# Association of Latent Tuberculosis Infection in Health Care Workers with Allergy and Allergic Sensitization to Common Aeroallergens

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#### ABSTRACT

Health care workers (HCW) are at increased risk of a latent tuberculosis infection (LTBI) due to occupational exposure to Mycobacterium tuberculosis. In order to investigate the mutual influence of a  $T_{\rm H}1$  type immune response caused by LTBI and T helper 2 ( $T_{\rm H}2$ ) type immune response caused by allergy, we conducted a study examining the prevalence of common inhaled allergen sensitization in the HCW population with different levels of exposure to tuberculosis (high and low). HCW with possible exposure to tuberculosis (TB) were tested with QuantiFERON-TB Gold (QFT-G) and tuberculin skin test (TST), while skin prick test (SPT) was performed for inhaled allergens. The antigen (Ag) response at QFT-G was inversely correlated with participants` allergy anamnesis (p=0.039). Sensitization to inhaled allergens (positive SPT and number of positive allergens at SPT) was more prominent in the low exposure group (p=0.0066 and p=0.0065, respectively). Ag response at QFT-G test was significantly higher in participants with no medical history of allergy (p=0.048). Our results demonstrate that exposure to TB and LTBI are associated with inhaled allergen sensitization in HCW, possibly inhibiting allergic sensitization by mediating the T-helper type 1 (Th1) immune response.

**Key words:** allergy and immunology, health personnel, interferon-gamma, latent tuberculosis, skin test, tuberculin test

### Introduction

Health care workers (HCW) in contact with patients in a contagious state of tuberculosis (TB) are at an increased risk of contracting TB infection when compared to the general population. The prevalence of latent tuberculosis infection (LTBI), a condition of ongoing immune response to *Mycobacterium tuberculosis* (MTB) without a progression to active TB disease<sup>1</sup>, ranges among HCW from 33 % to 79 % in low- and middle-income countries and from 5 % to 55 % in high income countries<sup>1,2</sup>. Early diagnosis and usage of adequate treatment is of a particular importance in controlling the TB<sup>3</sup>. Since 1948, the Childhood Vaccination Program in Croatia has included mandatory neonatal *Bacillus Calmette-Guérin* (BCG) vaccination<sup>4</sup>. In 2018, the overall incidence of TB in Croatia was 8.4/100.000 and 350~TB cases were reported  $^5.$ 

It is reported that between up to 80 % of TB infections among HCW are associated to their occupational exposure to MTB<sup>6</sup>. MTB, the causative agent of TB, is a strong activator of the T-helper type 1 (T<sub>H</sub>1) immune response, characterized by a strong cell-mediated immunity and production of interleukin-2 (IL-2), interferon- $\gamma$  (IFN- $\gamma$ ) and tumor necrosis factor (TNF- $\alpha$ )<sup>7</sup>.

On the other hand, one of the hallmarks of allergic diseases, as an immune systems response against nonhazardous substances of the environment, are production of allergen-specific immunoglobulin E (IgE) and prolifera-

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tion of allergen-specific T-cell populations ( $T_H^2$  dominant)<sup>8</sup>. The first phase of allergic disease development is the allergic sensitization. This refers to the process of excessive allergen-specific IgE production and its binding to the tissue mast cells and peripheral blood basophils via fragment crystallizable  $\varepsilon$  receptor I (FccRI). Upon a repeated allergen exposure, antigen cross-linking of FccRI occurs, and mast cells and basophils become activated causing allergic diseases development. Allergic sensitization is manifested as immediate skin test reactivity. As opposed to  $T_H^1$  type immune response, the  $T_H^2$  type immune response is defined by an increase in production of IL-4, -5, and -13, and a decrease in IFN-Y<sup>9</sup>.

The hygiene hypothesis states that the  $T_H 1$  and  $T_H 2$  type immune responses are inversely balanced<sup>10</sup>. Exposure to microbial agents and subsequent infections are thought to stimulate  $T_H 1$  immune response type and to promote the development of variety of regulatory T cells subpopulations, which are held responsible for securing a balanced immune response. Contrarily, in reduced microbial exposure during early life, the predisposed individuals may develop  $T_H 2$  type response to otherwise harmless antigens present in their environment<sup>11</sup>.

