Established in 1871
Swiss Medical Weekly
Formerly: Schweizerische Medizinische Wochenschrift
The European Journal of Medical Sciences

Original article | Published 14 August 2014, doi:10.4414/smw.2014.13988
Cite this as: Swiss Med Wkly. 2014;144:w13988

Contact tracing investigation after professional exposure to tuberculosis in a Swiss hospital using both tuberculin skin test and IGRA

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Summary

SETTING: A 950 bed teaching hospital in Switzerland.
AIM: To describe the result of a contact investigation among health care workers (HCW) and patients after exposure to a physician with smear-positive pulmonary tuberculosis in a hospital setting using standard tuberculin skin tests (TST) and Interferon-gamma release assay (IGRA).
METHOD: HCW with a negative or unknown TST at hiring had a TST two weeks after the last contact with the index case (T0), repeated six weeks later if negative (T6). All exposed HCW had a T-SPOT.TB at T0 and T6. Exposed patients had a TST six weeks after the last contact, and a T-SPOT.TB if the TST was positive.
RESULTS: Among 101 HCW, 17/73 (22%) had a positive TST at T0. TST was repeated in 50 at T6 and converted from negative to positive in eight (16%). Twelve HCW had a positive T-SPOT.TB at T0 and ten converted from negative to positive at T6. Seven HCW with a positive T-SPOT.TB reverted to negative at T6 or at later controls, most of them with test values close to the cut-off. Among 27 exposed patients tested at six weeks, ten had a positive TST, five of them confirmed by a positive T-SPOT.TB.
CONCLUSIONS: HCW tested twice after exposure to a case of smear-positive pulmonary TB demonstrated a possible conversion in 10% with T-SPOT and 16% with TST. Some T-SPOT.TB reverted from positive to negative during the follow-up, mostly tests with a value close to the cut-off. Due to the variability of the test results, it seems advisable to repeat the test with values close to the cut-off before diagnosing the presence of a tuberculous infection.

Key words: *tuberculosis; outbreak management; latent tuberculosis infection; contact investigations; IGRAs*

Introduction

Patients with smear-positive pulmonary tuberculosis may contaminate persons with whom they come in contact, some of whom (about 10% according to the literature) will progress to disease and transmit the infection further. Screening exposed contacts for latent tuberculosis infection (LTBI) and offering preventive treatment before the disease develops is considered as one of the effective methods for controlling tuberculosis, particularly in countries where tuberculosis is a rare disease, and where resources and equipment allow it [1–4]. As contacts of cases with contagious pulmonary tuberculosis have a high risk of developing the disease in the near future, particularly if they have immunological markers of infection [5], contact tracing and preventive treatment of infected contacts is recommended whenever a case of smear-positive tuberculosis is detected [6].
A case of smear-positive tuberculosis was observed in a health-care worker (HCW) at a large teaching hospital in Switzerland. A contact tracing procedure was performed among other HCW and patients in contact with the index case. This paper describes the procedure using both tuberculin skin test (TST) and an Interferon Gamma Release Assay (IGRA), the results and some open questions arising in this setting.

Case report

A junior medical doctor from Cameroun arrived in Switzerland in January 2005 and started working in the University Hospital in Lausanne (CHUV). He was healthy on arrival, but had prior contacts with patients with tuberculosis in his country of origin. Because of misunderstanding, he did not undergo the pre-employment screening for TB. By the 15th of April he noted the abrupt onset of productive cough, weakness and malaise. He sought medical

attention two weeks later, and was diagnosed with smear-positive pulmonary tuberculosis. Cultures confirmed the presence of a fully susceptible *M. tuberculosis* strain. Isolation under negative pressure was ordered and a four drug regimen with isoniazid, rifampicin, pyrazinamid and ethambutol was started immediately. The patient was cured at the end of therapy.

Method

As the onset of cough was abrupt beginning on the 15th of April, the index case was considered as potentially infectious during a period ranging from the 1st April and the beginning of May when diagnosis was made and the index case was isolated (one month period). All HCW working in the same department as the index case during that period, all workers in other departments with whom he was in contact (operating theatre, emergency rooms) and all patients treated by him during that period were identified and contacted. All HCW exposed to the index case were asked to fill out a questionnaire with demographic data, information about prior BCG vaccination, prior exposure to tuberculosis and the self-estimated length of exposure to the index case. Since the period of communicability extended over a month and since most HCW had multiple contacts with the index case during that time, the date of exposure for all HCW was set at 15th of April as a proxy.

