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Research Article

The Benefit of Quantiferon-TB Gold Plus in The Incidence of Tb Disease in Health Care Workers (Environment Control)

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Abstract

This study detected the benefit of using a calculated air change model to prevent TB organisms' transmission in Healthcare workers. The high-risk group contained Health care workers who usually contacted TB patients. 659 of 1351 Health care workers of Central Chest Institute of Thailand were enrolled and separated to 3 groups: 257 health care workers in high-risk group who work in the area which highly developed air change model, 55 health care workers in the high-risk group with the underdeveloped air change and 347 Health care workers in the low-risk group. This study used the QuantiFERON-TB Gold Plus test to diagnose Latent TB infection (LTBI). Result: 87 (13.2%) health care workers had positive results with IGRA, cut off point ≥ 0.35 iu/ml). Positive IGRA participants had an increased risk of active TB in one year, RR 13.10 (95% CI 2.4- 70.47), p=0.0001 (multivariate analysis- adjusted age, sex, a period of employment, workplace). Sensitivity and specificity of IGRA ability to predicted TB disease was 66.7% (95% CI 22.3- 95.7%) and 87.3% (95% CI 84.4 - 89.7%). 38 of 257(14.7%) high-risk group with highly developed air change model, 13 of 55 (23.6%) high-risk group with underdeveloped air change model, and 36 of 347 (10.3%) low-risk groups were positive IGRA. There was no significant difference in LTBI between high-risk patients with the highly developed area and low-risk, p= 0.33. 4 of 43 abnormal CXR participants and 2 of 45 positive IGRA results in last 2 years had positive IGRA in TB2-TB1 difference group. One participant who was in both of the mentioned groups had TB disease (interferon-γ concentration in TB2-TB1 difference was 2.59 iu/ml). Participants who positive in TB1 Ag, TB2 Ag and

TB2- TB 1 difference group had proportion of TB disease in 11.1 %, 16.7% and 50%, respectively, significant difference p= 0.04. Summary: Having a Good environment, more than 12 ACH, was one of the best ways to prevent airborne transmission especially TB infection. In some situations, such as the high prevalence of TB infection, detecting CD8+ T lymphocyte response (in TB2-TB1 difference) would be better.

Keywords: Latent tuberculosis infection, Air change per hour, Quantiferon-TB Gold plus

Introduction

Thailand was one of 14 high burden countries of the world in TB disease during 2016-2020. Health care workers have a high-risk of being infecte [1]. In high burden countries, such as Kenya, LTBI was 60% among healthcare worker [2]. The diagnosis of recent LTBI is controversial in areas of a high prevalence of TB disease. Previous versions of IGRA, such as QuantiFERON-TB Gold In-Tube (QFT-GIT), used a single mixture of synthetic ESAT-6, CFP-10, and TB7.7 peptides to stimulate CD4+ T helper lymphocyte to release interferon-γ [3-7]. The previous study, which compared M.TB specific CD8+ T cell function between LTBI and active TB disease, showed that the percentage of MTB –specific CD8 T cell responders were higher in active TB disease than CD4 + T helper and CD8 T lymphocyte [8-12]. Using both CD4+ T helper lymphocyte and specific CD8 T cells to predict ongoing active TB disease would be better than using only CD4+ T helper lymphocyte. QuantiFERON-TB Gold Plus (QFT-Plus) was the new version of IGRAs which stimulate both CD4+ T helper lymphocyte and CD8 T cell to release interferon-γ by specific TB Antigen (Ag). TB1 tube and TB2 tube contains TB Ag to elicit cell-mediated immune responses from CD4+ T lymphocytes and both CD4+ and CD8+ T-cells [13], respectively.

Many factors determine the likelihood of airborne transmissions, such as the number of organisms, length of time exposed to contaminated air, the immune status, and the concentration of organisms in the air. Decreasing the concentration of TB organisms by using properly ventilated space would induce low M.TB transmission [14]. Recommended ventilation, a minimum of 12 air changes per hour (ACH) and one-way airflow direction from a clean area to a dirty area, would have low concentration and fast removal of the organism [15,16].

The study's primary purpose is to detect environmental control's benefit by using calculated air change per hour, more than 12 ACH, and one-way airflow direction. QuantiFERON-TB Gold Plus test was executed to detect LTBI in health care workers.

