A systematic review on the role of gender in tuberculosis control

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Summary

Many questions exist on the role of gender in tuberculosis (TB) epidemiology and control. Sex is the term used to differentiate men and women on the basis of their biological characteristics. Gender on the other hand refers to the socially constructed features that are associated with this differentiation, such as roles, behaviors and expectations. Gender configures both the material and symbolic positions that men and women occupy in the social hierarchy, and shapes their life experiences. From previous studies and reviews it seems likely biological and socio-cultural factors play a role in the higher TB notification rates among men, and that these have different contributions in different settings. The focus of this systematic literature review is on gender-specific barriers in help seeking and access to health services, diagnosis and initiation of treatment, treatment adherence and treatment outcomes, for which interventions may help to reduce gender differences.

To carry out a systematic review of studies assessing gender related issues in TB control, we searched Pubmed and the Social Science Citation Index (SSCI). In April 2010 we included papers (both articles and reports) prior to the search date. In Pubmed, the keywords (tuberculosis OR mycobacterium tuberculosis) AND (gender OR sex) were used as search terms in titles and abstracts. The literature was restricted to studies in human subjects. SSCI was searched through the ISI web of knowledge for literature with the search term "tuberculosis" in the title and "gender" or "women" or "men" in the topic. As a first step, data were extracted on title and abstract. Literature describing original research in the English language, potentially fitting any of the four topics (health seeking and access to health services, diagnosis and initiating treatment, treatment adherence and treatment outcome) was retrieved. Papers with a title or abstract that mentioned that gender, sex, or demographic characteristics were taken into account were included. A template was used to extract data from the full text, which included information on the objective, geographical location, study period, sample size, study design and methods, main findings and recommendations made by the authors. Papers were excluded if they were not in English, not on *M. tuberculosis,* focused on the effects of BCG vaccination, not on original research, did not contain relevant information on one of the topics, or did not include gender stratified data (which could be on men or women only).

From the current review it became clear that there are important differences in the limitations experienced by men and women when trying to access TB care, and in the patterns they follow in the help seeking process. Male patients tend to delay seeking care longer than female TB patients. Female TB patients in general encounter greater barriers to receive appropriate medical attention as women are more likely to seek help but tend to do this firstly with more easily accessible, but less qualified providers, thereby delaying access to appropriate diagnosis and care. Female TB patients more often presented with symptoms not specific for TB. This may be one of the reasons why they are inclined to visit easily accessible health care workers and delay visiting a general health care clinic or TB clinic. Non-specific TB symptomatology may decrease the chance a physician includes TB in the differential diagnosis, and thus orders sputum smear examination. From our review it appeared that in general health care provider delay was similar in men and women who were diagnosed with TB. However, some studies show that more women than men experience extraordinary health care provider delay. Most probably, this is due to a combination of more frequent 'treatment shopping' and non-specific TB symptomatology and a decreased sensitivity of smear microscopy among female TB patients. It is not clear which of these factors that may affect gender differences in TB diagnosis are most important, and this also may differ in various settings. Smear microscopy in itself is not a sensitive diagnostic method for TB, but even has a lower sensitivity among women than men. More sensitive diagnostic methodologies than microscopy seem to be able to diminish gender differences among TB suspects in reaching a TB diagnosis to a large extent. With recent developments in molecular tests to diagnose TB, methods are in sight to improve case detection in both men and women, ánd make gender differentials in TB diagnosis disappear once TB is in the differential diagnosis. Upon diagnosis, the delay before start

of treatment was minimal both for men and women. When on treatment, women generally are better adherent and, at least partly as a consequence, have better treatment outcomes. It was hypothesized that a lack of autonomy that may impair women's ability to seek healthcare from appropriate providers as mainly observed in south-east Asia, could at the same time make it more difficult to interrupt treatment. Male TB patients on average more frequently die and default during treatment. Women on average less often default, despite the fact that serious adverse events and liver injury are more commonly observed among women than men. Alternative treatment strategies, making directly observed therapy more feasible, e.g. at the workplace, may be especially useful in males. Use of a comprehensive supportive approach, which may include the provision of incentives, transportation, feeding, and others, may also improve treatment success.

In our review on gender-specific issues in TB control, no studies on the effects of gender-specific interventions to improve either access to health care, TB diagnosis and treatment adherence and outcomes were identified. One study on the effects on active case finding [1], which could be seen as a temporary intervention, aimed to identify gender based differences in patients with pulmonary TB. However, no operations research studies implementing and evaluating gender-specific effects of interventions could be identified. In our opinion it is crucial that TB control programs build on existing knowledge and move on from research to action, specifically addressing the gender-related barriers to TB diagnosis and care. These actions should be informed by action-oriented research that helps identify the most appropriate strategies for each particular context, and later evaluate their effectiveness. Showing improved performance may accelerate scale-up of effective policies and actions.

Areas for interventions can be identified by mixed methods studies focused on quantitatively assessing gender-specific access to health care in general and TB diagnostics specifically, treatment adherence and successful treatment outcomes and by means of qualitative research methods assess reasons for any differences observed. As a first step, data on sex, age, and preferably other socio-economic factors, within the health care sector, including TB programs, should be collected and analyzed. Data should be analyzed on all levels, from district to regional to country to continental level, and should be compared between them. This would allow tracking gender disparities within specific contexts and their interaction with factors such as access to care, ethnicity, particular forms of TB, the HIV co-epidemic, etc. Interdisciplinary studies are also necessary in order to better explain the interplay of these factors.

One field that may benefit both women and men, includes interventions promoting and optimizing partnerships between different public and/or private health care facilities and workers, to facilitate access to health care staff which recognizes TB suspects and will refer them to an appropriate clinic. Furthermore, there is still a need for additional research examining the relationship between gender and TB in the context of the HIV epidemic. The strong relationship between TB and HIV, especially in settings of high-HIV prevalence, like sub-Saharan Africa, makes it essential to further examine how the co-epidemic influences men and women in terms of TB and health seeking behaviors and access to care, diagnosis, initiating and adherence to treatment, and outcomes. Another field that may benefit both women and men, is implementation and assessment of the additional value of new, more sensitive, diagnostic techniques for TB. It would be very helpful to know by how much the more sensitive fluorescent microscopy using LED-lamps, and molecular tools remove gender differences. A third field that may benefit both women and men is to assess different possible strategies for a comprehensive approach to treatment, including incentives, in order to reduce gender-related obstacles to treatment adherence and treatment success.

In conclusion, there is a need for TB programs to identify, implement and evaluate innovative strategies to improve TB detection and shorten the pathway to TB diagnosis and treatment for men and women at both local and national levels. Action-oriented research is required to optimize these strategies.

Acknowledgements

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Introduction

Many questions exist on the role of gender in tuberculosis (TB) epidemiology and control. Sex is the term used to differentiate men and women on the basis of their biological characteristics. Gender on the other hand refers to the socially constructed features that are associated with this differentiation, such as roles, behaviors and expectations. Gender configures both the material and symbolic positions that men and women occupy in the social hierarchy, and shapes their life experiences [2]. While gender is associated with differences between the sexes, it also gives a particular meaning to these differences and influences the interpretation of the biological characteristics in which these differences are based.

Hypothetically, gender may influence the epidemiology of TB in various ways. Differences between sexes in social and economic roles may lead to differential exposure to TB, while differential health status, especially in low income countries, may lead to altered progression rates to TB disease. The rate of progression to disease is equal or greater in women during reproductive years while at older ages the rate of progression is higher in men. In some societies women can be expected to have less access to health care (primary and TB-specific) which may lead to delays in detection and treatment. Socio-economic and cultural differences may have an effect of gender-specific treatment adherence and thus on treatment outcomes. HIV/AIDS in sub Saharan Africa is most prevalent among the female population, which may affect gender-specific prevalence of TB infection and disease. Also, women make up 70% of the world's poor, and poverty is known to affect access to health care.

Starting from adolescence, the prevalence of TB infection as measured with the tuberculin skin test, is usually higher in men than in women [3]. Both prevalence surveys and notification rates tend to show higher TB disease rates in men. Possible explanations for the higher TB rates in men are:

- Biological function: sex hormones, genetic background and HIV including reduced immune response to tuberculin
- Difference in exposure due to behavioral risk factors (smoking, occupation, indoor air pollution, dietary differences)
- Socio-cultural components (awareness, stigma, income, differential access to health care and health care seeking behavior)

Several reviews have been published on the topic in the last 15 years [2-14]. We did a systematic literature review to provide an update on gender-specific issues in TB control as input for the development of a research agenda presenting priorities for gender related issues within TB control.

We used a framework identifying gender-specific barriers at the different steps in TB control [2], which is a modified framework developed by Uplekar [4] (see Figure 1). This modified framework consolidates some of its elements that are not amenable for individual study and covers the following topics:

- TB occurrence and epidemiology
- Help seeking and access to health services
- Diagnosis and initiating treatment
- Treatment adherence
- Treatment outcome

The focus of this systematic literature review is on gender-specific barriers for which interventions may help to reduce gender differences. As TB occurrence and epidemiology is something that cannot be modified by TB control interventions in a narrow sense, we excluded this topic from the current review.

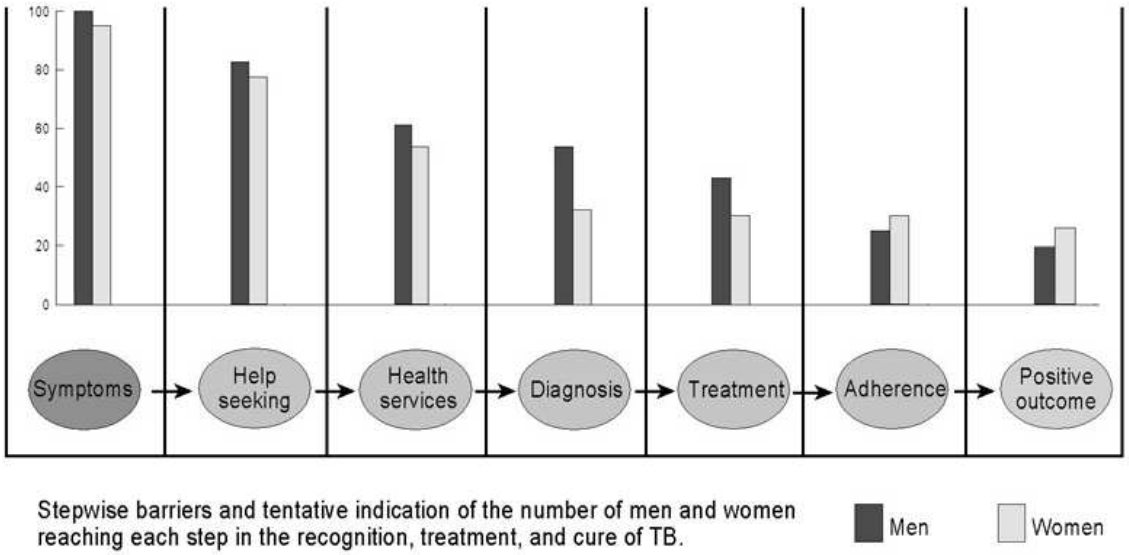

Figure 1. Gender differentials for clarification and study at each step in the course of effective control. Reproduced from [4]. For this review, a modified version [2] was used combining the seven elements into five: TB occurrence and epidemiology; Help seeking and access to health services; Diagnosis and initiating treatment; Treatment adherence; Treatment outcome. This review focuses only on the last four elements of this modified framework as these may be modified by specific TB control interventions.

Methods

To carry out a systematic review of studies assessing gender related issues in TB control, we searched Pubmed and the Social Science Citation Index (SSCI). In April 2010 we included papers (both articles and reports) prior to the search date. In Pubmed, the keywords (tuberculosis OR mycobacterium tuberculosis) AND (gender OR sex) were used as search terms in titles and abstracts. The literature was restricted to studies in human subjects. SSCI was searched through the ISI web of knowledge for literature with the search term "tuberculosis" in the title and "gender" or "women" or "men" in the topic.

As a first step, data were extracted on title and abstract. Literature describing original research in the English language, potentially fitting any of the four topics (health seeking and access to health services, diagnosis and initiating treatment, treatment adherence and treatment outcome) was retrieved. Papers with a title or abstract that mentioned that gender, sex, or demographic characteristics were taken into account were included.

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To identify additional relevant papers, we searched reference lists of reviews and included papers reporting on original research. The numbers of referenced papers included per topic are summarized in Figure 2.

As a number of reviews on gender in TB had been published before, we summarized relevant information for each of the themes before describing results from identified literature. In the discussion section, conclusions are drawn per topic and directions for future research are provided.

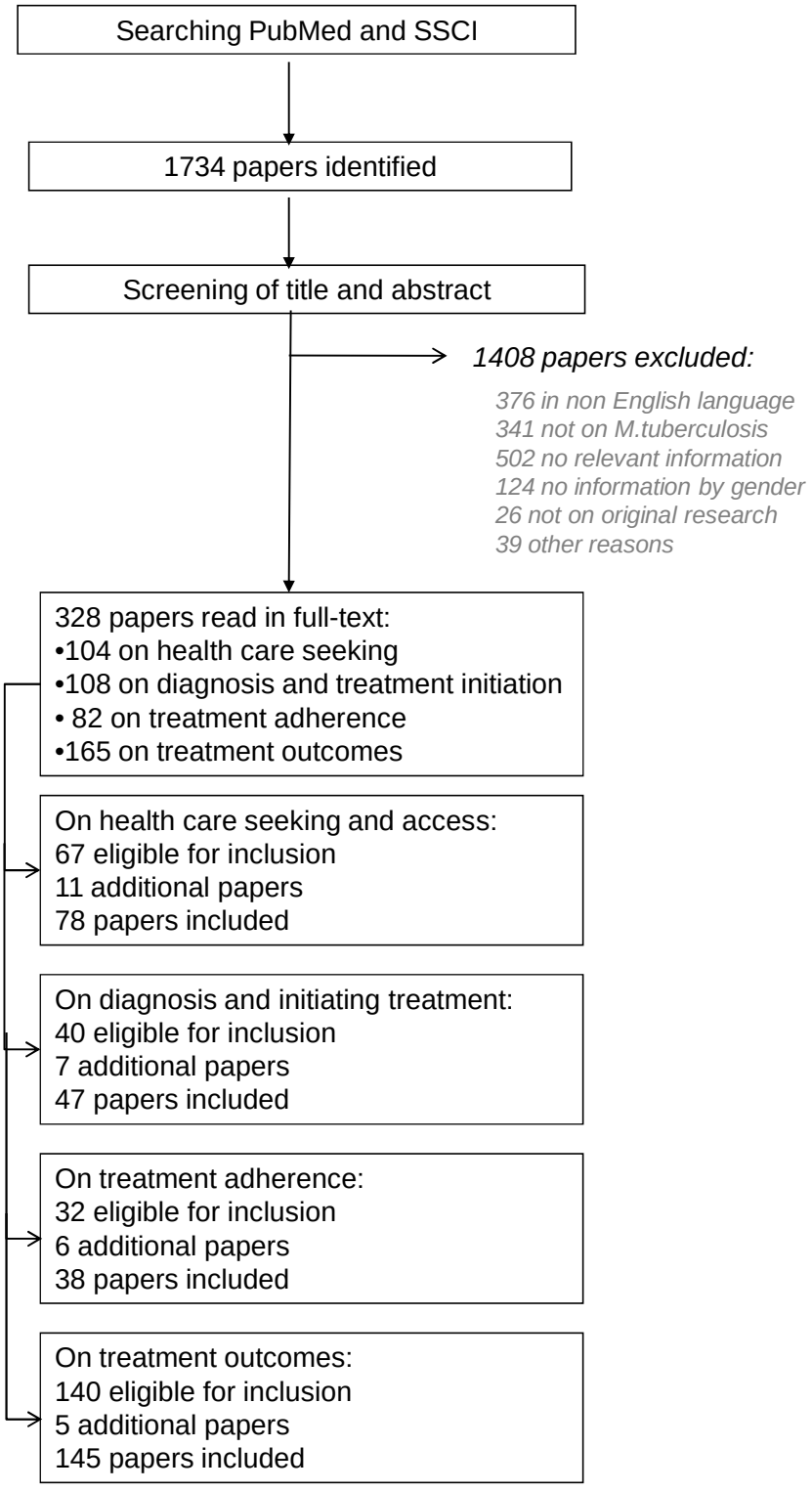

Figure 2. Selection of articles included in the review, by topic. As many articles were included for more than one topic, the total number of papers read in full-text is smaller than the sum of the numbers per topic.

Results

Help seeking and access to health services

Out of the 1734 papers (articles and reports) found in the search, 104 were selected, based on the titles and abstracts, as containing relevant information on help seeking and access to health care. After reading the full text of the selected papers, 37 were excluded, for the following reasons:

- 19 articles were not on help-seeking and access to TB care
- 10 articles were not based on original research
- 8 articles did not sufficiently consider gender differences

Sixty-seven of the initially selected articles were therefore included in this category. Additionally, 12 studies that were potentially relevant for this section were identified in the references of other articles, 11 of which were included after reading the full text. A total of 78 papers that addressed help seeking behavior and access to health services were thus included in this systematic literature review.

Previously published reviews

Uplekar et al. [4], in an article published in 2001, highlight the need for research that helps determine the extent to which the higher TB notification rates in men reflect epidemiological differences or arise from distinctive obstacles faced by men and women to access TB care. Based on a literature review and field visits, the authors developed a framework that suggests a strategy for research to explain gender differentials in TB control. The authors also point to several factors that influence care seeking behavior among men and women: self-image, status in family and society, access to resources, manifestation and expression of symptoms, and stigma associated with TB. They suggest the development of a multi-site investigation, incorporating qualitative and quantitative research methods, and employing a generic protocol adapted for local use, in order to identify common and distinctive gender-related barriers to access and ways to surmount them.

In 2008, Storla et al. [5] published a systematic review on delay in diagnosis and treatment of TB. Out of the fifty-eight studies included in the review, twelve concluded that women experience increased diagnostic delay, while four studies made the opposite conclusion. Other factors associated with diagnostic delay were negative sputum smear, low access to healthcare, and initial visitation of a government low-level healthcare facility, private practitioner, or traditional healer. The authors also found major differences in the ways diagnostic delay was defined in the studies reviewed.

In 1998, Holmes et al. [6] published a review on sex differences in the epidemiology of tuberculosis, with the aim of providing a baseline of what was already known regarding sex differences in the prevalence and annual risk of *M. tuberculosis* infection, disease notification, progression to disease, case fatality and mortality, and TB/HIV co-infection. According to these authors, the lower notification rates reported among women living in low-income countries, as opposed to the excess in notifications in women in industrialized settings earlier in the century, raise the possibility that women are being underreported in the former, perhaps due to inadequate care-seeking related to time and financial constraints, insufficient access to income, and inequalities in legal rights, social status and education. The authors suggest that TB programs should evaluate age- and sex-specific data and establish if access to care is lower for either sex due to structural and/or social barriers, or under-diagnosis. They also recommend making services more 'user friendly', especially for

reproductive age women, for example, incorporating TB in maternal health and HIV prevention and care programs.

Hudelson (1996) [3] conducted a review of the English-language literature, in order to determine what was known about the role that socio-economic and cultural factors play in determining gender differentials in tuberculosis and tuberculosis control. The review showed that barriers to early detection and treatment of TB are different for women and men. Women's heavy workload, as well as lack of mobility, independence and access to cash all act as deterrents to seeking care from TB treatment services. In order to improve women's access to TB care, the author recommends reducing transport and time costs, promoting integration of health services, and integrating and supporting 'traditional practitioners'.

In 2004, Bates et al. [7] published a review aimed at identifying potential pro-poor disease-control strategies that could simultaneously influence the three Global Fund priority diseases—malaria, tuberculosis, and HIV disease. Through this review, the authors found that the timing and method of accessing tuberculosis care can be affected by gender. In Southeast Asia, tuberculosis is perceived as a largely male disease and this perception might prevent women from recognizing and seeking care for tuberculosis-related symptoms. Women fear social isolation and tend to self-medicate at an early stage of the symptoms, whereas men are more worried about the cost, seek help late, and prefer to use formal health services. Women are more inhibited by poor-quality services and lack of confidentiality than men; these feelings could account partly for their preference for traditional healers and self-medication, which delays diagnosis and treatment.

In 1999, Ogden et al. [8] published a review that was mainly focused on the reasons for treatment failure, but also provided interesting insights on help-seeking and access to TB care. The authors report that women of reproductive age are less likely and able to seek and obtain care than men of the same age. In many societies, younger women have relatively junior status in their households and communities, less mobility, less autonomy and greater constraints in accessing resources for treatment than older or higher status women. Moreover, the social repercussions of a TB diagnosis for women (e.g. rejection, harassment, desertion, divorce, inability to marry and dismissal from work) become barriers to accessing healthcare.

In a 1996 article on women and tuberculosis, Connolly and Nunn [9] state that it is unclear whether the higher rates of TB notification in men are due to biological mechanisms placing them at higher risk or to undernotification in women, or both. While an active-case finding study conducted in India [15] showed the incidence of TB in women to be 30% of that in men, suggesting that the higher notification rates in men may be explained by biological mechanisms, studies in Nepal [16] comparing active and passive case-finding showed that a higher proportion of women were undiagnosed in the community. This suggests that under-diagnosis for women may occur in programs that rely on passive case-finding, possibly due to socio-economic and cultural factors. Studies have shown that women tend to wait longer to report their illness and they consult with traditional healers more frequently than men. The stigma associated with tuberculosis has greater impact on women than on men, making them more likely to be divorced or to have difficulty in finding a marriage partner. Studies in India found that married men and single women with TB perceived a greater level of family support than married women (Nair, D. Tuberculosis in Bombay: new reasons for concern, unpublished document), and that single women often try to hide their illness for fear of desertion, rejection or blame [17].

In an editorial article published in 2007, Allebeck [10] notes that studies from Malaysia [18], China [19] and Vietnam have shown that treatment is often delayed due to poor knowledge, particularly among persons of lower socioeconomic standing, who lack awareness of the risks associated with long-standing cough, are not reached by national programs and do not recognize the need for prompt case detection, follow-up and treatment. The author also identifies among the main barriers to access to health services the distance to healthcare facilities, lack of insurance coverage and costs for visits, and language and other cultural barriers. A study Shanghai has shown that fear of losing one's job is also an important barrier among immigrant workers [20].

Vissandjee and Pai [11] published an article in 2007 about the way in which gender and other social processes operate in causing health inequalities in the case of TB management and control. Drawing from studies conducted in India, the authors establish a link between delays in help seeking, gender disparities to access and entitlement to care, and stigma and social discrimination. Social discrimination on the basis of TB disease status may result from various factors, such as perceived danger and contagiousness, as well as adverse judgments which may attribute the condition to behaviors that are considered immoral (such as sex with sex workers and menstruating women) and blame the victim for acquiring the disease. The way people respond to TB unveil the moral basis of the judgments on risk and vulnerability to this disease, suggesting a causal web of interactions linking ethnicity, culture and gender.

In the *Encyclopedia of Medical Anthropology*, Shrestha-Kuwahara et al. [21] present a review of TB-focused anthropological and social science literature. In their review the authors found a number of studies that report that women tended to seek care from providers they felt comfortable with rather than visiting government TB clinics and often delayed obtaining appropriate treatment. A study in Nepal showed that women sought traditional health care services before seeking care in government clinics, due in part to the proximity of services [22]. The authors of the review also address the cultural meanings of the diseas, and report on a study conducted in Mexico, which found that working-class people from similar socioeconomic strata share a humoral explanatory model of TB, and that women shared much stronger agreement on this view than men. This could be related to women's role in taking care of the family health and the influence that this has in the distribution of traditional health knowledge [23]. The authors of the review also highlight the social consequences of a TB diagnosis for women in societies in which women occupy a lower status and how this may result in undertreatment and increased mortality, providing evidences from studies conducted in different contexts.

Original research

Although all 78 articles selected for the topic included some relevant information on the relationship between gender and help-seeking behavior and access to healthcare, only 29 of them specifically addressed the study of gender differences as part of their objectives [24] [25] [26] [27] [28] [29] [30] [31] [32] [33] [34] [35] [36] [37] [38] [39] [40] [41] [42] [43] [44] [45] [46] [47] [48] [49] [50] [22] [51]. Fifty-two of the studies used quantitative methods, 17 qualitative used qualitative methods, and 9 had a mixed methods approach. There were three articles that compared passive case finding strategies regularly used in TB care services with other strategies based on outreach and active case finding, and in that sense these can be considered intervention studies [16] [52] [53].

The selected articles can be classified in four categories, according to the aspects of help-seeking behavior and access to healthcare for tuberculosis that they focus on. These categories are not mutually exclusive and there is considerable overlap between them, since many of the articles address more than one aspect.

1) Gender differences in access to healthcare
2) Gender differences in help-seeking patterns
3) Gender differences in patient delay
4) Gender-related influencing factors: the articles in this category can be further classified in three subcategories
    a) Socio-cultural and economic barriers to access TB care
    b) TB-related perceptions, attitudes and stigma
    c) Knowledge about TB

Gender differences in access to healthcare

It has been hypothesized that the lower TB notification rates in women might be due, at least in part, to a reduced access to healthcare, and particularly diagnostic services for women. In order to explore this, Borgdorff et al. [29] conducted a meta-analysis that compared age- and sex-specific smear-positive TB prevalence rates and TB notification rates in 14 countries. In most countries the female/male ratio in prevalent TB cases was similar or lower than that in notified cases (except in the African region), which would suggest that female/male differences in notification rates are not due to differential access to diagnosis, but to true differences in epidemiology. However, the authors caution that this conclusion cannot be generalized to individual regions or countries.

This caution is supported by the divergent findings of five studies conducted in four countries. On the one hand, studies in Bangladesh and India showed that the proportion of TB cases in women found during population and community surveys was not higher than that observed through routine diagnosis [36] [26], suggesting that gender differences in TB notification are not due to underreporting in women, or even that women are more likely to report TB than men. On the other hand, two studies in Nepal and one in Peru showed a significantly higher proportion of female smear-positive TB patients detected through active case finding and temporary outreach TB diagnosis camps, compared to those detected through passive case finding and regular services, such as health posts and clinics [16] [52] [53]. One of these studies also reported female sex as a strong risk factor for failure to self-report in multivariate analysis [52]. The findings of these three studies support the hypothesis that women face greater limitations than men to access TB care.

Gender differences in help-seeking patterns

In our systematic review we identified a number of studies that focused on different facets of the patterns of help-seeking behavior in men and women. Five quantitative studies found that, compared to men, women more often took or intended to take help-seeking actions when they presented with TB-related symptoms, such as prolonged cough [54] [55] [56] [37] [47]. Alternatively, in a study conducted in China the participants in focus group discussions (FDG) perceived women as less likely to seek care than men, and less likely to be prioritized within the family for care seeking. However, this difference was not statistically significant in a related survey [57].

Studies in The Gambia and Vietnam showed that, compared to men, women took more help-seeking actions and saw a larger number of healthcare providers [58] [41] [55]. There were also important differences regarding the type of help-seeking actions undertaken by men and women. All but one of the studies [58] that touched upon this subject found that women were more likely than men to use home remedies and self-medication, and to visit traditional healers, pharmacists, private practitioners, less qualified providers and lower level healthcare facilities. Conversely, men sought healthcare in public hospitals, more qualified providers, specialty services and upper level healthcare facilities more often than women [54] [59] [60] [58] [55] [56] [50] [22] [37] [61] [25] [62] [26] [27] [39] [38] [32] [63] [64] [19]. There was one study conducted in The Gambia that partially deviates from this trend, in which men were found to be more likely than women to visit hospitals, but also pharmacist and private doctors, while women were more likely than men to visit government health centers [58].

Some authors present possible explanations to and perceived consequences of these gender differences in help-seeking patterns, based on the results of qualitative and mixed methods researches. That women sought care with traditional healers and pharmacists more often than men was thought to be related to stronger traditional beliefs, more time constraints and a greater interest in privacy and confidentiality among women [32]. Some of the perceived reasons for women's preference for private healthcare providers were that these were considered more convenient, accessible, familiar, trustworthy and effective [50] [62]. In contrast, FGD participants in Vietnam thought that men more often go straight to public health services, without self-

medicating or visiting private practitioners first, because they tended to initially neglect their TB symptoms [38]. Related to this, studies in Colombia [51] and Peru [65] suggest that men might be more reluctant to seek help because this is perceived as a sign of weakness, which conflicts with the values of traditional masculinity. The perceived result of these gendered patterns of behavior was a longer and more circuitous history of healthcare seeking among women, that led to longer delays to TB diagnosis and treatment [32] [35].

There were four quantitative and two qualitative studies that found no evidence of gender differences in help-seeking patterns [41] [66] [30] [24] [34] [67].

Gender differences in patient delay

Thirty-two of the articles included in this systematic review addressed the issue of patient delay, which was generally understood as the period of time between the onset of symptoms related to TB and the first visit to a healthcare provider. However, there were important variations in this definition in the types of healthcare providers considered by each author; some authors considered any type of healthcare provider (including traditional healers), while others only considered the first contact with a medical, public and/or specialized TB healthcare facility. For example, while Yamasaki-Nakagawa et al. defined patient delay as "the period from the onset of symptoms to the first visit to a health care provider, including traditional healers" [22], Meintjes et al. understood it as "the time from the first symptom to seeking medical attention in the formal health services" [68].

Besides these discrepancies in the definition of patient delay, several authors used related but distinct notions to describe delay, some of which also varied considerably in the way each author defined them. Concepts such as health-seeking delay, test-seeking delay, diagnostic delay, traditional healer delay, healthcare system delay, doctor's delay, treatment delay, delay to hospitalization and total delay often overlapped with and were difficult to distinguish from patient delay.

Notwithstanding the difficulties posed by the divergent ways of understanding patient delay, comparing the findings of the studies that dealt with this topic provides interesting insights. While 15 articles reported no gender differences in patient delay, there were 7 quantitative and 3 qualitative studies that showed evidence of longer patient delays among women, and 5 quantitative and 1 qualitative studies that found longer patient delays in men.

South-East Asia and the Western Pacific were the two regions in which fairly consistent gender differences in patient delay were reported across the different articles. Although seven of the studies conducted in these regions found no association between gender and patient delay [69] [26] [22] [70] [41] [56] [71], there were eight others (six quantitative and two qualitative) that provided evidence of a longer patient delay among women [35] [40] [25] [59] [55] [72] [49] [63]. From these regions, only two articles reported a longer patient delay among men, one in India [51], and one in Thailand (however, the latter did not state whether the difference had statistical significance or not) [73].

The articles that reported on studies from countries in the four remaining regions (Africa, the Americas, Eastern Mediterranean and Europe) showed more divergent findings regarding gender differences in patient delay. Eight articles reported no differences between men and women [74] [75] [76] [31] [39] [77] [78] [79], three studies (two quantitative and one qualitative) found longer patient delay among women [80] [35] [32], and five others (four quantitative and one qualitative) found it among men [65] [81] [27, 68] [82].

Six of the articles reviewed reported on the delay between the onset of symptoms and the diagnosis or initiation of treatment. It was therefore not possible to distinguish patient delay from the delay related to the healthcare providers. It is interesting to note, however, that four of these studies found no differences in delay between men and women [58] [30] [83] [84], while two of them found it to be longer among the latter [46] [85].

Gender-related influencing factors

Socio-cultural and economic barriers to access TB care

A number of studies have also focused on how gender imbalances within the family and in society at large can also influence differences in access to healthcare and help-seeking behavior. All the articles that dealt with these issues concur that women face greater socio-cultural and financial barriers to access TB care, given their subordinate position in relation to men.

Travel and treatment costs can have a more limiting effect for women, due to their financial dependence, lower income and lack of control over the family resources [32] [33] [35] [86] [49] [50] [25] [87]. A study in India about gender differences in the costs of TB care found that women spent significantly more money for care seeking than men [26]. Another study conducted in Zambia concluded that, although men spent more money in accessing TB care than women, it was still more affordable for them when taken in the context of their ability to pay and the great disparities in the median individual income between men and women [88].

Qualitative data has revealed that men were more frequently focused on financial concerns and the effects of TB on the family economy, such as interference with livelihood activities, the loss of wages, financial difficulties, reduced capacity for work, poor job performance, and the consequences of long absence from work [50] [63] [45] [43] [51]. These findings seem to be supported by the research conducted in Nepal by Yamasaki-Nakagawa et al. [22], who found that men were significantly more likely to visit the government medical establishment first if they knew that TB treatment was free than if they did not know, while women did not follow this pattern. This does not necessarily mean that financial barriers are more important for men than for women, but could indicate that women face other types of socio-cultural barriers that limit their access to TB care, in addition to the financial ones. Johansson et al. [63], for example, highlight the particular social and economic effects of TB confronted by women who are heads of household.

Some of the qualitative studies reviewed showed that traditional gender roles that grant men a higher status as the 'breadwinner' or the 'pillar of the family', cause women to be perceived as less important. Women's health is therefore not prioritized and they may receive less support (including financial support) for their healthcare, compared to other family members [38] [49] [34] [89] [45] [19] [57]. The time constraints related to the heavy workload of women, their domestic social responsabilities and their role as care-takers can also restrict their access to healthcare [40] [49] [51].

Women's lack of independence, reduced decision-making power and restricted mobility also constitute important limitations for seeking healthcare [40] [86] [49] [89]. This is illustrated by the fact that women often need to ask permission to their husbands or elders and/or be accompanied by a family member, in order to visit a healthcare provider [32] [35] [25] [27] [50] [24] [26].

Gender imbalances in society also exert an influence and tend to be reproduced in the patient-doctor relations, as Fochsen et al. [33] have shown. Weiss et al. [51] also found that often health provider's instructions were not given directly to the female patients, but to an accompanying person. This also limits women's access to healthcare and their control over the healthcare encounter.

TB-related perceptions, attitudes and stigma

Most of the studies reviewed provided evidence that women had to confront greater TB-related stigma and social consequences than men. Four quantitative, fourteen qualitative and one mixed methods studies provided evidence that women had more experiences and greater fear of social isolation, rejection, abuse, harassment, humiliation, conflict with spouses and family members, abandonment, divorce and difficulty in finding marriage partners (probably related to the ideas that TB is hereditary or that it affects pregnancy and breastfeeding), related to tuberculosis [25] [54] [26] [39] [60] [89] [48] [62] [50] [34] [38] [67] [63] [45] [43] [87] [51]. Some studies related this with a particular interest among women in keeping their TB diagnosis a secret, and feeling inhibited and ashamed of discussing their illness with family and friends [25] [54] [26] [35] [38] [63] [45] [49] [67] [64]. These feelings of shame and greater interest in secrecy might be related to the gendered patterns of help-seeking discussed before, in which women tended to use self-medication, traditional healers and private practitioners more than men.

However, there were interesting exceptions to this pattern of greater TB-related stigma for women found in most studies. Concerns about the effects TB-related stigma in marital status and marriage prospects where not completely absent among men [39]. In China, Zhang et al. [57] showed that unmarried young men worried more that a TB diagnosis would make it difficult for them to find a marriage partner, while unmarried women felt that they would still be able to find a marriage partner, although their parents might receive fewer betrothal gifts than usual. In Thailand, higher TB stigma was significantly associated with an increase in patient delay among men, and a decrease in patient delay among women. The authors hypothesize that women seek care more quickly in order to minimize the social consequences of the disease [73].

Four of the articles reviewed reported that men were more concerned about the financial and work-related consequences of the TB stigma, such as losing their job, reduced income and the effects that this would have in the family economy [38] [63] [62], all of which could also lead to loss of social status within the family and the community [48]. In a multi-country study conducted in India, Bangladesh, Malawi and Colombia, Somma et al. [48] found financial and work-related issues to be associated with the stigma of TB among men at all sites.

Some articles explored the links between TB-related stigma and discrimination with other forms of stigma and with social norms, particularly those related to gender roles. Several studies found that respondents associated TB with poverty, dirtiness, prostitution, 'free' sex practices 'promoted' by contraceptive use, breaking cultural norms regarding sexual behavior (e.g. sexual abstinence after the death of a relative, after delivering a child or after a miscarriage), and smoking and drinking alcohol [32] [60] [50] [34] [62] [51]. Smoking and alcohol consumption as causes of TB were more often associated to men [34] [62] [50] [51], whereas the perceived association of TB and sexual practices was stronger for women in some contexts [32] [50], and for men in others [34] [48], and was sometimes mediated through local beliefs about HIV and AIDS [50] [48] [51]. Atre et al. showed that men and women typically identified sexual experience as the cause of TB for the opposite-sex [62].

Beliefs in non-medical causes of tuberculosis may also have an influence in stigma and discourage help-seeking in medical healthcare facilities, with important differences between women and men. While Promtussananon et al. [90] found these non-medical beliefs to be more present among men than among women in South Africa, Atre et al. [62] reported that in India more women identified supernatural and karma-related causes of TB, compared to men. In some contexts, traditional beliefs about the causes of TB are closely related to gender roles. Weiss et al. [51] found that TB in women was thought to be associated with cooking smoke exposure, overwork, childbearing and taking care of other TB patients. In Vietnam, men were thought to be more affected by two 'types' of TB that are caused by hard work and by germs, whereas women were thought to be more

affected by a 'type' of TB that is caused by too much worrying [42]. As in other contexts, some people also believed that TB can be hereditary [42] [62] [57].

Other studies conducted in the USA, Ecuador and the Democratic Republic of Congo found no evidence of gender differences regarding perceptions, attitudes and stigma related to TB [91] [92] [28].

Knowledge about TB

Knowledge about TB can also have an influence in help-seeking behavior. Studies have found a significant association between knowledge of TB and both health care actions and seeking care in hospitals and government medical establishments [54] [37] [22].

Although six of the articles reviewed reported that there were no gender differences in knowledge about TB [93] [66] [94] [95] [92] [27], there were two quantitative studies in Vietnam, and one in China that found a significant association between male gender and increased knowledge about TB [56] [54] [37]. In The Gambia, the lack of knowledge about TB was perceived as worse among women, who were thought to have stronger traditional beliefs [32].

The two studies in Vietnam also found differences between men and women regarding the sources of information about TB. While men had more access to TB information through media, such as TV, radio, newspapers and loudspeakers, women had more access through relatives and friends. Furthermore, people who received TB information through friends and relatives had lower knowledge scores than those who received it through TV, radio or loudspeakers [54] [37].

Diagnosis and initiation of treatment

In order for a TB patient to get a TB diagnosis, patients need to go to the health facility and their symptoms must be recognized as potentially related to TB in order for them to be referred for TB diagnostic procedures. Data on gender differences in health care seeking and general access to health care are described in the previous chapter, this chapter will focus on gender in relation to access to and results of TB diagnostics after having sought care, and initiation of treatment.

Of all original research papers (articles and reports) found in the search, based on the title and abstract, 108 were selected as containing potentially relevant information on diagnosis and initiation of treatment. After reading the full text, 68 were excluded for the following reasons:

- 32 papers contained information on TB epidemiology, not on diagnosis and treatment initiation
- 15 papers contained information on one of the other topics included in this review, but not on diagnosis and treatment initiation
- 4 papers were on technical performance of tests for TB diagnosis, without reference to gender
- 3 papers were on diagnosis and treatment initiation but did not contain relevant information on gender specifics
- 2 papers only gave information on total diagnostic delay, not split out in patient and health care system delay. They are included in the previous chapter on health care seeking
- 2 papers did not fit into any of the themes

In addition to the 40 identified and eligible articles, an additional 7 relevant papers were identified in the references of these papers and in references of previously published reviews containing information on this topic. Thus, in total, 47 papers were included in this review.

Previously published reviews

In their review published in 1996, Connolly and Nunn [9] mention a non-published active case-finding study conducted over two years in India which showed the incidence of TB in women to be 30% of that in men. Another active case finding study described, from Nepal, observed that a higher proportion of women were undiagnosed in the community.

In a review of the English literature, Hudelson (1996) [3] attempts to explore how socio-economic and cultural factors may lead to gender differentials in TB. Hudelson refers to the same two studies in southeast Asia as Connolly and Nunn, showing that active case-finding revealed more additional cases among women than men(reducing the F:M prevalence ratio). A study from the early 1960's in India found that men with TB reported symptoms more often than women with TB (Banerji et al., 1963). The researchers felt that this was due to more difficult communication between interviewers and women. An unanswered question is whether this would also apply to interaction of women and health care workers.

In a letter in 1999, Diwan [12] notes that the lower prevalence of TB infection in women than men at least partly is due to socio-cultural differences leading to a wider social network but another part may also be due to a reduced immune response and therefore lower sensitivity of the tuberculin skin test in females after adolescence. In a review of literature concerning gender and TB in 1999 and 2000, Thorson [96] noted the same.

