Open Forum Infectious Diseases

MAJOR ARTICLE

Tuberculosis Infection and Disease Among Pregnant People Living in Sweden With Origin in Tuberculosis-Endemic Countries

Ylva Båtshake,[1] John Walles,[1,2,3] Niclas Winqvist,[1,4] and Per Björkman[1,5]

[1]Clinical Infection Medicine, Department of Translational Medicine, Lund University, Malmö, Sweden, [2]Clinical Microbiology, Infection Prevention and Control, Office for Medical Services, Region Skåne, Lund, Sweden, [3]Department of Infectious Diseases, Central Hospital, Kristianstad, Sweden, [4]Skåne Regional Office for Infectious Disease Control and Prevention, Malmö, Sweden, and [5]Department of Infectious Diseases, Skåne University Hospital, Malmö, Sweden

Background. Pregnancy has been associated with elevated incidence of tuberculosis (TB) disease. Since 2014, people living in Sweden with origin in TB-endemic countries have been offered screening for TB infection in antenatal care (ANC) using Quantiferon-TB assays. We assessed factors associated with TB infection in this population and determined the incidence of TB disease during pregnancy and postpartum periods with regard to ANC Quantiferon-TB results.

Methods. Quantiferon-TB results obtained during ANC in Sweden, 2014–2018, were linked to data from national registers (Pregnancy Register, Patient Register and Tuberculosis Register). Factors associated with TB infection (defined as Quantiferon-TB ≥0.35 IU/mL) were identified using logistic regression analysis. Incidence of TB disease was determined with regard to pregnancy, postpartum and subsequent periods, and ANC Quantiferon-TB results.

Results. Among 7638 screened individuals, 1424 (18.6%) had TB infection. Tuberculosis infection was independently associated with higher age at immigration (adjusted odds ratio, 1.04 [95% confidence interval, 1.03–1.05]; $P < .001$), and was more common among people originating from Africa compared to other world regions (845/3088 [27.4%] vs 579/4550 [12.7%]; $P < .001$). In total, 16 participants were diagnosed with TB disease (10 during pregnancy, 4 at <6 months after delivery, 2 at >6 months after delivery); among these, all diagnosed during pregnancy/postpartum had positive ANC Quantiferon-TB results (constituting 14/1424 [1%] of people with TB infection).

Conclusions. Among pregnant people screened in Swedish ANC, TB infection was associated with higher age and African origin. All cases of TB disease reported in persons with TB infection at ANC screening occurred during pregnancy or postpartum.

Keywords. antenatal; pregnancy; screening; Sweden; tuberculosis.

One-fourth of the world population is estimated to have tuberculosis infection (TBI), with a lifetime 5%–10% risk of progression to tuberculosis (TB) disease [1, 2]. The World Health Organization End TB strategy recommends systematic screening for TBI in population groups at elevated risk of disease progression, such as close contacts of patients with pulmonary TB and people with human immunodeficiency virus (HIV) [3]. In high-income countries with low TB incidence, most cases of TB are due to progression of preexisting TBI rather than de novo infection, with a majority of cases occurring in immigrants from high-incidence countries [4, 5]; for example, 87% of notified TB cases in Sweden during 2019 belonged to this category [6]. For this reason, TB elimination strategies for low-incidence countries emphasize targeting immigrant populations [7]; however, the prevalence of TBI is likely to vary widely among immigrants from different world regions. In addition, immunosuppressive conditions other than HIV can influence the risk of disease progression in people with TBI and may also motivate TBI screening [8, 9].

During pregnancy, physiological immune adaptations occur in order to ensure tolerance to fetal antigens—for example, suppression of $CD4^+$ and $CD8^+$ T cells, as well as increased activity of T regulatory cells [10]. Registry-based studies performed in low-endemic countries have shown increased incidence of TB disease in connection to pregnancy, with most cases diagnosed postpartum [11, 12], suggesting that pregnancy-induced immunological changes increase the risk of TB progression. For these reasons, guidelines in some low-endemic countries recommend TBI screening during antenatal care (ANC) for women with risk factors for TB exposure [13, 14].

Received 18 May 2023; editorial decision 03 July 2023; accepted 09 July 2023; published online 11 July 2023

Correspondence: Ylva Båtshake, MD, MSc, Clinical Infection Medicine, Department of Translational Medicine, Lund University, Ruth Lundskogs gata 3, 214 28, Malmö, Sweden (ylva.batshake@skane.se); Per Björkman, MD, PhD, Clinical Infection Medicine, Department of Translational Medicine, Lund University, Ruth Lundskogs gata 3, 214 28, Malmö, Sweden (per.bjorkman@med.lu.se).

