Screening and treatment of tuberculosis among pregnant women in Stockholm, Sweden, 2016–2017

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Systematic TB screening of pregnant women in Stockholm was feasible with high yield of unknown latent TB and mostly asymptomatic active TB. Optimised routines improved referrals to specialist care. Adherence to treatment of latent TB was very high. http://bit.ly/2NrhEwk

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ABSTRACT Swedish National tuberculosis (TB) guidelines recommend screening of active and latent TB (LTBI) among pregnant women (PW) from high-endemic countries or with previous exposure to possibly improve early detection and treatment.

We evaluated cascade of care of a newly introduced TB screening programme of pregnant women in Stockholm county in 2016–2017. The algorithm included clinical data and Quantiferon (QFT) at the Maternal Health Care clinics and referral for specialist care upon positive test or TB symptoms.

About 29 000 HIV-negative pregnant women were registered yearly, of whom 11% originated from high-endemic countries. In 2016, 72% of these were screened with QFT, of which 22% were QFT positive and 85% were referred for specialist care. In 2017, corresponding figures were 64%, 19% and 96%, respectively. The LTBI treatment rate among all QFT-positive pregnant women increased from 24% to 37% over time. Treatment completion with mainly rifampicin post-partum was 94%. Of the 69 registered HIV-positive pregnant women, 78% originated from high-endemic countries. Of these, 72% where screened with QFT and 15% were positive, but none was treated for LTBI. 9 HIV-negative active pulmonary TB cases were detected (incidence: 215/100 000). None had been screened for TB prior to pregnancy and only one had sought care due to symptoms.

Systematic TB screening of pregnant women in Stockholm was feasible with a high yield of unknown LTBI and mostly asymptomatic active TB. Optimised routines improved referrals to specialist care. Treatment completion of LTBI was very high. Our findings justify TB screening of this risk group for early detection and treatment.

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Introduction

Pregnancy is a state of relative immunosuppression characterised by anti-inflammatory cellular responses that promote tolerance to fetal antigens. Pregnancy induces a down regulation of the T-helper type 1 (Th1) immunity leading to impaired cell-mediated immunity with decreased levels of interferon (IFN)-γ and tumour necrosis factor (TNF)-α and therefore a theoretically increased susceptibility to activation and/or *de novo* infections of certain intracellular microbes such as *Mycobacterium tuberculosis* [1, 2]. Quiescent or subclinical tuberculosis (TB) with few and non-specific symptoms is more common during pregnancy with an abrupt onset of a pro-inflammatory response after delivery which may lead to overt clinical manifestations, *i.e.* immune reconstitution syndrome (IRS) [3, 4]. Pregnancy and, in particular, the post-partum period have been debated as linked to a higher risk of active TB and contributors to both maternal, fetal and newborn morbidity and mortality, especially among HIV-positive women [5–11].

As part of the global End TB strategy [12], screening and treatment of latent TB infection (LTBI) is now recommended in low-endemic middle- and high-income countries for certain risk groups, such as immunosuppressed individuals from high-endemic countries [13, 14]. In line with this strategy, the Public Health Agency of Sweden recommends screening for LTBI among pregnant women from high-TB endemic countries (incidence ⩾100/100 000) or exposed to known/suspected contagious TB [15]. In Sweden, asylum seekers are offered a health examination upon arrival, including TB screening for high-risk groups. However, coverage is only about 50% [16] and other migrants, such as reunification family members, are only entitled to a health examination upon their own request, while other immigrants, *e.g.* labour immigrants and European Union (EU) migrants are not entitled to examination. Therefore, many pregnant women from high-endemic countries have not been screened for TB after arrival in Sweden and routine check-ups at the Maternal Health Care (MHC) clinics therefore offer a good opportunity to screen for unknown TB in this group.