Exposure to MTB is therefore thought to be a potential modifier of the  $\rm T_H1/T_H2$  balance and the onset and course of the allergic diseases. It might inhibit allergic sensitization and clinical development of atopic allergic diseases by modifying the immune profile, i.e. downregulating undesirable  $\rm T_H2$  immune response by activation of regulatory T-cells and induction of anti-inflammatory cytokine response<sup>12</sup>. However, little is known about the impact which exposure to MTB may have on allergic diseases development and vice versa – data is scarce about potential influence which allergic sensitization may have on the development and course of TB.

In order to provide more information about mutual influence of a  $T_H 1$  type immune response caused by LTBI and  $T_H 2$  type immune response caused by allergy we conducted a study examining the prevalence of common inhallatory allergen sensitization and clinically relevant allergic disease in a HCW population with different levels of exposure to TB.

#### **Subjects and Methods**

#### **Subjects**

The study was conducted at Srebrnjak Children's Hospital in Zagreb, Croatia, which is the Ministry of Health Reference center for clinical allergy in children, with circa 40–50 annual admissions of patients with TB. This study included 40 female HCW: nurses, laboratory technicians, physicians, physiotherapists and cleaning personnel with mean (SD) age of 44.1 (8.0) years (range 25–60 years), taking part in high or low risk work activities regarding TB transmission. They were recruited during the obligatory yearly medical examination. The level of TB exposure broadly differs among health care occupations, so according to the exposure of HCW to the patients in a contagious

state of TB, they were divided in high risk (TB+) and low risk (TB-) subgroup. High risk subgroup included personnel from a tuberculosis ward for infants and children up to 7 years of age, and personnel from tuberculosis ward for school children and adolescents, which were directly exposed to tuberculosis patients during office hours for a period of time longer than 5 years. Low risk subgroup involved HCW from nontuberculosis wards without direct exposure to tuberculous patients. All participants were clinically healthy and with no history of clinically manifested TB. They had all received mandatory BCG vaccination in childhood according to the national vaccination calendar, comprising neonatal vaccination with BCG vaccine SSI-0.0375 mg Mycobacterium bovis, Danish strain 1331 (attenuated) dissolved in diluted Sauton SSI injected intradermally. All of them were retested at the age of 13 in accordance with Croatia's Childhood Vaccination Program and revaccinated later if necessary.

The study was approved by the Srebrnjak Children's Hospital Ethics Committee. All subjects involved were acquainted with study objectives and the methods used and signed the informed consent for the study. The study protocol was executed according to the ethical principles of the World Medical Association Declaration of Helsinki<sup>13</sup>.

#### Methods

Determination of blood IFN-y was performed by the commercial QuantiFERON-TB Gold (QFT-G) (Cellestis/ Qiagen, Valencia, CA, USA). QFT-G is an IFN-y release assay, commonly known as IGRA, and was used according to manufacturer's instructions<sup>14</sup>. Prior to TST, blood was extracted for IFN-y determination into three evacuated heparinized test tubes: antigen-free tube (nil or negative control); tube with specific antigens for MTB (ESAT-6, CFP-10 and TB7.7; TB antigen tube); and tube with mitogen phytohemagglutinin (PHA) (mitogen or positive control). Only samples with the required blood volume  $(1\pm0.1)$ ml) were referred to the laboratory. Within 5 h of venipuncture, all test tubes were incubated at 37 °C for 22 h. After incubation, the tubes were centrifuged and plasma was stored at +4 °C. The concentration of IFN-y was determined within 7-10 days by enzyme-linked immunosorbent assay (ELISA) according to manufacturer's instructions. IFN-y concentration in the TB antigen tube and mitogen tube was reduced by the IFN-y concentration in nil tube. The cut-off value for positive finding (TB antigen minus nil) was 0.35  $kIUl^{-1}$  and by  $\geq 25$  % higher than the nil value. The TB antigen tube finding was interpreted if the values of negative and positive control met the following criteria: nil <8.0  $kIUl^{-1}$  and mitogen minus nil  $\geq 0.50 kIUl^{-1}$ . The subjects with mitogen minus nil <0.50 kIU $l^{-1}$  and/or nil negative control >8.0 kIUl<sup>-1</sup> were classified as indeterminate.