Open Forum Infectious Diseases®

https://doi.org/10.1093/ofid/ofad353

Individuals seeking asylum in Sweden are offered health examination, including TB screening for people from high- and medium-incidence countries [14]. However, the coverage is estimated to be <50% (personal communication, Knut Lönnroth, Karolinska Institute, Solna), and immigrants who are not asylum seekers are not routinely offered health examination [14]. TB screening of people attending ANC has been recommended in Sweden since 2012 [15] and has gradually been introduced in all regions of the country. In the antenatal TB screening program, people originating from TB-endemic countries are offered Quantiferon-TB (QFT) testing to determine TBI status [14]. Persons with positive QFT results, as well as those with suspected TB disease, are referred to infectious disease clinics for further management. In an evaluation of the antenatal TB screening program in Stockholm in 2016–2017 (comprising approximately 58 000 women), 20.6% had TBI, with 9 cases of TB disease detected during pregnancy or postpartum [16]. Moreover, a Swedish registry–based study found increased incidence of TB disease among women during pregnancy and postpartum periods [12]; however, data on TBI status were not reported.

In this study, we aimed to determine the prevalence of TBI among pregnant people living in Sweden with origin in TB-endemic countries who had been screened with QFT testing during ANC attendance in 2014–2018 and to assess factors associated with TBI. In addition, we investigated the incidence of TB disease with regard to ANC QFT test results and timing with regard to pregnancy and the postpartum and subsequent periods.

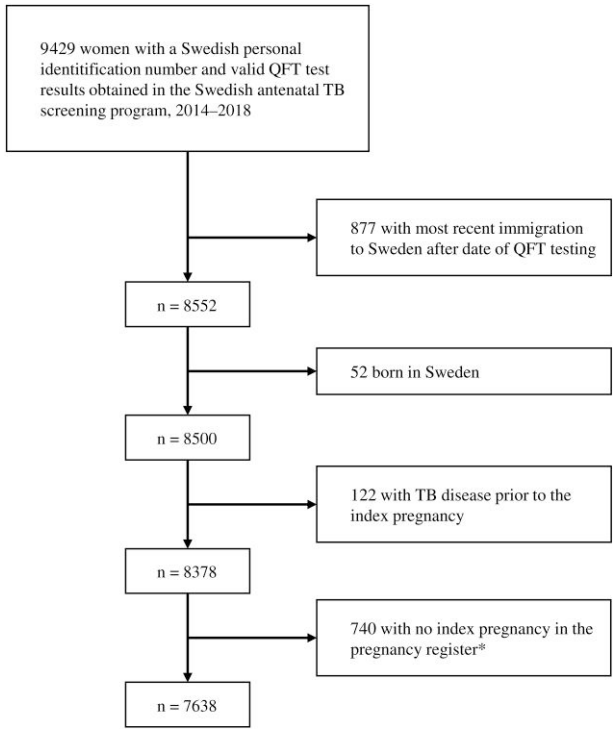

Figure 1. Flowchart illustrating inclusion and exclusion of people screened for tuberculosis infection during antenatal care, 2014–2018. *Miscarriages and abortions before gestational week 22 are not included in the Pregnancy Register. Abbreviations: QFT, Quantiferon-TB; TB, tuberculosis.

METHODS

Study Design and Setting

For this register-based study, people with a national identity number (NIN) and available valid QFT results obtained during 2014–2018, coinciding with record of pregnancy from the Swedish Pregnancy Register or the Patient Register, were eligible for inclusion. People with history of TB disease, people born in Sweden, and people who had been tested before their most recent immigration to Sweden were excluded (Figure 1).

QFT results were retrieved from the regional microbiology laboratories of Lund, Kalmar, Stockholm, Karlstad, and Linköping and linked to register data based on NIN in 2020 (with follow-up until 2019 to allow for detection of TB disease occurring >6 months after delivery). The following national registers were used for linkage:

- The Swedish Pregnancy Register, which includes detailed information on outcome for all registered pregnancies not interrupted before gestational week 22. This register also includes information on the pregnant person's geographic origin, as well as date of the most recent immigration to Sweden.
- The national TB Register (SmiNet), which contains data on all cases of TB disease notified in Sweden.
- The national Patient Register, which contains medical data on both inpatients and outpatients.
- The Swedish Cause of Death Register, which contains data on all registered deaths in Sweden.
- TBI was defined as a positive QFT result. Test results were categorized as positive or negative based on the cutoff recommended by the manufacturer (nil-corrected interferon-γ ≥0.35 IU/mL) [17]. Indeterminate results were not considered. TB disease was defined according to diagnosis in the Patient Register and/or notification of TB disease in the national TB Register. The pregnancy period was defined as the period 280 days before a delivery and postpartum period as 6 months after a delivery.

Statistical Analysis

All analyses were performed in R software, version 4.2.0 [18]. Descriptive statistics were applied to characterize the study population in relation to relevant variables. For comparison between groups, we applied cross-tabulation analysis with χ^2 tests, independent *t* tests, and Wilcoxon signed-rank tests.

To investigate the associations between TBI status and the independent variables, we used univariable and multivariable logistic regression analysis, including immigration year, age at immigration, and region of birth as independent variables. In a subsequent analysis, restricted to participants with complete data, education was included as an additional independent variable. *P* values <.05 were considered statistically significant.

Ethical Statement

Ethical approval for this study was granted from the Swedish Ethical Review Authority (2019-01448). Data linkage was performed by the Swedish Health and Welfare Board and returned to the researchers on a password-protected USB flash drive. Study data were managed and analyzed in a pseudonymized form with a key code.