In 2001, Uplekar et al. [4] formulated their theoretical framework describing seven aspects of TB control which can also contain gender-specific barriers in access to TB control (as described firstly in a 1999 WHO report by the same authors). Uplekar et al. applied routinely available data from

seven different sites in diverse South-east Asian settings (Nepal, Bangladesh and India), and all sites showed a lower prevalence of sputum positivity among females compared to males.

The 2004 WHO report on Tuberculosis in the series on 'Gender in Health Research' [2] summarizes findings from several studies in Asia which found that even in settings where more women than men present for care, they experience longer provider delays in TB diagnosis. Physician respondents reported that female suspects often returned home for approval before providing a sputum sample while men were more likely to demand a comprehensive diagnostic evaluation. Three other referenced studies from Asia show that fewer women undergo sputum microscopy when they seek treatment for comparable respiratory symptoms. There are indications that screening of sputum may be less sensitive in women. One study found that use of a bronchodilator, oral salbutamol, increased the rate of positive TB diagnosis and that sensitivity was increased most in women but this was not confirmed in another study in Chennai, India.

In a 2008 article on gender in TB research, Allotey [13] states that the general reported trend that TB is more a disease of men than women highlights the effect of poverty on access to diagnostic facilities, a factor that disproportionally affects women. Other social barriers for women to TB diagnosis include roles such as care of others, which hinders their opportunities to access diagnosis, services which are insensitive to gender-specific needs and greater experiences of stigmatization and discrimination in women identified as having TB.

Original research

Of the 42 articles that included relevant information on the relationship between gender and diagnosis of TB and initiation of treatment upon TB diagnosis, 19 of them specifically addressed gender as part of their objectives. Out of the 42 studies, 37 used quantitative methods only, three used qualitative methods only, and two used a mixed method approach. Three of the articles described the results of an intervention, of which one had included the topic gender in the objective. One study assessed the feasibility and yield of active case finding among household members of smear positive TB index cases, and compared the yield to that in household members of two neighboring households [52]. Another study had introduced active case finding in a community, by community nurses, and compared actively and passively detected TB suspects on some aspects like gender [1]. In the third intervention study, the effect of a course of oral salbutamol on sputum positivity was assessed [97].

We classified the results into five categories related to different aspects of TB diagnosis and initiation of treatment:

1. Access to TB diagnostics
2. Health care system related delay in TB diagnosis
3. Results of TB diagnostics, further divided into:
    a) Sex and age distribution among suspects and cases
    b) Sputum microscopy versus culture
4. Initiation of treatment after diagnosis
5. Interaction between health care staff and patients

Access to TB diagnostics

Three studies, from Vietnam, South Africa and Bangladesh, compared male to female (M:F) ratios in the general population to the ratios in TB suspects ([98],[99] and [100]). The M:F ratio in the general population was close to one (0.97, 0.94 and 1.05), while the ratio among TB suspects were 1.36, 1.45 and 1.9. One of these studies also gave the M:F ratio among outpatients with

respiratory symptoms, which was 1.27. Another study [26] compared the M:F ratio among the general population and outpatients. Among the general population it was 0.96 while it was 0.68 among outpatients, and 1.6 among outpatients with respiratory symptoms. The lower ratio among all outpatients indicates that women visited health clinics more often than men, but not for respiratory symptoms. In accordance with this finding, the prevalence of respiratory symptoms in a community survey was observed to be higher among men than women.

Overall, in four studies including data from seven countries, higher rates of sputum submission for TB diagnosis among male inhabitants were observed in Malawi [101] (OR=1.17, 95%CI 1.14–1.20), Kenya [87] (M:F ratio 1.5), and India [102] (M:F ratio 1.9). In contrast, in an analysis of routine laboratory records in Benin, Malawi, Nicaragua and Senegal [103], in all four countries the greatest proportion of suspects was found in young adults, and the age distribution of suspects in general was comparable between men and women, so rates of sputum submission among men and women did not seem to differ greatly. The study in Vietnam [98] noted that in the 30 districts, in all age groups, a greater proportion of men than women had sputum smear examination done, although there was no significant difference in 0-14 and 25-34 year groups.

Five studies compared data of actively and passively detected TB cases. In Peru [52], not previously detected TB cases identified through screening of household contacts of an index case were more likely to be female (3 males vs. 8 females) and more likely to be aged ≥55 years than cases who had self-reported at the clinics (119 males vs. 93 females). It is unclear whether this under-notification occurred because older women delayed seeking medical care for their symptoms or because health care providers failed to make prompt diagnoses when these individuals did seek care. In Vietnam [104], the M:F ratio among actively detected cases was 0.7:1 compared to 2.7:1 in cases detected passively by the NTP. Case detection was low overall, but seemed to be higher among men than women (39% vs. 12%, with wide confidence intervals due to low numbers). In Nepal [16], more males were detected both by passive and active case finding and cases detected through active case finding had a lower M:F ratio than self-referred cases (1.2:1 compared to 2.6:1). Particularly noticeable in Nepal was the difference in the number of older females (≥ 45 years). In contrast, in India [26], the M:F ratio was 6.5:1 among patients detected in a large community survey compared to 4.1 for those notified by health facilities. Borgdorff et al.[29] compared M:F ratios in notification and prevalence survey data in available data from 14 countries. In most countries in the South-East Asian and the Western Pacific region, the M:F sex ratio in prevalent cases was, in general, greater than 1 and similar to or higher than that in notified cases, but not in sub-Saharan Africa, suggesting that M:F differences in notification rates may be largely due to epidemiological differences and not to differential access to TB diagnosis. The authors noted themselves that this conclusion cannot be generalized to individual regions or countries, as confirmed by the study results mentioned above.

In the US[105], male TB cases were more often diagnosed after death than female TB cases (aOR=1.52, 0.98-2.46). This may have to do with the fact that male cases more often belong to a risk group like injecting drug users.

Differences between men and women in the presentation of TB symptoms might influence the decision of seeking help in people infected with *M. tuberculosis*, and might also influence the chance of suspicion of TB by clinicians. Five studies, with data from London [106], India and Bangladesh[50], India, Bangladesh, Malawi and Colombi [51], Nairobi, Kenya [107], and Vietnam [44] reported on symptoms in pulmonary TB patients. Four studies did find a difference in clinical presentation between men and women. The study from London [106] found that female patients more often did not present with the systemic TB symptoms of fever, sweats and weight loss. Female patients in India and Bangladesh reported more diverse ("vague") physical symptoms more often than male patients and also reported a higher mean number of categories of physical distress, and more females in Malawi reported 'other' symptoms than males. In a study in Vietnam [44], general symptoms (such as fever, tiredness, anorexia and headache) were significantly more common in women than men, whereas symptoms suggesting pulmonary TB (PTB) (such as cough,

sputum expectoration and hemoptysis) were significantly less common in women than men. In all four countries in the multi-country study[51], women presented to the clinic with a greater diversity of nonspecific physical symptoms. In India, characteristic symptoms of cough and blood in sputum were as frequent among men as among women, but non-specific symptoms were more often reported by women. In Nairobi[107], no difference in symptoms was observed between male and female patients.

Two studies reported on radiographic presentations in pulmonary TB patients. In Nigeria[108], 50% of PTB patients presented with cavitations without differences between male and female patients. In Vietnam[109], men presented with advanced CXR findings more often than men, despite a similar disease duration. This could correspond to a slower rate of progression to smear positive disease among women. The authors conclude that this would have implications for the possibilities for women to obtain a timely TB diagnosis.

In another study among TB patients among TB patients from Vietnam [55], the proportion of patients who were ordered to have sputum smear examinations for TB symptoms at their first health care encounter was examined. A higher proportion of men had smear examinations than women (36% vs. 14%, P<0.001). This was due to the fact that women less often went to the hospital when first seeking health care.

Three studies looked at completion of the TB diagnostic process. In a study from India [102], among those who reported for sputum smear examination at the laboratory, a similar proportion of males and females did not provide three sputum smears (7.7% vs 6.8%). In Mexico [1] upon active case detection of suspects by community nurses, the overall proportion of suspects providing three samples was lower than in India, and slightly higher than among male suspects than female suspects (86.4% vs. 84.6%). Only in Kenya [107], male suspects less often produced at least one specimen (male: female ratio 0.8).

Health care system related delay in TB diagnosis

Studies in eight countries (i.e. Bangladesh, India, Malaysia, Mexico, Norway, Rwanda, South Africa, Tajikistan, Vietnam) did not find differences in health care system related TB diagnostic delays between men and women [1, 26, 68, 72, 76-77, 110-111]. The typical average delays were in the order of one month, but with a wide variation in individual delays. Only a study in Bangladesh showed minimal diagnostic delays as delay was measured upon arrival in a TB clinic. In contrast, six studies with data from seven countries did show differences in health care system delay. In a study in four provinces in China [112], a statistically significant difference in experiences of >2 weeks of health care provider related diagnostic delay was found only in Liaoning province, where 25% of male patients (40/158) and 35% of female patients (23/65) experienced delayed diagnosis (*P*=0.04). In Vietnam [59], female patients more often had a health care provider delay between onset of cough and onset of treatment of ≥6 weeks but the difference was small and not significant (aOR 1.2, 95% CI 0.8-1.7). A study in Spain [113] also found that sex was not associated with a health system delay greater than the median (aOR 1.12, 0.97-1.29), but female gender was associated with a health care system delay greater than the 75th percentile (aOR 1.26, 1.06-1.49). The authors think that this probably is due to lower index of suspicion among females. Another study from Vietnam [41] observed significantly longer delays between first visit to any health care provider and TB diagnosis was longer in women than men (average 7.7 vs. 5.5 weeks), as well as the delay from visiting a qualified medical doctor or a hospital to TB diagnosis (5.4 vs. 3.8 weeks). In multiple regression analysis, rural residence was a risk factor for longer doctor delay in men while highland residence was associated with a longer health care provider delay in women. Women visited more health care providers before TB diagnosis (mean 1.7 vs. 1.5). In the multi-country study [51], health care provider delay was longer for women than men in all three countries (not studied in Colombia), which was mainly due to the longer duration between first help

seeking and visiting a primary health center in women. A study in Nepal [22], also found that women had a longer health care provider delay (median 1.3 vs. 0.8 months, *P*=0.05). Over 75% of both men and women who had attended the government medical establishments directly received TB diagnosis within a few days of their visit, whereas many subjects received a diagnosis much later if they initially visited a private health care provider or traditional healer. Visiting a traditional healer first was associated with a longer health care provider delay in men than women (*P* = 0.030); however, the delay did not differ significantly by sex when they visited a private health care provider (*P* = 0.11) or government medical establishments first (*P*= 0.63). The median health care provider's delay was 1.5 months for men and 3.0 months for women when they visited a traditional healer first, whereas it was 1.3 months and 1.7 months, respectively, when they visited a private provider first.

Three studies from the US looked at gender differences in diagnostic delays among special groups. Two studies were done among hospitalized patients. In the first delays in smear orders were more often observed in female patients (aOR 1.66, 95% CI 1.06-2.60) as well as borderline significance in delays in isolation (aOR 1.40, 95% CI 0.98-1.99) [114], which is probably due to a lower suspicion of TB among women than men. The other study on hospitalized patients [115] did not show a lower suspicion among women. Against a background of an increasing TB incidence during the early phase of the AIDS epidemic, the proportion of patients for whom TB was considered in the first two days increased significantly for male patients from 66% in 1987 to 74% in 1990, while no trend was observed for females (average 77%), even when adjusting for HIV status. Among inmates who should all be screened for TB [116], the median time from intake to tuberculin skin test was 3 days for men and 2 days for women. Median time from referral to chest x-ray (CXR) was 2 days for men and 7 days for women; the recommendation is that this should be done within 3 days. Among those referred for CXR, more women than men were released before the CXR was made (34% vs. 6%) and more women did not get a CXR within 90 days (6% vs 0.01%).

Results of TB diagnostics

Sex and age distribution among suspects and cases

Almost all studies comparing TB suspects and TB cases observed a higher proportion of males among TB suspects, and a higher proportion of male suspects to be cases [29, 87, 98, 100-101, 117-118]. In a multi-country study in Bangladesh, India, Malawi and Colombia [51], the F:M ratio among patients in the clinic registers decreased consistently at each of the three steps of the clinical process, from symptomatic presentation with suspected TB, to submission of diagnostic sputum, to obtaining a positive result for sputum. Only in Malawi, no difference was observed in the F:M ratio between TB suspects and those submitting sputum. There, the relative decrease in the F:M ratio among those smear positive also was smallest (11%). Observers more frequently identified discomfort about producing sputum among women (39%) than men (15%) in Malawi but not in India and Banglades (this was not studied in Colombia). Dandona et al. [102] also found a higher proportion of male suspects in India, but the proportion of patients diagnosed as sputum positive was similar among men (68.8%) and women (68.2%). Jiménez-Corona [1] found that among PTB suspects detected actively in Mexico, the proportion of men was 44% while it was 59% among those diagnosed as having PTB. Among actively detected cases in Kampala, Uganda, Sekandi [119] noted an even sex distribution. Ramsay et al. [107] noted that in Nairobi 45% of suspects were male but that regardless of the definition applied, more men than women were found to be smear-positive.

Three studies, from Bangladesh [100], Kenya [87] and South Africa [99], compared M:F ratios among TB suspects and TB cases. All three studies found that the M:F ratio's among both TB suspects and TB cases were above 1, and that the ratio was bigger among cases (>2 for smear-positive cases) than suspects (1.5-1.9). In Kenya, the ratio was higher among smear-positive

cases (2.1-2.4, depending on definition applied) than among all culture-positive cases (1.8). In South Africa, the M:F ratio increased for smear grade+ 1.8:1 to 2.5:1 for smear grade+++.

Several studies analyzed both sex- and age-distributions and the results varied greatly. In the South African study mentioned above [99], the M:F ratio among confirmed TB cases was 1.7-3.6 in age groups between 25-74 years but was around 1 in younger and older age groups. Rieder et al [103] found that age-and gender-specific distributions of TB suspects in four countries were, in general, similar among men and women, but that in contrast, age- and gender-specific distributions of cases among suspects showed large differences between countries. Overall, in all four countries, a higher proportion of male suspects turned out to be cases compared to females. The proportion of females among cases was similar in children but in adults decreased with increasing age. Thus the M:F ratio increased with age. Also in a study in Bangladesh [100], the M:F ratios among both suspects and cases increased with age. This is in accordance with another study from the same country [111] which noted that among women in Bangladesh, more teenagers were diagnosed with TB, while among men TB was more prevalent among the elderly (data not shown). Also in accordance with this, Borgdorff [29] observed that M:F notification ratio's were above 1 and increased with increasing age in almost all countries. Also, in India [26], the overall sputum positivity rates were significantly higher among men than women (15.3% vs. 6.9%; $P < 0.001$) but differed with age. Among men, the sputum positivity rate increased with age, reaching a peak in the age group 35–44 years, and then decreased with age. Among women, the sputum positivity rate decreased significantly with age (chi-square linear trend, $P < 0.001$). This led to an increasing M:F ratio with increasing age. In Vietnam [98], in the age groups 25-54 years, men were approximately twice as likely to be smear-positive, whereas there was no sex difference in the youngest (0-24 years) and oldest (>65 years) age groups. The sex differences remained after stratification for specimen appearance, timing of collection and number of smears examined. In contrast, in Tanzania [100], a significantly higher proportion of female cases (61%) were aged 15–34 years compared with males (45%, $P < 0.05$), probably due to a higher HIV infection rate in young women.

Sputum microscopy versus culture

In a recent study in Moldova, Mongolia, Uganda and Zimbabwe, Rieder [120] concluded that although there were larger differences in the prevalence of sputum smears with low-grade bacillary counts between countries and age groups than between men and women, there was a tendency towards females having lower bacillary counts. Countries with high HIV-prevalence more often observed low-grade results, as well as patients at the extremes of age. Stratified by sex, female cases had slightly greater proportions of low-positive results in all countries except Zimbabwe. Stratified by age and sex, females aged <35 years and >64 years had a greater proportion of low-positive results, while between 35 and 64 years the inverse was the case. Stratified by country, age and sex, in all countries, women ≥65 years had a higher proportion of low-grade results than men although this difference was significant only in Moldova. In Uganda, girls had a significantly greater proportion of low-grade positive results than boys.

Several other studies also showed that sputum smear microscopy seemed to be less sensitive for women than men. Lawson [118] observed that male and female patients were as likely to have a positive culture (OR 1.12, 0.89-1.40), but male patients more often were smear positive (52% vs. 42%, P-0.003). This may at least in part be due to the higher HIV prevalence among women (58% vs. 49%, P=0.02). Kivihya-Ndugga [87] also observed that the M:F ratio among culture positive cases was lower (1.8) than among smear microscopy positive cases (2.1-2.4). Murthy [97] observed that among TB suspects with dry cough or scanty sputum, a short course with a β2-agonist (salbutamol) led to a two-fold enhancement in sputum positivity was observed in women with salbutamol intervention, which made the gender distribution in TB diagnostics near equal. Of note, more women than men needed a second course of salbutamol. Ramsay [107] found that regardless of the definition applied in Nairobi, more men than women suspects were found to be

smear-positive but that the increase in detection with less strict criteria was higher for women. In a sub-selection of those who produced a set of good quality specimens, the differences became smaller and borderline significant (*P*=0.05-0.06). Also, more men produced a set of three good quality specimens (based on macroscopic classification): 64% vs. 54%, *P*=0.01. This was not observed by Kivihya-Ndugga in another study in Kenya, where gender was not associated with sputum quality. Here sputum volume was associated neither with culture positivity nor ZN smear positivity.

Initiation of treatment after diagnosis

In the four country study [51], the F:M ratio for smear positive patients was no different from those starting treatment in all countries. Both in a study from India [26] and one from Bangladesh [100], the rate of initial default after diagnosis among smear-positive TB patients was similar among men and women. In the Indian study, this was both true for those patients diagnosed in a community survey and those who had presented themselves at health facilities.

Delay in starting treatment after TB diagnosis was found to be slightly longer among men than women among patients detected through active case finding in Mexico (median 6 vs. 1 day) but the difference was not statistically significant [1]. In Egypt [39], treatment delay among self-referred patients was only slightly longer for men than for women (median 1.4 vs. 1.2 weeks). In Bangladesh, treatment delay overall was similar for self-referred men and women (median 1 day for both), but it was longer for older women.

Among Asian born TB patients in New York city [121], participation in directly observed treatment (DOT) was significantly associated with male sex (47% vs. 30%, aOR 1.86, 95% CI 1.30-2.66). However, as the researchers did not know which proportion of male and female patients were offered DOT before start of treatment, no conclusions can be drawn on whether there is a differential acceptance of DOT by gender.

Interaction between health care staff and patients

Five articles describe gender specific results on the interaction between patients and health care staff. In Syria [27], the satisfaction with services providing TB care was very similar between men and women. In a follow-up on the study showing longer doctor delays for female than male patients in Vietnam [49], TB doctors proposed that the observed longer doctor delays for female than men TB patients was not caused by delays in recognizing symptoms or proposing investigations, but instead by the fact that women are thought to delay their own diagnostic process. Reasons provided were socio-cultural, like stigma, and practical concerns, such as women not being able to come to the clinic by themselves and their lack of decision-making power. In another study from Vietnam [63], several male doctors described the meeting with female TB patients as difficult as women presented their symptoms in a "less concrete" way, making it more difficult to examine and diagnose women than men. Female doctors did not report this. Similar results were reported in India [33]: the dominance of doctors seemed to be more pronounced in consultations with female patients, and as a result, female patients' own accounts of their illness tended to be neglected, which may explain female patients' greater difficulties in receiving sputum investigations and being diagnosed with TB once they present to the health care system. The doctors' interactions with female patients were often restricted by other social structures, e.g. when a senior family member was present during the consultation, the expected behavior of the women would be to keep silent and let her attendant talk to the doctor. In Bangladesh[51], female clinicians gave direct instructions before start of treatment to nearly all male patients (90%) but to

only 33% of female patients-more often instructions were directed to a guardian. In India[51], consultations were longer than 15 minutes for 30% of female and 20% of male patients.

Treatment adherence

Of the 1734 identified studies, 82 were categorized as reporting on the topic 'adherence' based on title and abstract. We aimed to obtain the full text papers of all these 82 studies. After reviewing the full text we further excluded 44 papers because of the following reasons:

- paper did not report on treatment adherence (n=19);
- paper did not include any gender analyses in treatment adherence(n=9);
- paper clearly focused on treatment outcome categories and was therefore categorized into the topic 'treatment' outcome (n=16);
- the reference was not an original study (n=1);

As of September 30th 2010 we could not obtain the full text of 1 article [122].

The 32 eligible papers were selected, and three additional papers identified as eligible based on title and abstract were added later. Six papers identified in the references of the selected papers were also added.

Previously published reviews

In 1996 a review article was published by Hudelson [3] on gender differentials in TB including 51 articles published in the period between 1975 and 1995. The author found that gender differences may exist in rates of compliance but that there is no consensus among the studies reviewed as to whether men or woman are more compliant. It appeared to depend on the particular socio-economic and cultural context. Barriers to compliance especially relevant for woman included lack of time, cash, transportation and replacement labor. Stigma associated with TB, and knowledge about TB and its appropriate treatment are also important influences on compliance.

In 1996, Conolly et al [9] published an article on women and tuberculosis, in which a few studies on treatment compliance were described. It was reported that once on treatment, women may face greater difficulties maintaining compliance. A study in the Philippines is referenced in which a high default rate among pregnant or lactating woman was reported due to the fear that the drugs could cause miscarriages and reduce the ability to breast feed or harm the baby [123]. Another study in India is referenced showing that parents of girls of marriageable age were reluctant to continue sending their daughters to the TB clinic once the symptoms subsided. It was felt that knowledge of the disease among the communities reduced their daughters' chances of marriage [17].

In 1999, Ogden et al [8] wrote a review paper based on literature from India and key contributions from social science, attempting to answer the question 'who is to blame for treatment failures in TB?'. Authors report that a number of studies, mainly from the Indian subcontinent, indicate that gender effects are significant obstacles to woman's ability to adhere to treatment, although the evidence is largely anecdotal. No further details on gender differences regarding TB treatment adherence are reported.

In an article published in 2001, Uplekar et al [4] call attention to the need for research that helps determine the extent to which gender inequalities in TB are due to distinctive problems of access faced by men and women, so that TB programs can better address these issues. Adherence is included as one of the pieces of their framework for a research strategy to explain gender differentials in TB control. Regarding adherence, the authors note that women tend to comply better with the treatment. As part of the proposed research strategies, clinical record reviews and case studies could help answer questions regarding patient treatment behavior, including adherence to treatment.

In 2007 a systematic review of qualitative research on patient adherence to TB treatment was published by Munro et al. [14]. The aim of this systematic review of qualitative studies was to understand factors considered important by patients, caregivers and health care providers in contributing to TB medication adherence. Nineteen electronic data bases were searched for qualitative studies examining adherence or non adherence to preventive or curative TB treatments and describing the perspectives of patients, care givers, or health care providers, published between 1966 and February 2005. A meta-ethnographic approach was followed to synthesize findings across the 44 studies. Across these studies eight major themes were identified: organization of treatment and care, interpretations of illness and wellness, the financial burden of treatment, knowledge, attitudes, and beliefs about treatment, law and immigration, personal characteristics and adherence behavior, side effects, and family, community and household support. Among the personal characteristics and adherence behavior it was reported that female patients were perceived as being more motivated, but in some countries required permission from men or head of household to attend treatment. Further it was reported that two studies indicated that female patients who were, or wanted to be pregnant, were less likely to adhere to treatment as they perceived the treatment to be harmful [124] [125]. Among 'family, community and household support' one result was reported that husbands and other male support was considered important for female patients, but the influence on difference in treatment adherence are not reported.

The authors reported that in future research it should be explored how gender shapes experiences of treatment and how differing gender roles may influence adherence. This aspect was reported less frequently than expected in the primary studies in this review and would benefit from further exploration.

Original research

A review of the identified original studies showed that they can be classified into the following four categories:

1) Cross sectional and cohort studies examining factors associated with adherence to TB treatment
2) Cross sectional and cohort studies examining factors associated with adherence to treatment latent TB infection
3) Qualitative studies including focus group discussions or in depth sociologic evaluation aimed at finding reasons/explanations related to adherence
4) Prospective studies to assess the impact of different interventions on adherence to TB treatment or to treatment for latent TB infection.

It is also important to note that eight of the reviewed articles were specifically aimed at examining gender differences related to TB treatment adherence. Six articles reported on intervention studies; one of them did not report on the effects of the intervention by gender.

Treatment adherence is a critical determinant of successful TB control; poor adherence may result in both treatment failure and development of resistance to TB medicines [2].

The identified studies used different terminologies to describe the concept of adherence. For example some studies used the terminology 'adherent or compliant to treatment' and defined this as clients who did not come to the clinic and did not respond to follow up phone calls [126], or not completing the full doses of treatment by pill count [127] [128-129]. While other studies used the term 'defaulted' and defined this as interruption of treatment for two consecutive months, a definition similarly used when describing TB treatment outcomes [26, 130].

The results of our systematic literature review show that, in contrast to the findings of the three review articles published in the 1990s [3, 8, 131], the majority of studies that report on gender

differences in adherence to either IPT or TB treatment found a higher likelihood of compliance among females compared to males.

Ten studies did not identify a difference in adherence rates between males and females [17-18, 27, 126-127, 132-136] while one study reported that being male was significantly associated with default in the univariate analyses but no existing differences when multivariate analyses were conducted [132]. Eight studies found effect that being male was associated with default in multivariate analyses [130] [137] [138] [102] [139] [128] [140] [129], five in univariate analysis [31] [141] [142] [143] [51], or showed a similar but not statistically significant trend [144] [145]. A study in Saudi Arabia found that, although female patients were less likely to default than male patients, when only Saudi Nationals were considered, non compliance was seen more frequently in females [142].

The majority of the studies did not investigate the reasons for the observed gender differences in adherence to treatment. Only a few studies discussed the gender differences and came up with possible explanations. Lavigne et al [128] hypothesized that males may be less compliant to LTBI treatment for economic reasons. In various cultures, men are the main contributors to the family income and cannot afford to take time out for a medical visit to a clinic. Other studies also mention the fact that men are largely responsible for financial family support [146] or their bread winner status [139], and that this was one of the most common reasons cited by men for choosing to work instead of complying with TB treatment.[147]. Besides work-related pressure, alcohol and drug addiction was also reported as a reason for non-compliance among men[34, 45].

Feeling responsible for taking care of their children and family was found to be a motivation to adhere to treatment regimes among some women [34, 129]. Alternatively, the pressure of housework can also lead some women to drop out of treatment [45]. Barnhoorn and Adriaanse [17] hypothesize that social rejection could also be a stronger deterrent to adherence for women, especially those of marriageable age, whose parent might be reluctant to send them to the clinic, as this might bring the disease to light. Nair et al [45] reported that the strain of keeping their disease a secret affected women's adherence to treatment, particularly when the reasons for their movements outside the home were routinely questioned.

For women, the quality of the interaction with the staff, the physical conditions of the TB units, and the quality of the initial reception at the health facility were reported as factors that could influence the likelihood of compliance to treatment [147]. Khan et al [89] reported that women in rural areas were particularly disadvantaged by problems associated with travel; duration and costs of travel and being unable to travel alone were mentioned as factors contributing to default. An ethnographic study in the Philippines concluded that the local belief that TB medicines can cause miscarriage, dry up breast milk or harm lactating babies, can dissuade women from complying with TB treatment [123]. Weiss et al. [51] also reported beliefs that TB treatment can have harmful effects in pregnancy and breastfeeding.

Treatment outcomes

Using titles and abstracts, a total of 165 papers were selected based on their including information about tuberculosis treatment outcomes. Thirty-five studies were excluded after reading the full text of the selected papers because: 1) 25 studies were not related to gender and tuberculosis outcomes, 2) 2 studies were not original research, 3) 2 studies related to treatment of latent tuberculosis infection, 4) 5 studies focused only on multi-drug resistant tuberculosis, 5) 1 study did not sufficiently define the outcome.

Therefore, a total of 140 papers were included and read. While reviewing the selected papers, an additional 5 articles were identified in the references and were later included after reading the full text. Thus, ultimately, a total of 145 papers were included in the final review of treatment outcomes.

Previously published reviews

Acknowledging the need to consider the broader impact of gender on health in 2001 Uplekar et al developed a seven step model of gender differentials with the aim of clarifying and examining each step in the course of TB control. Building off other barriers, the final step of the model and the ultimate aim of TB control was for patients to obtain a positive treatment outcome [4].

In a 2004 WHO Tuberculosis Report [2], authors highlighted two studies in Africa and Asia in which more males than females had unsuccessful outcomes. For example, in one study conducted in three urban and rural districts in Tanzania, 5% of females and 6% of males defaulted from tuberculosis treatment and 67% of females and 63% of males were found to be free of TB following treatment [148]. Similarly, in Thailand, being male was a strong risk factor for unsuccessful treatment outcome, even after controlling for other variables in the analysis[149]. Authors linked adherence and treatment outcomes and emphasized the need to critically examine the subjective 'cost-benefit analysis' which TB patients personally undergo when weighing the personal, social and financial burdens against the expectations of a cure.

In a 1996 review article of gender differences in tuberculosis Hudelson discussed gender differences in tuberculosis outcomes [3]. The author pointed out a study from Pakistan which examined reproductive-age mortality in women in Karachi and found that tuberculosis accounted for 40 percent of infectious disease deaths[150]. Based on verbal autopsies, authors of this study found that many women stopped treatment early because of the high cost. In another study cited by Hudelson, Cassels et al. found that patients identified through active case finding were more likely to default than those who self-referred and that older female patients were more likely to default than older male patients [16].

In two articles by Connolly and Nunn and Holmes, Hausler and Nunn authors suggest that in settings where women occupy a lower status, the consequences of TB may result in higher mortality. Examples were provided from two studies from China and India to illustrate gender differences and death from TB [9] [6]. In China, higher mortality and case-fatality rates from tuberculosis were found in younger females and in females of reproductive age than males of the same age[151]. Similarly, authors refer to a study from India in which younger females had case-fatality rates over 35% greater than males of the same age[152]. Authors posed the explanation that young women may have increased biological susceptibility to tuberculosis related to child bearing. Also, younger women may have had lower awareness about tuberculosis resulting in delays in treatment, or more constraints in accessing care than men.

In their report from a study conducted in four countries, Weiss et al addressed aspects of TB control with reference to a gender-specific barrier framework including treatment outcomes [51].

Using registry data, across sites (Bangladesh, India ,Malawi, and Colombia), authors found consistent findings showing that men were less likely than women to successfully complete treatment. They highlighted the need for gender sensitivity and TB control and for further study of the relationships between the following: health policy, stigma, responsibility, ethics, and outcomes.

Original research

Review of the selected studies revealed they could be classified into the following topics:

- Successful treatment outcomes – Cure and/or Treatment completion
- Death
- Default
- Failure
- Smear and culture conversion
- Adverse events
- Other outcomes
    - Radiologic outcomes
    - Pharmacokinetics/Biochemical outcomes
    - Body Mass Index
    - Quality of Life
    - Hospitalizations
    - Relapse
    - Other outcomes

According to the WHO, a cured case is defined as a patient with pulmonary tuberculosis who had completed treatment with a negative bacteriology result during the course of treatment and at the end of treatment. A case with completed treatment is defined as a patient with pulmonary tuberculosis who had finished treatment, but with no bacteriology result at the end of treatment. Within this review, successful treatment was reported many ways. Death as a treatment outcome is defined as a patient who died from any cause during treatment. Defaulted is for a patient whose treatment was interrupted for two consecutive months. A failed case is assigned to patients who were initially smear-positive and who remained smear-positive at month five or later during treatment. Transferred out is for a patient who transferred to another reporting usit and for whom the treatment outcome is not known. In this review, while most studies used the above definitions, some studies varied their outcome definitions. For example, when comparing treatment success, authors sometimes varied their reference group and included died, default, and treatment failure, while others included transferred out cases and lost to follow-up. Furthermore, studies had variations in follow-up times for outcomes.

Successful treatment outcomes – Cure and/or Treatment completion

Seventeen studies found more females than males had a successful treatment outcome [153] [154] [155] [27] [156] [100] [157] [158] [138] [102] [31] [159] [160] [161] [146] [162] [163]. Many of these studies reported the relationship between gender and treatment success to be statistically significant [153] [154] [155] [27] [156] [157] [158] [138] [102] [31] [159] [161] [146] [162]. In one study out of England, Wales and Northern Ireland, a larger proportion of females than males completed treatment and sex was significantly associated with treatment success, although authors used a modified criteria to define successful tuberculosis treatment outcome [164].

In seven studies, no association was found between gender and treatment success [165-166] [167] [168] [160] [39] [169] [163, 170].

Three studies reported significantly higher cure rates in females than males [102] [171] [172]. One study among children from India reported higher treatment completion rates in males, but no test of significance was reported [173].

Other studies found no association between gender and cure [174] or treatment completion [135].

Death

Studying the relationship between gender and death in TB patients is important in order to identify and target persons most at risk of dying. In twenty-eight studies multivariate analyses were used to explore factors related to mortality among TB patients. Of these, gender was not found to be associated with mortality at the bivariate level in five studies [175] [132] [166] [176] [177] or in the final model in eight studies [178-183] [184-186]. In thirteen studies, males were significantly more likely to die than females in multivariate analyses [1, 156, 187-190] [191-196] [197]. In only one study among hospitalized pulmonary TB patients in Bolivia, females were found to be more likely than males to die, after controlling for other variables, including coexisting pathology and extent of lung disease [198].

In a descriptive study of new pulmonary tuberculosis patients in England and Wales, significantly more male patients died from tuberculosis than female patients [199]. Thirteen other studies described sex differences in mortality, but no statistical differences were reported. In seven of these studies more males than females with tuberculosis died [154] [200] [160, 168, 201-203] [204] whereas more females than males died in three studies [22, 205-206]. In three studies, the proportion of deaths among males and females was not provided [171-172, 207]. Pérez-Perdomo et al reported no significant differences in median survival time between males and females following AIDS diagnosis among AIDS cases with active tuberculosis, Puerto Rico, 1981–1998 [208].

A number of studies examined mortality rates over time. Overall, findings from ten studies from Brazil, South Africa, Spain, Hong Kong, Singapore, Taiwan, India, and Japan have shown that males had higher mortality rates than females, even when taking age into account [209] [210] [211] [212] [213] [214] [182] [215] [216] [217]. Authors speculate about the reasons for these differences. Kolappan suggest the higher mortality rates in males reflect the higher treatment defaults occurring among men possibly due to factors such as smoking and alcoholism. Hino et al also offer alcohol consumption among men as a possible reason for their higher mortality, as well we their tendency to take longer to seek health care, compared to females who authors suggest are more health-conscientious.

Several studies attempt to examine why mortality is different in males and females. One study examined the role of smoking, a known risk factor for TB, on death in South Korean men and women, and found smoking was associated with an approximately 50% increase in risk of mortality from tuberculosis in both males and females, with male and female current smokers having equally heightened risks of death from tuberculosis [218]. In a retrospective study in San Francisco in 1986-1995, DeRiemer et al. found that male TB cases more often were diagnosed after death than females, which may be related to injecting drug use, which was also independently associated with diagnosis after death [105]. Bang et al investigated occupations and industries with elevated respiratory tuberculosis mortality in the United States during 1990-1999 and found elevated proportionate mortality ratios in more industries for white males than for any other groups [219]. Authors attributed this finding to more TB deaths that were documented in white males than in other groups. A study by Burke et al examined tuberculosis mortality and its relationship with recent childbirth in a retrospective study of Gibraltarian women, 1874-1884 [220]. Even after controlling for age at death, marital status, and religion, recent childbirth did not increase the risk of tuberculosis mortality among women; however, the odds of tuberculosis mortality increased to eight to one among widowed women. Authors attempted to explain this finding with the possibility that the deceased husbands of widowed women had died of tuberculosis, thereby increasing the women's likelihood of contact with TB. Alternatively, widows may have been faced with increased financial and emotional stress, which may have enabled tuberculosis the opportunity to take hold

prior to their own death. Elender, Bentham, and Langford examined the association of poverty, ethnicity and AIDS on tuberculosis mortality in England and Wales during 1982-1992 [221]. They found overcrowding at the household level and poverty to be significant predictors of TB mortality for males and females. Authors suggest that because women have traditionally spent more time in the home than men, they may be at increased risk of infection from exposure to the tuberculosis bacillus for longer periods of time. Furthermore, authors implicate the psychological and physical stress induced by living in poverty in enhancing disease susceptibility. Gragnolati et al recognizes the use of BCG vaccine, TB treatment, health care system improvements, health education, and improved nutrition and sanitation as important interventions which have helped to reduce TB mortality over time [213].

Default

Authors of fourteen quantitative studies and one qualitative study discussed the relationship between gender and default. In the majority of the quantitative studies, authors reported more males than females defaulting from treatment [154] [26] [132] [130, 158] [144] [137] [139] [222] [1] [171] [223]. Authors found a statistical association between sex and default in seven of these studies [26] [132] [130] [137] [139] [1] [171] [223]. Alternatively, Kamel et al found slightly more females than males defaulted or did not complete treatment in Egypt, but the numbers were very small and the relationship was not significant [39].

Several other studies in Spain, Singapore, and Italy found no association between default and gender [132] [144] [190]. In the study by Fautstini et al, patients who failed or defaulted from treatment were grouped together. More males than females defaulted, but there was no association between sex and failure or default compared with other outcomes [190].

Some authors presented possible reasons for why males are more likely to default. One reason may be related to their primary role as bread-winners in the family and in society [158] [139]. Because of the nature of their work and the need to commute or leave their home early to work and provide for their families, males may find it difficult to comply with daily clinic attendance, especially during the continuation phase of treatment.

Other possible treatment barriers that were suggested related to time and money. For example, Van der Werf et al examined factors influencing adherence to therapy in a rural service program in Ghana, and reported longer home-to-clinic distances, along with male gender, significantly associated with higher default rates [223]. Alternatively, in a qualitative study examining socio-cultural constraints and treatment opportunities in Pakistan, Khan et al, found rural women were particularly disadvantaged by problems associated with travel, namely the duration and cost of travel and being unable to travel alone as factors contributing to default [89].

Failure

Three studies from Egypt, Vietnam and The Gambia found no statistical differences between males and females in relation to treatment failure [39] [224] [171]. A study from Saudia Arabia, however, found that treatment failure was almost three times more common among male patients than female patients [146]. Failure was assigned to TB cases with cultures that remained positive for *M.tuberculosis* at the end of the initial phase of treatment and also failed to show radiologic and clinical improvement. Authors attribute the higher failure rate in males to their higher prevalence of non-compliance, as no differences between gender in symptoms, radiologic findings, clinical presentation (pulmonary or extra-pulmonary), social background or drug resistance were found.

Smear and culture conversion

There were mixed results on the association between sex and smear and/or culture conversion in the seven articles included in this review. At the end of two months of treatment, three studies reported no association between gender and smear conversion [225] [27] [226], whereas a study from the Gambia found a significantly higher proportion of females than males had negative smears during the same time period [39]. A study conducted in Egypt found males were significantly more likely than females to have a positive smear at end of follow-up (10% vs 7%), but there were no sex differences in culture at end of treatment [39].

There were differences across studies in terms of gender and culture conversion at the end of two months. Güler et al [226] found no differences in males and females in culture conversion at two months after controlling for other factors in Turkey. However, in a study among smokers in Spain, culture was positive after two months in 23% of males and 44% of females; females were over five times more likely than males to have a positive culture at two months in multivariate analysis [227].

Two studies found that time to sputum smear conversion was significantly greater in males than females, while Guler et al found no sex difference in time to culture conversion [226, 228].

Adverse events

Twenty-one studies included in this review addressed the issue to adverse events among patients being treated for tuberculosis disease. In twelve studies, authors made comparisons between males and females in terms of liver injury during tuberculosis treatment [229-231] [232-235] [236] [237] [238] [239] [240]. Of the four studies in which significant sex differences were found after controlling for age [230, 232, 239] [240], females were more likely than males to experience hepatotoxicity as a side effect in three of the studies from Denmark, Singapore and Argentina [232, 239] [240]. In all four studies in which an association was seen, patients were given standard anti-tuberculosis treatment. However, in the study by Chang et al which found males more at risk of liver injury, approximately 20 percent of the cohort in Hong Kong were administered pyrazinamide with isoniazid and rifampin during the continuation phase of treatment [230]. Moreover, authors found a considerable difference in the unadjusted risk of hepatotoxicity for pyrazinamide-containing regimens was seen between males and females (3.2% vs. 0% among ages 35–49, and 5.0% vs. 0.6% among ages > 49 years, respectively).

