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

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Summary:
Systematic TB screening of pregnant women in Stockholm was feasible with high yield of unknown latent TB and mostly asymptomatic active TB. Optimized routines improved referrals to specialist care. Adherence to treatment of latent TB was very high.

Abstract

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

We evaluated cascade of care of a newly introduced TB screening program of PW in Stockholm county 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 29000 HIV negative PW were registered yearly, where of 11% originated from high-endemic countries. In 2016, 72% of these were screened with Quantiferon® (QFT), of which 22% were QFT positive and 85% were referred for specialist care. In 2017, corresponding figures were 64%, 19% and 96%. LTBI treatment rate among all QFT positive PW increased from 24% to 37% over time. Treatment completion with mainly rifampicin postpartum was 94%. Of the 69 registered HIV positive PW, 78% originated from high-endemic countries. Of these, 72% where screened with QFT and 15% were positive, but none was treated for LTBI. Nine HIV negative active pulmonary TB cases were detected (incidence 215/100000). None had been screened for TB prior to pregnancy and only one had sought care due to symptoms.

Systematic TB screening of PW in Stockholm was feasible with high yield of unknown LTBI and mostly asymptomatic active TB. Optimized 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.

Introduction

Pregnancy is a state of relative immunosuppression characterized 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 IFN-γ and TNF-α and therefore a theoretically increased susceptibility to activation and/or de novo infections of certain intracellular microbes such as *M. tuberculosis* (*Mtb*) [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 postpartum 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 (PW) 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. labor immigrants and EU-migrants are not entitled to examination. Therefore, many PW from TB 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 PW from high endemic countries (Fig 1) in collaboration between MHCs, Dept of Communicable Diseases, the TB Center and HIV Center, Department of Infectious Diseases, Karolinska University Hospital (Karolinska). 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 minimize 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 month (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 month (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 Swedish Communicable Disease Act.

Our objective was to evaluate cascade of care of the newly introduced TB screening program among PW in Stockholm 2016-2017.

Material and Methods

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

At MHC, mainly during the 1st 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 PW was immediately referred to the TB Center at Karolinska for diagnostic procedures according to routine clinical practice. Asymptomatic PW from high TB endemic countries or 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/ml), information was given to the PW by the midwife. If the QFT was positive (≥0.35 IU/ml), information was given to the PW at an appointment with a MHC physician and thereafter referred for CXR and then specialist care.

In June 2016, some adjustments were introduced to screening criteria as a consequence of QFT positive PW referred for specialist care, but who after assessment were not recommended treatment. Adjustments were made regarding QFT which was not recommended if the PW a) had been previously 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 was recommended *in parallel*, as some PW had been unwilling to perform CXR with delayed/absent referral to specialist care as a consequence.

Referred PW with symptoms and/or abnormal CXR were seen by a specialist/resident physician in infectious diseases within one week for further diagnostic work-up. Asymptomatic PW with normal CXR were seen within four weeks, mainly during 2nd trimester. PW with a QFT borderline positive result (0.35-0.99 IU/ml) or indeterminate result were re-tested [25]. PW 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 PW was <30 years old and had migrated to Sweden within 2 years *or* visited her home country *or* another high-endemic country >3 months 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, 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 >30 years and arrival to Sweden >2 years ago.

All PW were planned to initiate LTBI treatment within one month after delivery. To minimize loss to follow-up, PW recommended for treatment were scheduled for an appointment with a physician 1-2 weeks after estimated time of delivery and a letter to the midwife with LTBI information and instructions to contact the TB Center after delivery. PW exposed to contagious TB recently (<2 years) started LTBI treatment already during pregnancy. During treatment, the PW had check-up appointments with a TB nurse at two 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 (AEs) 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. PW with CXR infiltrates without activity were recommended 9H.

