Tuberculin Skin Testing in a Elementary School in Taiwan

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The two major uses of tuberculin skin test (TST) are for surveying the infection prevalence of tuberculosis (TB) the pathogen and for diagnosing the latent infection of TB the disease. In the past, however, due to worrying about possible interference in the test from BCG vaccination, we seldom made use of TST as a tool in TB-related studies here in Taiwan, especially on child TB situations. This study was initiated by an incidence close to the end of 2005 when an elementary school teacher was suddenly diagnosed, confirmed, and notified as an open type TB sufferer. To fulfill the required contact search protocol, we conducted a TST (2 TU PPD) screening project among the pupil population of the school. The findings are quite interesting. Firstly we saw that all 5 claimed “intimate” contacts – the five pupil officers of the teacher’s own class – showed positive TST reactions, and 3 out of the five (60%) had swollen masses $\geqq$15 mm in diameter. Secondly, the first round TST screening involved almost all pupils attending the teacher’s class, or to them he was the homeroom teacher, and pupils of two

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other classes in the nearest vicinity of the first one, in which the percentages of having TST positive results turned out to be 56.7% (17/30), 43.8% (14/32), and 34.5% (10/29), respectively. The figures show that pupils attending the teacher's class seemed to have a higher positive rate, but a chi-square test told us the differences were not statistically significant. Thirdly, a second round TST screening was also carried out which had 347 (21.2% of the entire pupil population excluding the aforementioned three classes) voluntary pupils completed the test, including 42 1st graders, 69 2nd graders, 44 3rd graders, 66 4th graders, 63 5th graders, and 63 6th graders, and the outcome showed their positive rates to be 26.2% (11/42), 26.1% (18/69), 36.4% (16/44), 48.5% (32/66), 42.9% (27/63), and 39.7% (25/63), respectively. In short, those data showed the lower grades had the lowest TST positive rate, but such seemly trend turned out to be not statistically meaningful according to our further analysis. When we conducted a regression analysis on the TST data of all participating pupils, the results said that sex and grade (age) were marked determinants for TST positive rate, but not TB contact history and BCG vaccination history because data of the latter two were not statistically significant. This article is a record of the TST screening effort, and hopefully it can provide some useful information for future TST applications and TB control on school grounds.

Keywords: tuberculosis (TB), Bacille Calmette-Guérin (BCG), tuberculin skin test (TST)

Introduction

Tuberculosis (TB) is the leading killer of all infectious diseases around the globe as no other disease causes nearly as many deaths as it does. It is estimated that in the entire world at this moment there is one person contracting TB in every

4 seconds and one getting killed by the disease in every 10 seconds [1]. In Taiwan particularly, both the incidence and mortality of TB rank number one among those of all notifiable communicable dieseases. The etiologic agent of TB in human is a bacterium named *Mycobacterium tuberculosis*, and TB is spread from person to person through a principal transmitting route of airborne droplet nuclei. Often when a person with infectious TB is spitting, talking, coughing, singing, or even laughing, tiny particles containing *M. tuberculosis* are expelled into the air. These particles with diameters less than 5 μm, called droplet nuclei, can remain suspended in the air for several hours. Once inhaled by a person, these droplets will enter the pulmonary alveoli through the respiratory tract and effect infection there [2]. However, there is another key characteristic of the TB infection, i.e. the infection is by no means to come by easily due to a fact that *M. tuberculosis* can hardly reach the peripheral part of lung. Consequently, transmission of TB would most likely take place between much more intimate contactors, who are often close family members or roommates. Not everyone infected develops the full-blown disease, so asymptomatic or latent TB infection is most common. However, a latent infection has a chance of 10 to 20% to progress into an active TB disease during the person's life time [3].

In the recent years, there seemed to be a universal trend of bouncing back of TB prevalence in countries all over the world, and this trend is no exception among children. Not too long ago in the United States, the incidence of child TB registered an 18% increase over a period of a decade (from 1985 to 1994) [4]. In Taiwan, researchers were astounded by their own finding that in just four years (from 1998 to 2002) the local incidence of child TB rised by a whopping 56%, which indicates that at least over those specified years, Taiwan child TB was not under effective control as it should be. Child TB is an important public health

indicator of a society because 75% of the patients in such category are newly infected for the very first time in their young life, rather than reactivation of some latent cases from previous infection [5]. That is to say, it suggests that some devastating known or unknown infection sources definitely exist out there in the environment where the young people spend their daily life, and most of such sources are very close and dear to them.