Tuberculin skin test (TST) was performed by intradermal injection of 2 tuberculin units (TU) of standardized PPD solution Tuberkulin RT23 SSI (Statens Serum Institut, Copenhagen, Denmark) on the volar surface of the left forearm. The transverse diameter of the indurated area was measured after 72 h. Induration diameter  $\geq$ 15 mm was defined as a positive reaction. For all subjects, the test was performed by the same trained professionals. No repeated TST were performed.

The presence of clinically manifested allergy (allergic rhinoconjunctivitis, atopic dermatitis, allergic asthma and/or food allergy) in personal medical history was self reported using a questionnaire. Besides covering above mentioned diseases and their associated symptoms, participants gave detailed data on eventual use of allergy medication, previously conducted allergy tests, lifestyle habits and their sociodemographic characteristics.

Skin prick test (SPT) was performed after QFN-G and TST on the volar surface of the right forearm with extracts of 11 inhalant allergens: house dust mite (*Dermatophagoides pteronysinnus*), animal dander (dog and cat), cocksfoot (*Dactylis glomerata*), mugwort (*Artemisia vulgaris*), ragweed (*Ambrosia elatior*), birch (*Betula alba*), hazel (*Corylus avellana*), *Alternaria alternata*, and Cladosporium mix (*Cladosporium cladosporioides* and *C. herbarum*), with histamine hydrochloride (10 mg/ml) and phenolated glycero-saline used as positive and negative controls (Stallergenes, Marcy l'Etoile, France). A mean wheal diameter of  $\geq$ 3 mm was defined as a positive SPT reaction<sup>15</sup>.

#### **Statistics**

Shapiro-Wilk's normality test was used to test the distributions of inducation size (mm) at TST, Ag response (U/L) at QFN-G and total positive urtica diameter (mm) at SPT for normality. Data with normal distribution were expressed by arithmetic mean and standard deviation (mean±SD), and those with asymmetric distribution by median and range.

Groups of participants positive vs. negative at TST, and groups of participants positive vs. negative at QFN-G were compared by Fisher's exact test for the presence of allergy and positive SPT result (at least 1 positive allergen) and by Student's t-test for age. Nonparametric Mann-Whitney U test was used to compare the same groups for total positive urtica diameter (mm) at SPT and groups of participants positive vs. negative at SPT for induration size (mm) at TST and Ag response (U/L) at QFT-G. Spearman non-parametric test was used to assess the association between continuous variables. All statistical tests were performed using GraphPad Prism 6.01 (GraphPad Software, La Jolla, CA, USA). Values of p<0.05 were considered statistically significant.

#### Results

The determination of IFN- $\gamma$  in the total population of BCG vaccinated HCW revealed an LTBI prevalence rate (positive QFT-G test) of 17/39 (43.59 %), with a median value for IFN- $\gamma$  response upon TB antigen stimulation 2.80 (range 0.40–12.41) kIU/L. Fourteen (35.90 %) participants tested positive at TST with a median induration diameter of 23.5 (range 15–40) mm. No significant difference was found between groups of participants positive vs. negative at TST, and groups of participants positive vs. negative at QFT-G test for age (p=0.707; p=0.053), the history of allergy (p=0.458; p=0.701) and positive SPT result for at least 1 allergen (p=0.482; p=0.883) (Table 1).

Twelve (28.21 %) subjects were positive at SPT for at least 1 allergen with a median total positive urtica diameter of 11 (range 4–27) mm, while 22 (56.41 %) subjects had a medical history of allergy (Table 1). IFN-g concentration (Ag response at QFT-G) was inversely correlated with participants` allergy anamnesis (Spearman rho = -0.331, p = 0.039). Ag response (IFN-y concentration) at QFT-G test was significantly higher in participants with a negative medical history of allergy (p = 0.048, Figure 1).

When comparing subgroups with high and low risk of TB exposure we found no significant difference history of allergy between these groups (p = 0.301), while a positive SPT to at least one allergen was more frequent in the low risk TB exposure group (p = 0.006, Table 2). The number of positive allergens at SPT was significantly higher in the low risk vs the high risk group of participants (p = 0.0065, Figure 2).