At that time the current policy for TB screening in HCW in the hospital (at pre-employment and at regular intervals for those in high risk settings or after occupational contact with a patient with smear-positive TB) was to use TST. For this investigation an IGRA (T-SPOT-TB®, Oxford Immunotec, Oxford, UK) was also used for the first time. Both tests were performed according to the following protocol:

Protocol of investigation:

- HCW: prior TST (TST performed at pre-employment health evaluation or at the last periodic control) was used as baseline. HCW with no prior TST, or negative prior TST or TST older than five years were retested shortly after exposure (T0). Because T-SPOT.TB was never used before in the routine contact-tracing in the hospital and in order to obtain a baseline value it was performed at T0 for all HCW in contact regardless of the prior TST. The blood was drawn at the same day as the application of the TST. Six weeks later (T6), a TST was offered to all HCW with a negative TST at T0 and a second T-SPOT.TB to all. T-SPOT.TB was re-checked ten weeks later (T16) in 8 HCW in cases of conversion.
- Patients: patients in contact with the index case were contacted individually by a community nurse and were informed about the investigation. According to the usual procedure in Switzerland [7], they all had a TST at T6. Contacts with a positive TST were tested at the time of reading with T-SPOT.TB.

The TST was performed using the Mantoux method with two units of RT23 tuberculin. A TST was considered positive if the induration was ≥10 mm. The T-SPOT.TB was performed according to the manufacturer's instruction. The test was considered positive if the sample demonstrated the presence of six spots more than the negative control. Conversion was defined as a change from negative to positive, reversion as a change from positive to negative, whatever the values.

According to the current Swiss procedure [7], contacts with a positive T-SPOT-TB test have to pass a medical examination and a chest X-ray. Those with a normal image are considered as possibly infected and offered a preventive treatment with isoniazid for nine months or rifampicin for four months. Contacts with an abnormal X-ray are assessed for the possible presence of active tuberculosis. Contacts with a positive TST not confirmed by T-SPOT.TB are informed that they probably have not been contaminated and offered clinical surveillance.

Statistical analysis

Descriptive statistics with absolute values and proportions are presented. Odds ratios (OR) with the corresponding 95% confidence intervals (95%-CI) for TST and IGRA at T0 and T6 depending on vaccination status and on prior exposure to tuberculosis were calculated. To assess the binary concordance among TST and IGRA at T0 and T6 kappa statistics were presented [8]. All statistics were performed using the Stata version 12.1 software (StataCorp. LP, College Station, TX, USA)

Results

HCW

The total number of contacts to be investigated was 101. The demographic data, distribution by professional categories, risk factors for prior exposure to TB, the estimated time of exposure and the distribution of the test results at initial and repeated screening are reported in table 1. The majority (68%) of HCW had been vaccinated with BCG (time elapsed since vaccination not known). Vaccinated HCW had a higher rate of TST positivity at T0 compared to non-vaccinated (29% vs 0% OR not calculable because there was nobody with prior BCG in one group) but about the same rate of positivity of T-SPOT.TB at T0 (10% and 11% respectively, OR 0.92 (95%-CI 0.17–4.90). Both groups showed a comparable rate of conversion between T0 and T6 with both TST and T-SPOT-TB (13% resp. 8%). HCW with a known prior exposure to TB were more likely to show a T-SPOT-TB positivity at T0 than non-exposed although this was not statistically significant (20% vs 9% respectively, OR 3.11 (95%-CI 079–12.27), whereas there was no difference in the TST positivity at T0 (OR 0.82 with a 95%-CI 0.17–4.90). There was a very low inter-rate agreement between TST and T-SPOT.TB both at T0 (.k = 0.09) and at T6 (.k = 0.13).

Conversion by both TST and T-SPOT.TB appear not to correlate with the self-estimated duration of the exposure to the index patient (table 1), although we were not able to perform a multivariate logistical regression analysis due to the low conversion rate both by TST and T-SPOT.TB (table 1).

In the whole studied population, a possible conversion of the TST (change from negative to positive) was observed,

in 6/43 (14%) HCW from T0 to T6. T-SPOT.TB was positive at T0 in twelve and converted from negative at T0 to positive at T6 in ten. Among the six HCW with a TST conversion none were confirmed by T-SPOT.TB and among ten T-SPOT converters, none demonstrated a TST conversion (0% correlation). Furthermore T-SPOT-TB reverted from positive at T0 to negative at T6 in two cases (table 2). The T-SPOT.TB reverted to negative values in six patients with prior conversion (T0–T6) 3 of them being in the "grey zone" between six and nine spots and all with 15 spots or less.

