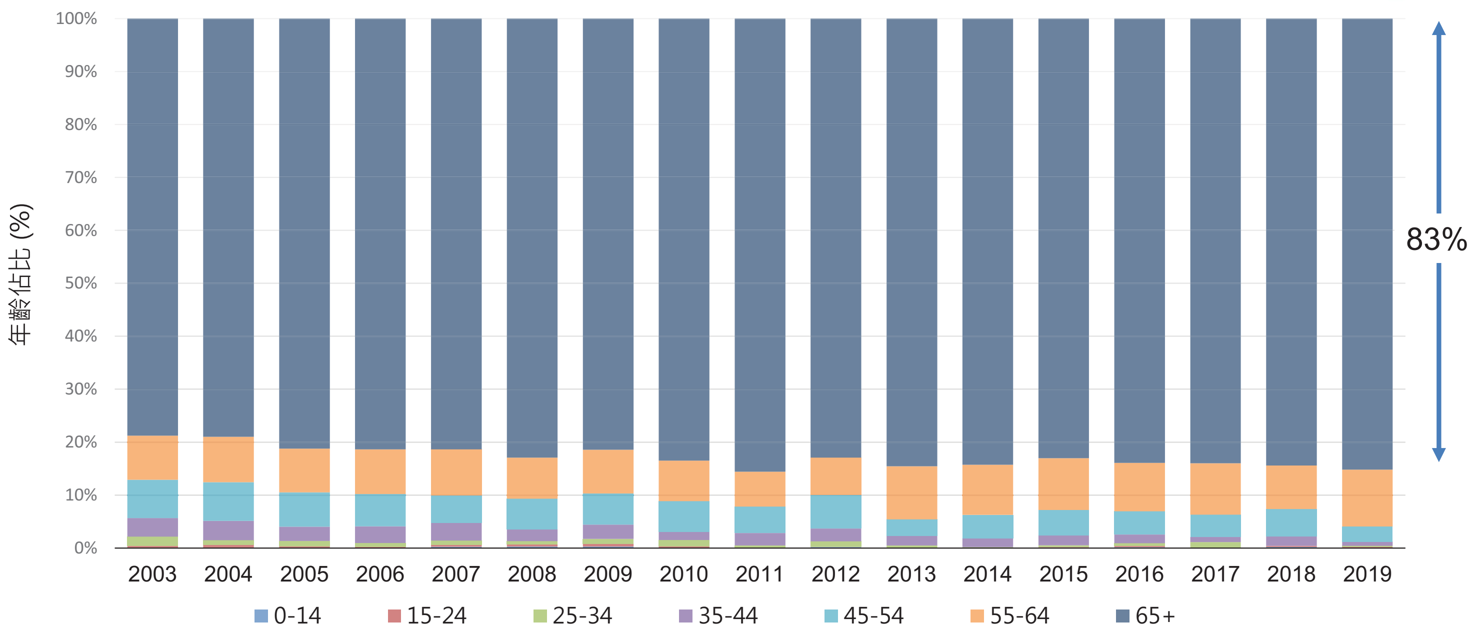
結核病年齡別發生率(2005-2019)

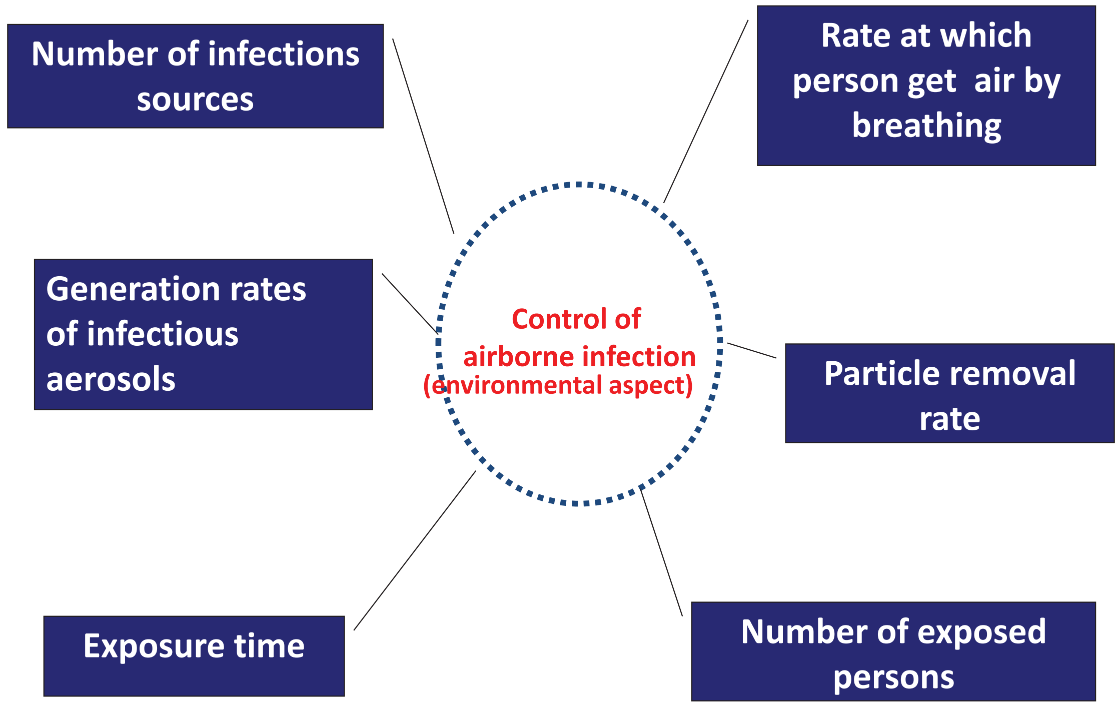
	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
<15	3.5	3.5	3.3	4	3.2	2.6	3.3	2.2	2.7	2.2	1.5	1.7	1.6	1.2	1.2
15-19	22.7	21.7	19.9	17.5	20.2	17.7	17.5	14.6	14.9	15.6	10.2	9.5	9.2	7.7	7.6
20-24	31	27.9	26.5	28.4	22	21.8	23	19.9	19.1	15.4	12.9	13	12.3	10.7	10.6
25-29	33.2	26.9	26.4	27.3	23.3	24.2	20	19	17	16	15.3	11.9	12.5	11.4	10
30-34	34.9	29.6	26.3	26.2	22.2	22.1	22.3	20.1	19.3	18.9	14.7	14.9	12.8	13.3	11.3
35-39	35.1	32	31	31.2	27.1	25.2	25.3	23.8	23	20.2	16.9	15	15.9	14	13
40-44	45.5	40.3	38.6	37.5	31.6	31.7	29.1	28.8	27.6	24.3	20.1	18.3	19.0	16.1	15.5
45-49	56	51.4	48.5	44.3	40	39.1	38.2	37.2	33.8	31.9	27.6	26.4	24.1	21.7	21.5
50-54	72.8	64.8	58.8	55.9	52.7	50.9	47.9	47.8	42.2	42.4	37.7	36.9	35.2	32.7	29.8
55-59	98.3	95.5	83	73.4	69.9	66.2	61.9	58.1	53.3	53	47.8	47.1	45.3	38.8	37.3
60-64	131.2	110.8	110	102.9	92.2	93.7	82.8	86.6	67.2	69.8	69.6	61.5	54.8	54.1	53
≥65	385	356.5	323	314	291.3	283.1	263.5	250.5	230.9	220	208.3	191.3	173.4	159.2	143.7