In studies from Tanzania, Germany, and the United Kingdom ,authors found significant differences between males and females in the development of rashes during treatment [241-242] [243]. In two of these studies patients were treated with standard regimens, and females were more likely than males to develop rash, which was largely attributed to pyrazinamide[242] [243]. In the study by Ipuge, Rieder and Enarson, females in Tanzania were half as likely as males to develop adverse cutaneous reactions to thiacetazone [241].

Two studies from the Netherlands and South Africa found no association between sex and evidence of ototoxicity in tuberculosis patients receiving aminoglycosides [244] [131], and similarly no sex differences were found in hearing-related side effects among patients administered streptomycin as part of their standard treatment in Turkey [233].

In two studies of patients with tuberculosis meningitis, female sex was associated with permanent neurologic sequelea at the end of treatment in adults in Turkey [205] and male sex was a predictor of poor neurologic outcome after six months of treatment among children in South Africa [245].

In a study of non-HIV infected persons with peripheral lymph node tuberculosis in Korea, authors examined paradoxical responses, which they defined as clinical or radiological worsening of pre-

existing TB lesions, or development of new lesions in a patient who had received anti-TB therapy for two weeks or more [246]. Being male, younger age and presence of local tenderness at the time of diagnosis were independently predictive of paradoxical response in lymph node TB patients.

Two studies reported on sex differences in serious adverse events, which was defined as an event which led to at least the discontinuation of one or more standard anti-tuberculosis drugs [247] [243]. In Montreal, time to a serious adverse event was significantly more rapid in females and older patients, and their occurrence was associated with female sex, as well as older age, being born in Asia, and HIV positivity [247]. In Germany, the proportion of females with severe side effects was higher than males, but gender not significant in the final model predicting adverse events [243].

Other outcomes

Radiologic outcomes

Radiologic outcomes were linked to gender in Saudia Arabia, where chest radiographs of 1080 patients with pulmonary TB were examined at the end of treatment. Female gender was associated with poor radiological outcome, along with older age, delayed diagnosis, poor treatment adherence and previous TB [248]. Authors suggested that the worse radiological outcomes in females could be attributed to the stigma of TB in women, which may pressure female patients to hide their illness and refrain from seeking medical attention until late in the course of the disease.

A study from Egypt examining gender differences in outcomes in pulmonary TB patients found no sex differences x-ray status at end of treatment [39].

Pharmacokinetics/Biochemical outcomes

A number of studies have been conducted investigating the pharmacokinetics of TB treatment and biochemical outcomes in TB patients. Five different studies examining the effect of sex and AIDS on plasma concentrations of anti-TB medications conducted in the U.S. found that sex had no significant effect on the intrapulmonary concentrations of rifampicin, isoniazid, ethambutol, ethionamide, or pyrazinamide in plasma [249] [250] [251-253].

Two studies explored gender differences in the pharmacokinetics of rifampicin during treatment. Iwainsky et al investigated the influence of sex on intermittent rifampicin administration and found both the serum concentration and the urinary excretion of rifampicin were significantly higher in women than in men [254]. Another study examined the pharmacokinetic interactions between rifampicin and antiretroviral therapy and found that efavirenz concentrations during rifampicin administration were not associated with gender [255]

Another study sought to determine whether ethambutol usage alters serum copper concentration in patients with tuberculosis and whether there is any relationship between age, sex, and smoking habit. Abbasi et al found there was a significant difference in Cu levels but no relationship between changes in Cu concentration with sex, age, and smoking [256].

Body Mass Index

Weight gain is often used as part of the assessment of a patient's response to treatment, and two studies reported on the relationship of sex and weight change during treatment. In Tanzania,

authors examined factors related to weight gain and body mass index (BMI) during treatment for tuberculosis, and found that, in addition to length of hospital stay, drug regimen, HIV status, and tribe, sex was an independent determinant of weight gain, with women gaining more weight than men [257]. Although authors found that weight gain was ultimately a poor predictor of outcomes in tuberculosis patients in their study, they emphasized the importance of good nutritional status for morbidity, quality of life, and human performance in TB patients, which were not captured in their study.

Cakir et al measured changes in weight and BMI in males and females in Turkey during treatment for TB to assess if these related to changes in serum leptin and TNF alpha levels , which have been associated with anorexia [258]. While authors found a significant increase in BMI between pretreatment and posttreatment for tuberculosis, leptin and TNF alpha levels did not show the expected rise in parallel to weight gain in men and women.

Quality of Life

In addition to traditional outcomes of TB morbidity and mortality, some studies have expanded their assessment of health status to include other measures, such as the impact of TB disease and its impairment on daily activities, behavior, perceived health and functional state. To measure the impact of tuberculosis treatment on patients' lives, three studies discussed how sex related to quality of life. In China, Chamla et al used the SF-36 scores before, during, and at the end of treatment to assess tuberculosis patients' health related quality of life, and found sex was significantly associated with the total SF-36 score at completion of treatment. SF-36 scores showed a gradual increase over the course of treatment, indicating the positive effect on patients' quality of life [259].

Using a similar study design, Dhuria et al used a different tool (WHOQOLBREF) to assess the quality of life of TB patients at the onset of treatment, after 3 months of treatment, and at completion of treatment in Delhi. By the end of treatment, the mean scores for overall quality of life and in the physical domain were higher in females than males but the difference was not significant [260].

Another study from India examined the physical, mental and social well-being of tuberculosis patients [261]. Authors found that, for patients who were cured or completed treatment, measures of physical, mental and social well-being increased from start to end of treatment for both men and women. For example, patients' perceived health status increased from 5% and 7% to 78% and 82% in males and females, respectively (sig trend chi square). However, at the end of treatment 52% of males and 38% of females continued to have symptoms. The persistence of symptoms was not related to sex. Authors suggest the higher proportion of males with persistent symptoms is likely due to the high prevalence of chronic smokers among male patients and highlight the need for patients with persistent symptoms to receive appropriate medical evaluation and follow-up to ensure cure.

Hospitalizations

Hospitalization may be an indication of severity of tuberculosis disease, or hospitalized patients may differ from outpatients in terms of burden of co-morbid illness and contraindications to anti-tuberculosis drugs. Two studies examined differences in hospitalizations by gender. Chu et al examined the risk factors associated with early unplanned readmission to the emergency department within 28 days of discharge among newly diagnosed tuberculosis in Hong Kong [262]. However, sex was not independently associated with early readmission. Furthermore, Thierfelder et al examined what factors determined hospitalization among patients with pulmonary tuberculosis in

Tajikistan and found that independent predictors for hospitalization were male gender, smear status and age [163]. Authors suggest that health care providers may be more inclined to hospitalize men, because they are less self sustained when they are sick at home in the Tajik culture. Also, males are more likely to consume drugs and excessive alcohol, which are risk factors for hospitalization in patients with TB.

Relapse

Another yardstick for measuring treatment outcomes is to assess the recurrence of tuberculosis in previously treated persons. Understanding risk factors for recurrence of TB makes it possible to take measures to ensure treatment success. Six studies included in this review included gender in their examination of recurrent rates in TB cases [1] [263-264] [265-266] [267]. Four studies from Brazil, India, United Kingdom, and the United States found no differences between males and females in relapse rates, but found that inadequate or irregular treatment was the key predictor of recurrent TB [264-265] [263] [266]. Alternatively, two studies found higher relapse rates among males. Jiménez-Corona et al found males were over three times likely than females to have recurrent TB and be retreated in Mexico, after controlling for diabetes and drug resistance among bacteriologically confirmed pulmonary TB patients in Orizaba, Veracruz [1]. Authors attribute the higher relapse rate in males to their higher default rates. Tam et al. evaluated two rifapentine regimens in a clinical trial in Hong Kong and after 5 years found that elderly males were more like to experiences relapses (or failures)[267].

Other outcomes

In a retrospective study of adult patients at Korean teaching hospitals, Park et al examined clinical outcomes of spinal tuberculosis according to the severity of disease [268]. A favorable outcome was assigned to patients having no symptoms, full physical activity at work, no evidence of central nervous system involvement, no remaining sinus or abscess that was clinically or radiologically detectable, and radiologic evidence of healing of the spinal lesion. An unfavorable status included at least one of the following conditions: not radiographically quiescent, limited physical activity, presence of a sinus or clinical abscess, myelopathy with functional impairment, or a need for additional chemotherapy for spinal disease. Among patients with spinal TB, authors found no relationship between sex and use of radical or nonradical surgery and outcomes at the end of TB treatment.

Discussion and conclusions

To reach the Millenium Development Goal to halt and reverse the incidence of TB by 2015, cure rates and case detection rates need to be improved greatly in many parts of the world. It seems evident that gender-specific interventions may contribute to improving case detection rates and treatment success. However, which interventions may work best in different parts of the world, is not yet clear. Policy making regarding gender within TB control is scarce and this review shows that intervention studies specifically focused on gender-specific issues in TB control are virtually non-existent.

In order to design gender-sensitive TB control policies and programs, a detailed analysis of the different steps in the course of disease and the various gender-related factors that influence each one of these steps is essential. A multitude of such factors are revealed in the studies reviewed here. These factors are located at the broader structural level, as well as the interpersonal and individual levels, and they are related to biological aspects and the material conditions of TB patients, as well as the cultural meanings associated with the disease. When analyzing how these factors operate, it is important to take into account, on the one hand, the more general dynamics of gender in which they take place, and on the other hand, the way in which gender interacts with other axes of social differentiation, such as age, class, ethnicity, educational level, rural or urban residence, HIV status, etc. Further exploration of the interrelations in different setttings between these factors, levels and axes could prove useful for TB research and interventions.

While the articles reviewed provide important information about the gender-specific social, economic and cultural constraints to access healthcare for TB, it is important not to disregard the insights that they also offer into the different strategies used by men and women to face those constraints and to overcome the particular obstacles they encounter throughout the course of disease, from the onset of symptoms until the disease outcomes. TB control interventions could build upon some of these strategies, while still tackling the gender inequalities that make these strategies necessary in the first place. As research has shown, for instance, that women's lack of social and economic independence makes them more likely to visit traditional healers and private practitioners, TB control programs could collaborate more closely with these providers in order to enhance women's access to appropriate TB care, and at the same time address the conditions that restricts women's autonomy to seek healthcare.

Although outside the scope of this review, a number of studies included in this systematic review have attempted to elucidate to what extent the higher TB notification rates observed in men can be attributed to epidemiological differences or to gender differentials in access to TB care. However, as concluded in other reviews [2-3, 6-7, 9], a generalizable conclusion has proved difficult to reach. While the meta-analysis of data from 14 countries [29] and some country-specific studies [36] [26] seem to support an epidemiological explanation, comparisons between active and passive case finding have shown that women were more likely to be under-diagnosed, presumably due to a lower access to TB care [16] [52] [53]. Therefore, the relative contribution of epidemiological differences, on the one hand, and gender-specific barriers to TB care, on the other, to the gender differences in TB notification rates needs to be assessed for each specific context.

Before moving on to the conclusions for each one of the specific topics, it is appropriate to address the limitations of this systematic review. Although the search strategy used for this review yielded an important amount of relevant articles, it is not exempt of limitations. There might be articles that include important findings on TB and gender, but not as their central topic, and therefore might have not been retrieved in our search. For instance, based on title and abstracts, about one in ten papers were considered to be on TB epidemiology, but in the sidelines may have included some information on one or more of the topics covered in this review. In case of doubt, we retrieved the full text articles and only very few of these articles were in the end included in the

review. Moreover, the fact that our search relied on databases of academic journals implies that it lacked access to grey literature, such as reports by organizations or government institutions that do not enter the regular publication and distribution channels. Also, while Pub Med and SSCI are extensive and capture published literature across many themes, including papers in biomedical and social science fields, literature included elsewhere were not captured. By reviewing and using literature referenced in other articles, we were able to broaden our search somewhat. Also, because there are many ways to describe gender (e.g. sex, gender, male, females, men, women, etc) our choice of search terms may have missed studies with relevant findings. However, we conducted several 'sensitivity analyses' to determine if any articles were missed or findings would be altered when changing the various search terms, but the sensitivity analyses did not yield extra relevant articles. We should also consider the possibility of a publication bias of negative findings: studies that explored gender differences but did not find any could be regarded as less interesting to publish.

There are other limitations that have to do with the particularities of the studies on which the retrieved articles reported. There were relatively few qualitative and mixed methods studies that could suggest possible interpretations for the findings of the quantitative studies. Besides, the variability in the methods and the definitions used in different studies (e.g. the definitions of patient delay,adherence to treatment, and outcomes) posed a difficulty for making comparisons and trying to identify and propose explanations for similarities and differences within and across contexts.
Finally, this review focused on the broad topic of gender and TB, so no systematic distinctions were made in the presentation of results in regards to geography, type of TB (e.g. pulmonary or extra-pulmonary TB, age, HIV and non-HIV infected populations, drug resistance, or quality of study.

Health care seeking and access

Whatever the contribution of gender differentials in access to healthcare to the uneven TB notification rates, what has become apparent, based on the results of our review, is that there are important differences in the limitations experienced by men and women when trying to access TB care, and in the patterns they follow in the help seeking process. Our findings agree with previous reviews [3] that female TB patients encounter greater barriers to receive appropriate medical attention. The articles reviewed provide evidence that women's access to TB care is limited by their subordinate status within the family and in society at large, reduced access to and control over economic resources, heavy workloads associated with their role as caretakers, lack of independence, restricted mobility, deficient knowledge about TB, less appropriate sources of TB information and increased vulnerability to the social consequences of TB related stigma, which leads to a greater interest in hiding the disease.

This may explain the gendered patterns in help seeking behavior observed in many of the studies reviewed. Gender comparisons showed that women were more likely to seek help for their TB symptoms and to take a larger number of healthcare seeking actions, but they tended to do this with less qualified providers and in lower level healthcare facilities. This may often translate into longer and more convoluted paths to appropriate TB care, as shown by the fact that more articles reported a longer patient delay among women, especially in the Western Pacific and Southeast Asia, compared to those that reached the opposite conclusion.

At the same time, the social organization of gender may also have negative effects in men's help seeking behavior. The longer patient delay observed among men in some countries may be related to financial and work-related concerns, which seem to have a greater relative importance for them than for women, or to traditional standards of masculinity that regard seeking medical attention as a sign of "weakness". Paradoxically, men's tendency to initially neglect symptoms until they become more serious, combined with their increased autonomy and income, could also explain why they more often go directly to higher level healthcare facilities as their first help seeking action, compared to women.

Some of the articles reviewed provide important insights gender-related factors in health care seeking behaviors and obstacles to access to TB care, by exploring the interactions of variables such as gender, age, education and income, but further efforts would be necessary. Regarding TB-related stigma and discrimination, for instance, it would be useful to have a deeper analysis of the way in which these phenomena are grounded on existing (gender) inequalities, and at the same time contribute to strengthening and reproducing them. This type of analysis of the stigma of TB could profit significantly from recent developments in other areas of social and health research [269].

Diagnosis and initiating treatment

In almost all articles reviewed, TB suspects presenting for smear examination more often are men than women, and male TB suspects more often have a positive TB diagnosis than female suspects. The issue whether the male preponderance among TB suspects is due to lower access to TB health care services for women and/or due to a lower incidence and prevalence of TB among women remains a question. The issue of TB epidemiology was not a subject of the current review and as concluded before, this question remains unanswered. From the current review it is clear however that more sensitive diagnostic methodologies seem to be able to diminish gender differences among TB suspects in reaching a TB diagnosis to a large extent. In most low and middle income countries, TB diagnosis relies on sputum smear examination. Application of less strict criteria for smear examination, culture, and β2-antagonist for those with dry cough or low bacillary load in sputum, all diminished differences in a positive identification of TB between male and female suspects. This important finding highlights the potential to improve case detection among female suspects using more modern diagnostic techniques.

The results of this review show how gender can also exert an influence in symptoms such as cough and sputum expectoration, that are often thought of as solely dependent on physiological factors. The norms and expectations about what is considered as appropriate behavior for men and women may influence the way TB symptoms are presented and experienced, contributing to the differences in access to TB diagnosis and treatment.

Most studies observed very similar health care service related delays in TB diagnosis and initiation of treatment for men and women. Studies that did find differences, usually observed small differences to the disadvantage of women. Women more often visited less qualified health care facilities and in lower level healthcare facilities than men and this seemed to account for the differences observed in some of the studies. This is in agreement with the conclusions on health care seeking behavior, showing that women more often first visit under-qualified health care workers, such as traditional healers.

In female and male cases diagnosed with TB, women more often presented with symptoms not specific to TB. This may be one of the reasons why they are inclined to visit easily accessible health care workers and delay visiting a general health care clinic or specific TB clinic. Studies from Asia reported on the interaction between health care staff and patients. These studies observed that in Asia, especially the interaction between male doctors and female patients sometimes was problematic due to socio-cultural factors, like the subordinate role of women.

Only a few studies assessing delays between diagnosis and initiation of treatment existed. According to the results, delays in general were very short and did not differ much between men and women.

Treatment adherence

Whereas many of the studies presented in this section found women to be more likely to comply with TB treatment than men, there was only one that would reach the opposite conclusion, and only for a subsample of its population. This is all the more striking because, as it has already been discussed in previous sections, other researches provide evidence about the important obstacles women face to seek TB care and have an appropriate diagnosis. This supports what Uplekar et al. [4] have already suggested: while more men than women are diagnosed with TB, among those who receive treatment, women generally tend to comply better.

As for the reasons why this may happen, one of the studies reviewed provides an interesting insight when discussing the role of men's supervision in women's adherence to treatment [31]. Paradoxically, the same dependence and lack of autonomy that may impair women's ability to seek healthcare from appropriate providers, could at the same time make it more difficult for those who can access treatment to decide to interrupt it before completion. Men, alternatively, who generally enjoy greater independence, might as well use it to decide they won't continue with the treatment once the symptoms have disappeared. It would be important to reflect on how interventions could benefit from the follow-up that a strong family network can provide for TB patients, without inadvertently reinforcing an oppressive gender arrangement.

The fact that women are usually the primary caretakers and that their value within many societies often depends on their ability to fulfill this role may also constitute an important motivation to successfully complete anti-TB treatment, especially where female TB patients are stigmatized and regarded as unsuitable for marriage, having children, breastfeeding or taking care of a family. On the other hand, the particular social consequences that TB has for women, which make them more interested in keeping the diagnosis secret, might also explain why, for them, the quality of the interaction with healthcare staff seems to be more of a determinant of compliance with treatment, compared to men [147]. Social and financial constraints on mobility can also be particularly limiting for women's compliance with treatment [89].

Men's traditional role as primary income providers could also be related to their lower adherence, leading them to stop visiting the healthcare facilities in order to avoid loss of wages or employment. Besides, the sense of 'invulnerability' that is often associated with traditional ideas of masculinity could also cause men to be more prone to neglect treatment.

Treatment outcomes

Results from the studies included in this review show that females tend to have better treatment outcomes, while males more frequently die and default during treatment. These findings highlight the importance of improving clinical management for male TB patients who may be at increased risk of death and default. Additional time and effort may be necessary to educate males about the importance of adhering to treatment, and in investigating other social and financial support strategies, to reduce their chances of defaulting. Alternative treatment strategies, such as the use of family members to oversee treatment, may be useful in males. Default rates may be minimized through community health workers and volunteers, who may be effective in educating patients, contact tracing, and tackling stigmatizing factors. There is also a need to shorten duration of treatment, as well as decentralizing treatment and making directly observed therapy more feasible. Use of a comprehensive approach, which may include the provision of incentives, transportation, feeding, and others, can also improve treatment success.

Both TB control programs and other public health programs should be strengthened and should interact with each other to improve the TB treatment outcomes and to prevent unnecessary deaths. For example, to reduce the influence of smoking on TB mortality in both males and females, tuberculosis control programs and policies should in the future incorporate tobacco control as a preventive intervention. Also, detailed cause of death associated with tuberculosis should be collected by surveillance systems in order to provide better understanding of treatment outcomes.

This corresponds with the importance of implementing comprehensive national vital registration systems for accurate and reliable documentation for TB deaths.

Due to the limited studies available about the relationship between sex and treatment failure, it is difficult to make conclusions about whether failure is more common in males or females. Furthermore, the data show no consistent pattern for gender by smear or culture conversion. Moreover, no distinct patterns were found in terms of gender and relapse, although previous treatment was determined to be the most important factor in predicting recurrent tuberculosis. These findings highlight the importance of ensuring both males and females finish treatment, and the need for better confirmation that every TB patient is cured to decrease the incidence of recurrent disease.

Liver injury and serious adverse events were more common among women, suggesting the importance of closer monitoring for the side effects related to anti-TB drugs. Better understanding who may be at increased likelihood of developing adverse events during treatment may help with identifying and monitoring high-risk patients prior to starting treatment. Findings highlight the limitations of current anti-TB therapy and emphasize the need for urgent action to develop new, less-toxic anti-TB drugs with shorter regimens to treat patients with tuberculosis.

Quality of life also an important outcome for males and females, as it is important to examine all the domains of health to treat patients comprehensively and addressing issues relevant to the quality of life will provide added value to TB programs. This will require investments in support services to ensure care and counseling for patients beyond the status quo treatment strategy. Health care workers should be sensitized to the special needs of women affected by TB so that they can help the patients to combat its negative impact.

Recommendations for future research

A gender approach to tuberculosis policy and control programs may lead to improvements in effectiveness of TB control. Suggestions for future avenues of research are provided below. Before we give recommendations per topic, we describe some matters applicable to several of the components reviewed.

What has been concluded before[270] is that routinely collecting data on sex, and preferably other socio-economic factors, within the health care sector, including TB programs, would enable and promote analysis of the data by gender. This would provide important knowledge into the roles of gender in the different steps towards diagnosis and treatment of TB and make it possible to study these roles in different settings, which would greatly enhance insights.

Most research included in this review had a quantitative nature. Most studies using qualitative methods were included in the section on health care seeking behavior and access. A relatively small number of studies used both quantitative and qualitative methods. Application of mixed methods enables both quantifying the nature of the subject under study and at the same time assess reasons for these findings.

As concluded above, almost no studies on the effects of gender-specific interventions have been performed. One field that may benefit both women and men, includes interventions promoting partnerships between different public and/or private health care facilities and workers, to facilitate access to health care staff which recognizes TB suspects and will refer them to an appropriate clinic.

Furthermore, there is still a need for additional research examining the relationship between gender and TB in the context of the HIV epidemic. The strong relationship between TB and HIV, especially in settings of high-HIV prevalence, like sub-Saharan Africa, makes it essential to further examine how the co-epidemic influences men and women in terms of TB and health seeking behaviors and access to care, diagnosis, initiating and adherence to treatment, and outcomes.

It is crucial that TB control programs build on existing knowledge and move on from research to action, specifically addressing the gender-related barriers to TB diagnosis and care. These actions should be informed by action-oriented research that helps identify the most appropriate strategies for each particular context, and later evaluate their effectiveness. This action-oriented research could benefit greatly from a analyses of routinely collected TB data from the sub-national, national, and global program levels as suggested by Ottmani et al. [270]. Studying routine records and reports can help further focus the TB research and control agendas through the examination of the distribution of TB by gender. This would allow tracking gender disparities within specific contexts and their interaction with factors such as access to care, ethnicity, particular forms of TB, the HIV co-epidemic, etc. Interdisciplinary studies are also necessary in order to better explain the interplay of these factors.

Health care seeking and access

More research is needed to assess the gender-specific barriers to access TB healthcare and how much they contribute to male/female differences in notification rates, in each particular context. This research should consider gender-related influencing factors at the more structural, as well as the interpersonal and individual levels, related to both material conditions (e.g. economic resources, physical access) and subjective and cognitive dimensions (e.g. perceptions, attitudes, stigma, knowledge), and the way in which this gender-related factors intersect with other axes of social differentiation (e.g. age, ethnicity, class, educational level, occupation, HIV status). In doing so, the research should focus not only in the constraining effects that certain social, economic and cultural conditions have on peoples access to TB care, but also in the actions people undertake in order to overcome these constraints.

The variations in the way patient delay is defined make it difficult to compare the results of different studies on this subject. In order to conduct a more detailed analysis of the relative contribution of different types of delay and the factors that influence them, it would be important that future research considers, whenever possible, six different moments in the course of disease: onset of symptoms, first visit to non-medical or under-qualified providers (e.g. pharmacy, traditional healers), first visit to lower level providers, both public and private, which do not have the laboratory and X-ray capacities to diagnose TB (e.g. health centers, health posts), first visit to specialized or higher level public providers that are equipped to diagnose TB (e.g. TB clinics, hospitals), diagnosis of TB and initiation of treatment.

In terms of action-oriented research, it would be helpful for TB programs to identify and evaluate innovative strategies to improve TB detection and shorten the pathway to TB diagnosis and treatment for men and women at both local and national levels. For example, TB programs may work to implement and improve referral systems within the informal (e.g. traditional healers) and private (e.g. pharmacists, private practitioners) sectors. To improve awareness about TB and help address TB-related stigma, TB programs should develop health promotion and communication strategies to enhance equal access to and uptake of quality information about TB for men and women.

Diagnosis and initiating treatment

To reduce health system delays in TB diagnosis, public private partnerships, including partnerships with less qualified providers like traditional healers, may decrease the time needed to refer those with symptoms indicating the possibility of TB, to health care facilities with diagnostic and appropriate treatment possibilities.

Health care system strengthening aimed at integration of TB diagnostic and treatment services in relatively often frequented and relatively easy to reach health care clinics (e.g. maternity and child welfare centers or work-based clinics) might reduce delays and improve case detection. Research is needed to optimize integration of TB care into general or specific forms of health care.

Policy at the clinic level should address gender-specific barriers to obtaining quality smear microscopy. For example, patients should be provided private and well-ventilated spaces to produce sputum, and these procedures should be routinely evaluated and feedback provided to clinical staff and patients. Furthermore, monitoring of symptoms, x-ray and sputum requests, and diagnoses should be routinely collected and analyzed to evaluate gender differences at different steps of the diagnosis process [51, 270].

As more sensitive diagnostic methods for TB may remove gender differences in detection of TB among suspects, future research aimed at identifying the additional value of new diagnostic techniques are needed. No studies on new phenotypic and molecular techniques were identified for this review. It would be very helpful to know by how much the more sensitive fluorescent microscopy using LED-lamps removes gender differences. Molecular tools such as the Hain-test and the Cepheid GeneXpert are even more sensitive than microscopy, and may remove most differences. This would be useful to know, although in the near future, these molecular tools are not expected to be available for the majority of the population in low and middle income countries.

Treatment adherence

More research is needed to deepen our understanding of the gender-specific barriers to TB treatment adherence, which seem to result in lower adherence for men. Explanations advanced by previous studies should be further investigated, such as the increased financial concerns that would make it more difficult for men to miss work in order to attend healthcare facilities, or the greater TB-related stigma and social consequences that could make women feel more motivated to successfully complete the treatment.

Quantitative studies should consider the exploration of gender differences since the design, ensuring enough power and defining a priori which other variables that might be influencing adherence will be adjusted. This would provide stronger evidence of the possible interaction between gender and other variables with treatment adherence, while qualitative studies could shed light on the socio-cultural processes through which these factors exert their influence.

Intervention studies would be useful for assessing different possible strategies to reduce gender-related obstacles to treatment adherence, such as education on TB treatment and the importance of treatment adherence, stigma and discrimination reduction strategies (specially towards women), flexible or alternative treatment programs (e.g. involving health promoters, patient's family and other community members, offering flexible times, community-based DOTS or workplace-based DOTS).In this review, we found a paucity of published literature examining different modes of providing TB treatment and how that interacts with adherence and gender. For example, an important area for future research would be to implement and evaluate different models for provision of TB medication (e.g. family, friends, and/or community health workers as treatment supporters, use of empowerment strategies, number of days of observation, etc) and assess how these influence men and women and their adherence to treatment.

Treatment outcomes

The examination of sex differences in treatment outcomes is essential for targeting TB prevention and control programs at groups at higher risk. Quantitative research looking at gender differences through the use of interactions that clarify gender-specific effects of independent factors on treatment outcomes can be useful. For factors which may not be common in both males and females in some societies, such as alcohol and smoking, it would be important to power the study to be able to stratify by sex.

To improve treatment success among males, there is a need to identify why males are defaulting and develop interventions to improve their treatment success. Qualitative studies would be useful

to better understand the role, perceptions and practices of health care workers in regards to these gender differences. Qualitative studies are also helpful prior to implementing a program to assess barriers to change and to help develop better implementation strategies. Further studies are needed to develop and evaluate interventions that reduce default and mortality among TB patients, particularly among males. Innovative strategies which are acceptable and feasible, and therefore likely to be effective, are needed to help in reducing smoking in males and females and poverty reduction programs need to be linked with tuberculosis programs. Studies on treatment completion are needed for planning health strategies for TB control, to decide which patients should be given priority for DOT, and in devising new strategies to improve completion rates, improving quality of life and in evaluating the effectiveness of control programs. For example, developing and evaluating health systems and programs to provide treatment for TB in the workplace may improve treatment adherence and outcomes for working patients. Future research should focus on identifying causes of treatment failure in tuberculosis patients.

To better understand the relationship between gender and mortality, it is important to analyze program data by sex. To ensure accurate data are recorded, there is a need to assess the quality of surveillance data for deaths. Evaluations of vital registration systems are needed, as well as studies to determine why there are differences in survival. Furthermore, there is the need for socio-economic information on the patient program forms or in medical records to assess whether the treatment completion rates are affected by socio-economic factors and whether this is related to sex.

As liver injury and serious adverse events were more common among women, further investigations are needed focusing on more detailed timing of the onset of the symptoms, their severity, and their persistence after adverse event resolution. Further prospective studies are necessary to test for viral hepatitis in male and female patients on TB treatment. Also further studies are required to explore possible relationships between sex hormones or aging, pregnancy and immunologic response and outcomes.

Conclusions

From previous studies and reviews it seems likely biological and socio-cultural factors play a role in the higher TB notification rates among men, and that these have different contributions in different settings. From the current review it became clear that there are important differences in the limitations experienced by men and women when trying to access TB care, and in the patterns they follow in the help seeking process. Male patients tend to delay seeking care longer than female TB patients. Female TB patients in general encounter greater barriers to receive appropriate medical attention as women are more likely to seek help but tend to do this firstly with more easily accessible, but less qualified providers, thereby delaying access to appropriate diagnosis and care. Female TB patients more often presented with symptoms not specific for TB. This may be one of the reasons why they are inclined to visit easily accessible health care workers and delay visiting a general health care clinic or TB clinic. Non-specific TB symptomatology may decrease the chance a physician includes TB in the differential diagnosis, and thus orders sputum smear examination. From our review it appeared that in general health care provider delay was similar in men and women who were diagnosed with TB. However, some studies show that more women than men experience extraordinary health care provider delay. Most probably, this is due to a combination of more frequent 'treatment shopping' and non-specific TB symptomatology and a decreased sensitivity of smear microscopy among female TB patients. It is not clear which of these factors that may affect gender differences in TB diagnosis are most important, and this also may differ in various settings. Smear microscopy in itself is not a sensitive diagnostic method for TB, but even has a lower sensitivity among women than men. More sensitive diagnostic methodologies than microscopy seem to be able to diminish gender differences among TB suspects in reaching a TB diagnosis to a large extent. With recent developments in molecular tests to diagnose TB, methods

are in sight to improve case detection in both men and women, ánd make gender differentials in TB diagnosis disappear once TB is in the differential diagnosis. Upon diagnosis, the delay before start of treatment was minimal both for men and women. When on treatment, women generally are better adherent and, at least partly as a consequence, have better treatment outcomes. It was hypothesized that a lack of autonomy that may impair women's ability to seek healthcare from appropriate providers as mainly observed in south-east Asia, could at the same time make it more difficult to interrupt treatment. Male TB patients on average more frequently die and default during treatment. Women on average less often default, despite the fact that serious adverse events and liver injury are more commonly observed among women than men. Alternative treatment strategies, making directly observed therapy more feasible, e.g. at the workplace, may be especially useful in males. Use of a comprehensive supportive approach, which may include the provision of incentives, transportation, feeding, and others, may also improve treatment success.

In our review on gender-specific issues in TB control, no studies on the effects of gender-specific interventions to improve either access to health care, TB diagnosis and treatment adherence and outcomes were identified. One study on the effects on active case finding [1], which could be seen as a temporary intervention, aimed to identify gender based differences in patients with pulmonary TB. However, no operations research studies implementing and evaluating gender-specific effects of interventions could be identified. In our opinion it is crucial that TB control programs build on existing knowledge and move on from research to action, specifically addressing the gender-related barriers to TB diagnosis and care. These actions should be informed by action-oriented research that helps identify the most appropriate strategies for each particular context, and later evaluate their effectiveness. Showing improved performance may accelerate scale-up of effective policies and actions.

Areas for interventions can be identified by mixed methods studies focused on quantitatively assessing gender-specific access to health care in general and TB diagnostics specifically, treatment adherence and successful treatment outcomes and by means of qualitative research methods assess reasons for any differences observed. As a first step, data on sex, age, and preferably other socio-economic factors, within the health care sector, including TB programs, should be collected and analyzed. Data should be analyzed on all levels, from district to regional to country to continental level, and should be compared between them. This would allow tracking gender disparities within specific contexts and their interaction with factors such as access to care, ethnicity, particular forms of TB, the HIV co-epidemic, etc. Interdisciplinary studies are also necessary in order to better explain the interplay of these factors.

One field that may benefit both women and men, includes interventions promoting and optimizing partnerships between different public and/or private health care facilities and workers, to facilitate access to health care staff which recognizes TB suspects and will refer them to an appropriate clinic. Furthermore, there is still a need for additional research examining the relationship between gender and TB in the context of the HIV epidemic. The strong relationship between TB and HIV, especially in settings of high-HIV prevalence, like sub-Saharan Africa, makes it essential to further examine how the co-epidemic influences men and women in terms of TB and health seeking behaviors and access to care, diagnosis, initiating and adherence to treatment, and outcomes. Another field that may benefit both women and men, is to identify the additional value of new, more sensitive, diagnostic techniques for TB. It would be very helpful to know by how much the more sensitive fluorescent microscopy using LED-lamps, and molecular tools remove gender differences. A third field that my benefit both women and men is to assess different possible strategies for a comprehensive approach to treatment, including incentives, in order to reduce gender-related obstacles to treatment adherence and treatment success.

In conclusion, it is important for TB programs to identify, implement and evaluate innovative strategies to improve TB detection and shorten the pathway to TB diagnosis and treatment for men and women at both local and national levels. Action-oriented research is useful to evaluate and optimize these strategies.

Summary table on gender, help seeking and access to TB care

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
Agboatwalla, 2003 [24]	To study the differences in knowledge of cause, spread and treatment of TB; to compare male and female health-seeking behaviors; and to compare urban and rural perspectives regarding knowledge of and attitude towards TB.	754 adult men and women (20 to 45 years of age), from urban and rural areas. Pakistan. Time not specified.	Cross-sectional, descriptive study, using a semi-structured questionnaire.	Knowledge about TB symptoms was particularly deficient among rural females (compared to rural males, $p < 0.001$). No significant gender differences were observed in the type of healthcare facility the respondents would visit, but more female than male said that they would visit the healthcare facility accompanied by their husbands or other family members.	
Ahsan, 2004 [25]	To investigate gender differences in the epidemiological factors associated with the treatment seeking behaviors of TB cases in the rural communities of Bangladesh.	307 new TB cases, from 11 rural health centers and 1 community. Dhaka, Bangladesh. Time not specified.	Descriptive cross-sectional study.	More males, compared to females, had chosen treatment from health centers as their first choice (aOR 4.2, 95%CI 2.0 – 8.4), and more females than males had taken treatment from traditional healers before attending the health centers (70.4% vs. 32.4%, $p = 0.000$). More women compared to men had a patient delay of more than 60 days (50% vs. 29.8%, $p = 0.001$). Women had to face significantly more socio-cultural and financial barriers for TB care than men: want to diagnose secretly, need to ask permission to seek treatment, need for accompaniment to attend a health center, problems to cover travel costs, and an association between TB diagnosis and social isolation, problems in the relationship with their spouses and other family members, and problems in finding a marriage partner ($p \leq 0.001$ for each one of them).	Develop an appropriate gender strategy for developing a TB control program, comprised of operational, socio-cultural and community awareness interventions aimed at treating undiscovered cases of TB among women in rural Bangladesh.

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
Ali, 2003 [95]	To explore the level of awareness about tuberculosis amongst patients and their families, and recommend strategies for increasing understanding of the disease.	213 TB patients. Karachi, Pakistan. Time not specified.	Descriptive cross-sectional survey based on a structured questionnaire using convenience sampling.	No significant differences in knowledge and awareness were found with respect to gender.	
Armijos, 2008 [92]	To explore knowledge, beliefs, perceptions, and attitudes about tuberculosis (TB) in a high-risk group in Ecuador.	212 adults undergoing diagnostic TB testing. Quito, Ecuador. 1999-2000	Data were collected from a convenience sample using a structured questionnaire, and subjected to statistical and qualitative analyses.	No gender differences in knowledge of symptoms and fear of social stigma is reported.	
Aspler, 2008 [88]	1) To estimate patient costs for tuberculosis (TB) diagnosis and treatment and 2) to identify determinants of patient costs.	103 adult TB patients who had been on treatment for 1–3 months. Lusaka, Zambia. 2006	A cross-sectional survey, using a standardised questionnaire.	Men spend more money in accessing care than women ($p = 0.028$ in multivariate linear regression) (includes care-seeking and treatment costs). However, TB diagnosis and treatment was more affordable for males when taken in the context of their ability to pay. The total direct costs, expressed as a proportion of median individual income, were 92% higher for women than for men ($p < 0.001$).	
Atre, 2004 [62]	To specify the distribution of TB-related illness experiences, meanings and behaviors, examining categories of personal	80 men and 80 women who personally and whose immediate family members did not	Semi-structured Explanatory Model Interview Catalogue interviews were conducted, and	Social problems were more often considered for women with TB (rejection by husband, problems arranging marriages, social isolation, and inability to care for children and family). Job loss and reduced income were	

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
	distress, perceived causes, and help seeking with reference to narrative contexts of respondents' accounts, as reported by the general population of people without TB.	currently have active TB. Pune District, Maharashtra, India. November 1998 – June 1999.	analyzed using qualitative and quantitative methods.	regarded as most troubling for men. Men and women typically identified sexual experience, as well as heredity, as the cause of TB for the opposite-sex. Addictions were more often identified as a cause of TB for men. More women respondents identified supernatural and karma-related causes. With wider access to information about TB, male respondents more frequently recommended allopathic doctors, specialty services, and the higher levels of health services (rural Hospitals [$p < 0.01$], government hospitals [$p < 0.01$], TB hospitals [$p < 0.01$], and District TB centers [$p < 0.05$]). The reasons for recommending private practitioners were their easy accessibility and confidence in their effectiveness.	
Aye, 2010 [110]	To investigate the extent and determinants of patient and health system delays for TB.	204 newly diagnosed PTB patients, enrolled in DOTS. 12 districts in Tajikistan. December 2006 – March 2007.	Questionnaire administered to a cohort of TB patients.	No significant gender differences were found in patient's delay (hazards ratio women to men 0.745, $p = 0.103$).	
Balasubramanian, 2004 [26]	To examine gender differences in tuberculosis among adults aged >14 years with respect to infection and disease prevalence, health care service access, care seeking behavior,	76 011 adults > 14 years of age for community survey, 2115 TB patients. Self-referred out-patients attending	Data were collected from 1) community survey, 2) self-referred out-patients seeking care at governmental PHIs, 3) TB suspects	The comparison of the proportion of women with TB infection and smear-positive TB, between the community survey results and patients notified at PHIs suggest that women are more likely than men to access health services for TB, despite facing greater stigma and inconvenience. More women than men felt inhibited discussing their illness with	

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
	diagnostic delay, convenience of directly observed treatment (DOT), stigma and treatment adherence.	peripheral health institutions (PHIs). TB suspects. Tiruvallur District, south India. 1998-2002.	referred for sputum microscopy at PHIs, and 4) TB patients notified under DOTS. Community survey results were compared with those for patients notified at PHIs.	family and friends (21% vs. 14%, $p < 0.05$), felt unwelcome at social activities (18% vs. 12%, $p < 0.05$), and needed to be accompanied for health encounters (11% vs. 6%; $p < 0.01$). Women were more likely than men to first consult a private provider (63% vs. 51%; $p < 0.05$). The median patient delay was similar among male and female tuberculosis patients (14 days). Women spent significantly more money for care seeking than men (Rs [Rupees] 500 vs. Rs 300; $p < 0.001$).	
Bashour, 2003 [27]	To determine whether there are sex differences in diagnosis, compliance with treatment and/or treatment outcomes; to identify TB patients' knowledge, beliefs and attitudes towards TB; and to identify gender related factors and/or barriers that may influence patients' compliance with TB treatment and utilization of health care services.	552 new smear-positive TB patients. Syrian Arab Republic. 2002.	Prospective study, with 6 month follow-up, using a semi-structured questionnaire and review of treatment cards.	Mean patient delay was significantly longer for men than for women (63.3 days vs. 40 days). Regarding the first place where patients sought care, a higher proportion of men than women went to public hospitals (19.6% vs. 7.6%), and a higher proportion of women than men went to private physicians (66.4% vs. 81%, $p = 0.005$). There were no gender differences in knowledge about TB. There were significant differences in attitudes and perceptions of health seeking behavior: more women than men agreed they needed permission to go to the TB center (71.3% vs. 28.5%, $p < 0.001$) and referred that they had to be accompanied by someone (86.8% vs. 29.3%, $p < 0.001$).	
Becerra, 2005 [52]	To assess the feasibility and yield of a simple active case finding strategy in a high incidence population in	208 case subjects with PTB, 1094 household contacts and 2253 neighboring household contacts.	Screening of household contacts and neighboring households for symptomatic	The comparison of case subjects detected throught active and passive case finding showed, in multivariate analysis, that female sex (aOR 3.9, 95% CI 0.93 – 23.1, $p = 0.053$) and age >55 years (aOR 5.3, 95% CI	

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	northern Lima, Peru.	Lima, Peru. January 1996 – April 1997.	individuals and sputum examination.	1.2 – 22.8, p = 0.026) were a strong risk factor of failure to self-report.	
Bennstam, 2004 [28]	To explore and describe the underlying attitudes toward TB and to describe the context of TB in a Congolese society, with special interest applied to gender differences.	4 groups, with a total of 23 women and 26 men, with and without TB. Mai Ndombe District, Democratic Republic of Congo. Time not specified.	Grounded theory methodology, using focus group discussions for data collection.	No gender differences were observed regarding TB-related attitudes, perceptions and stigma.	
Borgdorff, 2000 [29]	To explore whether lower tuberculosis notification rates among women are due to a reduced access to health care, particularly diagnostic services, for women.	Meta-analysis of data from 14 countries from South East Asian, Western Pacific, African and East Mediterranean regions.	Age- and sex-specific TB prevalence rates of smear-positive TB from 29 surveys from 14 countries were compared to age- and sex-specific notification rates from the same countries in 1996.	In most countries the F/M sex ratio in prevalent cases was similar or lower than that in notified cases (except in the African region), suggesting that F/M differences in notification rates may be largely due to epidemiological differences and not to differential access to diagnosis. However, this conclusion cannot be generalized to individual regions or countries.	Additional research would be instrumental in obtaining firmer conclusions on gender bias in TB case detection, related to health seeking behavior and/or to steps within the health systems in suspecting and diagnosing TB.
Breen, 2008 [106]	To determine how frequently these features and blood test evidence of inflammation were absent in individuals with TB.	175 adult unselected subjects with TB Lodon, UK 2003-2006	Prospective, observational cohort study.	In a multivariable model, absence of systemic TB symptoms, such as fever, sweats and weight loss, was significantly associated with female sex (aOR 3.15, 95% CI 1.45 – 6.83, p = 0.004).	