In January 2016, Stockholm county introduced systematic screening of both active TB and LTBI among all pregnant women from high-endemic countries (figure 1) in collaboration between MHCs, the Department of Communicable Diseases Control and Prevention at Stockholm County Council and the TB centre and HIV centre at Department of Infectious Diseases, Karolinska University Hospital (Karolinska, Sweden). QFT was preferred before the standard tuberculin test (TST) because of the advantage of only one visit needed for testing, as well as better performance to detect assumed LTBI during pregnancy [17–21]. Treatment of LTBI was initiated after delivery (if not recently exposed to contagious TB) [15] to minimise the risk of adverse events during pregnancy. Shorter LTBI treatments such as rifampicin (RIF) once daily (OD) for 4 months (4R), isoniazide (INH) plus RIF OD for 3 months (3HR) and high-dose INH and rifapentine (RPT) once weekly for 12 weeks (3HP) have been shown to be as efficacious and safe as INH with pyridoxine substitution OD for 9 months (9H) and significantly associated with increased completion rates [22, 23]. 3HP is at present not a validated option in pregnancy or breast feeding; however, trials are on-going (www.clingovtrials.com). TB care and treatment is free of charge according to the Swedish Communicable Disease Act.

Our objective was to evaluate cascade of care of the newly introduced TB screening programme among pregnant women in Stockholm in 2016–2017.

Material and methods

This was a retrospective, observational study of pregnant women screened for active TB and LTBI in Stockholm during 2016 and 2017. HIV-negative pregnant women were screened at the regular MHC clinics in Stockholm and referred to the centralised TB centre at Karolinska upon a positive screening result (figure 1). HIV-positive pregnant women were screened and followed up at the specialist MHC clinic and the HIV centre at Karolinska.

At MHC, mainly during the first trimester, information was registered on country of birth, year of arrival to Sweden, previous history and/or contact with active TB, previous testing and/or treatment for LTBI and symptoms of active TB, *i.e.* fever, night sweats, weight loss and/or cough. If symptoms of active TB were detected, the subject was immediately referred to the TB centre at Karolinska for diagnostic procedures according to routine clinical practice. Asymptomatic pregnant women from high-endemic countries or with known TB exposure were tested with QFT and analysis was performed according to the manufacturer's instructions at the Karolinska TB laboratory. If QFT was negative (<0.35 $IU \cdot mL^{-1}$), information was given to the subject by the midwife. If the QFT was positive (⩾0.35 $IU \cdot mL^{-1}$), information was given to the subject at an appointment with an MHC physician and thereafter referred for chest radiograph (CXR) and then specialist care.

In June 2016, some adjustments were introduced to the screening criteria as a consequence of QFT-positive pregnant women referred for specialist care, but who, after assessment, were not recommended treatment. Adjustments were made regarding QFT which was not recommended if the subject: a) had been previously