#### **Discussion and Conclusion**

The aim of this study was to examine the prevalence of allergen sensitization in health care workers with high or low risk of contracting the TB, and with positive or negative results at TST and QFT-G. We wanted to examine if there is a difference in the prevalence of allergic

 TABLE 1

 RESULTS OF SKIN PRICK TEST, TUBERCULIN TEST AND QUANTIFERON GOLD TEST BY AGE AND ALLERGY DIAGNOSIS

	TST+ (n=14)	TST- (n=25)	Two-tailed/ sided <i>p</i> -value	QFT-G+ (n=17)	QFT-G-(n=22)	Two-tailed/ sided <i>p</i> -value
Age: mean±SD*	$44.5.0{\pm}5.19$	$43.48 {\pm} 9.27$	0.707	$46.65 \pm 5.20$	$41.68 \pm 9.14$	0.053
No. of subjects positive at SPT**	3 (21.43%)	8 (32.00%)	0.482	5 (29.40%)	6 (27.27%)	0.883
No. of subjects with allergy in personal medical record**	9 (64.29%)	13 (52.00%)	0.458	9 (52.94%)	13 (59.09%)	0.701

\* unpaired t-test; \*\* Fisher's exact test

QFT-G = Quantiferon-Tb Gold; SD = Standard Deviation; SPT = Skin Prick Test; TST = Tuberculin Skin Test.



Fig.1. Number of positive (pos) allergens at skin prick test (SPT) in participants with high or low exposure to TB patients. Mann-Whitney U test, median (0 mm) and interquartile range are shown. U = 103.5, p = 0.0065.

sensitization in HCW exposed to TB and conversely – will HCW with the presence of allergy be less susceptible to TB infection. As to our knowledge, this is the first study which underlines this question.

Our results indicated the prevalence of LTBI in HCW to be lower than the respective literature data on healthcare professionals in low- and middle-income countries<sup>2</sup> not exceeding the World Health Organization estimates for the general world population<sup>18</sup>. Previously conducted study on HCW exposed to patients with TB in our facility demonstrated that the rate of IFN- $\gamma$  positive HCW was not significantly higher in HCW at high exposure to TB infection<sup>16,17</sup>. This is probably due to the fact that children under 10 years of age rarely develop microscopically positive TB and forceful cough like adult patients do<sup>18</sup>, so HCW in children's hospital may be presumed to be less exposed to TB infection.

We found that QFT-G results (Ag response) were inversely correlated with the participants' personal medical history of allergy and that IFN-g concentrations were significantly higher in participants with negative medical history of allergy. Additionally, when the participants were categorized into 2 groups according to their risk of exposure to TB (high and low risk), we found that a positive SPT result to at least one allergen was more common in in the low exposure group, as is consistent with our previous findings on paediatric population<sup>16</sup>. Moreover, the sensitization rate (number of allergens positive at SPT) was significantly higher in the low risk group of partici-



Fig. 2. Antigen response (IFN-y concentrations, U/l) in participants with positive (Allergy +) vs. negative (Allergy-) personal medical history. Median (0 mm) and interquartile range are shown. U = 109.0, p = 0.048. Ag response = antigen response.

pants compared to those with high risk of exposure to TB. It is known that  $T_H 1$  and  $T_H 2$  responses are mainly mutually inhibitory and reciprocally regulated7. The so-called "hygiene hypothesis" suggests that early childhood exposure to microorganisms and infections reduces susceptibility to allergy by driving pro- or anti-inflammatory immune responses<sup>20,21</sup>. Exposure to microbial agents and infections such as MTB stimulates the Th1 type of immune response which is inversely balanced with Th2 response characteristic for atopy allergy<sup>22</sup>. Continuous exposure to pathogens results in the induction of regulatory pathways involved in the maintenance of immune tolerance tolerance through the interaction with the innate immunity, including regulatory T cells (Tregs), innate lymphoid cells (ILCs), dendritic cells (DCs), epithelial cells, effector lymphocytes, natural killer T cells (NKT) and B lymphocytes<sup>23</sup>. Additonally, microbial endotoxins are powerful adjuvants that can enhance these immune responses and serve as protective factors against the development of allergy<sup>24,25</sup>. Moreover, the ability of MTB to persist in the lungs throughout a patient's lifetime, causing LTBI and preventing active disease forms by the host's ongoing immune response, may indicate that a persistent immune challenge by pathogens immune system robustness and reduces causes it not to overreact otherwise unharmful environmental agents (allergens). Indeed, previ-

