**Risk of tuberculosis in pregnancy:**
A national, primary care based cohort and self-controlled case series study

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Risk of tuberculosis in pregnancy: 
A national, primary care based cohort and self-controlled case series study

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Contributors
DZ undertook the analysis and wrote the paper with contributions from MK, NR and IA. IA conceived the idea and NR supervised the statistical analysis. All authors have approved the final manuscript. IA is guarantor.

Funding
We received a grant from the Medical Research Council (09_084R, 12/11/2009) to access the GPRD database. Internal HPA funding was used to cover salaries and on-costs.

At a glance commentary

Scientific Knowledge on the Subject
• TB disease during pregnancy has adverse effects on mother and child.
• Risks of TB far outweigh the risk of TB treatment during pregnancy
• Current evidence of TB incidence in pregnancy is inconclusive, but local studies indicated a potentially high TB incidence during pregnancy.

What this study adds to the Field
• The study found a significantly increased incidence of TB diagnosis in mothers postpartum which probably reflects an increase in TB incidence during pregnancy.
• The self-controlled case series found an increased TB risk post-partum, adjusting for individual confounders.
Abstract

Objective
Tuberculosis (TB) disease adversely affects mother and child, and strategies to control TB in this group are important. The aim of this study was to analyse the epidemiology of TB in pregnancy, and establish whether pregnancy is an independent risk factor for TB.

Methods
The UK-wide cohort study was based on the General Practitioner Research Database (GPRD), enrolling all women with pregnancies between 1996 and 2008. Incidence rates (IR) and ratios (IRR) of TB events during pregnancy, 6 months post-partum, and outside pregnancy were calculated and compared using Poisson regression. A nested self-controlled case series (SCCS) compared the risk of TB in these periods, adjusting for individual and time-bound confounders.

Results
The crude TB rate for the combined pregnancy and post-partum period was 15.4 per 100,000 person years (py), significantly higher than outside of pregnancy (9.1 per 100,000 py, p=0.02). Adjusting for age, region and socio-economic status the post-partum TB risk was significantly higher than outside pregnancy (IRR 1.95, CI 1.24-3.07), whereas there was no significant increase during pregnancy (IRR 1.29, CI 0.82-2.03). These observations were confirmed in the SCCS (IRR 1.62, CI 1.01-2.58 and 1.03, CI 0.64-1.65 respectively).
Conclusions

The incidence of TB diagnosis is significantly increased post-partum. Although we did not find an increase during pregnancy, the post-partum incidence may reflect an increase during pregnancy given diagnostic, immunological and administrative delays. Clinicians’ awareness should be improved and the effectiveness of public health policy measures such as targeted screening of pregnant and post-partum women in high-risk groups should be evaluated.

Mesh Terms: Pregnancy, Tuberculosis, Risk Factors, incidence studies
Introduction

Globally, tuberculosis (TB) is a leading cause of morbidity and premature mortality, and one of the most important causes of death amongst 15-44 year old women. In developed countries a rise in the number of pregnant patients with tuberculosis has been described, as a result of increasing numbers of cases amongst migrants and ethnic minority groups with younger age distribution.

In the United Kingdom, recent rises in TB incidence have been associated with a change in the epidemiology of TB with the disease now affecting younger age groups and immigrants from high prevalence countries. TB rates in pregnant women are expected to be higher because of the different demographic composition of this group, and the fact that women from high prevalence areas often have a higher total period fertility rate. Two local studies from large London teaching hospitals provided incidence estimates in pregnant women between 3-5 times higher than the respective local background rate (153 to 252 per 100,000 maternities). It, however, remains unclear whether pregnancy increases the risk of TB or if this observation relates to the higher occurrence of the disease in high-risk groups.

Pulmonary as well as extra-pulmonary Tb adversely affect the health of mother and child. TB in pregnancy has been shown to respond to standard treatment, but considerable delays in diagnosis have been observed amongst these women, and delays in treatment initiation are associated with poorer outcomes for mother and foetus. A possible intervention to avoid these adverse outcomes will be to promote active case finding for TB in pregnant women. This will, however, only be appropriate if pregnancy itself increases the risk of TB. In
the UK screening is recommended for HIV positive mothers and those with recent exposure to active TB only\textsuperscript{12}. However, literature from elsewhere has promoted the screening of the wider pregnant population\textsuperscript{13}.