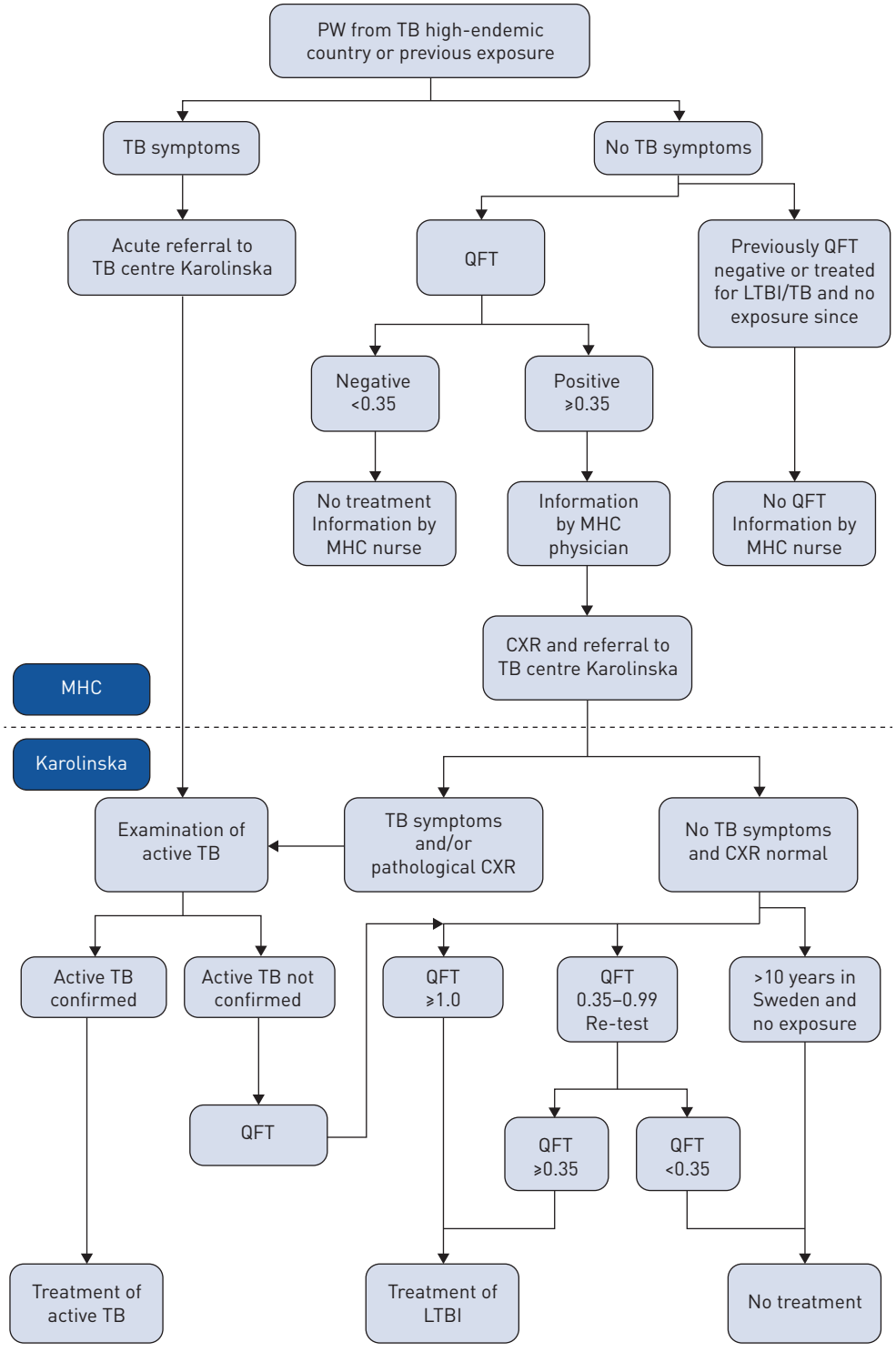

FIGURE 1 Flow chart of tuberculosis (TB) screening algorithm for pregnant women (PW) from high-endemic countries or previous exposure. QFT: Quantiferon test; MHC: Maternal Health Care.

tested TST-/QFT-negative and not been exposed to TB thereafter; or b) had been previously treated for LTBI or active TB (but still referred if exposed to contagious TB thereafter) [24]. Further, referrals to CXR and specialist care were recommended in parallel, as some pregnant women had been unwilling to perform CXR with delayed/absent referral to specialist care as a consequence.

Referred pregnant women with symptoms and/or abnormal CXR were seen by a specialist/resident physician in infectious diseases within 1 week for further diagnostic work-up. Asymptomatic pregnant

women with normal CXR were seen within 4 weeks, mainly during the second trimester. Pregnant women with a QFT borderline-positive result (0.35–0.99 IU·mL^{-1}) or indeterminate result were re-tested [25]. Pregnant women with no CXR performed were thoroughly informed by the physician about the harmlessness and importance of the examination.