Material and Methods

The prospective Cohort study was conducted from June 2019-May 2020 at Central Chest Institute of Thailand. 659 of 1351 Health care workers who worked in outpatient and inpatient departments were enrolled. Health care workers were separated into 3 groups

- High-risk Health care workers who work in areas with a highly developed air change model
- High-risk Health care workers who work in areas with an underdeveloped air change model
- Low-risk Health care workers

The high-risk group is defined by Health care workers who usually contact TB patients e.g. Chest clinic, TB clinic, Bronchoscopy unit, respiratory inpatient ward, respiratory critical unit, and et.al.

The low-risk group is defined by Health care worker who never or rarely contacted TB patients (≤ 1 case per month)

The area with a highly developed air change model is defined as an area with routinely checked airflow direction and calculated ACH.

QuantiFERON-TB Gold Plus was the new version of IGRA. The antigen in the TB1 tube elicited cell-mediated immune responses from CD4+ T lymphocytes. Ag in TB2 tube elicited cell-mediated immune responses from CD4+ and CD8+ T lymphocytes.

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Positive interferon-gamma release assay (IGRA) results defined by interferon-γ concentration- response to TB1 Ag and/or TB2 Ag, are ≥0.35 iu/ml.

The interferon-γ concentration of the TB difference group is measured by the difference between interferon-γ concentration in TB2 tube and TB1 tube. This phenomenon shows the response of cell-mediated immune responses CD8+ T lymphocytes.

The ethical committee of Central Chest Institute of Thailand approved this study. Informed consent was obtained from all Health care workers.

QuantiFERON-TB Gold Plus and Chest X-Ray were performed. Followed up chest X-ray was done in 6 and 12 months.

Statistical Analysis

The baseline characteristic was described by descriptive analysis. The result was that Fisher's exact test made a comparison between the two groups. The correlation was calculated by regression analysis risk by program Stata 15.1.

Results

Six hundred fifty- nine participants were enrolled in this study, and the number of participants was Five hundred eighty-seven (89%). All participating Health care worker's baseline characteristic is shown in Table 1. Eighty-seven participants (13.2 %) had positive IGRA results. Seventy-one, ten and nine participants got positive IGRA results in TB1 and TB2 Ag tubes, only TB1 Ag tube, and only TB2 Ag tube, respectively. The interferon-γ concentration value range was determined between -7.84 to more than 10 and -6.42 to more than 10 in TB1 and TB2 Ag tubes. Positive IGRA participants had an increased risk of active TB in one year, RR 13.10 (95% CI 2.4-70.47), p=0.0001 (multivariate analysis- adjusted age, sex, a period of employment, workplace). Sensitivity and specificity of IGRA result's ability to predicted TB disease were 66.7% (95% CI 22.3-95.7%) and 87.3% (95% CI 84.4 - 89.7%).

- Eighty-one (12.3%) participants had positive IGRA in the TB1 Ag group. There were 4 TB disease patients in this setting.
- Eighty (12.1%) participants were positive IGRAs in the TB2 Ag group. There were 3 TB disease patients in this setting.
- Seventeen (2.6%) participants were positive IGRAs in

Table 1: Baseline characteristics.

Characteristics	Number (%)
Participants	659
Female	587 (89%)
Period of employment	
- <5 years	147 (22.3.%)
- 5-10 years	191 (28.9%)
- > 10 years	285 (43.2%)
- undetermined	37 (5.6%)
Abnormal chest X-ray	
- Active TB	3 (0.5%)
- Old TB scar	43 (6.5%)
- Other disease	70 (10.6%)
- Denied CXR	26 (3.9%)
Previous TB disease	14 (2.1%)
History of IGRA result (QuantiFERON-TB Gold In-Tube) in 2017	45 (6.8%)
- positive IGRA	
- negative IGRA	18 (2.7%)
Workplace	27 (4.1%)
- Chest Department	
- Cardiovascular Department	207 (31.4%)
- Cardiothoracic Surgery Department	179 (27.2%)
- Other e.g. Radiology, Dental, Pharmacy Department	131 (19.9%)
Risk group and working area	142 (21.5%)
- High-risk Health care workers who work in areas with a highly developed air change model	257 (38.9%)
- High-risk Health care workers who work in areas with a developing air change model	55 (8.3%)
- Low-risk Health care workers	347 (52.8%)

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the TB difference group. There was 1 TB disease patient in this setting. Five (0.1%) participants were all positive IGRAs test in TB1 Ag tube, Th2 Ag tube, and TB difference group. There was 1 TB disease patient in this setting.

