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Increased risk of active tuberculosis during pregnancy and postpartum: a register-based cohort study in Sweden

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Author's contribution:

JJ and SKB planned the study. SKB and JJ did the statistical analyses.
JJ produced the tables.
JJ, IB and JB contributed to the interpretation of the results. JJ wrote the first draft of the manuscript and all authors contributed to subsequent revisions.

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Abstract

Rationale

Studies investigating the risk of active tuberculosis (TB) in association with pregnancy have not been conclusive. We aimed at investigating this risk in a large retrospective register-based cohort study in Sweden.

Methods

Data from women 15-49 years of age who had given birth in Sweden 2005-2013 were extracted from the National Childbirth Register and linked to the national TB register. Cohort time was divided into three exposure periods: during pregnancy, six months postpartum, and time neither pregnant nor postpartum. We calculated incidence rates (IR) per 100 000 person-years for each period, and incidence rate ratios (IRR) with IR neither pregnant nor postpartum as reference.

Results

The cohort included 649 342 women, of whom 553 were registered as cases of active TB: 389 when neither pregnancy nor postpartum, 85 during pregnancy and 79 during postpartum. Overall IR were 9, 12 and 17 cases per 100 000 person-years respectively, giving an incidence rate ratio (IRR) of 1.4 (95% CI 1.1–1.7) during pregnancy and 1.9 (95% CI 1.5–2.5) postpartum. Stratification by TB incidence in country of origin showed that the increased risk was concentrated to women from countries with a TB incidence of 100 or higher where incidence rates per 100 000 person-years were 137 when neither pregnancy nor postpartum, 182 during pregnancy and 233 postpartum.

Conclusion

We show a significant increase in risk of active TB during both pregnancy and postpartum in women from high incidence countries and recommend TB screening in pregnant women belonging to this risk group.

Introduction

Until the middle of the 20th century, active tuberculosis (TB) during pregnancy was considered a serious complication of both conditions[1] and as a consequence, sometimes even an indication for termination of pregnancy. In addition, women who had survived TB were often dissuaded from having children. With the introduction of effective TB medication this changed [2,3] and after adequately treated TB in women of reproductive age, no increased risk of relapse during pregnancy has been observed [4].

During pregnancy there is, among other cytokine changes, a significant decrease in TNF-α secretion from NK-cells. These changes occur gradually over the course of the pregnancy to be more pronounced in the 2nd and 3rd trimester [5]. There is an increased risk of TB activation associated with treatment with TNF-α inhibitors [6,7], illustrating the importance of TNF-α in containing *Mycobacterium tuberculosis* infection.

Studies investigating an increased risk of active TB in association with pregnancy have not been conclusive [8-10]. While some studies have shown no increased risk or even a reduced risk of active TB during pregnancy, a study from 2012 showed an increased risk in particular during postpartum, defined as within 6 months after delivery [9]. The increased risk of active TB postpartum has been interpreted as possibly due to delayed diagnosis, as symptoms of active TB can be mistaken for symptoms related to the pregnancy itself. In addition, symptoms might not appear until after delivery due to unmasking of TB when a normal

immune response is restored [11-14]. A delayed diagnosis of active TB is a danger not only to the pregnant woman but also to the newborn child [15-17]. Transmission in utero is considered to be rare [18] and the main risk to the child occurs after birth from a mother with pulmonary TB. An early diagnosis of active TB before delivery is therefore important to reduce this risk. Screening for latent TB infection (LTBI) during pregnancy could also be a good opportunity for prevention, if pregnancy and postpartum constitute an increased risk of activating LTBI.