Treatment of LTBI was initially recommended if the subject was <30 years old and had migrated to Sweden within 2 years; or visited her home country or another high-endemic country for >3 months in the previous 2 years; or was previously exposed to contagious TB within 2 years; or had co-morbidity with a higher risk of TB activation, such as severe diabetes mellitus, kidney failure, underweight or immunosuppressive treatment; or pathological CXR indicating previous TB (and where active TB was excluded). In June 2016, the age-limit was removed as criteria and the limit of >2 years in Sweden or since exposure was adjusted to >10 years, due to several cases of active TB among pregnant and post-partum women aged >30 years with arrival to Sweden >2 years ago.

All pregnant women were planned to initiate LTBI treatment within 1 month after delivery. To minimise loss to follow-up, pregnant women recommended for treatment were scheduled for an appointment with a physician 1–2 weeks after the estimated time of delivery and a letter to the midwife with LTBI information and instructions to contact the TB centre after delivery. Pregnant women exposed to contagious TB recently (<2 years) started LTBI treatment already during pregnancy. During treatment, the pregnant women had check-up appointments with a TB nurse at 2 weeks after initiation and then usually every month. Adherence was assumed if self-reported and if the woman complied with the monitoring including blood tests for liver enzymes. Severe adverse events or other concerns were reported to the physician for assessment. First-line treatment of LTBI for pregnant and post-partum women during the study period was 4R with 3HP as an alternative for post-partum women who did not breast feed. Pregnant women with CXR infiltrates without activity were recommended 9H.

The study included only ordinary management procedures covered by the regular patient insurance. All compiled data were anonymised to obtain minimal integrity intrusion for the patient. MHC data was collected and compiled by the Department of Communicable Diseases Control and Prevention, Stockholm County Council, and then stored together with data from the specialised care in a safe database at Karolinska for centralised analyses (table 1). Ethical permission was granted from Stockholm Regional Ethics committee (Dnr 2018/555-31) who waivered the necessity of informed consent.

Results

Screening and treatment of LTBI among HIV-negative pregnant women

In 2016, a total of 29 459 pregnant women were registered in Stockholm (table 1); 3054 (10%) originated from high-TB endemic countries and, of these, 2184 (72%) were screened with QFT at the regular MHC clinics. Of the screened pregnant women, 479 (22%) were QFT positive, which is in line with estimated LTBI prevalence in high-endemic countries [14]. Of these, 407 (85%) were referred to the TB centre at Karolinska.

In 2017, the corresponding figures were 28 805 pregnant women, 3140 (11%) originated from high-endemic countries, 1994 (64%) were screened with QFT, 383 (19%) were QFT positive and 367 (96%) were referred.

TABLE 1 Yield of screening and treatment of latent tuberculosis (LTBI) among HIV-negative and HIV-positive pregnant women in Stockholm, 2016–2017

	2016	2017	HIV 2016–2017
Pregnant women total[#]	29 459	28 805	69
High endemic origin[#]	3054 (10)	3140 (11)	54 (78)
Screened with QFT[¶]	2184 (72)	1994 (64)	39 (72)
QFT positive[¶]	479 (22)	383 (19)	6 (15)
Referred[+]	407 (85)	367 (96)	na
Initiated LTBI treatment[+]	113 (28); (24% of QFT-positive)	142 (39); (37% of QFT-positive)	0
Completed LTBI treatment[+]	106 (94); (22% of QFT-positive)	128 (90); (33% of QFT-positive)	na

Data are presented as n or n (%), unless otherwise stated. QFT: Quantiferon test; na: not applicable. Data collected by [#]Department of Growth and Regional Planning Stockholm County Council, [¶]Karolinska University Laboratory and [+]TB centre, Department of Infectious Diseases, Karolinska University Hospital.