The objective of tuberculin skin test (TST) is to find out whether an individual has a postponed allergic reaction towards tuberculosis bacilli, but this allergic reaction may either come from a natural TB infection taking place at least 3-8 weeks previously or an artificial one (BCG vaccination) taken more than 2-12 weeks in advance. The two major uses of TST are helps in estimating TB infection prevalence and for diagnosis of latent tuberculosis infection (LTBI) [6]. Since 2001, Taiwan has adopted a purified protein derivative (PPD) of the pathogen called RT23 2 TU (TU standing for tuberculin units) to be used in TST. According to an age old recommendation given by Would Health Organization (WHO), countries with high incidence of TB should adopt a BCG preventive immunization policy, and this policy has been faithfully followed and a long-term, nationwide BCG vaccination program has been implemented in Taiwan for more than 50 years in the past and the coverage is excellent, exceeding 98% [7]. Furthermore, since the infection rate and disease prevalence of TB were already quite high when we decided to do something about it 50 years ago, and about 80% of the adult population over 20 years of age were already TST positive in those days, so nowadays the older a person is, TST is a less helpful tool for TB diagnosis. Therefore, under the combined influences of BCG vaccination policy and the reality of high prevalence of TB, to find out the true meaning of Taiwan TST results is getting more complicated [3].

In December 2005, this particular elementary school somewhere in Taiwan had its entire staff of 103 teachers and other employees take a regular physical. One check item was a preliminary chest X-ray checkup (with small size film), and it turned out that 15 people among the entire school staff had somewhat dubious and questionable images and needed re-examination. After they were asked to return to the hospital for large film chest X-ray picture taking, the specialist examining those negtive films spotted one teacher as a active TB infected case and duly reported the newly found case to the local health authority right away, whereas the rest 14 suspects were ruled out as active TB bearers. This particular teacher not only had hollow holes evident on his X-ray films, on further examination, his sputum smear test and sputum culture both gave positive results, i.e. he was a confirmed open type TB case. Through a session of sputum information gathering interview, we got to know that this particular teacher started coughing about 3 months before in September 2005. After that, he went to see a doctor in more than one occasion in the vicinity of his residence. However, none of those physicians he visited diagnosed him as a possible TB sufferer, let alone a real one. Because this teacher was found to be a sputum-positive TB case and according to the TB control regulations issued by Taiwan CDC, it's a mandatory follow-up measure that a school pupil contact screening must be carried out to find out if anyone among those pupils under the teacher's direct supervision was infected. This article is a record of the investigation and analysis of the TST results gathered from certain pupils of that school, and we hope it will serve as a helpful reference for the future TST applications and TB control on school grounds.

Materials and methods

A. Subjects of the study

The entire school pupil population of a certain elementary school in Taiwan where a teacher was unexpectedly diagnosed as an infectious TB case

B. When this study was carried out

December 2005 to January 2006.

C. Methods used in this study

During the study, we started an outbreak investigation focused on the newly found and notified TB case, an elementary teacher. What we urgently wanted to know was information concerning his symptom onset, the details of his journey of seeking medical help after he felt sick, and who were his close contacts on a regular basis. Besides, in order to better understand the potential of that school's pupils being infected by TB, after consulting with the local health bureau and the parents of school pupils, we accepted the suggestion by the health bureau and took the requests from the parents into consideration, and carried out a two-step TST screening scheduled on December 19, 2005 and January 16, 2006. Based on considering the right of privacy of the new case as well as protecting those pupils exposed to the greatest possibility of TB infection, the local health bureau sent a team to the school without prior notice but claiming to give a TST to three so-called "randomly selected" classes (but the truth was otherwise, i.e. they were purposely selected to include the class under the direct supervision of the sick teacher as its homeroom teacher, and two other classes next to it geographically). Thus, in the first round of TST we only focused on the selected three classes: Class A (the notified sick teacher being its homeroom teacher), Class B, and Class C (they are next door to Class A). The second round TST checkup would take samples from the entire pupil

population of the school (but excluding the three classes already taking part in the first round) and the approach was a little different from that of the first round. This time we sent out a notice with consent paper attached to each parent, telling him or her the purpose and method of the test. The parents were given an option, i.e. should a parent want his or her child to participate in this screening activity, by returning the consent paper and the child would receive the test, but should the parent disagree to the idea or in any doubt, by withholding the paper and the child would be left out of the test. In this study, we used a PPD called RT23 2 TU in our TST. It was done by a specially assigned trained technician to inoculate the tuberculin dose at the center location of the palm side of left forearm. Seventy two hours after the inoculation, the swollen skin spot or mass would be checked, measured, and recorded by the specialist