No HCW had a radiological abnormality or symptoms suggestive of TB at control. As all HCW had a confirmed recent exposure, we assumed that all contacts with a stable or increasingly positive T-SPOT.TB test had an indication for preventive chemotherapy. A preventive therapy was offered but rejected by most of them.

Patients

Twenty-seven patients (all adults) were contacted and tested by TST and T-SPOT six to eight weeks after the last contact with the index case. Ten had a positive TST, five of whom were confirmed by a positive T-SPOT.TB. All patient with a negative TST and five with a positive TST had a negative T-SPOT.TB. A preventive therapy was offered to all patients with a positive T-SPOT.TB and accepted by four. One patient with a positive TST but negative T-SPOT.TB was also offered a preventive treatment.

Discussion

In a contact investigation performed among 101 HCW exposed to a case of smear-positive tuberculosis in a hospital and tested twice at six week intervals, we observed six TST conversions and ten IGRA conversions between T0 and T6. Globally, 21 HCW workers had at least one positive IGRA, eight of whom reverted to negative values between T0 and T6 or between T6 and T16. Thirty percent of them had a possible previous exposure to TB. Two had received a treatment for tuberculosis in the past but none had received a preventive treatment.

Among 27 adult patients exposed to the same index case and tested more than six weeks after the last contact, ten had a positive TST, five of whom also had a positive IGRA. No patient with a negative TST had a positive IGRA.

This contact investigation in a hospital setting among HCW and patients posed several problems for the management and interpretation of test results.

Choice of test procedure

As 68% of HCW had received a BCG vaccination in the past and 30% had a possible prior exposure to tuberculosis, the reliability of the TST as a tool for assessing the presence of infection was considered inappropriate, as a large proportion of false positive results was expected, with a risk of generating unnecessary anxiety, examinations and preventive treatment in uninfected contacts [9]. Therefore, all contacts were offered a test with T-SPOT.TB, considered

Table 1: Study population and distribution of positive test results (TST and T-SPOT.TB) at initial screening and at control (by frequency of positivity related to number of tests performed). The risk factors for TB infection prior to the current exposure were defined as: 1) birth in a country with a high prevalence of TB. 2) travel in such countries for more than six months. 3) previous exposure to any person known to have TB. Immunodeficiency was defined as having HIV/AIDS, solid or bone marrow transplantation or any other immunosuppressive drug (steroids, anti-TNF, etc). *OR and 95%-CI were calculated and the results are presented in the text.

Categories	**Total (Nr)**	**Positive at T0**		**Conversion T0 to T6**	
		by TST (n = 73)	by T-SPOT.TB (n = 100)	by TST	By T-SPOT.TB
Age (mean/median in years)	(35/38)				
Gender					
m	39	6/25 (24%)	8/38 (21%)	1/12 (8%)	4/27 (15%)
f	62	11/48 (23%)	4/62 (6%)	5/31 (16%)	6/55 (11%)
Age category					
<35y	50 (50%)	8 (16%)	5 (10%)	3 (6.0%)	5 (10%)
35–50y	34 (34%)	6 (18%)	3 (8.8%)	2 (5.8%)	5 (10%)
50–65y	17 (17%)	3 (18%)	4 (3.5%)	1 (5.8%)	0 (0%)
>65y	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
BCG vaccination					
yes	68 (68%)	15/51 (29%)*	7/68 (10%)*	5/27 (18%)	8/59 (13%)
no	19 (19%)	0/13 (0%)	2/18 (11%)	1/9 (11%)	1/13 (8%)
unknown	14 (14%)	2/10 (25%)	3/14 (21%)	0/7 (0%)	0/10 (0%)
Prior exposure to TB					
yes	30 (30%)	4/20 (20%)*	6/30 (20%)*	1/14 (7%)	4/23 (17%)
no	68 (68%)	12/52 (23%)	6/67 (9%)	5/29 (17%)	6/56 (11%)
unkonwn	3 (3%)	1/1 (100%)	0/3 (0%)	0/0 (0%)	0/3 (0%)
Time of exposure					
<3h	63 (63%)	9/48 (18%)	9/63 (14%)	3/32 (9%)	9/51 (17%)
3–8h	26 (26%)	5/15 (33%)	2/26 (8%)	3/8 (37%)	1/22 (4%)
>8h	11 (11%)	2/9 (22%)	1/11 (9%)	0/3 (0*)	0/9 (0%)
unknown	1 (1%)	1/1 (100%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
HCW categories					
Physicians	19 (19%)	2/14 (14%)	2/19 (10%)	1/5 (20%)	0/14 (0%)
Nurses	43 (43%)	9/31 (29%)	4/43 (9%)	3/20 (15%)	4/29 (14%)
Others	39 (39%)	6/28 (21%)	6/38 (16%)	2/18 (11%)	6/29 (21%)
HCW with known immunodeficiency	0 (0%)	0	0	0	0
Total nr. HCW	**101**	**17/73 (23%)**	**12/100 (12%)**	**6/43 (14%)**	**10/82 (12%)**