There is currently insufficient evidence on the epidemiology of TB in pregnancy globally, and no data on whether pregnancy increases the risk of TB. The UK General Practice Research Database (GPRD) provided a suitable cohort to investigate the epidemiology of TB in pregnancy in the UK and determine whether TB is an independent risk factor for TB in order to inform future public health and screening policy. Some of the results of the study have been previously reported in the form of an abstract\textsuperscript{14}

**Methodology**

We estimated incidence rates for TB in pregnancy, six months postpartum and outside of pregnancy, modelled adjusted incidence rate ratios in a retrospective cohort study and performed a nested self-controlled case series (SCCS) analysis, which adjusts for all non-time-dependent confounders (see analysis and figure 1).

*Please insert here figure 1: schematic of study populations (a) and exposure times (b) for cohort and self-controlled case series studies*
Study population

The study used the General Practice Research Database (GPRD), which contains records from 460 Practices across the UK, forming a generalisable dataset of 5.5% of the UK population. Data derived from GP practices are audited, tested and checked for quality assurance by GPRD staff and independent testers.

For the cohort study, all women with pregnancies occurring between 1996 and 2008 were enrolled in the study with their entire individual cohort time potentially ranging from December 1987 to December 2009. Women had to have at least one clinical code (Read or OXMIS codes in the UK General Practice coding systems) associated with pregnancy in their medical records. We included all stillbirths, terminations and miscarriages. Women with insufficient information to determine either start or end date of the pregnancy were excluded from the study.

For the nested SCCS approach, pregnant women with at least one Read code for TB were selected from the cohort. For individuals enrolled in this analysis, TB could have occurred before, during or after pregnancy.

Defining exposure and outcome

Pregnancy was defined as any conception, regardless of the outcome. The start of the pregnancy was defined using the recorded last menstrual period (LMP) or calculated from the expected delivery date (EDD). The pregnancy end date was defined as the date of the recorded pregnancy outcome. If the start of a subsequent pregnancy overlapped with the
end of a previous one, the start date of the second pregnancy was considered the end of the first pregnancy.

TB disease was either culture-confirmed disease caused by any species from the *Mycobacterium tuberculosis* complex or, in the absence of culture confirmation, the presence of clinical and/or radiological signs and/or symptoms compatible with tuberculosis, and/or a decision by the clinician to treat the patient with a full course of anti-tuberculosis treatment.

These definitions were operationalised by choosing the respective Read codes from the database (TB events). We used the recording date for the TB diagnosis as our best estimate for the onset of TB disease. We counted repeated TB codes as new episodes if they were entered more than 12 months after the initial event. This rule excludes new episodes in women, who are currently on TB treatment. Socio-economic status was measured using the UK index of multiple deprivations, a composite indicator based on employment, wealth and assets in a small area.

Individual-level exposure factors, such as BCG status, socio-economic status, region, and marital status were available from the patient’s records. Time-bound exposure factors, such as age and time period (before 2000, 2001-2005, 2006-2010) were calculated using the mid year point of the patient’s birth year.

Individuals entered the cohort either 90 days after their first practice registration, the up to standard date of the practice, or reaching the age of 13, whichever came last. Person time
and events were censored at the end of practice registration (including death), last collection date for the practice, transfer-out date from the practice, or reaching the age of 50, whichever came first.

The database was cleaned and cross-checked. Other information from the individual’s record, such as birth outcome, birth year, other pregnancies, death date or practice transfers were used to validate pregnancy and TB dates. The GPRD helped cross-checking death data against UK death records. Pregnancies with identical start or end dates were removed as duplicates.

Data analysis

Estimation of incidence

The crude incidence rate of TB disease in the cohort overall, during pregnancy, in the immediate post-pregnancy period and outside of pregnancy were calculated as the number of TB events per person-time at risk. The countrywide estimate was also weighted for different population sizes across UK regions.

We compared the incidence rates (IR) in pregnancy and post-partum with the rate outside of pregnancy, calculating IR ratios. A Poisson regression model was built, allowing the effect of these three strata to be adjusted for confounding factors. Each was added stepwise to the model and retained, if it changed the IR rates for the strata and a likelihood ratio test was significant (p<0.05), indicating the model with confounder explains the data better than the
Variables where effect modification is clinically plausible were tested for interaction, taking the magnitude of the observed effect and the width of confidence intervals into account in order to decide whether associations are clinically as well as statistically significant.