Referred pregnant women who initiated treatment increased from 113 (28%) out of 407 in 2016 to 142 (39%) out of 367 in 2017 (table 1). Upon the physicians' decision, 109 (21%) of all women were not recommended treatment due to previous treatment of TB/LTBI, 93 (18%) due to migration to Sweden >10 years ago, 45 (9%) due to negative QFT result upon retesting and 29 (6%) due to other causes, *e.g.* miscarriage/abortion, frequent travels to high-risk countries, MDR exposure or elevated liver enzymes. In addition, in June 2016, the inclusion criteria for treatment was adjusted as described previously and, therefore, 83 (16%) women were not recommended treatment due to age >30 years and/or arrival to Sweden >2 years ago. Furthermore, 22 (4%) women emigrated/moved, 38 (7%) were unwilling to undergo treatment and/or were lost to follow-up. In total, the proportion of all QFT-positive pregnant women that initiated LTBI treatment increased from 113 (24%) out of 479 in 2016 to 142 (37%) out of 383 in 2017. In total, six pregnant women started treatment during pregnancy, while the remaining started after delivery.

A total of 255 women initiated LTBI treatment in 2016–2017 (table 2). Five women still on treatment (3 RIF and 2 INH) were excluded from further analyses. The mean (range) age was 30.1 (20–41) years and time in Sweden was 4.9 (0–31) years. In summary, 156 (62%) pregnant women originated from Africa, 86 (34%) from Asia, seven (3%) from Europe and <1% from America. The majority, 224 (90%), was treated with 4R and remaining with 9H, 3HR or 3HP.

A total of 234 (94%) women completed treatment, while remaining discontinued due to adverse events (6 out of 16), re-location (3 out of 16) or loss to follow-up (7 out of 16).

Cascade of care for all HIV-negative pregnant women intended for screening is presented in figure 2.

Screening and treatment of LTBI among HIV-positive pregnant women

A total of 69 HIV-positive pregnant women were registered in Stockholm in 2016–2017 (table 1), 54 (78%) originated from TB high-endemic countries, of those 59 (72%) were screened with QFT and of these six (15%) were QFT positive, but with no clinical or radiological signs of TB. None was treated for LTBI. One subject started treatment for suspected lymph node TB but was instead diagnosed with lymphoma, two had elevated liver enzymes due to chronic hepatitis, one had a legal abortion and two did not start due to prolonged travels abroad.

Detection and treatment of active TB

A total of nine microbiologically confirmed active pulmonary TB cases were detected during pregnancy or post-partum (table 3). All were HIV negative. The mean (range) age was 29.2 (23–33) years. Five had their first child. Seven originated from high-endemic countries and time in Sweden was 4.2 (1–12) years. None had been screened for TB after arrival to Sweden. Five had previously been exposed to TB and two had been treated for active TB previously, but one of them had discontinued treatment after 4 months.

Six of the active TB cases were referred to Karolinska from MHC *via* the screening programme and were diagnosed in the second trimester. Of the remaining three cases, one case had not been included in the MHC screening due to uncertain migration status and was detected post-partum in asylum screening. One case had been abroad during pregnancy and was detected post-partum when seeking primary health care

TABLE 2 Outcome of treatment of latent tuberculosis infection (LTBI) among HIV-negative women in 2016 and 2017

LTBI treatment	2016	2017	Total
Completed	106 (94)	128 (93)	234 (94)
RIF	86 (95)	124 (93)	210 (94)
INH	7 (78)	3 (100)	10 (83)
INH+RIF	12 (100)	1 (100)	13 (100)
INH+RPT	1 (100)	0	1 (100)
Discontinued	7 (6)	9 (7)	16 (6)
RIF	5 (5)	9 (7)	14 (6)
INH	2 (22)	0 (0)	2 (17)
INH+RIF	0	0	0
INH+RPT	0	0	0
Total	113	137	250

Data are presented as n (%) or n. Proportion (%) that completed or discontinued of all treated as well as for each respective drug. RIF: rifampicin; INH: isoniazid; RPT: rifapentine.