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Cassels, 1982 [16]	To compare the results of active case-finding and passive case-finding both in terms of patient compliance and of eventual outcome.	159 new smear-positive self-referred (SR) patients, and 111 smear-positive patients found through ACF among 2843 symptomatic patients, out of a 67068 population over 15 years of age. Nepal 1978-1980	Comparison of ACF carried out by mobile teams and self-referral of patients to the existing services.	The overall male : female ratio in ACF patients was 1.2 : 1, compared to 2.6 : 1 in the SR group ($p < 0.001$). Particularly noticeable was the difference in the number of females aged 45 and older.	
Chang, 2007 [72]	To determine the length of delay, and factors linking the delay from the onset of symptoms of PTB until the commencement of treatment in Sarawak, Malaysia.	316 new smear-positive PTB patients over 15 years of age Sarawak, Malaysia June 2003 - May 2004	Institution based cross-sectional study, using a semi-structured questionnaire.	Significantly fewer male respondents (36%) had a patient delay, compared with female respondents (57%) ($p = 0.006$). Using logistic regression analysis, only being male was associated with reduced patient delay (aOR 0.49, 95% CI 0.30 – 0.78). This might be related to women's dependence on male family members to take them for treatment.	
Crampin, 2004 [30]	To explore possible explanations for the excess of TB in young women and older men that is observed in may populations, concentrating on HIV status, pregnancy, smoking, cooking smoke exposure, contact with TB	598 new TB cases and 992 controls. Karonga District, Malawi 1996 – 2001	Case control study, using interviews and HIV testing.	There were no differences between men and women regarding delay between the onset of cough and starting treatment, or the health service first used (hospital, health center, private practitioners and traditional healers, in order of importance).	

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	cases within the household or outside, and gender differences in health service usage and diagnostic delay.				
Date, 2005 [31]	To examine how gender and literacy influence TB diagnosis and treatment.	74 smear-positive pulmonary TB patients visiting the National Tubercuosis Insititute. Sana'a, Yemen. 2001 – 2003	Individual interviews and data collection about treatment outcomes in the following 8 months	There were no gender differences in patient delay.	
Dhingra, 2002 [70]	To assess the health seeking delay in chest symptomatic with TB	301 PTB patients New Delhi, India. March – August 2001	Cross-sectional study using semi-structured questionnaire	No gender differences were found in health seeking delay.	
Díez, 2004 [80]	To study patient delay and its determinants.	A cohort of TB patients: 10,053 TB cases were identified, of which 7,037 were included in the final analysis. 13 Autonomous Regions in Spain. May 1996 – April 1997.	Data were obtained from medical records, and the association between patient delay with different factors was estimated using unconditional logistic regression with two different cut-off points to define 'patients delay' (the median and 75th	Median and 75th percentile patient delay were 22 and 57 days respectively. In multivariate analysis, female gender emerged as a factor linked with extreme patient delay (aOR 1.15, 95% CI [1.01-1.30]; p≤0.05), which could be related with problems in accessing medical care and proneness to having the disease at certain extra-respiratory sites.	Further study the association between extreme delay and female gender, as both sex and gender effects could be at work.

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			percentile).		
dos Santos, 2005 [84]	To investigate factors associated with total delay in treatment of tuberculosis.	1105 adult cases of PTB diagnosed over a 2 year period. Recife, Brazil. 2001 - 2003	A cohort of adult cases of PTB diagnosed over a 2 year period was interviewed using a standard questionnaire and had sputum and blood samples examined.	Sex was no associated with treatment delay (the time between the onset of symptoms and the initiation of treatment).	
Eastwood, 2004 [32]	To explore gender differences in care seeking behavior, access to treatment, and knowledge and perceptions about TB.	15 government health workers (age 25 to 65), 15 female and 15 male TB patients at different stages of treatment (age 15 to 59), mostly urban. Fajar, The Gambia. 2002	Qualitative semi-structured interviews were conducted and then analyzed using the thematic framework method.	Patients initially seeking care with traditional healers and pharmacies was thought to cause diagnostic delay, and to be more common among women, due to stronger traditional believes, time constraints and more interest in privacy and confidentiality. Treatment and transport costs were perceived to reduce access, especially for women, who have lower income. Interference with work also limits access, and for women, having to ask permission to their husbands or elders. Lack of knowledge and the consequences of TB-related stigma, that associates TB with poverty, dirtiness and prostitution, were perceived as worse among women.	Increase decentralization to improve access to care, lengthen opening hours, health clinics and increase privacy, and provide education on TB to patients, general public and health providers (including traditional healers). This education should consider TB-related stigma, especially towards women.
Edginton, 2002 [60]	To describe the beliefs, attitudes and experiences about tuberculosis of patients and community members, in an attempt to understand how these could impact on presentation to health	TB patients and community members, community leaders, traditional healers, student nurses and male manual road workers.	A descriptive study using structured interviews with 327 individual patients, and 14 focus group interviews with an approximate total of 160 patients and	The places patients said they attended first were, in order of importance, hospitals, traditional healers, clinics and private doctors, and women were more likely than men to attend a clinic first ($p = 0.03$). Respondents believed there are types of TB caused by breaking cultural norms, including norms about women's sexual behavior (sexual	Collaboration between traditional and western healers, in order to accommodate patients' cultural needs, avoid conflicting messages and make patients more comfortable consulting

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	services and treatment adherence.	Rural Tintswalo district of the Northern province in South Africa. July 1994 – January 1996.	community groups.	abstinence after the death of a relative, after delivering a child or after a miscarriage). 'Free' sex practices, such as those promoted by contraceptive use, were thus considered a risk for acquiring TB. Sexual abstinence is also expected from people with TB, which can lead to conjugal conflicts.	both types of healers. Make interventions more accessible and acceptable to local people.
Enkhbat, 1997 [71]	To compare the influence on delay in the TB case finding process according to the type of medical facilities initially visited.	107 patientes 16 years and older diagnosed with bacteriologically confirmed PTB. Ulaanbaatar, Mongolia. May 1995 – March 1996.	Statistical analysis of interviews and medical record reviews.	Sex was not significantly associated with patient's delay.	
Farah, 2006 [76]	To assess the delays in the start of treatment for TB patients in Oslo / Akershus region, Norway and to analyze risk factors for the delays.	83 TB cases reported to the hospitals of those two regions. Oslo and Akershus regions, Norway. July 1, 2003 – February 6, 2004.	The cases were identified by reviewing notifications to the National TB Registry. Patient, health care system and total delay were calculated, and their association to sex, birthplace, site of the disease and age group was analyzed by multiple	Median patient delay was 28 days, and multiple regression analysis showed no significant difference between men and women.	There is a need of awareness of TB in the general population and among health personnel.

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
			regression.		
Fochsen, 2006 [33]	To explore health care providers' experiences and perceptions of their encounters with male and female patients in a rural district in India with special reference to tuberculosis (TB) care.	22 healthcare providers, 17 men and 5 women, from the public and private health care sector. Ujjain district, Madhya Pradesh, India. Time not specified.	Semi-structured interviews, analyzed using latent content analysis.	Power imbalances in the doctor-patient relationship are influenced by gender factors, and tend to limit access to health care. The dominance of doctors in their relationships with patients, by virtue of the perceived lack of knowledge of the latter, tend to reproduce gender imbalances in Indian society. Power imbalances within the family curtail women's control over the medical encounter. Male patients were sometimes perceived as less cooperative, since they were more challenging of doctor's authority. In doctor-patient relationships increasingly defined by consumerism and by patients' financial situation, women's social and financial dependence limits their access to healthcare, because of their limited resources and the tendency to prioritize the needs of other family members.	Medical encounters in TB control activities should be guided by a patient-centered approach, acknowledging patients' experiences and shared decision making.
Ford, 2009 [65]	To determine the psychosocial factors associated with delayed test-seeking among tuberculosis patients	The city of Iquitos, in the 108 newly diagnosed pulmonary TB patients, 14 years of age or older. Peruvian Amazon. Time not specified.	Cross-sectional, quantitative survey. Delay in TB test-seeking behavior was calculated, and its association with different factors assessed through univariate and multiple linear regressions.	The median delay in test-seeking behavior was 61 days and the mean was 95 days. Multiple regression analysis showed that male gender was associated with 48% longer test-seeking delay ($p = 0.02$). This may be related to a perception that seeking medical attention as a sign of weakness in the "macho" Latin culture, and the long absences from home due to the work that some men do in this region.	Encourage men to seek testing in tuberculosis health promotion and ensure that health services are "male-friendly".
Ganapathy, 2008 [34]	To find out gender differences in understanding of TB with	Adult community members, divided into 4 groups	Qualitative study using focus group discussion.	Men were seen as more vulnerable because of smoking, alcohol consumption, contact with polluted surroundings and extra marital	

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	reference to symptoms, causes, spread and cure, perceptions about vulnerability to TB, gender differentials in care seeking, type of providers consulted, reasons for choice and perceptions about TB services, implications of TB on marriage, pregnancy and lactation.	according to gender and two age groups. Amount of FDGs and total participants not specified. Chennai City, south India. Time not specified.		relationships. Men and children get priority in receiving care during an illness, because of men's status as breadwinners and because of women's domestic responsibilities. Both men and women initially approached private doctors more, but sought government health facilities for more serious illenesses. Women were thought to face greater social consequences for a TB diagnosis, especially since it would affect their possibilities of getting married, more than it would affect men's.	
Godfrey-Faussett, 2002 [79]	To describe the distribution and risk factors for delay among patients presenting with a cough to the urban health centres.	427 adult patients presenting with a cough to urban health centers. Lusaka, Zambia. Time not specified.	Problem analysis workshop, and cross-sectional survey.	Gender was not clearly associated with increased delay, unlike an earlier study in Lusaka that showed that diagnostic delay was significantly greater in women. It is suggested that the process of decentralization has lead to greater gender equity.	
Gosoniu, 2008 [35]	To compare the interval from symptom onset to diagnosis of TB for men and women, and to assess socio-cultural and gender-related features of illness explaining diagnostic delay.	Approximately 100 patients of TB control programmes of each country. India, Bangladesh and Malawi. Time not specified.	Mixed-methods quantitative-qualitative study. Semi-structured Explanatory Model Interview Catalogue (EMIC) interviews were administered to 100 or more patients at each site, assessing categories of distress, perceived causes and help	The only common cross-site determinants of problem delay were related to female sex and gender roles. With adjustment for confounding, female sex in Bangladesh (estimate = 8.08; P = 0.01), status of married woman in India (estimate = 4.03; P = 0.04), and occupational status of housewife in Malawi (estimate = 2.76; P = 0.04), were associated with diagnostic delay. In India, prior use of a druggist or pharmacy was associated with problem diagnostic delay for female patients compared to males (estimate = 1.49; P = 0.01). In the second adjusted analysis of grouped EMIC variables, female	Further research is needed to study these issues in people not yet enrolled in TB control programs and to distinguish patient delay from provider delay.

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			seeking.	sex was a significant explanatory variable in India (adjusted estimate = 5.72, P < 0.001). In Bangladesh, narrative accounts indicated that a lack of control of household resources and need for their husband's permission contributed to delayed help seeking for some women. In India, fear of stigma lead women to hide their illness from their husbands and families. Pregnancy as a perceived cause of TB in Malawi was also related with problem delay. Long and circuitious history of health seeking (i.e. going to pharmacy first) was also seen as cause of problem delay among women.	
Hamid Salim, 2004 [36]	To determine whether the observed gender difference is epidemiologically true or whether it is due to accessibility barriers for women.	266189 population. Bangladesh. January – March 2001.	Two-stage random sampling population survey, including interview about the presence of symptoms of TB, and examination of one early morning sputum specimen of all those identified TB suspects.	The female/male ratio (0.33:1) of cases found during the survey was not higher than that observed through routine diagnosis (0.42:1), which suggest that gender differences in TB case notification are epidemiologically true, and not due to accessibility barriers for women.	
Harper, 1996 [53]	To increase case-finding without decreasing case-holding, by expanding outreach services into remote areas away from existing health services.	4009 patients with symptoms attending camps and 8288 attending Health Posts (HPs) or Clinics.	Patients attending 45 temporary outreach TB diagnostic 'microscopy camps' were compared to those attending HPs/Clinics. Camp-	A higher proportion of women attended the camps as opposed to HPs/Clinics (56% vs. 43%, RR 1.31, 95% CI 1.22 – 1.40). A greater proportion of diagnoses of smear-positive TB made at camps were women compared to HP/Clinic diagnoses (53% vs. 35%, RR 1.51, 95% CI 1.19 – 1.92).	

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		Nepal 1990 - 1993	diagnosed patients were followed up by cohort.		
Hoa, 2003 [37]	To describe the knowledge of TB among men and women with a cough for more than three weeks and how that knowledge affected their health-seeking behavior.	35,832 adults aged 15 years or over Bavi District, Vietnam. 2000	population-based cross-sectional survey carried out within a demographic surveillance site.	Men had a significantly higher knowledge score than women (3.04 and 2.55 respectively, $p < 0.001$) and better knowledge about symptoms and about cause of TB was significantly related to taking a healthcare action ($p = 0.002$ and $p = 0.004$ respectively) and seeking hospital care ($p = 0.001$ and $p = 0.05$ respectively). More men than women reported TV and radio as sources of TB information (54% of men, 46% of women, $p < 0.001$), and the people who reported these sources had higher knowledge scores compared with those who reported receiving information from friends or relatives (mean score: 3.39 vs 2.05 respectively, $p < 0.001$). More women (94.6%) than men (78.8%) reported that they took healthcare action for their symptom of cough ($p < 0.001$). Significantly more women than men chose self-medication or a visit to the pharmacy as their first healthcare action (33% vs 20%, $p < 0.02$) and significantly more men than women sought care at a hospital at any point during their disease period (26% vs. 16%, $p < 005$). In logistic regression models health care action was associated with being a woman ($p < 0.001$) and having a higher knowledge score ($p < 0.05$), and seeking hospital care was associated with higher knowledge score ($p < 0.05$), longer cough	Promote equal opportunities for education and media access. Understand the knowledge base of the population and relate traditional beliefs to modern medical knowledge.

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				duration ($p < 0.001$), more disease symptoms ($p < 0.002$) and having health ensurance ($p < 0.001$). Among men, compared to women, the mean duration of cough was significantly longer (21.1 weeks vs. 16.2 weeks, $p < 0.001$) and sputum production was more common (61% vs. 50%, $p < 0.01$). More men (22%) than women (13%) reported having health insurance ($p < 0.01$).	
Hoa, 2009 [54]	To describe the TB knowledge in the general population and to analyze which methods and tools should be used for health education in community.	12,143 adult population (15 years old or older) Rural district in Vietnam July – September 2005	A population-based cross-sectional survey within a demographic surveillance site.	Knowledge about TB was generally poor. In multiple linear regression analysis, male gender was significantly associated with increased knowledge scores (coefficient = 0.52, 95% CI [0.45 – 0.59], P = 0.001). Hospital care seeking was significantly associated with mean knowledge score ($p < 0.01$). More women than men associated heavy stigma with a TB diagnosis (48.7% vs. 35.1%, $p < 0.0001$). More women than men would hide their TB diagnosis from friends and neighbors (12.8% vs. 10.9%, $p < 0.01$). More women than men would take health-care actions (including self-medication) if they had cough for more than 2 weeks ($p < 0.001$), but more men than women would seek care at the district hospital (31.7% vs. 24.2%, $P < 0.001$). Men have more access to TB information through TV ($p < 0.001$), radio ($p < 0.001$), newspapers ($p < 0.001$) and loudspeakers ($p < 0.05$), and women had more access through relatives and friends ($p < 0.001$). People who received information from friends or relatives had a lower average knowledge score than those who received it from TV or loudspeakers ($p < 0.001$).	Health education needs to be design in order to approach traditional believes in a sensitive way, addressing the context and specific needs of the targeted population.

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Huong, 2007 [59]	To assess the patient, health care provider and total delay in diagnosis and treatment of new smear-positive pulmonary tuberculosis patients, and the risk factors for long delay, in Vietnam.	2093 smear positive pulmonary TB patients. 70 districts in Vietnam. 2002	A cross-sectional survey of new patients treated by the National Tuberculosis Control Programme was conducted in 70 randomly selected districts in Vietnam.	Men reported earlier with TB symptoms than women (4.4 and 5.6 weeks respectively, $p < 0.005$). In uni- and multivariate analysis, female sex was an independent risk factor for long patient delay (aOR 1.3, 95% CI [1.0 – 1.7]). This may indicate lower access to diagnosis and treatment for women compared to men. Women tend to report with cough to private providers earlier than men, but this does not result in shorter overall delays, supporting earlier findings that health care providers visited by women tend to be less qualified.	Efforts should be made to further reduce diagnostic delays by improving the referral from the private to the public health sector.
Johansson, 2000 [38]	To explore and describe perceptions of factors influencing health-seeking behaviour in Vietnam, with specific reference to gender differentials in delay in health seeking	Vietnamese men and women, with and without TB. Four provinces of Vietnam. 1996	16 focus group discussions for data collection and modified grounded theory technique for analysis.	Fear of social isolation caused by TB was thought to be more common among women. Traditional gender-roles that conceive men as the 'pillar of the family' cause women to be perceived as less important, which leads to neglect their health problems. Denial and concealment, caused by fear of stigma, social isolation and separation from partner, was thought to be more common among women. Denial of the disease in men was related to poverty and fear of losing one's source of income. Men were believed to initially neglect symptoms, and then go straight to public health services, while women were believed to resort to a private practitioner and/or self-medication first. Women were also believed to be more sensitive to deficiencies in conditions of health care facilities and attitudes of staff than men.	Patient and system-related factors that intervene in help seeking behavior can be influenced with health education, reduction of total costs of treatment for patients, decentralization of TB services and improvement of salaries and working conditions for staff. Teaching health workers about behavioral, sociological and gender aspects of TB control.
Johansson, 2002	To elucidate	24 TB patients and	In-depth	The lower status of women within the family	Increase awareness of

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[63]	understanding of mechanisms of the tuberculosis sickness trajectory in Vietnam.	16 health care providers involved in TB care. Quang Ninh Province, Vietnam. Time not specified.	interviews. Modified grounded theory was used for the analysis.	made them more vulnerable to rejection, humiliation and divorce, if diagnosed with TB. Men expressed more concern about the effects of TB on the family economy. Women described fear of disease, isolation and stigma, appeared to wait longer before accepting a suspicion of being sick with TB, and tended more to self-medication. Women, felt and enacted stigma, and its impact. Female TB patients who are heads of household confront particular social and economic difficulties.	the importance of quality interaction based on transparency and trust among patients, family, society, and providers, paying particular attention to the differences between men and women with regard to their social situation and need for social support.
Jurcev Savicevic, 2008 [93]	To investigate knowledge about tuberculosis (TB) and to identify target groups for information, education and communication activities.	386 patients of 5 general practitioners. Split, Croatia. January – February 2007.	Cross-sectional survey based on a structured questionnaire using a convenience sampling among subjects aged ≥ 18 years.	There were no significant gender differences in knowledge about TB.	
Kamel, 2003 [39]	To determine the sex ratio among registered PTB cases; to describe and compare the utilization patterns of TB services and between male and female patients; to describe and compare outcomes of TB treatment between male and female TB patients; to identify	334 PTB patients who were on anti-TB therapy. Alexandria, Egypt. 2001-2002	Cross-sectional comparative study design, using a structure interview questionnaire and data collection from records and control cards; cases were prospectively fallowed-up during 8 months.	Significantly more women than men attended a private clinic for the diagnosis of TB (28.8% vs. 14.7%), whereas more men than women had visited a public chest clinic (51.5% vs. 42.7%) or public chest hospital (32.5% vs. 20.4%) ($p < 0.001$). There were no significant gender differences in the first facility the patients sought. A significantly higher proportion of women used traditional medicines for treatment of TB compared with men (35% vs. 24.2%, $p = 0.043$). There	

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	factors behind gender differences in health seeking behavior, diagnostic delay, TB treatment adherence (compliance behavior) and subsequent treatment outcomes.			were no significant gender differences in the time elapsed from the appearance of symptoms until seeking health care, or in terms of access to health care facilities (distance to clinic, mean commuting time and means of transport). Men and women had similar perceptions regarding the social consequences of TB. However, regarding family relationships, more women did not agree at all that TB affects marital status ($p = 0.044$), and more men did not agree at all that TB decreases the chance of marriage ($p = 0.009$). More women than men thought that TB affects pregnancy and breastfeeding ($p < 0.05$).	
Karim, 2007 [40]	To assess the gender variations in delay from symptom onset to help seeking, diagnosis and treatment of tuberculosis (TB) using DOTS at community level, in 10 subdistricts of Bangladesh with 2.5 million people under a non-governmental organization's (BRAC) DOTS programme for TB control.	1000 newly diagnosed PTB patients (500 men and 500 women) 10 subdistricts of the BRAC TB control program, in Bangladesh. 2001 – 2002	A cross-sectional survey of a conveniently selected sample.	Women compared to men had significantly longer mean (51.9 vs. 48.7; $p = 0.015$) and median (50 vs. 42; $p = 0.002$) patient delay than men. The multiple linear regression analyses indicated a significant association between the sex of patients and patient's delay ($p = 0.023$). The analysis of sex by age interaction showed that women of older age experience significantly longer patient's delay ($p = 0.031$). The heavy workload of women, their restricted mobility, lack of independence, powerlessness in decision making, inaccessibility to financial resources, and fear of divorce or abandonment, may provide potential explanations.	Develop and implement appropriate health education on TB symptoms, diagnosis, curability and social stigma. Better integration of the private sector into the TB control programme. Further research is necessary to study the impact of socio-economic and cultural factors in delays.
Khan, 2000 [89]	To explore the extent to which factors related to individuals, the care provision process, and the cultural context influence	36 new TB cases, balanced over sex, stage of treatment, and urban/rural residence.	In-depth, semi-structured interviews. Responses to open questions were	Access to TB services for women is limited by the restrictions to their mobility, the unwillingness to pay for a treatment for them, and the stigma associated with TB, which appears to be much greater for women. It is	Factors related to access to service must be taken into account when designing a DOTS strategy, i.e. the

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	the behavior of tuberculosis patients attending TB clinics in rural Pakistan, and examines the effects of disease on their personal lives.	Three districts in Pakistan. Time not specified.	reviewed and coded, and quantitative data was analyzed using SPSS-PC.	feared that a TB diagnosis will affect a woman's chances of getting married or will put her at risk of being expelled of her marriage home.	necessity of accompanying 'chaperons' for women patients.
Lawn, 1998 [74]	To determine the factors affecting the delay from the onset of symptoms of PTB until the initiation of treatment	100 adults with newly diagnosed smear-positive PTB Kumasi, Ghana 1995	Retrospective questionnaire survey	No significant differences in patient delay were seen in the comparison of males and females	
Liam, 1997 [69]	To investigate patient and doctor delay in the diagnosis and treatment of pulmonary tuberculosis in patients attending a tertiary teaching hospital.	97 patients with newly diagnosed PTB Kuala Lumpur, Malaysia 1994-1995	Data was collected through interviews using a standard questionnaire, and subjected to statistical analysis	There was no sex differentiation in patient delay	
Liefooghe, 1995 [87]	The aim of the research was to explore the cultural factors influencing perceptions of TB and their effect upon treatment adherence.	3 groups of male and 3 groups of female smear-positive PTB in-patients; each group had 8 participants. Sialkot, Punjab Province, Pakistan. Time not specified.	Focus groups discussions; content analysis.	While both male and female TB patients face many social and economical problems, female patients are more affected. Divorce and broken engagements seem to occur more often in female patients. Females are usually economically dependent on their husbands and family in law, and need the cooperation to avail of treatment. The belief that pregnancy enhances the risk for relapse decreases their marriage prospects.	

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
Liefooghe, 1997 [64]	To understand the community's beliefs and knowledge about the causation, transmission and symptomatology of TB; to determine treatment-seeking behavioral patterns in TB suspects; and to asses attitudes towards the disease and the afflicted patients.	41 male and female, rural and urban community members and 8 male TB patients. Uasin Gishu District, Kenya 1994	5 focus group discussions were conducted.	Some rural and urban community members, and rural women in particular, perceived traditional healers as a valid alternative for TB care. Female community members believed that the delay in receiving TB treatment was due to patients concealing their health status for fear of isolation.	
Lienhardt, 2001 [58]	To estimate the time delay between onset of symptoms and initiation of treatment and identify the risk factors influencing the delay in patients with TB.	152 TB patients over 15 years of age. Rural and urban health centers in The Gambia. 1997	Structured interviews with newly diagnosed TB patients aged over 15 years presenting to TB control staff in four health centres.	The median total delay to treatment was 8.6 weeks, and there was no effect of sex. This is different in other countries, such as Ghana, were longer delays are found among women. This could be related to the fact that women in The Gambia regularly attend health centers for antenatal care and child immunization. Total median delay varied with subject's occupation, being longer among housewives (10 weeks), unemployed persons (12 weeks) and farmers (14 weeks). Female patients had seen a larger number of health providers than male patients (5 vs. 4, $p = 0.01$), and were more likely to have visited government health centers (OR 4.71, 95%CI 1.62-14.2), while male were more likely to have gone to a hospital, a pharmacist or a private doctor (OR 2.12, 95%CI 0.95-4.81).	Improving referral systems and access to diagnostic facilities. Increase awareness of the signs and symptoms of TB among the general population and health providers at all levels.
Long, 1999 [41]	To describe and compare health seeking behaviour between men and women and to measure delays in	1027 patients aged 15-49 with new smear positive pulmonary TB	Inteviews with structured questionnaire with all new TB cases in	Mean total delay to TB diagnosis was significantly longer in women than in men (13.3 and 11.4 weeks, respectively), but this difference seemed to be more in the provider	Develop appropriate health education programs on TB symptoms, diagnosis

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
	tuberculosis (TB) diagnosis.	detected. 23 districts in four provinces of Vietnam. 1996	a stratified random sample of districts.	side. There were no gender differences regarding patient delay and pattern in health care seeking behavior (types of health care providers visited). Multivariate analysis showed that, to receive a correct diagnosis, women had to visit more providers than men (average 1.7 vs. 1.5, p = 0.02). Women with higher education were more likely to self-medicate and to attend the hospital; the choice of a district hospital was associated among men with higher income and shorter travel time to hospital.	and cure for the general population and health providers. Women with symptoms suggestive of TB should receive more attention from health providers. Health service provision should be studied from a gender perspective, to understand the longer provider delay for women.
Long, 1999 [42]	To describe the perceptions and beliefs of Vietnamese people regarding TB and its risk factors with special reference to differences between men and women.	16 groups of men and women, TB patients and non-TB participants. 4 districts in Vietnam. Time not specified.	Focus group discussions. The data were analysed by applying open coding and constant comparisons.	There are traditional beliefs in four types of TB. Men are thought to be more affected by the types of TB that are caused by hard work and by germs transmitted through the respiratory system. Women are thought to be more affected by a type of TB caused by too much worrying. 'Hereditary TB' is believed to affect both sexes equally. Men were perceived to get TB more often than women, as they were more exposed to risk factors during both work and leisure time (eating out, smoking, drinking, wider social contacts, pollution). Some participants mention 'female' risk factors (too much thinking, poorer health status, being dependent on in-laws, pregnancy and delivery). These traditional beliefs are closely related to the different roles of men and women, and may contribute to long delays to TB diagnosis and increased social stigma and isolation of TB patients and their families due to erroneous beliefs in transmission routes.	

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
Long, 2001 [43]	To describe the socio-economic consequences of tuberculosis (TB) in Vietnam with special reference to gender differentials concerning social stigma and isolation.	16 groups with men and women, TB patients and non-TB patients, with 8 to 10 participants each. Vietnam. Time not specified.	Data was collected using focus group discussions, and analyzed using grounded theory technique.	Male patients often worried about economic-related problems, while female patients worried more about social consequences of the disease, since they were often socially and economically dependent on their husbands and in-laws. Female patients tended to isolate themselves more than men, since they wanted to protect other family members from the disease. Divorce was a more important worry for women than it was for men. Unmarried women with TB were likely to have more difficulty finding a marriage partner than unmarried men with TB. This was related to the belief held by some people that TB was a hereditary disease or that TB could cause sterility. Severe isolation and other social consequences were described as important factors causing delay in TB diagnosis, especially among women.	
Long, 2002 [44]	To describe and compare clinical symptoms of new smear-positive pulmonary TB among men and women, how these symptoms influence TB diagnostic delays, and estimate the rate of improvements in clinical symptoms for both sexes.	1027 new smear-positive PTB cases aged 15 years and over (757 men and 270 women) Vietnam 1996	All the 1027 were interviewed using a structured questionnaire after confirmation of diagnosis, and 540 were selected for follow-up 2, 5 and 8 months after start of treatment.	While general symptoms, such as fever, tiredness, anorexia and headache, were significantly more common in women than men ($p = 0.049$, $p = 0.003$, $p = 0.000$, $p = 0.009$, respectively), symptoms suggesting PTB, such as cough, sputum expectoration and hemoptysis, were significantly less common in women than in men ($p = 0.021$, $p = 0.006$, $p = 0.033$, respectively). Although bivariate analysis showed a higher mean number of symptoms in women than in men (5.3 vs. 5.0, $p = 0.04$), the difference was no longer significant after controlling for cofounding variables.	

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
Lorent, 2008 [77]	To evaluate delays in the diagnosis and treatment of TB and associated risk factors	104 TB patients Rwanda June – September 2006	Prospective data collection of patients treated for TB	No association was found between patient delay and sex.	
Meintjes, 2008 [68]	To describe patient and provider delay in the diagnosis of TB in patients with suspected TB requiring admission, and to determine the risk factors for this delay and the consequences.	125 patients with suspected TB. Cape Town, South Africa. February-September 2003.	Cross-sectional study, using a structured questionnaire and medical records.	In multivariate analysis male gender was an independent risk factor associated with longer patient delay ($p = 0.02$).	
Motta, 2009 [271]	To evaluate access to TB diagnosis for users of the Family Health Program (FHP) and Reference Ambulatory Units (RAU).	100 TB patients registered with the TB Control Program. Itaboraí Municipality, Rio de Janeiro, Brazil. July-October 2007	Cross-sectional study. Interviews were conducted using the primary care assessment tool.	There was no difference in health-seeking behavior regarding sex between patients that used family and community oriented health services and those who used traditional centralized reference ambulatory units.	
Nair, 1997 [45]	To explore the health seeking behavior of poor male and female tuberculosis patients in Bombay, and to examine their perceptions of the causes and effects of the disease on their personal lives.	16 adult newly diagnosed TB patients treated in NGO's clinic. Bombay, India. 1993 – 1994	In-depth interviews.	Men worried about loss of wages, financial difficulties, reduced capacity for work, poor job performance, and the consequences of long absence from work. Women were concerned about rejection by husband, harassment by in-laws, and the reduced chances of marriage (for single women), in addition to their concerns about dismissal from work. The wage-earning capacity of both men and women was affected, but women	Tuberculosis control programs which are responsive to the constraints faced by women (particularly married women) in seeking health care by creating conditions which will facilitate treatment-seeking, will

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
				feared loss of employment whereas men, being self-employed, lost wages but not employment. Married men and single women perceived a greater level of family support to initiate and complete treatment. Married women tried, often unsuccessfully, to hide their disease condition for fear of desertion, rejection or blame for bringing the disease.	have greater success in identifying women tuberculosis patients and enabling them to complete treatment.
Needham, 2001 [46]	To clarify if socio-economic, gender and health service system factors are associated with patients' diagnostic delay for tuberculosis within a typical urban African setting	202 adults newly registered with PTB at the centralized Chest Clinic. Lusaka, Zambia. Time not specified.	Cross-sectional survey.	Median diagnostic delay was 8.6 weeks, and it was significantly associated with female sex ($p = 0.02$). Lower education among women may be a confounding factor. Other potential explanations could be the heavy workload of women, lack of mobility, independence and financial resources and the associated stigma, specially considering the high rates of TB-HIV co-infection. Other factors associated with longer diagnostic delay were: having visited a private doctor ($p = 0.05$) or a traditional healer ($p < 0.001$), and more than six health-seeking encounters ($p < 0.001$).	Integration of TB screening services for women into existing primary health care or pediatric clinics. Address the stigmatization affecting women through health education directed at women.
Odusanya, 2004 [78]	To determine the patterns of delay amongst tuberculosis patients seen at a tuberculosis clinic in Lagos, Nigeria.	141 newly diagnosed cases of PTB. Lagos, Nigeria. September 2000 – January 2001	Longitudinal recruitment using a health worker administered protocol to determine time interval from onset of symptoms to initiation of treatment.	Patient delay was not found to be significantly associated with gender.	
Pehme, 2006 [81]	To estimate the determinants of patient delay in conditions of	185 newly detected symptomatic culture-positive patients aged	Cross-sectional study, using structured	Male gender was associated with prolonged patient delay (aOR 2.12, 95%CI 1.06-4.23) and extreme patient delay (aOR 3.28, 95%CI	Education about cough as an important TB symptom.

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
	negligible HIV infection, insignificant immigration and free access to medical care with TB.	=> 16. 6 counties of southern Estonia. January 2002-December 2003.	questionnaire, and logistic regression with 2 cut-off points for analysis.	1.30-8.26).	
Peterson Tulsky, 1999 [91]	To measure knowledge and perceived susceptibility to tuberculosis among homeless adults in San Francisco and attitudes toward control measures used to improve adherence to treatment for tuberculosis.	292 homeless shelter residents. Five homeless shelters in San Francisco, California, USA. 1993	A cross-sectional survey via interview of homeless shelter residents.	Perceived susceptibility to TB did not differ by sex.	
Pirkis, 1996 [83]	To examine delay in initiation of treatment for tuberculosis	142 notified TB patients. Victoria, Australia. January 1991 – December 1993.	Retrospective record review.	The median time between onset of symptoms and initiation of treatment was longer in females than in males (62 vs 41 days for all TB patients, and 49 vs 39 days for pulmonary TB patients). However, this difference was not significant.	
Portero, 2002 [66]	To investigate general knowledge about TB and intended health-seeking behavior for TB symptoms among the general population of Metro Manila, and how they are determined by socioeconomic factors.	3970 subjects aged 18 and older, from different socio-economic status. Fiver urban communities in Metro Manila, Philippines.	Cross-sectional survey. Multivariate analysis with standard logistic regression.	Knowledge about TB and intended health-seeking behavior did not differ by sex.	

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
		March – May 2001.			
Promtussananon, 2005 [90]	To investigate public perceptions about causes, suggested means of risk reduction, and preferred treatment of tuberculosis.	80 members of semi-urban communities. Limpopo, South Africa. Time not specified.	Cross-sectional study with participants chosen by quota sampling.	The perception of biomedical causes of TB was significantly higher among women, while more men held local cultural beliefs about TB ($p = 0.02$).	TB education particularly targeted to men in this communities.
Pronyk, 2001 [75]	To examine patterns of health seeking behavior among hospitalized tuberculosis patients.	298 hospitalized patients diagnosed with PTB, aged over 10 years. South Africa 1999	Hospitalized patients diagnosed with PTB were identified in hospital records, and were interviewed using a semi-structured questionnaire.	No gender differences were found in patient delay.	
Pungrassami, 2010 [73]	To estimate the association of TB and acquired immune-deficiency syndrome (AIDS) stigma on delay in seeking care for TB symptoms.	432 newly diagnosed adult patients with TB. Thailand. 2005-2006	Cross-sectional survey.	The median patient delay time among men was 1 week longer than among women (28 vs. 21.5 days). Among men, those with higher TB stigma had a small increase in patient delay times (mean difference per one point stigma score 0.012, 95% CI -0.001 – 0.025), while women had a small decrease in patient delay (mean difference per one point stigma score -0.009, 95% CI -0.026 – 0.007; $p = 0.05$). These findings suggest that women who report higher levels of TB stigma may seek care more quickly in an effort to relieve their symptoms and minimize any social consequences due to disease.	