The study included only ordinary management procedures covered by the regular patient insurance. All compiled data was anonymized to obtain minimal integrity intrusion for the patient. MHC data was collected and compiled by Department of Communicable Diseases Control and Prevention, Stockholm County Council and then stored together with data from the specialized care in a safe database at Karolinska for centralized 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 PW

In 2016 a total of 29459 PW 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 screened PW, 479 (22%) were QFT positive, which is in line with estimated LTBI prevalences in high TB endemic countries [14]. Of these, 407 (85%) were referred to the TB Center at Karolinska.

In 2017, the corresponding figures were 28805 PW, 3140 (11%) originated from high TB endemic countries, 1994 (64%) were screened with QFT, 383 (19%) were QFT positive and 367 (96%) were referred.

Referred PW who initiated treatment increased from 113/407 (28%) in 2016 to 142/367 (39%) in 2017 (Table 1). Upon 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. Further, 22 (4%) women emigrated/moved, 38 (7%) were unwilling to treatment and/or lost to follow-up. In total, the proportion of *all* QFT positive PW that initiated LTBI treatment increased from 113/479 (24%) in 2016 to 142/383 (37%) in 2017. In total, six PW 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. Mean age was 30.1 (range 20 – 41) years and mean time in Sweden was 4.9 (range 0 – 31) years. In summary, 156 (62%) PW originated from Africa, 86 (34%) from Asia, 7 (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 (6/16), re-location (3/16) or loss to follow-up (7/16).
Cascade of care for all HIV negative PW intended for screening is presented in Fig 2.

Screening and treatment of LTBI among HIV positive PW

A total of 69 HIV positive PW 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 6 (15%) were QFT positive, but with no clinical or radiological signs of TB. None was treated for LTBI. One PW started treatment for suspected lymph node TB but was instead diagnosed with lymphoma, two women 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 microbiological confirmed active pulmonary TB cases were detected during pregnancy or postpartum (Table 3). All were HIV negative. Mean age was 29.2 years (range 23 – 33 years). Five had their first child. Seven originated from high TB endemic countries and average time in Sweden was 4.2 years (range 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 four months.

Six of the active TB cases were referred to Karolinska from MHC via the screening program and were diagnosed in 2nd 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 postpartum when seeking primary health care for prolonged cough and weight loss. One case was detected in contact tracing at Karolinska and at the same time also diagnosed as pregnant in 1st trimester.

Only one of the PW with active disease had experienced symptoms associated with TB and two PW reported slight cough when questioned for symptoms, while the remaining were asymptomatic. Eight were tested with QFT and all were positive (range 2.13 – 9.83 IU/ml). Seven had pathological CXRs with infiltrates and/or pleural effusions. The symptomatic case had cavitary upper lobe infiltration and was smear microscopy (SM) positive in sputum, while the remaining were SM negative. Three were PCR positive and all were *Mtb* 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 program among PW in Stockholm in 2016 and 2017 (Fig 2). The choice of TB screening among PW originating from countries with an incidence of >100/100000 is in line with recent reviews by Pareek, Greenaway and co-authors [26, 27] where screening of LTBI in migrants 16–35 years old and originating from countries with a TB incidence of >150/100000 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 PW 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 PW to QFT and/or loss to follow-up was uncommon. Further, 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 PW not recommended for treatment upon specialist decision and a rather large drop-off from "referrals" to "initiated treatment".

However, these drop-offs were smaller as compared with a recent meta-analysis by Alsdurf and co-authors [28], where the proportion of eligble 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 completed treatment. Corresponding figures among HIV negative PW in our study were 68% and 27%.

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 PW. Knowledge and perceptions improved with continued information and feed-back to the screening units (Jansson L. et al. IJTLD 2019, accepted for publication).