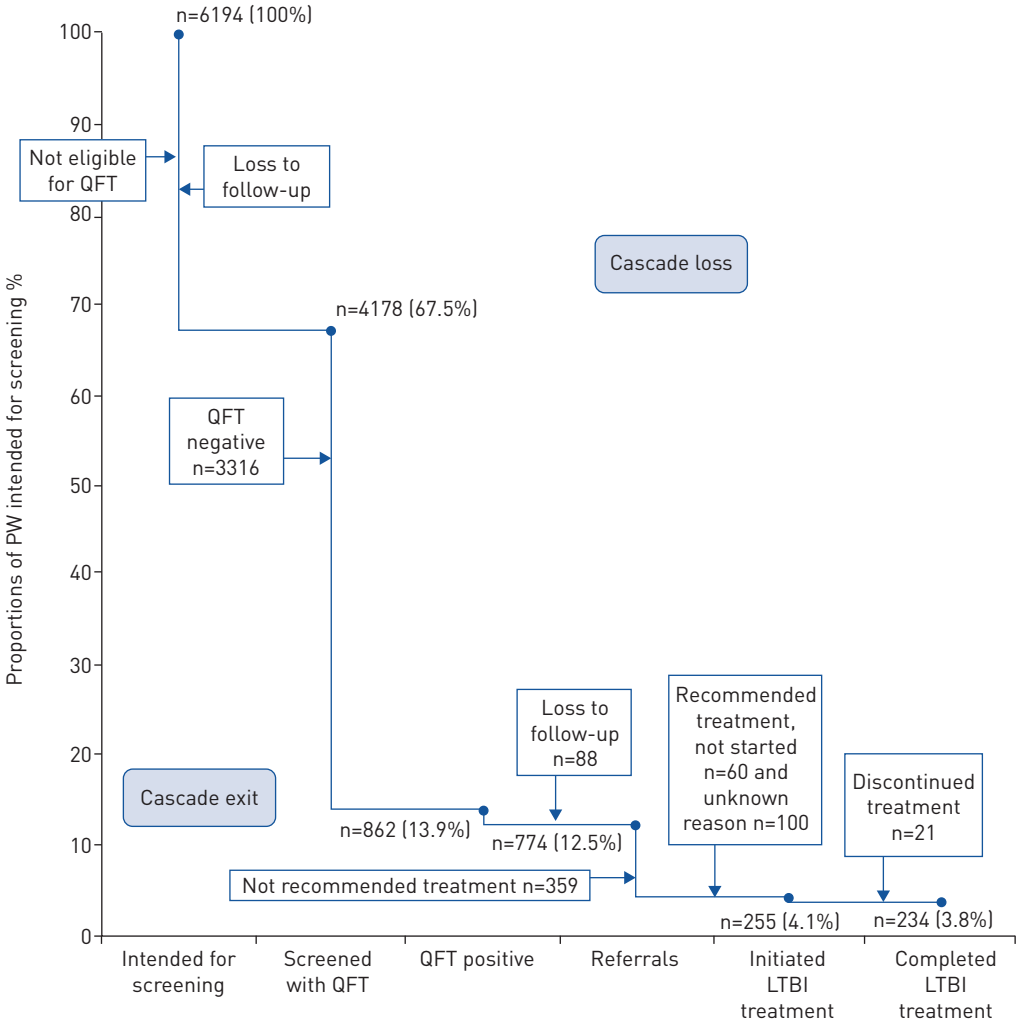

FIGURE 2 Proportions (%) of all HIV-negative pregnant women (PW) from high-endemic countries (intended for screening) through the cascade of care in Stockholm county, 2016–2017.

TABLE 3 Details of active tuberculosis (TB) cases detected during pregnancy or post-partum in Stockholm 2016–2017

