Tuberculosis in pregnancy: an estimate of the global burden of disease

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Summary

Background The estimated number of maternal deaths in 2013 worldwide was 289 000, a 45% reduction from 1990. Non-obstetric causes such as infectious diseases including tuberculosis now account for 28% of maternal deaths. In 2013, 3·3 million cases of tuberculosis were estimated to occur in women globally. During pregnancy, tuberculosis is associated with poor outcomes, including increased mortality in both the neonate and the pregnant woman. The aim of our study was to estimate the burden of tuberculosis disease among pregnant women, and to describe how maternal care services could be used as a platform to improve case detection.

Methods We used publicly accessible country-level estimates of the total population, distribution of the total population by age and sex, crude birth rate, estimated prevalence of active tuberculosis, and case notification data by age and sex to estimate the number of pregnant women with active tuberculosis for 217 countries. We then used indicators of health system access and tuberculosis diagnostic test performance obtained from published literature to determine how many of these cases could ultimately be detected.

Findings We estimated that 216 500 (95% uncertainty range 192 100–247 000) active tuberculosis cases existed in pregnant women globally in 2011. The greatest burdens were in the WHO African region with 89 400 cases and the WHO South East Asian region with 67 500 cases in pregnant women. Chest radiography or Xpert RIF/MTB, delivered through maternal care services, were estimated to detect as many as 114 100 and 120 300 tuberculosis cases, respectively.

Interpretation The burden of tuberculosis disease in pregnant women is substantial. Maternal care services could provide an important platform for tuberculosis detection, treatment initiation, and subsequent follow-up.

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Introduction

In the past two decades, there have been major declines in maternal mortality. The estimated number of maternal deaths in 2013 worldwide was 289 000, a 45% reduction from 1990.[1] Globally, the leading causes of maternal death include direct obstetric causes, such as haemorrhage and hypertensive disorders; however, other non-obstetric causes including infectious diseases are now responsible for 28% of maternal mortality worldwide.[2] Despite widespread implementation of the DOTS strategy and progress towards the tuberculosis-specific targets articulated in the Millennium Development Goals, tuberculosis remains a significant global public health challenge. In 2013, 3·3 million tuberculosis cases and 510 000 tuberculosis deaths were estimated to occur in women globally.[3]

The presence of tuberculosis disease during pregnancy, delivery, and post partum is known to result in unfavorable outcomes for both pregnant women and infants.[4,5] These outcomes include a roughly two-fold increased risk of premature birth, low birthweight, intrauterine growth retardation, and a six-fold increase in perinatal death,[6,7] especially in women who are co-infected with HIV.[4,8–11] Tuberculosis disease in the infant is also an outcome of concern. In the high tuberculosis and HIV prevalence setting of Durban, South Africa, 15% of mothers with active tuberculosis transmitted the infection to their newborns within the first 3 weeks of life.[6]

Clinical diagnosis of tuberculosis in pregnant women can be difficult due to non-specific symptoms related to the physiological response to pregnancy.[4] For pregnant women in most countries with a high tuberculosis burden, the current standard practice of care for tuberculosis screening and diagnosis is the same as that used to detect disease in the general population. Recommended diagnostic tests may include smear microscopy, culture, and molecular DNA detection methods such as Xpert MTB/RIF.[4] Shielded chest radiography, which poses minimal risk to the fetus, is also recommended in women with a recent tuberculosis contact.[4–6] In settings of high HIV burden, the WHO symptom screen and Xpert MTB/RIF are recommended. Once diagnosis is confirmed, the WHO recommendation for tuberculosis treatment in pregnant women is the same as for non-pregnant women,[12] even for HIV-positive women on antiretroviral therapy (ART).[5,12]

The burden of tuberculosis disease among pregnant women is not known. Consequently, there are few data to guide efforts to reduce the tuberculosis burden in this population. Therefore, the objectives of this paper were to

(1) estimate the global and country-level burden of tuberculosis disease among pregnant women; (2) determine how many pregnant women could benefit from tuberculosis diagnosis integrated with maternity care; and (3) estimate the number of cases that could be detected using three different diagnostic tests.

