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Dépistage et traitement de l'infection tuberculeuse latente chez les requérants d'asile récemment arrivés dans le canton de Vaud

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Dépistage et traitement de l'infection tuberculeuse latente chez les requérants d'asile récemment arrivés dans le canton de Vaud

THÈSE

préparée sous la direction du Docteur Patrick Bodenmann

(avec la collaboration du Docteur Jean-Pierre Zellweger)

et présentée à la Faculté de biologie et de médecine de

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DOCTEUR EN MEDECINE

Par

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Madame le Professeur Stephanie Clarke
Directrice de l'Ecole doctorale

Résumé de la publication de thèse

Cette thèse a fait l'objet de deux publications peer review :

I. Facteurs associés avec l'infection tuberculose latent chez les requérants d'asile entrant dans le canton de Vaud : Une étude transversale dans le canton de Vaud.

Objectifs : Les objectifs de cette étude étaient l'identification des facteurs associés à l'infection tuberculeuse latente (ITBL) chez les requérants d'asile récemment arrivés au Canton de Vaud et leur utilisation pondérée pour l'élaboration d'un score prédictif qui pourrait permettre la meilleure sélection des individus à dépister avec les Interferon Gamma Release Assays (IGRA).

Méthode : Le protocole de l'étude prévoyait l'inclusion des requérants d'asile de plus de 16 ans, récemment arrivés dans deux centre de requérant du canton de Vaud ceux de Sainte-Croix et de Crissier. De septembre 2009 à juillet 2010 les requérants d'asile ont bénéficié lors des visites au centre de soins infirmier (CSI) d'informations sur l'ITBL et le protocole et les enjeux de l'étude. Les requérants d'asile ont d'emblée été informées que leur participation à l'étude n'aurait pas d'impact sur le débouché de leur dossier d'asile et qu'il n'y aurait pas de compensation financière à leur participation. Après avoir signé le consentement éclairé les requérants d'asile bénéficiaient d'une entrevue avec l'infirmière du centre où un questionnaire démographique et médical était remplit. 10cc de sang étaient prélevés à la fin de l'entrevue pour l'examen IGRA. Les patients présentant des symptômes évocateurs de tuberculose active ou un anamnèse de traitement pour une tuberculose active étaient exclus de l'étude et adressés au médecin référant du centre pour une visite médicale. Selon les résultats du test T-SPOT.TB (IGRA), les requérants étaient classés en deux groupes : positifs et négatifs. Le groupe IGRA positif était adressé au médecin référant. L'analyse statistique des données de l'étude a été réalisée par le logiciel STATA 11.2. Les β coefficients de l'analyse multivariée ont été combinées pour la création d'un score pronostic dont la puissance de discrimination a été évaluée par une courbe ROC. Le protocole de l'étude avait reçu l'aval de la commission d'éthique de l'Université de Lausanne.

Résultats : Durant la période de l'étude, 788 requérants d'asile ont été hébergés dans les deux centres de l'étude. 639 avaient plus de 16 ans et 393 d'entre eux ont participé à l'étude (61.50%). 295 (75.06%) avaient un IGRA négatif et 98 (24.93%) étaient positifs. A noter que parmi les 98 positifs, 5 avaient une tuberculose active non détecté précédemment. Les analyses univarié et multivarié ont permis d'identifier 6 facteurs associées à l'ITBL : Région d'origine, moyen de transport, état civil, âge, toux et antécédent d'exposition à la tuberculose. Le score élaboré en combinant ces 6 facteurs présente un AUC de 81% avec une sensibilité de 80%, une spécificité de 70% et des valeurs prédictive positive et négative respectivement de 45% et 92% quant un seuil de 13 est utilisé.

Conclusion : Les requérants d'asile qui immigrent en Suisse proviennent de pays où l'incidence de la tuberculose est supérieure à celle des pays de l'Europe occidentale et présentent un risque élevé pour l'infection tuberculose latente (ITBL). L'origine comme seul facteur n'est pas suffisant pour stratifier le risque d'ITBL et ne peut pas justifier la prescription d'un traitement préventif d'ITBL. L'introduction des tests de détection, hautement spécifiques de l'infection au *M. tuberculosis* tel que les IGRA ainsi que le taux élevé de réussite des traitements préventifs de l'infection latente ont ouvert la voie à un dépistage précoce de l'ITBL qui compléterait le dépistage de la tuberculose active actuellement effectué à la frontière. Afin de mieux cibler le dépistage par ces tests une meilleure sélection des individus à dépister est impérative. Elle pourrait se faire en évaluant le score individuel de risque ITBL par requérant.

II. Taux élevé d'adhérence au traitement préventif de l'infection tuberculeuse latente prescrit à un collectif de requérants d'asile dans un canton suisse.

Objectifs: L'efficacité du traitement préventif de l'infection tuberculeuse latente dépend de l'adherence du sujet au traitement. Un traitement bien conduit pour une duré prévue est en mesure de prévenir l'activation des cas d'infection tuberculeuse latente (ITBL). Le plus grand enjeu dans un programme préventif pour la tuberculose est, outre de cibler la détection des individus les plus à risque pour l'ITBL, de pouvoir traiter efficacement le collectif dépisté positif. Cette étude évaluait la faisabilité d'un traitement préventif court parmi un collectif de requérants d'asile porteurs d'une ITBL dans le canton de Vaud.

Méthode: Nous avons effectué une étude prospective de cohorte parmi des requérants d'asile récemment attribués dans le canton de Vaud, âgés de plus de 16 ans et qui avaient été dépistés positifs par IGRA. L'ensemble du collectif selon le protocole de l'étude était adressé au médecin référant afin d'exclure une tuberculose active et pour discuter du traitement préventif si le diagnostic d'ITBL était confirmé. Lors de la première visite médicale, outre l'examen clinique, un bilan radiologique avec une radiographie du thorax et un bilan de la biologie hépatique ainsi qu'un test de dépistage HIV était proposé à l'ensemble du collectif. En cas de suspicion clinique ou d'image radiologique suspecte de tuberculose active le sujet était adressé pour des examens complémentaires. Les sujets porteurs d'ITBL se voyaient proposés, en l'absence de contre indications, un traitement de rifampicine de quatre mois. En acceptant de participer à l'étude ils s'engageaient de se présenter à leur contrôle médical mensuel où était évaluée l'adhérence au traitement et l'apparition d'effets indésirable ou de complications. Si l'adhérence était jugée correcte l'ordonnance du traitement était renouvelée d'un mois et le requérant recevait son prochain rendez-vous de contrôle. L'adhérence était considéré satisfaisante si le patient était adhérent à son schéma de visites médicales et demandait le renouvellement de son ordonnance. Si le requérant d'asile ne se présentait pas à deux contrôles il était considéré comme non adhérent et son traitement est suspendu.