- Positive IGRA in TB1 Ag, TB2 Ag and TB difference participants had an increased risk of active TB in one year, RR 14.22 (95% CI 2.65-76.41) p<0.0001, RR 7.21 (95% CI 1.48-35.13), p=0.004, RR 7.53, (95% CI 0.93- 61.02), p=0.03. (univariate analysis).

There were only six TB patients throughout the research, 4 positive IGRA, and 2 negative IGRA. One of the TB patients in this group had TB Lymphadenitis. All TB patients had a negative result in the sputum smear, molecular test, and culture. The diagnosis of Tuberculosis disease is defined by using chest X-ray responses after treatment. The characteristic of TB patients was shown in Table 2.

Thirty-eight of 257(14.7%) High-risk Health care workers who work in areas with a highly developed air change model, 13 of 55 (23.6%) High-risk group with underdeveloped air change model, and 36 of 347 (10.3%) low-risk health care workers had positive IGRA result. There was no significant difference in LTBI between high-risk patients with the highly developed area and low-risk, p= 0.33, but there was a significant difference between high-risk with underdeveloped and low-risk, p=0.02. Data was shown in Figure 1

Four-five participants had undergone previous IGRA detection in 2017 by the QFT-GIT test, with 18 positive results. Eight of 18 previously positive IGRA participants still got positive IGRAs in TB1 Ag tube, 5 in TB2 Ag, only 2 in the TB2- TB 1 difference group. One participant had TB disease, abnormal CXR (old TB scar) 2 years before enrollment, and previous positive IGRA result 2 years before (interferon-γ concentration in TB1 tube, TB2 tube, and TB2-TB1 difference was 0.81, 3.4, 2.59 iu/ml). Participants who were positive in TB1 Ag, TB2 Ag and TB2- TB 1 difference group had proportion of TB disease in 11.1 %, 16.7% and 50%, respectively, significant difference p= 0.04. One of 27 previous negative IGRA results turned to positive IGRAs result in this study, and there was no TB disease found after follow-up 12 months.

Forty-one Health care workers had previous abnormal CXR, old TB scar patterns. 20 participants (48%) had positive IGRAs result in any TB Ag tube. Previous abnormal CXR before enrollment in a positive IGRA group ranged between 0.5 to more than 10 years. Four (20%) and Eight (40%) of 20 positive IGRA participants had previous abnormal CXR one year and 5 years before enrolment, respectively. Nineteen participants who had previous abnormal CXR (old scar TB) were positive IGRA results in TB1 Ag, 17 in TB2 Ag, and 4 in the TB2- TB 1 difference group. Participants who

Table 2: TB patients Characteristic of CCIT health care worker

Partici-pant	Diagnosis	interferon-γ concentration value (iu/ml)				Previous abnormal CXR	Previous TB disease
		(iu/ml)					
		TB1 Ag tube	TB2 Ag tube	TB difference	Previous QFT-GIT test in the year 2017		
1	TB LN	1.71	1.75	0.04	N/A	No	No
2	TB lung	0.01	0.01	0	N/A	No	No
3	TB lung	0.36	0.28	-0.08	N/A	Yes	No
4	TB lung	0.81	3.4	2.59	0.99	Yes	No
5	TB lung	0.1	0.11	0.01	N/A	No	No
6	Progressive bronchiectasis	1.88	2.17	0.29	N/A	Yes	No
	(TB like pattern)						