Methods

Estimating the burden of tuberculosis in pregnant women

We derived an estimate of the number of pregnant women with active tuberculosis in 217 countries using publicly accessible country-level estimates of the following parameters: total population,[13] distribution of the total population by age and sex,[13] crude birth rate,[14] estimated prevalence of active tuberculosis,[15] and case notification data by age and sex.[15] In each country, the estimated tuberculosis prevalence rate was adjusted to reflect more accurately the prevalence of tuberculosis among women of childbearing age (15–44 years) by using the ratio of smear-positive cases notified in women of childbearing age relative to the smear positive notification rate in the full population. The calculated adjusted tuberculosis prevalence rates by region are shown in table 1 together with case notification rates in women aged 15–44 years, and in the full population (as reported by WHO).[16] The point estimate of tuberculosis cases in pregnant woman was obtained using the following formulae:

Formula 1·1:

$$\textit{Case notification rate women (age 15–44 years) smear positive} = \frac{\textit{Total N new smear positive cases notified woman (15–44 years)}}{\textit{Full country population} \times \textit{proportion of population women age 15–44 years}}$$

Formula 1·2:

$$\textit{Estimated tuberculosis prevalence rate women (age 15–44 years)} = \frac{\textit{Case notification rate woman (age 15–44 years) smear positive}}{\textit{Full country case notification rate smear positive} \times \textit{Full country tuberculosis prevalence rate}}$$

Formula 1·3:

$$\textit{Estimated number of tuberculosis cases in pregnant women} = \textit{Total population} \times \textit{crude birth rate} \times \frac{\textit{280 days per pregnancy}}{\textit{365 days per year}} \times \textit{Estimated tuberculosis prevalence rate women (age 15–44 years)}$$

We multiplied the total population by the crude birth rate, and then by the average gestational period (280 days), to calculate the number of pregnant days, per country, in 2011. By dividing this number by 365 days, we estimated the number of women pregnant on any given day during the year. Finally, by multiplying this number by the age-specific and sex-specific tuberculosis prevalence, we calculated a point estimate of the number of pregnant women with active tuberculosis in each country in 2011. In summary, formula 1·1 was used to calculate the case notification rate in women aged 15–44 years. This rate was used to estimate the total prevalence in women aged 15–44 years (formula 1·2). Formula 1·3 was then used to estimate the total number of tuberculosis cases in pregnant women. Country-level estimates were added together to generate regional and global estimates of tuberculosis burden.

Monte Carlo simulations were used to define the uncertainty ranges (UR; 2·5 and 97·5 percentiles) around point estimates. To calculate ranges, we used formulas 1·1 to 1·3, and randomly and individually sampled three key parameters (crude birth rate, total population, and estimated prevalence of tuberculosis) 1000 times. Reported maxima and minima for each key input informed the variability of the distributions, which were assumed to be Gaussian based on best fit in comparison to other two-tailed distributions. For each distribution, the mean was selected as the medium-level estimate of the primary data.[12,13] The variance was defined as three standard deviations from the mean, as the primary data sources provided high-level and low-level data that represented the highest and lowest possible data points.[12,13]

Estimating the burden of tuberculosis in pregnant women among those who access maternal health services

We estimated the proportion of tuberculosis cases with access to antenatal and labour or delivery care in each country by multiplying the country-level estimate of tuberculosis cases by two different indicators of access: at least one antenatal care visit (antenatal care services),[17,18] and birth attended by skilled health professional (labour and delivery services).[18] The WHO regional averages for these statistics are shown in table 1.