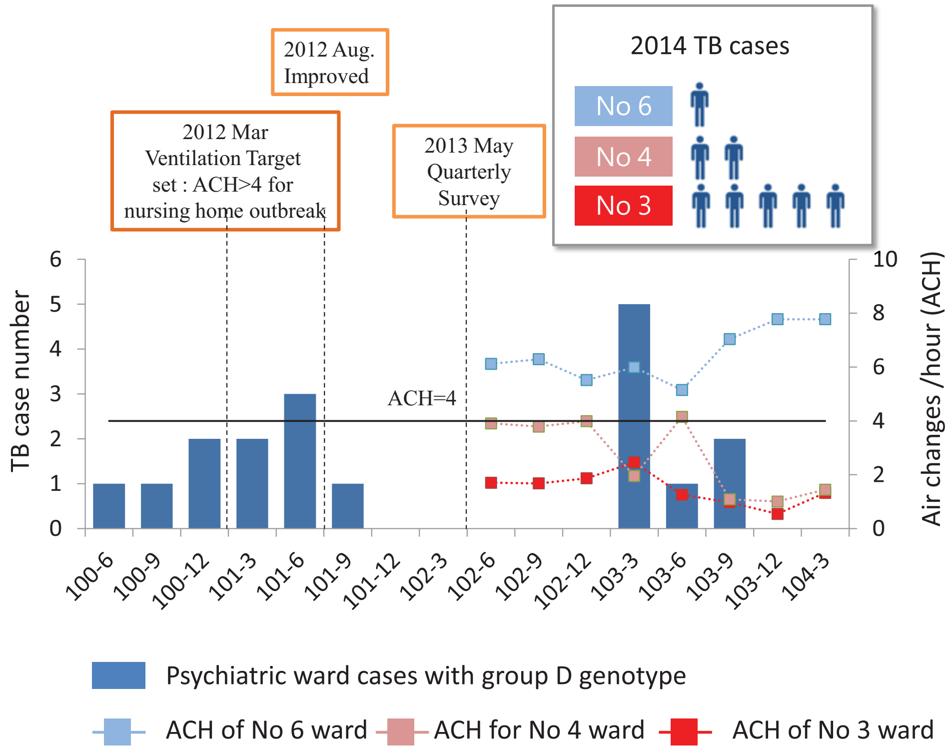
單位：每10萬人口



結核病死亡個案之年齡分佈(2003-2019)




Number of infections sources
Rate at which person get air by breathing
Generation rates of infectious aerosols
Control of airborne infection (environmental aspect)
Particle removal rate
Exposure time
Number of exposed persons


2012 Aug. Improved
2012 Mar Ventilation Target set : ACH>4 for nursing home outbreak
2013 May Quarterly Survey
2014 TB cases
No 6
No 4
No 3
TB case number
Air changes /hour (ACH)
ACH=4
0
1
2
3
4
5
6
0
2
4
6
8
10
100-6
100-9
100-12
101-3
101-6
101-9
101-12
102-3
102-6
102-9
102-12
103-3
103-6
103-9
103-12
104-3
Psychiatric ward cases with group D genotype
ACH of No 6 ward
ACH for No 4 ward
ACH of No 3 ward

Congregate settings were high risk populations are

- Congregate settings
  - School
    - Basement
    - No window
  - Long term care facility
    - Recycle fan
    - Split-Type Air-Conditioners

High risk populations

Elderly

Nursing home

Long term care facility

Hospital

Common risks

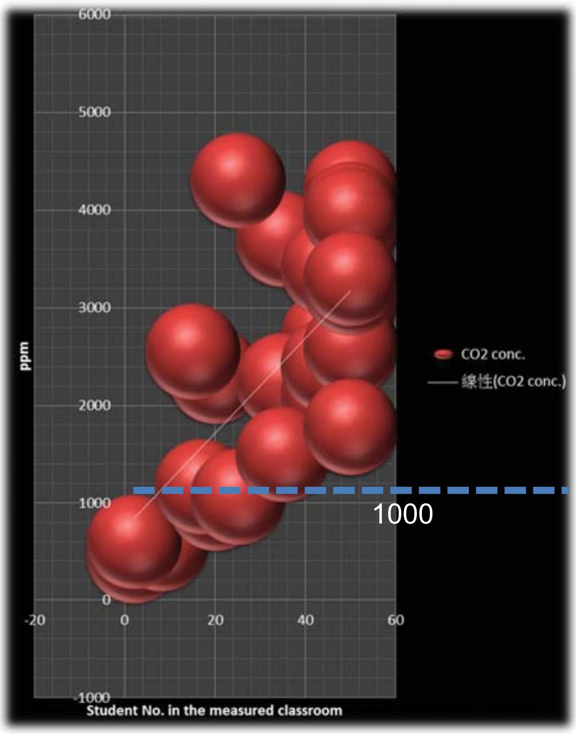
✓ Crowded

✓ Long time shared

✓ Poor ventilation

CO_2 concentration in 28 classrooms at the S building

- >=1000ppm: 89%
- < 1000ppm in 3 because of <10 students in the rooms
- This is the second set of surveillance data for CO2 concentration gathered after the outbreak => no improvement at all



建築技術規則建築設備編 102條

第 102 條 建築物供各種用途使用之空間，設置機械通風設備時，通風量不得小於左表規定：

房間用途	樓地板面積每平方公尺所需通風量（立方公尺／小時）	
臥室、起居室、私人辦公室等容納人數不多者。	8	8
辦公室、會客室	10	10
工友室、警衛室、收發室、詢問室。	12	12
會議室、候車室、候診室等容納人數較多者。	15	15
展覽陳列室、理髮美容院。	12	12
百貨商場、舞蹈、棋室、球戲等康樂活動室、灰塵較少之工作室、印刷工場、打包工場。	15	15
吸煙室、學校及其他指定人數使用之餐廳。	20	20
營業用餐廳、酒吧、咖啡館。	25	25
戲院、電影院、演藝場、集會堂之觀眾席。	75	75
廚房 營業用	60	60

民國 106 年 10 月 18 日

(108/5/29修訂)

可考慮的環境監測措施:
設立二氧化碳顯示面版
由於二氧化碳的濃度會與換氣頻率和室內的人數有關, 因此量測時應注意當時的室內人數

環保署室內空氣品質標準

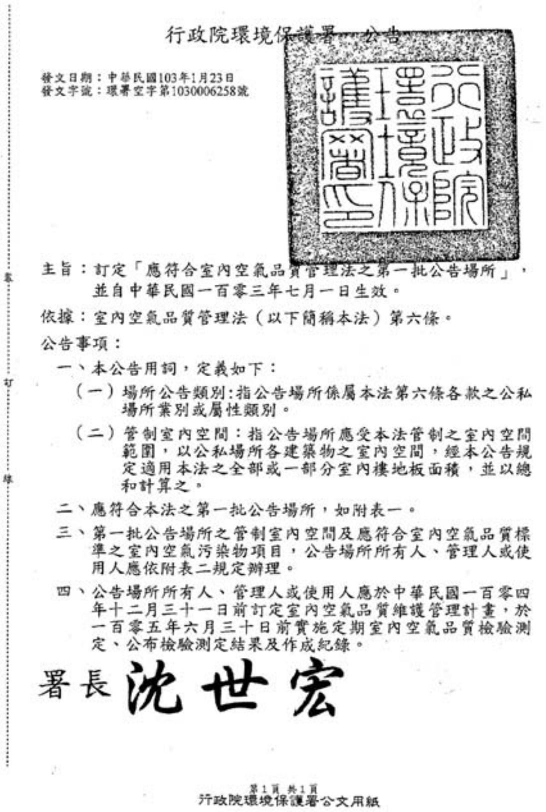
項目	標準值		單位
二氧化碳（CO_2）	八小時值	一〇〇〇	ppm（體積濃度百萬分之一）
一氧化碳（CO）	八小時值	九	ppm（體積濃度百萬分之一）
甲醛（HCHO）	一小時值	〇・〇八	ppm（體積濃度百萬分之一）
總揮發性有機化合物（TVOC，包含：十二種揮發性有機物之總和）	一小時值	〇・五六	ppm（體積濃度百萬分之一）
細菌(Bacteria)	最高值	一五〇〇	CFU/m^3（菌落數/立方公尺）
真菌(Fungi)	最高值	一〇〇〇。但真菌濃度室內外比值小於等於一・三者，不在此限。	CFU/m^3（菌落數/立方公尺）
粒徑小於等於十微米（μm）之懸浮微粒（PM_{10}）	二十四小時值	七五	$\mu g/m^3$（微克/立方公尺）
粒徑小於等於二・五微米（μm）之懸浮微粒（$PM_{2.5}$）	二十四小時值	三五	$\mu g/m^3$（微克/立方公尺）
臭氧（O_3）	八小時值	〇・〇六	ppm（體積濃度百萬分之一）