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
Rintiswati, 2009 [67]	To document patient journeys toward TB diagnosis and treatment and factors that influence health care seeking behavior.	67 TB patients, 22 family members and 6 focus grupo discussions with community members. Jogjakarta, Indonesia. Time not specified.	In-depth interview and focus group discussions with TB patients, family and community members.	Patients showed no apparent difference in care-seeking behavior according to gender. However, in the rural area, males were more comfortable informing their friends and neighbors regarding their illness than females. Most spouses of TB patients stated the need to separate sleeping, eating and cooking.	
Rodger, 2003 [85]	To estimate the delays in diagnosis of tuberculosis and to investigate the factors independently associated with delays.	853 smear-positive PTB patients. London, UK 1998 - 2000	Analysis of surveillance data collected by doctors (1999-2000) and an anonymized national survey (1998)	Women were more likely than men to have a delay in diagnosis greater than the median (57% of women vs. 48% of men; aOR 1.46, 95% CI, 1.1 – 1.9, p = 0.01)	
Rodríguez-Reimann, 2004 [47]	To investigate gender and acculturation differences in TB-specific Health Belief Model (HBM) constructs, and the applicability of the HBM's traditional configuration to Mexican Americans.	166 adult Mexican Americans who had a relative with a positive TB skin test. San Diego, California, USA Time not specified.	Cross-sectional self-report survey	Univariate analysis revealed that women perceive more benefits to taking health-related actions (p = 0.004), report greater attention to TB-related cues to act (newspaper articles, and radio and TV spots) (p < 0.001), and indicate a greater intent to engage in preventative health behavior than men (p < 0.0001).	
Sanou, 2004 [86]	To explore patients' and community members' perceptions and problems associated with accessing	TB patients, community representatives, members of the	28 focus group discussions and 68 in-depth interviews.	Women were perceived to have limited financial autonomy to make decisions about health care, which restricted their access to TB treatment. In some cases women's health	

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
	formal tuberculosis (TB) treatment; and to identify patients' and community members' perceptions and problems associated with adhering to formal TB treatment.	health centre management committee, traditional healers and health professionals. 3 districts in Burkina Faso. 2002		seeking behavior was dependent on the will and money of fathers, husbands or husbands' families.	
Skordis-Worrall, 2010 [82]	To explore the ways in which provider and patient behaviors interact to exacerbate diagnostic delay in Cape Town, South Africa.	Members of communities with high TB prevalence, including 2 with high HIV co-prevalence. Cape Town, South Africa. 2004	Focus group discussions, with groups stratified by sex, ethnicity and TB status. The analysis was made using grounded theory and thematic analysis.	Men were more likely to delay communication about a suspected illness. These delays appeared to delay treatment seeking. Female family members, particularly mothers, seem to play a key role in guiding care-seeking strategies.	
Somma, 2008 [48]	Assess indicators of TB-related stigma and socio-cultural and gender-related features of illness associated with stigma.	Approx. 100 TB patients in each site. Bangladesh, India, Malawi and Colombia. Time not specified.	Semi-structured explanatory model interviews; cross-site statistical analysis.	The overall stigma index was greater for women in Bangladesh ($p = 0.04$). Women, particularly in South Asia, experienced considerable TB-related social disqualification and feelings of rejection associated with gender roles, and were particularly vulnerable and fearful of abuse, abandonment, divorce and other marriage-related problems. In India and Malawi, women were more likely to be concerned about impact on marital prospects. However, female sex as a determinant of more stigma was a significant finding in multivariate analysis only in Bangladesh ($p =$	Exaggerated perceptions of risk, realistic precautions against spread and the effects of enacted, anticipated and internalised stigma should be informed by public education and mitigated by efforts to promote social support. Development of community-based care,

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
				0.02). Associations with HIV/AIDS were linked to TB stigma in Malawi, where sexual contact as a perceived cause was more associated with stigma for men and less for women. Financial and work-related issues were associated with the stigma of TB among men at all sites: having to stop working for social reasons and disability, contributed to loss of income and social status within the family and the community.	treatment programmes at work and income-generating programmes are all likely to stimulate effective support for patients and their families.
Thorson, 2000 [55]	To assess health-seeking behavior in adults with long term cough.	34,127 people aged 15 and over. Ha Tay province, Vietnam. Time not specified.	Population-based survey; household interviews with structured questionnaire.	Among individuals with long-term cough, more women than men took health-care actions ($p = 0.05$), and they were more likely to take three or more health-care actions ($p = 0.02$). However, women were more likely to use self-medication and visit private practitioners, and to chose less-qualified providers (self-medication, pharmacist or private practitioner) as the first health-care action, while more men than women visited a hospital. Regression analysis indicated that being a woman was associated with an increase in the number of health-care actions taken, an increased delay to first hospital visit and lower total cost per health-care action ($p = 0.01$).	Sex-sensitive strategies taking into account the observed sex differences in health-seeking behavior and addressing the neglect of case detection thus need to be developed.
Thorson, 2004 [49]	To explore doctors' views and explanations for a longer doctor's delay among female TB patients in order to eventually contribute to improved case detection.	Medical doctors from various departments. Quanh Ninh Province, Vietnam. 2001	Focus group discussions and in-depth interviews.	Longer diagnosis delay among female patients was attributed to limited autonomy and resources for women in terms of money and time, due to their inferior position in the household and their role as care-takers. Women were seen as more ashamed of talking about their symptoms, more afraid of stigma and less knowledgeable about TB. Men, being the primary providers, where	Patient-doctor encounters guided by gender-specific needs can contribute in reducing barriers for help-seeking behavior in women.

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
				perceived as having more access to money and decision-making power, and being more daring and open.	
Wandwalo, 2000 [94]	To determine patients' general knowledge of TB and the management of the disease.	296 newly diagnosed PTB patients. Mwanza, Tanzania. May - July 1997	Health facility based study using structured questionnaire.	There were no significant differences in knowledge about TB between men and women.	
Wang, 2008 [56]	To understand whether and to what extent people in rural China know TB and are aware of the pro-poor DOTS program, and further to understand the collation between rural people's knowledge and awareness of TB and their health-care seeking behaviors from a gender perspective.	1083 people from general population for survey on knowledge of TB. 33549 people for help-seeking among TB suspects. Yangzhong County, a rural area in China. Time not specified.	Two cross-sectional studies (one for TB knowledge and one for help-seeking among TB suspects).	Significantly more men than women actively learned knowledge about TB (20.1% vs. 11.7%, $p < 0.001$), knew about the appointed health facility for TB diagnosis and treatment (69.9% vs. 57.8%, $p < 0.001$), and knew about the local policy for free TB diagnosis (46.8% vs. 38.6%, $p = 0.007$) and treatment (44.6% vs. 34.4%, $p < 0.001$). Significantly more women than men sought healthcare for the current prolonged cough (79.2% vs. 58.6%, $p = 0.005$). However, men preferred to visit upper level health facilities, whereas women preferred to visit lower level health facilities in their first and second health-care-seeking action. There was no gender difference in the delay to the first visit to a health care facility.	Gender issues should be considered in promoting patients' health-care seeking behavior and to shorten the delay of diagnosis.
Weiss, 2006 [51]	To document sex differences in key aspects of TB control; to identify gender-specific barriers to early case detection, appropriate treatment, adherence, and cure; to	42 focus group discussions (5 to 11 participants each); 20394 patients registered at local TB control programs; clinical observation of	A multi-methods approach guided plans for six components of the research at all four sites: situational analysis of health-	The study shows that for women, delays in seeking care often result from domestic social responsibilities that restrict their access to resources. The reasons why men delay seeking care typically focused on interference with livelihood activities.	Health-care professionals should be trained to consider the possibility of TB in female patients presenting with more atypical symptoms.

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
	compare and contrast findings from studies in Asia, Africa, and South America; and to recommend policy and interventions for enhancing the gender sensitivity of TB control programmes.	512 patients; outpatient survey of 2529 TB patients; EMIC interviews with 427 patients currently in treatment. Bangladesh, India, Malawi and Colombia Time not specified	services infrastructure and TB control programmes; focus group discussions to examine community views; examination of data from patients registered in local TB control programs; observation of patient-provider interaction; survey with TB out-patients; Explanatory Model Interview Catalogue.	The study also found substantial TB related stigma at all sites, which was associated with HIV/AIDS in hyperendemic settings, and with difficulties in arranging marriages for women with TB in South Asia. Stigma, social discrimination, family rejection, risk of divorce and interference with marriage prospects were greater for women, especially in South Asia. Perceived causes of TB: sexual contact with an infected person, extramarital sex and promiscuous sexual activity; smoking and drinkin, more associated with men; smoke from cooking, overwork, childbearing or taking care of TB patients, more associated with women. Perceived negative effects of TB in pregnancy and breastfeeding. In Colombia, men were reluctant to seek help because it would be interpreted as weakness, which would go against traditional values of masculinity. In Bangladesh, more often the health providers instructions were not given directly to the female patients, but to an accompanying person. In India, there was a significantly longer mean delay from symptom onset to first help seeking among men, compared to women (57.2 days vs. 48.1 days, $p < 0.01$).	Control program site studies are needed to relate the prevalence and sex ratios of men and women with TB in communities and clinics. Health information should clearly distinguish appropriate public health precautions to minimize spread from unfounded concerns that contribute inappropriately to TB stigma. It should also clarify the relationship between HIV/AIDS and TB, and their distinctive modes of transmission. National and local strategies to improve detection of patients with TB, with particular attention to reducing patient delay for men and provider delay for women, should consider the impact of strategically reorganizing health and community services. Local options for restructuring critical features of health

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
				Women more frequently acknowledged the seriousness of TB, compared to men, specially in Bangladesh and Malawi.	systems should be considered, including planning for gender-sensitive active or semi-active case finding.
Weiss, 2008 [50]	To identify and compare socio-cultural features of TB and the distribution of TB-related experiences, meanings and behaviors with reference to gender across cultures in three high-endemic low-income countries.	Approx. 100 patients from each site. Bangladesh, India and Malawi. Time not specified.	Semi-structured explanatory model interviews.	Female patients reported a wider range of symptoms less specific for TB. Men more frequently focused on financial concerns. In South Asia, TB-related stigma and social discrimination were particularly troubling for women because they threatened their ability to marry or put them at risk of divorce. Men emphasised smoking and drinking alcohol as causes of TB, and women in Malawi reported sexual causes associated with HIV/AIDS. Women compared to men were more likely to use home remedies and self-medication in Bangladesh (76% vs. 36.5%, $p < 0.01$, and 30% vs. 15.4%, $p < 0.1$), private health care providers in India (80.3% vs. 63.3%, $p < 0.05$). The last-mentioned were preferred because they were considered more convenient, familiar and trustworthy. Women in particular mentioned the cost of transportation and the need to be accompanied by the husband or brother as limitations to access health care.	Clarifying modes of transmission and perceived risk in the community may help to reduce stigma and shorten patient delay. Effective collaboration between public services and private practitioners. Training the clinical health staff in local presentations of TB.
Xu, 2004 [19]	To obtain an in-depth understanding of factors that influence the health seeking behavior of TB patients, and access to tuberculosis (TB) care in counties with or without National TB Control	9 female and 21 male TB patients, 3 female and 25 male village health workers, and 15 female and 15 male health providers.	Data was collected using focus group discussions, and analyzed through qualitative content analysis.	Women were perceived as more reluctant to seek help, especially when the family is poor, because they prioritize the health of husband and children. This was related to the higher status granted to men within family, for being the providers, and to the lower value attributed to women's work at home and their contribution to the family.	

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
	Program (NTP) in rural China.	Jiangsu Province, China Time not specified.		Women were thought to seek help in village health stations first, because of their closeness and convenience, having minor symptoms and the cheaper cost of medicines.	
Yamasaki-Nakagawa, 2001 [22]	To examine delays in TB diagnosis and compare health care seeking behavior between men and women.	265 men and 125 women newly diagnosed with TB who began to receive DOTS. Nawalparasi district, Nepal. December 1997 – June 1999.	A cross-sectional analysis of patient interviews.	Significantly more women than men visited a traditional healer at some time prior to their TB diagnosis (35% vs. 18%, p = 0.001), and were more likely to receive more complicated charms from traditional healers. Men tended to visit the government medical establishment first if they knew that free TB treatment was available than if they did not know (30.4% vs. 16.4%, p = 0.021). Women did not fallow this pattern. There was no gender difference in patient's delay (the median was 0.8 months for men, and 0.6 for women).	Development of suitable links between modern and traditional, private and public health services, through education and a good referral system.
Yimer, 2009 [61]	To describe and analyze health care seeking among TB suspects and pulmonary TB (PTB) cases in a rural district of the Amhara Region in Ethiopia.	1006 TB suspects (542 women), 15 years and above. Amhara Region, Ethiopia. 2008.	Cross-sectional study. House-to-house visits were conducted and TB suspects were interviewed using a semi-structure questionnaire.	In logistic regression women were found to be less likely to visit a medical (more qualified) health provider (health post, clinic, health centers and hospitals) than men (aOR 0.8, 95% CI 0.6 - 0.9).	
Zhang, 2007 [57]	To explore perceptions of TB, and health care seeking pathways, among poor rural communities in Inner Mongolia.	20 focus groups, with 105 farmers; survey with 614 farmers. Inner Mongolia Autonomous Region, China.	Focus group discussions and a structured interview questionnaire survey.	Social stigma associated with TB influenced marriage prospects (related to the idea that TB is inherited) and impeded important social interactions within the community. Unmarried young men felt that it would be difficult for them to find a marriage partner if they were diagnosed with TB, at least until they were completely cured. The reason for this was the	

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
		Time not specified.		perception that TB would harm their offspring, and TB treatment would be unaffordable, as mentioned above. In contrast to unmarried men, unmarried women felt that even if they had TB they would still be able to find a marriage partner, even during diagnosis and treatment, but their parents would receive fewer betrothal gifts than usual. Some FDG participant said they would try to keep it a secret if a member of their family or themselves had TB. Although the FGDs participants perceived that women were less likely to seek care than men, and less likely to be prioritized within the family for care seeking, gender difference was not statistically significant in the survey.	

Summary table on gender, TB diagnosis and initiation of treatment

Reference	Aim	Person, place time	Design & methods	Main findings	Recommendations
Ahidjo, 2005 [108]	To assess the radiographic appearance and frequency of distribution of cavitations in the lungs	116 (71.6% male) adult patients diagnosed bacteriologically as PTB, in two hospitals in northeastern Nigeria , April 2003 to March 2004	Retrospective review of chest radiographs	Overall, 50% of PTB patients presented with cavitations with no differences between male and female patients (P=0.837)	
Austin, 2004 [99]	To describe the sex and age distribution of sputum submission and smear positivity	38566 initial sputum smear tests for TB suspects (59% male) ≥15 years in the Western Cape region, South Africa, in 1999	Review of laboratory registers	The M:F ratio among the general population was 0.94:1; 1.45: 1 among TB suspects and 2.08:1 among confirmed TB cases. This ratio increased for smear grade+ 1.8:1 to 2.5:1 for smear grade+++. The M:F ratio was 1.7-3.64 in age groups between 25-74 years but similar in younger and older age groups	
Ayé, 2010 [110]	To investigate the extent and determinants of patient and health system delays for TB.	December 2006 – March 2007. 12 districts in Tajikistan. 204 (56% male) newly diagnosed PTB patients, enrolled in DOTS.	Structured patient interviews	No significant gender differences were found in health system delay in TB diagnosis (HR for women 1.2, 0.91-1.59). The type of facility for first contact was the main determinant of health system delay.	
Balasubramanian, 2004 [26]	To examine gender differences in TB among adults aged > 14 years with respect to infection and disease prevalence,	Several studies between 1998 to 2002 including individuals from community, out	Data were collected from: 1) community survey; 2) self-referred out-patients attending	1. The M:F ratio in the surveyed population was 0.96 while it was 0.68 in outpatients, indicating that more women than men attended governmental health facilities. 2. Among out-patients with chest symptoms, the	Elderly patients, especially elderly women, need additional support to access diagnostics and

Reference	Aim	Person, place time	Design & methods	Main findings	Recommendations
	health care service access, care seeking behavior, diagnostic delay, convenience of DOT, stigma and treatment adherence	patients and TB patients in rural sub-district in Tiruvallur, south India	primary health institutions; 3) TB suspects referred for sputum microscopy; 4) TB patients notified under DOTS	M:F ratio was 1.6, while it was 2.7 among TB patients registered for DOTS. 3. In the community survey, the prevalence of respiratory symptoms (cough ≥3 weeks) was significantly higher among men than women (7.2%, vs. 3.3%; *P*< 0.001). Similarly, among self-referred patients attending health facilities, men were significantly more likely to have respiratory symptoms than women (5.0%, vs. 2.2%, *P*< 0.001). 4. Significantly more female than male tuberculosis suspects submitted the required three sputum samples for smear microscopy (85% vs. 83%; *P* <0.05). but the sputum positivity rate was significantly higher among men than women (15.3% vs. 6.9%; *P* < 0.001). 5. Among men, the sputum positivity rate increased with age, reaching a peak in the age group 35–44 years, and then decreased with age. Among women, the sputum positivity rate decreased significantly with age (chisquare linear trend, *P* <0.001). 6. The median health system delay did not differ significantly for male and female patients (median delay 30 vs 37 days, P=0.6). 7. Both among smear-positive patients diagnosed in the community survey (29%) and diagnosed at the peripheral health institutes (15%), the rate of initial default was similar among men and women.	DOT services. Qualitative research is needed to identify and address barriers to care seeking and treatment completion among men and the elderly.
Bashour, 2003 [27]	To determine whether there are sex differences in diagnosis, compliance with treatment and/or treatment outcomes of TB patients	552 (70% male) smear-positive TB patients in the Syrian Arab Republic, diagnosed from Jan to July 2002	Prospective cohort study; patient interviews and review of treatment cards	Satisfaction with the service provided (99.7% vs. 97.8%), convenience of visits (93.6% vs. 87.4%), and long waiting times 10.9% vs. 12.4%) were similar for men and women. The mean score for satisfaction with care was higher among men than women (2.8 ± 0.4 vs. 2.7 ± 0.5, P=0.02)	

Reference	Aim	Person, place time	Design & methods	Main findings	Recommendations
Becerra, 2005 [52]	To assess the feasibility and yield of a simple active case finding strategy in a high incidence population in northern Lima, Peru.	208 case subjects with PTB, 1094 household contacts and 2253 neighboring household contacts in Lima, Peru, January 1996 – April 1997.	Active TB case finding among household members of smear-positive TB index cases and household members of 2 neighboring households	Case subjects detected through active case finding (3 males and 8 females) differed from those who self-reported (119 males and 93 females) in that they were more likely to be female and more likely to be aged ≥55 years. Older women diagnosed with TB did not report longer duration of cough than other groups in the study. It is unclear whether this under-notification occurred because older women delayed seeking medical care for their symptoms or because health care providers failed to make prompt diagnoses when these individuals did seek care.	Further work is needed to define the barriers to accessing appropriate health care faced by older women with TB in this community.
Begum, 2001 [100]	To assess gender differences in access to tuberculosis diagnosis and in TB treatment outcome	TB suspects and patients in 59 thanas in Bangladesh in 1997	Retrospective review of outpatient (42,877 patients with respiratory symptoms), TB laboratory (first 10 per month; n=5,665), and treatment (all 5,632 new sputum smear-positive patients) registers	The F/M ratio was 0.95 among the general population, 0.79 among outpatients with respiratory symptoms, 0.52 in those undergoing sputum smear microscopy, 0.36 among those found to be smear-positive, and 0.35 among those starting TB treatment. All ratios declined with age. The number of sputum smears taken per suspect patient was similar for both men and women.	Gender bias in incidence of respiratory symptoms and access to public health facilities may be important and further studies and interventions appear indicated, taking into account the possible role of age. Special attention may need to be given to the quality of sputum submitted by women for examination.
Boeree, 2000 [101]	To examine gender differences in sputum submission and sputum smear positivity	All TB diagnostic units in eight geographically representative districts in Malawi,	Retrospective review of laboratory registers	Significantly more males submitted sputum and were smear-positive compared with females. Rates of sputum submission per 100 000 adults were 1203 for males and 1032 for females (OR=1.17, 95%CI 1.14–1.20). Rates of smear-	

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		1995 and 1996		positive sputum per 100 000 adults were 153 for males and 123 for females (OR= 1.24, 95%CI 0.97–1.59). A significantly higher proportion of female cases (61%) were aged 15–34 years compared with males (45%, *P* < 0.05), probably due to a higher HIV infection rate in young women	
Borgdorff, 2000 [29]	To explore whether lower TB notification rates among women are due to a reduced access to health care, particularly diagnostic services, for women	14 countries from South East Asian, Western Pacific, African and East Mediterranean regions.	Age- and sex-specific TB prevalence rates of smear-positive TB from 29 surveys from 14 countries were compared to age- and sex-specific notification rates from the same countries in 1996.	The F/M notification rate ratio was below 1 and decreased with increasing age in almost all countries. The F:M prevalence ratio's were <0.5 in surveys in the south-east Asian and western Pacific region and approximately 1 in the African region. In most countries in the South-East Asian and the Western Pacific region, the F/M sex ratio in prevalent cases was similar or lower than that in notified cases, but not in sub-Saharan Africa, suggesting that F/M differences in notification rates may be largely due to epidemiological differences and not to differential access to diagnosis. However, this conclusion cannot be generalized to individual regions or countries.	Additional research, both quantitative and qualitative, would be instrumental in obtaining firmer conclusions on gender bias in TB case detection, related to health seeking behavior and/or to steps within the health systems in suspecting and diagnosing TB.
Breen, 2008 [106]	To determine how frequently fever, sweats and weight loss, and blood test evidence of inflammation were absent in individuals with TB.	143 (48% male) adult unselected subjects with culture confirmed TB at a TB service in London, UK, 2003-2006	Prospective, observational cohort study.	Absence of the systemic TB symptoms fever, sweats and weight loss, was significantly associated with female sex (aOR 3.15, 1.45-6.83)	
Bruchfeld, 2002 [117]	To study the prevalence of PTB and HIV among PTB suspects, and to compare clinical and epidemiological characteristics between	509 consecutive outpatients (60% male) evaluated with sputum smear on clinical suspicion of PTB in a hospital in	Cross-sectional study	39% of male suspects vs. 26% of female suspects had positive cultures (aOR 1.9, 1.3-2.9). The findings of a male:female ratio of 1.3 among non-TB patients, compared to a ratio of 2.1 in the PTB patients, as well as the trend towards an increased risk of PTB in HIV-	

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	confirmed PTB patients and non-PTB subjects	Addis Ababa, Ethiopia, March-Nov 1996		positive women seem to favor biological or transmission explanations, as a gender-based selection bias for these patient groups is unlikely.	
Cassels, 1982 [16]	To compare the results of active case-finding (ACF) and passive case-finding both in terms of patient compliance and of eventual outcome.	159 new smear-positive self-referred (SR) patients, and 111 smear-positive patients found through ACF among 2843 symptomatic patients, out of a 67068 population over 15 years of age, in Nepal, 1978-1980	Comparison of ACF carried out by mobile teams and self-referral of patients to the existing services.	The overall male : female ratio in ACF patients was 1.2:1, compared to 2.6:1 in the SR group ($p < 0.001$). Particularly noticeable was the difference in the number of females aged 45 and older.	
Cegielski, 1997 [115]	To assess the degree to which, from 1987 to 1990, physicians suspected tuberculosis (TB) in the first 2 hospital days in human immunodeficiency virus (HIV)-infected patients with pulmonary disease.	2174 adult patients (93% male) with AIDS, generally with unknown diagnosis at admission, and discharged with a diagnosis of *Pneumocystis carinii* pneumonia from 1987 to 1990 in 96 hospitals in five US cities	Retrospective cohort study; review of medical records for which patients TB was suspected (a physician wrote TB as a possible diagnosis or ordered sputum smear and culture for AFB in the first two hospital days)	Against a background of an increasing TB incidence during the early phase of the AIDS epidemic, the proportion of patients for whom TB was considered in the first two days increased significantly for male patients from 66% in 1987 to 74% in 1990, while no trend was observed for females (average 77%). Adjusted for HIV and city, the result was similar.	Physicians must be aware of epidemiological trends and of their practice patterns, so that they may more quickly identify patients with TB and institute appropriate isolation, treatment, and public health measures
Chang, 2007 [72]	to determine the length of delay, and factors linking the delay from the onset of symptoms of pulmonary tuberculosis (PTB) until the	316 (61% male) patients from 10 TB clinics in randomly selected divisions in Sarawak, Malaysia from June 2003 to	Institution based cross-sectional study; semi-structured patient interviews and review of outpatient	The median health care diagnosis delay was 22 days, and gender was not associated significantly associated with diagnostic delay (aOR 1.24, 95%CI 0.71-2.1)	

Reference	Aim	Person, place time	Design & methods	Main findings	Recommendations
	commencement of treatment	May 2004.	cards		
Dandona, 2004 [102]	To provide baseline information on the utilization of the Revised National TB Control Program (RNTCP) services by men and woman, barriers to utilization and to recommend actions to optimize this utilization.	83,099 (65% male) TB suspects listed in the laboratory and 21,592 (69% male) TB patients in the TB register. Data from representatively selected TB service units from relatively good and relatively poor functioning district TB programs in 4 states in India.	Data were collected on suspects examined in 2002 and patients starting treatment in 2002. Randomly selected patients from the period July 2001-Dec 2002 who had discontinued the diagnostic evaluation and who were diagnosed with TB but did not start treatment were interviewed	The F:M ratio in TB suspects who reported at the laboratory for diagnosis was 0.54. Among those who reported, a similar proportion of males and females did not complete the diagnostic process (7.7% vs 6.8%). The proportion among TB patients diagnosed as sputum positive was similar among men (68.8%) and women (68.2%).	
DeRiemer, 1999 [105]	To identify the characteristics of persons in whom TB was diagnosed after death, and determine whether secondary cases of TB resulted from them	3102 TB cases reported in San Francisco, in 1986-1995, of which 120 (3.9%) were diagnosed after death	Retrospective review of reporting registers	Male TB cases more often were diagnosed after death (aOR=1.52, 0.98-2.46). This may have to do with risk groups like injecting drug users	
Díez, 2005 [113]	To study health system delay in TB diagnosis and its determinants.	5184 (70% male) culture-confirmed TB cases in 13 (out of 17) autonomous Regions in Spain, May 1996 – April 1997.	Clinical record review	Sex was not associated with a health system delay greater than the median (aOR 1.12, 0.97-1.29), but female gender was associated with a HSD delay greater than the 75th percentile (aOR 1.26, 1.06-1.49)	

Reference	Aim	Person, place time	Design & methods	Main findings	Recommendations
Farah, 2006 [76]	To assess (patient and) health care provider delays in start of treatment for TB patients	83 (44 male) TB cases aged ≥15 years in the period July 1 2003-Feb 6 2004 in Oslo/Akershus region, Norway	Cross-sectional review of notification data, laboratory data and referral case notes to identify cases, patient delay and health care system (HCS) delay	HCS delay did not differ significantly between the 44 male and 39 female patients. Median HCS delays were 22 vs. 35 days (aOR 0.84, 95% CI 0.49-1.45)	
Fochsen, 2006 [33]	To explore health care providers' experiences and perceptions of their encounters with male and female patients with special reference to TB care	22 health care providers (17 males and 5 females) working in outpatient practice and with experience of consulting with both male and female patients with complaints suggestive of PTB, purposively selected from the public vs. private sector and rural vs. urban areas from a rural district in India (Ujjain district, Madya Pradesh).	Cross-sectional study with semistructured interviews on personal experiences, with use of probing. Latent content analysis	The dominance of doctors seemed to be more pronounced in consultations with female patients, and as a result, females patients' own accounts of their illness tended to be neglected which may explain female patients' greater difficulties in receiving sputum investigations and being diagnosed with TB once they present to the health care system. The doctors' interactions with female patients were often restricted by other social structures, e.g. when a senior family member was present during the consultation, the expected behavior of the women would be to keep silent and let her attendant talk to the doctor	A patient-centered approach, acknowledging patients' experiences and shared decision making, should guide medical encounters in TB control activities. This will be crucial to the achievement of an equitable treatment of TB, and will be of special importance to those female patients whose voices were not heard in the medical encounter.
Huong, 2006 [98]	To assess the yield of sputum smear microscopy by sex	29,243 smears from TB microscopy centers in 30 randomly selected (proportional to size) districts in Vietnam,	Review of laboratory record data of TB suspects	Men were more likely to present for sputum smear examination in all age groups although not significant in 0-14 and 25-34 year groups (overall male: female ratio among suspects 1.36, 95% CI 1.19-1.54 compared to 0.97 in the general population). The proportion of	

Reference	Aim	Person, place time	Design & methods	Main findings	Recommendations
		in 1998		cases among suspects was higher among men than among women (overall 11.6% vs. 8.4%). In the age groups 25-54 years, men were approximately twice as likely to be smear-positive, whereas there was no sex difference in the youngest (0-24 years) and oldest (>65 years) age groups. The sex differences remained after stratification for specimen appearance, timing of collection and number of smears examined	
Huong, 2007 [59]	To assess (patient and) health care provider delay in diagnosis and treatment, and risk factors for delay	2093 (71% male) new smear-positive pulmonary TB patientstreated by the National TB Control Programme in 70 randomly selected districts in Vietnam, in one quarter in 2002	Structured interviews shortly after start of treatment	Female patients more often had a health care provider delay of ≥6 weeks but the difference was small and not significant (aOR 1.2, 95% CI 0.8-1.7)	
Jiménez-Corona, 2006 [1]	To identify gender based differences in patients with PTB	8195 (44% male) individuals with a cough >2 weeks, as detected by community workers, in all health care centers in 12 municipalities in Veracruz state, Mexico in March 1995-April 2003, of which 829 were diagnosed with TB. Of those 623 had genotyping results	Laboratory records on TB suspects and prospective follow-up of TB patients	The proportion of female suspects providing three samples was slightly higher than among male suspects (86.4% vs. 84.6%, P=0.03). Among PTB suspects, the proportion of women was 56% while it was 41% among those diagnosed as having PTB. Between men and women there were no differences in diagnostic delay (median 2.9 vs 2.78 months, P=0.46) and treatment delay between men and women (median 0.2 vs 0.02 months, P=0.22).	

Reference	Aim	Person, place time	Design & methods	Main findings	Recommendations
Johansson, 2002 [63]	To elucidate understanding of mechanisms of the tuberculosis sickness trajectory in Vietnam.	24 TB patients and 16 health care providers involved in TB care, in Quang Ninh Province, Vietnam. Time not specified.	In-depth interviews. Modified grounded theory was used for the analysis.	Several male doctors described the meeting with female TB patients as difficult as women presented their symptoms in a "less concrete" way, making it more difficult to examine and diagnose women than men. Female doctors did not report this.	Increase awareness of the importance of quality interaction based on transparency and trust among patients, family, society, and providers, paying particular attention to the differences between men and women with regard to their social situation and need for social support.
Kamel, 2003 [39]	To determine the sex ratio among registered PTB cases; to describe and compare the utilization patterns of TB services and between male and female patients; to describe and compare outcomes of TB treatment between male and female TB patients; to identify factors behind gender differences in health seeking behavior, diagnostic delay, TB treatment adherence (compliance behavior) and subsequent treatment outcomes.	334 (69% male) PTB patients who were on anti-TB therapy, in Alexandria, Egypt, 2001-2002	Cross-sectional comparative study design, using a structured interview, questionnaire and data collection from records and control cards; cases were prospectively followed-up during 8 months.	The pattern of TB symptoms at the time of the interview (>1 month after start of treatment) was similar for both sexes. Only purpura was reported more often by women (14.6% vs. 2.6%, P=0.0003). Treatment delay after diagnosis was shorter for women than men (delay after diagnosis 1.4 vs 1.2 weeks, P=0.0001)	
Karim, 2007 [111]	To assess gender	100 PTB patients	Programme record	Among women, more teenagers were	The programme should

Reference	Aim	Person, place time	Design & methods	Main findings	Recommendations
	variations in (patient and) health system delay: doctor's delay and treatment delay (after diagnosis)	(500 men and 500 women) conveniently selected from 10 subdistricts of Bangladesh from March 2001 to September 2002	review and patient interviews within 4 weeks of diagnosis	diagnosed with TB while among men, TB was more prevalent among the elderly (data not shown). Doctor's delay was similar for men and women (median 2 vs. 3 days), as well as treatment delay (median 1 day for both). Women of older age had longer treatment delays.	mobilize social support, especially for women patients.
Kivihya-Ndugga , 2005 (#1771)	To determine to what extend the performance of smear microscopy is responsible for sex differences in notification rates	998 (60% male) TB suspects (history of cough ≥3 weeks, night sweats, fever for 1 month, weight loss and/or loss of appetite) who had provided three sputum samples with at least one positive or three negative culture results in a major TB diagnostic health centre in Nairobi, Kenya. Nurse counselors explained the importance of providing good quality sputa.	Examination by Ziehl-Neelsen microscopy, and in case of negative smears, chest X-ray was performed. Re-examination of all smears by fluorescent microscopy and Löwenstein-Jensen culture	Among all suspects, the M:F ratio was 1.5, while it was 1.8 among the 559 culture-positive cases, and 2.1-2.4 among culture-positive, ZN-positive cases. This difference was largely compensated by XCR on ZN-negative cases, as ZN followed by CXR yielded 93% of all culture-positive men and 89% of women (F:M ratio 1.9). FM increased overall sensitivity compared to ZN and decreased sex differences (F:M ratio 1.9). Among those tested, more women (49/92, 53%) were positive than men (53/166, 32%). Among ZN-negative cases, men more often had cavities. Sputum volume was associated neither with culture positivity nor ZN smear positivity. Gender was not associated with sputum quality.	
Lawson, 2008 [118]	To describe the differences in clinical presentation (and risk factors for) TB in male and female PTB patients	1186 (±60% male) patients ≥15 years with cough >3 weeks and sputum culture results upon attending hospitals in Abuja, Nigeria in Sep 2003-Dec 2004.	Prospective data-collection using structured patient interviews, clinical data including smear and culture, chest X-rays	Male and female patients were as likely to have a positive culture (OR 1.12, 0.89-1.40), but male patients more often were smear positive (52% vs. 42%, p-0.003). This may at least in part be due to the higher HIV prevalence among women (58% vs. 49%, P=0.02)	There is a need to carry out a prevalence study of TB in this community to confirm gender differences as many patients who do not present in hospitals are missed.

Reference	Aim	Person, place time	Design & methods	Main findings	Recommendations
Liu, 2005 [121]	To identify factors associated with directly observed therapy (DOT) participation and to quantify how early use of DOT affected treatment outcomes	731 Asian-born patients with drug-susceptible TB (61% male) in New York city between 1993-1997 who completed treatment	Retrospective review	DOT participation was significantly associated with male sex (47% vs. 30%, aOR 1.86, 95% CI 1.30-2.66). This may (in part) be due to gender-specific health care professional's role in offering it as researchers were unable to know which patients were offered DOT.	
Long, 1999 [41]	To describe and compare health seeking behavior between men and women and to measure delays in tuberculosis (TB) diagnosis.	1027 (74% male) patients aged 15-49 with new smear positive pulmonary TB detected, in 23 districts in four provinces of Vietnam, 1996	Interviews with structured questionnaire with all new TB cases in a stratified random sample of districts.	Women visited more health care providers before TB diagnosis (mean 1.7 vs. 1.5, P=0.02). The delay from first visiting any health care provider to TB diagnosis was longer in women than men (7.7, 6.8-8.5 vs. 5.5, 5.1-5.9, P=0.003), as well as the delay from visiting a qualified medical doctor or a hospital to TB diagnosis (5.4, 4.2-6.6 vs. 3.8, 3.3-4.3, P=0.003). In multiple regression, rural residence was a risk factor for longer doctor's delay in men while highland residence was associated with a longer health care provider's delay in women.	Develop appropriate health education programs on TB symptoms, diagnosis and cure for the general population and health providers. Women with symptoms suggestive of TB should receive more attention from health providers. Health service provision should be studied from a gender perspective, to understand the longer provider delay for women.
Long, 2002 [44]	To describe and compare clinical symptoms of new smear-positive pulmonary TB among men and women, how these symptoms influence TB diagnostic delays, and estimate the rate of	1027 new smear-positive PTB cases aged 15 years and over (757 men and 270 women) Vietnam	All the 1027 were interviewed using a structured questionnaire after confirmation of diagnosis, and 540 were selected for follow-up 2, 5 and 8	While general symptoms, such as fever, tiredness, anorexia and headache, were significantly more common in women than men (p = 0.049, p = 0.003, p = 0.000, p = 0.009, respectively), symptoms suggesting PTB, such as cough, sputum expectoration and hemoptysis, were significantly less common in women than in men (p = 0.021, p = 0.006, p	

Reference	Aim	Person, place time	Design & methods	Main findings	Recommendations
	improvements in clinical symptoms for both sexes.	1996	months after start of treatment.	= 0.033, respectively). Although bivariate analysis showed a higher mean number of symptoms in women than in men (5.3 vs. 5.0, p = 0.04), the difference was no longer significant after controlling for cofounding variables.	
Lorent, 2008 [77]	To evaluate (patient and) health services delays in the diagnosis and treatment for TB	104 adult patients (43% male) treated at the main referral center for TB in Rwanda (Kigali university hospital), between June and September 2006	Questionnaire survey and review of case files and referral letters	Median health service diagnostic delay was 28 days overall: a median of 18 days at the health facilities visited before the referral hospital and a median of 6 days at the referral hospital. Male sex was not associated with a delay >6 days at the referral hospital (aOR 1.14, 95%CI 0.52-2.50)	
Meintjes, 2008 [68]	To describe (patient and) provider delay and its risk factors and consequences	104 TB cases admitted to a secondary level hospital serving communities with high HIV prevalence in Cape Town, South Africa, between Feb and Sept 2003	Structured patients interviews	No difference in provider delay by gender was observed (median delay 30 days, IQR 10-60)	
Murthy, 2000 [97]	To assess the effect of administering oral salbutamol (a β2-agonist) in increasing sensitivity of smear microscopy	250 TB suspects with dry cough (no sputum) or scanty sputum smears	Oral salbutamol 1 mg twice daily for 3 days; and repeated if sputum yield was still not adequate	More women than men needed a second course of salbutamol. A two-fold enhancement in sputum positivity was observed in women with salbutamol intervention, and made the gender distribution in TB diagnostics near equal.	
Ramsay, 2009 [107]	To evaluate the impact of specimen quality and different smear-positive TB case (SPC) definitions	644 patients (45% males) ≥15 years with cough >2 weeks who produced ≥1	Structured patient interviews and collection of 3 sputum specimens	No differences in TB treatment history and clinical presentation of symptoms such as sputum production, fever, etc.) between males and females. Male suspects less often produced	The effects of HIV infection, coaching in specimen production, specimen volume and

Reference	Aim	Person, place time	Design & methods	Main findings	Recommendations
	on detection by sex	specimen for microscopy, in Mathare, Nairobi, Kenia between Feb and Dec 2005	over 2 consecutive days (spot-morning-spot) after coaching on sputum expectoration. SPC detection by sex was compared using different definitions based on AFB cut-off to define a positive smear and required number of positive smears	at least one specimen (male: female ratio 0.8). More men produced a set of three good quality specimens (based on macroscopic classification): 64% vs. 54%, P=0.01. Regardless of the definition applied, more men than women were found to be smear-positive. The increase in detection with less strict criteria was higher for women. In a sub-selection of those who produced a set of good quality specimens, the differences became smaller and borderline significant (P=0.05-0.06).	fluorescence microscopy on sex and gender-specifc impact of reduced thresholds for case definition requires further study.
Rieder, 1997 [103]	To ascertain workload, yield from serial smear examination, and demographic characteristics of sputum smear examinees	Sputum smears from 36,919 TB suspects from 42 laboratories performing sputum smear microscopy in Benin, Malawi, Nicaragua and Senegal. Laboratories were non-randomly selected from laboratories perceived as registering accurately	Retrospective review of TB laboratory registers	In all four counties, the greatest proportion of suspects was found in young adults, and the age distribution of suspects in general was comparable between men and women. In all countries, a higher proportion of male suspects turned out to be cases compared to females but there were big variations by age. The proportion of females among cases decreased with increasing age. In 35 of the 42 laboratories, females constituted a higher proportion among TB suspects than among cases. This effect became more pronounced with increasing age. In the group under 25 years of age and approximately equal number of females compared to males needed to be examined to identify one case of TB while the relative number of females that had to be examined to identify one case increased steadily with age	A characterization of what constitutes a TB suspect in actual practice, and a determination of the final diagnosis in such suspects, might help to elucidate the phenomenon of potentially higher prevalences of non-specific resp symptoms in women
Rieder, 2009 [120]	To examine the influence of age and sex on the	107 nationally representative	Analysis of individual smear	Country (inverse correlation with HIV prevalence) and age (more often at the	Particular emphasis should be given to

Reference	Aim	Person, place time	Design & methods	Main findings	Recommendations
	grading of tuberculosis (TB) sputum smear microscopy results.	samples of laboratory registers (between 1999 and 2003) in Moldova, Mongolia, Uganda and Zimbabwe. Of 89362 suspects with diagnostic samples, 13577 (15%) were TB cases with 27859 quantified, positive smear examinations (10633 cases with 20549 quantified positive smear examinations had complete age and sex information)	examinations by country, age and sex	extremes of age) were more important in differences in low-grade results, but there was a tendency towards females having lower bacillary counts. Stratified by sex, female cases had slightly greater proportions of low-positive results in all countries except Zimbabwe. Stratified by age and sex, females aged <35 years and >64 years had a greater proportion of low-positive results, while between 35 and 64 years the inverse was the case. Stratified by country, age and sex, in all countries, women ≥65 years had a higher proportion of low-grade results than men although this difference was significant only in Moldova. In Uganda, girls had a significantly greater proportion of low-grade positive results than boys.	appropriate instructions on how to produce high quality sputum (not sex specific)
Rozovsky-Weinberger, 2005 [114]	To investigate patient-level and hospital-level factors associated with delays in TB suspicion and isolation among inpatients with pulmonary TB	937 (69%) patients hospitalized with culture-positive PTB during 1996 and 1999 in Chicago, Los Angeles and Southern Florida that provided care for at least 5 TB patients per year	Analysis of AFB smear orders within 48 hours of admission and isolation rates within 24 hours of admission	Delays in smear orders were more often observed in female patients (aOR 1.66, 95% CI 1.06-2.60) as well as borderline significance in delays in isolation (aOR 1.40, 95% CI 0.98-1.99)	
Rutz, 2008 [116]	To evaluate adherence to tuberculosis control guidelines, published by the Centers for Disease Control and Prevention	A large urban jail, Baltimore, USA, in 1996.	Observation of symptom screening at intake; review of medical records of 225 (143 men) with positive TST; review of isolation	Median time from intake to TST was 3 days for men and 2 days for women. Median time from referral to CXR was 2 days for men and 7 days for women (recommendation within 3 days). Among those referred for CXR, more women than men were released before the CXR was made (34% vs. 6%) and more women did not	

Reference	Aim	Person, place time	Design & methods	Main findings	Recommendations
			records	get an CXR within 90 days (6% vs 0.01%)	
Sekandi, 2009 [119]	To identify undetected smear-positive TB cases by means of screening for ≥2 weeks of cough and describe characteristics of cases detected hereby	930 individuals ≥15 years identified through a house-to-house survey in five randomly selected villages in Kampala, Uganda, between June and Aug 2005	Structured interview and smear microscopy of three sputum specimens from those with cough ≥2 weeks	Among the 20% of those with cough ≥2 weeks, 33 (18%) were newly detected smear-positive cases. They had an even sex distribution (P=0.47)	
Thorson, 2000[55]	To assess health seeking behavior in adults with cough >3 weeks during the last 3 months	492 (213 men) individuals with long-term cough among 34127 individuals ≥15 years in Ha Tay province, Vietnam (period unknown)	Household interviews on cough and health-care seeking for cough	Sputum smear examinations were done more often in men than women after seeking health care (36% vs. 14%, P=0.0006), due to differences in healthcare seeking behaviors (they less often went to the hospital during first actions)	
Thorson, 2004 [104]	To estimate the gender-specific prevalence of tuberculosis (TB) through screening, and calculate case detection within the Vietnamese National TB program.	35,832 individuals (47% men) ≥15 years identified through a household survey in 67 districtes selected by randomized stratified sampling in Bavi district, Northern Vietnam in April-June 2000	Population-based survey within an existing sociodemographic longitudinal study. Cases were identified by a screening question about cough ≥3 weeks and further diagnosed with sputum examination and a chest X-ray	1.6% of men and 1.5% of women reported cough ≥3 weeks. Ten male and 15 female smear-positive cases were detected for a similar prevalence of 60/100,000 among men and 79/100,000 among women. The M:F prevalence ratio was 0.7:1. The M:F ratio for TB prevalence based on notification data was 2.7:1. Case detection was 39% (95% CI 20-76%) for male and 12% (95% CI 6-26%) for female TB cases. Among the actively detected cases, women had a higher frequency in number of visits per person to private providers, 1.3 compared to 0.7 among men. Only 20% of both men (n=2) and women (n=3) had gone to the hospital.	urgent development of gender-sensitive TB case detection strategies, promoting equity in all aspects of the health care seeking chain leading to TB diagnosis and treatment. To improve global TB control strategies more population-based studies on TB prevalence and case detection among women and men are needed.