Sweden is a low TB incidence country (5,3 /100 000 inhabitants in 2017) [19], and the majority of TB cases are diagnosed in individuals originating from high TB incidence countries likely infected before migrating to Sweden. The risk of active TB decreases with time in Sweden due to the reduced risk of new exposure when living in a low incidence country.
Few large studies on risk of TB in association with pregnancy have been conducted [9], and prospective cohort studies are both costly and time-consuming. In Sweden, national registers with excellent coverage over time are available for pregnancies and childbirth [20], as well as for active TB [21], immigration and death [22], and can be linked through unique personal identity numbers. The aim of this retrospective study was to investigate if pregnancy and postpartum constitute risk factors for active TB by using available registers.

Methods

This was a national retrospective register-based cohort study. The cohort consisted of all women in reproductive age, defined as between 15 to 49 years old, who gave birth at least once in Sweden during the study period 1 January 2005 to 31 December 2013. There was no programmatic TB screening in pregnant women in Sweden during the study period, regardless of risk group. A priori we calculated that a yearly TB incidence among pregnant women of at least 7.0 per 100 000 in a one-sided two-sample Poisson test was sufficient to detect a

significant difference to the population yearly TB incidence in Sweden of 6.0 per 100 000 inhabitants with 80% power, 5% significance level, and given an average of 100 000 births per year.

Women contributed time from the date they turned 15 years old or date of immigration to Sweden if they were older than 15 years. Time contribution ended when the first of the following occurred: date they turned 50 years old; date they emigrated from Sweden; death or end of study period. We excluded women with incomplete identity number, or lacking date of birth or date of delivery.

The cohort was grouped according to TB incidence in the respective country of birth based on the average of WHO country estimates during the study period [23] as follows (table S.1 in supplement):

Low incidence: < 25 cases per 100 000 inhabitants and year

Medium incidence: 25 to 99 cases per 100 000 inhabitants and year

High incidence: 100 or more cases per 100 000 inhabitants and year

The person-time contributed by each woman was divided into three periods of exposure: pregnancy, postpartum (180 days after delivery) and time neither pregnant nor postpartum. If a new pregnancy started before the end of the 180 days postpartum of the previous birth, the subsequent time was counted as during pregnancy.

For the women from high incidence countries, we also investigated the influence of time in Sweden for the risk of active TB, assuming that the majority of them had been exposed to TB before immigration to Sweden and that their risk of active TB was highest during the first years in Sweden, whether pregnant or not. In order to test this hypothesis, the time neither pregnant nor postpartum was divided in time before 1st pregnancy (i.e. 1st included in the

study period) and other time neither pregnant nor postpartum (Figure 1). In this group of women the time contributed was also stratified by age groups 15-19, 20-29, 30-39 and 40-49 years of age.

Figure 1. Timeline for the study of TB risk in pregnant women aged 15-49 years in Sweden 2005-2013, with two examples of how contribution of time was stratified.

* Time was divided in three different periods; during pregnancy, postpartum and time not pregnant or postpartum.
In the analysis of women from high incidence countries, time not pregnant or postpartum was divided in two periods; before 1st pregnancy and other time not pregnant or postpartum, and also stratified by age group.

Woman A was 22 years at the start of the study and contributed time in age group 20-29 until she turned 30 years and then contributed to age group 30-39.
Woman B entered the study when she turned 15 years old and contributed time in age group 15-19 until she turned 20 and then contributed to age group 20-29.

Registers

The cohort was extracted from the Swedish Medical Birth register (MBR) [20] held at the National Board of Health and Welfare, which includes all registered births in Sweden occurring later than gestational week 22. The register contains information on date of birth and country of birth of the mother, as well as date of delivery and estimated length of pregnancy.

Data on TB diagnosis was extracted from the TB-register in SmiNet [21] at the Public Health Agency of Sweden (PHAS), containing all reported cases of active TB. Laboratory confirmed cases have a positive culture of *M. tuberculosis* or a sample with positive microscopy for acid-fast bacteria paired with a positive polymerase chain reaction test (PCR-test) for the *M. tuberculosis* complex. For cases with no laboratory confirmation, the clinical criteria for

reporting are symptoms and/or radiological findings consistent with active TB and a clinician's decision to treat with a full course of TB medication. For cases with no date of diagnosis reported, the date of the first laboratory report was used as a proxy. For cases lacking laboratory confirmation, we used the date of the clinical report if date of diagnosis was lacking.