as more specific (no influence of prior BCG vaccination and environmental mycobacteria) and potentially reducing the need for further examination and preventive treatment [10, 11]. It is generally assumed that IGRA have a higher negative and positive predictive value for progression to tuberculosis than TST, contacts with a positive IGRA result having a significantly higher risk of progression to tuberculosis than contacts with a negative result [12, 13]. In our study we found a very low inter-rate agreement between TST and T-SPOT.TB both at T0 and at T6 possibly due to the high rate of BCG vaccination in HCW. We also found no correlation among conversion by TST and conversion by T-SPOT.TB between T0 and T6. We are not able to explain these findings, which, translated in to clinical practice means that a contact screening performed only with TST would have identified a different population to which a preventive treatment potentially would have been offered. Nonetheless in practice we considered that a conversion by T-SPOT.TB was more relevant because we avoided false TST results due to BCG vaccination.

Timing of the tests

Because of the high level of anxiety in the HCW and the hospital management, the screening was organised rapidly after the diagnosis of the index case and the first testing was performed soon after the last possible contact (in average two weeks, defined as T0), in spite of the fact that some tests results may have been positive as a consequence of a prior infection. As the immune reaction after contact establishes after several weeks, it was decided to repeat the tests (TST in contacts with negative results and IGRA in all) six weeks later, considering that this time would allow for the development of an immune reaction in infected contacts [14, 15]. The T-SPOT.TB tests which were positive at T0 could have been the result of prior infection or the consequence of the recent contact with the index case prior to the diagnosis. The T-SPOT.TB tests which became positive between T0 and T6 were considered as a sign of recent infection. Due to this uncertainty, all contacts with a positive test result at any time had a medical examination and a chest X-ray before taking a decision of preventive treatment or information and observation.

Degree of exposure and test results

It is generally admitted that close contacts of infectious patients have a higher risk of being infected than casual contacts, the highest risk being in relatives sharing the same habitation [5]. In this context, it may seem surprising that there was apparently no correlation between the number of hours of contact of the HCW with the index case (less than three hours, three to eight and more than eight hours), but this may reflect the fact that the contacts took place in well ventilated hospital rooms and were not very close (work in the same room without direct contact). On the other hand, adults who were born in a country with a high prevalence of tuberculosis may have been infected during childhood and have a positive test result, as has been repeatedly demonstrated among migrants [16]. In our study group, persons with a prior exposure to TB (related to birthplace or occupation) seem to have a higher frequency of positive T-SPOT than those without exposure.

Conversions and reversions

The change from a negative to a positive test result (with TST and with IGRA), defined as a conversion, is considered as a marker of a recent infection and an indication for further examinations and proposal of a preventive treatment. An intriguing phenomenon, which was frequently ignored in the period where only the TST was available for contact investigations, is the observation of a variation in

Table 2: Evolution of the number of spots between T0 and T6 among all HCW who had at least one positive test result with the current definition of cut-off (six and more spots) and with a modified cut-off (16 spots and more). Contacts with positive IGRAs at T0 were considered as having a prior infection of unknown origin, contacts with a change from negative to positive were considered as possible conversions, contacts with a change from positive (at T0 or T6) to negative (at T6 or T16) were interpreted as reversion.