Reference	Aim	Person, place time	Design & methods	Main findings	Recommendations
Thorson, 2004 [49]	To explore doctors' views about and explanations for the previously observed longer doctor's delay in female patients than in male patients	Key informants selected from clinical staff in one general hospital and TB units in two rural districts of Quanh Ninh province, Vietnam	Five focus group discussions and three in-depth interviews. Qualitative thematic content analysis of data.	The doctors' views on longer doctor's delay for female TB patients was that it is not caused by delays in recognizing symptoms or proposing investigations, but instead by the fact that women are thought to delay their own diagnostic process. Reasons are socio-cultural, like stigma, and practical concerns, like women not being able to come to the clinic by themselves and lack of decision-making power on the part of the individual woman.	Interventions are needed in order to reduce delay to TB diagnosis especially for women. The possibility of getting a TB diagnosis should be governed by an equity principle (a differential approach when needed) instead of the currently employed equality principle (an identical approach). Increasing the awareness of gender inequities among doctors is needed.
Thorson, 2007 [109]	To analyse chest X-ray (CXR) findings among men and women with smear positive pulmonary tuberculosis (TB)	366 (299 men) smear positive pulmonary TB patients diagnosed during 6 months in 23 districts selected by stratified random sampling, in four province of Vietnam, in January-June 1996	Cross-sectional study with structured interviews of cases with 3 sputum smear microscopy examinations and a CXR	At the time of diagnosis, women reported general symptoms more often than men. Weight loss (94 vs 88%) and lack of appetite (79 vs 66%), were more frequently reported by women, whereas men more commonly reported local symptoms such as chest pain (74 vs 68%) and dyspnoea (52 vs 48%). Miliary findings and pleuritis were more often observed among men, also after adjustment for age and symptoms duration.	
Weiss, 2006 [51]	To document sex differences in key aspects of TB control; to identify gender-specific barriers to early case detection, appropriate treatment,	42 focus group discussions (5 to 11 participants each); 20394 patients registered at local TB control programs;	A multi-methods approach guided plans for six components of the research at all four sites: situational	At all sites, the F:M ratio among patients in the clinic registers decreased at each of the three steps of the clinical process, from symptomatic presentation with suspected TB, to submission of diagnostic sputum, to obtaining a positive result for sputum. Only in Malawi, no difference	Health-care professionals should be trained to consider the possibility of TB in female patients presenting with more

Reference	Aim	Person, place time	Design & methods	Main findings	Recommendations
	adherence, and cure; to compare and contrast findings from studies in Asia, Africa, and South America; and to recommend policy and interventions for enhancing the gender sensitivity of TB control programmes.	clinical observation of 512 patients; outpatient survey of 2529 TB patients; Explanatory Model Interview Catalogue (EMIC) interviews with 427 patients currently in treatment. The study was done in Bangladesh, India, Malawi and Colombia. Time is not specified	analysis of health-services infrastructure and TB control programmes; focus group discussions to examine community views; examination of data from patients registered in local TB control programs; observation of patient-provider interaction; survey with TB out-patients; EMIC	was observed in the F:M ratio between TB suspects and those submitting sputum. Also, the relative decrease in the F:M ratio among those smear positive was smallest (11%). At all four sites, the F:M ratio for smear positive patients was no different from those starting treatment. Only in Malawi (not studied in Colombia), observers found that discomfort about producing sputum was more frequently identified among women (39%) than men (15%). In Bangladesh, female clinicians gave direct instructions to nearly all male patients (90%) but to only 33% of female patients-more often instructions were directed to a guardian. In India, consultations were longer than 15 minutes for 30% of female and 20% of male patients. In India, characteristic symptoms of cough and blood in sputum were as frequent among men as among women, but non-specific symptoms were more often reported by women. Health care provider delay was longer for women than men in all three countries (not studied in Colombia), which was mainly due to the longer time between first help seeking and visiting a primary health center. At all four sites, women presented to the clinic with a greater diversity of nonspecific physical	atypical symptoms. Control program site studies are needed to relate the prevalence and sex ratios of men and women with TB in communities and clinics. Health information should clearly distinguish appropriate public health precautions to minimize spread from unfounded concerns that contribute inappropriately to TB stigma. It should also clarify the relationship between HIV/AIDS and TB, and their distinctive modes of transmission. National and local strategies to improve detection of patients with TB, with particular attention to reducing patient delay for men and provider delay for women, should consider the impact of strategically reorganizing health

Reference	Aim	Person, place time	Design & methods	Main findings	Recommendations
				symptoms.	and community services. Local options for restructuring critical features of health systems should be considered, including planning for gender-sensitive active or semi-active case finding.
Weiss, 2008 [50]	To identify and compare social-cultural features of TB and the distribution of TB illness related experiences, meanings, and behaviors with reference to gender across cultures in three high-endemic countries	Approximately 100 TB patients from (rural) Bangladesh, (Chennai city) India and (Lilongwe city) Malawi (period unknown)	Quantitative comparisons and qualitative phenomenological analysis of illness narratives through semi-structured explanatory model interviews	Female patients in India and Bangladesh reported more diverse ("vague") physical symptoms more often than male patients. Female patients in India and Bangladesh also reported a higher mean number of categories of physical distress, and more females in Malawi reported 'other' symptoms than males.	As health staff may be less able to identify TB among patients presenting with atypical symptomology, documenting local patterns of phsycial distress associated with TB benefits clinical management and ensures the relevance of training for clinical health staff and their sensitivity to local presentations of TB.
Yamasaki-Nakagawa, 2001 [22]	To examine delays in TB diagnosis and compare health care seeking behavior between men and women	336 (238 male) new patients on DOTS treatment in a rural area of Nepal from mid-Dec 1997 to mid-June 1999	Patient interviews	Overall, women had a slightly longer health care provider's delay (median 1.3 vs. 0.8 months, P=0.054). Over 75% of both men and women who had attended the government medical establishments directly received TB diagnosis within a few days of their visit, whereas many subjects received a diagnosis much later if they initially visited a private	As the difference in case detection by sex was most significantly related to the type of health care providers visited first after becoming ill, an effective means of

Reference	Aim	Person, place time	Design & methods	Main findings	Recommendations
				health care provider or traditional healer. Visiting a traditional healer first, was associated with a longer health care provider's delay in men than women (P = 0.030); however, the delay did not differ significantly by sex when they visited a private health care provider (P = 0.11) or government medical establishments first (P= 0.63). The median health care provider's delay was 1.5 months for men and 3.0 months for women when they visited a traditional healer first, whereas it was 1.3 months and 1.7 months, respectively, when they visited a private provider first.	shortening the delay among women is thought to be to develop suitable links between modern and traditional health services.
Yan, 2006[112]	To understand contextual barriers to accessing timely TB diagnosis after first seeking care, especially among the poor and vulnerable in rural China.	Maximum variation selection of townships within purposively selected poor, rural districts (3 per province) of four provinces in China, in 2004	Structured interview with community residents, PTB patients, and TB suspects. Narrative individual interviews with TB patients and suspects, and with policy makers and health workers; focus group discussions with residents and health providers; observation of doctors	Within the four provinces, a statistically significant difference in experiences of >2 weeks of health care provider related diagnostic delay was found only in Liaoning province, where 25% of male patients (40/158) and 35% of female patients (23/65) experienced delayed diagnosis (P=0.04). Gender influences 'system' diagnosis delay through shaping women's and men's access to resources for TB treatment as well as experiences of social stigma, which may constrain care seeking at specialist facilities. When asked in the questionnaire which members of their family would get priority for TB treatment, the overwhelming majority of respondents mentioned male members of the family. In focus group discussions participants explained that males are seen as the backbone of the family workforce, so their health is prioritised.	Efforts to raise awareness about TB symptoms and services provided by TB dispensaries amongst the rural population are also important in encouraging care seeking at TB dispensaries, with a particular focus on poor women and the elderly.

Summary table on gender and adherence to TB treatment

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
Ailinger, 2006 [126]	To examine adherence to and risk factors associated with latent TB infection therapy (LTBI).	53 adult immigrants from Latin America; resident of a county with ≥ 20% Latino population who started LTBI therapy within last 3 months at a public health clinic in Washington DC (USA). Study period is not mentioned.	Cross-sectional study of non probability sample of medical records of eligible immigrants. Adherence was defined as number of months individual has completed therapy. Non adherence: individual did not come to clinic and did not respond to follow up phone call or letter from public health nurse.	There was no significant difference in adherence by gender, country of origin or languages spoken.	Future research should investigate the association of other basic conditions factors as health care system factors, pattern of living, resource availability, and family systems with adherence.
Ailinger, 2007 [127]	To examine predictors of adherence to LTBI therapy.	153 Latino immigrants seen at a public health clinic for LTBI in 2004-2006 in the USA. City is not mentioned.	Cross sectional review of randomly selected records of Latino clients at a public health clinic in the US. Full adherence was defined as completion of 270 doses of INH in 12 months.	There was no statistically significant difference in mean number of months adherence or doses by gender.	
Al-Hajjaj, 2000 [142]	To define factors that affect compliance rate and to determine the appropriate methods to modify these factors.	628 TB patients (385 males and 243 females) Taif, Saudi Arabia 1996-1997	Design and test of retrieval system. Review of files and records of patients.	In this study, female patients were less likely than male patients to default from treatment (34.2% vs. 49.9%; p = 0.0001). However, when only Saudi Nationals were considered, non-	

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
				compliance was seen more frequently in females than in males (42.7% and 29.7%, respectively), with a statistically significant difference (P ≤ 0.05).	
Atun 2005 [141]	To establish whether admissions, discharges and hospital utilisation for tuberculosis (TB) in Russia are independent of sex, age, disability and employment status.	PTB patients admitted to and discharged from hospitals in Samara Region of theRussian Federation, 1999-2002	Analysis of hospital admissions, discharges and in-patient utilisation using linked routinely collected data on TB notifications and hospital admissions	Interruption of hospital care (treatment) was more frequent among male than female patients (completed hospital episodes was 81.4% in male and 93.0% in female patients, P<0.001)	
Balasubramanian, 2004 [26]	To examine gender differences in TB among adults aged > 14 years with respect to infection and disease prevalence, health care service access, care seeking behavior, diagnostic delay, convenience of direct observed treatment strategy (DOTS), stigma and treatment adherence.	Several studies between 1998 to 2002 including individuals from community, out patients and TB patients in rural sub-district in Tiruvallur (south India)	Data were collected from: 1) community survey; 2) self-referred out-patients attending primary health institutions; 3) TB suspects referred for sputum microscopy; 4) TB patients notified under DOTS	Smear positive males more likely to default compared to smear positive females (19% vs 8%; odds ratio (OR) 2.5; 95% confidence interval (CI) 1.4-4.3) Being male was independently associated with default in multivariate analyses ($OR_{adjusted}$ 2.1; 95% CI: 1.1-3.9)	Qualitative research is needed to identify and address barriers to care seeking and treatment completion among men and the elderly
Barnhorn, 1992 [17]	To compare and contrast health beliefs, demographic and socio-economic variables, causative beliefs, supports and barriers of compliant and noncompliant tuberculosis patients.	52 compliant and 50 non-compliant TB outpatients. Wardha District, India. September 1988 – February 1989.	Interviews using structured questionnaires, and statistical analysis.	Although no statistically significant gender difference was found in compliance to treatment, the authors state that parents of girls of marriageable age may be reluctant to send their daughters to the clinic, since this may bring the disease to light.	

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
Bashour [27]	To determine whether there are sex differences in TB diagnosis, compliance with TB treatment and/or TB treatment outcomes.	552 new smear-positive TB patients seen at all provincial TB centers in the Syrian Arab Republic during 2 January 2002 to 31 July 2002	Prospective study in which TB patients were followed up for 6 months, including semi-structured questionnaire at stud entry. Review of treatment cards to assess TB treatment compliance. Compliance was defined as 0 of 60 days missed during 2-month initial phase; 0 of 120 days missed during 4-month continuation phase.	Review of 96% (528/552) TB treatment cards did show that compliance with TB treatment did not differ significantly between males and females. Mean number of days missed during initial phase was 10.4 among males and 9.3 among females. Mean number of days missed during continuation phase was 39.2 among males and 26.8 among females. 8.7% males and 5.8% females defaulted TB treatment.	
Cayla, 2004 [132]	To determine TB treatment completion and to analyze factors associated with treatment default and fatality.	1,515 TB patients initiating TB treatment between 1 June 1999 and 31 May 2000 in areas where members of the SEPAR TB and Respiratory Infection Group work (Spain).	Multicentre prospective cohort in which pulmonologists recorded treatment outcome. Logistic regression analyses to assess risk factors for default.	Male sex was significantly associated with defaulting in univariate analyses (OR 3.17; 95% CI:1.54-6.68), but not in multivariate analyses when only drug addiction and being an immigrant was significantly associated with risk of defaulting.	
Chan-Yeung, 2003 [130]	To assess the prevalence and predictors of default from TB treatment.	442 defaulted TB patients and 1,768 TB patients who completed TB that were registered for TB treatment in 1996 at the Chest Service in Hong Kong	Nested case control study. For each defaulted case (failure to collect medication for > 2 consecutive months after day of last attendance) 4 randomly cases from all TB patients	Being male was significantly associated with default (OR 1.4; 95% CI: 1.1-1.8) in multivariate analyses among all TB patients; and the Ors was 1.5 (95% CI: 1.1-2.1) among pulmonary TB (PTB) patients. History of default from treatment was strongest predictor of non-compliance (OR 8.2, 95%CI:4.7-14.3)	

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
			completing treatment were selected.		
Chee, 2000 [144]	To identify demographic, social, disease or treatment-related characteristics which may be predictive of patients defaulting TB treatment.	TB patients registered for TB treatment at the TB Control Unit (TBCU) in Singapore with case notes on default as of 1996.	Retrospective, patient record based case control study. 44 defaulters (cases): patients on TB treatment who failed to turn up for scheduled appointments. 44 controls (non defaulters): randomly selected patients who initiated TB treatment at same day as case.	A non significant trend towards to the association that males are more likely to default than females (OR 2.1; 95% CI: 0.8-5.7)	
Chuah, 1991 [143]	To study factors associated with poor patient compliance with anti-tuberculosis therapy	219 TB patients Northwet Perak, Malaysia 1982-1984	Retrospective study, using review of patient records.	Male patients were significantly more likely to default than female patients ($p < 0.01$)	
Comolet, 1998 [137]	To increase the understanding of the determining factors of default in an urban environment.	Defaulted TB patients in 2 cities in Madagascar in 1993.	Retrospective case control study including active tracing of 38 defaulted TB patients and 111 'treatment completed' controls.	Treatment default was significantly higher in males (76%) compared to females (56%) OR:2.51 (95% CI: 1.02-6.31)	
Connolly, 1999 [138]	To determine trends and risk factors for interruption of TB treatment.	3,610 TB patients completing or interrupting TB treatment, diagnosed in the Hlabisa health districts (South Africa) between July 1991 and December	Retrospective analyses of the notified TB patients' database.	Being male was positively associated with failure to complete TB treatment (OR: 1.3; 95% CI: 1.1 to 1.6) in the multivariate analyses.	

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
		1996.			
Dandona, [102]	To provide baseline information on the utilization of the Revised National TB Control Program (RNTCP) services by men and woman, barriers to utilization and to recommend actions to optimize this utilization.	TB units in 4 states in Southern India, data collection from April to November, 2003.	TB registers and interviews with sample of TB patients among TB patients who had defaulted in different phases TB patients listed in the laboratory and TB register from July 2001 to December2002 and 'cured' and 'treatment completed' TB patients registered for treatment January to June 2002	Among 744 patients not completed TB treatment the odds of not completing treatment were significantly higher for men (23.7%) compared to females (13.2%) (OR: 2.15; 95% CI:1.76-2.62) in multiple logistic regression analyses.	
Daniel, 2006 [139]	To determine risk factors associated with default from TB treatment.	777 TB patients registered for TB treatment at TB hospital in Sagamu local government area (Nigeria) during January 1997 and December 2003.	Retrospective review of 777 adults registered for TB treatment of which 178 (23%) defaulted. Default: not collecting treatment for 2 consecutive months after date of last attendance for collecting treatment.	Men (58.4%) were more likely to default than woman (46.1%). In multivariate analyses male sex was only factor significantly associated with default (OR: 1.64; 95% CI: 1.15-2.34).	
Date, 2005 [31]	To examine how gender and literacy influence TB diagnosis and treatment.	74 newly diagnosed smear-positive PTB patients. Sana'a, Yemen. December 2001 – March 2002; September 2002 – March 2003.	Interviews with TB patients and review of treatment outcomes after treatment was completed. Statistical analysis was performed.	More females than males completed treatment (P > 0.046, univariate logistic regression analysis). Supervision by male relatives contributed to completion of treatment among female patients.	

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
Davidson, 2000 [133]	To identify the effect of increasing the value of incentives and altering their distribution schedule, and other characteristics on adherence to TB treatment.	384 TB patients from 6 TB DOT programs in New York City (USA) between October 1992 and March 1996.	Prospective study in which TB patients participated in TB DOT incentives program. Patients were considered adherent if they attended 80% of the prescribed visits every month of the TB treatment.	Age, sex, education, marital status, race, employment or income was not associated with adherence.	
Eidlitz-Markus, 2003 [134]	To apply the Arkansas color method in order to evaluate drug compliance and factors that could predict adherences in patients daily treated for LTBI.	105 persons receiving LTBI treatment and who are at increased risk of developing active TB referred to the ambulatory Tel Aviv (Israel) TB centre during September 1999 to April 2000.	Interviews took place with these patients. Non-adherence to TB treatment is measured as the absence of metabolites of INH in the urine as measured by the Arkansas color test.	No statistically significant correlation between compliance and gender.	
Ganapathy, 2008 [34]	To find out gender differences in understanding of TB.	16 focus groups (FGs) including members of the community from Chennai city (India). FGs started after December 2000, but further specification of time period is not reported.	Qualitative study using focus group discussions (FGDs)	Most of the females were of the view that woman would be more regular in taking treatment as they had the responsibility of taking care of the family. Many of the woman and some of the men were of the opinion that men would be irregular for treatment due to pressure of work and dependence on alcohol.	
Johansson, 1999 [147]	To explore perceptions, knowledge and attitudes about compliance with	16 FGDs, including 8 to 10 individuals with and without previous	Qualitative study using focus group discussions (FGDs)	Among *'understanding of compliance'* it was reported that, especially by men and elderly, the necessity of a long	

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	TB treatment among men and woman.	TB experience, in 4 purposively selected districts in 4 provinces in Vietnam, 1996		treatment period, especially after symptoms were gone, were poorly comprehended. Although some woman also brought up financial aspects of non-compliance, financial difficulty was the most common reason cited by men among *'individual costs'*. Regarding *'staff attitudes and quality of health facilities'* woman seemed to be more sensitive to the quality of interaction between staff and patient, and the quality of physical condition of the buildings in which the TB units were located. Furthermore, it was conveyed, that if woman were initially received well at the health facilities, they were more likely to comply.	
Kamel, 2003 [39]	To study gender differences in health care utilization and outcome of TB treatment.	260 newly diagnosed PTB patients commencing TB therapy during December 2001 and November 2002 in Alexandria (Egypt) and 74 patients starting treatment 3 months preceding the study	Prospective cohort of newly diagnosed TB patients initiating treatment and followed up for 8 months including retrospectively record review of 74 TB patients initiating TB treatment 3 months prior to commencing study. Treatment non compliance was defined as performing 80% or less of the required treatment	86.4% females and 84.4% males said they had been adherent to treatment in the past.. Non compliance with TB treatment was not statistically different between males (13.5%) and females (14.2%).	
Khan, 2000 [89]	To understand the extent to which factors related to individuals, the care provision process, and	36 new TB patients attending 3 TB clinics selected from 3 districts in Pakistan	In-depth sociologic evaluation including semi-structured interviews among	Limited description of gender differences included that rural woman were particularly disadvantaged by problems associated with travel: all 9 rural woman	

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	the cultural context influenced the behavior of TB patients.	during an unknown time period.	purposively selected TB patients to give balance over sex, stage of treatment and urban/rural residence.	respondents named duration/cost of travel and being unable to travel alone as factors contributing to default. The numbers in rural man are not reported.	
Kohn, 1996 [135]	To compare compliance between directly observed preventive therapy (DOPT) and daily treatment for students with inactive TB.	105 purified protein derivate (PPD) positive students receiving DOPT at school based clinic and 22 PPD positive students referred to Department of Health for non-DOPT therapy in New York, 1993	Cohort study of students exposed to two different treatment protocols.	Age, sex and immigrant status did not affect treatment completion.	
Lavigne, 2006 [128]	To document the impact of smoking on adherence to LTBI treatment.	337 patients initiating LTBI treatment at specialized TB clinic in Montreal (Canada)	Convenience sample of consecutive patients initiating TB treatment. Adherence was assessed through pill count, patient-self report and attendance to scheduled visit.	Being female was positively associated (OR =1.9; 95% CI:1.1-3.3) with adherence when adjusting for smoking and age.	
Lertmaharit, 2005 [140]	To study the level of compliance and associated factors among TB patients	487 newly diagnosed adult TB patients in 4 regions in Thailand, during unknown study period	Cross sectional descriptive study including interviews of 487 adult Compliance categorized as: 'excellent'= punctual; 'good' = missing ≤2 consecutive weeks; 'poor' = missing > 2 consecutive weeks.	Female patients (74.5%) were more likely to have 'excellent' compliance than male patients (62%) (p=0.02). In multivariate analyses female patients were also more likely to have 'excellent' compliance (OR:1.87 (95% CI: 1.17-2.99)	

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
Liam, 1999 [18]	To describe knowledge and attitude of patients towards TB, their perception of TB and treatment and which factors have an effect on non-directly supervised TB treatment.	135 TB patients commenced on TB treatment from September 1994 to February 1996 (before DOTS initiating) in University teaching Hospital in Kuala Lumpur.	Retrospective review of hospital clinical records. Patients were considered non-compliant if they failed to return for scheduled clinic visits and in the total duration of uninterrupted therapy was at least 1 one month shorter than prescribed duration.	Gender was not associated with compliance.	
Mishra, 2005 [145]	To analyse the contribution of socioeconomic status to non-adherence to DOTS.	50 cases (non-adherent) and 100 controls (adherent) Nepal Unknown study period.	Case-control study, using questionnaire-based interviews.	Men were more often non-adherent to treatment, compared to women (OR 1.4, 95% CI 0.6-3.5), but this difference was not statistically significant ($p > 0.2$).	
Murphy,2000 [272]	To assess perception of TB infection rates, physician TB behavior, and patient knowledge of TB transmission and TB adherence.	199 HIV positive adolescents recruited from clinical care sites in 3 USA cities during 1993-1994 and 133 adults living with AIDS in New York	Cross sectional study including questionnaires as part of large assessment in a psychosocial intervention study. Self reported treatment completion.	Higher compliance rates were reported among the older, adult sample, who were primarily woman.	
Nair D et al. 1997 [45]	To explore the health seeking behavior of poor TB patients, to understand their perceptions of the cause of the disease, and to examine the effects of Tb on their personal lives	An opportunistic sample of 16 (9 male) of 72 adult TB patients who attended PATH's TB clinic in Bombay during April 1993-1994	clinical record reviews, patient interviews, and interviews with clinic staff	Men dropped out of treatment because of pressures to return to wage work or due to alcohol and drug addiction. Women dropped out because of the pressure of housework, and the strain of keeping their condition secret, particularly when the reasons for their movements outside the home were	We need more studies which capture genderdisaggregated lay concerns with the interface between the physical and mental tensions of city life, and its manifestation as

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
				routinely questioned.	health problems. Women and men experienced differing amounts of family support, which was expressed in terms of rest, and lighter workloads. More specifically, family support was also manifest in early contact with a physician (irrespective of his competence to diagnose and treat tuberculosis) and the duration and regularity of treatment, with more support being experienced by men, and unmarried women who werc staying in their natal homes. Married women did not appear to have as much support for the treatment of tuberculosis as unmarried women. Cases of desertion and temporary abandonment highlighted the discrimination they faced. Special efforts should be made to identify women tuberculosis patients, and to create facilities which enable them to complete treatment. Tuberculosis control programmes which are responsive to the constraints faced by

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
					women in seeking health care by creating conditions which will facilitate treatment-seeking, will have greater success in identifying women tuberculosis patients and enabling them to complete treatment.
Ngamvithayapong, 1997 [129]	To determine the level and reasons associated with adherence to TB preventive therapy among asymptomatic HIV-infected individuals.	412 asymptomatic HIV infected individuals referred for preventive therapy in a clinic in Thailand from November 1993 until August 1994	Prospective cohort study. Level of adherence was measured by pill count and considered 'good' if >80% pills were taken during the 9 month follow up period.	Females were more likely to adhere to the therapy than males (OR: 1.56, 95% CI: 0.95-2.56), especially when commercial sex workers were excluded from the analysis (OR: 3.45, 95% CI: 1.79-67). Adjusted for source of participants and history of physical symptoms OR was 3.00 (95% CI:1.56-5.88)	
Nichter, 1994 [123]	To document the weak lungs/TB complex, a specific ambiguous illness category, and discuss how it has influenced perceptions of TB medication leading to drug misuse.	Opportunistic sample of 60 lower class literate mothers, 13 groups (5 participantes each), including men, former TB patients and government midwives. Oriental Mindoro, Philippines. Time not specified.	Ethnographic study, using interviews, focus group discussions and rapid rural appraisal techniques.	Pregnant women fear that the TB medicines will cause miscarriage and lactating mothers fear the medicine will dry up their breast milk or harm their baby.	
Nyamathi, 2008 [273]	To determine whether a validated nurse case management intervention would improve adherence to	520 homeless adults residing in 12 homeless shelters and residential recovery sites in LA	Prospective 2-group site-randomized intervention in which 279 and 241 homeless adults respectively	Gender differences were not analyzed. Raw data showed that 61% males and 65% females completed treatment in the control group and 37% males and 33% females in control group.	

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
	latent TB infection treatment.	(USA) from 1998 to 2003	formed the intervention and control group.		
Ormerod, 1991 [263]	To examine the inter-relationships between treatment, compliance, age and calendar year of treatment and relapse.	1,009 notified TB patients in Blackburn (UK) between 1978 and 1987.	Multiple linear logistic regression analyses of notified TB patients.	The result section does not mention gender sub analyses, but the discussion section contains the statement that sex, among others (site of disease, presences of multiple sites) were not related to relapse or compliance.	
Piyaworawong, 2001 [274]	To study the risk factors for default in IPT in an integrated care setting.	412 people living with HIV in Mae Chan Hospital, Thailand	Retrospective cohort study, 1995-1999	Female sex was associated with lower default: relative risk 0.65 (95% CI: 0.49 to 0.87)	
Samman, 2003 [146]	To assess the impact of multidrug resistant (MDR) TB and other factors on TB treatment outcome.	147 MDR TB patients admitted to the TB referral hospital in Jedda (Saudi Arabia) from June 1993 to June 1999	Retrospective cohort study including review of clinical files and chest X rays. Chi-square test to compare proportions of compliance and MDR TB among subgroups. Patient was considered as compliant when there was a record that he or she completed treatment without interruptions.	Poor compliance was significantly more common among males (44.0%) subjects than females (15.3%)	Further studies to explore the various factors involved in non-compliance among Saudi males and females are needed.
Salami, 2003 [275]	To review factors predisposing to poor drug compliance.	Newly diagnosed PTB patients seen at outpatient department of university hospital in Ilorin (Nigeria) between January	Analyzing medical records of 769 non compliant and 761 compliant TB patients	Male sex was associated with defaulting (OR:1.68; 95% CI: 1.37 -2.07)	

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
		1991 and December 1999.			
Sass, 1996 [136]	To compare compliance of IPT among 2 groups of PPD positive students.	202 students with positive PPD test attending a high school in Brooklyn (New York, USA). Data collected in the time period January 1993 to July 1994.	Non randomized study in which 28 students started with DOPT at the school health center and 146 students with self-administered daily therapy. Noncompliance was defined as missing 14 days of therapy once or missing > 5 days of therapy for 2 months	Completion of therapy did not differ by gender, age, or years.	
Tanke, 1994 [276]	To assess the impact of different automated telephone reminders for appointments in a public health TB clinic.	2,008 TB patients with scheduled TB appointments in the TB Control Program of Santa Clara County Health Department (California, USA) over a period of 6 months (year unknown).	quasi experimental study	The overall effectiveness of using an automated reminder nor the relative impact of four different messages on attendance to the clinic, on TB treatment adherence, did not differ as a function of gender.	
Weiss, 2006 [51]	To document sex differences in key aspects of TB control; to identify gender-specific barriers to early case detection, appropriate treatment, adherence, and cure; to compare and contrast findings from studies in Asia,	42 focus group discussions (5 to 11 participants each); 20394 patients registered at local TB control programs; clinical observation of 512 patients; outpatient survey of 2529 TB patients;	A multi-methods approach guided plans for six components of the research at all four sites: situational analysis of health-services infrastructure and TB control programmes; focus group discussions to	Consistent cross-site findings from registry data showed that more women drop out during the course of diagnosis, while men who are diagnosed with TB are less likely to successfully complete treatment.	

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
	Africa, and South America; and to recommend policy and interventions for enhancing the gender sensitivity of TB control programmes.	EMIC interviews with 427 patients currently in treatment. Bangladesh, India, Malawi and Colombia Time not specified	examine community views; examination of data from patients registered in local TB control programs; observation of patient-provider interaction; survey with TB out-patients; Explanatory Model Interview Catalogue.		
White, 2003 [277]	To characterize LTBI patients from high-risk referral sites who received directly observed preventive therapy (DOPT) or self-administered therapy (SAT) and to compare therapy completion in patients before and after implementation of this treatment strategy	764 patients on therapy for LTBI in San Francisco during 1993-1994 and 1997 to June 1998	Retrospective cohort study	Being male was negatively associated with treatment completion (OR:0.67, 95% CI: 0.49-0.90) adjusted for treatment strategy, age, ethnicity, cohort	

Summary table on gender and TB treatment outcomes

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
Abal, 2005 [225]	To examine the effect of smoking on sputum smear conversion in tuberculosis patients	339 patients out of the 526 sputum positive patients registered January 1998 to December 2000 in Kuwait.	Patients with sputum positive status at the time of diagnosis, during a 3-year period from January 1998 to December 2000 were enrolled in the study. Basic data, smear and culture result at presentation, smoking history, history of diabetes, drug abuse and alcoholism were entered in a profoma. Logistic regression analysis was carried out using sputum status as the binary-dependent variable and the other variables as independents	Gender was not related to sputum smear conversion in tuberculosis at the end of 2 months in logistic regression. Smoking did not influence the chances of an early sputum conversion when other factors remained stable. Number of cigarettes smoked or the sex difference did not influence smear conversion.	
Abbasi, 2009 [256]	To determine (1) whether ethambutol usage can alter serum Cu concentration in patients with tuberculosis and (2) whether there is any relationship between age, sex, and smoking habit of patients with changes in serum Cu	Sixty adult inpatients (26 women and 24 men) with diagnosis of pulmonary tuberculosis in Tehran, Iran. (year unknown)	Blood samples were obtained before treatment (baseline) and 10 days after starting anti-tuberculosis therapy. The amounts of serum Cu were determined in all samples by atomic absorption	There was a significant difference in Cu levels but no relationship between changes in Cu concentration with sex, age, and smoking.	