The mother's country of origin, dates of immigration, dates of emigration, and date of death were obtained from Swedish Population Register at Statistics Sweden [22]. For asylum seekers, the date of immigration registered did not always correspond to the date of entering Sweden as registration had been delayed for some women. This was evident in 14 women registered as giving birth in Sweden before the official date of immigration, which then was changed to one day before giving birth. The same occurred in nine cases of active TB diagnosed in Sweden before their official date of immigration, which then was set to the immigration date stated in the TB register.

All data were linked using the Swedish unique national identity number. In women lacking a Swedish national identity number, a temporary identity number given for health care matters was used. After linkage, Statistics Sweden deleted the identity numbers before data was analysed at PHAS.

Statistical methods

The incidence rates (IR) were calculated as number of TB events per person-time-at-risk for each of the exposure periods. The incidence rate ratio (IRR) was calculated as the IR during pregnancy or postpartum divided by the IR during time neither pregnant nor postpartum. Both IR and IRR were reported with 95% confidence intervals and considered statistically

significant if they did not include one. In the analysis of the subgroup of women from high incidence countries, the IRR was calculated as the IR during time before 1st pregnancy, pregnancy and postpartum divided by the IR during other time neither pregnant nor postpartum.

Statistical analysis was conducted in R v. 3.4.1. [24]

Complementary analysis of background population

In order to confirm that the results were reasonable, we compared them with an estimate of IR for TB in the different exposure periods for the population of all women aged 15-49 years in Sweden, i.e. including also all women who did not give birth during the study period. Population data per year to obtain person-years was retrieved from Statistics Sweden, and the total number of TB cases among women in this age group, from the TB register at PHAS.

Ethical considerations

The Regional Ethics committee in Stockholm granted ethical permission, Dnr 2014/1504-31/3, and waived the need for informed consent as the study was retrospective and only used anonymized data from already existing registers.

Results

Main analysis

The total number of registered deliveries in Sweden between 1 January 2005 and 31 December 2013 was 951 672. After applying the exclusion criteria the final cohort consisted of 649 342 women contributing time during the study period with a total of 951 530 deliveries (Table 1). The average time contribution of each women was 8.5 person-years of which 1.1 person-years were during pregnancy and 0.7 person-years during postpartum.

Table 1. Number of women and total time contributed (person-years) by TB incidence in country of birth, Sweden 2005-2013

TB incidence in country of origin	Women	Person-years
Low (<25 cases /100 000)	546 980	4 792 201
Medium (25-99 cases /100 000)	57 326	426 995
High (≥100 cases /100 000)	44 536	305 249
Unknown origin	500	3 677
Total	**649 342**	**5 528 112**

The mean age at first delivery during the study period was 29.9 years (median 30 years old, range 15-49) and the mean number of deliveries per woman was 1.5 (range 1-7).
During the study period, 553 of the women were reported as diagnosed with active TB, of which 452 (82%) were verified by mycobacterial culture. There were 85 cases diagnosed during pregnancy, 79 during postpartum and 389 when neither pregnant nor in postpartum (Table 2).

There was an overall significantly increased risk of active TB both during pregnancy (IRR=1.4; 95% CI 1.1–1.7) and postpartum (IRR=1.9; 95% CI 1.5–2.5) compared to when neither pregnant nor postpartum (Table 2). When stratifying by incidence in country of birth, the increased risk was only confirmed in women from high incidence countries and corresponded to TB incidence rates per 100 000 person-years of 182 during pregnancy, 233 postpartum and 137 when not pregnant or postpartum (Table 2).

Table 2. Number of TB cases, incidence rates and incidence rate ratios in women during pregnancy, postpartum or when not pregnant or postpartum, by TB incidence in country of origin, Sweden 2005-2013.