The self-controlled case series

In order to determine whether pregnancy is an independent risk factor for TB we performed a nested SCCS. This method, which has been validated elsewhere\textsuperscript{17,18}, only includes individuals who have an event and exposure (n=177, figure 1). It compares the incidence of the event (i.e. TB) during exposure time to the respective incidence in a “control time” (i.e. comparing incidence in the same person during a risk period with a non-risk period). The exposure times in this study are times during pregnancy and the six months following pregnancy, and control times all other person times before and after pregnancy (figure 1). The method implicitly controls for all non time-dependent confounders of TB, such as country of origin or ethnicity. Age and period were adjusted for by including these variables in the model. The model was fitted using conditional Poisson regression and has similar statistical power compared with cohort studies\textsuperscript{17}.

We carried out a sensitivity analysis by excluding the 6 months before each pregnancy from calculating the background risk as per protocol and in keeping with the literature\textsuperscript{8}. This is because there is a theoretical possibility that women with worse health (e.g. unrecognised TB) are less willing to conceive, hence artificially lowering the pregnancy rate during this period. All data analysis was carried out using STATA 11.1.
Sample size considerations

For the incidence study we estimated that about 35,000 person years or 50,000 pregnancies would be needed to detect the threefold higher TB incidence rate in pregnancy seen in some local studies\(^8\text{-}^9\) with 80% power and 5% significance, assuming a UK background rate of 13 per 100,000.

For the SCCS we estimated that 25 exposure-time events and 150 control-time events would be sufficient to detect a risk ratio of 1.7, whereas 100 and 700 events would allow detecting a risk ratio of 1.33 with 80% power at a 5% significance level.

Results

A total of 192,801 women with a total of 264,136 pregnancies (1-14 per woman) were included in the cohort study. Of the 516,589 women with pregnancies in the GPRD, about 271,625 (52.6%) were excluded, because their pregnancies were outside of the 12-year observation period and a further 52,163 (10.1%), because pregnancy dates could not be accurately determined from their records. Table 1 shows that the geographical and age distribution of included women is similar to all pregnancies ever reported to the GPRD.

Please insert here table 1: Comparison of geographical and age characteristics between pregnancies in the cohort and all pregnancies in the GPRD.
Average follow up time was 9.1 years (7 days to 21.8 years) giving a total of 1,745,834 person years. Of this time, 171,765 years were spent during pregnancy and 114,866 years in the 180 days post pregnancy. The median pre-pregnancy follow up time was similar for women with TB (2.57 years, intraquartile range 0.7-5.19 years) and women without TB (median 2.28 years, intraquartile range 0.74-5.2 years, p=0.4).

The mean age at pregnancy was 29.5 years (range 13-50). The mean age for cohort entry was 25.6 years (range 13-48.9) and cohort exit 35.1 years (range 13.7-50). The median length of pregnancy was 39.6 weeks (range 2-45), and two peaks of gestational length were observed, a smaller at 10.6 and a larger at 39.9 weeks. Most pregnancies resulted in a not further specified birth (79%), a miscarriage (9.1%), a caesarean section (6.2%), or an assisted (e.g. instrumental) delivery (5.2%). There were 405 records (0.15%) of neonatal deaths.

A total of 177 TB events were identified in the cohort, 22 of these occurring during pregnancy (8, 7 and 7 in the first, second and third trimester respectively) and 22 in the 180 days after pregnancy. The mean age at TB diagnosis was 30.1 years (range 13.4-44). None of the women had more than one TB episode. Most TB events were recorded in London (31%), followed by the Midlands (25%), North England (20%), South England (16%) and Scotland, Wales and Northern Ireland (9%).

61.6% of the TB events were not further specified. Amongst the remainder, extra-pulmonary TB (n=43) was more frequent than pulmonary TB (n=25). This seemed more pronounced in the TB events during or 180 days after pregnancy, where extra-pulmonary TB was found in
13 of 44 cases compared to 30 of 133 cases outside of pregnancy. The most common sites of extra-pulmonary TB were genitourinary (n=11) and lymphatic TB (n=8).

Only one patient with a TB event in the cohort died and was censored 7 years after her pulmonary TB was diagnosed (outside pregnancy); it is improbable that the death was related to the TB.

The cohort study

The overall crude incidence rate of TB diagnosis was 10.1 (CI 8.7-11.8) per 100,000 person years. Taking into account the different representations of the regions, the weighted crude incidence rate over the cohort time (1987-2009) for the UK was 10.5 per 100,000.