D. Definition

(A) TST result determinant: According to the relevant WHO recommendation and also referring to the advice cited in the guidelines for TB diagnosis and treatments published by Taiwan CDC, for a child older than 6 and its most recent BCG inoculation was done more than 6 years ago, or has never received BCG before, a TST positive result is defined as showing a swollen mass with a diameter equivalent to or larger than 10 mm [3, 8].

(B) Grade variable: Divided into three groups, i.e. higher, mid, and lower grades.

(C) TB contact history variable: All tested pupils were divided into three categories, i.e. “intimate” denotes those pupils not only attending the notified teacher’s class, but also having more frequent than normal interactions with the teacher in the teacher’s opinion; “normal” means

pupils attending the same class but other than those “intimate” ones in the teacher’s opinion; and “none” marks all pupils attending the other two classes.

E. Data analysis

The determined TST results of all tested subjects in this study were provided in writing by the health team that carried out the test. Then one of our researchers used Microsoft Excel 97 software to execute keying in, weeding errors, and verifying, and then applied the data onto SAS 9.1 edition software to process statistic tests. In this study, we made use of chi-squire test (also called χ^2 test) to determine if there is any sort of relationship between the two nominal variables, and here for instance, between the variation in contact history (whether the pupil was attending the class under the direct supervision of the sick teacher) and the positive rate of the TST results. Furthermore, since the participating pupils of the second round or the expanded TST were not from a random sampling process, its representative nature was in question and was checked by using “chi-squire test” as well. Another task to find out if there is any differences in sex and grade between pupils agreed to take part the test and those disagreed rather, we used “chi-squire test for trend in proportion” instead to compare the TST positive rate trends of various grades. As to the aspect of deduced statistic analysis, we adopted the “logistic regression analysis” approach, using whether it’s a TST positive case or not as a dependent variable, but treating sex, grade, TB contact history, and BCG vaccination history as independent variables, to probe whether each of these independent variables being predominant factor and significantly affecting the turning out of TST positive cases, as well as to calculate the Odd’s Ratio (OR) of forming TST positive results in contrast to TST negative cases when

relevant factors being maneuvered.

Results

According to a general survey, except the 1st Grade was divided into 9 classes, each of the other grades of the said elementary school had 10 classes, and throughout the school each class was attended by anywhere from 25 to 32 pupils. Therefore, the entire school had a total of 59 classes with 1728 pupils, among which 802 were girls and 926 boys. The TB teacher, without knowing the outcomes of the TST test, told us that 5 pupils in his class (Class A) had more frequent contact with him and were appointed officers. The TST results revealed that all five officers of Class A, who had more close contacts with the teacher, gave positive reaction, and 60% (3 pupils) showed swollen masses ≧15 mm in diameter. The subjects of the first round TST were supposed to include 95 pupils, but 4 pupils failed to complete the test. There was one pupil each of the three classes happened to ask for leave of absence to attend some legitimate activities and one of Class A was on sick leave (getting chickenpox). Therefore, the completion rate of the test was 96% (91/95), and the number of pupils received the test was 30 for Class A, 32 for Class B, and 29 for Class C. The percentage of pupils displayed positive results, i.e. with a swollen mass equivalent to or larger than 10 mm, was 56% (17/30), 43.8% (14/32), and 34.5% (10/29), respectively. These figures appeared indeed that Class A had a higher positive rate than Class B or Class C had. However, checking them with a chi-square test, the differences involved did not qualify to be significant statistically (*P* value > 0.05) (see Table 1). Among pupils of Classes A, B, and C, there were 4 pupils displayed PPD≧18 mm results. We paid visits to their households but found that none of them had family members infected with TB. Those 4 pupils were

then asked to visit the local hospital to have a re-examination. They were examined by a specialist physician, had chest X-ray picture taken, and sputum checked, but all failed to show any active signs of suspected TB infection. The only exceptions were 2 pupils of Class A due to their having "intimate" contact history with the sick teacher, the physician weighted the circumstances and decided to prescribe some preventive anti-TB drugs for them to take.