台灣的室內空氣品質法規演進

- In 2011, the Environmental Protection Agency released its indoor air quality standards.
- In 2012, detailed enforcement procedures for these of standards were put in place. However, these procedures were not fully enforced until 2014, and only a limited number of places were required to meet the standards.
- That being said, in 2016, libraries in all colleges, payment area and waiting rooms in medical centers and regional hospitals, living rooms in public elderly social welfare care facilities were made to meet the standards.
- If suggested CO2 threshold level—which is much in line with the indoor air quality standards—gains wider acceptance, organizations might start self-monitoring CO2 levels and improve ventilation to keep outbreaks from occurring.

A Collaboration between EPA and MOHW

- 2016年討論醫院院感查核標準有固定空氣品質的自我評核機制
- 建議依照室內空氣品質標準來自我管理 (對於環保署尚未公告之區域及型態的醫療院所)
- 2020年建議長照機構先有換氣通風概念再鼓勵測量 CO2 來做為客觀的標準



行政院環境保護署 公告

發文日期：中華民國103年1月23日
發文字號：環署空字第1030006258號

主旨：訂定「應符合室內空氣品質管理法之第一批公告場所」，並自中華民國一百零三年七月一日生效。

依據：室內空氣品質管理法（以下簡稱本法）第六條。

公告事項：

一、本公告用詞，定義如下：

（一）場所公告類別:指公告場所係屬本法第六條各款之公私場所業別或屬性類別。

（二）管制室內空間：指公告場所應受本法管制之室內空間範圍，以公私場所各建築物之室內空間，經本公告規定適用本法之全部或一部分室內樓地板面積，並以總和計算之。

二、應符合本法之第一批公告場所，如附表一。

三、第一批公告場所之管制室內空間及應符合室內空氣品質標準之室內空氣污染物項目，公告場所所有人、管理人或使用人應依附表二規定辦理。

四、公告場所所有人、管理人或使用人應於中華民國一百零四年十二月三十一日前訂定室內空氣品質維護管理計畫，於一百零五年六月三十日前實施定期室內空氣品質檢驗測定、公布檢驗測定結果及作成紀錄。

署長 沈世宏

第1頁 共1頁
行政院環境保護署公文用紙

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ORIGINAL ARTICLE

WILEY

Effect of ventilation improvement during a tuberculosis outbreak in underventilated university buildings

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Abstract

The role of ventilation in preventing tuberculosis (TB) transmission has been widely proposed in infection control guidance. However, conclusive evidence is lacking. Modeling suggested the threshold of ventilation rate to reduce effective reproductive ratio (ratio between new secondary infectious cases and source cases) of TB to below 1 is corresponding to a carbon dioxide (CO_2) level of 1000 parts per million (ppm). Here, we measured the effect of improving ventilation rate on a TB outbreak involving 27 TB cases and 1665 contacts in underventilated university buildings. Ventilation engineering decreased the maximum CO_2 levels from 3204 ± 50 ppm to 591-603 ppm. Thereafter, the secondary attack rate of new contacts in university dropped to zero (mean follow-up duration: 5.9 years). Exposure to source TB cases under CO_2 >1000 ppm indoor environment was a significant risk factor for contacts to become new infectious TB cases (P < .001). After adjusting for effects of contact investigation and latent TB infection treatment, improving ventilation rate to levels with CO_2 <1000 ppm was independently associated with a 97% decrease (95% CI: 50%-99.9%) in the incidence of TB among contacts. These results show that

Pei-Chun Chan and Chi-Tai Fang are contributed equally.

maintaining adequate indoor ventilation could be a highly effective strategy for controlling TB outbreaks.

KEYWORDS

carbon dioxide, contact investigation, isoniazid preventive therapy, outbreak control, tuberculosis, ventilation

1 | INTRODUCTION

Tuberculosis (TB) is currently the leading global epidemic, causing more than 1.6 million deaths worldwide in 2017.[1] Despite the advances in molecular diagnosis, effective drug treatment, and directly observed treatment, short-course (DOTS) program, the worldwide TB incidence declined very slowly, 2% per year at the present time—but is consistent with model predictions for the impact of the DOTS strategy.[1,2] Additional strategies are urgently required to achieve the global End TB target.

Tuberculosis is an airborne disease which spread through infectious aerosol generated by patients during cough.[3] In an indoor environment, infectious aerosol progressively accumulates and put everyone in the room at risk unless the indoor air is continuously replaced with the fresh outdoor air by ventilation.[4] Poor ventilation is associated with increased risk of tuberculin skin test (TST) conversion.[5] The role of ventilation in preventing TB transmission has been widely proposed in infection control guidance.[2,6-8] However, conclusive evidence is lacking.[8,9]

Theoretically, improving ventilation rate decreases the probability of TB transmission exponentially, but never to zero.[10] Nevertheless, to stop the TB epidemic, it only needs to reduce the effective reproductive ratio (ratio between new secondary infectious cases and source cases) to less than one, rather than to zero.[11] Modeling work, based on parameters from South Africa high schools, suggested that this threshold is 8.6 L/s per person, corresponding to an indoor carbon dioxide (CO_2) level of 1000 parts per million (ppm).[12] However, this theoretical threshold has not been tested in real world.

Taiwan has advanced public health services. The national directly observed therapy program and contact investigation system ensure all TB patients and their contacts are diagnosed promptly and treated effectively.[13] Nevertheless, a large outbreak involving 27 active TB cases and 1665 contacts occurred at a poorly ventilated university building during 2010-2013. Investigation found that the university building had an indoor CO_2 level up to 3204 ppm as the outbreak unfolded. We aimed to measure the effect of improving ventilation to levels with indoor CO_2 <1000 ppm on this TB outbreak, focusing on the risk of contacts to become new secondary infectious TB cases.

Practical Implications

- Tuberculosis (TB) is the leading global epidemic, causing 1.6 million deaths worldwide in 2017. Despite advances in molecular diagnosis, effective drug therapy, and directly observed treatment, short-course (DOTS) programme, the global incidence declined very slowly, only 2% per year––but is in line with predicted impact of DOTS strategy. Additional strategies are urgently required.
- This study provides the first empirical data showing that improving indoor ventilation to levels with CO2 <1000 ppm is highly effective in controlling a TB outbreak which occurred in poorly ventilated indoor environment. A refocusing on the importance of adequate indoor ventilation in TB control could be the game changer for achieving the global End TB target.