The crude incidence rates for TB during pregnancy were 12.8 per 100,000 (CI 8-19.4). TB rates during the 180-day postpartum period (19.2 per 100,000, CI 12-29) were higher than outside of pregnancy (9.1 per 100,000, CI 7.6-10.8, p=0.001). TB events during pregnancy and the 180 day postpartum combined (15.4 per 100,000, CI 11.2-20.6) were significantly more common compared to the rate outside of pregnancy (crude incidence rate ratio 1.68, CI 1.17-2.38, p=0.02).

TB incidence rate ratios (IRR) adjusted for age, socio-economic status, region of residence and BCG vaccination status show a significantly increased incidence of TB in the 180 days after pregnancy (IRR 1.95, CI 1.24-3.07, p=0.004), but not during pregnancy (IRR 1.29 CI 0.82-2.03, table 2). The model also shows increased TB rates in London and more deprived areas.
and decreased rates amongst those with a record of BCG immunisation (Table 2). Ethnicity and country of birth are not included in the Poisson model (insufficient data); however these individual level confounders are adjusted for in the SCCS model.

Please insert here table 2: Poisson model of incidence rate ratios for TB

**The self-controlled case series**

The final SCCS model confirmed the results of the Poisson analysis (table 3). Adjusting for all non-time bound confounders, the time period of observation and patients’ age, the incidence rate ratio of TB during pregnancy (IRR 1.03, CI 0.64-1.65) is not significantly increased compared with the risk outside of pregnancy. However, the TB risk is significantly increased in the 6 month period after pregnancy (IRR 1.61, CI 1.01-2.58, p=0.04).

Please insert here table 3: Analysis of the self controlled case series showing incidence rate ratios for TB

The postpartum period was explored in greater detail, using the same methodology. We found an upward trend immediately post pregnancy peaking at 90 days postpartum (IRR 1.74, CI 0.95-3.19) and a gradual decrease to an IRR of 1.53 (CI 0.79-2.96) and 1.19 (CI 0.55-2.58) at 180 days and 270 days postpartum respectively (Fig. 2).

Please insert here fig. 2: Incidence rate ratios for different time periods.
Compared to the background risk, we did not find a significantly decreased TB risk in the six months prior to pregnancy (IRR 0.53, CI 0.24-1.15, p=0.11), and exclusion of this time period to calculate background risk had a minor effect on model estimates.

Discussion

This is first primary care based cohort study, which quantifies the risk of TB during pregnancy and postpartum. We found a significantly increased risk in the six months following the pregnancy, but not during pregnancy. Considering diagnostic, administrative and immunological delays, TB risk during pregnancy is almost certainly also increased. The risk remained significantly elevated when adjusted for all individual-level risk factors and known time-dependent risk factors as demonstrated in the SCCS.

This study benefits from using a very large, representative and well maintained primary care database, but remains an observational study based on data recorded for clinical purposes. Our overall TB incidence rate was slightly lower than current UK TB rates because it represents an average over the cohort time (1987-2009). Demographically, our cohort is similar to the entire cohort of pregnancies ever reported to the GPRD. Adjustment for confounding in the Poisson model was limited to well-recorded variables in the GPRD; however these subject characteristics were adjusted for by design in the nested SCCS.

Following cleaning and cross-validation, systematic misclassification is unlikely for exposure or outcome variables. Underascertainment of pregnancies is possible, because diagnosis and
recording of early miscarriages can depend on health seeking behaviour. We may have underestimated TB risk during pregnancy, because TB is associated with adverse birth outcomes\textsuperscript{10,11,19} and probably miscarriage. The effect of this is likely minimal and primary care data are probably less vulnerable to underrecording miscarriages compared with other data sources\textsuperscript{20} and our descriptive analysis demonstrated that we captured many miscarriages. We limited analysis to women with pregnancies between 1996 and 2008 and those where a start and end date of the pregnancy could be ascertained. This could have led to underestimating TB episodes during pregnancy, especially in patients born abroad/in high prevalence countries, because of late pregnancy presentations and poorer recording of miscarriages. However, recording of TB and pregnancies is done independently in UK primary care. Our sampling method is therefore unlikely to have introduced significant bias (table 1).