As to the second round TST campaign, a notice letter was sent out to the parents of all 1633 pupils (once again, not including those took part in the first round TST). So, 359 parents chose to return the consent paper that accounted for 22.0% of the total. Since those participating in the second round TST were not sampled in a random fashion, the first thing striking our mind was wondering if those pupils agreed to participate in the test differed from those disagreed to do so as far as their sex and grade are singled out. After running a chi-square test, we discovered that the differences in their sex and grade between the two groups were not statistically significant enough ($P > 0.05$) (see Table 2). Then, not all 359 pupils whose parents gave the consent and who did go on to take the TST completed the test after all, i.e. 12 of them failed to give a kind of result we expected – for some reason the test reactions of 6 out of those 12 pupils were not read and registered, and the other 6 pupils' data were found somewhat incomplete or inappropriate in the database. As a result, we have only 347 pupils who went through the test and whose results were duly read and registered in the database in a meaningful and proper way, and they included 42 1st graders, 69 2nd graders, 44 3rd graders, 66 4th graders, 63 5th graders, and 63 6th graders. The percentages of positive TST results, which was represented by having a swollen mass equivalent to or larger than 10 mm in diameter, among tested pupils in each grade of the school were 26.2% (11/42), 26.1% (18/69), 36.4% (16/44), 48.5% (32/66), 42.9%

(27/63), and 39.7% (25/63), respectively. Also it is shown by the TST results that pupils in the lower grades had a lower positive rate than those of the mid grades and the higher grades. We carried out a chi-square test for trend and found the TST positive rate increased along with the advance of grades. This relationship turned out to be statistically meaningful in a significant way (*P* value < 0.05) (Table 3).

In order to further understand all relevant factors that may influence the outcomes of the schoolchild TST, we used logistic regression analysis in this study. Our findings are as follows: It shows that those school girls had a marked higher TST positive rate than their male counterparts, which means the school girls had a considerable higher risk of getting a positive TST result than that of the school boys, and more precisely, the former was 1.49 folds of the latter. It was also found that the odd of TST positive in the lower graders was noticeably lower than that among the mid and higher graders, and the risk ratios were 2.02 and 2.00 folds, respectively. However, the other two factors, TB contact history and BCG vaccination history, were found not statistically significant in this case (Table4).

Discussion

Whether BCG inoculation will affect the reading of TST is still controversial and full of uncertainty since there are a few factors needed to be considered: such as vaccination age and dose of BCG, dose and type of tuberculin, and length of lapse of time between the BCG vaccination and the TST [9-13]. Although in this study it turned out through regression analysis that BCG vaccination was not likely a risk factor to cause TST positive results, but in view of the fact that only 6 pupils in this study had not been vaccinated. Therefore, it is extremely possible

that the statistical power was inadequate in this case due to too small was the number of samples. Bearing this in mind, we believe that in order to ascertain if BCG vaccination or TB infection do have a significant impact on the school children's TST positive rate, we should get a big enough number of samples to start with in our future test and analysis.

TB transmission often takes place from an infectious TB case to a healthy individual when the two have had prolonged and intimate contacts, especially in a more crowded or not well-ventilated environment setting. Therefore, normal, casual social contacts seldom lead to TB infection. However, most school grounds are rather crowded and without much empty space, and it has been reported in the past that outbreaks of TB transmission occurred on school grounds [14, 15]. This study happens to be an investigating report of a TB transmission outbreak at an elementary school in Taiwan. In this particular event, we discovered that all those pupils having had intimate contacts with the diseased teacher gave positive results in the screening TST. Even the rest pupils of his class though having no such so-called intimate contacts with their sick teacher, the overall positive rate turned out to be higher than its neighboring classes. These data seem to further substantiate the accuracy of the theory stressing that effective TB transmission needs prolonged contacts. In other words, common casual contacts on school ground will not effectively evoke TB transmission. In addition, since the local health authority chose to make an effort in protecting the privacy of the involved teacher and pupils, they deliberately included two neighboring classes in the imperative contact investigation to camouflage their real intention. However, now we know better from out TST screening results that confirmed once again that communication of TB indeed requires longtime contacts. If for a certain excuse of, say, privacy rights of some individual cases to expand the contact