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 PW 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 PW a higher proportion originated from high TB endemic countries as compared with HIV negative PW (78 vs 11%). The proportion of QFT positive PW was 15% and not significantly different from HIV negative PW. However, Konig Walles and co-authors observed lower levels of IFN-γ in HIV positive PW as compared with HIV negative PW [18]. This may indicate a higher risk of false negative QFT results among HIV positive PW with LTBI. In a recent report by Norrby and co-authors [30], the incidence of active TB among HIV positives was 80 times higher than the general population in Stockholm, which emphasizes the importance of TB screening and treatment of PW 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 and co-authors [31], where median yield was 431/100000 among twenty-one studies reporting on post-arrival community based screening of migrants. This can be compared with 93/100000 for pre-entry screening, 29/100000 for screening at port-of-arrival and 119/100000 for screening at reception centers. Further, active TB among PW 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, as compared with pre- or peri-migration screening (64% vs 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 and co-authors [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 336/100000 screened was seen among migrants originating from very high TB incidence countries (>350/100000), while for high incidence countries (150-250/100000) the yield was 166/100000. In our study 7/9 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 [32], but the yield with CXR screening in all PW from high incidence countries (>100/100000), 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 215/100000 screened PW yearly. Only one had been in contact with health care due to suggestive TB symptoms and this patient was the only case which was SM positive i.e. highly contagious. This suggests that symptoms of TB disease during pregnancy are either mild or absent which emphasizes the importance of active questioning of symptoms and TB exposure, as well as a liberal sputum sampling for *Mtb* verification including culture. This is

supported in a recent study from south of Sweden by Bullarbo and co-authors [33], where only one active TB case out of 902 screened PW was detected due to symptoms.

Conclusions

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

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	2016	2017	HIV 2016-2017
PW total[1]	29459	28805	69
High endemic origin[1]	3054 (10%)	3140 (11%)	54 (78%)
Screened with QFT[2]	2184 (72%)	1994 (64%)	39 (72%)
QFT positive[2]	479 (22%)	383 (19%)	6 (15%)
Referred[3]	407 (85%)	367 (96%)	na
Initiated LTBI treatment[3]	113 (28%) (24% of QFT pos)	142 (39%) (37% of QFT pos)	0
Completed LTBI treatment[3]	106 (94%) (22% of QFT pos)	128 (94%) (33% of QFT pos)	na

Table 1. Yield of screening and treatment of latent tuberculosis (LTBI) among HIV negative and HIV positive pregnant women in Stockholm 2016 – 2017. PW; pregnant women. QFT; Quantiferon® test. Na; not applicable. Data collected by [1]Department of Growth and Regional Planning Stockholm County Council, [2]Karolinska University Laboratory and [3]TB Center, Department of Infectious Diseases, Karolinska University Hospital.

LTBI treatment	2016 N (%)	2017 N (%)	Total N (%)
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

Table 2. Outcome of treatment of latent TB (LTBI) among HIV negative women 2016 and 2017. N; number. RIF; rifampicin. INH; isoniazid. RPT; rifapentine. Proportion (%) that completed or discontinued of all treated as well as for each respective drug.

Age	Parity	Origin/ TB incidence	Years in SE	Previous TB expo/tx	Symptoms	QFT (IU/mL)	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)

Table 3. Details of active tuberculosis (TB) cases detected during pregnancy or post-partum in Stockholm 2016-2017. SE; Sweden. Expo; esposure. Tx; treatment. QFT; Quantiferon® test. CXR; chest x-ray. PE; pleural effusion. AI; apical infiltrate. SM; smear microscopy. PCR; polymerase chain reaction. GL; gastric lavage. BAL; Broncho-alveolar lavage. TB incidence; high >100/100000, middle 25-100/100000, low <25/100000. 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. 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.