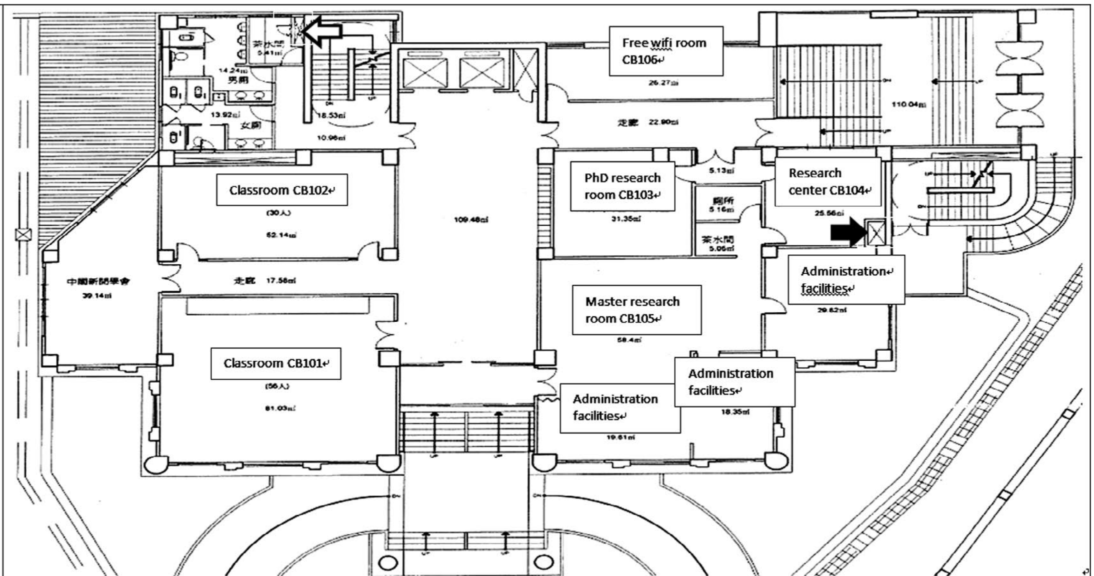
2 | METHODS

2.1 | Study settings

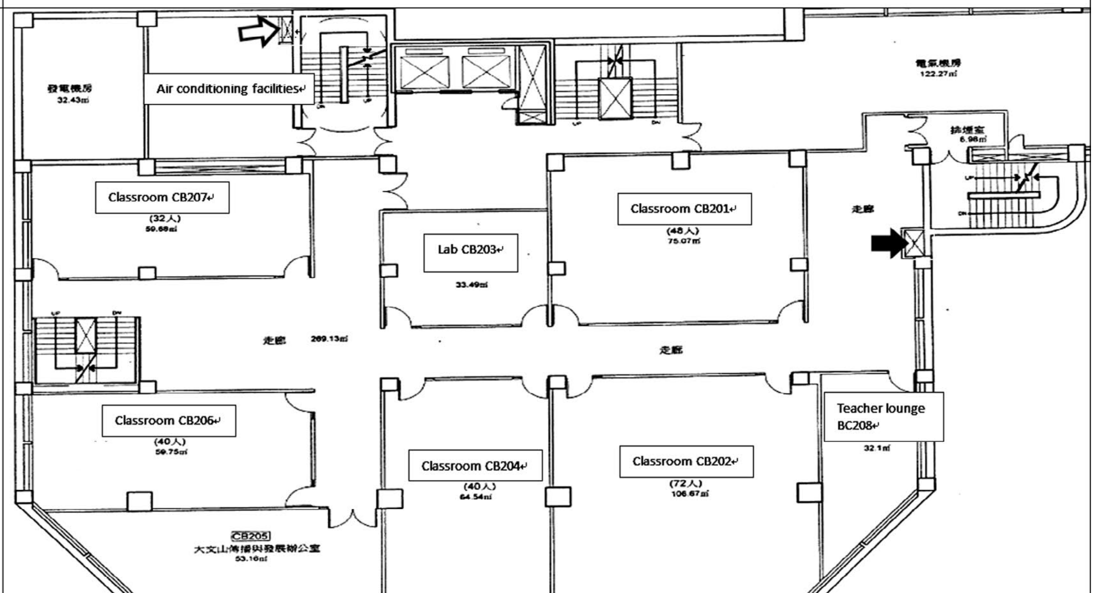
University A, located at suburbs of Taipei, has around 10 000 students. The university building used a central mechanical ventilation and air-conditioning system to maintain temperature within a comfortable range in a hot and humid climate. The air circulates between classrooms. None of the classrooms has an independent ventilation system. To minimize electricity cost, no extractor ventilation machines had been installed for underground floors (Figure 1). The lack of air outflow created a positive indoor pressure that prevented the inflow of fresh hot air.

FIGURE 1 Building C underground floorplan. The locations of the very small outward grille and inward grille of this central ventilation system in each floor are labeled with black arrow (outlet) and white arrow (inlet), respectively. There were 2, 5, and 4 classrooms on basement 1 (CB1F), basement 2 (CB2F), and basement 3 (CB3F), respectively, plus administrative offices and graduate student research rooms. Before ventilation engineering, this ventilation system did not have any extractor machines. The four 2850 cubic-feet-per-min (CFM) supply machines and one 2300 CFM supply machines created a positive pressure which minimized inflow of hot fresh air. On October 28, 2011, three 3000 CFM extractor machines were installed, along with five 3000 CFM supply machines. During November 2011, two more supply machines were installed, along with a revision of a direct type air inlet duct to increase the inward air flow

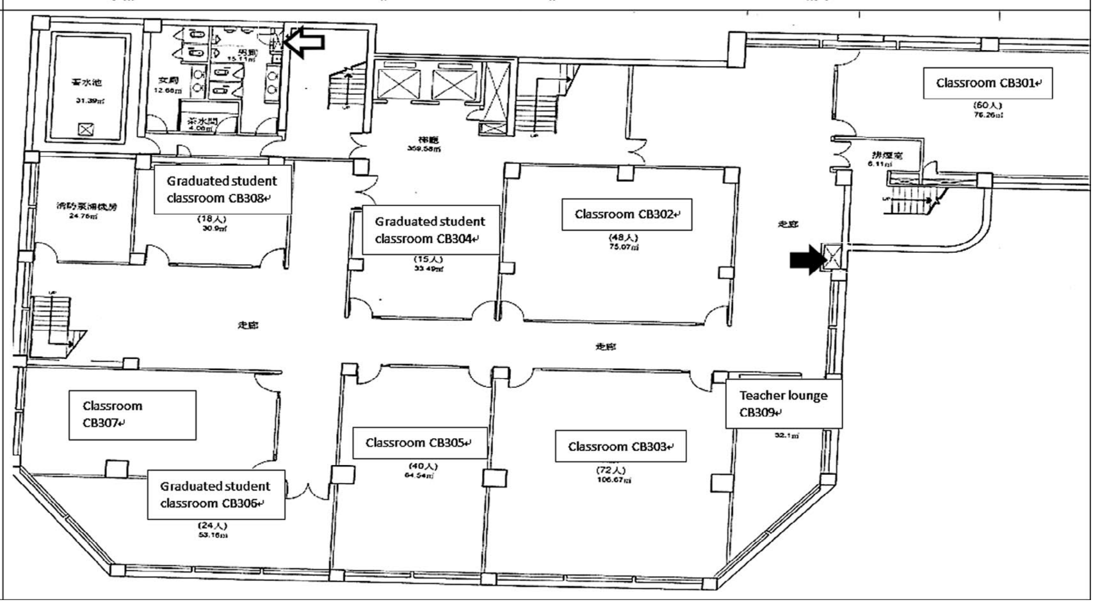
CB1F



CB2F



CB3F



2.2 | The outbreak

The outbreak began at classrooms (Figure 2) in the underground floors of the Building C. Figure 1 shows a diagram of rooms in the floorplan. The index case (Case 0, a student who presented with a productive cough for 1 month) was diagnosed with smear-positive non-cavitary TB in November 2010. The index case was immediately put on sick leave and began treatment. Initial chest radiography (CXR) screening of 44 classmates, 3 teachers and 4 family members, found no additional cases. However, from April to September 2011, 11 new cases emerged. Most of these cases had been in the same classroom but never had close contact with the index case. The National Reference Laboratory of Mycobacteriology performed DNA fingerprinting with standard IS*6110* restriction fragment length polymorphism,[14] which showed an identical genotype for all collected strains isolated from the index case and the subsequent 11 cases, including 7 secondary cases related to the index case, 2 tertiary cases related to Case 3, and two cases of uncertain sources (Figure 3). The ongoing transmission, despite the early removal of the index case, prompted investigation of possible environmental factors.