TB incidence in country of origin	Exposure period	No of TB cases (n=553)	Person-years	Incidence rate per 100 000 person-years (95% CI)	Incidence rate ratio (95% CI)
All women	Pregnancy	85	689 288	12 (10–15)	**1.4 (1.1–1.7)**
	Postpartum	79	456 102	17 (14–21)	**1.9 (1.5–2.5)**
	Not pregnant or postpartum	389	4 382 732	8.9 (8.1–9.9)	1.0 reference
Low <25 cases /100 000	Pregnancy	1	584 836	0.17 (0.04–0.63)	0.20 (0.03–1.49)
	Postpartum	2	386 420	0.52 (0.16–1.44)	0.62 (0.15–2.58)
	Not pregnant or postpartum	32	3 820 945	0.84 (0.59–1.15)	1.00 reference
Medium 25-99 cases /100 000	Pregnancy	2	58 862	3.4 (1.1–9.5)	0.25 (0.06–1.05)
	Postpartum	7	39 343	18 (9–33)	1.3 (0.6–3.0)
	Not pregnant or postpartum	44	328 790	13 (10–18)	1.00 reference
High ≥100 cases /100 000	Pregnancy	82	45 081	182 (147–223)	**1.32 (1.04–1.69)**
	Postpartum	70	30 017	233 (184–290)	**1.70 (1.31–2.20)**
	Not pregnant or postpartum	313	230 151	137 (123–153)	1.00 reference
Unknown origin	Pregnancy	0	509	0	-
	Postpartum	0	322	0	-
	Not pregnant or postpartum	0	2 846	0	-

Of the 313 cases diagnosed when neither pregnant nor postpartum, 172 (55%) were diagnosed before start of the first pregnancy (Figure 2).

Figure 2. TB incidence rate ratios with 95% confidence intervals in women from high TB incidence countries, Sweden 2005-2013; before 1st pregnancy, during pregnancy and postpartum, compared to other time neither pregnant nor postpartum.

When stratifying time contributed by women from high incidence countries by age group, IRR for all exposures were statistically significant for age groups 20-29 and 30-39, with the exception of 30-39 years during pregnancy, which was borderline. Although all confidence intervals overlapped with each other, there was a tendency of a higher IRR postpartum as compared to before first pregnancy (table S.2 in supplement and figure 3).

Figure 3. Incidence rate ratios with confidence intervals; before 1st pregnancy, during pregnancy and postpartum compared to other time not pregnant or postpartum, in women from high TB incidence countries, age groups 20-29 and 30-39 years, Sweden 2005-2013.

Complementary analysis of background population

The complementary analysis of the background population analysis showed a significant increase in risk of active TB during pregnancy and an even higher increase in risk during postpartum, compared to during time not pregnant or postpartum (table 3). The person-years included in the study cohort constituted 29 percent of the person-years from the background population.

Table 3. Number of TB cases, person years, incidence rates and incidence rate ratios by exposure period, in all women aged 15-49 years, Sweden 2005-2013.

Exposure period	No of TB diagnosis	Person-years	Incidence rate per 100 000 person-years (95% CI)	Incidence rate ratio (95% CI)
Pregnancy	85	689 213	12.3 (9.9-15.3)	**1.6** (1.5-1.7)
Postpartum	79	456 364	17.3 (13.7-21.6)	**2.3** (2.2-2.4)
Time not pregnant or pp	1339	17 738 509	7.6 (7.2-8.0)	1.0 reference
Total	1503	18 884 086	8.0 (7.6-8.4)	

Discussion

In this study we show a significantly increased risk of active TB during pregnancy and postpartum, in a cohort of women aged 15-49 years who had given birth in Sweden, a low endemic setting (6.8/100 000 population average during study period). Even though the overall TB incidence rates were low, we validated these findings by analysis of the total Swedish population of women aged 15-49 years old during the same study period, which resulted in similar IRR's but with more narrow confidence intervals.
When stratifying by incidence in country of birth, these risks were significant in women originating from countries with a high TB incidence, i.e. more than 100 cases per 100 000 inhabitants and year. In women from low TB incidence countries (less than 25/100 000) of which the vast majority was born in Sweden, the scarcity of cases resulted in incidences of less than 1 /100 000 for all periods.