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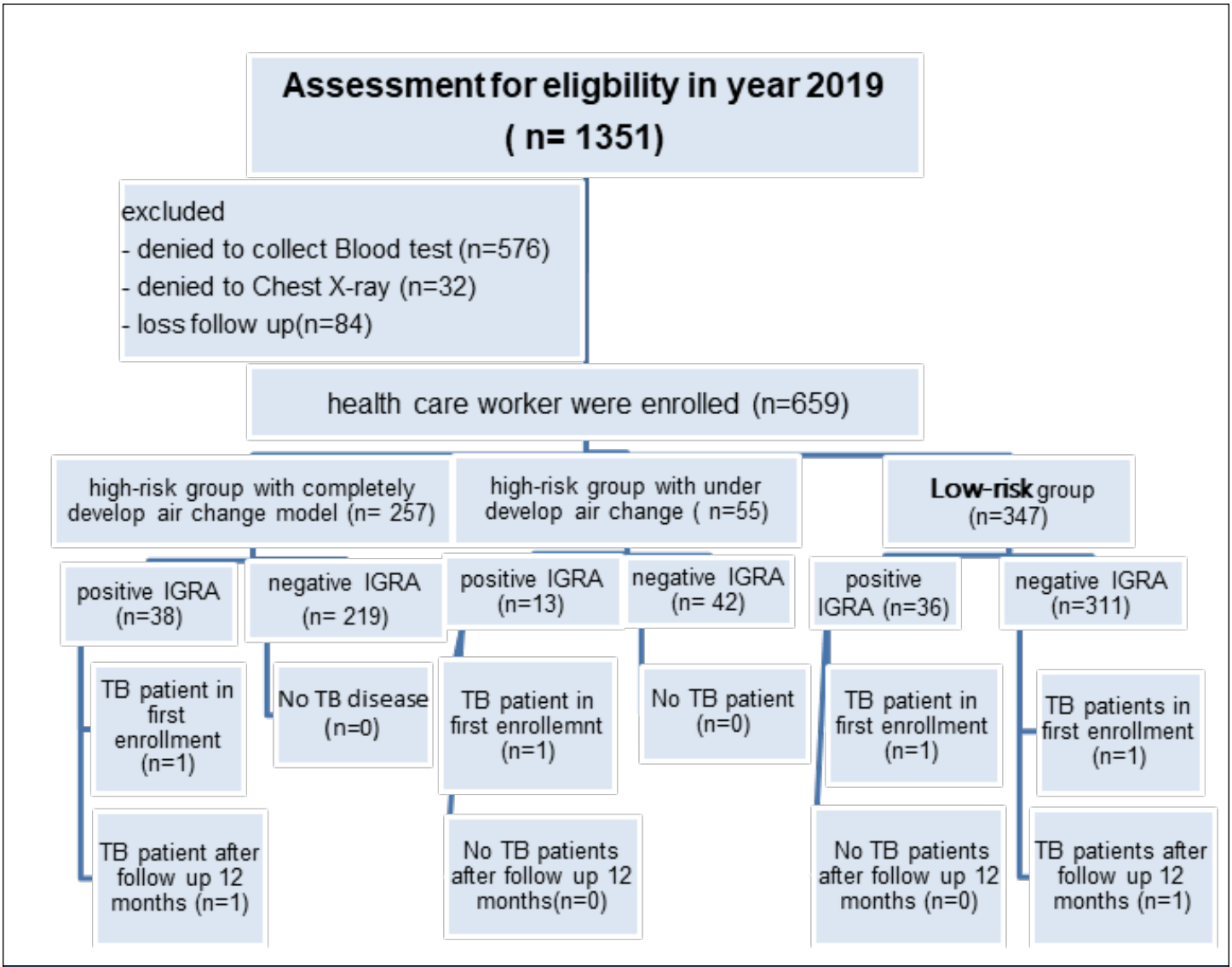

Figure 1: Latent tuberculosis infection and TB disease of CCIT health care workers separated by the risk of TB infection and area

positive in TB1 Ag, TB2 Ag and TB2- TB 1 difference group had proportion of active TB disease in 5.2 %, 5.8% and 25%, respectively, no significant difference p= 0.47.

Discussion

Minimum of 12 ACH in an area with a high-risk of airborne transmission was better at reducing transmission of TB organism, which was confirmed by showing no significant difference between the number of participants who had positive IGRAs in high-risk group with work in the area of highly developed air change model (14.7%) and low-risk participants (10.3%), p= 0.33, but there was a significant difference between high-risk group with underdeveloped air change model (23.7%) and low-risk group, p= 0.02

This prospective study showed that QuantiFERON-TB Gold Plus by interferon-γ concentration ≥0.35 iu/ml was a predictor of TB disease, the relation between interferon-γ concentration value and increased risk of active TB disease had a risk ratio of 13.10 (95% CI 2.4- 70.47), p=0.0001. The previous study illustrated that using both CD4+ and CD8+ T lymphocyte cells will predict recent TB disease than CD4+ T lymphocyte,[9-11] but this study showed that using CD4+ T helper lymphocyte was better than using both CD4+ T and CD8 + T lymphocyte or only CD8+ T lymphocyte.