The debate about an association between TB and pregnancy is unresolved\textsuperscript{21}, although early studies failed to demonstrate a clear association\textsuperscript{22}. Internationally there are no recent incidence estimates in non-HIV infected pregnant populations. A previous UK-wide study of TB in pregnancy based on an obstetric card return scheme\textsuperscript{20} (4.2 per 100,000) may have underestimated incidence\textsuperscript{23}, because additional case finding was limited and it was restricted to obstetricians, who do not normally see miscarriages. Comparatively\textsuperscript{8,9} low extra-pulmonary TB rates in this study\textsuperscript{20}, suggested an under-ascertainment of clinically less obvious cases. Our incidence estimates were lower than previous estimates from high risk areas within London\textsuperscript{8,9}, explainable by the different setting in our study.
Complex maternal immune system changes during pregnancy prevent allograft rejection of the foetus. One mechanism is the partial inhibition of the cellular immune system via cytokines (e.g. IL-10, TGF-β)\textsuperscript{24,25} through an increase of specific T regulatory cell populations. The susceptibility for specific infections such as influenza can increase during pregnancy\textsuperscript{26}.

Mycobacteria cause a predominantly cellular immune response and recent studies found an up-regulation of specific T-cell inhibiting cytokines (IL-10, TGF-β) during TB reactivation\textsuperscript{27}.

The physiological down-regulation of the cellular immune system is one possible explanation of the higher incidence rates of TB during and immediately after pregnancy.

The significantly increased risk in the 6 month postpartum period may reflect a delay between pregnancy and risk increase for TB. Likely explanations fall into three categories – administrative, immunological and medical. Since we took the first recorded TB date on the GPRD as event date, an administrative delay between diagnosis and recording of TB disease is possible. It is also likely that immunological changes gradually increase TB susceptibility during pregnancy as the expression of T-regulator cells are partially oestrogen-dependent\textsuperscript{25} and increasing throughout the pregnancy\textsuperscript{25,28}. After delivery, these changes gradually normalise again.

Diagnostic delays have been described elsewhere\textsuperscript{8,9}, despite the high level of access to healthcare enjoyed by pregnant women. Late presentations\textsuperscript{8,9}, an ambiguity of symptoms, frequently mimicking physiological pregnancy changes\textsuperscript{29} and a conservative approach to investigations (e.g. X-rays) have been blamed for these delays\textsuperscript{30}. Delays in treatment initiation are associated with poorer outcomes for mother and foetus\textsuperscript{10,19} and can be more pronounced in women of minority ethnic background or those who recently arrived from
high prevalence areas\textsuperscript{31}. These delays present a limitation to this study, and the combination of these delays is a possible reason for the failure to demonstrate a significant TB risk during pregnancy and the anticipation of these prompted us to propose an analysis of the six months post-pregnancy in our protocol.

In conclusion we found that there was an increased incidence of TB diagnosis in mothers postpartum which probably reflects an increase in TB incidence during pregnancy, given the diagnostic, immunological and administrative delays described above. About 25\% of all events occurred during pregnancy and the postpartum (16\% of total person time). To avoid adverse outcomes for mother and child it is vital to recognise and treat TB in pregnancy early\textsuperscript{9-11;19} making diagnostic delays unacceptable. This suggests that further research is needed on the cost effectiveness of active case finding for TB in pregnant women. Research from Zimbabwe\textsuperscript{32} found that untargeted active case finding in a high TB incidence area may be an effective tool for increasing case detection and the role of simple and cheap interventions such as sputum smears during antenatal care should be evaluated in high TB incidence countries. Replication of our observations in cohort studies from TB high burden countries may provide support for such an approach. In low incidence countries clinicians should have an elevated index of suspicion for TB during the pregnant and postpartum period, aiming to exclude this diagnosis particularly in those from high incidence countries. Our results may prompt a rethink of current TB prevention strategies and increase clinical awareness of TB during pregnancy and the postpartum period.