Résultats : Notre collectif comptait 98 sujet présument atteint de ITBL sur la base du test T-SPOT.TB ce qui représentait 24.9% du collectif initial. L'âge moyen était de 26.7 ans, 74% était des hommes. La majorité étaient des africains: 66 %, 17% étaient asiatiques et les populations balkaniques et de l'ex-union soviétique étaient représentés à part égale d'huit pourcent. Parmi notre collectif nous n'avions pas de sujet immunodéficient notamment HIV positif. Des 98 sujets, 11 ne se sont pas présenté à leur visite médicale initiale. La visite médicale initiale a permis la détection de 8 patients porteurs d'une tuberculose active, dont cinq ont reçu un traitement antituberculeux, ou d'une autre affection pulmonaire non tuberculeuse. Chez deux patients il y avait une contre-indication au traitement préventif et deux avaient un anamnèse positif de traitement antituberculeux non précédemment déclaré. Le traitement préventif a été prescrit à 74 requérants d'asile. Durant le suivi mensuel trois requérants ne se sont pas présentés lors de la première visite de suivi, trois lors de la seconde et sept lors de la troisième pour un total de 13 sujets. Chez deux sujets le traitement préventif a du être suspendu à cause d'une adhérence problématique secondaire à des abus de substances illégales. Durant le suivi, nous n'avons pas eu de sérieuses complications ni d'effets indésirables au traitement qui auraient nécessité son arrêt. En final 60/75 des sujets ont achevé leur traitement soit 80% du collectif.

Conclusion: Malgré la vulnérabilité et la volatilité inhérente à cette population qui est d'ailleurs la plus à risqué de réactivation d'une ITBL, cette étude montre que il est possible d'obtenir de taux d'adhérence très élevés au traitement préventif. Nous considérons que les conditions qui ont permis ces résultats sont la prescription d'un schéma de traitement préventif court, un suivi médico-soignant régulier et l'hébergement contrôlée et stable où résidait notre collectif.

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RESEARCH ARTICLE Open Access

Factors associated with latent tuberculosis among asylum seekers in Switzerland: a cross-sectional study in Vaud County

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Abstract

Background: Screening and treatment of latent tuberculosis infection (LTBI) in asylum seekers (AS) may prevent future cases of tuberculosis. As the screening with Interferon Gamma Release Assay (IGRA) is costly, the objective of this study was to assess which factors were associated with LTBI and to define a score allowing the selection of AS with the highest risk of LTBI.

Methods: In across-sectional study, AS seekers recently arrived in Vaud County, after screening for tuberculosis at the border were offered screening for LTBI with T-SPOT.TB and questionnaire on potentially risk factors. The factors associated with LTBI were analyzed by univariate and multivariate regression.

Results: Among 393 adult AS, 98 (24.93%) had a positive IGRA response, five of them with active tuberculosis previously undetected. Six factors associated with LTBI were identified in multivariate analysis: origin, travel conditions, marital status, cough, age and prior TB exposure. Their combination leads to a robust LTBI predictive score.

Conclusions: The prevalence of LTBI and active tuberculosis in AS is high. A predictive score integrating six factors could identify the asylum seekers with the highest risk for LTBI.

Keywords: Asylum seeker, Latent tuberculosis infection, Tuberculosis, Risk factors, Predictive score, Interferon gamma release assay

Background

Most of the asylum seekers entering in Switzerland lived in countries with higher incidence rate of tuberculosis than in Western Europe and have a high risk of latent tuberculosis infection (LTBI) [1]. Persons with LTBI are at risk of developing an active tuberculosis mostly during the first years after infection [2]. A preventive treatment of infected but asymptomatic individuals lowers the risk of reactivation of latent infection and therefore decreases the pool of future active tuberculosis in a population [3]. Those principles are the basis of screening protocols for the management of individuals exposed to patients with active tuberculosis. Since the majority of asylum seekers are young adults the presence of LTBI among them would point to a recent contamination. Screening migrants for LTBI and treating those at risk of reactivation has been proven to be effective [4,5]. As most cases of active tuberculosis among asylum seekers occur within 5 years of entering Western countries and are due to the reactivation of a LTBI, screening and preventive treatment of LTBI, may be a complement to the screening for active tuberculosis in destination countries [6].

The current screening procedure for asylum seekers at the Swiss border consists on a standardized questionnaire on symptoms associated with tuberculosis, history of contact or prior treatment for active TB and an evaluation of the risk associated with the incidence in the country of origin. Migrants with symptoms or high risk of active tuberculosis are assessed by a physician. Those

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who are asymptomatic are transferred in a local center in a county. Screening for LTBI with tuberculin skin test (TST) was used during several years but was suspended after a study demonstrated the limited implications of a positive test result, particularly the weak observance of the treatment for LTBI by physicians and asylum seekers with a positive TST [7].

The introduction of Interferon-Gamma Release Assays (IGRAs) as a screening tool for tuberculosis infection changed the concept of screening individuals exposed to active TB and potentially infected [8]. IGRAs are highly specific, not influenced by prior BCG vaccination or contact with most non-tuberculous mycobacteria. They therefore help the physician to restrict the need for further examinations and prescription of preventive treatment.

Screening asylum seekers born in countries with high prevalence of tuberculosis upon entering Switzerland with IGRA is limited by the cost of the test and by the low number of migrants eligible for preventive treatment. Since individuals with LTBI are asymptomatic a screening based on clinical approach is not an option. A better definition of the factors associated with LTBI and reactivation of infection among asylum seeker might lower the cost of the screening procedure. The screening with IGRA of the asylum seekers presenting those factors could be cost-effective since the proportion of positive IGRA in this group would be higher than of the rest of the asylum seeker population. A recent prospective study from The Netherlands confirms the high rate of positive IGRA test results in immigrants and demonstrates that immigrants with a positive test result have a much higher risk of developing tuberculosis within two years after entry, irrespective of age and origin [9]. The authors consider the possible usefulness of a preventive treatment in this population group.

Based on such an assumption, some countries have introduced a selective screening for groups of asylum seekers considered at high risk of LTBI and reactivation [10,11]. The aims of this pilot study were to assess the prevalence of LTBI among asylum seekers entering Vaud County and to define the factors associated with latent infection among them.