RESULTS

In total, 9429 people with NIN had valid QFT results obtained during pregnancy in 2014–2018. Among these, 1791 were excluded (Figure 1), resulting in 7638 participants with available QFT results obtained after their last registered immigration to Sweden, who had not been diagnosed with TB disease before the index pregnancy, and who had a pregnancy recorded in the Swedish Pregnancy Register corresponding to the time of QFT testing. Baseline characteristics of the study participants are presented in Table 1.

The mean age of participants was 30.8 years (standard deviation, 5.6 years). The most common regions of birth were Asia (3870 [51%]) and Africa (3088 [40%]). The median duration of residence in Sweden before ANC TB screening was 4.2 years (interquartile range, 1.6–8.5 years). HIV infection was present in 44 persons, 9 of whom had TBI.

Prevalence of TBI and Associated Factors

Among 7638 participants, 1424 (18.6%) met our definition of TBI. Of 3088 people originating from Africa, 845 (27.4%) had TBI, compared to 498 of 3870 (12.9%) people from Asia and 58 of 541 (10.7%) from Europe ($P < .001$; Table 1). Compared to all other world regions, TBI was significantly more common among people of African origin (27.4% vs 579/4550 [12.7%]; $P < .001$). Among people of African origin, TBI was most common in people from the Horn of Africa (ie, the countries of Djibouti, Eritrea, Ethiopia, and Somalia) and other sub-Saharan African countries (27.8% and 30.2%, respectively) compared to North Africa (17.4%).

Region of birth was associated with TBI in both univariable and multivariable regression analysis. Origin from Africa was independently associated with TBI, with significantly lower adjusted odds ratios (AORs) for origin from Asia, South America, and Europe. As for age at immigration, the AOR was 1.04 (95% confidence interval [CI], 1.03–1.05), corresponding to increased odds of having TBI by 4% per additional year of age. Furthermore, immigration during 2014–2017 was negatively correlated with TBI compared to immigration before 2010 (Table 2). In multivariable analysis including participants with complete data on educational level (missing values [n = 1701] not included in analyses), these associations remained. In addition, higher education level showed a weak negative association with TBI (AOR, 0.78 [95% CI, .63–.98], $P = .031$ for college compared to no education; Table 2).

Incidence of TB Disease in Relation to Pregnancy Periods and ANC TBI Test Results

Overall, during follow-up until the end of 2019, 16 participants had been diagnosed with TB disease. Among these, 10 had been diagnosed during the index pregnancy, 4 during the postpartum period, and 2 at >6 months after delivery. All 14 cases notified during pregnancy or postpartum occurred in persons with positive ANC QFT results, whereas the 2 individuals diagnosed >6 months after delivery (7 months and 3 years after delivery, respectively) had negative QFT results at ANC screening (Table 3). None of these 16 persons had registered comorbidities. The odds ratio for subsequent diagnosis of TB disease was 30.8 (95% CI, 7.0–136) for people with positive ANC QFT results compared to those with negative QFT results at ANC screening. Overall, 14 of 1424 people with positive ANC QFT results (0.98%) developed TB disease during pregnancy or postpartum, corresponding to an incidence rate of pregnancy-related TBI progression to TB disease of 7.8 (95% CI, 4.6–13.2) cases per 1000 person-years during pregnancy and postpartum. Three deaths were registered among the study participants; none of these were due to TB, nor to obstetric complications.

DISCUSSION

In this study based on people with origin in TB-endemic countries attending ANC in Sweden, 18.6% of screened individuals had positive QFT results, showing high TBI prevalence in this population. Although no comparative data on TBI prevalence in the general Swedish population are available, the ANC TB screening program clearly targets a group of people in which TBI is common.

Our findings are in agreement with previously published data from Stockholm, which showed positive QFT results in 20.7% of pregnant persons from TB-endemic countries screened 2016–2017 [16]. In a smaller study performed in western Sweden in 2008–2012 [19], TBI prevalence was even higher (36%); however, in that study TBI status was determined by tuberculin skin test, which is less accurate than QFT [20]. In the United States, rates of TBI ranging between 14% and 48% have been reported among pregnant people, with considerably higher prevalence among foreign-born persons, in particular those of Asian American race or Hispanic ethnicity [21].

Table 1. Baseline Characteristics of 7638 People Screened for Tuberculosis Infection During Antenatal Care in Sweden