2.3 | Study design

We used a retrospective cohort study of all contacts (n = 1665) involved in this outbreak (follow-up to July 31, 2018, with a mean follow-up time of 5.9 years) to examine the effect of ventilation improvement on the risk for contacts to become new infectious TB cases. We obtained cases, contacts, and follow-up data from the National Surveillance of Notifiable Contagious Diseases (NSNCD), a centralized cloud-based case management database to ensure that all new TB cases from the list of university students, employees, and TB patients' contacts were included.

2.4 | Contact investigation

In addition to household contacts, all persons who had a cumulative 30-40-hour exposure to shared air (defined as staying in the same floor or within the same building with any infectious TB patients) were considered as contacts for whom clinical and radiographic evaluations and follow-up were provided to detect active TB.[13] Public health nurses used lists of students/faculties/employee, curriculum, and class rosters to identify contacts as many as possible. To analyse the chain of transmission, all contacts were linked to the first source case he/she had been exposed to. Per national policy, contacts <13 years of age received a TST, using a cutoff point of 10 mm.[13] In response to this outbreak, the authority expanded TST to all contacts regardless of age beginning in October 2011. Isoniazid preventive therapy (isoniazid 10 mg/kg once daily [max. 300 mg] for 9 months) was offered to all asymptomatic contacts with latent TB infection (LTBI, defined as having a positive TST >10 mm, and normal chest radiographs). However, LTBI contacts could choose not to receive treatment.

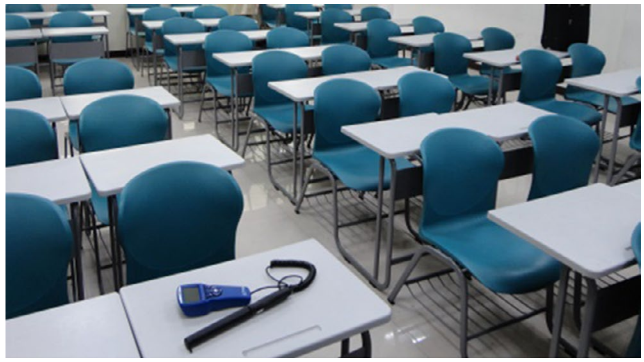


FIGURE 2 One of the crowded and poorly ventilated 56-seat underground classrooms, where the index case had attended class, with a carbon dioxide level up to 2936 parts per million (ppm) at peak hours (the photograph was taken after the students have left)

2.5 | Measurement of indoor CO_2 levels

Standard portable CO_2 meters, TSI-8760 (TSI Incorporated, with precision range of ±50 ppm),[15] were used to measure CO_2 levels. The CO_2 meters were calibrated using the National Institute of Standards and Technology standard gases (0/910/3010 ppm). All CO_2 measurements were conducted during peak hours (10 AM to noon or 1 PM to 5 PM) when almost every classroom was occupied (20-50 students per class, Appendix S1). Measurements were taken beginning 30 minutes after the commencement of a class and lasted until the end of a class. One to four sites were sampled, based on classroom size. The measurement was repeated every 10 seconds for 5-15 minutes. The maximum, minimum, and average CO_2 levels, classroom population, and numbers of open windows and doors (at the time of measurement), were recorded (Appendix S1). Because indoor CO_2 in congregate settings rarely achieve steady state,[16] we used the monthly maximum of daily averages of indoor CO_2 levels as the best estimate[17] for the theoretical steady-state value in calculating the corresponding ventilation rate. We performed a sensitivity analysis which uses monthly median of daily averages of indoor CO_2 levels in estimating the effect of ventilation on infection risk.

2.6 | Estimation of ventilation rate

The relationship between the steady-state indoor CO_2 level (which represents the per person ventilation) and room ventilation rate Q is given by Issarow et al[17]:

$$CO_2\,(\text{steady state}) = C_E + npC_a/Q.$$

Here, Q is ventilation rate (L/s), which we wanted to estimate. C_E is the CO_2 level of outdoor ambient air (400 ppm), n is the number of room occupants, p is the breathing rate, and C_a is the concentration in exhaled breath. For a standard classroom (180 m^3)

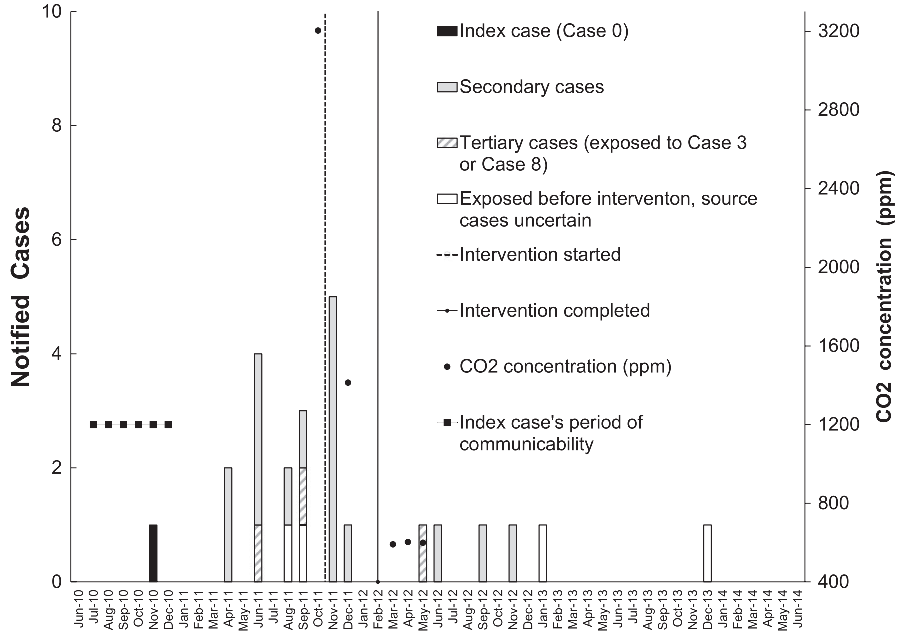


FIGURE 3 Epidemic curve by notification date of active tuberculosis (TB) cases and carbon dioxide (CO_2) concentration (the monthly maximum values of daily average) in the underground floors of Building C before and after ventilation engineering intervention. Index case (black), secondary cases (gray), and tertiary cases (diagonal) are shown by different color or pattern. Four additional cases caused by the same strain (white) were found by cross-checking 20 392 employees and students who had stayed at University A campus before the ventilation engineering was completed on January 16, 2012: Case 9 was exposed to Case 0 in the CB2 classroom for only 20 h, but exposed to Case 3 in Building M on the same floor (but not in the same room) for 62 h; Case 22 exposed to Case 0 for 32 h, to Case 3 for 39 h, to Case 8 for 14 h, and Case 23 was exposed to Case 0 for 30 h, Case 3 for 39 h, Case 8 for 14 h, Case 9 for 8 h, all in Building M on the same floor but not in the same room. The curriculum of Case 7 could not be matched to any TB cases. The final four cases (one notified in 2016, 2017, and two in 2018, respectively, not shown in the Figure) were contacts of the index case (contact occurred in poorly ventilated environments before the ventilation engineering). All these four patients had been diagnosed to have latent TB infection in late 2011 but refused to receive isoniazid preventive therapy

with 30 students, substituting pC_a by average CO_2 generation rate (0.0048 L/s per person),[18] a CO_2 level of 3204 ppm (before intervention) is equivalent to 1.7 L/s per person. After ventilation engineering, the CO_2 levels decreased to 591-603 ppm, equivalent to 23.6-25.1 L/s per person.