Estimating the burden of tuberculosis detected in pregnant women

We present three hypothetical diagnostic scenarios, each using a different single test that could be implemented in the maternal care setting. Tests considered include: (1) the present standard of care for tuberculosis diagnosis in most settings (sputum smear microscopy); (2) a test that is currently recommended in pregnant women with high sensitivity but only moderate specificity (chest radiography for detection of active tuberculosis); and (3) a recently recommended test with high sensitivity and excellent specificity (Xpert RIF/MTB). WHO symptom screen with subsequent Xpert RIF/MTB was not explicitly

	Epidemiological data (rate per 100 000)				Health system access (%)	
	Case notification smear positive, 2011[16]	New smear positive case notification (women aged 15–44), 2011[16]	Estimated prevalence of tuberculosis, all forms, 2011[15]	Estimated prevalence of tuberculosis (women aged 15–44), all forms*	Antenatal care services[17,18] (at least one antenatal care visit)	Labour and delivery services[18] (births attended by skilled health personnel)
African Region	70	96	293	411	84	60
Region of the Americas	13	11	36	34	95	90
Eastern Mediterranean Region	28	35	171	219	78	75
European Region	9	8	56	52	97	99
South-East Asia Region	59	54	271	250	83	68
Western Pacific Region	32	22	131	92	90	85

*Calculated using methods described in main text.

Table 1: **Epidemiological prevalence data and health system access by WHO region**

considered because our Xpert RIF/MTB test scenario assumes that the full population would get Xpert RIF/MTB as the initial test. These tests serve as examples, that could be more or less relevant, depending on the local epidemiology of the setting.

To assess the potential range of effect of different tests, we assumed that, in each country, all pregnant women with access to antenatal and labour or delivery care would receive only the single tuberculosis test described in each diagnostic scenario. We assumed that women were only being diagnosed within the framework of maternal care services, and that the test offered in these settings may differ from testing algorithms routinely offered through the national tuberculosis programme.

We estimated the proportion of cases that could be detected using these tests for initial case detection by multiplying each country-level estimate (after adjustment for access to maternal health services) by the reported test sensitivity. Before investigating case detection by test, the adjusted country-level tuberculosis prevalence estimate was subdivided into different types of disease (pulmonary-smear positive, pulmonary-smear negative, or extra-pulmonary) with WHO data for disease classification by country.[15] Estimates of test performance were obtained from the literature[19,20] and are summarised in appendix. Test sensitivity in pregnant women was assumed to be the same as in the general population because there are no data to support other assumptions. At all stages of the analysis, any missing data were imputed with the average regional values from which the country in question was located. A summary of missing data by variable is shown in the appendix. All analysis was done in Microsoft Excel.

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	Mean (95% uncertainty range)	Rate per 1000 pregnant women (95% uncertainty range)	Percentage of global burden
All countries combined	216 500 (192 100–247 000)	2·1 (1·8–2·4)	..
African Region	89 400 (74 200–110 500)	3·6 (3·0–4·5)	41%
Region of the Americas	4800 (3900–6000)	0·4 (0·3–0·5)	2%
Eastern Mediterranean Region	28 500 (19 700–41 900)	2·3 (1·6–3·4)	13%
European Region	4900 (3800–6300)	0·6 (0·5–0·8)	2%
South-East Asia Region	67 500 (52 000–87 100)	2·4 (1·9–3·1)	31%
Western Pacific Region	21 400 (19 400–23 700)	1·1 (1·0–1·2)	10%

Table 2: **Total number of active tuberculosis cases in pregnant women, rate per 1000 pregnant women and percentage of global burden by WHO region and combined**

Results

We estimated that there were 216 500 (95% UR 192 100–247 000) pregnant women with tuberculosis globally in 2011. The number of tuberculosis cases estimated in each of the 217 countries is provided in appendix. As shown in table 2, the Africa WHO Region and South East Asia WHO Region carry the greatest burden of tuberculosis cases among pregnant women, with 89 400 (41% of global burden) and 67 500 (31% of global burden) cases, respectively. The country with the highest number of cases in pregnant women was India (44 500 or 21% of the global tuberculosis burden), which reflects the high tuberculosis burden in the general population, the country's large population, and its high birth rate. Estimates for each of the 22 WHO high tuberculosis burden countries are shown in table 3.