screening process to include more pupils who are not required by the laws and regulations, we are afraid this may infringe upon the human rights of those innocent pupils. Therefore, we would like to make a recommendation that the future contact screenings should basically follow the regulations of TB control issued by Taiwan CDC -- only applying to the pupils of the class when their homeroom teacher is notified infectious disease sufferer. Besides, we'd like to make another recommendation that in the future studies on TST and intimacy of contacts, attention may be paid to both categorized and isometric indexes at the same time since linear index is more sensitive than categorized index, and easier to reflect the relevance. Because in this study we failed to collect the linear index of the two variables (TST result of mass diameter and TB contact frequency survey), it is probably the major reason why the statistical test was not so inconspicuous.

This study was a cross-sectional study, and there was no long-term traceable, repeated measurement of the pupils' TST results. The positive result rate was only the prevalence at that particular time point, so it was not able to clarify the timing nature of cause and effect. Hence, the pupils' TST positive results were not necessarily related to the TB teacher in the first place. Another notable detail of this study was that we did not use the international standard, two-stage TST, thus the apparent positive rate obtained, when used in estimating latent TB infection prevalence, may very well underestimate the true situation. Once again we have to mention the fact here that for the second round of TST test, the participating pupils were by no means selected in a random fashion but according to their parents' free will. This might lead to possible selective deviations. However, due to limited time and space available, we could not come out with a setup with random sampling, and in view of the fact that the voluntary group's

composition turned out not too different from the rest as far as grade and sex were concerned, we preliminarily assumed those participants should be able to represent the entire pupil population of that school.

The main tasks of TB control are to find TB and cure TB. Only there are no obvious symptoms in the early disease onset stage after being infected. In case the attending physician is not alert enough towards TB diagnosis, the good doctor may let it slip and fail to spot the infected early in time, this kind of delay in diagnosis could considerably increase the risk of pulmonary TB transmission. Research has pointed out that in Taiwan, the number of days in TB health system delay is far more serious than that in TB patient delay as their averages are 23 days and 7 days, respectively. Although our average TB health system delay is shorter than those in South Korea and Malaysia [16], but look at the devastating effect it causes that each and every day of delay, an undetected sputum positive TB case would unknowingly spread TB bacterium in his community for one more day!! In the incident we dealt with in this study, we learnt that the diseased teacher had sought physician's help in the vicinity of his residence, but the doctors he visited did not make an accurate diagnosis. From his description, it is estimated his health system delay was a amazing 90 days. Of course we do have excuses for this unbelievable situation, such as most basic clinics having no X-ray facility and being not able to give chest X-ray examination, but if those physicians were a little more conscious and alert about TB possibilities while checking their patient, and if they were willing to take advantage of the referral system, we believe that is the most effective way to slow down the rampant TB spread.

From previous studies, we see that 80% of child TB cases were discovered through contact screening, and 98% of their infection sources were adults suffered

from open-type pulmonary TB, among them 88% were the child's family and close friends [17]. Therefore, the future child TB prevention and control should emphasize on the finding and management of adult open-type pulmonary TB cases since any improvement in such direction will definitely decrease the exposure risk of children at large to TB bacterium. One notable risk factor of school ground TB control is general lacking of accurate knowledge in the contagious nature of pulmonary TB. Some studies revealed that knowledge of and attitude toward pulmonary TB have a profound influence on the individual to adopt effective preventive behaviors, and increase in health education is helpful to enhance the positive awareness of TB and lower down the uneasy sentimental reaction towards TB [18]. At the beginning of the incident, it was originally planned the contact screening process would only cover all pupils of the sick teacher's own class and the two classes next door, and no arrangement to expand such activity to the entire school pupil population. However, the lack of or correct knowledge, or cognitive deficit toward TB, got the entire school into a huge panic. Although the local health authority made multiple efforts including health education campaigns, explaining sessions, and negotiation meetings, teachers as well as parents of the school could not quiet down their uproarious anxieties and worries and they insisted on asking for a school wide pupil screening. Because of this unexpected development, we finally gave in and arranged the second round TST screening to cover all pupils with insisting parents. From this lesson we'd like to make a recommendation here says that if you want to conduct school ground TB control smoothly, you have to first set up an accurate cognition of pulmonary TB in the community well in advance, then when outbreak takes place the responsible health worker can focus on whatever mandatory and perform them swiftly without waste any efforts to overcome some

unnecessary interference.