Characteristic	TBI	TB Uninfected	Total	*P* Value
Total	1424 (18.6)	6214 (81.4)	7638	
HIV				.721[a]
Yes	9 (20.5)	35 (79.5)	44	
No	1415 (18.6)	6179 (81.4)	7594	
Missing	…	…	0	
Region of birth[b]				<.001[a]
Africa[c]	845 (27.4)	2243 (72.6)	3088	
North Africa	50 (17.4)	237 (82.6)	287	
Horn of Africa	521 (27.8)	1355 (72.2)	1876	
Other sub-Saharan Africa	191 (30.2)	440 (69.7)	631	
Africa, country not specified	83 (28.2)	211 (71.8)	294	
Asia[d]	498 (12.9)	3372 (87.1)	3870	
Central	8 (11.9)	59 (88.1)	67	
Eastern	44 (22.4)	152 (77.6)	196	
Southeastern	93 (19.4)	386 (80.6)	479	
Southern	188 (13.9)	1164 (86.1)	1352	
Western	122 (8.5)	1315 (91.5)	1437	
Asia, country not specified	43 (12.7)	296 (87.3)	339	
Europe[e]	58 (10.7)	483 (89.3)	541	
South America	19 (16.0)	100 (84.0)	119	
Other	4 (20.0)	16 (80.0)	20	
Missing	…	…	0	
Immigration year				<.001[a]
Before 2000	62 (11.8)	463 (88.2)	525	
2001–2005	92 (18.8)	397 (81.2)	489	
2006–2010	369 (23.2)	1220 (76.8)	1589	
2011–2012	201 (21.6)	728 (78.4)	929	
2013–2014	268 (19.9)	1077 (80.1)	1345	
2015–2016	304 (15.9)	1604 (84.1)	1908	
2017–2018	128 (15.0)	725 (85.0)	853	
Missing	…	…	0	
Education				<.001[a]
None or <9 y	200 (24.9)	602 (75.1)	802	
Elementary school, 9 y	222 (19.0)	949 (81.0)	1171	
High school, 10–12 y	387 (18.0)	1771 (82.0)	2158	
College/university, >12 y	266 (14.7)	1540 (85.3)	1806	
Missing	349	1352	1701	
Years in Sweden				<.001[f]
Median (IQR)	4.9 (2.1–8.5)	4.0 (1.5–8.5)	4.2 (1.6–8.5)	
Proportion <2 y	23.9	30.9	29.6	
Missing	…	…	0	
Age, y				
Mean ± SD	31.2 ± 5.8	30.6 ± 5.6	30.8 ± 5.6	<.001[g]
Range	14.6–52.3	14.9–51.6	14.6–52.3	
Missing	…	…	0	
Age at immigration, y				
Mean ± SD	25.7 ± 6.6	24.4 ± 7.3	24.7 ± 7.2	<.001[g]
Missing	…	…	0	
QFT test pregnancy week				
Mean ± SD	15.0 ± 7.4	15.4 ± 7.4	15.3 ± 7.4	.168[g]

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: HIV, human immunodeficiency virus; IQR, interquartile range; QFT, Quantiferon-TB; SD, standard deviation; TB, tuberculosis; TBI, tuberculosis infection.

[a] χ^2 test.

[b] Region of birth was further categorized based on United Nations subregions for Africa and Asia. Due to the high proportion of African people with origin in the Horn of Africa (ie, the countries of Djibouti, Eritrea, Ethiopia, and Somalia), participants from this region were categorized separately. Due to low numbers of participants from other African regions, participants with origin in other parts of East Africa, Central or Middle Africa, Southern Africa, and Western Africa were merged into 1 category (other sub-Saharan African countries).

[c] Most common countries: Somalia (31%), Eritrea (20%), and Ethiopia (9%).

[d] Most common countries: Syria (23%), Afghanistan (11%), and Pakistan (10%).

[e] Most common countries: Romania (20%), Serbia (8%), and Bosnia and Herzegovina (8%).

[f] Wilcoxon test.

[g] *t* test.

Table 2. Results of Univariable and Multivariable Logistic Regression Analyses

	Univariable Logistic Regression Analysis			Multivariable Logistic Regression Analysis			Multivariable Logistic Regression Analysis on Part of Data Set[a]		
Variable	OR	(95% CI)	*P* Value	AOR	(95% CI)	*P* Value	AOR	(95% CI)	*P* Value
Region of birth									
Africa	Ref	…		Ref	…		Ref	…	
Asia	0.39	(.35–.44)	<.001	0.41	(.36–.46)	<.001	0.42	(.36–.49)	<.001
Europe	0.32	(.24–.42)	<.001	0.33	(.25–.44)	<.001	0.39	(.28–.53)	<.001
South America	0.50	(.30–.81)	.007	0.52	(.30–.83)	.010	0.57	(.32–.97)	.048
Other	0.77	(.19–1.82)	.5	0.62	(.18–1.71)	.4	0.68	(.19–1.88)	.5
Immigration year									
1980–2010	Ref	…		Ref	…		Ref	…	
2011–2012	1.10	(.91–1.32)	.3	0.99	(.82–1.20)	>.9	0.95	(.76–1.19)	.7
2013	1.18	(.95–1.45)	.13	1.04	(.83–1.29)	.8	0.96	(.74–1.24)	.8
2014	0.84	(.68–1.04)	.12	0.76	(.60–.95)	.018	0.77	(.59–.99)	.043
2015	0.77	(.63–.95)	.014	0.69	(.55–.86)	.001	0.63	(.48–.81)	<.001
2016	0.74	(.61–.89)	.002	0.66	(.53–.81)	<.001	0.66	(.51–.84)	<.001
2017	0.62	(.49–.79)	<.001	0.57	(.44–.74)	<.001	0.59	(.43–.79)	<.001
2018	0.99	(.68–1.42)	>.9	0.87	(.59–1.27)	.5	0.62	(.36–1.02)	.071
Age at immigration	1.03	(1.02–1.03)	<.001	1.04	(1.03–1.05)	<.001	1.04	(1.03–1.05)	<.001
Education									
None or <9 y	Ref	…		…	…		Ref	…	
Elementary school, 9 y	0.70	(.57–.87)	.002	…	…		0.84	(.68–1.06)	.14
High school, 10–12 y	0.66	(.54–.80)	<.001	…	…		0.85	(.70–1.04)	.12
College/university, >12 y	0.52	(.42–.64)	<.001	…	…		0.78	(.63–.98)	.031