See Online for appendix

When we considered the proportion of tuberculosis cases with access to maternity services in each country that could potentially benefit from tuberculosis screening and diagnosis through either antenatal care or labour and delivery services, the number of tuberculosis cases that could be reached globally was 167 200 (antenatal care) or 123 500 (labour and delivery; table 4). Results for each of the 217 countries are shown in the appendix.

	Mean (95% uncertainty range)	Rate per 1000 pregnant women (95% uncertainty range)	Percentage of global burden among pregnant women*
Afghanistan	6100 (3200–11 000)	7·2 (3·7–12·8)	2·8%
Bangladesh	8100 (4100–14 300)	3·5 (1·8–6·1)	3·8%
Brazil	800 (400–1600)	0·4 (0·2–0·7)	0·4%
Cambodia	1700 (1400–2000)	5·9 (5·0–7·0)	0·8%
China	9500 (8100–11 100)	0·7 (0·6–0·8)	4·4%
DR Congo	16 200 (8700–26 900)	7·2 (3·9–12·1)	7·5%
Ethiopia	8000 (6500–9600)	3·7 (3·0–4·4)	3·7%
India	44 500 (30 600–62 000)	2·3 (1·6–3·1)	20·6%
Indonesia	9500 (4700–16 400)	2·7 (1·3–4·6)	4·4%
Kenya	4300 (2200–7100)	3·8 (2·0–6·4)	2·0%
Mozambique	4300 (2300–7400)	5·9 (3·2–10·4)	2·0%
Myanmar	2500 (2000–3200)	3·9 (3·1–5·0)	1·2%
Nigeria	10 900 (3000–27 700)	2·1 (0·6–5·4)	5·0%
Pakistan	14 800 (7200–26 300)	4·3 (2·1–7·7)	6·8%
Philippines	6600 (5700–7500)	3·7 (3·2–4·2)	3·0%
Russia	1200 (500–2400)	0·9 (0·4–1·8)	0·5%
South Africa	8400 (4400–14 300)	10·3 (5·4–17·6)	3·9%
Tanzania	3100 (1700–5200)	2·2 (1·2–3·7)	1·4%
Thailand	500 (200–900)	0·9 (0·4–1·6)	0·2%
Uganda	2600 (1400–4400)	2·3 (1·2–3·8)	1·2%
Vietnam	900 (700–1100)	0·8 (0·7–1·0)	0·4%
Zimbabwe	2400 (1400–4100)	7·9 (4·6–13·4)	1·1%
Total	166 200 (143 000–195 500)	2·5 (2·1–2·9)	77·0%

*Total percentage does not sum to 100% because list only shows % of global burden in pregnant women for each of the WHO 22 high tuberculosis burden countries.

Table 3: **Total number of active tuberculosis cases in pregnant women, rate per 1000 pregnant women and percentage of global burden amongst pregnant women for the 22 high tuberculosis burden countries as classified by the WHO**

	Health system indictor	
	Antenatal care services (at least one antenatal care visit)	Labour and delivery services (births attended by skilled health personnel)
African Region	71 100	49 600
Region of the Americas	4400	3500
Eastern Mediterranean Region	17 000	11 100
European Region	4700	4800
South-East Asia Region	51 000	37 200
Western Pacific Region	19 100	17 200
All countries combined	167 200	123 500

Table 4: **Number of active tuberculosis cases in pregnant women who access antenatal and labour and delivery services, by WHO region and combined**

When test sensitivity was taken into account, the total number of cases that could potentially be detected further declined (table 5). Sputum smear microscopy yielded the fewest cases, because no smear-negative cases would be detected using this approach to diagnosis. A nucleic acid amplification test such as Xpert MTB/RIF would detect

	Maternity care access indicator	
	Antenatal care services (at least one antenatal care visit)	Labour and delivery services (births attended by skilled health personnel)
Smear microscopy		
Smear positive	85 000	62 600
Smear negative	0	0
Total	85 000	62 600
Chest radiography		
Smear positive	80 000	58 900
Smear negative	34 200	25 600
Total	114 100	84 500
Xpert MTB/RIF		
Smear positive	83 300	61 400
Smear negative	37 000	27 600
Total	120 300	89 000

Table 5: **Number of active tuberculosis cases detected with different diagnostic tests in pregnant women—all countries combined**

120 300 active tuberculosis cases in antenatal care settings and 89 000 in labour and delivery settings. Chest radiography was estimated to detect a similar number of cases: 114 100 and 84 500 respectively.