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
	levels				
Abós-Hernández, 2002 [198]	To identify risk factors for dying among adult patients hospitalized with pulmonary TB	466 patients (305 males), mean age 33.1, in a public hospital in Santa Cruz, Bolivia from Nov 1993 -Feb 1996	Hospital-based cross-sectional study of patients admitted consecutively with pulmonary tuberculosis. Multiple logistic regression analysis was used.	The following predict death: coexisting pathology (odds ratio OR 2.88; 95% CI 1.48–5.36), female sex (OR 2.08; 95%CI 1.23–3.52), and number of lobes affected (OR 1.48; 95%CI 1.23–1.79). The number of lobes affected did not differ between males and females (mean [SD]: males 3.1 [1.5]; females 3.2 [1.5]; P 0.78)	
Al-Hajjaj, 2000 [248]	To explore clinical factors associated with poor radiological outcomes	1,080 patients from an inpatient specialty chest hospital in Saudi Arabia over a 14-month period from the 1st of December 1994 until the end of January 1995	Chest radiographs of 1,080 patients with pulmonary tuberculosis were reviewed. Post-treatment residual changes were classified from 1 to 5 according to the severity of these changes. Data analysis was done by tabulating these classes against different variables that were likely to influence the final radiological appearance at the end of the treatment period.	Older age, female gender, delayed diagnosis, poor Tx adherence and previous TB associated with poor radiological outcome. It is not clear to us why female patients had worse radiological outcome than males but it can be speculated that in a society like ours, tuberculosis still carries a stigma and the problem becomes even worse if it occurs in females. This may pressure female patients to hide their illness and refrain from seeking medical attention until late in the course of the disease.	
Antoine, 2007 [153]	To estimate treatment success and identify factors associated with non-completion of treatment in study setting in 2001	6514 tuberculosis cases (pulmonary and extrapulmonary) in England, Wales, Ireland between 1 January and 31 December 2001, including cases with a postmortem	At 12 months after the start of treatment, outcome was assessed according to a protocol based on standardised European recommendations. 95% confidence interval (CI), and	Males more likely to not complete treatment, missing outcome information for 21% of cases. Non-completion of treatment in multivariate analysis was associated with male sex (AOR 1.2 (1.1-1.5)), age > or =65 years, recent entry into UK for those born abroad, residence outside London, pulmonary disease and	

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
		diagnosis	significance was taken to be p(0.01. Predictors of non-completion of treatment were analysedusing univariable and multivariable (logistic regression) methods	drug resistance	
Antunes, 1999 [209]	To characterize tuberculosis mortality trends in the Municipality of São Paulo, Brazil, from 1900 to 1997	TB cases and census data from the municipality of São Paulo, Brazil, from 1900 to 1997	Standardized tuberculosis mortality rates and proportional mortality ratios were calculated and stratified by gender and age group based on data provided by government agencies. These measures were submitted to time-series analysis	Time-series for tuberculosis mortality rates (pulmonary form, per 100,000 inhabitants) stratified by gender and age group, São Paulo, Brazil, 1900-97. For each period, gender, and age group, results show the ratios of yearly increase or decrease in tuberculosis mortality, Reporting of tuberculosis deaths remained higher for males in the adult and older age groups, and to a lesser extent among children under 5 years. This observation may be tempered by studies reporting greater under-reporting of the disease among females (Connolly & Nunn, 1996), although there are no such observations on record for Brazil. Women aged 20 to 49 years experienced a sharper downward trend in tuberculosis death rates than men of the same age in the intermediate period. The same was true for women over 50 years, but with a less marked contrast.	
Aparna, 2009 [154]	To evaluate the drug resistance in pulmonary TB patients from a community and its effect on therapeutic response.	605 TB patients registered for treatment at LEPRA Society TB clinics in Andra Pradesh, India during 2004—2005.	record-based analysis of TB patients treated at LEPRA Society TB clinics. A multivariate logistic regression model was constructed	Females recorded slightly higher (95%) favourable response (cured or completed) than males (90%). Twice as many males had unfavorable result (failed, died, default) (10%) than females (5%). Default (4 vs 1%) and	Higher default rate among males has contributed to the unfavourable response. This gives an insight to address the default as one of the

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
			with the associated variables. Significance of association for drug resistance pattern and treatment category was calculated.	deaths (3 vs 2%) were higher among males. 51 (8%) patients showed unfavourable outcome to anti-TB treatment. In multivariate analysis, there was an association between unfavourable outcome with male gender and MDR (gender, OR 2.126, 95% CI 1.09—4.1; MDR, OR 4.5, 95% CI 1.98—10.4).	important issues in the DOTS programme.
Apers, 2004 [175]	To evaluate the accuracy of the diagnosis of pulmonary TB in operational conditions	300 PTB patients (108 female and 192 male) in Gweru, Zimbabwe, during 2000-2001	Prospective cohort study of routinely diagnosed PTB patients between September 2000 and September 2001. Comparing routine sputum smear microscopy, with two sensitive laboratory tests: the concentration method and the Mycobacterium Growth Indicator Tube (MGIT) culture technique.	Risk of dying was not associated with sex, age, culture results or HIV status but was higher in patients who were negative on smear microscopy	
Baghaei, 2010 [229]	To assess the incidence, risk factors, and outcome ofhepatitis due to anti-TB drugs	761 patients documented as new cases of TB at the national TB referral center in Tehran, Iran, January 2006 to January 2008	All patients received standard anti-TB treatment. If drug-induced hepatitis (DIH) occurred, all drugs were discontinued and reinitiated after liver function tests (LFT) normalization in a stepwise way.	Among TB cases with hepatits, 57.6% were female and 42.4% were male. There was no difference in sex (p=.237), nationality, marital stattus, smoking, or opium use history between the hepatitis group and non hepatits group (P > 0.05) IH development is associated with old age, certain clinical manifestations, and higher death rates.	
Balasubramanian, 2004 [26]	To examine gender differences in TB among adults	76 011 adults were surveyed in Tiruvallur District India, from	Data were collected from 1) community survey, 2) self-referred	Among new smear positive TB patients, males had twice the risk of treatment default than females(19% vs. 8%; OR	In this study, working men and alcoholics were more likely to default

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
	aged >14 years with respect to infection, disease prevalence, health care service access, care seeking behavior, diagnostic delay, convenience of DOT, stigma and treatment adherence	December 1998 to June 2001	out-patients seeking care at governmental primary health institutions (PHIs), 3) tuberculosis suspects referred for sputum microscopy at PHIs, and 4) tuberculosis patients notified under DOTS. Community survey results were compared with those for patients notified at PHIs.	2.5; 95%CI 1.4–4.3; P 0.001). Among new smear negative TB patients, 15% of males and 9% of females defaulted; P < 0.05). No difference in outcomes in EP cases and relapse smear-positive cases, but in other retreatment smear-positives, 41% of males and 10% of females defaulted (p.001). In multivariate analysis, the independent risk factors for default were previous history of treatment (adjusted odds ratio [AOR] 3.9; 95%CI 2.6–5.6; P 0.001), alcoholism (AOR 2.2; 95%CI 1.5–3.3; P 0.001), being male (AOR 2.1; 95%CI 1.1–3.9; P 0.02) and being employed (AOR 1.7; 95% CI 1.1–2.4; P 0.01). Among smear-positive patients diagnosed in the community survey, the rate of initial default was similar among men and women (P 0.8), but increased significantly with age (2 linear trend, P 0.02), increase in both men and women. Among smear-positive patients diagnosed at PHIs, the rate of initial default did not differ by age or sex.	from treatment, indicating a need to develop DOT services that are acceptable and convenient to these groups. Men and elderly patients need additional support to access diagnostic and DOT services.
Bang, 2005 [219]	To identify occupations and industries with elevated respiratory tuberculosis (TB) mortality in the United States	7686 deaths due to respiratory TB in the United States for the period 1990-1999	Used National Center for Health Statistics multiple-cause-of-death data, restricted to certain states for which information on decedents' usual industry and occupational information was available and limited to US residents aged > or	Because more TB deaths were documented in white males than in other groups, elevated PMRs were shown in more industries for white males than for any other groups. For males, elevated PMRs occurred for miscellaneous personal services and agricultural production, crops. Among black males, but not among white males, elevated PMRs were found in miscellaneous repair services, hotels and motels, and sanitary services. Among white females, an	

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
			=15 years. Proportionate mortality ratios (PMRs), adjusted for age, sex, and race, were calculated from US census occupation and industry classifications	elevated PMR was seen for hospitals. Among black females, an elevated PMR occurred for agricultural production, crops. In addition, white female clinical laboratory technologists and technicians had a PMR of 3.14 (95%CI 1.15–6.83). Two other HCW groups with elevated TB mortality in our study were white female registered nurses (PMR 5 1.37; 95%CI 1.04–1.81) and white male nursing aides, orderlies, and attendants (PMR 5 2.72; 95%CI 1.31–5.00) (data not shown). Industries and occupations involving potential contact with infected cases (e.g., health care workers), those with silica exposure and silicosis (e.g., mining and construction), and those associated with low socioeconomic status had significantly elevated TB mortality	
Barker, 2002 [155]	To illustrate successes and difficulties for the South African National TB Program in a rural area (also compared Tx outcomes between those receiving DOT in community vs. facility.	1476 patients diagnosed with tuberculosis (TB) in the catchment area of four rural hospitals in Sekhukhuneland, Northern Province, South Africa, between January 1997 and June 1999	Prospective cohort study. Standard outcomes for TB treatment as defined by the World Health Organisation. Treatment failure, treatment interruption and death were grouped as poor outcomes. Risk factors for pOOF treatment outcome were assessed among 1 038 patients with smear-positive PTB.	1476 were diagnosed with TB. The majority (76%) had smear-positive pulmonary disease. Male gender (odds ratio 1.38, 95% confidence interval 1.02, 1.87) was significantly associated with a poor outcome. This difference was because of higher numbers of men failing and interrupting treatment, an effect that has been observed elsewhere in rural South Africa and elsewhere. Possible reasons for the high interruption rates are the need to find employment outside an area where the unemployment rate is around 60%, and alcoholism, whichis common, particularly among men	

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
Bashour, 2003 [27]	To determine sex differences in diagnosis, treatment compliance, outcomes between men and women; identify TB patients' knowledge ,beliefs, attitudes; identify gender-related factors and/or barriers that influence compliance and utilizaion of services	552 newly diagnosed smear-positive patients (366 males and 186 females) from 14 centers throughout the Syrian Arab Republic (country wide) Jan - July 2002	a prospective study of gender and TB outcomes. TB patients were interviewed at recruitment (from January 2002 to July 2002) and followed until the end of treatment.	78.6% of males and 77.2% of females had smear negative conversion after 2 months (p=0.8); 52.2% of males and 66.7% of females had smear negative conversion after3 months(p=.2); 86% of males and 90% of females had successful treatment outcomes (not sig different). Male sex is significant predictor of negative treatment outcome (OR 2.9) after controlling for confounders. Tx success rate was better among women.	Need for qualitative studies. Interventions are needed that rectify any gender imbalances or inequalities in connection to TB treatment. Interventions need to be designed according to local context. A gender approach to TB policy and control program may lead to improvement in effectiveness of TB control.
Bassey, 2005 [200]	To evaluate the pattern of sputum smear positivity and assessed the effects of directly observed treatment short course (DOTS) among tuberculosis (TB) patients	1391 patients seen in six DOTS clinics in the Federal Capital Territory (FCT), Abuja Nigeria between January and December 2003	sputa were screened microscopically for the presence of acid-fast bacilli (AFB) using the Ziehl-Neelsen staining technique.	In total, 160 of the men screened were AFB positive (75% new cases, 25% follow-up cases). In comparison, 136 women were AFB positive (59.6% new cases, 40.4% follow-up cases). During the 1-year study period, two deaths were recorded (both men vs 0 women).	
Baussano, 2008 [156]	To identify predictors of unsuccessful treatment of PTB	1564 pulmonary tuberculosis cases, 600 (38.4) females and 964 (61.6) males, in the Piedmont Region of Italy during 2001-2005	cohort of pulmonary tuberculosis (PTB) cases resident between 2001 and 2005 in the Piedmont region of Italy	Larger proportion of women had a successful treatment outcome (65%) than men (51%). Among new cases, women were significantly less likely to have an unsuccessful treatment outcome OR 0.48, 0.37-0.63); Among all cases, women were significantly less likely to have an unsuccessful treatment outcome (aOR 0.53, 95%CI 0.42-0.68), and die during treatment (aOR 0.42, 95%CI 0.25-0.69)than men	
Begum, 2001 [100]	To assess gender differences in access to tuberculosis	42,877 out-patients with respiratory complaints (5,632 TB	Information on the age and sex of a sample of patients in	Successful treatment outcome (i.e., cure or treatment completed) was reported for 86% of women and 84% of men who	Focus further research on exploration of sex differences in the

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
	diagnosis and in tuberculosis treatment outcome in Bangladesh.	patients) within the Public health sector services in 59 thanas in 3 divisions in Bangladesh in 1997	1997 was collected from out-patient registers and tuberculosis laboratory and treatment registers	had started treatment. Little difference in treatment outcome was observed between female and male patients in all age categories, although treatment success was lower in males aged 65 years or more, largely because of a strongly increased case fatality ratio in that age group (data not shown).Ratio of females to males in every subset of suspect and patient is less than 1; No gender bias was observed in tuberculosis treatment outcome. Treatment was successful (cured or treatment completed) in 86% of female and 84% of male patients. Treatment success was lower in males aged 65 years or more (males 68% versus 81% in females), largely because of a strongly increased case fatality ratio in that age group (data not shown)	incidence of respiratory conditions,identification of constraints among women in accessing out-patient clinics and verification of the quality of sputum submitted by women for examination.
Bernatas, 2003 [157]	To evaluate decentralisation based on the success rate by site of treatment and according to certain critical variables.	1125 new smear-positive tuberculosis patients recorded in the registers, 948 were included in the study (84%), mean age was 30.1 years, in Djibouti City, Djibouti from 3 urban centers, from April 2000 until April 2001.	Comparative evaluation of the success rate of smear-positive patients followed in all treatment centres	In multivariate analysis, females sex is related to treatment success. Authors attribute this to the role of women in African societies, as well as the lack of work and the high consumption of khât among men. Three factors interact negatively on treatment success: Djibouti nationality, age under 20 years and male sex.	
Borgdorff, 1998 [187]	To estimate excess mortality among tuberculosis patients in the Netherlands and identify risk factors for tuberculosis-	4,340 TB patients diagnosed in the Netherlands in the period 1993–1995	national tuberculosis register was reviewed retorspectively and Excess mortality in tuberculosis cases, according to age and	258 died within 1 yr while on treatment. SMR for males 9.4 (8.1–11) and SMR for females 6.8 (5.4–8.4). Gender was an independent risk factors for mortality within 12 months after diagnosis in multivariable analysis-risk of death was	

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	associated mortality		sex, was determined by comparison with national mortality rates. Risk factors were identified and adjustment for confounders was carried out using Cox's proportional hazard analysis.	somewhat lower in females than in males (adjusted hazard ratio (AHR) 0.8)	
Burke, 2003 [220]	To explore the possibility that the physiological and social strains of recent childbirth and the early mothering of infants may have been risk factors in adult female tuberculosis mortality	244 reproductive age women who died in Gibraltar between 1874 and 1884	case study combines the methods of family reconstitution and a retrospective case-control study design	In general, males and females reflect a similar pattern in the risk of tuberculosis mortality over the life span in late 19th-century Gibraltar. O f reproductive-age Gibraltarian women who died between 1874 and 1884, the cause of death was reported to be TB in 136/244 (55.7) women. Almost 12% of the women who died had given birth within the year preceding their death. Factoring in the effects of age at death, marital status, and religion, the logistic regression results indicate that recent childbirth did not increase the risk of tuberculosis mortality among these women. However, even after controlling for age, the regression indicates that, relative to never married women, the odds of dying from tuberculosis rise to eight to one among widowed women. Authors offer offer at least two reasonable alternative explanations, both of which will require further scrutiny. First, there is the possibility that the deceased husbands of widowed women were, themselves, struck down by tuberculosis. Living in close proximity to sick husbands and	A more detailed analysis of reproductive histories based on a re-defined cohort of child-bearing (as opposed to the more general ‘‘reproductive age’’) women, focusing on the total number of children and the spacing of pregnancies, may be useful to implicate pregnancy risks at a more detailed level.

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
				possibly caring for them over the course of their illness could have compromised the health of the women who were eventually left widowed by the death of their spouse. A examination of husband's cause of death, however, does not seem to support this possibility. Alternatively, having lost their husbands, widows may have found themselves living under less supportive circumstances prior to their own death. Being widowed, and having to overcome increased financial and emotional stress, tuberculosis may have been given the opportunity to take hold.	
Cagatay, 2004 [205]	To describe tuberculosis meningitis (TM) in Turkey	42 inpatients with tuberculosis meningitis ;28 females, 14 males, mean age 33, in Istanbul Turkey, during 1991 - 2002	Clinical and laboratory findings of 42 patients with TM, followed between 1991 and 2002, were evaluated retrospectively.	Significantly more females (<0.05); 7.1% died and all were females with stage III disease. Female gender associated with permanenet neurological sequelae in TM	
Cakir, 1999 [258]	To investigate whether leptin and TNFalpha levels change with improvement in body weight with antituberculotic therapy in active tuberculosis patients	30 patients (8 females and 22 males) with active pulmonary tuberculosis and 25 sex- and age-matched healthy subjects (8 females and 17 males) in Ankara, Turkey	case control study, Body weight, body mass index (BMI) and serum leptin and plasma TNFalpha levels are measured before and in the sixth month of therapy in all patients.	In the pretreatment period, there was a significant correlation between leptin and TNFalpha levels in the whole patient group ($r = 0.78$, $p < 0.001$), and in female ($r = 0.74$, $p < 0.001$) and male patients separately ($r = 0.74$, $p = 0.035$). Leptin and TNF alpha levels are increased in TB, leptin may be responsible tor weight loss in TB patients, no relationship between leptin and BMI though	
Caylà, 2004 [132]	To determine treatment completion among patients with tuberculosis (TB), and	1515 cases in Spain in areas where there were members of the SEPAR Tuberculosis	A prospective cohort study of TB patients. Factors associated with treatment default and	Sex not associated with fatality or default	

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
	to analyse factors associated with treatment default and fatality	and Respiratory Infections Group work, during 1 June 1999 - 31 May 2000	fatality were studied using logistic regression, calculating odds ratios (OR) and their 95% confidence intervals (95%CI).		
Chailleux, 1996 [188]	To analyze predictors of survival for patients receiving home long-term oxygen therapy (LTOT) or prolonged mechanical ventilation (PMV) according to the cause of chronic respiratory insufficiency (CRI) and the patients physiologic data.	There were 26,140 patients receiving LTOT or PMV in the national nonprofit network for home treatment of patients with CRI in France between January 1, 1984 and January 1, 1993	Analysis of a nationwide database (ANTADIR Observatory), Survival analysis was performed using the actuarial and the Cox's semiparametric model.	1599 males with TB sequelae; 748 females with TB B sequelae. For tuberculous sequelae, female sex (OR 0.68; 0.60-0.77), is an independent factor associated with death in final model.	
Chamla, 2004a [259]	To validate the SF-36 questionnaire in a Chinese population and to assess the patients' health-related quality of life (HQoL) during tuberculosis (TB) treatment.	102 TB cases with mean age of 39.9 years in Wuhan District TB Centre, a governmental institution specialising in the treatment and prevention of TB between November 2001 and April 2002	TB cases were examined prospectively.The SF-36 (Chinese version) scores of 102 TB cases before treatment, after the initial phase and at the end of treatment were compared with those of 103 control subjects.	In regression model, at completion of treatment, sex was associated with the total SF-36 score (OR 0.25, 95%CI 0.15–0.44)	
Chamla, 2004b [174]	To determine the rate and associated factors of adult tuberculosis (TB) in the central Chinese city of Wuhan	286 males and 131 females with mean age 35 in Wuhan, China, in an urban, hospital during 1 January to 31 December 2001	A retrospective descriptive study of 417 patients registered for TB treatment	The mean age of admission was 38.47 (median 35) years, with males aged 20-40 years mostly affected. Cure not associated with sex.	

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
Chang, 2007 [231]	To examine whether dosing schedules of standard pyrazinamide-containing anti-tuberculosis (TB) treatment (standard treatment) might affect hepatotoxicity.	All patients with hepatitis from a cohort of 3,007 clinic patients who commenced anti-TB treatment in Hong Kong from January 1 to June 30, 2001.	A nested case-control study, each case with hepatitis between 1-9 weeks post-TB treatment was compared using conditional logistic regression analysis with two controls selected randomly from patients without hepatitis in the same period and matched by sex, age and standard treatment. Impacts of sex and age were examined by logistic regression analysis of cases and patients without hepatitis.	3/4 patients who died of drug induced hepatitis were male. Logistic regression analysis in TB cases showed that sex was nonsignificant in its association with hepatitis. After controlling for age, the corresponding risk of hepatitis for females increased from 2.3% (1.4–3.7%) to 4.7% (2.9–7.5%) and from 2.8% (1.9–4.2%) to 3.9% (2.9–5.3%) for males.	
Chang, 2008 [230]	To compare continuation-phase regimens incorporating pyrazinamide, isoniazid, and/or rifampin with those containing isoniazid and rifampin to evaluate the hepatotoxicity of pyrazinamide.	3,007 patients (1,953 (64.9) males) with active tuberculosis (TB) managed at government chest clinics under a TB control program in Hong Kong with treatment started from January 1 through June 30, 2001. Included all patients with probable hepatotoxicity from 12 or more weeks after starting	Cohort analyses were conducted on a cohort of TB cases. Hepatotoxicity was considered probable when serum alanine transaminaseexceeded three times the upper limit of normal.	Risks of hepatotoxicity for standard continuation-phase regimens comprising isoniazid and rifampin were 0.8%, 0.9%, and 0%among females younger than 35 years, from 35 to 49 years, and older than 49 years, respectively. The corresponding risks for standard continuation-phase regimens among males were 0.9%, 0.9%, and 0.8%. Thec orresponding risks for pyrazinamide-containing continuation-phase regimens were 0%, 0%, and 0.6% among females, and 0%, 3.2%, and 5.0% among males (P 5 0.24 for x2 test of trend). Logistic regression showed that hepatotoxicity from 12 or more weeks after starting treatment was	

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
		treatment.		significantly associated with males 2.1 (1.0–4.4). The case fatality rate of hepatotoxicity from 12 or more weeks after starting treatment was 1 (0.16%) out of 617 patients taking pyrazinamide, isoniazid, and/or rifampin, and 1 (0.04%) out of 2,327 patients taking isoniazid and rifampin. Both fatal cases were males older than 49 years. Restricting the analysis to males older than 49, the corresponding risks were 0.42% and 0.12%. Neither difference was significant statistically.	
Chan-Yeung, 2002 [158]	To examine sex differences in the rate and clinical presentation and compliance with treatment of tuberculosis in Hong Kong	5757 patients registered for tuberculosis treatment with the Hong Kong Department of Health Government Tuberculosis and Chest Service (Chest Service), Hong Kong from 1 January 1996 to 31 December 1996 were compared to past five decades	Notification rates of tuberculosis during the past five decades were obtained from the Hong Kong Tuberculosis and Chest Service, Department of Health, Hong Kong. In addition, all patients registered with the Chest Service for treatment of tuberculosis in 1996 were studied.	For PTB, more women than men were cured or had completed treatment at 6 months (53.6% vs. 41.0%),however, there was no difference between the sexes at 12 months. More men had relapse (15.1% vs. 8.0%), and a history of previous default (2.8% vs. 0.7%) . A higher proportion of men than women defaulted from treatment at 12 months (8.7% vs. 6.5%). For those with extra-pulmonary disease, only about a quarter of patients, both men and women, had completed treatment at 6 months, but by 12 months more women had completed treatment than men (82.8% vs. 75.9%). The proportion defaulting from treatment was also higher in men than women. One possible reason for the higher percentage of men defaulting may be the fact that they were the only bread-earners in the family and some had to commute between China and Hong Kong because of the nature of their work.	Study of sex differences is essential for targeting prevention programmes at groups at higher risk. Need to further study how sex hormones affect the pathogenesis of tuberculosis and its manifestation. Need for socio-economic information on the patients on the programme forms or medical records to assess whether the treatment completion rates are affected by socio-economic factors.The results of this study indicate that special attention should be paid to elderly men in any tuberculosis treatment or prevention programme in

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
					Hong Kong. It is important for each region to identify sex issues relevant to the management of tuberculosis in order to develop a more effective control programme.
Chan-Yeung, 2003 [130]	To determine the prevalence and risk factors of default from tuberculosis treatment in Hong Kong	5757 TB patients in hospital and clinics in Hong Kong Government Tuberculosis and Chest Service and Hong Kong chest clinics in 1996	Retrospective study. Data were obtained from programme forms and medical records completed by physicians. Patients who defaulted treatment were defined as those who had failed to collect medication for more than 2 consecutive months after the date of the last attendance during the course of treatment. Demographic and clinical characteristics, including history, treatment, and outcome, were compared between defaulters and non-defaulters, both among the whole group and among those with pulmonary disease	Male sex associated with treatment default (1.4;1.1-1.8)	
Chee, 2000 [144]	1) To identify any demographic, social,	44 treatment defaulters in	A retrospective, patient record based case-	There was no significant association of defaulting with sex - (OR 2.1, 95%CI	

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	disease or treatment-related characteristics which may be predictive of patients defaulting from treatment; 2) to assess the effectiveness of home visits as a means of defaulter recall; 3) to ascertain outcome in these patients.	Singapore Tuberculosis Control Unit in 1996	controlled study of TB treatment defaulters, defined as patients who missed their scheduled appointments and required a home visit to recall for treatment. Controls were randomly selected, non-defaulting patients who started treatment on the same dates as the defaulters.	0.8–5.7, Table 1).	
Chemtob, 2001 [165]	To provide an epidemiological basis necessary for any new national TB control policy, and to bring it to the attention of the medical profession in Israel and abroad since its results led to a change in Israel's TB control policy.	1990 to September 1992, n = 820 new cases and 57 retreatment cases, Israel	reviewed all TB cases notified during the period 1990 to September 1992. "New cases" (820 cases, 93.5%) and "re-treatment cases" (57 cases, 6.5%) were analyzed according to three mutually exclusive groups: "successful outcome," "death," and "potentially unsatisfactory outcome" (according to WHO/IUATLD definitions).	no association between outcome and gender	
Cho, 2009 [246]	To evaluate the clinical characteristics and risk factors for the paradoxical response (PR) in non-HIV-	275 patients with lymph node TB, non HIV infected, > 16 years old; 75% female from a	Medical records of non-HIV-infected patients aged > or =16 years with peripheral lymph node TB treated in a	Male gender, n (%) 22/54 (41) with PR and 38/181 (21) without PR (p <0.01). In multivariate analysis, younger age (OR 0.96), male gender (OR 2.60), and the presence of local tenderness at the	Further studies are required to explore possible relationships between sex hormones or aging, and immunologic

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	infected patients with peripheral lymph node tuberculosis (TB)	Tertiary hospital in Korea during January 1997 - August 2007	tertiary hospital between January 1997 and August 2007 were analysed. PR was defined as clinical or radiological worsening of pre-existing TB lesions, or development of new lesions in a patient who had received anti-TB therapy for at least 2 weeks.	time of diagnosis (OR 2.90) were independently predictive of PR in lymph node TB patients	response.
Chu, 2001 [262]	To examine whether patients with newly diagnosed tuberculosis (TB) discharged to ambulatory treatment are at risk of unplanned readmission through the emergency department within 28 days of discharge, and the risk factors associated with such readmission	134 patients admitted to an acute medical department with TB; mean age was 64.1 years ; 33 females (24.6%) and 101 males (75.4%), in Hong Kong during January 1996 to March 1998	retrospective record review for unplanned readmission in 28 days of TB cases. Potential risk factors associated with the readmission were recorded during hospital stay and follow-up visits, including age, sex, length of stay, substance abuse, need of assistance in the activities of daily living (ADL), comorbidities, non-compliance, drug complications and use of non-standard drug regimen.	Sex was not independently associated with early unplanned readmission.	
Chung, 2007 [166]	To compare care quality among different healthcare institutions in Southern Taiwan	421 patients, 311 male (73.9%) and 110 female (26.1%), were included, from one tuberculosis	population-based retrospective cohort design, medical records were reviewed, level of conformance with	Gender not associated with treatment success or fatality when controlling for age and the patients treated by the pulmonologists and treated at Chest Specialty Hospital in Taiwan	

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
		sanatorium, 2 medical centers, 11 regional hospitals, and 15 district hospitals and primary practitioners in Southern Taiwan registered from January 1 to June 30 2003.	diagnostic guidelines, efficiency of diagnostic and treatment process, and treatment were measured as main outcome. Association was investigated using Chi-square tests, Kruskal Wallis tests, Mann-Whiteney U tests, and multiple logistic regression analysis to evaluate outcome differences among different levels of institutions.		
Comolet, 1998 [137]	To increase the understanding of the determining factors of default in an urban environment where medical facilities are accessible	38 patients who did not complete treatment compared with 111 controls who did complete treatment in Tamatave, Madagascar in 1993	Risk factors for default were assessed by a retrospective case-control study in a sample of 38 patients who had not completed treatment for pulmonary tuberculosis, compared with 111 controls who had completed treatment under comparable conditions. Different kinds of determinants were studied: objective socio-demographic factors, subjective psychological factors, attitudes and behaviour of patients in	Default associated with sex of patient; 76% of defaulters versus 56% of non-defaulter (controls) were male, OR 2.51 (1.02 OR 6.31), $P < 0.0281$	

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			relation to chemotherapy, quality of relationships with the medical staff, knowledge and attitudes regarding tuberculosis.		
Connolly, 1999 [138]	To determine trends in and risk factors for interruption of tuberculosis treatment	3610 patients, 629 did not complete treatment, Hlabisa, South Africa, during 1991-1996	Data were extracted from the control programme database starting in 1991. Temporal trends in treatment interruption are described; independent risk factors for treatment interruption were determined with a multiple logistic regression model, and Kaplan-Meier survival curves for treatment interruption were constructed for patients treated in 1994-1995.	in Hlabisa, South Africa, 1991–1996, more men (19%) failed to complete treatment than women (16%; P 0.02). Males at higher risk for failure to complete treatment, male versus female sex (OR 1.3, 95%CI 1.1-1.6). Treatment interruption was more frequent among patients known to be HIV-infected, but this pattern was unaffected by sex.	
Conte, 1999 [249]	To compare the steady-state plasma and intrapulmonary concentrations of orally administered pyrazinamide in normal volunteers and subjects with AIDS.	40 adult volunteers (10 men with AIDS, 10 normal men, 10 women with AIDS, and 10 normal women) in San Fransisco for 5 days (date unknown)	Pyrazinamide was administered at 1 g once daily for 5 days. Subjects with AIDS and with more than four stools per day were excluded. Blood was obtained prior to administration of the first dose, 2 h after the last dose, and at the	Gender had no significant effect on the concentrations of pyrazinamide in plasma, or in ELF or AC. the absorption of pyrazinamide is not affected by gender or by the presence of AIDS, as defined in our subjects. Plasma drug concentrations were higher in women than in men in this study, but the difference is explainable by the higher weight-adjusted dose received by the women.	

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
			completion of bronchoscopy and bronchoalveolar lavage, which were performed 4 h after the last dose. Standardized bronchoscopy was performed without systemic sedation. The volume of epithelial lining fluid (ELF) recovered was calculated by the urea dilution method. The total number of alveolar cells (AC) was counted in a hemocytometer, and differential cell counting was performed after cytocentrifugation. Pyrazinamide was measured by high-performance liquid chromatography		
Conte, 2000 [253]	To determine the effects of AIDS and gender on steady-state plasma and intrapulmonary ethionamide concentrations.	40 adult volunteers (10 men with AIDS, 10 normal men, 10 women with AIDS, and 10 normal women) in San Fransisco (date unknown)	Ethionamide, 250 mg every 12 h for a total of nine doses, was administered to 40 adult volunteers (10 men with AIDS, 10 healthy men, 10 women with AIDS, and 10 healthy women). Blood was obtained for drug assay prior to	The presence of AIDS or gender was without significant effect on the concentrations of ethionamide in plasma, AC, or ELF.	

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
			administration of the first dose, 2 h after the last dose, and at the completion of standardized bronchoscopy and bronchoalveolar lavage, which were performed 4 h after the last dose. Ethionamide was measured in epithelial lining fluid (ELF) and alveolar cells (AC) using a new mass spectrometric method.		
Conte, 2001 [250]	To study the steady-state plasma and intrapulmonary orally administered ethambutol concentrations in healthy volunteers and subjects with AIDS.	40 adult volunteers (10 men with AIDS, 10 normal men, 10 women with AIDS, and 10 normal women) in San Fransisco (date unknown)	Ethambutol (15 mg/kg of body weight) was administered orally once daily to 10 men with AIDS, 10 healthy men, 10 women with AIDS, and 10 healthy women. The mean (+/- standard deviation [SD]) CD4 cell count for the 20 subjects with AIDS was (350 +/- 169) x 10(6) cells per liter. Blood was obtained for drug assay 2 h after the last dose and at the completion of bronchoalveolar lavage, performed 4 h after the last dose. Standardized bronchoscopy was	Two- and 4-h concentrations of ethambutol in plasma were not affected by AIDS status or gender.	

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
			performed without systemic sedation. The volume of epithelial lining fluid (ELF) was calculated by the urea dilution method. The total number of alveolar cells (AC) was counted in a hemocytometer, and differential cell counting was performed after cytocentrifugation. Ethambutol was measured by a new, sensitive and specific liquid chromotography-mass spectrometry method. The presence of AIDS, as defined in this study, or gender was without significant effect on the concentrations of ethambutol in plasma at 2 or 4 h or in ELF at 4 h following the last dose.		
Conte, 2002 [252]	To evaluate the effects of gender, AIDS, and acetylator status on the steady-state concentrations of orally administered isoniazid in plasma and lungs	80 adult volunteers in San Fransisco (date unknown)	Isoniazid was administered at 300 mg once daily for 5 days to 80 adult volunteers. Subjects were assigned to eight blocks according to gender, presence or	The concentrations of orally administered isoniazid in plasma were not affected by gender or the presence of AIDS($P < 0.05$)	

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
			absence of AIDS, and acetylator status. Blood was obtained prior to administration of the first dose, 1 h after administration of the last dose, and at the completion of bronchoscopy and bronchoalveolar lavage (BAL), which was performed 4 h after administration of the last dose. The metabolism of caffeine was used to determine acetylator status. Standardized bronchoscopy was performed without systemic sedation. The volume of epithelial lining fluid (ELF) recovered was calculated by the urea dilution method. Isoniazid concentrations in plasma, BAL fluid, and alveolar cells (ACs) were measured by high-performance liquid chromatography. AIDS status or gender had no significant effect on the concentrations of		

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
			isoniazid in plasma at 1 or 4 h.		
Conte, 2004 [251]	To compare the steady-state plasma and intrapulmonary concentrations of oral rifampicin (rifampin) in men and women with and without AIDS.	40 adult volunteers (10 men with AIDS, 10 normal men, 10 women with AIDS, and 10 normal women) in San Fransisco (date unknown)	Prospective nonblinded pharmacokinetic study.	Sex had no effect on plasma concentrations of rifampicin at 2 hours, 4 hours, or in epithelial lining fluid. Alveolar cell concentrations of rifampicin were significantly greater in women (13.9 ± 6.7 mg/L) than in men (6.6 ± 4.1 mg/L) [p = 0.0003]. Alveolar cell rifampicin concentrations were 78% greater in smoking women (17.8 ± 7.0 mg/L) than in nonsmoking women (10.0 ± 2.4 mg/L), but the difference was not significant (p > 0.05).	
Cullinan, 1991 [201]	To study fatality in pulmonary tuberculosis in England and Wales	1222 of patients notified as having TB confined to the lungs in England and Wales in 1983	mortality up to the time of finishing chemotherapy calculated.	Comparison with a referent population showed that the all cause mortality among people with pulmonary tuberculosis was 10 times greater than that of the age and sex matched general population. In both sexes, case fatality rates rose with increasing age. Of the 158 deaths, 124 (78%) occurred in male patients, almost of all them white; male case fatality within each age group was consistently higher than female. The overall number of deaths in patients of Indian subcontinent origin was small (6% of all deaths), and a smaller proportion died than of white patients, but the trends of increasing case fatality with age and ofhigher rates in men than women cases were also present. To assess the effect of disease severity, case fatality rates by radiographic extent of disease (based on number of lung zones or equivalent area affected) were calculated - generally, male case fatality	

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				rates were higher than female in each radiographic category and in each age group. Logistic regression analysis of four clinical variables confirmed increasing age and radiographic evidence of extensive disease (p < 0-01 for each) and to a lesser extent male sex (p = 0-06) as important independent risk factors for death during chemotherapy. The relation to male sex, which is slightly weaker, may be attributable to a higher prevalence of coexistent disease, alcoholism, or poorer social circumstances in the men. (speculation)	
Dandona, 2004 [102]	To assesse the utilization of and barriers to the Revised National Tuberculosis Control Programme (RNTCP) services based on DOTS in 4 states of India, and recommend actions to optimize utilization of the RNTCP services	83,099 (65% male) TB suspects listed in the laboratory and 21,592 (69% male) TB patients in the TB register. Data from representatively selected TB service units from relatively good and relatively poor functioning district TB programs in 4 states in India.	Two districts each in 4 states with more than 50% of the population covered under the RNTCP in 2002, representing diverse levels of general health indicators, were selected. Sex-disaggregated data on patients who reported to the RNTCP facilities for the diagnosis and treatment of tuberculosis in 2002 were reviewed from the laboratory and tuberculosis registers to assess the utilization of these services. Data on barriers to utilization of the RNTCP	A total of 83,099 patients had reported for the diagnosis of tuberculosis in the study areas, of whom 29,279 were women (35.2%). Among new smear-positive tuberculosis patients, 79.9% of women (95% CI 78.4%-81.4%) and 74.4% of men (95% CI 73.4%-75.4%) were cured. Males and females who did not complete treatment were 535 (24%) and 209 (13%) In logistic regression, odds of not completing treatment were higher for men than women 2.2, 1.8-2.6, (as well as never married. did not know duration of treatment, did not know TB was curable and were not satisfied with DOTS provider).	

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			services were collected through interviews of 4310 patients with tuberculosis who were 16 years of age or older.		
Daniel, 2006 [139]	To determine the risk factors associated with default from tuberculosis treatment in Sagamu, Nigeria	777 TB patients registered for TB treatment at TB hospital in Sagamu local government area (Nigeria) during January 1997 and December 2003.	retrospective study of adults registered for antituberculosis DOTS therapy	Off 774, 178 (23%) defaulted. Defaulting was higher in men than women, 58% versus 46%, p<0.01).Men more likely to default. Risk factor associated with non-compliance was male sex 9 OR 1.64: CI. 1.15-2.34; p < 0.01) in multivariable analysis. Author's speculate that the higher default rate in men compared with wormen can be attributed to their status as breadwinners in the society. Men tend to leave their home early to provide for their families and as a result may find it difficult to comply with daily clinic attendance, especially during intensive phase.	Important that treatment programs are flexible to accomate working men. Alternative strategies such as the use of family members to oversee treatment may be desirable in men. There is also a need to shorten duration of treatment, decentralize and make DOTS more accessible, and ensure adequate uninterrupted drug supply to TB treatment centres.
Date, 2005 [31]	To examine how gender and literacy influence TB diagnosis and treatment	74 newly diagnosed smear-positive PTB patients. Sana'a, Yemen. December 2001 – March 2002; September 2002 – March 2003.	Individual interviews and data collection were conducted for TB patients. The treatment outcome for each patient was checked from September 2002 to March 2003.	More females than males completed treatment (P = 0.046, univariate logistic regression analysis). 12 of 41 male patients (29%) were missing before registration compared to only three of 33 female patients (9%, P 5 0.042). Univariate logistic regression found the only factor related to treatment outcome was sex (P 5 0.046). Twenty-three of 33 female patients (70%) completed treatment compared to 19 of 41 (46%) male patients. This finding may be linked to the gender roles of the tribal society. Supervision by male relatives contributed to completion of treatment	Lack of education does not hinder women from receiving TB diagnosis and treatment. The concept of traditional illness, however, causes a longer diagnostic delay among illiterate patients, and the role of male relatives positively influences treatment outcomes for female patients.