Methods

Vaud County is host to 9% of the total Swiss asylum seeker population. A cross-sectional study was conducted in two host centers (Sainte-Croix and Crissier) where the asylum seekers have to stay after the initial screening for active TB at the border. For financial and practical reasons (turnover of entries of AS in Switzerland and staff holidays), sampling lasted 10 months from September 2009 to July 2010.

All participating individuals were volunteers aged above 16 years, lodging in Sainte – Croix and Crissier host centers. All were recently arrived in Switzerland and had already been screened at the border for active tuberculosis two to three months before. They received detailed information on the study goals and on tuberculosis infection and signed a written consent form, translated in English, French, German, Russian and Arabic. For those asylum seekers who did not understand those languages a live translation was provided. The study was approved by the ethic commission of the University of Lausanne.

Certified nurses on each of the host center interviewed the individuals about their origin, demographic, travel conditions and medical history. Individuals mentioning a previous tuberculosis treatment were excluded from the study and addressed to the local health center to be assessed by a physician. In asylum seekers without a previous history of tuberculosis, 10ml venous blood was taken for T-SPOT-TB. The blood tubes were addressed with same day post mail to the laboratory.

The asylum seeker population was divided in two groups, positive and negative, according to the T-SPOT. TB results. Cases with 6 to 8 spots were considered according to the Swiss recommendations, as positive. No case was indeterminate.

Asylum seekers with a positive T-SPOT.TB result were addressed to the local health center for medical assessment. A physician examined them, asking for medical history of active tuberculosis or TB contact, performed a clinical examination and ordered a chest X-ray. HIV screening was proposed to all positive individuals, and women were offered pregnancy tests.

The asylum seekers presenting with cough, compatible with tuberculosis symptoms or abnormal chest X-ray had a sputum examination and culture. All asylum seekers with active tuberculosis were treated and excluded from the study. All asylum seekers with positive T-SPOT.TB without signs suspect of active TB or abnormal X-ray were considered as carriers of LTBI and were offered a preventive treatment. The follow-up and feasibility of LTBI preventive treatment is presented in a different paper.

The statistical data analysis was performed using STATA 11.2 (College Station, Texas 77845 USA). The data were summarized as mean (sd) for the age and as number (percentage) for categorical data. Univariate logistic regression analysis was performed to assess the association of the demographic, immigration history and medical factors associated with LTBI. Significant predictors at the level of 20% were used in a backward procedure to elaborate a multivariate model and to develop a prognostic scoring system to predict LTBI cases.

The β coefficients (β =log (OR)) derived from the multivariate logistic regression model were used to develop an overall prognostic scoring system. To simplify the

calculation of the score, each β- coefficients were multiplied by 3 and were rounded to the closest integer. The score was calculated as the sum of the weighted scores from the six related factors. The discriminatory power of the score was assessed with a ROC curve.

Results

Among 788 asylum seekers registered in two dedicated centers during the study period, 639 were adults over 16 years old. 393 of them agreed to be screened (61.50% of the eligible population). In this group, 295 (75.06%) asylum seekers had a negative T.SPOT.TB, and 98 (24.93%) had a positive T-SPOT.TB of which 5 (5.1%) had active tuberculosis (3 culture-proven) previously not detected at the border and 2 had already been treated for active tuberculosis prior to the entry in Switzerland (Figure 1). The spot distribution is provided on Figure 2 (Figure 2). The characteristic of the 5 cases with active tuberculosis are shown on Figure 3 (Figure 3). The remaining 38, 5% did not agree respond to the proposed screening or left the country before any investigation. Detailed data on the unscreened collective is scarce but their median age is of 29.26 years, 25% were women and their origin distribution is shown on Figure 4.

In the univariate analysis (Table 1) balkanic origin was set as reference since the tuberculosis incidence rate in balkanic countries is close to the western European countries. Associated with LTBI variables were: origin from FSU and Africa, ground/sea transit pattern, previous TB exposure and cough. The variables Age, Sex, Asian origin, being married, the existence of siblings and offspring as well as prior stay in congregate settings, addictions and immunosuppression were not associated with an increased risk of LTBI.

The multivariate logistic regression (Table 2) identified origin from the Former Soviet Union 12.54 (2.02, 77.9), Asia 2.63 (0.49, 14.12) and Africa 26.11 (5.04, 135.43), ground transit 2.42 (1.34, 4.37), married status 2 (1.01, 3.82), and cough 8.08 (2.63, 24.87) as the major factors associated with LTBI. Prior TB exposure 1.94 (0.65, 5.72) and age by 10 years 1.37 (0.99, 1.88) were considered as minor factors related with LTBI because of their almost significant CI 95% interval.

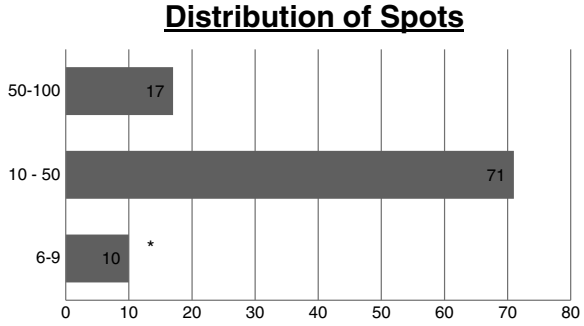

Figure 2 Spot distribution among positive IGRA. *During the study period we followed the actual Swiss Guidelines and the cases with 6–9 spots were counted as positive. The recent CDC recommendations differ and propose to consider tests results between 6 and 9 spots as borderline.

The values of our predictive score (Figure 5.) ranged from 2 to 23 (median (11.5), IQR (6.3)). The probability of having a positive IGRA increases with score value. The score had a good discriminatory power (AUC=81%) with a sensitivity of 80%, a specificity of 70%, a PPV of 45% and a NPV of 92% when using the cutoff-score=13 (Figure 6).

Discussion

The main objectives of this study were to assess the factors associated with LTBI among asylum seekers entering Vaud County. A robust score combining six factors (country of origin, travel conditions, age, marital status, cough, prior TB exposure) allowed the identification of AS with the highest risk of LTBI.