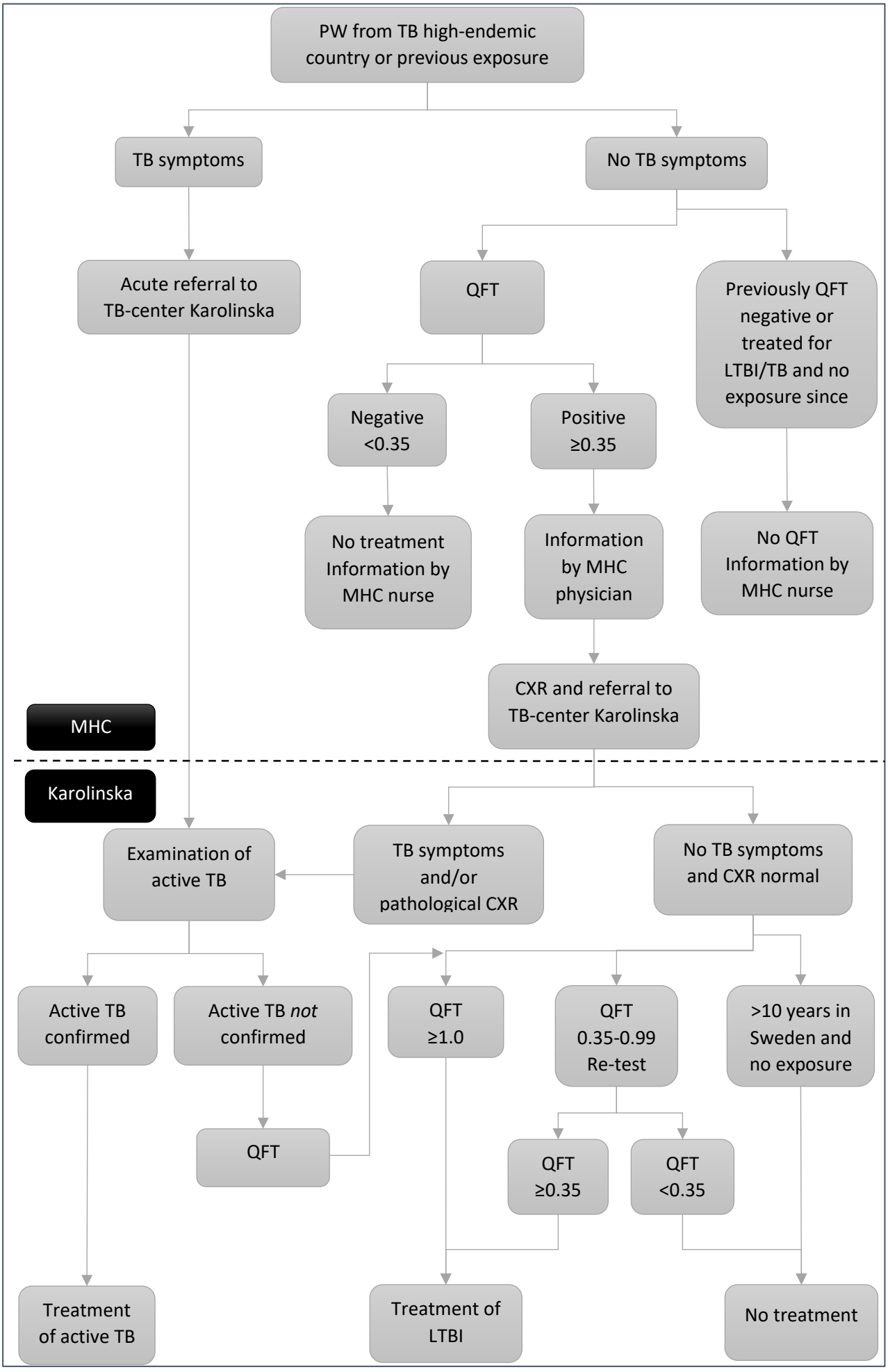

Figure 1. Flow chart of TB screening algorithm for pregnant women (PW) from high-endemic countries or previous exposure. QFT; Quantiferon test, MHC; Maternal Health Care.