Our results confirm findings from a study in the United Kingdom by Zenner et al [9], which demonstrated an increased risk of active TB in women postpartum, although an increased risk during pregnancy could not be shown. A stronger statistical power in our study is a possible explanation for this difference with an overall of 553 TB cases included in our study as compared to 177 TB cases in the study by Zenner and co-workers. A more recent European cross-sectional study also concluded that TB was diagnosed more frequently after delivery [25], and possible reasons stated was delayed diagnosis due to pregnancy or late or poor attendance to antenatal care that might be more common in risk groups for TB.

In Sweden during the study period, almost 90 percent of diagnosed TB cases were born outside of Sweden, and the majority of them originate from high incidence countries [19]. In our study, 84 percent (465/553) of the TB cases were born in high incidence countries. According to observations from the national TB surveillance [19], the majority of active TB cases in migrants is diagnosed within the first five years after arrival in Sweden. We could

confirm this observation among women from high incidence countries aged 20-29 and 30-39 years old, where we showed a significantly increased IRR for active TB before the first pregnancy, but also during pregnancy and postpartum, compared to other time neither pregnant nor postpartum. In a low incidence setting like Sweden, the risk for re-infection after completed treatment, for LTBI or active TB, is very low and thus, the women diagnosed with TB before pregnancy, had a much reduced risk of developing active TB again, pregnant or not.

Maternal health controls represent an excellent opportunity to screen women belonging to risk groups for TB in order to initiate early diagnosis and treatment of active TB, or preventive therapy when indicated, as has been recommended in scientific publications [26,27]. Mother and child will benefit from an early diagnosis of both active TB and LTBI, preferably well before the child is born. As LTBI is a continuous source of new cases of active TB, LTBI treatment is an important part of WHO's End TB strategy [28] aiming at a 90 percent reduction of the TB incidence rate by 2035 as compared to 2015. Consequently, the WHO has issued guidelines on LTBI screening and treatment in 2014 with a recent update in 2017. However, TB screening during pregnancy or postpartum is not recommended in these guidelines [29]. Our data provide robust evidence that women from high TB prevalence countries are at substantially elevated risk of developing active TB in both pregnancy and during the post-partum period. We believe that introduction of routine LTBI screening, preferably in early pregnancy, should be considered by public health bodies in countries with low TB prevalence. Notably, it is far more probable that active TB in pregnancy is the result of LTBI activation/progression than of re-activation of adequately treated active TB although definitive proof is currently lacking.

Limitations

The national childbirth register we used does not include pregnancies shorter than 22 weeks and may reflect a reduced time-period during pregnancy. However, it is not likely that this biased the results since immunological changes during pregnancy, that theoretically could explain the increased risk of TB activation, are more pronounced during the last two trimesters [5], something that was not investigated here.

The register data did not include any information on other health conditions that might have influenced the risk of developing active TB such as HIV, underweight or nutritional deficiencies. Neither was there any information on possible factors that might have increased the risk of TB exposure, like for example time spent in refugee camps or imprisonment. In Sweden however, all pregnant women are offered screening for HIV[30] and to our knowledge there has been no report of active TB and HIV co-morbidity in pregnancy in Sweden, to date. We had no means to control for events like earlier pregnancies or TB diagnosis occurring outside of Sweden before immigration. As the risk of exposure is greatly reduced after moving to a low TB incidence country, we believe our results underestimate the added risk of active TB during pregnancy and postpartum.