The prevalence of LTBI of 24.9% observed in this study among asylum seekers is close to the estimates reported in the literature. Winje and et al. reported a 29% [12] prevalence while Hardy AB and al, reported 38% [13]. Pareek [1] demonstrated that the proportion of asylum seekers in UK with a positive IGRA was between 3 and 28%, related to the incidence of tuberculosis in the home country and Mulder [9] reported a similar

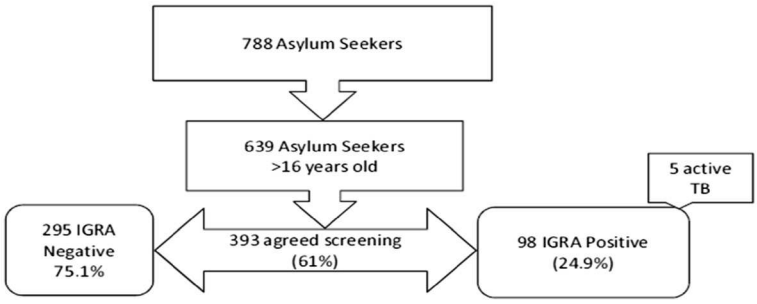

Figure 1 Study flowchart.

Active TB Characteristics

N°	ORIGIN	SEX	AGE	SPOTS
1	FSU	F	47	30-50
2	AFRICA	M	18	50-100
3	AFRICA	M	24	50-100
4	AFRICA	M	20	50-100
5	AFRICA	M	20	10-20

Figure 3 Characteristics of cases with active TB.

result with 20% positive QuantiFERON(®)-TB Gold In-Tube assay among AS.

A striking figure is the detection of 5 subjects with active tuberculosis that passed undetected through the border screening performed several weeks before. We assume that these subjects progressed from a recently acquired infection after border screening according to the natural history of TB. Considering the fact that the majority of cases of tuberculosis among asylum seekers are notified after entry, this is not surprising but underlines the fact that migrants with complaints or health problems should have rapid access to health care and tuberculosis diagnosis. A recent study by Ricks [14] highlighted the importance of LTBI screening and treatment in order to reduce the burden of TB among foreign born individuals in the US.

The multivariate logistic regression permitted to identify the major factors associated with LTBI. Married individuals from an African or an FSU country that crossed multiple borders to reach Switzerland border and who cough are mostly at risk of being infected. Two minor factors (age and positive history of TB exposure) were also highlighted. Using those six factors we elaborated a predictive model for screening asylum seekers for LTBI resulted in a score with an AUC=81%.

The risk of LTBI increases with age. Indeed the longer a person lives the greater are the risk of being in contact with an individual with active TB. The main feature of using age as LTBI predictor is the presumed time of infection. Due to their young age and to the travel conditions, frequently in very close contact with other persons during prolonged periods, we assume that these individuals have been infected recently.

	screened	not screened	total
FSU	20	33	53
Balkan	62	45	107
Asia	127	50	177
Africa	184	118	

Figure 4 Distribution of the collective by region of origin.

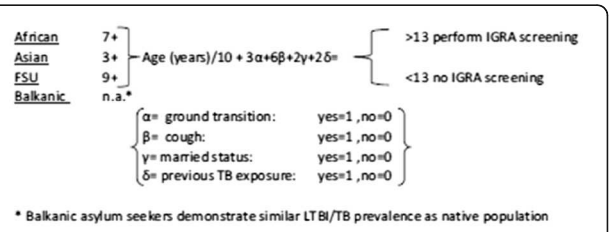

Figure 5 Predictive score calculation. Example: The score for an asylum seeker from former Soviet Union, aged 47 without ground transit, no cough, married with previous exposure to TB is equal to: 7+4.7+2+2=15.7. In such case, screening with IGRA is justified.
* balkanic asylum seekers demostrate similar LTBI/TB prevalence as native population.

In our study married individuals also had a higher risk of being infected with an odd ration of 2.0. This is a quite interesting finding since demographic data on disease shows an opposite relation [15]. Although no solid explanation can be given for this finding our collective showed a clear association with LTBI.

The prevalence of tuberculosis in the home country is correlated with a risk of having LTBI. The NICE guidelines suggest LTBI screening for all asylum seekers migrating from countries with a TB prevalence higher than 50/100.000 [11]. Applying this rule to Switzerland would mean screening the majority of asylum seekers and would imply high costs and logistical problems. Due

Table 1 Univariate analysis

Factors	Positive n(%)	Negative n(%)	Odd ratio	(95% Conf. interval)	p<0.05
Age , mean(sd)	29.09	27.63	1.02	0.99 , 1.04	0.179
Age (by 10 years)	29.09	27.63	1.18	0.93 , 1.49	0.179
Sex					
Male	214	72	1.05	0.62 , 1.76	0.858
Origin					
balkanic origin (ref)	54	8	ref.	ref.	ref.
FSU	12	8	4.5	1.41 , 14.4	0.011
Asia	110	17	1.04	0.42 , 2.57	0.927
Africa	119	65	3.69	1.65 , 8.22	0.001
Ground transit	109	60	2.49	1.54 , 4.02	0.000
Married	124	48	1.34	0.84 , 2.12	0.219
Siblings	243	73	0.53	0.30 , 0.92	0.025
Offspring	111	46	1.45	0.91 , 2.32	0.116
Congregate settings	96	34	1.1	0.68 , 1.78	0.695
Addictions	138	54	1.4	0.88 , 2.21	0.154
Immunosuppresion	19	7	1.3	0.46 , 2.78	0.79
Prev. TB exposure	12	9	2.38	0.97 , 5.84	0.057
Cough	17	12	2.3	1.05 , 5.01	0.036

Table 2 Multivariate logistic regression

Risk factor	Odds ratio	(95% Conf. interval)	p<0.05
Age (by 10 years)	1.37	0.99 , 1.88	0.054
Origin			
balkanic (ref)	ref.	ref.	ref.
FSU	12.54	2.02 , 77.9	0.007
Asia	2.63	0.49 , 14.12	0.26
Africa	26.11	5.04 , 135.43	0.000
Ground transit	2.42	1.34 , 4.37	0.003
Married	2	1.01 , 3.82	0.038
Prev. TB exposition	1.94	0.65 , 5.72	0.233
Cough	8.08	2.63 , 24.87	0.000

to the limited population of this study the independent evaluation of each country of origin was not possible. Therefore we studied those countries mainly represented in the Swiss asylum seeker population. Bias due to the addition of populations like North Africans (low risk) and sub Saharan Africans (high risk) to the statistical analysis could not be avoided. Due to the absence of asylum seeker from Latin American origin in our collective, we could not assess the risk in this population.

The travel conditions to reach Switzerland were clearly related to the risk of LTBI infection. Individuals travelling directly to destination using airplane meet fewer migrants in their journey and therefore have a lower risk of TB infection. A long and hazardous journey through several borders using ground and/or sea transportation increases the risk of TB contacts and infection. Although the socioeconomic status of the asylum seeker might influence the travel pattern it is difficult to argue that ground/sea transit is less expensive than airplane but it is seems clear that access to airplane is limited to persons with higher socio-economic status and access to official (or fake) documents.