HCW nr.	T0 n spots	T6 n spots	T16 n spots	Interpretation Cut-off 6 spots	Interpretation Cut-off 16 spots
1	47	68		infection	infection
2	43	80		infection	infection
3	34	3		reversion from positive	reversion from positive
4	19	16		infection	infection
5	16	20		infection	infection
6	12	16		infection	infection
7	12	7		infection	negative
8	12	6		infection	negative
9	10	8		infection	negative
10	8	11	25	infection	conversion
11	6	7		infection	negative
12	6	0		reversion	negative
13	2	8	2	reversion	negative
14	2	7		conversion	negative
15	1	12	12	conversion	negative
16	1	11	5	reversion	negative
17	1	6		conversion	negative
18	0	15	0	reversion	negative
19	0	12	0	reversion	negative
20	0	10		conversion	negative
21	0	9	0	reversion	negative

the level of positivity of the blood tests, some tests turning from positive to negative if they are repeated. Changes in level after a short time interval may be due to biological variability [17, 18] or technical factors [19] or be the consequence of a transient immunological stimulation in subjects able to eliminate the mycobacteria soon after the contact [20] or due to some other unknown factors. High rates of both conversions and reversions are particularly noticeable in serial testing context such as TB screening in HCW [21–23]. Most of the changes in level or reversions are observed for tests with values close to the cut-off defined by the manufacturer. Therefore, some authors propose that the cut-off be set at a higher level, for instance doubling the level for positivity, particularly for repeated testing without documented exposure to tuberculosis [24, 25]. Using 16 spots as a cut-off for positivity instead of six, 15 out of 21 tests results would have been considered as negative, including seven of eight cases with an apparent reversion and only one would be considered as a conversion. There is currently no consensus about the optimal cut-off level for serial testing and individual testing after contact, and the elevation of the cut-off may have as a consequence a decrease in sensitivity of the test [26, 27]. Reversal of transiently positive tests may explain why the majority of contacts with a positive test result never progress to tuberculosis. If only contacts with a strong and stable immunological reaction have a significant risk of developing tuberculosis, then the repetition of the tests, particularly in cases with borderline results, may increase the efficiency of preventive treatment. In a study of contacts tested three times over an observation period of 18 months, 54 among 134 untreated contacts reverted from positive to negative at three months and 28/78 reverted to negative at 18 months [28]. In spite of this, the exact definition of latent tuberculosis infection and the interpretation of positive immunological tests remain somewhat elusive [29, 30].

Indication to preventive treatment

There is a general consensus that infected contacts of index cases with smear-positive pulmonary tuberculosis have a high risk of developing tuberculosis at a later date and would therefore benefit from a preventive treatment [4, 31, 32]. The main obstacle to an efficient prevention is the low rate of acceptance of preventive treatment by healthy contacts, including health care workers [33–35]. Short treatments, for instance four months of rifampicin instead of nine months of isoniazid, are better accepted and have a higher completion rate [36, 37]. Furthermore, a better definition of infected contacts, for instance by selecting for preventive treatment only the contacts with a stable or strongly positive reaction, or with individual risk factors, may improve the rate of adherence.

Limitations of the study

The study has several limitations. One of them is the fact that the procedure for contact investigation was not the same in all contacts (TST only for some of them) and that most HCW had two T-SPOT.TB and only some of them had three tests. Therefore, the role of prior exposure to TB before the current outbreak and the exact number of reversions of positive tests cannot be assessed.

Another major limitation of our study is the fact that the time of exposure to the index case was unknown for most HCW and had to be set arbitrarily. We cannot exclude that some HCW were exposed earlier than indicated and that the TST and T-SPOT.TB-test performed at T0 were actually performed four to six weeks after exposure.

As we used T-SPOT.TB for the first time in our institution within the context of a contact investigation, we did not consider the possibility of reversion and false positivity and did not repeat the positive or borderline tests, as would be the case now. Therefore we were not able to assess the assay variability.

Conclusions

1. Contact tracing among HCW and patients exposed to a staff member with pulmonary tuberculosis is difficult, as many adults have been vaccinated with BCG or have already been exposed to tuberculosis in the past and may have a remote infection. Tuberculin skin test is considered unreliable in this setting. IGRAs are more specific but their interpretation is still subject to controversy.
2. In our setting and using the current definition of positivity, T-SPOT.TB demonstrated 22% of latent infection, 10% probably recent (T-SPOT.TB conversions). Among exposed patients, the rate of possible infection was 19%.
3. Contacts tested several times with T-SPOT demonstrate a reversion in seven of 21 cases. This may be due to variations of the test value close to the cut-off or to a spontaneous elimination of the mycobacteria by the organism. Re-testing the contacts with a weakly positive test result and setting a higher cut-off for the definition of conversion may increase the efficiency of the procedure.

Funding / potential competing interests: No financial support and no other potential conflict of interest relevant to this article was reported.

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