Almost all pregnant women in Sweden are in contact with the national health program of antenatal and post-natal care. This introduces a possible risk of bias of TB diagnosis while pregnant and postpartum due to closer contact with health services as compared with when not pregnant or postpartum. In most cases though, the contact with health services focuses more on the woman during pregnancy compared to postpartum. However, TB incidence was higher postpartum, which contradicts a possible bias.

Information on preventive treatment for LTBI in our study cohort is lacking. As the largest target group for LTBI treatment in Sweden is recent immigrants from high incidence countries, the effect of LTBI treatment in our cohort could possibly lead to a lower TB

incidence per 100 000 person-years in this group, however this should not affect the incidence rate ratios.

For women who had events (TB-diagnosis or childbirth) registered that occurred in Sweden before their official immigration date, we corrected the erroneous dates of immigration from Statistics Sweden. For the remaining, less time when not pregnant or postpartum might have been registered, possible increasing the reference incidence and thus underestimating the increase in risk of active TB associated to pregnancy.

Conclusions

Our findings of an increased risk of active TB during pregnancy and postpartum in women from high TB endemic countries is probably generalizable to other settings. In addition, an even more pronounced increase is likely in a high incidence setting, where there is a continuous risk of renewed TB exposure. Active TB during pregnancy and postpartum poses severe risks for both mother and child. Our study adds knowledge to a controversial field, and we consequently recommend screening for latent TB in pregnant women from TB risk groups, such as women from high TB incidence countries or with known recent TB exposure. For any woman, being in child-bearing age increases motivation for chemoprophylaxis in latently infected individuals. Clinicians should also apply a low threshold when considering active TB (and investigate accordingly) in pregnant women and in women in the postpartum period belonging to TB risk groups.

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Country	average TB incidence per year, 2005 to 2013	Group
Albania	17	1. Low (< 25)
Antigua and Barbuda	6,2	1. Low (< 25)
Australia	6,4	1. Low (< 25)
Austria	10	1. Low (< 25)
Bahamas	14	1. Low (< 25)
Barbados	2,4	1. Low (< 25)
Belgium	10	1. Low (< 25)
Canada	5,2	1. Low (< 25)
Chile	17	1. Low (< 25)
Costa Rica	14	1. Low (< 25)
Cuba	7,9	1. Low (< 25)
Cyprus	5,0	1. Low (< 25)
Czechia	7,9	1. Low (< 25)
Denmark	7,1	1. Low (< 25)
Dominica	13	1. Low (< 25)
Egypt	19	1. Low (< 25)
Fiji	24	1. Low (< 25)
Finland	6,7	1. Low (< 25)
France	9,2	1. Low (< 25)
Germany	6,4	1. Low (< 25)
Greece	5,7	1. Low (< 25)
Grenada	2,8	1. Low (< 25)
Hungary	16	1. Low (< 25)
Iceland	4,1	1. Low (< 25)
Iran	17	1. Low (< 25)
Ireland	10	1. Low (< 25)
Israel	5,9	1. Low (< 25)
Italy	7,1	1. Low (< 25)
Jamaica	4,9	1. Low (< 25)
Japan	21	1. Low (< 25)
Jordan	7,1	1. Low (< 25)
Lebanon	13	1. Low (< 25)
Luxembourg	7,7	1. Low (< 25)
Malta	10	1. Low (< 25)
Mauritius	22	1. Low (< 25)
Mexico	21	1. Low (< 25)
Monaco	2,0	1. Low (< 25)
Netherlands	6,9	1. Low (< 25)
New Zealand	8,0	1. Low (< 25)
Norway	7,3	1. Low (< 25)
Oman	13	1. Low (< 25)
Poland	23	1. Low (< 25)
Saint Lucia	9,3	1. Low (< 25)
Samoa	12	1. Low (< 25)
Saudi Arabia	16	1. Low (< 25)
Seychelles	19	1. Low (< 25)
Slovakia	11	1. Low (< 25)
Spain	17	1. Low (< 25)