Factors associated with tuberculosis infection (TBI) among people screened for TBI during antenatal care during 2014–2018.

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio; Ref, reference category.

[a]Missing values (n = 1701) not included in analyses.

Table 3. Characteristics and Details of Tuberculosis Disease Cases Among People Screened for Tuberculosis Infection During Antenatal Care, 2014–2018

Country of Birth	Years in Sweden	Age, y	TB Manifestation	Time of TB Diagnosis in Relation to Pregnancy
Previous TBI				
Africa (NS)	2	29	Pulmonary	During pregnancy
Africa (NS)	1	36	Pulmonary	1 wk postpartum
Burundi	10	35	Pulmonary[a]	During pregnancy
Eritrea	2	24	Pulmonary	During pregnancy
Eritrea	2	28	Pleuritis	During pregnancy
Ethiopia	1	29	Pulmonary	During pregnancy
Somalia	9	27	Lymphadenitis	During pregnancy
Somalia	<1	26	Pulmonary	During pregnancy
Somalia	4	26	Pulmonary	2 mo postpartum
Morocco	7	31	Lymphadenitis[a]	1 mo postpartum
Afghanistan	1	22	Pulmonary	3 mo postpartum
India	1	26	Pulmonary	During pregnancy
Mongolia	5	33	Pulmonary	During pregnancy
Nepal	6	33	Pulmonary	During pregnancy
No previous TBI				
Somalia	3	30	Pulmonary	3 y after delivery
Somalia	4	17	Pulmonary	7 mo after delivery

Abbreviation: NS, not specified; TB, tuberculosis; TBI, tuberculosis infection.

[a]Not microbiologically verified.

In our study population, TBI was independently associated with African origin. More than half of people with TBI (59%) were from Africa, and in this category, 27% had TBI. These findings are consistent with data from the Swedish Public Health Agency on TB incidence; in 2019, 48% of all individuals diagnosed with TB disease originated from sub-Saharan Africa, compared to 7% from North Africa and the Middle East, 22% from Asia, and 13% from Sweden [6].

Screening of immigrants from TB-endemic countries is recognized as a key component of TB programs in low-incidence countries, and is recommended by the European Centre for Disease Prevention and Control [7, 22]. However, such screening is also challenging, not least with regard to identifying and reaching groups at high likelihood of having TBI [23, 24]. In this regard, ANC is a suitable screening platform for people with origin in TB-endemic countries. In the Swedish context, the yield was highest among people from Africa. Interestingly, people from regions with lower TB incidence also had relatively high rates of TBI (eg, ranging from 8.5% to 19.4% for participants from different parts of Asia), possibly reflecting higher risk of TB exposure among persons immigrating from these countries than in the general population of the respective countries, or acquisition of TBI during migration in refugee camps or other high-risk conditions. Unfortunately, our data sources did not allow for further investigation of underlying reasons for this.

In addition, we observed variations in TBI prevalence among participants screened at different time points during the study period, with significantly lower prevalence among people who had immigrated during 2014–2017. This may be due to changes in origin and characteristics of immigrants, which in turn are linked to likelihood of TBI [25] (Supplementary Figure 1). For example, a high proportion of persons from Syria (a country with comparatively low TB incidence) immigrated to Sweden during this time period. Moreover, higher age at immigration was independently associated with increased odds of TBI. This suggests cumulative acquisition of TBI in people living in TB-endemic settings, in line with results from a cohort study of Ethiopian pregnant women, in which only increasing age was associated with TBI prevalence among HIV-negative individuals [26] (Figure 2).

Studies from Sweden and other high-income countries indicate that TB screening of migrants from high-burden countries is cost-effective [27, 28]. In our study, ANC-based screening led to detection of TBI in almost 1 in 5 individuals tested. Furthermore, screening programs should ideally be linked to evidence-based interventions for participants with abnormal findings. In this regard, the optimal management of TBI in pregnant people remains unclear, with uncertain benefit of TB preventive therapy (TPT) for pregnant people with TBI [29, 30]. Due to concerns of increased risk of hepatotoxicity and potential misclassification of women with unrecognized TB disease, both the Centers for Disease Control and Prevention and the Swedish Public Health Agency recommend deferral of TPT until 2–3 months after delivery, unless other established risk factors for progression exist [13, 14].