A previous exposure to TB is an obvious factor related with LTBI. A personal history of recent exposure to presumed or confirmed active TB person enhances the risk of LTBI and its reactivation potential mostly during the following two years.

That cough was identified as a risk factor for LTBI is surprising since by definition LTBI is an asymptomatic infection. This could be due to the fact that smokers (who are very prevalent in this population group) have a higher risk of LTBI and tuberculosis than non smokers [16]. Other plausible explanation for this finding could be the congregated way of living, especially during winter months in asylum seeker centers with high exposure to passive smoking as well as the lack of stratification during statistical analysis between chronic and acute coughing due to sample limitations. When present, chronic cough was extensively assessed to rule out disease while acute coughing was usually self-limited.

The limitations of our study are the local setting, the inherent characteristics of this mobile population, the cross sectional design and the voluntary pattern of enrolment. This study provided a realistic description of actual collective of asylum seekers arriving in Vaud county. As the asylum seeker population is randomly allocated in the different regions of Switzerland, we assume that this population group was representative of the demographic details of the whole asylum seeker population in Switzerland. Nevertheless in this study

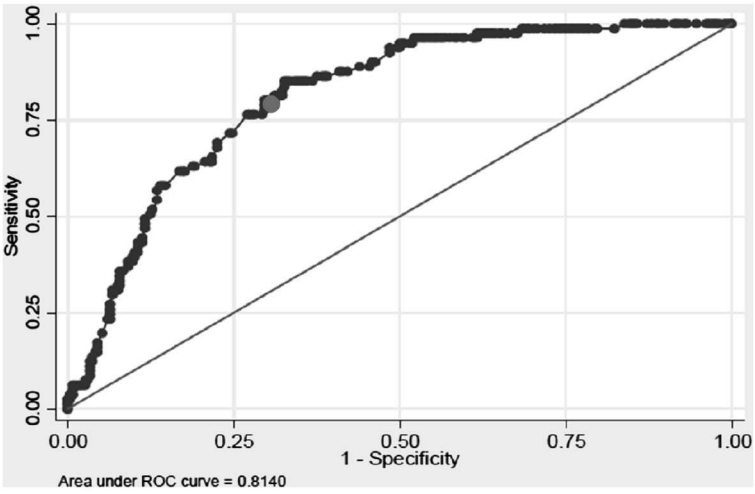

Figure 6 The area under the ROC curve (AUC=81%) gives a measure of the discriminative power of the score between the infected and the control group. The red dot corresponds to the sensitivity/specificity at a cut-off of 13.

61% of the recently arrived asylum seeker population was screened using IGRA qualifying this study as representative of the study population. In addition to this, since no selection was applied to the study population, the travel condition and characteristics of the asylum seeker entering Vaud County match those of asylum seekers entering in other western European countries. Some bias could result from the voluntary pattern of enrollment with an over-representation of sick migrants but this setting was essential for the ethical acceptance of the study protocol. As the proportion of migrants with positive IGRAs was similar as in comparable studies, we assume that this was not a bias. Moreover, among AS who entered in the centre, the actual number of eligible persons was lower since many of them left the territory or were rejected before the enrollment procedure could be started. We have decided to include all the asylum seekers that were present on the asylum seekers registry to the study collective to better describe the reality. Finally since this study is time and country specific the collective characteristics are subject to change over time following the shift in immigration pattern.

Conclusions

This study highlights the factors associated with LTBI among asylum seekers entering Vaud County, Switzerland. The observed prevalence of LTBI (24.9%) matches with the prevalence from the literature. The prevalence of TB previously undetected at the border in asylum seekers with LTBI was also high (5.1%). The factors associated with LTBI identified in this population (age, origin from FSU, Asian and African countries, ground transportation; married status; prior TB exposure and cough) were combined to create a predictive score of LTBI for asylum seekers which could be used at border screening. The application of this score to an asylum seeker population could help discriminating those most at risk for LTBI permitting a limitation of the number of IGRA to be performed in a border screening setting.

Abbreviations

LTBI: Latent tuberculosis infection; AS: Asylum seekers; TB: Tuberculosis; IGRA: Interferon Gamma Release Assay; AUC: Area under the curve; PPV: Positive predictive value; NPV: Negative predictive value; FSU: Former Soviet Union.

Competing interests

No authors declared any competing interest in the performance of this study.

Authors' contributions

AS acquired the study data and helped to the results interpretation, drafted the manuscript and revised it. JPZ conceived and designed the study, helped in the study coordination, interpretation of the results and revised the study manuscript. MF performed the statistical analysis and interpretation. OD participated in the study coordination. CD carried out the initial assessment and blood sampling; PB helped in the study coordination, contributed to the interpretation of results and revised the manuscript. All authors read and approved the final manuscript.

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High rate of completion of preventive therapy for latent tuberculosis infection among asylum seekers in a Swiss Canton

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Summary

BACKGROUND: Preventive treatment may avoid future cases of tuberculosis among asylum seekers. The effectiveness of preventive treatment depends in large part on treatment completion.

METHODS: In a prospective cohort study, asylum seekers of two of the Swiss Canton Vaud migration centres were screened with the Interferon Gamma Release Assay (IGRA). Those with a positive IGRA were referred for medical examination. Individuals with active or past tuberculosis were excluded. Preventive treatment was offered to all participants with positive IGRA but without active tuberculosis. The adherence was assessed during monthly follow-up.

RESULTS: From a population of 393 adult migrants, 98 (24.9%) had a positive IGRA. Eleven did not attend the initial medical assessment. Of the 87 examined, eight presented with pulmonary disease (five of them received a full course of antituberculous therapy), two had a history of prior tuberculosis treatment and two had contraindications to treatment. Preventive treatment was offered to 75 individuals (4 months rifampicin in 74 and 9 months isoniazid in one), of whom 60 (80%) completed the treatment.

CONCLUSIONS: The vulnerability and the volatility of this population make screening and observance of treatment difficult. It seems possible to obtain a high rate of completion using a short course of treatment in a closely monitored population living in stable housing conditions.

Key words: *rifampicin; tuberculosis; asylum seekers; LTBI; preventive treatment*

Introduction

Latent tuberculosis infection (LTBI) is a widespread condition among asylum seekers born in or who have lived in countries with a high prevalence of tuberculosis [1]. Persons with LTBI have a known risk of developing active tuberculosis at a later stage [2] and can be screened by tuberculin skin testing or by one of the new Interferon Gamma Release Assays (IGRA), which offer a greater specificity [3]. Among the persons with positive IGRA, those most at risk of developing an active infection are children, immunosuppressed persons and those with recently acquired infection. The highest risk for the development of tuberculosis among infected persons is during the first few years following infection. The risk of reactivation, defined as the progression from latent infection to active disease can be decreased by preventive treatment [4].