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Conflict of Interest

None to declare

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Contributors

DZ undertook the analysis and wrote the paper with contributions from MK, NR and IA. IA conceived the idea and NR supervised the statistical analysis. All authors have approved the final manuscript. IA is guarantor.
Figure 1: schematic of study populations (a) and exposure times (b) for cohort and self-controlled case series studies

Figure 1a Study population

Figure 1b Exposure times*

*The schematic provides an overview for censoring and risk periods used in the cohort study as well as the self-controlled case series study.
Table 1: Comparison of geographical and age characteristics between women included in the cohort and all pregnancies in the GPRD

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<th>Geographical region</th>
<th>included women (pregnancies 1996-2008)</th>
<th>all women (pregnancies 1987-2009)</th>
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<tr>
<td>North England</td>
<td>38169 19.8%</td>
<td>99034 19.2%</td>
</tr>
<tr>
<td>Midlands</td>
<td>52882 27.4%</td>
<td>124861 24.2%</td>
</tr>
<tr>
<td>South England</td>
<td>53043 27.5%</td>
<td>139027 26.9%</td>
</tr>
<tr>
<td>London</td>
<td>25879 13.4%</td>
<td>79280 15.3%</td>
</tr>
<tr>
<td>Scotland, Wales and Northern Ireland</td>
<td>22828 11.8%</td>
<td>74387 14.4%</td>
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<th>all women (pregnancies 1987-2009)</th>
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<td>&lt;15 years</td>
<td>287 0.1%</td>
<td>1631 0.3%</td>
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<td>15-19 years</td>
<td>15917 8.3%</td>
<td>57918 11.2%</td>
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<tr>
<td>20-24 years</td>
<td>31640 16.4%</td>
<td>96045 18.6%</td>
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<td>25-29 years</td>
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<td>30-34 years</td>
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<td>27347 14.2%</td>
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<td>40-44 years</td>
<td>4648 2.4%</td>
<td>17432 3.4%</td>
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<tr>
<td>45-50 years</td>
<td>250 0.1%</td>
<td>4378 0.8%</td>
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| All                            | 192801                                  | 516589                            |
Table 2: Poisson model of incidence rate ratios for TB

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<tr>
<th>Category</th>
<th>TB events (n)</th>
<th>person years</th>
<th>IR</th>
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<th>IRR</th>
<th>95% CI (IRR)</th>
<th>p Value</th>
<th>LR Test</th>
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<td>Outside of pregnancy*</td>
<td>133</td>
<td>1,459,203</td>
<td>9.11</td>
<td>7.63</td>
<td>10.8</td>
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<td>During pregnancy</td>
<td>22</td>
<td>171,765</td>
<td>12.81</td>
<td>8.03</td>
<td>19.39</td>
<td>1.29</td>
<td>0.82</td>
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<td>6 month post pregnancy</td>
<td>22</td>
<td>114,866</td>
<td>19.15</td>
<td>12</td>
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<td>1.95</td>
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<td>Aged 20-29*</td>
<td>80</td>
<td>630,464</td>
<td>12.69</td>
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<td>Aged up to 19</td>
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<td>162,586</td>
<td>6.77</td>
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<td>BCG vaccination</td>
<td>16</td>
<td>286,571</td>
<td>5.58</td>
<td>3.19</td>
<td>9.07</td>
<td>0.58</td>
<td>0.34</td>
<td>0.98</td>
</tr>
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<td>South England*</td>
<td>29</td>
<td>469,422</td>
<td>6.18</td>
<td>4.14</td>
<td>8.87</td>
<td>1.00</td>
<td>reference category</td>
<td></td>
</tr>
<tr>
<td>London</td>
<td>54</td>
<td>185,829</td>
<td>29.06</td>
<td>21.83</td>
<td>37.92</td>
<td>3.63</td>
<td>2.28</td>
<td>5.76</td>
</tr>
<tr>
<td>Midlands</td>
<td>43</td>
<td>487,822</td>
<td>8.81</td>
<td>6.38</td>
<td>11.87</td>
<td>1.17</td>
<td>0.72</td>
<td>1.90</td>
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<td>Northern England</td>
<td>35</td>
<td>384,548</td>
<td>9.1</td>
<td>6.34</td>
<td>12.66</td>
<td>1.05</td>
<td>0.63</td>
<td>1.75</td>
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<tr>
<td>Scotland Wales and NI</td>
<td>16</td>
<td>218,213</td>
<td>7.33</td>
<td>4.19</td>
<td>11.91</td>
<td>0.96</td>
<td>0.51</td>
<td>1.78</td>
</tr>
<tr>
<td>Deprivation quintile 1*</td>
<td>12</td>
<td>341,793</td>
<td>3.51</td>
<td>1.81</td>
<td>6.13</td>
<td>1.00</td>
<td>reference category</td>
<td></td>
</tr>
<tr>
<td>Deprivation quintile 2</td>
<td>18</td>
<td>304,738</td>
<td>5.91</td>
<td>3.5</td>
<td>9.34</td>
<td>1.50</td>
<td>0.72</td>
<td>3.12</td>
</tr>
<tr>
<td>Deprivation quintile 3</td>
<td>35</td>
<td>317,481</td>
<td>11.02</td>
<td>7.68</td>
<td>15.33</td>
<td>2.61</td>
<td>1.35</td>
<td>5.05</td>
</tr>
<tr>
<td>Deprivation quintile 4</td>
<td>53</td>
<td>367,564</td>
<td>14.42</td>
<td>10.8</td>
<td>18.86</td>
<td>2.98</td>
<td>1.57</td>
<td>5.65</td>
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<tr>
<td>Deprivation quintile 5</td>
<td>59</td>
<td>414,258</td>
<td>14.24</td>
<td>10.84</td>
<td>18.37</td>
<td>3.94</td>
<td>2.08</td>
<td>7.46</td>
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</tbody>
</table>