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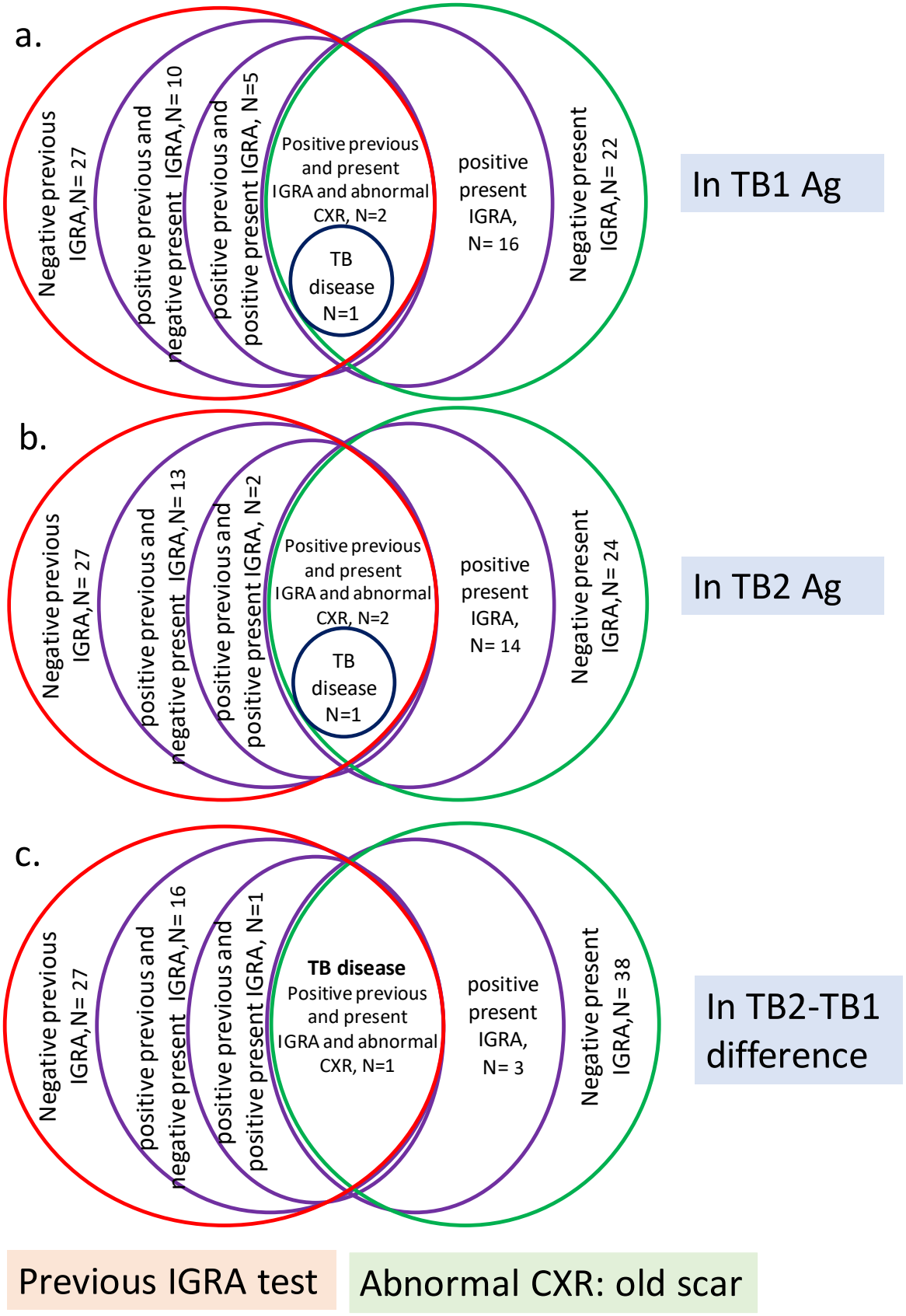

Figure 2: Diagram of IGRA results in participants who previous IGRA test (n=45) and abnormal CXR (n=41). a. result in TB1 Ag, b. result in TB2 Ag, and c. result in TB2-TB1 difference.