Sweden	6,8	1. Low (< 25)
Switzerland	7,1	1. Low (< 25)
Syrian Arab Republic	24	1. Low (< 25)
Tonga	15	1. Low (< 25)
Trinidad and Tobago	20	1. Low (< 25)
United Arab Emirates	2,5	1. Low (< 25)
United Kingdom of Great Britain and Northern Ireland	15	1. Low (< 25)
United States of America	4,4	1. Low (< 25)
Uruguay	24	1. Low (< 25)
West Bank and Gaza Strip	1,08	1. Low (< 25)
Algeria	75	2. Medium (25-99)
Argentina	26	2. Medium (25-99)
Armenia	66	2. Medium (25-99)
Bahrain	27	2. Medium (25-99)
Belarus	69	2. Medium (25-99)
Benin	68	2. Medium (25-99)
Brazil	45	2. Medium (25-99)
Bulgaria	41	2. Medium (25-99)
Burkina Faso	59	2. Medium (25-99)
China	82	2. Medium (25-99)
China	82	2. Medium (25-99)
Colombia	31	2. Medium (25-99)
Dominican Republic	70	2. Medium (25-99)
Ecuador	62	2. Medium (25-99)
El Salvador	34	2. Medium (25-99)
Estonia	31	2. Medium (25-99)
Guatemala	29	2. Medium (25-99)
Honduras	54	2. Medium (25-99)
Iraq	46	2. Medium (25-99)
Jugoslavia countries; Slovenien, Serbien, Bosnien, Makedonien, Kroatien and Montenegro	29	2. Medium (25-99)
Kuwait	30	2. Medium (25-99)
Latvia	57	2. Medium (25-99)
Libya	40	2. Medium (25-99)
Lithuania	75	2. Medium (25-99)
Malaysia	76	2. Medium (25-99)
Maldives	42	2. Medium (25-99)
Mali	64	2. Medium (25-99)
Nicaragua	52	2. Medium (25-99)
Palau	69	2. Medium (25-99)
Panama	56	2. Medium (25-99)
Paraguay	43	2. Medium (25-99)

Portugal	30	2. Medium (25-99)
Qatar	40	2. Medium (25-99)
Republic of Korea	94	2. Medium (25-99)
Rwanda	89	2. Medium (25-99)
Singapore	38	2. Medium (25-99)
Solomon Islands	91	2. Medium (25-99)
Sri Lanka	66	2. Medium (25-99)
Togo	73	2. Medium (25-99)
Tunisia	30	2. Medium (25-99)
Turkey	27	2. Medium (25-99)
Venezuela	29	2. Medium (25-99)
Yemen	59	2. Medium (25-99)
Afghanistan	189	3. High (>100)
Angola	379	3. High (>100)
Azerbaijan	179	3. High (>100)
Bangladesh	225	3. High (>100)
Bhutan	192	3. High (>100)
Bolivia	140	3. High (>100)
Botswana	563	3. High (>100)
Burundi	156	3. High (>100)
Cabo Verde	148	3. High (>100)
Cambodia	452	3. High (>100)
Cameroon	272	3. High (>100)
Central African Republic	491	3. High (>100)
Chad	151	3. High (>100)
Congo	399	3. High (>100)
Cote d'Ivoire	212	3. High (>100)
Democratic People's Republic of Korea	375	3. High (>100)
Democratic Republic of the Congo	327	3. High (>100)
Djibouti	529	3. High (>100)
Equatorial Guinea	126	3. High (>100)
Eritrea	112	3. High (>100)
Ethiopia	282	3. High (>100)
Gabon	503	3. High (>100)
Gambia	181	3. High (>100)
Georgia	138	3. High (>100)
Ghana	186	3. High (>100)
Guinea	192	3. High (>100)
Guyana	115	3. High (>100)
Haiti	239	3. High (>100)
India	254	3. High (>100)
Indonesia	420	3. High (>100)
Kazakhstan	153	3. High (>100)
Kenya	313	3. High (>100)
Kyrgyzstan	163	3. High (>100)
Lao People's Democratic Republic	232	3. High (>100)