Importantly, pregnancy may confer increased risk of TB disease progression, an association that is supported both by epidemiological and immunological studies [11, 12, 31–33]. However, none of the hitherto published register-based studies have included data on TBI status of participants before diagnosis of TB disease. To our knowledge, our study is the first to use this approach, which provides greater precision in the estimates of TB progression in relation to pregnancy.

In our study, all 14 individuals diagnosed with TB disease during pregnancy or postpartum had positive QFT results at ANC screening, corresponding to a TB incidence of 7.8 per

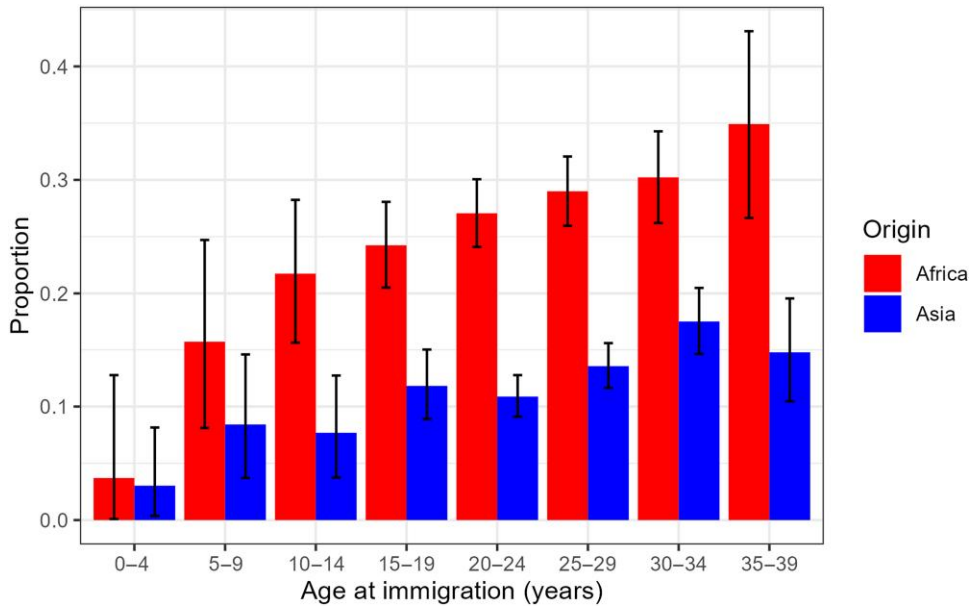

Figure 2. Proportion of tuberculosis (TB) infection by age at immigration and continent of origin. In people of African and Asian origin, the proportion of TB infection was strongly influenced by the age at immigration.

1000 pregnancy-influenced person-years (95% CI, 4.6–13.2) in women with TBI. In contrast, no cases of TB disease presenting after the postpartum period were observed in women diagnosed with TBI at ANC screening. A meta-analysis reported overall TB incidence of 0.3/1000 person-years in people with TBI, with corresponding figures of 17.0 among TB contacts, 16.9 in people with HIV, and 4.8 in people receiving immunosuppressive treatment, respectively [34]. Hence, our findings support that pregnancy is associated with progression of TBI. Furthermore, in low-endemic countries such as Sweden, a negative QFT result during ANC in people with origin in TB-endemic countries appears to have strong negative predictive value for incident TB disease during pregnancy and postpartum. None of the individuals diagnosed with TB disease had registered comorbidities that might have influenced the risk of progression; however, 5 of these persons had immigrated to Sweden <2 years before being diagnosed with TB disease. As the TB risk among immigrants from endemic countries is highest during the first year after arrival, with a gradual decline thereafter [35], it is possible that some of these cases were due to recently acquired TBI.

Interestingly, most TB cases in previous studies were reported postpartum [11, 12], whereas the majority of people with TB disease in our study had been diagnosed during pregnancy. Pregnancy confers physiological immune changes, which may increase the risk of progression of TBI [32, 33]. These immune modifications are restored shortly after delivery. Thus, it is plausible that progression to TB disease occurs during pregnancy, but that typical clinical manifestations do not appear until after delivery; a phenomenon that might be compared to "unmasking" TB after antiretroviral therapy initiation in people with HIV [36]. ANC TB screening could allow for more accurate and timely diagnosis of TB disease among pregnant people. Apart from the risk of TBI progression in connection to pregnancy, TB disease has been associated with increased risks of various adverse pregnancy outcomes [37], further supporting the importance of ANC-based TB screening.

Certain limitations of our study should be considered. It is possible that selection bias occurred, since people without national identity numbers could not be included. Newly arrived immigrants, undocumented immigrants, and people applying for asylum receive provisional identity numbers, which cannot be linked to national registers. TB incidence might have been even higher in such people, which could have led to underestimation of TB incidence. Although the cohort uptake area represents approximately 46% of the Swedish population, all Swedish regions were not included. Data were missing for relatively high proportions for some variables. To minimize the effect of missing data on education level, multivariable regression analyses were performed both with and without this variable included.