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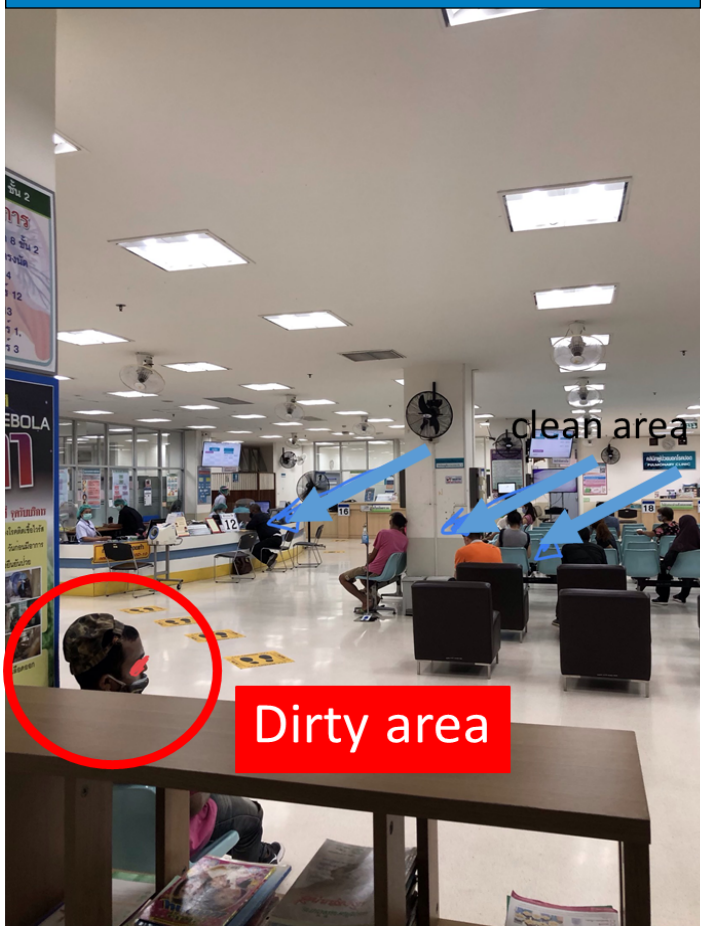
Our data showed that higher number of participants who had positive IGRAs in TB1 Ag group (CD4+ T lymphocyte) was ongoing to active TB disease than the others, risk ratio RR 14.22 (95% CI 2.65-76.41) p<0.0001 in TB1 Ag tube, 7.21 (95% CI 1.48-35.13), p=0.004 in TB2 Ag tube (CD4+ T and CD8 + T lymphocyte) and 7.53, (95% CI 0.93- 61.02), p=0.03 in TB difference group (CD8+ T lymphocyte), respectively. The response of CD4+ T lymphocyte to TB Ag is enough to diagnose LTBI. Two negative IGRA health participants in low-risk group had TB disease. It was difficult to explain why this happened. We found that one of two negative IGRA participants had TB disease after 12 months of follow-up. Is it possible that the patient got infected during the 1-year follow-up? The patient denied any household or close contact with TB patients. Because of this situation, sensitivity IGRA's ability to predicted TB disease was low (66.7%, 95% CI 22.3- 95.7%), and specificity was 87.3% (95% CI 84.4 - 89.7%).

The previous study showed a rapid decline in CD8+ T lymphocyte response during the initial phase of successful TB treatment [11]. QuantiFERON-TB Gold Plus detected CD4+ T lymphocyte and CD8+ T cell response in tube TB2 Ag and CD8+ T lymphocyte response in the TB2-TB1 difference group. If latent tuberculosis infection does not progress to active TB disease, interferon-γ concentration should drop after follow up in 12 months. We found that 8 of 18 previous positive IGRAS participants in the last 2 years were positive IGRAS in TB1 Ag tube (CD4+ T lymphocyte), Five participants in TB2 Ag tube (CD4+ T and CD8 + T lymphocyte), and 2 in TB2-TB1 difference group (CD8 T lymphocyte). The data was similar to previous abnormal CXR participants in which 19 participants had positive IGRAS in TB1 Ag tube (CD4+ T lymphocyte), 17 in TB2 Ag tube (CD4+ T and CD8 + T lymphocyte), and 4 in the TB2-TB1 difference group(CD8 T lymphocyte). One participant in the previous positive IGRAs and abnormal CXR group had TB disease. It showed that the positive TB2-TB1 difference group had a higher proportion of the TB disease than the others, a significant difference in the previous positive IGRA group, p= 0.04. It suggested that the use of positive IGRAs result in TB2-TB1 difference group was better than either TB1 Ag or TB2 Ag to predict active TB disease in special situations, such as previous TB disease or high suspected latent TB infection. It's a limitation in the number of active TB diseases.

Summary

Having a Good environment, more than 12 ACH, was one of the best ways to prevent airborne transmission especially TB infection. Detection of CD4+ T lymphocyte response for TB Antigen (TB1 Ag group) was recommended for latent tuberculosis infection in the general population. However, in some situations, such as the high prevalence of TB infection or previous TB disease, detecting CD8+ T lymphocyte response (in TB2-TB1 difference) would be better.

Picture 1: Area of highly developed air change. In open air, calculation and direction of air flow was shown.



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