Liberia	288	3. High (>100)
Madagascar	246	3. High (>100)
Malawi	344	3. High (>100)
Mauritania	145	3. High (>100)
Mongolia	428	3. High (>100)
Morocco	100	3. High (>100)
Mozambique	539	3. High (>100)
Myanmar	388	3. High (>100)
Namibia	715	3. High (>100)
Nepal	163	3. High (>100)
Niger	120	3. High (>100)
Nigeria	340	3. High (>100)
Pakistan	276	3. High (>100)
Papua New Guinea	432	3. High (>100)
Peru	137	3. High (>100)
Philippines	325	3. High (>100)
Republic of Moldova	168	3. High (>100)
Romania	116	3. High (>100)
Russian Federation	110	3. High (>100)
Senegal	137	3. High (>100)
Sierra Leone	316	3. High (>100)
Somalia	286	3. High (>100)
South Africa	938	3. High (>100)
Sudan	109	3. High (>100)
Swaziland	1220	3. High (>100)
Tajikistan	144	3. High (>100)
Thailand	192	3. High (>100)
Timor-Leste	498	3. High (>100)
Turkmenistan	120	3. High (>100)
Uganda	215	3. High (>100)
Ukraine	113	3. High (>100)
United Republic of Tanzania	441	3. High (>100)
Uzbekistan	102	3. High (>100)
Viet Nam	160	3. High (>100)
Zambia	516	3. High (>100)
Zimbabwe	452	3. High (>100)

Table S.2. Number of TB cases, person-years, incidence rates and incidence rate ratios with confidence intervals; before 1st pregnancy, during pregnancy and postpartum compared to other time not pregnant or postpartum, in women from high TB incidence countries, by age groups, Sweden 2005-2013.

Age group	Risk period	No of TB diagnosis (n=468)	Person-years	Incidence rate per 100 000 person-years (95% CI)	Incidence rate ratio (95% CI)
All age groups	Before pregnancy	175	82 687	212 (181-254)	**2.21** (1.77-2.76)
	During pregnancy	82	45 081	182 (145-226)	**1.90** (1.45-2.50)
	Postpartum	70	30 018	233 (182-295)	**2.44** (1.90-3.14)
	Other time not pregnant or postpartum	141	147 511	96 (80-113)	1.00 reference
15-19 years	Before pregnancy	21	6 885	305 (189-466)	0.55 (0.16-1.83)
	During pregnancy	2	975	205 (25-741)	0.37 (0.06-2.19)
	Postpartum	2	461	434 (53-1567)	0.78 (0.18-3.26)
	Other time not pregnant or postpartum	3	536	560 (115-1636)	1.00 reference
20-29 years	Before pregnancy	108	43 606	248 (203-299)	**1.70** (1.23-2.34)
	During pregnancy	53	21 128	251 (188-328)	**1.72** (1.18-2.50)
	Postpartum	39	13 134	297 (211-406)	**2.03** (1.45-2.85)
	Other time not pregnant or postpartum	56	38 354	146 (110-190)	1.00 reference
30-39 years	Before pregnancy	43	31 460	137 (99-184)	**1.60** (1.10-2.33)
	During pregnancy	25	21 092	119 (77-175)	1.39 (0.88-2.19)
	Postpartum	27	14 858	182 (120-264)	**2.13** (1.42-3.19)
	Other time not pregnant or postpartum	72	84 281	85 (67-108)	1.00 reference
40-49 years	Before pregnancy	3	736	408 (84-1191)	**9.92** (2.73-36.1)
	During pregnancy	2	1 887	106 (13-383)	2.58 (0.57-11.8)
	Postpartum	2	1 565	128 (16-462)	3.11 (0.72-13.5)
	Other time not pregnant or postpartum	10	24 340	41 (20-76)	1.00 reference