IR denotes the unadjusted incidence rates for all categories, 95% CI (IR) the 95% confidence interval for the incidence rates, IRR the adjusted incidence rate ratio from the Poisson model adjusting for the other variables in the model, 95%CI (IRR) the respective confidence interval, p values denote the significance for each variable within the Poisson model and LR Test the p value for the likelihood ratio test, which was used to decide whether variables should be included in the model. Deprivation quintile refers to the quintile in the UK Index of Multiple deprivation (IMD), where 1 is the least and 5 the most deprived quintile. Marital status (p=0.66) and time period (LRT p=0.57) were not included in the final model based on their LRT and the impact on the effect sizes. *denotes a reference category with a default IRR of 1.
Fig 2: Adjusted incidence rate ratios for different time periods

The adjusted incidence rate ratios for different pregnancy and post-partum periods from the self controlled case series model (adjusted for age and period). Bars denote 95% confidence intervals. Reference is the time outside of pregnancy (IRR 1), denoted by the x axis line.

Table 3: Analysis of the self controlled case series showing incidence rate ratios for TB

<table>
<thead>
<tr>
<th></th>
<th>TB events</th>
<th>person yrs</th>
<th>IRR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outside of pregnancy*</td>
<td>133</td>
<td>1448</td>
<td>1</td>
<td>reference category</td>
<td></td>
</tr>
<tr>
<td>During pregnancy</td>
<td>22</td>
<td>167</td>
<td>1.03</td>
<td>0.64</td>
<td>1.65</td>
</tr>
<tr>
<td>6 month post pregnancy</td>
<td>22</td>
<td>113</td>
<td>1.62</td>
<td>1.01</td>
<td>2.58</td>
</tr>
<tr>
<td>Aged 20-29*</td>
<td>80</td>
<td>681</td>
<td>1.00</td>
<td>reference category</td>
<td></td>
</tr>
<tr>
<td>Aged up to 19</td>
<td>11</td>
<td>125</td>
<td>0.81</td>
<td>0.32</td>
<td>2.06</td>
</tr>
<tr>
<td>Aged 30-39</td>
<td>74</td>
<td>742</td>
<td>0.79</td>
<td>0.44</td>
<td>1.42</td>
</tr>
<tr>
<td>Aged 40-49</td>
<td>12</td>
<td>179</td>
<td>0.68</td>
<td>0.23</td>
<td>2.04</td>
</tr>
<tr>
<td>Before year 2000*</td>
<td>53</td>
<td>555</td>
<td>1.00</td>
<td>reference category</td>
<td></td>
</tr>
<tr>
<td>years 2000-2005</td>
<td>77</td>
<td>676</td>
<td>0.83</td>
<td>0.52</td>
<td>1.34</td>
</tr>
<tr>
<td>years 2006-2010</td>
<td>47</td>
<td>497</td>
<td>0.59</td>
<td>0.30</td>
<td>1.14</td>
</tr>
</tbody>
</table>

IRR denotes the adjusted incidence rate ratio from the conditional Poisson model of the SCCS, 95% CI the respective 95% confidence interval. *denotes a reference category with a default IRR of 1
Fig 2: Adjusted incidence rate ratios for different time periods
248x140mm (300 x 300 DPI)
Figure 1a Study population
338x270mm (96 x 96 DPI)
Figure 1b Exposure times*
228x135mm (96 x 96 DPI)