Asylum seekers (AS) from high incidence countries entering in low incidence countries have a higher rate of LTBI than the local population, therefore some of them may develop TB after entering the country, by reactivation from remote infection. In some low incidence countries AS or migrants are screened for active TB and LTBI upon entry. In Switzerland AS are screened at the border for active TB only. Cases with LTBI are not detected and not offered a preventive treatment so that the possible progression from infection to disease after entry is not prevented. The treatment of latent tuberculosis infection (LTBI) is generally considered costeffective and a component of the strategy towards elimination of tuberculosis in low-incidence countries [5–7]. The key features of a cost effective LTBI screening strategy are proper screening, selection of persons at highest risk of progression and the completion of preventive treatment by eligible persons with LTBI who are expected to follow a long treatment in spite of being asymptomatic [8].

The low adherence to LTBI treatment is the main challenge in the preventive strategy. According to various studies the completion rate of preventive treatment varies from 10% to 86% [9, 10]. The duration and side effects of preventive treatment along with the lack of awareness on active tuberculosis disease by people with LTBI, and the high social and economical vulnerability of some population groups like asylum seekers render adherence to treatment a highly challenging issue for both the physician and the patient. No factor seems to reliably predict the adherence to pre-

ventive treatment [11]. Our study aims to assess the rate and conditions of adherence to preventive treatment in a population of asylum seekers with latent tuberculosis infection recently arrived in Canton Vaud. All aspects regarding screening results, demography and treatment decision were described in a separate paper [12].

Methods

We conducted a prospective cohort study to assess the feasibility and adherence of preventive treatment in a population of asylum seekers (AS) with LTBI newly arrived in the Swiss Canton Vaud, who had recently passed a border screening for the detection of active TB. The AS resided in two migrant centres at Sainte – Croix and Crissier. AS aged over 16 years were offered a free IGRA screening for LTBI by T-SPOT.TB (Oxford Immunotec, Abingdon, UK). All asylum seekers received written information about tuberculosis and the aims of the study were translated into five major languages (English, French, German, Russian and Arabic). All participants signed a consent form. A translator was used if needed. The study was approved by the ethics commission of the University of Lausanne.

The results of IGRAs were categorised as positive, indeterminate or negative. An additional SPOT.TB was offered to AS with an indeterminate result.

AS with a positive test result were referred for further examination to a physician for the exclusion of active TB and a decision on preventive treatment. The physician obtained a detailed history of TB exposure or treatment, and performed a clinical examination. A chest X-ray was taken and human immunodeficiency virus (HIV) screening was offered to the IGRA positive participants. AS with suspect clinical manifestations or abnormal radiological findings had further investigations including sputum examination. AS with documented or possible active tuberculosis were treated according to the current Swiss guidelines [13].

AS with LTBI without evidence of active disease were offered a preventive treatment according to the current Swiss recommendation with four months of rifampicin (first choice) or nine months of isoniazid. The rifampicin scheme was preferred over the isoniazid because of its simplicity of prescription (no need for vitamin substitution, short treatment time) and follow up (better tolerance, no need for routine liver function test assessment, visible urine colouration) advantages that could enhance compliance with treatment [6]. We did not use incentives. Adherence to treatment was evaluated during the monthly visit to the physician where clinical examination, side effects and symptom assessment was performed. If normal, the preventive treatment prescription was renewed. In cases of abnormality, blood tests were requested. The treatment was self-administered but the nurse in charge of the centre met regularly (if possible daily) with the treated AS and reinforced the treatment instructions. If the physician was not assured of the adherence to the treatment directly observed treatment (DOT) for a month was prescribed.

The adherence to treatment was considered as satisfactory if the AS were compliant with all scheduled visits and asked for a repeat prescription. No tablet count was performed. Individuals who did not attend two of the scheduled appointments were considered as non-adherent. The treatment was suspended in individuals with poor or problematic adherence.

Results

The screening assay with T-SPOT.TB among 393 adult AS living in two asylum seeker centres in Canton Vaud revealed positive IGRA results in 98 (24.9%), who were referred for further medical examination. The mean age of the AS with LTBI was 27.63 years. 74% were men, 66% were Africans, and 17% were Asians. Balkanic and former Soviet Union nationals were both 8% and 8% of the collective. No AS with LTBI had a known immunosuppressive treatment or condition, notably HIV infection.

Of them, 11 did not attend the first scheduled medical evaluation. After examination, documented or possible tuberculosis or another pulmonary disease was discovered in 8/87 AS (of whom 5 were prescribed an antituberculosis treatment). Two other patients had a history of prior treatment for active tuberculosis. Of the 77 IGRA positive asymptomatic individuals with normal chest X-ray, 2 had counter indications (severe liver disorder and pregnancy) for preventive treatment (fig. 1).

An LTBI treatment with daily rifampicin for four months was offered to 74 AS, one received isoniazid for 9 months due to counter indication to rifampicin. During the follow up three participants defaulted on the first follow-up visit, three on the second and seven on the third (total 13 cases). In two individuals preventive treatment was suspended because of poor compliance and substance abuse. During the follow-up, no serious adverse event was observed and no treatment was interrupted for medical reasons. The final rate of completion of preventive treatment in our cohort was 80% (60/75) (fig. 2).

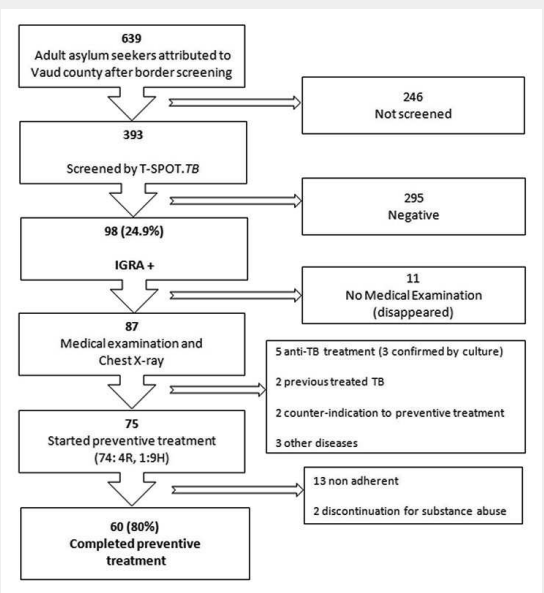

Figure 1

Preventive treatment completion flowchart.
* IGRA = Interferon Gamma Release Assay

Discussion

In this prospective study, the rate of adherence to LTBI preventive treatment in AS was high with 80%.