Discussion

Because access to maternity services has improved in low-resource settings and indirect causes contribute to a larger proportion of maternal deaths, it is important to understand the burden of infectious diseases such as tuberculosis among pregnant women. This study estimates that, in 2011, more than 200 000 pregnant women had active tuberculosis globally. More than 70% of these tuberculosis cases occurred in Africa and South East Asia, where access to quality maternity services remains limited and case detection rates are lower in the general population.[3] This is the first study that has attempted to quantify the burden of tuberculosis disease among pregnant women, a key population for which specific interventions to reduce morbidity and mortality are urgently needed in low-resource settings.[4] It is a comprehensive study using consistently reported data across 217 countries based on routinely collected information provided to international authorities.

The active case finding scenarios we describe offer the advantage of detecting tuberculosis in those with minimal clinical disease who would otherwise not be detected. It also offers the additional advantage as a platform for isoniazid preventative therapy. Treatment for latent tuberculosis infection is recommended for pregnant women who are at high risk of disease progression.[4] Maternity services provide a unique opportunity for tuberculosis screening and subsequent follow up, in view of a pregnant woman's ongoing contact with the health system during antenatal care, labour and delivery, and afterwards, through maternal

and child health services. Provision of treatment to women with active tuberculosis who are already integrated into the health system should optimise outcomes, offering improved protection to both the mother and potentially reducing tuberculosis transmission to the neonate as well. This approach has proved to be successful for other infectious diseases. For example, malaria programmes have successfully leveraged these platforms to promote intermittent preventive treatment of malaria during pregnancy and provide insecticide-treated nets,[21,22] which have benefits beyond pregnancy and the postpartum period.

This study had several limitations. First, our estimates of burden among those who access the health system assume that access only occurs within maternity care settings (antenatal and labour and delivery). We do not account for pregnant women who could have been diagnosed through the national tuberculosis programme or other programmes because we have no data to estimate the extent to which they could gain access through other programmes. In many settings, especially among persons living with HIV, the prevalence of undiagnosed tuberculosis in pregnant women has been noted to be high.[4,23] Because of our assumption about health system access, the number of pregnant women that could benefit from the integration of tuberculosis screening and diagnosis in maternal health settings will vary by setting. In settings where there is little coverage of the national tuberculosis programme or lower case detection in the general population, the added value of integration will be increased in terms of yielding cases among pregnant women—eg, where coverage of tuberculosis diagnosis services is limited to district hospitals, but pregnant women access antenatal care at more peripheral health services.

Second, the role of the private sector in provision of all of the relevant services for this model—tuberculosis screening and diagnosis, routine antenatal care, labour and delivery care—is not known at the global level, but is likely to be significant in high tuberculosis burden settings in Asia. The integration of these services should be considered in view of these programmatic contexts. Third, most of the data we used to derive our estimates were obtained from publicly accessible databases that have uncertainty arising from different sources. For example, for epidemiological data, in settings such as India, where as many as half of patients with tuberculosis are treated in the private sector,[24] under-reporting leads to underestimates of the true burden of tuberculosis disease. Related to this, we assumed that tuberculosis cases were not systematically undernotified in any particular sex or age group. We do not have data to support other assumptions, but if in fact tuberculosis cases are undernotified in women of reproductive age, the estimates presented will be an underestimate of the true burden of disease in pregnant women. Finally, when considering different diagnostic tests, we assumed that chest radiography, a recommended test for initial detection of tuberculosis disease in pregnant women,[6] is accessible wherever skilled birth attendants are practising. Although it might not be used in all settings in current practice, evidence shows that use of this technology in countries with low or middle income, especially in high HIV burden settings, could be advantageous.[25,26] Additionally, if active tuberculosis can be ruled out with radiography, other abnormalities consistent with previous tuberculosis infection (eg, apical fibronodular scarring) might be detected and isoniazid preventative therapy can be offered.