2.7 | Secondary attack rate

We compared the secondary attack rate in contacts of TB cases notified before the completion of ventilation engineering on January 16, 2012, (before intervention) and the secondary attack rate in contacts of TB cases notified after the completion of ventilation engineering on January 16, 2012, (after intervention). All contacts were followed up to July 31, 2018.

2.8 | Effect of ventilation improvement

The effect of ventilatory improvement on reducing TB incidence among contacts was estimated by the following formula:[11]

$$\text{Relative effect} = 1 - (1/\text{adjusted hazard ratio for exposure under low ventilation}).$$

2.9 | Statistical analysis

Proportions and rates were compared with chi-square (or Fisher's exact test) and chi-score test, respectively. For time-to-event analysis, the zero time of follow-up for each contact is the diagnosis date of the source case (index date). The end of follow-up was the date when the contact was notified as an active TB case (event), the date of mortality due to non-TB-related causes (censored), or July 31, 2018 (censored). To control the effect of isoniazid preventive therapy (100% effective, none of the 173 [0%] contacts who received isoniazid preventive therapy acquired TB), person-time after the date of starting isoniazid preventive therapy was censored. Probabilities of TB were estimated by Kaplan-Meier method and compared using log-rank test. Cox regression and logistic regression were used to adjust for covariates. All analyses were conducted using SAS ver. 9.2 (SAS Institute). A two-sided $P < .05$ was considered statistically significant.

2.10 | Ethical statement

The Institutional Review Board of Taiwan Centers for Diseases Control (Taipei, Taiwan) approved the study procedure as public health surveillance, which does not require informed consent.

3 | RESULTS

3.1 | Epidemiological investigation

A total of 27 active TB cases (mean age:23 years, all previously healthy) were identified. Fifteen cases were confirmed by sputum culture of strains with an identical DNA fingerprint. Twelve cases were confirmed by serial CXR findings and response to anti-TB treatment as well as epidemiological link to one of DNA fingerprinting-confirmed cases. Figure 3 shows the chains of transmission (index case, secondary cases, and tertiary cases). There were four DNA fingerprinting-confirmed active TB case whose source case was uncertain (see Figure 3 legend for details).

3.2 | Initial ventilation assessment

Ventilation specialists from the Taiwan Institute of Labor, Occupational Safety and Health (ILOSH) inspected the classrooms in the underground floors of Building C on October 13, 2011. The CO_2 level measured at Classroom CB307 (in B3 floor) where the index case had attended the class was as high as 3204 ppm. The CO_2 level measured at Classroom CB202 in B2 floor was 2926 ppm (Appendix S1). Furthermore, the CO2 level measured at the inlet of air flow (see the floorplan in Figure 1) was 1600 ppm, which indicates that the airflow in underground floors were nearly 100% recirculation, with little inflow of fresh air from the outside. The authority enforced ventilation engineering.

3.3 | Ventilation engineering

The intervention consisted of: (a) for the ground floor and above, keeping the windows open (to serve as air outlets) to facilitate both natural and mechanical ventilation; and (b) for the underground floors, installing extractor ventilation machines to improve air outflow (see Figure 1 legend for details), along with constructing new ventilatory circuits for Building C to normalize the outflow of exhaled air so that the pre-existing inlet pipes from the roof could function as designed (see Figure 1 and Appendix S2). The above intervention decreased ground floor CO_2 levels to 700-800 ppm (measured on December 9, 2011), but the CO_2 levels on underground floors were still up to 1413 ppm (Appendix S1). A glass wall at the ground floor door in Building C (Figure 4A) blocked the outflow of exhaled air (through a stairway) from classrooms on the three underground floors. The outbreak coordination committee therefore recommended removing the aforementioned glass wall, which was subsequently removed on January 16, 2012 (Figure 4B). After these interventions, the ventilation levels in Building C improved to 370-400 ppm on the ground floor and 591-603 ppm (23.6-25.1 L/s per person) on the underground floors (Figure 3). The same ventilation engineering work were implemented in other buildings as well.

3.4 | Impact of ventilation on secondary attack rate in University A

After ventilation engineering, the secondary attack rate of university contacts dropped to zero (contacts of TB cases notified before January 16, 2012:20/728 [2.7%] vs contacts of TB cases notified after January 16, 2012:0/278 [0.0%], $P = .002$, follow-up to July 31, 2018, for a mean of 5.9 years). The drop in secondary attack rate was not due to CXR screening that may detect less infectious cases (20/634 [3.0%] vs 0/275 [0.0%], after excluding contacts of cases detected by mass CXR screening, $P < .001$), nor was it caused by treatment of LTBI (20/1 480 411 vs 0/544 752 person-days, after excluding person-time after starting isoniazid preventive therapy, $P = .007$).

3.5 | Ventilation levels and risk for contacts to become new infectious TB cases

Table 1 shows demographic and epidemiological information for 1665 contacts (including 1006 school contacts, 214 contacts at a private tutoring class [where Case 8 attended], 96 household contacts, and 352 contacts in other settings) involved in this outbreak. Exposure to source cases under indoor CO_2 >1000 ppm (n = 942, including the 728 school contacts exposed before January 16, 2012, and 214 contacts at a private tutoring class where an indoor CO_2 level of 1022 ppm, Table S4) was associated with a higher risk for the contacts to become

FIGURE 4 The un-openable glass wall at the front door of the ground floor of Building C, which obstructed the ventilation of underground floor classrooms. (A), before intervention and (B) after removal of upper two-third glass (replaced with insect screen)

new infectious TB cases (P < .001, median time from exposure to TB notification: 11 months,[19] interquartile range: 6-18 months, person-time after the start of LTBI treatment was censored, Figure 5). One of the 214 contacts at the private tutoring class acquired active TB (Table 1). Therefore, CO_2 level of 1022 ppm was not safe. The only one contact in the CO_2 level <1000 ppm category who acquired active TB (Table 1) was the index patient's younger sister, who had prolonged close household contact with the index patient.

3.6 | Effect of ventilation improvement

After adjusting for exposure to "super spreader" (the index case, Case 0), proximity of contact (household) and LTBI treatment (by censoring person-time after the start of LTBI treatment), Cox regression revealed that among 1035 contacts of smear-positive source cases, exposure to source cases under indoor CO_2 >1000 ppm was a major risk factor for contacts to become new infectious TB cases (adjusted hazard ratio 32.8 [95% CI:2.0-540.3]) (Table 2). Ventilation improvement to levels with CO_2 <1000 ppm was associated with a 97% decrease in incidence of infectious TB cases among contacts (95% CI:50%-99.9%).