Although we could control for several variables of relevance, a possibility for residual confounding remains, similar to all register-based studies. Miscarriages and abortions occurring before gestational week 22 are not included in the Pregnancy Register, and the potential effect on such pregnancies on TB incidence could therefore not be analyzed. Finally, we did not have access to data on TPT for participants; however, since such therapy is recommended for pregnant people in Swedish guidelines only if certain risk factors exist [14], we consider the potential impact of this factor on our results to be low.

CONCLUSIONS

Among 7638 pregnant people with origin in TB-endemic countries screened with QFT in Swedish ANC, TBI was diagnosed in 1424 (18.6%). TBI was associated with African origin, higher age at immigration, and immigration year. Among people with TBI at ANC screening, 14 developed TB disease, with all cases reported during pregnancy and postpartum. These findings show that screening during ANC leads to detection of TBI in a high proportion of the targeted population, and provide further evidence for increased risk of TBI progression in connection to pregnancy.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Acknowledgments. The authors wish to thank Dr Jerker Jonsson, MD, PhD (Swedish Public Health Agency) for helpful assistance in verifying the total cases of TB from the national TB Register. We also thank Dr Knut Lönnroth, MD, PhD (Karolinska Institute, Solna) for valuable input regarding coverage in the Swedish TB infection screening program for migrants.

Data availability. Data are not publicly available.

Financial support. This work was supported by the Swedish Heart-Lung Foundation (grant number 20170258 to P. B.); the Crafoord Foundation (grant number 20170537 to P. B.); the Alfred Österlund Foundation, Region Skåne research grants (grant number 41509 to P. B.); governmental funding of clinical research within the National Health Services Sweden (grant number 40103 to P. B. and J. W.); and the Research and Development Committee at the Northeastern Hospitals in Skåne (grant number 2019-F016 to J. W.).

Potential conflicts of interest. All authors: No reported conflicts.

References

1. Centers for Disease Control and Prevention. The difference between latent TB infection and TB disease. **2014**. Available at: https://www.cdc.gov/tb/publications/factsheets/general/ltbiandactivetb.htm. Accessed 3 May 2023.
2. World Health Organization. Global tuberculosis report 2022. **2022**. Available at: https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2022. Accessed 3 May 2023.
3. World Health Organization. The End TB strategy: Global strategy and targets for tuberculosis prevention, care and control after 2015. **2014**. Available at: https://www.who.int/teams/global-tuberculosis-programme/the-end-tb-strategy. Accessed 3 May 2023.
4. Guthmann J-P, Haas W. Tuberculosis in the European Union/European Economic Area: much progress, still many challenges. Euro Surveill **2019**; 24: 1900174.