#### TABLE 2

THE NUMBER OF SUBJECTS POSITIVE AT SKIN PRICK TEST AND THE NUMBER OF SUBJECTS WITH ALLERGY IN THE PERSONAL MEDICAL RECORD IN SUBJECTS WITH HIGH (TB+) OR LOW (TB-) RISK OF EXPOSURE TO TB PATIENTS

	TB-(n=22)	TB+ (n=17)	Two-sided <i>p</i> -value
No. of subjects positive at SPT*	10 (45.45%)	1 (5.88%)	0.006*
No. of subjects with allergy in personal medical record*	14 (63.64%)	8 (47.06%)	0.301
No. of subjects with allergy in personal medical record*	14 (63.64%)	8 (47.06%)	0.301

\* Fisher's exact test

TB = tuberculosis, SPT = skin prick test.

ous studies have shown that exposure to MTB may reduce the risk of developing asthma and other allergic diseases in both children and adults<sup>26–28</sup>.

Some precautions were made when planning the study. Because LTBI and active disease cannot be differentiated by IFN- $\gamma$  determination, the possible presence of active TB was ruled out by normal clinical findings recorded in all our IFN- $\gamma$  positive subjects. Participants with positive IFN- $\gamma$  findings received no TB chemoprophylaxis and were free from any signs of TB at 1 year after testing. Repeated HCW testings to TB infection did not affect the results because in the testing algorithm QFT-G venipuncture always precedes TST<sup>29</sup>.

The small sample size as well as gender bias (only female participants) represent the biggest limitations of our study, especially for identifying differences between subgroups; however, every HCW from the tuberculosis ward in our institution was included in the study. Addtionally, a study involving adult patients revealed that the protective effect of exposure to TB or previous MTB infection against the development of asthma and other allergic diseases later in life was only present in female participants, but not in males<sup>27</sup>. Existance of a period between MTB

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In conclusion, the results of this study demonstrate that there is a significant difference in allergic sensitization, SPT associated parameters and clinical manifestations of allergy in HCW with high vs low risk of exposure to TB patients. It is plausible that exposure to TB and LTBI may confer protection against allergic sensitization and allergic disease. Further studies involving larger groups of participants should be undertaken to confirm these associations in HCW exposed to TB.

#### Authorship and Conflict of Interest

The first two authors IB and SBL share first authorship. The authors declare no conflicts of interest.

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### LATENTNA TUBERKULOZNA INFEKCIJA U ZDRAVSTVENIH RADNIKA POVEZANA JE S ALERGIJAMA I SENZIBILIZACIJOM NA UOBIČAJENE INHALACIJSKE ALERGENE

## SAŽETAK

Zdravstveni radnici imaju povećan rizik od latentne tuberkulozne infekcije (LTBI) zbog profesionalne izloženosti *Mycobacterium tuberculosis*. Kako bismo istražili međusobni odnos imunološkog odgovora posredovanog stanicama Th1 uzorkovanog tuberkuloznom infekcijom i onog posredovanog limfocitima Th2 u alergijama, istražili smo prevalenciju senzibilizacije na uobičajene inhalacijske alergene u zdravstvenih radnika s različitim stupnjem rizika od izoloženosti tuberkulozi (visok i nizak stupanj). Izloženost tuberkulozi i LTBI u zdravstvenih radnika testirani su korištenjem QuantiFERON-TB Gold (QFT-G) i tuberkulinskog kožnog testa (TST), a senzibilizacija na inhalacijske alergene je utvrđena kožnim ubodnim testom. Antigenski (Ag) odgovor na QFT-G testu inverzno je korelirao s osobnom anamnezom alergija sudionika (p= 0.039). Senzibilizacija na inhalacijske alergene (pozitivan kožni ubodni test i broj pozitivnih alergena na kožnom ubodnom testu) bila je izraženija u skupini sudionika s niskim rizikom od izloženosti tuberkulozi (p= 0.0065, respektivno). Ag odgovor na QFT-G testu bio značajno viši u sudionika s negativnom osobnom anamnezom alergija (p= 0.048). Rezultati ove studije ukazuju na to kako su izloženost tuberkulozi i LTBI povezani sa senzibilizacijom na uobičajene inhalacijske alergene u zdravstvenih radnika, potencijalno inhibirajući alergijsku senzibilizaciju indukcijom imunološkom odgovora posredovanog stanicama Th1.