TABLE 1 Characteristics of the 1665 contacts involved in the outbreak[a]

	Acquired TB (n = 22)[b]	Did not acquire TB (n = 1643)	
Variables	No. (%)	No. (%)	*P* value
Age (y), median (min, max)	20.0 (15.9-39.8)	21.8 (2.4-94.0)	.441
<15	0 (0)	14 (0.9)	
16-25	21 (95.5)	1227 (74.7)	
26-35	0 (0)	120 (7.3)	
36-45	1 (4.6)	73 (4.4)	
46-55	0 (0)	129 (7.9)	
56-65	0 (0)	62 (3.8)	
≥65	0 (0)	18 (1.1)	
Sex			
Male	8 (33.4)	855 (52.0)	.144
Female	14 (66.7)	788 (47.9)	
Source patient sputum smear results			
Negative or scanty	0 (0.0)	630 (38.3)	<.0001
Positive	22 (100.0)	1013 (61.7)	
Context of contacts			
University contacts	19 (86.4)	984 (60.0)	.031
Household contacts[c]	2 (9.5)	94 (5.7)	
Private tutoring class	1 (4.8)	213 (13.0)	
Contacts in other settings[d]	0 (0)	352 (21.4)	
Contacts of the index case			
No	3 (13.6)	1522 (92.6)	<.0001
Yes	19 (86.4)	121 (7.4)	
Isoniazid preventive therapy			
No	22 (100.0)	1470 (89.5)	.158
Yes	0 (0)	173 (10.5)	
Contact under CO_2 level >1000 ppm[e]			
No	1 (4.6)[f]	722 (43.9)	<.0001
Yes	21 (95.5)	921 (56.1)	

Note: *P* value, by chi-square test or Fisher's exact test (if the sample size is smaller than five).

Abbreviations: CO_2, carbon dioxide; ppm, parts per million; TB, tuberculosis.

[a]All student, staff, and faculty with a cumulative 30-40 h exposure to shared air (defined as staying in the same floor or within the same building with any infectious TB patient) were considered as contacts. Public health nurses used administrative data (lists of students/faculties/employee, curriculum, and class rosters) and results from a structured questionnaire to identify contacts as many as possible. Initially, 40 h were used. However, one contact with 30 h exposure to the index case became Case 3. Thereafter, the authority updated the operative definition for university contacts to a cumulative 30 h exposure to shared air, due to the severely underventilated environment in University A.

[b]The total 27 TB cases in this outbreak include the index case (Case 0), twenty-two contacts who acquired active TB during follow-up, and four additional TB cases who had exposure to shared air with infectious TB cases but did not meet the operative definition of contact (see the legend of Figure 3).

[c]Three household contacts were also university contacts (one is the index case's sister, who acquired active TB, and two are Case 5's roommates who attended the same school).

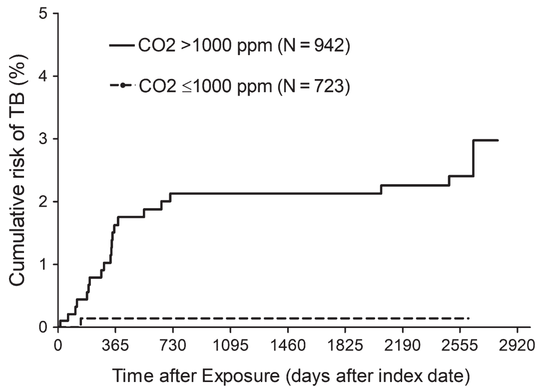
[d]Friends (n = 19), workplace contacts (n = 165), flight contacts (n = 3), contacts at another university (n = 165).

[e]Defined as having an indoor air CO_2 level >1000 ppm at the time of exposure. Contacts in this category include the 728 university contacts who were exposed to TB patients in this outbreak before the ventilation engineering was completed on January 16, 2012. One TB patient (Case 8) attended a private tutoring class. Public health inspectors found the tutoring class had a CO_2 level of 1022 ppm. Therefore, the 214 tutoring class attendees were also considered to have been exposed to TB patients in environment with a CO_2 level >1000 ppm.

[f]This is a household contact.

3.7 | Risk of LTBI

LTBI was diagnosed in 302 of the 667 contacts who received TST. Exposure under CO_2 >1000 ppm environment was associated with a significantly higher likelihood of LTBI (245/488 [50.2%] vs 57/179



Number at risk

CO2 >1000 ppm	942	805	776	776	776	776	775	276
CO2 ≤1000 ppm	723	697	695	695	694	670	323	77

FIGURE 5 Kaplan-Meier estimates for the risk of contacts to become new infectious tuberculosis (TB) cases, by ventilation status at the time of exposure to source cases (person-time after the start of isoniazid preventive therapy was censored)

[31.8%], $P < .001$). Logistic regression revealed that after adjusting for the higher infectiousness of the index case, exposure to source cases under CO_2 >1000 ppm in the university buildings before the intervention was also a risk factor for contacts to have LTBI (adjusted odds ratio 1.6 [95% CI:1.1-2.3], $P = .014$) (Table 3). Ventilation improvement to levels with indoor CO_2 <1000 ppm was associated with a 38% decrease in likelihood of LTBI among the contacts (95% CI: 9%-57%).

3.8 | Sensitivity analysis

Replacement of monthly maximum CO_2 value with monthly median CO_2 level (Figure S1) did not alter the exposure categories of contacts in Tables 1-3, and Figure 5 and therefore did not alter the analysis results.

4 | DISCUSSION

This study provides the first empirical data showing that improving indoor ventilation to levels with CO_2 <1000 ppm is highly effective in controlling a TB outbreak which occurred in poorly ventilated indoor environment. Improving ventilation to indoor CO_2 levels <1000 ppm was associated with a 97% decrease in risk for contacts to become new infectious TB cases and helped to end the TB outbreak in University A.

Prompt diagnosis, isolation, and treatment for both TB and LTBI are essential for the control of this outbreak. However, these chemotherapy-based interventions in University A were less successful than what should be expected. The role of poor ventilation in this outbreak was discovered precisely because of the ongoing occurrence of tertiary cases despite early removal of the index case 1 year ago. The worsening situation in October 2011 prompted investigations of indoor ventilation and the subsequent ventilation engineering. In retrospect, infectious aerosol accumulated in the poorly ventilated environment. Without the ventilation improvement, the outbreak in University A would be more prolonged and more difficult to control. The limitation of chemotherapy-based interventions is further highlighted by four cases who did not have identifiable sources but nevertheless acquired the outbreak TB strain (Figure 3). They may have entered a classroom or a floor for unrecorded activity and breathed the exhaled air from prior occupants. In such scenarios, TB transmission may occur even when the sources were not there. This makes contact investigation and preventive therapy not the answer for controlling of TB in congregate settings.

A major strength of this study is the comprehensive epidemiological investigation. The outbreak investigation team found that TB transmission can occur following an exposure to shared air as short as 30 hours under poorly ventilated environments. Another strength is the comprehensive contact tracing and long-term follow-up based on Taiwan's highly effective public health system.[13] The TST and clinical/radiographic evaluation to detect active TB also followed standardized protocols. With the assistance of civil registration and a centralized cloud-based contagious disease database, the NSNCD, follow-up was nearly complete.

The NIOSH and other governmental agencies had recommended indoor air quality standards based on CO_2 levels of 600-1500 ppm for schools and workplaces.[20-22] The considerations for these recommendations are for comfort and learning/working efficiency. Our results support the hypothesis that there is a threshold of ventilation rate that stop TB epidemic. However, our data are not precise enough to exactly define this threshold, which could be in between 600 and 1000 ppm CO_2 in this outbreak. Moreover, the threshold could vary across different TB outbreak—a higher ventilation rate would be required to neutralize the hazard from a more infectious index case.