5. European Centre for Disease Prevention and Control. Tuberculosis surveillance and monitoring in Europe 2021–2019 data. **2021**. Available at: https://www.ecdc.europa.eu/en/publications-data/tuberculosis-surveillance-and-monitoring-europe-2021-2019-data#no-link. Accessed 3 May 2023.
6. Public Health Agency of Sweden. Tuberkulos—Årsrapport [in Swedish]. **2020**. Available at: https://www.folkhalsomyndigheten.se/folkhalsorapportering-statistik/statistik-a-o/sjukdomsstatistik/tuberkulos/?tab=tab-report&rid%5B%5D=69298. Accessed 3 May 2023.
7. Lönnroth K, Migliori GB, Abubakar I, et al. Towards tuberculosis elimination: an action framework for low-incidence countries. Eur Respir J **2015**; 45:928–52.
8. World Health Organization. Latent tuberculosis infection: updated and consolidated guidelines for programmatic management. **2018**. Available at: https://www.who.int/publications/i/item/9789241550239. Accessed 3 May 2023.
9. Centers for Disease Control and Prevention. Who should be tested for TB infection. **2016**. Available at: https://www.cdc.gov/tb/topic/testing/whobetested.htm. Accessed 3 May 2023.
10. Abu-Raya B, Michalski C, Sadarangani M, Lavoie PM. Maternal immunological adaptation during normal pregnancy. Front Immunol **2020**; 11:575197.
11. Zenner D, Kruijshaar ME, Andrews N, Abubakar I. Risk of tuberculosis in pregnancy: a national, primary care-based cohort and self-controlled case series study. Am J Respir Crit Care Med **2012**; 185:779–84.
12. Jonsson J, Kuhlmann-Berenzon S, Berggren I, Bruchfeld J. Increased risk of active tuberculosis during pregnancy and postpartum: a register-based cohort study in Sweden. Eur Respir J **2020**; 55:1901886.
13. Centers for Disease Control and Prevention. Latent tuberculosis infection: a guide for primary health care providers. **2014**. Available at: https://www.cdc.gov/tb/publications/ltbi/pdf/LTBIbooklet508.pdf. Accessed 3 May 2023.
14. Public Health Agency of Sweden. Rekommendationer för preventiva insatser mot tuberkulos—Hälsokontroll, smittspårning och vaccination. **2022**. Available at: https://www.folkhalsomyndigheten.se/publikationer-och-material/publikationsarkiv/r/rekommendationer-for-preventiva-insatser-mot-tuberkulos-halsokontroll-smittsparning-och-vaccination/. Accessed 3 May 2023.
15. Swedish National Board of Health and Welfare. Rekommendationer för preventiva insatser mot tuberkulos—hälsokontroll, smittspårning och vaccination. Stockholm: Swedish National Board of Health and Welfare; **2012**.
16. Froberg G, Jansson L, Nyberg K, et al. Screening and treatment of tuberculosis among pregnant women in Stockholm, Sweden, 2016–2017. Eur Respir J **2020**; 55:1900851.
17. QuantiFERON-TB Gold. QuantiFERON-TB Gold. **2017**. Available at: https://www.quantiferon.com/products/quantiferon-tb-gold/. Accessed 3 May 2023.
18. R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; **2021**.
19. Bullarbo M, Barnisin M, Vukas Radulovic N, Mellgren Å. Low prevalence of active tuberculosis among high-risk pregnant and postpartum women in Sweden: a retrospective epidemiological cohort study using and evaluating TST as screening method. Infect Dis Obstet Gynecol **2018**; 2018:3153250.
20. Diel R, Goletti D, Ferrara G, et al. Interferon-γ release assays for the diagnosis of latent *Mycobacterium tuberculosis* infection: a systematic review and meta-analysis. Eur Respir J **2011**; 37:88–99.
21. Malhamé I, Cormier M, Sugarman J, Schwartzman K. Latent tuberculosis in pregnancy: a systematic review. PLoS One **2016**; 11:e0154825.
22. European Centre for Disease Prevention and Control. Public health guidance on screening and vaccination for infectious diseases in newly arrived migrants within the EU/EEA. **2018**. Available at: https://www.ecdc.europa.eu/en/publications-data/public-health-guidance-screening-and-vaccination-infectious-diseases-newly. Accessed 3 May 2023.
23. Pareek M, Greenaway C, Noori T, Munoz J, Zenner D. The impact of migration on tuberculosis epidemiology and control in high-income countries: a review. BMC Med **2016**; 14:48.
24. Kunst H, Burman M, Arnesen TM, et al. Tuberculosis and latent tuberculous infection screening of migrants in Europe: comparative analysis of policies, surveillance systems and results. Int J Tuberc Lung Dis **2017**; 21:840–51.
25. Lönnroth K, Mor Z, Erkens C, et al. Tuberculosis in migrants in low-incidence countries: epidemiology and intervention entry points. Int J Tuberc Lung Dis **2017**; 21:624–37.
26. Walles J, Tesfaye F, Jansson M, et al. Tuberculosis infection in women of reproductive age: a cross-sectional study at antenatal care clinics in an Ethiopian city. Clin Infect Dis **2021**; 73:203–10.
27. Shedrawy J, Deogan C, Öhd JN, et al. Cost-effectiveness of the latent tuberculosis screening program for migrants in Stockholm region. Eur J Health Econ **2021**; 22: 445–54.
28. European Centre for Disease Prevention and Control. Cost-effectiveness analysis of programmatic screening strategies for latent tuberculosis infection in the EU/EEA. **2018**. Available at: https://www.ecdc.europa.eu/en/publications-data/cost-effectiveness-analysis-programmatic-screening-strategies-latent-tuberculosis. Accessed 3 May 2023.
29. Miele K, Bamrah Morris S, Tepper NK. Tuberculosis in pregnancy. Obstet Gynecol **2020**; 135:1444–53.
30. Centers for Disease Control and Prevention. Treatment for TB during pregnancy. **2020**. Available at: https://www.cdc.gov/tb/topic/treatment/pregnancy.htm. Accessed 3 May 2023.
31. Rendell NL, Batjargal N, Jadambaa N, Dobler CC. Risk of tuberculosis during pregnancy in Mongolia, a high incidence setting with low HIV prevalence. Int J Tuberc Lung Dis **2016**; 20:1615–20.
32. Tesfaye F, Sturegård E, Walles J, et al. Dynamics of *Mycobacterium tuberculosis*–specific and nonspecific immune responses in women with tuberculosis infection during pregnancy. Microbiol Spectr **2022**; 10:e0117822.
33. Saha A, Escuduero J, Layouni T, et al. *Mycobacterium tuberculosis*–specific T-cell responses are impaired during late pregnancy with elevated biomarkers of tuberculosis risk postpartum. J Infect Dis **2022**; 225:1663–74.
34. Campbell JR, Winters N, Menzies D. Absolute risk of tuberculosis among untreated populations with a positive tuberculin skin test or interferon-gamma release assay result: systematic review and meta-analysis. BMJ **2020**; 368:m549.
35. Kristensen KL, Ravn P, Petersen JH, et al. Long-term risk of tuberculosis among migrants according to migrant status: a cohort study. Int J Epidemiol **2020**; 49: 776–85.
36. Lapadula G, Soria A, Bandera A, et al. Unmasking tuberculosis in the era of antiretroviral treatment. Eur Respir J **2012**; 39:1064–75.
37. Sobhy S, Babiker Z, Zamora J, Khan KS, Kunst H. Maternal and perinatal mortality and morbidity associated with tuberculosis during pregnancy and the postpartum period: a systematic review and meta-analysis. BJOG **2017**; 124:727–33.