Age years	Parity n	Origin/TB incidence	Years in Sweden	Previous TB expo/tx	Symptoms	QFT IU·mL^{-1}	CXR	Sputum (SM/PCR/culture)	GL/BAL	Diagnosis
29	2	Africa/high	2	–/–	No	3.48	PE	–/–/+		PTB (S)
33	1	Asia/high	6	+/–	No	2.13	Normal	–/–/+		PTB (PZA-R)
23	1	Europe/middle	1	+/–	No	0.56/2.69	PE+AI	–/–/–	+/+	PTB (S)
33	3	Africa/very high	3	+/–	No	5.53	AI	–/–/+	+/	PTB (S)
29	1	Africa/high	1	–/–	Slight cough	3.50	Normal	–/–/+		PTB (S)
27	1	Asia/high	1	–/+	No	9.83	PE+AI	–/+/+	+/	PTB (RIF-R)
33	3	Europe/low	7	–/–	Cough, weight loss	na	AI+cavity	+/+/+		PTB (S)
33	3	Asia/high	5	+/–	No	2.04	AI	–/–/+	+/	PTB (MDR)
23	1	Asia/high	12	+/+	Slight cough	2.90	AI	–/+/+	–/	PTB+LNTB (S)

Expo: exposure; tx: treatment; QFT: Quantiferon test; CXR: chest radiograph; SM: smear microscopy; GL: gastric lavage; BAL: broncho-alveolar lavage; PE: pleural effusion; AI: apical infiltrate; PTB: pulmonary TB; LNTB: lymph node TB; S: sensitive TB; PZA-R: Pyrazinamide resistant TB; RIF-R: Rifampicin resistant TB; MDR: multi-drug resistant TB; na: not applicable. TB incidence: high >100/100 000, middle 25–100/100 000, low <25/100 000; Generally, standard treatment was given for 6 months or prolonged to 9–12 months for mono-resistant cases. The MDR-TB case has been on adjusted regiments due to different adverse events.

for prolonged cough and weight loss. One case was detected in contact tracing at Karolinska and at the same time diagnosed as pregnant in the first trimester.

Only one of the pregnant women with active disease had experienced symptoms associated with TB and two reported slight cough when questioned for symptoms, while the remaining women were asymptomatic. Eight were tested with QFT and all were positive (range 2.13–9.83 IU·mL^{-1}). Seven had pathological CXRs with infiltrates and/or pleural effusions. The symptomatic case had cavitary upper lobe infiltration and was smear microscopy positive in sputum, while the remaining were smear microscopy negative. Three were PCR positive and all were *M. tuberculosis* culture verified in sputum and/or gastric/bronchoalveolar lavage.

Six patients had drug-sensitive TB. Two patients had mono-resistant TB *i.e.* RIF and Pyrazinamide (PZA), respectively. One patient had multi-drug resistant (MDR) TB.

Discussion

We evaluated cascade of care of the recently introduced TB screening programme among pregnant women in Stockholm in 2016 and 2017 (figure 2). The choice of TB screening among pregnant women originating from countries with an incidence of >100/100 000 is in line with recent reviews by Pareek *et al.* [26] and Greenaway *et al.* [27] in which screening of LTBI in migrants 16–35 years old and originating from countries with a TB incidence of >150/100 000 was the most cost-effective strategy to prevent one active TB case.

In June 2016, several adjustments in the recommendations for screening, referral and LTBI treatment were introduced as described previously. This adjustment resulted in fewer pregnant women eligible for QFT and thus probably a "false" higher drop-off in the cascade of care from "intended for screening" to "QFT screened". However, we do not have information on these figures but according to the MHC nurses, unwillingness by pregnant women to undergo QFT and/or loss to follow-up was uncommon. Furthermore, parallel referrals to CXR and to specialist care markedly decreased drop-off from "QFT positives" to "referred". The wider recommendations for screening as well as the more narrow inclusion criteria for LTBI treatment before June 2016 resulted in many pregnant women not recommended for treatment upon specialist decision and a rather large drop-off from "referrals" to "initiated treatment".

However, these drop-offs were smaller than in a recent meta-analysis by Alsdurf *et al.* [28], in which the proportion of eligible individuals that completed the different steps in the cascade of care was highly heterogeneous between identified risk groups. For migrants, only 43% completed testing and 14% of eligible individuals completed treatment. Corresponding figures among HIV-negative pregnant women in our study were 68% and 27%, respectively.