In response to the nosocomial multidrug-resistant (MDR) TB outbreaks crisis in 1990s, the United States Centers for Disease Control and Prevention (CDC) issued a 3-tiered strategy: administrative control (prompt isolation of TB patients), environmental control (isolation room, ventilation and germicidal ultraviolet), and personal protective equipment (mask).[6,7,23] CDC recommended that airborne infection isolation rooms should have a ventilation rate of at least 12 air changes per hour (ACH), based on engineering specifications for removing airborne particles, with high-efficient particulate air (HEPA) filtering for re-circulated air if non-recirculating local exhaust ventilation is not feasible.[6] After implementation, no more new cases occurred.[23,24] The respective contribution from each tier in this strategy cannot be separately evaluated. Nevertheless, this success is in keeping with our observation that improving ventilation rate to 23.6-25.1 L/s per person (equivalent to 14-15 ACH) helped to end the TB outbreak in University A.

Since 2009, World Health Organization (WHO) recommend healthcare facilities should be built to have a natural ventilation rate of at least 12 ACH.[8,25] WHO recently reviewed evidence on effect of ventilation in TB control and identified 10 observational studies which reported the impact of multi-tiered control strategy on TST conversion rate among healthcare workers.[8] High heterogenicity in study design and compliance to environmental control guidelines precluded a meta-analysis. WHO considered further assessment on the effect of ventilation in TB control as a research priority.[8] Our results show that improving indoor ventilation rate to levels equivalent to 14-15 ACH is highly effective in controlling a TB outbreak. Our findings strengthen the evidence base for the current WHO recommendation on the ventilation requirement for healthcare facilities.

One limitation of our study is the lack of baseline TST data prior to the outbreak. Taiwan is a middle-burden country with an annual TB incidence of 53.0 cases per 100 000 residents in 2012.[26] TST is not required for new students upon admission to universities in Taiwan. The lack of baseline TST data before this outbreak makes it impossible to use TST conversion (ie, incident LTBI) to measure the impact of ventilation improvement on TB transmission. Given the limitation in interpretation, the analyses still show that the ventilation improvement was associated with 38% decrease in likelihood of LTBI. Another limitation of this study is the lack of information on Bacillus Calmette-Guerin (BCG) vaccine history,[27] HIV status,[28] comorbidities such as diabetes mellitus[29] or rheumatoid arthritis[30] for the contacts. This information is considered private and therefore inaccessible by public health surveillance in Taiwan; however, the above-stated host conditions were unlikely to confound the analyses. First, BCG has been a universal vaccination at birth in Taiwan since 1965,[27] with more than a 95% vaccination rate in this generation of college students. The student cohort in this outbreak only received single dose of BCG at their birth, although some teachers or employees might have received a booster dose while in elementary school.[27] Second, the HIV prevalence is very low in Taiwan (approximately 0.1%) and is concentrated in specific high-risk groups, that is, people who inject drug and men who have sex with men.[31] Third, an overwhelming majority of the contacts and the patients were healthy and

TABLE 2 Risk factors for 1035 smear-positive contacts to acquire active TB

Variates	No. of TB cases[a] in each category of the contact (%)	Univariable			Multivariable		
		HR	95% CI	*P* value	Adjusted HR	95% CI	*P* value
Contacts of index case							
No	3/895 (0.3)	1.0			1.0		
Yes	19/140 (13.6)	46.5	38.7-157.7	<.0001	27.9	8.1-96.9	<.0001
Household contacts							
No	20/995 (2.0)	1.0			1.0		
Yes	2/40 (5.0)	2.7	0.6-11.7	.1796	57.5	6.8-487.1	.0002
Contact under CO_2 level >1000 ppm							
No	1/449 (0.2)	1.0					
Yes	21/586 (3.6)	14.3	1.9-107.0	.0095	32.8	2.0-540.3	.0145

Abbreviations: CO_2, carbon dioxide; HR, hazard ratio; ppm, parts per million; TB, tuberculosis.

[a]We used Cox regression to estimate the hazard ratio associated with exposure to source cases under poorly ventilated (operatively defined as CO_2 levels >1000 ppm) environments among the contacts, adjusting for infectiousness of source cases (index case) or proximity of contact (household). For each contact, the zero time was the diagnosis date of the source case. The end of follow-up was the date when the contact was notified as an active TB case (event), the date of starting isoniazid preventive therapy (censored), the date of any mortality due to non-TB-related causes (censored), or July 31, 2018 (censored).

TABLE 3 Risk factors for 667 contacts to have latent TB infection

Variates	No. of LTBI cases[a] in each category of the contact (%)	Univariable			Multivariable		
		OR	95% CI	*P* value	Adjusted OR	95%CI	*P* value
Contacts of index case[b]							
No	222/565 (39.3)	1.0			1.0		
Yes	80/102 (78.4)	5.6	3.4-9.3	<.0001	4.9	2.9-8.1	<.0001
Contact under CO_2 level >1000 ppm							
No	57/179 (31.8)	1.0			1.0		
Yes	45/488 (50.2)	2.2	1.5-3.1	<.0001	1.6	1.1-2.3	.014

Abbreviations: CO_2, carbon dioxide; LTBI, latent TB infection; OR, odds ratio; ppm, parts per million; TB, tuberculosis.

[a]Number of latent TB infection cases, defined as a positive tuberculin skin test using a cutoff point of 10 mm.

[b]All 102 contacts of the index case were exposed under poorly ventilated environment (CO_2 levels >1000 ppm).

active 18-22-year-old young college students (Table 1), an age range during which comorbidities should be rare.

Until now, Global End TB Strategy has focused on early diagnosis and effective treatment of active TB and preventive therapy for LTBI in high burden resource-limited countries,[32] and so far had a limited impact on TB epidemic trajectory.[2] As a comparison, in developed countries, the improvement in indoor ventilation as part of a general improvement in public health from the nineteenth to twentieth centuries was followed by a dramatic reduction in TB incidence before the era of anti-TB chemotherapy.[12,33,34] Interventions to maintain adequate indoor ventilation (to decrease airborne TB transmission) act at an earlier stage in the chain of events and therefore would be synergistic in the current global effort to end TB by greatly reducing the task and burden of subsequent diagnosis and treatment.

In conclusion, the present study shows that maintaining adequate indoor ventilation could be a highly effective strategy for controlling TB outbreaks. Our findings highlight the need to assess indoor ventilation status in TB outbreak investigation. In congregate settings where there is known to be a high risk of TB, it may be beneficial to make pre-emptive improvements to building ventilation. A refocusing on the importance of adequate ventilation in TB control may prevent hundreds of thousands of TB cases from occurring[12,35,36] and therefore could be the game changer for achieving the global End TB target.

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CONFLICT OF INTEREST

All authors have no conflict of interest.

AUTHOR CONTRIBUTIONS

C-TF designed the study. C-RD oversaw the outbreak investigation and intervention. S-CW assessed the ventilation situation at University A and made critical recommendations. M-CY, T-FC, J-YW, and P-C Chan read chest radiographs of the patients and contacts, diagnosed active and latent TB, and treated the patients and contacts with latent TB. P-C Chuang and RWJ performed DNA fingerprinting. C-RD obtained ethical approval and verified baseline and follow-up information of patients and contacts. P-C Chan and C-RD did the statistical analysis. C-TF, P-C Chan, and C-RD wrote the manuscript. All authors read and approved the submitted version of the manuscript. P-C Chan and C-TF contributed equally to the study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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