One particular feature of the migrant population is the young mean age, allowing the assumption that many persons with LTBI must have been infected recently and are therefore still in a period with a high risk of reactivation. One argument for this is the fact that migrants arriving in Switzerland by land or sea/ land travel had a higher rate of LTBI than migrants travelling by air, indicating that travel conditions were a risk factor for TB exposure and recent infection (data in a separate publication) [12]. An indication for this is the fact that about 75% of all TB observed in AS in Switzerland occurs more than three months after the border screening, probably by progression from a recent infection in young adults.

Variable rates of completion are reported with partially contradictory conclusions regarding the risk factors for non-adherence. A recent study by Horsburgh et al. reported that 93.7% of contacts of patients with contagious TB accept the treatment, whereas only 48.3% of health-care workers with LTBI detected by routine screening accept it [9]. A study conducted in Arkansas, US, among patients treated with isoniazid for LTBI found no correlation between adherence and age, diagnosis, mode of administration and duration of treatment, but demonstrated that education at the first visit could improve the adherence rate for further treatment [11]. An analysis conducted by Hirsch-Moverman et al. in the US and Canada reported rates of completion from 35% to 64% among contacts with TB, 32% to 61% in prisoners and jail inmates, 22% to 90% among foreign-born persons, with better rates among recent migrants [10]. Reduction of treatment duration from six or nine months isoniazid to four months rifampicin was followed by an increase in the completion rate up to 91%. Another study by the same group reported a progressive increase of the completion rate from 37% in 1996–1999 to 56.1% in 2002–2005 with tighter follow-up of patients [14]. Trajman et al. confirmed that the overall completion rate was satisfactory (73%) but that the reduction of the treatment duration to four months improved the rate of completion [15]. Similar conclusions were made in a Swiss study comparing the tolerance and rate of completion in contacts with LTBI treated with isoniazid for six months or rifampicin for four months, where the rate of treatment interruption because of liver toxicity decreased from 6.1% to 2% and the rate of treatment completion increased from 74% to 83% [16].

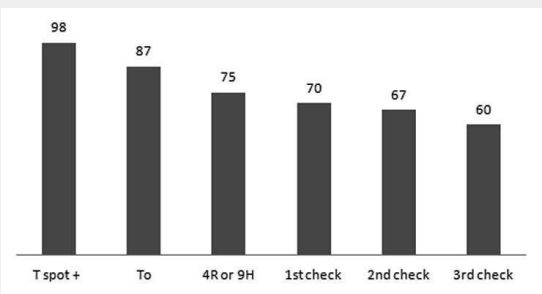

Figure 2

Monthly assessment and drop outs.
T spot+: Positive T-SPOT.TB, To: initial examination of the participants, 4R or 9H: Preventive treatment start either four months of rifampicin or nine months of isoniazid.

On the contrary, a prospective study conducted in Boston in 2006 reported a rate of completion of 28.6% (or 33.3% in recent contacts) [17]. In one study in South Africa, only 20% of children less than five years exposed to parents with TB completed the preventive treatment [18].

In Switzerland, the results varied. In a study of asylum seekers screened at the border with tuberculin skin test, where the subjects with a positive test result were supposed to have a medical examination and a prescription of preventive treatment, a large proportion were not prescribed a treatment or did not complete it [19]. Other reports were more favourable. A study conducted at the TB Dispensary in Lausanne reported a global completion rate of 76% among persons with a positive tuberculin skin test prescribed a preventive treatment with isoniazid for six months (70% among foreign-born persons, 93% among foreign workers and 90% in the local population) [20].

Several studies have reported a higher adherence and a lower rate of adverse events in subjects with LTBI who were prescribed a short treatment (four months of rifampicin) than among those who had to take a long treatment (six to nine months of isoniazid) [21, 22]. A report from the Centre Antituberculeux in Geneva reported an acceptance rate of 83% and a completion rate of 67% among the patients (mostly contacts of TB cases) who started the treatment with four months of rifampicin [23]. In underserved population groups, the results are less favourable. In a study of undocumented migrants in Lausanne, 10/22 persons with a positive IGRA test accepted the preventive treatment but only 5 completed it [24].

Not prescribing the preventive treatment in infected persons with a high risk of progression to active tuberculosis can be considered as a missed opportunity of reducing the pool of future cases of disease and the transmission of mycobacteria to contacts [25]. In a recent survey in the Netherlands, the risk of progression to TB among migrants with a positive IGRA was between 386 and 590/100,000, depending on the incidence rate in the country of origin [26].

Our study has some limitations. The screening and acceptance of preventive treatment for LTBI was voluntary. 39% of the AS were not screened and some of them may have been infected and at risk for progression to active tuberculosis disease [26]. Considering the fact that the screening was offered to all participants but that this population was extremely mobile, some staying for only few days in the centre, we consider that this pilot study was representative of the target population. Furthermore, AS were clearly informed that acceptance or refusal of the proposed screening and preventive treatment would have no impact on the final decision regarding granting refugee status or not. Also, although the efficacy of rifampicin is less extensively documented than isoniazid, because of the enhanced adherence to this preventive treatment scheme this option is a recommended alternative to the classical isoniazid scheme [16, 27].

Future uncertainties, difficulties of integration and in communication associated with a divergent representation of health and disease compared with locals are some of the problems AS need to overcome. The reasons for the high

rate of completion of LTBI treatment in this population of migrants in spite of social, economical and legal problems are probably related to the selection of a well-tolerated short treatment schedule (four instead of six or nine months), a stable environment (accommodation in a shelter with dedicated social workers and nurses caring for inmates), regular assessment of the drug intake by the nurses, close coordination with the medical staff of the referral hospitals and repeated information about the importance of treatment). This study demonstrates that a policy of screening for LTBI and preventive treatment can be implemented in a migrant population with a high rate of adherence if all obstacles are carefully considered in advance.

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Author's contribution: AS performed medical assessment, preventive therapy prescription and treatment follow-up, acquired the study data and helped to the results interpretation, drafted the manuscript and revised it. PB helped in the study coordination; contributed to the interpretation of results and revised the manuscript. EL and CL-F performed medical assessment, preventive therapy prescription and treatment follow-up of the study subjects. OD participated in the study coordination. JPZ conceived and designed the study, helped in the study coordination, interpretation of the results and revised the study manuscript. All authors read and approved the final manuscript.