With these considerations in mind, this study provides useful information for stakeholders at all levels as they work to optimise care for pregnant women and those with tuberculosis (panel). Getahun and colleagues[4] have urged the integration of tuberculosis care programmes and maternal, neonatal, and child health services to ensure the mainstreaming of tuberculosis services. We have shown that more sensitive tests such as Xpert RIF/MTB could be valuable tests in this population, and field trials from a study in Zambia have shown promising results.[27] Computer models of integrated screening with Xpert RIF/MTB have also been described in this setting.[28] However, further research is urgently needed in this vulnerable population,[5] especially around appropriate service delivery models to evaluate, integrate, and optimise uptake of services among providers and beneficiaries. When, how often, and where to screen during pregnancy are all questions that need to be considered. For example, should tuberculosis

***Panel:* Research in context**

Systematic review

We searched PubMed with the terms "tuberculosis", "pregnancy", and "burden" with no language or date restrictions. We identified 60 articles; however, none provided a quantitative estimate of the global burden of tuberculosis disease in pregnant women. We then search PubMed with the terms "tuberculosis" and "maternal child health". We identified several review studies that described the epidemiology of disease in pregnant women in countries with low and middle income and summarised the latest evidence on unfavourable outcomes associated with tuberculosis for both the pregnant women and infant. Published articles were also identified that provided information about present screening practices in pregnant women in high burden settings and about interventions designed to increase the detection of disease in this population. Further studies of relevance were identified through reports identified in the preliminary search.

Interpretation

This study adds to the present body of evidence by providing a quantitative estimate of the burden of tuberculosis disease in pregnant women. It also provides estimates of the potential effect of several diagnostic tests used in 217 countries, with different levels of access through maternal care platforms. Our study suggests that in many countries with low and middle income, pregnant women carry a substantial burden of tuberculosis, and that maternal care platforms could be an efficient way to detect additional cases that might otherwise remain undetected. The results can inform ongoing scale-up and integration of interventions that are intended to address a wide range of maternal health concerns related to infectious disease, including HIV and malaria.

diagnosis be available in the antenatal care setting, or should pregnant women be screened in these settings but visit another location for further testing? The question of cost should also be considered because more screening will increase costs to health systems, many of which are already financially strained.

In high HIV prevalence settings any active case finding for tuberculosis should have a substantial effect. In 2012, WHO estimated that 37% of incident tuberculosis cases in the African Region were co-infected with HIV. As many of these cases will be in women of reproductive age, focusing screening efforts on this population is essential. Routine HIV-related interventions such as Prevention of Mother to Child Transmission (PMTCT) could serve as a gateway to introduce tuberculosis screening, diagnosis, and treatment. How best to do this has already been considered in different areas of South Africa.[8,23,29,30] In many high tuberculosis burden countries, Option B+ (life-long treatment of HIV-positive pregnant women regardless of CD4 levels) has been fully adopted by WHO.[31] The programme is being rolled out in many countries, often integrated with routine antenatal and delivery care services. The rollout of these services could provide a unique opportunity for integrated service delivery to insure optimum care for all pregnant women.

Any improvement to tuberculosis services aimed at pregnant women will reduce transmission between mothers and infants, and should ultimately lead to a reduction in secondary cases in children, an important subpopulation in which the burden of disease is now thought to be much higher than originally estimated.[32] The substantial burden of disease estimated in pregnant women indicates there remains an urgent need to improve access to tuberculosis screening and diagnosis, especially in high tuberculosis and high HIV burden settings. More research is imperative to improve delivery and uptake of care in this vulnerable population.

Contributors

CC and AM conceived the study idea. JS, CC, and OO contributed to the study design. JS and OO did the literature review and data analysis. JS, OO, AM, and CC contributed to data interpretation. JS, CC, AM, and OO wrote the report and approved the final version of the report.

Declaration of interests

We declare no competing interests.

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