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Table 1. TST results of pupils attending Class A after their teacher being detected and notified as an open-type TB case as well as those of pupils attending the neighboring Classes B and C

Variable	Class A	Class B	Class C	Subtotal
Grade	6	6	3	—
Sex				
Female (%)	12 (40.0)	15 (46.9)	12 (41.4)	39 (42.9)
Male (%)	18 (60.0)	17 (53.1)	17 (58.6)	52 (57.1)
TST results				
≦9 mm (%)	13 (43.3)	18 (56.3)	19 (65.5)	50 (54.9)
10-14 mm (%)	10 (33.3)	10 (31.3)	4 (13.8)	24 (26.4)
15-17 mm (%)	5 (16.7)	4 (12.5)	4 (13.8)	13 (14.3)
≧18 mm (%)	2 (6.7)	0 (0.0)	2 (6.9)	4 (4.4)

Table 2. Distribution of sex and grade among pupils of the entire school (not including those of Classes A, B, and C) whose parents either agree or disagree to let their kids take the TST.

	All school pupils		
Variable	Agree	Disagree	Subtotal
Sample no	359 (22.0)	1274 (78.0)	1633 (100.0)
Sex			
Female (%)	175 (48.8)	586 (46.0)	761 (46.6)
Male (%)	184 (51.3)	688 (54.0)	872 (53.4)
Grade			
1st grade (%)	42 (11.7)	193 (15.2)	235 (14.4)
2nd grade (%)	71 (19.8)	196 (15.4)	267 (16.4)
3rd grade (%)	46 (12.8)	221 (17.4)	267 (16.4)
4th grade (%)	73 (20.3)	236 (18.5)	309 (18.9)
5th grade (%)	63 (17.6)	235 (18.5)	298 (18.3)
6th grade (%)	64 (17.8)	193 (15.2)	257 (15.7)

Table 3. Results of an extended TST covering all voluntary pupils of the entire school but not including pupils attending Classes A, B, and C

Variable	1st grade	2nd grade	3rd grade	4th grade	5th grade	6th grade	Sum
Sample no	42	69	44	66	63	63	347
Sex							
Female (%)	23 (54.8)	28 (40.6)	21 (47.7)	33 (50.0)	29 (46.0)	35 (55.6)	169 (48.7)
Male (%)	19 (45.2)	41 (59.4)	23 (52.3)	33 (50.0)	34 (54.0)	28 (44.4)	178 (51.3)
TST results							
≦9 mm	31 (73.8)	51 (73.9)	28 (63.6)	34 (51.5)	36 (57.1)	38 (60.3)	218 (62.8)
10-14 mm	7 (16.7)	15 (21.7)	7 (15.9)	21 (31.8)	19 (30.2)	21 (33.3)	90 (25.9)
15-17 mm	2 (4.8)	1 (1.5)	5 (11.4)	6 (9.1)	4 (6.4)	3 (4.8)	21 (6.1)
≧18 mm	2 (4.8)	2 (2.9)	4 (9.1)	5 (7.6)	4 (6.4)	1 (1.6)	18 (5.2)

Table 4. A logic regression analysis of the positive and negative data in this particular TST screening project

Variable	Sample no	Regression coefficient	Standard deviation	OR	*P* value
Constant	—	-7.92	468.0	—	0.99
Sex					
Male (control)	230	—	—	—	—
Female	208	0.20	0.10	1.49	0.049
Grade					
Lower (control)	111	—	—	—	—
Mid	139	0.36	0.14	2.04	0.01
Higher	188	0.35	0.14	2.00	0.01
TB contact history					
None (control)	408	—	—	—	—
Normal	25	0.16	0.22	1.38	0.46
Intimate	5	7.80	468.0	>999.99	0.99
BCG vaccination history					
No (control)	6	—	—	—	—
Yes	432	-0.29	0.42	0.56	0.49