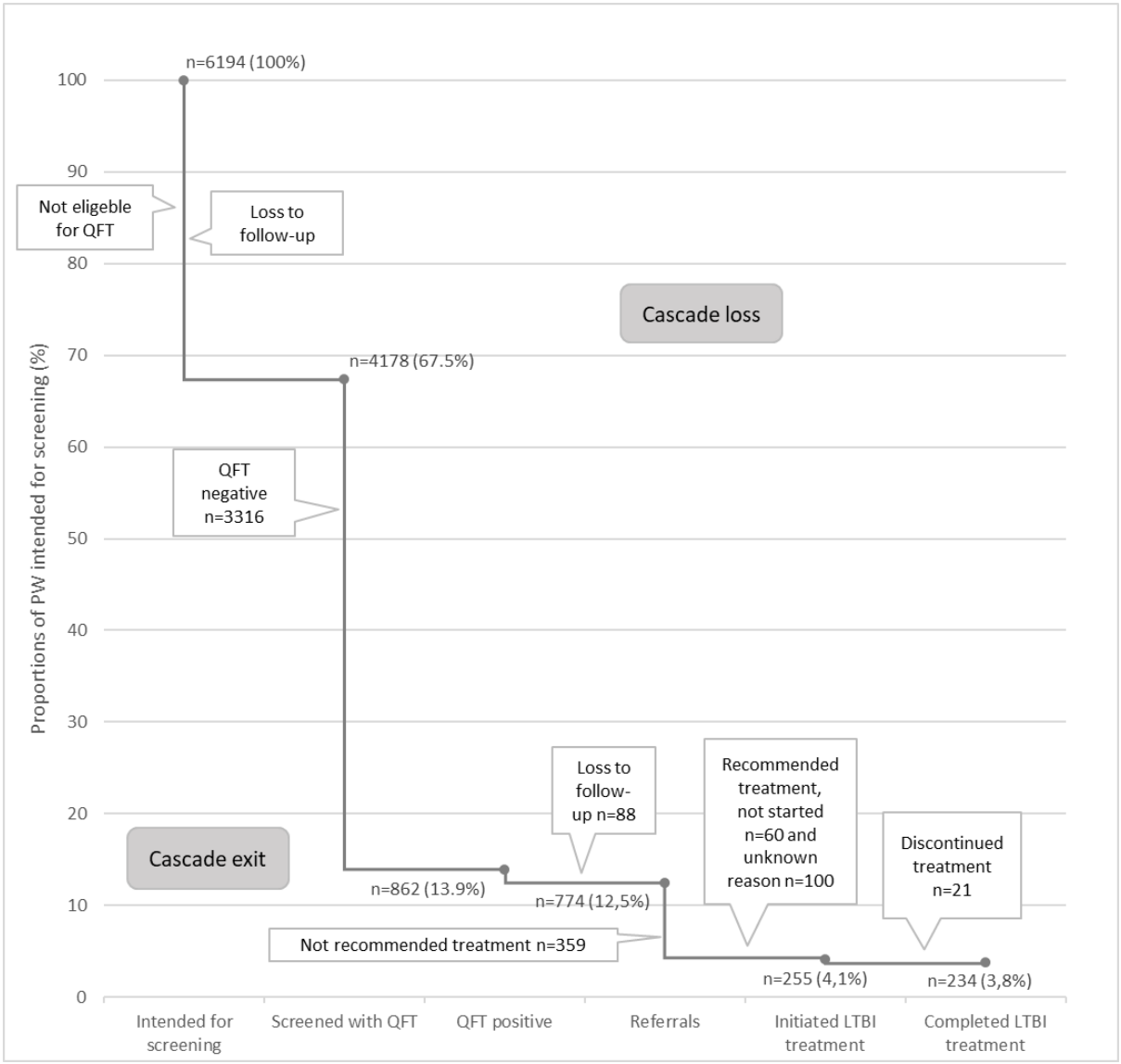

Figure 2. Proportions (%) of all HIV negative PW from high-endemic countries (intended for screening) through the cascade of care in Stockholm county 2016 – 2017.