Earlier identified difficulties in communicating a positive test result for LTBI, not being the same as active TB [29], was confirmed resulting in unnecessary anxiety among pregnant women. Knowledge and perceptions improved with continued information and feed-back to the screening units [30].

Treatment for LTBI was generally well tolerated with a high completion rate of 94%. Adherence was, however, not directly observed, but assumed if self-reported and fulfilled follow-up, which might be a limitation. Only 6% of patients treated with 4R discontinued and none discontinued with 3HR, while 17% of patients treated with 9H discontinued, which is in line with previous studies reporting higher completion rates with shorter LTBI treatments [22, 23]. All but six pregnant women initiated treatment after delivery. However, relative immune impairment and a possible quiescent TB activation during pregnancy may suggest that treatment should be initiated before delivery.

Among the HIV-positive pregnant women, a higher proportion originated from high-endemic countries compared with HIV-negative pregnant women (78 *versus* 11%). The proportion of QFT-positive pregnant women was 15% and not significantly different from HIV-negative pregnant women. However, Konig Walles *et al.* [18] observed lower levels of IFN-γ in HIV-positive pregnant women compared with HIV-negative pregnant women. This may indicate a higher risk of false negative QFT results among HIV-positive pregnant women with LTBI. In a recent report by Norrby *et al.* [31], the incidence of active TB among HIV-positive subjects was 80-times higher than the general population in Stockholm, which emphasises the importance of TB screening and treatment of pregnant women in this group.

In this study, MHC-based screening as a complement to the regular asylum screening, found a high yield of active TB. This is supported by Kunst *et al.* [32], in which median yield was 431/100 000 among 21 studies reporting on post-arrival community-based screening of migrants. This can be compared with 93/100 000 for pre-entry screening, 29/100 000 for screening at port of arrival and 119/100 000 for screening at reception centres. Furthermore, active TB among pregnant women is a high priority as it also include a vulnerable fetus/neonate, which is not the case for migrants in general. However, coverage was

lower for community-based screening, compared with pre- or peri-migration screening (64% *versus* 93%), which is in line with the regular asylum screening in Sweden [16] and is also reflected in the fact that none of the active TB cases in this study had been screened for TB after arrival to Sweden.

Greenaway *et al.* [27], showed that screening with CXR for active TB among migrants was highly sensitive (98%) but only moderately specific (75%). Yield results varied widely depending on country of origin, migrant type and screening setting. The highest yield of 336/100 000 screened was seen among migrants originating from very high TB incidence countries (>350/100 000), while for high-incidence countries (150–250/100 000) the yield was 166/100 000. In our study, seven out of nine TB cases had CXR pathology; however, only one had infiltrations with cavity formation, while the remaining had minor and non-specific findings. Low-dose CXR in pregnancy is considered harmless [33], but the yield with CXR screening in all pregnant women from high-incidence countries (>100/100 000), regardless of symptoms and QFT result, would be less cost-effective.

Nine HIV-negative pulmonary TB cases were detected, corresponding to a high incidence of 215/100 000 screened pregnant women yearly. Only one had been in contact with healthcare due to suggestive TB symptoms and this patient was the only case which was smear microscopy positive, *i.e.* highly contagious. This suggests that symptoms of TB disease during pregnancy are either mild or absent which emphasises the importance of active questioning of symptoms and TB exposure, as well as a liberal sputum sampling for *M. tuberculosis* verification including culture. This is supported in a recent study from south of Sweden by Bullarbo *et al.* [34], in which only one active TB case out of 902 screened pregnant women was detected due to symptoms.

Conclusions

Systematic TB screening of pregnant women from high-endemic countries was a feasible complement to regular asylum screening in Stockholm. The cascade of care revealed a high yield of previously unknown LTBI and mostly asymptomatic active TB. Information and optimised routines improved referral to specialised care. LTBI treatment completion was very high. Our findings justify TB screening of this risk group for early detection and treatment.

Conflict of interest: None declared.

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