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Figures (large format)

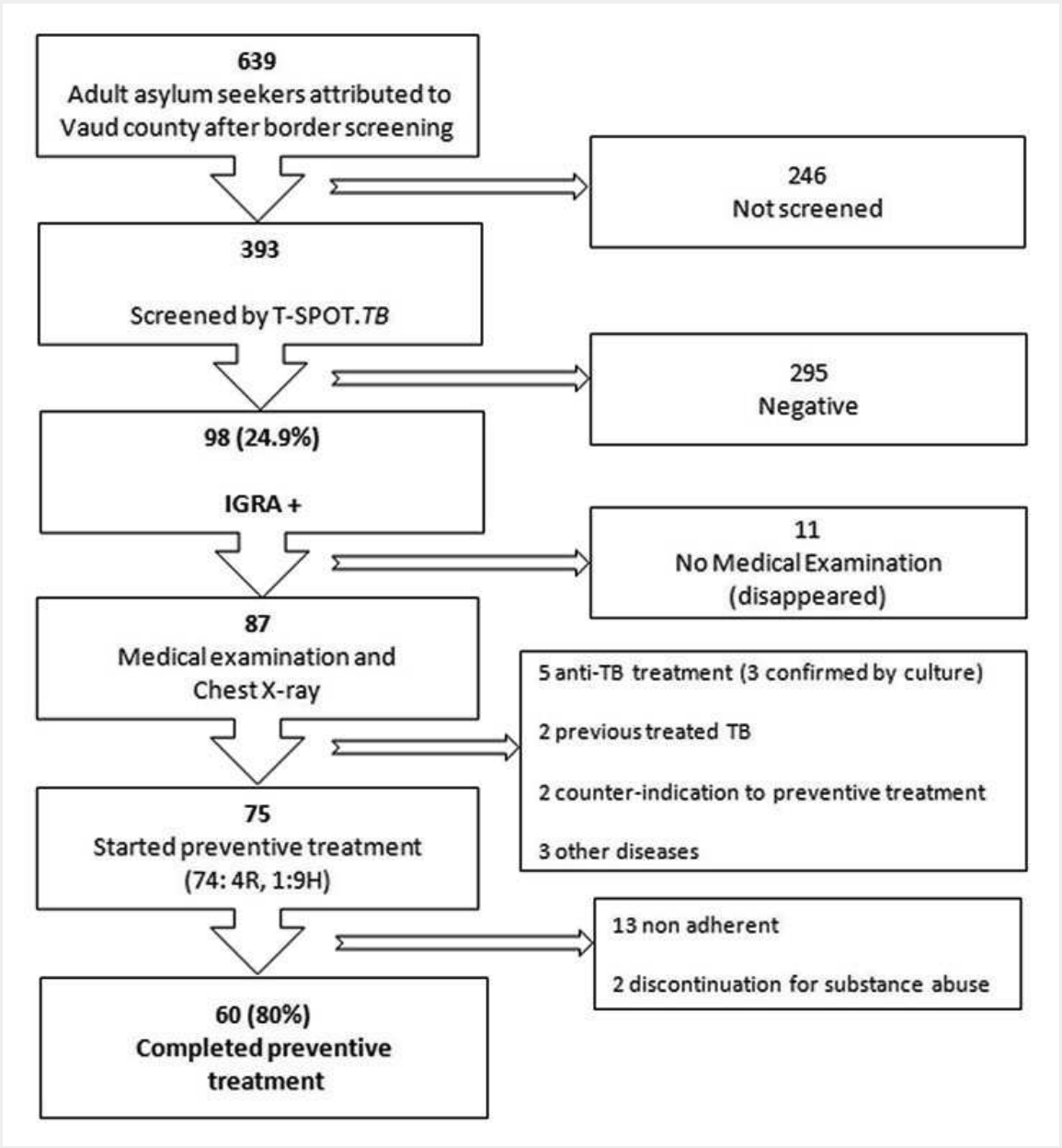

Figure 1

Preventive treatment completion flowchart.
* IGRA = Interferon Gamma Release Assay

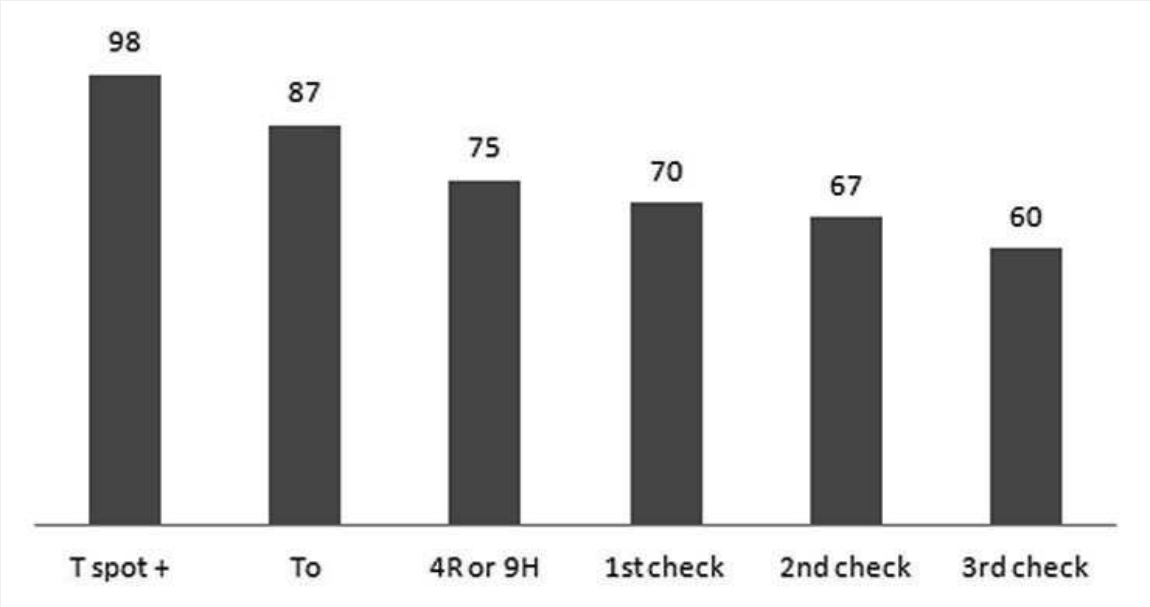

Figure 2

Monthly assessment and drop outs.
T spot+: Positive T-SPOT.TB, To: initial examination of the participants, 4R or 9H: Preventive treatment start either four months of rifampicin or nine months of isoniazid.