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				among female patients. One staff member said, however, that with strong support from male relatives female patients could complete their treatment under such difficult circumstances. In this study, all the female patients were accompanied to the NTI by male relatives. In contrast, the male patients visited alone or with male relatives. In the interviews, female patients identified themselves as weak and relied on their male relatives to understand the illness and care plan. The male relatives accepted the female's dependence. During the interview, they promised their support until the end of treatment because men are responsible for protecting women. This gender role seemed to contribute to successful treatment outcome for female patients. In contrast, male patients have no such support in their treatment. As a man has the option of making independent decisions, some may decide not to start or to stop treatment. For example, male patients who were missing before registration may have decided not to seek treatment at the health centres designated by the NTI staff. High literacy among males did not increase the percentage of men who completed treatment. In addition, it is of note that more than half of the illiterate male patients were less likely to complete treatment. gender roles dictate that men make decisions for their family and that women abide by these decisions. Female	

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				patients may have a better treatment outcome because they obey male family members who insist that they start and complete the 8-month treatment programme regardless of circumstances.	
de Jager, 2002 [244]	To investigate the ototoxic and nephrotoxic effects of long-term use of aminoglycosides.	110 patients treated with aminoglycosides; 81 (73.6%) men and 29 (26.4%) women, with a mean age of 35.7 years (range 10–83) in the Tuberculosis Centre Beatrixoord in the Netherlands, during January 1995 to July 2000	retrospective chart study. Patients treated for tuberculosis with aminoglycosides were evaluated for hearing loss and nephrotoxicity for a minimum of 14 days.	Sex was not found to be associated with hearing loss among patients taking aminoglycosides.	
DeRiemer, 1999 [105]	To identify the characteristics of persons in whom TB was diagnosed after death, and determine whether secondary cases of TB resulted from them	3102 TB cases reported in San Francisco, in 1986-1995, of which 120 (3.9%) were diagnosed after death	Retrospective review of reporting registers	Male TB cases more often were diagnosed after death (aOR=1.52, 0.98-2.46). This may have to do with risk groups like injecting drug users	
Devoto, 1997 [240]	To evaluate the risk factors involved in antituberculosis treatment-induced hepatotoxicity.	Sample of 456 patients in Argentina	In a retrospective study we analyzed the rate of drug-induced hepatotoxicity. Patients received a combination of drugs including isoniazid, rifampin, pirazinamide and streptomycin or ethambutol.	Female sex, alcoholism, HIV infection were associated with an increased risk of hepatotoxicity in this study. In the logistic model, the adjusted odds ratios (OR) and significance were found as follows: a) for alcoholism, OR = 17.31 (95% CI: 6.35-47.16), $p < 0.001$; b) for HIV infection, OR = 3.23 (95% CI: 1.47-7.11), $p = 0.003$ and c) for female sex, OR = 2.44 (95% CI: 1.22-4.86), $p = 0.011$. Age was not significantly	

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				associated with hepatotoxicity.	
Dhuria, 2009 [260]	To identify how TB affects QOL and how directly observed treatment short course (DOTS) therapy modifies this QOL in patients of TB attending DOTS centers.	90 adult patients of tuberculosis at 2 directly observed treatment short course (DOTS) cum microscopy centers in an urban area of Delhi between March 2004 and March 2005	A prospective study; case-control study. WHOQOLBREF (Hindi) questionnaire was used to assess the QOL at the onset of treatment, after 3 months of treatment under DOTS, and at completion of treatment	Among 51 males and 39 female TB cases, following treatment under DOTS, men though having lower overall QOL than women, had scored higher in the psychological, social, and environmental domains. Women also showed an improvement after treatment, but their scores in all the domains except physical were lower than those of men, implying the greater impact of the disease on the psychological, environmental, and social domain in women. at the end of treatment, the mean scores for overall quality of life and the physical domain were higher in the women patients than the men patients but the difference was not significant. Men scored better than women in psychological, social, and environmental domains but the difference was not significant.	the need to look into all the domains of health to treat the patient comprehensively considering all aspects. The health personnel of the facilities, who specifically cater to the female population, should be sensitized to the special needs of women affected by TB so that they can help the patients to combat the negative impact of TB.
Ditah, 2008 [164]	To evaluate tuberculosis treatment outcome in England, Wales and Northern Ireland by redefining the outcome criteria and investigate factors associated with unsuccessful treatment outcome 12 months after notification	13,048 cases, 2676 new SS+ cases; male (54.0%) in England, Wales, Ireland during 2000-2001	This was a prospective analysis of a cohort of patients diagnosed in England, Wales and Northern Ireland and reported to the Enhanced Tuberculosis Surveillance system in 2001 and 2002. Proportions of success and failure were calculated based on a new set of criteria following discussion with clinicians treating	Male sex associated with unsuccessful treatment outcome in multivariate analysis OR 1.27 (1.08-1.49)	

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			tuberculosis cases. Logistic regression was used to study risk factors for unsuccessful treatment outcome.		
Døssing, 1996 [232]	To evaluate routine procedure for the management of liver injury during antituberculosis treatment	765 patients(752 files), 485 were men (64%) treated in Municipality of Copenhagen, Denmark, Bispebjerg Hospital, during January 1983 to January 1994	From 1983-1986 they received a three-drug (9-month) regimen and from 1986-1993 a four-drug (6-month) regimen consisting of isoniazid, rifampicin, ethambutol + pyrazinamide. Data from a retrospective chart review.	Of 61 patients presenting with a normal pretreatment liver profile developed liver injury during treatment (50% men and 32% alcoholics, $P < 0.05$).Risk factors of hepatotoxicity included old age, female sex and extensive tuberculosis, and not alcohol consumption. We found a four times higher risk for women than men for drug hepatotoxicity requiring a modified antituberculosis regimen (Table 2) which cannot be explained by sex-related differences in age. This is in agreement with a recent study from Brazil, and consistent with several studies of hepatotoxicity associated with INH for pre- vention of tuberculosis. In the present study INH was associated with hepatotoxicity in three post-menopausal women among 11 cases in women proven by challenge with the drug.	
Duarte, 2009 [189]	To study the factors associated with death in incident cases of pulmonary tuberculosis (PT) during treatment.	all new cases of tuberculosis reported between January 2000 and December 2004	case-control study; cases were TB patients who died of any cause and controls were those cured after initial PT treatment. Data analyses included unconditional multiple hierarchical logistic regression.	factors associated with a higher risk of death included gender (males: odds ratio (OR) 1.4; 95% confidence interval (CI) 1.33 to 1.47), among others. Men are expected to present higher mortality rates than women, for example due to injuries. Because we were not able to differentiate deaths ''with'' PT from deaths ''due to'' PT, this may have generated an overestimation of the differences in the case fatality	

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				proportions between these and the reference groups in this study.	
Egbewale, 2007 [167]	To determine treatment outcomes and ascertain the effectiveness of the programme for TB	879 TB patients, 467 males and 412 females, mean age 33 years enrolled in the directly observed treatment-short course chemotherapy, Southwestern Nigeria, hospital patients, June 2000 and June 2004	Case registers of all TB patients enrolled were reviewed and data obtained analyzed by statistical methods.	Outcome was not significantly affected by gender (OR 0.8; 0.6-1.1)	
Elender, 1998 [221]	To determine standardised annual TB mortality rates	403 local authority districts, England and Wales 1982-1992,	an ecological analysis of standardised annual TB mortality rates for the 403 local authority districts between 1982 and 1992, disaggregated by age and sex. Social, demographic and ethnicity measures from the 1981 and 1991 censuses and standardised annual AIDS-related mortality rates for young men are used to calculate Poisson regression models	For men and women, TB mortality and overcrowding at the household level. Both poverty and AIDS-related mortality also associated for younger men. However, female tuberculosis deaths are less common than male deaths so the power to detect relationships with other variables is diminished.Whilst there is strong evidence that tuberculosis deaths are higher in areas with overcrowded housing, it should be stressed that the methodological constraints of an ecological study means that the outcome for individuals living in such circumstances is not addressed. This suggests that aspects of poverty over and above those encompassed by a measure of overcrowded households are also important in the etiology of tuberculosis. The exact causal mechan-ism is unclear but it is known that poverty often leads to poor nutrition, a signi®cant risk factor for the disease	

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Elliott, 2004 [202]	To examine the effect that prednisolone has on survival in HIV-1-associated pleural tuberculosis	adults (were 18 years) with HIV-1-associated pleural tuberculosis recruited at the National Tuberculosis Treatment Centre, Mulago Hospital (Kampala, Uganda), between November 1998 and January 2002, followup until July 2002.	We conducted a randomized, double-blind, placebo-controlled trial of prednisolone as an adjunct to tuberculosis treatment, in adults with HIV-1-associated pleural tuberculosis. The primary outcome was death. Analysis was by intention to treat.	Use of prednisolone as an adjunct to treatment for tuberculosis did not improve survival in the HIV-1–infected adults with pleural tuberculosis. The mortality rate was 21 deaths/100 person-years (pyr) in the prednisolone group and 25 deaths/100 pyr in the placebo group. Age-, sex-, and initial CD4+ T cell count-adjusted mortality rate ratio given. Mortality rates were also higher in participants who were older and in men (compared with women), but these 2 effects were not statistically significant. After adjusting for age, sex, and the natural logarithm of the initial CD4+ T cell counts, the mortality rate ratio for the prednisolone group, compared with the placebo group, was 0.99 (95% CI, 0.62–1.56 [Pp.95]).	
Epstein, 1987 [210]	To examine mortality rates (MRs) forpulmonary tuberculosis in relation to age, sex, ethnic group and year	in all ages/sex in South Africa 1978-1982	The reported mortality rates (MRs) for: (i) pneumonia and influenza; (ii) chronic obstructive lung disease and allied conditions; (iii) pulmonary tuberculosis; and (iv) carcinoma of the lung and bronchus over a 5-year period are examined in relation to age, sex, ethnic group and year.	The MR for TB was highest among coloured males and females of all ages and lowest among whites, and intermediate among Asians. MRs for males were higher than for females, especially in those over the age of 24 years. Age standardized MR for PTB for whites (M 12.3 F 3.9), coloureds (M 359 F 163), and Asians (M 61 F 24) per 100,000.	
Erhabor, 2003 [168]	To examine outcomes of patients on DOTS	571 TB patients (277 male, 294 female) in	Tuberculosis patients were placed on	A total of 26 patients died while on treatment, 18 (6.5%) of whom were	

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	and factors that may influence compliance	Ile-Ife, southwest Nigeria at the The Chest Clinic of Obafemi Awolowo University Teaching Hospitals Complex (OAUTHC)during 1996-1999,	different treatment regimens according to the recommendation of the International Union Against Tuberculosis and Lung Disease (IUATLD) and the Nigerian Tuberculosis and Leprosy Control Program (NTBLCP). The results were recorded and evaluated periodically by the clinic staff under central supervision. The outcome of treatment over a three-year period (1996-1999) was reviewed.	males and eight (2.7%) were females. The rate of cure/treatment completed, treatment default, transfer to other centers, and treatment failure was comparable between male and female patients. Age, sex category of treatment, and distance from hospital had no significant influence on drug compliance. Male vs Female %: Cured/completed Rx 84.1 vs 88.1; Defaulted 5.8 vs 6.5; Died 6.5 vs 2.7; Treatment failure 1.8 vs 1.0. The number of patients who die on treatment still needs to be minimized. Most of these patients report late to the hospital after they might have developed severe complications.	
Eugen-Olsen, 2002 [176]	To see if serum level of soluble urokinase receptor is elevated in tuberculosis patients and predicts mortality during treatment	262 individuals at the time of enrolment into a cohort based on suspicion of active tuberculosis and in 101 individuals after 8 months of follow-up 147 (56%) men and 115 (44%) women, in Guinea-Bissau, community study, between 1996 and 1998	suPAR was measured by ELISA in 262 individuals at the time of enrolment into a cohort based on suspicion of active tuberculosis and in 101 individuals after 8 months of follow-up.	No difference in suPAR levels between men and women (P 0.87). Sex did not appear to be associated with death or survival in a multivariate Cox model looking at suPAR levels, and controlling for HIV status, age, CD4 count and type of TB diagnosis.	
Façanha, 2006 [211]	To evaluate the evolution of tuberculosis-related mortality, as well as	All deaths from TB reported to the Ministry of Health via the Mortality	A descriptive study, based on secondary data, was conducted. All deaths from	Among the individuals who developed the active form of tuberculosis, the risk of death was lower for females than for males. The mean mortality rate per	

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	gender-related and age-related tendencies	Database among residents of Fortaleza, Brazil during 1980 to 2001	tuberculosis occurring among residents of Fortaleza in the 1980-2001 period and reported to the Ministry of Health via the Mortality Database were included. The evolution of tuberculosis-related mortality was compared with that of overall mortality and with that of mortality from all infectious diseases. The tendencies of the coefficients of overall mortality and of tuberculosis-related mortality, adjusted and unadjusted for age and gender, were calculated for the study period.	100,000 inhabitants was 7 among the males and 4.4 among females (OR: 1.59; 95% CI: 1.09-2.32). During 1980-2001, there was a tendency toward a decrease in the mortality rate for males ($y = -0.3175x + 10.971$) and females ($y = -0.1933x + 6.8051$). In 1990, there was a reduction in the tuberculosis-related mortality rate among males.	
Falzon, 2005 [159]	To analyse the determinants of TB treatment success in different countries using individual data	24 660 TB cases from surveillance data, Pooled tuberculosis (TB) notifications from 13 European countries, in 2000 and/or 2001.	We asked 18 European countries with both outcome data and individual TB records to code outcomes for cases notified. Cases completing treatment regardless of bacteriological proof of cure were considered successful. Logistic regression was used.	In logistic regression among cases with drug susceptibility results (n = 10 303), 'success' was associated with female sex (1.4, 95%CI 1.3-1.6),	

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
Farah, 2005 [160]	To evaluate the treatment outcome for new cases of culture positive pulmonary TB registered in Norway and to identify factors associated with non-successful treatment	655 patients (271 males ad 384 females) in Norway using surveillance data 1996-2002	a register-based cohort study. Treatment outcome was assessed according to sex, birthplace, age group, isoniazid (INH) susceptibility, mode of detection and treatment periods (1996-1997, 1998-1999 and 2000-2002). Logistic regression was also used to estimate the odds ratio for treatment success vs. non-success with 95% confidence interval (CI), taking the above variables into account.	The treatment success rates for women and men were 86% (95% CI 82%–90%) and 81% (95% CI 77%–85%) respectively. Mortality in men was 10.7% and in women was 6.3%. (no test for significance). In multivariate analysis, sex was not related to treatment success among new culture positive cases notified in Norway, 1996-2002. When considering the treatment outcome of TB, many studies including ours, include patients who never started treatment.	Early diagnosis of TB in elderly patients to reduce the death rate, abstaining from expulsion of patients on treatment and further measures to prevent default could improve the success rate further.
Faustini, 2008 [190]	To examine treatment outcomes including relapse in pulmonary tuberculosis patients	974 notified TB cases using surveillance data in Lazio, Italy during 1999-2001	Tuberculosis treatment was surveyed in the Lazio region (Italy) from 1999 to 2001; a six-year follow-up of notified cases was undertaken to detect relapses. The results were analyzed as a population-based case-control study comparing each unsuccessful outcome and relapse with eligible controls.	In multivariate analysis, death (OR 2.1; 95% CI 1.0—4.4) was associated with being male. There was no association between sex and being lost to therapy follow-up (OR 1.46; 0.89—2.38) or relapse (OR 1.98 0.30—12.83)	
Franco, 1998 [212]	To determine the trends of tuberculosis mortality in Spain	census and tb cases reported nationally in Spain during 1970 to	Official population figures and data on deaths from	During 1970-1993, the mean annual mortality rates over the study period were higher in men than in women for	

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
		1993	tuberculosis were used to calculate specific tuberculosis mortality rates by age and sex (per 100000 population). Causes of death from tuberculosis were grouped according to the International Classification of Diseases.	all disease sites and age groups, except CNS TB and the youngest age group (0-19 years). The mean annual mortality rate for all TB for men was 7.2/100,000 and for women 2.4/100,000) ($p<0.001$). In both men and women, mortality rates were higher in the elderly than younger groups ($p< 0.001$).	
Friedland, 2006 [255]	To examine pharmacokinetic interactions between rifampicin and ART on TB and HIV outcomes	Twenty African patients with newly diagnosed smear-positive pulmonary TB and HIV were enrolled [15 female, mean age 31 years], in Durban, South Africa for 6 months follow-up	Consenting patients with smear-positive pulmonary TB and HIV received once daily didanosine + lamivudine + efavirenz (600 mg), with rifampicin-containing TB regimen by directly observed therapy and self-administration at TB therapy completion. Trough efavirenz levels were measured by HPLC at 1, 2, 4 and 6 months while on rifampicin and after discontinuation. HIV and TB outcomes were monitored.	efavirenz exposure was not associated with gender ($P = 0.39$). Efavirenz concentrations on rifampicin were not associated with gender, body weight, or liver function. Despite wide variability in plasma efavirenz concentrations during rifampicin administration, excellent clinical outcomes were obtained.	
Gragnolati, 1999 [213]	To determine the diseases responsible for the existence and attenuation of sex differences in	Population and mortality data in Hong Kong, Singapore, and Taiwan 1960 and	Population and mortality data for Hong Kong and Singapore from WHO, for Taiwan from death certificates.	respiratory tuberculosis in all 3 countries accounts for the largest fraction of the sex difference in mortality and respiratory tuberculosis makes a larger contribution to the decline in the sex	

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	mortality	1990	Population figures are based on census or household registration systems. Cause of death grouped by ICD codes	difference than any cause of death. Resp TB is the single most important underlying cause of the existence and attenuation of the pattern. The reduction in death rates from TB in the mid-1990s was attributed to the use of BCG vaccine, TB treatment, health care system improvements, health education, and improved nutrition and sanitation.	
Gülbay,2006 [233]	To evaluate the side effects of and the risk factors for developing side effects against anti-TB drugs	1149 hospitalized patients (male total 876 (76.2%; mean age was 36.8) for tuberculosis in Ankara, Turkey at the Respiratory Ward of a University Clinic between 1984 and 2001	Records of 1149 patients with established tuberculosis who initially received anti-TB therapy were evaluated retrospectively. The major side effects, which resulted in a definitive termination from 1 or more drugs related to anti-TB therapy, and the risk factors associated with these side effects, were analyzed.	no gender or age differences were observed between patients who did and did not have side effects. No gender or age differences were observed between patients who did and did not have side effects. Ninety-five patients (8.3%), constituting 104 cases in total, experienced side effects. The frequency of drug reactions were increased from 0.6% at ages <20 to 5.2% at ages 20-40. Although there was no statistically significant difference in gender in those patients who developed hepatotoxicity compared with who those who did not (OR 1.071; 95%CI, 0.450–2.548; P ¼ 0:876), it was shown that male gender implied 1.07-fold more risks for developing hepatotoxicity.We found that the risk of hepatotoxicity was slightly higher in male patients, but this was not significant. Severe hepatotoxicity was more frequent in male gender. A similar occurrence rate of severe hepatotoxicity in male patients was found as in the study of Ohkawa et al.2 There was no significant distinction between ototoxicity and gender (OR 1.172; 95% CI 0.386–3.560; P ¼ 0:780).	

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
Güler, 2007 [226]	To identify the factors influencing both sputum smear and culture conversion time among patients with new case pulmonary tuberculosis (TB).	737 patients with pulmonary TB among hospitalised patients in a reference hospital evaluated 306 (193 men and 113 women) HIV-negative patients in Ankara, Turkey January 2000 and 2005	evaluated 306 human immunodeficiency virus-negative patients diagnosed with new case pulmonary TB. Factors associated with both sputum smear and culture conversion time (days) were investigated.	Men had longer time of sputum smear conversion than women (62.33 days in males and 54.64 days in females p = 0.04), but there was no difference in time for culture conversion; but sex was not related to either smear or culture conversion at two months in multivariate analysis.	
Gullón, 2009 [227]	To identify the factors influencing sputum culture conversion in smokers with pulmonary tuberculosis	All patients, current smokers with PTB in department all were HIV negative. 98 patients in Spain between May 1997 and December 2007	Ninety-nine patients with a smoking history and diagnosed with pulmonary tuberculosis were analysed retrospectively. The relationship between sputum culture status at the second month and the following variables: age, gender, pack-years index, comorbid diseases, number acid-fast bacilli (AFB) in sputum smear examination, radiological findings (cavitary, extensive or limited disease), drug susceptibility pattern and initial treatment, was analysed. The Student t-test, chi-square test and logistic regression model with forward stepwise	Culture was positive after one month 35% of males and 50% of females, after two months in 23% of males and 44% of females. Positive culture at 2 months was significantly associated with female gender in a logistic regression analysis (OR=5.63 95% CI 1.21-20.64-p=0.02).	

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			conditional methods were used for statistical analysis. A p value of <0.05 was considered to be statistically significant.		
Gutierrez, 2002 [207]	To describe and compare pulmonary pathology and proven causes of death in HIV-infected and non-HIV patients treated for tuberculosis, to identify the presence and extension of the lesions	246 adult patients (aged > 15) autopsied with tuberculosis and tested for HIV infection, 100 HIV-infected patients were matched with 44 non-HIV-infected patients in Sao Paulo, Brazil Hospital das Clinicas, School of Medicine, São Paulo University during January 1994 to December 1996,	Of 246 adult patients (aged > 15) autopsied with tuberculosis and tested for HIV infection at Hospital das Clinicas, School of Medicine, São Paulo University, from January 1994 to December 1996, 100 HIV-infected patients were matched with 44 non-HIV-infected patients.	Sex not found to be important for the histological outcome (lung parenchyma differences). Noncaseating generalized multibacillary tuberculosis was likely to be the primary cause of death in HIV-infected patients who died during therapy	
Haar CH, 2007 [178]	To examine HIV-related mortality among tuberculosis patients in The Netherlands	13269 tuberculosis (TB) patients reported in The Hague, The Netherlands. 542 HIV-positive patients, 400 were male (74%) during 1993-2001	Mortality was analysed as allcause mortality; multivariable analyses were done by logistic regression. To produce comparable mortality rates between patient groups in the three 3-year time periods, direct standardisation was used, taking the total patient population in the period 1993–2001 as the standard population.	Age and sex-standardised mortality rates among HIV-infected TB patients decreased significantly over time, from 22.9% in 1993-1995 to 11.8% in 1999-2001 (P < 0.001). Sex is not associated with death among 542 HIV-positive TB patients diagnosed in the Netherlands, 1993–2001 using multivariable analysis.	

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Hansel, 2004 [179]	To describe the characteristics of hospitalized patients with TB and to identify patient characteristics associated with in-hospital mortality	2,279 hospital admissions with a primary diagnosis of TB in the USA (based on 20% sample of US hospitalizations, representing 7,450,992 hospital admissions), mean age 50.2 in 2000	Using the 2000 Nationwide Inpatient Sample, representing 20% of US hospital admissions, we identified 2,279 hospital admissions with a primary diagnosis of TB (International Classification of Diseases, ninth revision, codes, 010.xx to 018.xx).	A disproportionate number of patients hospitalized with TB were men (64%). Unlike hospital admissions for primary reasons other than TB, the majority of hospital admissions for TB were in men (64% TB vs 41 other reasons); women results were 34% TB vs 59% all other reasons; p< 0.001. Sex did not relate to in-hospital mortality.	need for improved clinical management strategies that are targeted for high-risk populations.
Harries, 1998 [177]	To determine treatment outcome in an unselected cohort of TB patients in relation to human immunodeficiency virus serostatus	Eight hundred and twenty-seven adult TB patients (451 men and 376 women) in Malawi at Zomba Hospital during 1 July and 31 December 1995	prospective study was carried out to determine treatment outcome in an unselected cohort. Standardized treatment outcomes of treatment completion, death, default, and transfer to another district were assessed in relation to type of TB, human immunodeficiency virus (HIV) serostatus, age and gender.	Death rates increased with age but were similar in men and women.	
Harries, 1999 [203]	To compare twelve-month treatment outcome on patients with smear-negative PTB with 8-month treatment outcome in smear-positive PTB	4240 smear-negative and 4003 smear-positive pulmonary TB cases in all district and mission hospitals in Malawi in the National Tuberculosis	Twelve-month treatment outcome on patients with smear-negative PTB registered in all district and mission hospitals in Malawi during the	Outcome differences between patients with smear-negative and smear-positive PTB were similar when analysed by sex and by most age-groups. In patients with smear negative PTB, treatment outcome was no different between men and women. For patients with outcome	

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	patients	Control Programme in 1995	year 1995 was collected, and was compared with 8-month treatment outcome in smear-positive PTB patients registered during the same period.	data available, 34% of 1676 male patients and 32% of 154 1 female patients died before the end of treatment	
Hino, 2007 [214]	To describe Tuberculosis-related mortality in Brazil	TB cases reported to surveillance system in Brazil during 1980 and 2001	Time series analysis of data from the DATASUS related to cases in which Tuberculosis was the basic cause of death. The mortality rates were calculated per 100,000 inhabitants according to gender and age.	Decrease in tuberculosis mortality of approximately 42% for men and 54% for women during 1980-2001 (22 years). Tb death rates in men were consistently higher in men than in women, regardless of the age group. The Tb mortality rate (100,000 inhabitants) for men in 2001 was 5.7 for the age group from 20 to 59 years, and 20 for people aged 60 or older. On the other hand, rates for women were 1.8 and 6.8, respectively. Author speculate: Men usually take longer to seek health care when compared to women. This could suggest a higher lethality among men. It should also be highlighted that the high prevalence of Tb among men is also ascribed to life habits, including alcohol consumption, a factor strongly associated with Tb. It is also possible that women are more resistant than men and are more health-conscientious.	
Hiyama, 2000 [228]	To evaluate the frequency of drug resistance, (to elucidate factors influencing the response to chemotherapy, and (to	150 patients (115 males, 35 females) with pulmonary tuberculosis in Hiroshima, Japan at Kure Kyosai Hospital during 1990 to 1996	univariate analysis, Cox proportional hazard model	At bivariate level, male gender was related to increased sputum conversion time. Median duration of negative bacteriology in weeks for males was 8.6 and for females 5.4 (p=0.012). Gender did not appear in Cox multivariate analysis.	

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	attempt to improve the therapeutic approach				
Humphries, 1984 [199]	To describe deaths occurring in newly notified patients with pulmonary tuberculosis	1312 adult patients of white or Indian subcontinent ethnic origin with pulmonary tuberculosis only in England and Wales among reported cases via surveillance during October 1978 to March 1979	survey of the chemotherapy prescribed for adult patients with pulmonary tuberculosis	15% of the white patients died, 17% of the males and 11% of the females died from TB (stat sig). This contrasts with only 2% of the males and 2% of the females in the Indian subcontinent ethnic group. In all, 8% of the 748 white males and 6% of the 271 white females died from tuberculosis and 5% and 3%, respectively, with tuberculosis. Of the 6 Indian subcontinent patients, two died from tuberculosis, three died with tuberculosis and for one tuberculosis was not recorded on the death certificate. Among patients in whom TB was not diagnosed until after death, of the 51 patients, 48 were of white and three of Indian subcontinent ethnic origin. Considering the white patients, 23 (18 males, live females) were reported to have died from tuberculosis, three (one male, two female) with tuberculosis, and the remaining 22 (15 male, seven female) from non-tuberculous causes, tuberculosis not being mentioned.	
Hwang, 1997 [234]	To evaluate the incidence, predisposing factors and clinical course of antituberculous drug-induced liver injury in hepatitis B surface antigen (HBsAg)-positive carriers and	240 patients (154 male, 86 female; mean age 40 years) who had received daily isoniazid, rifampicin, ethambutol and pyrazinamide for the treatment of	prospectively followed patients. Patients with heavy alcohol consumption, with pretreatment serum alanine aminotransferase (ALT) elevation and who had less than 3 months	patient age > 35 years was the only independent variable for predicting antituberculous drug-induced liver injury, while sex, acetylator phenotype, HBsAg carrier status and severity of tuberculosis were not.	

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	non-carriers,	pulmonary tuberculosis in Taiwan in a hospital setting (date unknown)	post-treatment follow-up were excluded from the study.		
Ipuge, 1995 [241]	To conduct systematic surveillance for cutaneous thiacetazone-associated adverse reactions	patients on thiacetazone in the National TB program in Tanzania during 1 year period, between July 1, 1993, and June 30, 1994.	1 year of systematic surveillance within the national tuberculosis programme of Tanzania. Univariate and multivariate analyses were done of variables relevant to outcome.	Females were sig less likely to develop adverse reactions to thiacetazone (OR 0.5; 0.0-0.02)	
Iwainsky, 1976 [254]	To examine the effect of age and sex on pharmacokinetics of rifampicin during treatment with intermittent administration	75 patients receiving their first treatment for infectious lung tuberculosis in a clinical and lab setting (date unknown)	Pharmacokinetic investigations	Both the serum RMP-concentration and the urinary excretion of RMP aresignificantly higher in women than in men. Because of the higher serum RMP-concentration it is possible to reduce the RMP-dosage 10% in female patients, even with intermittent administration, and to diminish the risk of dose-dependent side effects.	
Jäger, 2008 [180]	To study which treatment mode is associated with the best survival in patients with the combination of respiratory failure and chest wall deformity from tuberculosis	Eighty-five patients received mechanical ventilation, and 103 received oxygen therapy alone at a University Hospital in Orebro, Sweden 1996 and 2004, 2006,	Swedish patients starting oxygen therapy or mechanical ventilation between 1996 and 2004 due to the combination of respiratory failure and chest wall deformity from tuberculosis were eligible for conclusion. They were followed up prospectively until October 2006, with death as the primary	A cohort of 188 patients was included. Eighty-five patients received mechanical ventilation, and 103 received oxygen therapy alone. Mechanical ventilation was associated with a significantly better survival than oxygen therapy alone, even after adjustments for age, gender, concomitant respiratory disease, blood gas tensions, and vital capacity, with an adjusted hazard risk of death of 0.35 (95% confidence interval, 0.17 to 0.70). Gender was not significantly related in final model.	

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			outcome.		
Jakubowiak, 2007 [222]	To identify risk factors for default and to evaluate possible impact of social support.	1805 cases of registered pulmonary TB in six Russian regions during second and third quarters of the 2003	Retrospective study of new pulmonary smear-positive and smear-negative TB patients registered during the second and third quarters of the 2003. Data were analysed in a case-control study including default patients as cases and successfully treated patients as controls, using multivariate logistic regression modelling.	68 (81.9) males defaulted and 15 (18.1) females defaulted, in bivariate analysis. Not significant 1.63 0.93–2.84. In multivariate analysis of association of social support and risk factors with default treatment outcome in newly diagnosed pulmonary smear-positive and smear-negative TB patients in Russia, social support reduced the default outcome (OR 0.13; 95%CI 0.06-0.28), controlling for age, sex, region, residence and acid-fast bacilli (AFB) smear of sputum. Sex was not significant.	
Jee, 2009 [218]	To explore the association of cigarette smoking with tuberculosis incidence, recurrence, and mortality	1,294,504 South Koreans during 1992-2006	Bivariate and multivariate methods	In men and women, smoking was associated with an approximately 50% increase in risk of mortality from tuberculosis. Male current cigarette smokers had a 40% increased risk of incident tuberculosis compared with nonsmokers and were 55% more likely to die of tuberculosis. In women, findings for mortality risk were similar, but current smoking was not associated with incidence. Former smokers, both males and females, were at increased risk of tuberculosis mortality and incidence. Smokers also had greater risk of recurrence. There was interaction between smoking and sex for incidence (P = 0.00047). We found that sex modified the risk of incident tuberculosis associated with smoking, such that	

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				women had no increase in risk while male current smokers had an approximately 50% increase in risk. However, male and female current smokers had equally heightened risks of death from tuberculosis. We found that sex modified the risk of incident tuberculosis associated with smoking, such that women had no increase in risk while male current smokers had an approximately 50% increase in risk. However, male and female current smokers had equally heightened risks of death from tuberculosis	
Jiménez-Corona, 2006 [1]	To identify gender based differences in patients with pulmonary TB	8195 (44% male) individuals with a cough >2 weeks, as detected by community workers, in all health care centers in 12 municipalities in Veracruz state, Mexico in March 1995-April 2003, of which 829 were diagnosed with TB. Of those 623 had genotyping results	Clinical and mycobacteriological information (isolation, identification, drug susceptibility testing and IS6110 based genotyping, and spoligotyping) was collected from those with bacteriologically confirmed pulmonary TB. Patients were treated in accordance with official norms and followed to ascertain treatment outcome, retreatment, and vital status.	568 patients for whom treatment completion could be evaluated. After completing treatment, men were more likely than women to have a subsequent episode of TB and to require retreatment (p=0.01, Mortality due to TB was higher in men (3.2 per 100 000 person-years) than in women (1.1 per 100 000 person-years,p=0.0003; Rate ratio was 2.91 (1.6-5.3). In multivariate analysis, men were more likely thanwomen to default from treatment [OR 3.30 (1.46 to 7.43)p= 0.004], to be retreated [HR 3.15 (1.38 to 7.22) p=0.007], and to die from TB [HR 2.23 (1.25 to 3.99) P=0.007) among bacteruilogically confirmed pulmonary TB patients in Orizaba, Veracruz, 1995-2003. The probability of death caused by TB among men more than doubled that of women when adjusted for variables known to be associated with mortality such as drug resistance and HIV infection.1	

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Kabra, 2004 [173]	To assess the feasibility of classification and treatment of various types of childhood tuberculosis in different categories	459 children registered in the TB clinic in North India in a Pediatric Tuberculosis (TB) Clinic of a tertiary care hospital (date unknown)	The study was conducted in the Pediatric Tuberculosis (TB) Clinic of a tertiary care hospital in North India. All children registered in the TB clinic were classified in four categories, similar to the categorization in World Health Organization's guidelines for treatment of tuberculosis in adults. All children with freshly diagnosed serious form of tuberculosis were included in category I. Category II included patients who had treatment failure, had interrupted treatment, relapse cases and those who were suspected to have drug resistant tuberculosis. Patients with primary pulmonary complex (PPC), single lymph node tuberculosis, minimal pleural effusion and isolated skin tuberculosis were included in category III. Category IV included patients who	The mean age of the children was 93 months and sex distribution was almost equal. 365 patients who completed treatment, No gender differences mentioned for outcomes; 202/290 for males and 163/263 for females completed treatment	

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			did not improve or deteriorated despite administration of 5 drugs (as per Category II) for at least 2 months.		
Kamel, 2003 [39]	To study gender differences in health care utilization and outcome of respiratory tuberculosis	334 (69% male) PTB patients who were on anti-TB therapy, in Alexandria, Egypt, 2001-2002	prospective study of tb patients	There were significantly more males than females with smear positive smear at end of follow-up (10% vs 7%, p<0.03). No sex differences in culture and x-ray status at end of treatment. No significant sex differences in treatment outcome were found: treatment completion for males (35%) vs females (33%); cure males 59% and 63% females; failure males (6% males vs 3% females); default	.
Keane, 1997 [224]	To assess the most important factors for predicting non-response to first-line treatment as treatment starts and whether any further indicators occur during the course of treatment which may enable more accurate prediction of non-response	130 subjects failing to respond to first-line therapy (cases) , compared with 673 subjects who responded to therapy (controls) in southern Vietnam in a supervised programme of TB treatment for intending migrants from Vietnam thru IOM during 1990 and 1995,	In all, 130 subjects failing to respond to first-line therapy (cases) between 1990 and 1995 were compared with 673 subjects who responded to therapy (controls) on various demographic and clinical characteristics using logistic regression to create a prognostic index. Variables analysed included the patient history of past TB treatment, weight, age, sex and radiological and	No sex difference in relationship between gender and non-response to first line therapy. (OR 0.9; 0.6-1.4)	

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			bacteriological findings. All subjects also tested negative for HIV status.		
Kennedy, 1996 [257]	To assess nutritional status in 200 adult Tanzanian patients with smear-positive pulmonary tuberculosis before, during, and after 6 months of tuberculosis treatment	200 adult Tanzanian TB patients with smear-positive pulmonary tuberculosis, 148 patients (74%) were successfully followed for 12 months	assessed nutritional status in 200 adult Tanzanian patients with smear-positive pulmonary tuberculosis before, during, and after 6 months of tuberculosis treatment	77% of males and 58% of females had a body mass index (BMI) below 18.5; approximately one-fifth had BMI < 16.0. Gender (p<0.002), length of hospital stay, drug regimen, HIV status, and tribe were determinants of weight gain during treatment. P<O.OOOl), even when other factors were accounted for. Sex was also an important determinant, women gaining more weight than men. At 12 months, 32% of male and 19% of female patients considered cured of tuberculosis had BMI < 18.5.	
Khan, 2000 [89]	To explore the extent to which factors related to individuals, the care provision process, and the cultural context influence the behaviour of tuberculosis patients attending TB clinics in rural Pakistan, and examines the effects of disease on their personal lives	Thirty-six tuberculosis patients attending TB clinics in rural Pakistan	Thirty-six patients attending three TB treatment clinics were interviewed in depth. These patients were stratified by stage of treatment (treatment proceeding, treatment completed, default), sex and by rural/urban status.	Rural women were particularly disadvantaged by problems associated with travel: all 9 rural women respondents named duration/cost of travel and being unable to travel alone (limited freedom to travel) as factors contributing to default in Pakistan.	designing DOTS interventions which are acceptable and feasible, and therefore likely to be e ective, in Pakistan. Most important of these are factors related the necessity of accompanying `chaperones' for women patients.
Knudsen, 2005 [181]	To examine the predictive value of soluble haemoglobin scavenger receptor CD163 serum levels for survival in verified	236 suspected tuberculosis (TB) cases, 113 cases, Guinea-Bissau with a median follow-up period of 3.3 years	Pre-treatment serum levels of sCD163 were measured in a cohort of 236 suspected tuberculosis (TB) cases from Guinea-Bissau,	In final model assessing the value of sCD163 as an independent predictor of long-term mortality, there was no significant relationship with age or gender in model predicting long-term mortality.	

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	tuberculosis patients		with a median follow-up period of 3.3 years (range 0-6.4 years).		
Kohn, 1996 [135]	To compare compliance between directly observed preventive therapy and daily treatment for students with inactive (class II) tuberculosis	105 purified protein derivate (PPD) positive students receiving DOPT at school based clinic and 22 PPD positive students referred to Department of Health for non-DOPT therapy in New York, 1993	Cohort analytic study and cost-effectiveness analysis. Students found to be positive for purified protein derivative and having no abnormal chest x-ray films on mandated screening were advised to have prophylactic treatment with isoniazid. Treatment was either directly observed in the school health clinic or provided as daily therapy by the Department of Health. Treatment completion, age, sex, ethnicity, and recent immigration were compared between the 2 treatment groups.	Sex did not significantly affect treatment completion.	
Kolappan, 2006 [182]	To measure the mortality rate and excess general mortality as well as identify groups at high risk for mortality among a cohort of tuberculosis patients	2674 patients (1800 males and 874 females) who were registered and treated under the DOTS strategy in Chennai Corporation clinics in Tamil Nadu, India 2000, follow-up period from the date	In this retrospective cohort study we followed up 2674 patients (1800 males and 874 females) who were registered and treated under the DOTS strategy in Chennai Corporation clinics in 2000. The	Males had a higher standardized mortality rate than female patients, which authors speculate reflects the liklihood of majority of treatment defaults occuring among men possibly due to additional factors such as smokng and alcoholism.	

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		of start of treatment to either the date of interview, or death was 600 days	follow-up period from the date of start of treatment to either the date of interview, or death was 600 days.		
Lee, 1993 [169]	To examine the family factors affecting the outcome of tuberculosis treatment in Taiwan	397 cases with PTB in Taiwan January – June 1990	interviewed 397 active pulmonary TB cases (274 males and 123 females) in Taiwan and followed up their treatment outcomes	57% of males and 63% of females had successful treatment outcomes (completed + cured) In males, the complete treatment group had a higher compliance score (mean +/- standard deviation = 13.45 +/- 2.80) and family apgar score (22.44 +/- 2.29) than the incomplete treatment group (11.61 +/- 3.21 and 14.77 +/- 3.92, respectively). In females, the complete treatment group had a higher cognition score (65.99 +/- 6.75), compliance score (13.65 +/- 2.55) and family Apgar score (22.78 +/- 2.30) than the incomplete treatment group (62.05 +/- 6.91, 11.70 +/- 3.04 and 14.84 +/- 3.80, respectively). In the logistic regression analysis, sex was not associated with treatment outcomes, after controlling for family Apgar score and compliance score, which were significantly related to the TB treatment outcomes, and other confounders.	
Lefebvre, 2008 [191]	To quantify the risk of dying associated with demographic and clinical factors	39.566 cases in the EU 2002-2004	Case-based data on 39,566 TB patients notified by 15 EU countries during 2002-2004 were analysed using logistic regression.	The association with male sex OR 1.48 (1.35–1.61) in multivariate analysis for death could be a consequence of repeated short treatment interruptions among males, as has been documented in different settings; better case-holding may improve outcomes [14]. Advancing age, resistance to isoniazid and rifampicin were strongest determinants	

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				of death while male sex (among others) was weakly associated	
Lienhardt, 1998 [171]	To identify factors determining the outcome of treatment of adult TB cases	1588 cases in health centers in the Gambia; 1238 with documented outcome during 1994-1995	Information on the outcome of treatment was collected on all tuberculosis cases registered with the Tuberculosis Control Programme in 1994 and 1995 and treated under supervision by tuberculosis control staff, nurses or village health workers. Treatment outcome was recorded as cured, completed treatment, failed, defaulted or died. Transferred-out patients were traced and their treatment outcome recorded at the health centre where they had last been seen.	Smear conversion at 2 months as higher in females than males (p>0.04). Female TB cases were more likely to achieve cure than males in multivariate analysis OR 1.7 (1.3-2.4) in multivariable analysis. No differences in death or failure by gender. Mles were more likely to default than females (p=0.003)	
Lienhardt, 2001 [58]	To estimate the time delay between onset of symptoms and initiation of treatment and identify risk factors influencing the delay	152 TB patients over 15 years of age in rural and urban health centers in The Gambia in 1997	Structured interviews with newly diagnosed TB patients aged over 15 years presenting to TB control staff in four health centres.	Cure was associated with sex (risk ratio [RR] for females 1.42, 95%CI 1.19–1.72, P 0.001), income (2 14.66, 3 df, P 0.002) and area of residence (RR for urban residence 1.29, 95%CI 0.98–1.69, P 0.04).	
Lockman, 2001 [192]	To study clinical outcome in MDR and pan susceptible TB patients	92 MDR TB and pan susceptible TB cases in Estonia January 1994 through	Clinical outcomes among 46 patients in Estonia with primary MDR tuberculosis and 46 patients with	male sex (hazard ratio, 5.8; 95% CI, 1.1-29.6; P = .03) were also associated with death due to tuberculos in multivariable analysis	

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		December 1996.	pansusceptible tuberculosis were compared.		
Low, 2009 [193]	To identify risk factors associated with mortality among TB patients on treatment in Singapore	7433 cases in Singapore during 2000-2006,	A retrospective cohort study of 7433 TB patients notified and started on TB treatment from 2000 to 2006 was conducted. Cox regression analysis was used to determine independent risk factors for mortality.	Male sex associated with all-cause mortality among TB patients. Male sex (among others) was risk factor for death due to TB OR 1.19 1.02–1.39	
Maree, 2007 [245]	To investigate mycobacterial genotypic diversity in children with TBM and analyzing the relationship among genotype, clinical presentation and outcome	59 children with tuberculous meningitis in South Africa 1992-2004,	Data were extracted from an ongoing prospective study on children with confirmed TBM from 1992 through 2003 at a referral hospital in the Western Cape Province, South Africa. Mycobacterial isolates were genotyped by standardized restriction fragment length polymorphism methodology. Clinical data at diagnosis, inflammatory progression during the first month of antituberculosis therapy and neurologic outcomes after 6 months of therapy	Advanced disease at diagnosis and male gender were predictors of poor neurologic outcome after 6 months of TB therapy in children with tuberculous meningitis. Mahadevan et al24 have also reported that boys with TBM were more likely to have poorer neurologic outcomes than girls; this association has not been specifically investigated in studies assessing clinical predictors of outcome in pediatric TBM. Possible immune-mediated gender differences are well-recognized as children enter into puberty;25 however, the median age of our patients was 2 years.	

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
			were analyzed according to the principal genetic group of the strain and the presence of the Beijing strain, respectively.		
Mert, 2001 [194]	To determine the clinical, radiographic and laboratory characteristics, diagnostic methods and prognostic variables in patients with miliary TB	38 miliary TB patients in Istanbul, Turkey 1978-1998,	The records of 38 patients (15 male, 23 female; mean age 41 years, range 16-76 years) with miliary TB from 1978 to 1998 were analyzed. Patients were evaluated also as to whether they presented with a fever of unknown origin (FUO). Criteria for the diagnosis of miliary TB were (i) miliary pattern on chest X-ray or (ii) biopsy or autopsy evidence of miliary organ involvement. Paraffin-embedded tissues with granulomata (n = 15) were re-evaluated for the presence of Mycobacterium tuberculosis DNA by polymerase chain reaction (PCR).	Mortality was significantly related to being male (P = 0.005), having atypical miliary pattern (P = 0.015), altered mental status (P = 0.002), and failure to treat TB (P = 0.00001). Stepwise logistic regression revealed that these variables were independent predictors of mortality.	
Noeske, 2002 [172]	To compare treatment outcome between individuals with drug-	560 smear positive PTB cases from Cameroon,West	compared treatment outcome in 410 patients with drug-	Female sex associated with cure OR 1.81 (1.11-2.97) after adjusting for age, HIV, prior treatment,and resistance. No	

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
	susceptible and drug-resistance TB	Province during 1997-1998,	susceptible tuberculosis (DS-TB) and 150 patients with drug-resistant tuberculosis (DR-TB) among 560 adult patients Information on treatment outcome was collected for all smear-positive TB patients having a positive culture with drug susceptibility tests performed for isoniazid, rifampicin, ethambutol and streptomycin.	association was found between death rate and sex. Smear conversion rate and cure rate were higher in females than in males.	
Nunn, 1992 [195]	To compare mortality reats, risk factors and cause of death in HIV1+ and HIV1- TB patients	Patients in HIV+ and HIV- TB centers in Kenya	a prospective cohort study of patients with tuberculosis in Nairobi, Kenya, to compare mortality rates, risk factors, and causes of death in HIV-1 positive and HIV-1 negative patients	Sex not associated with mortality in HIV pos or HIV neg cases after controlling for education and age in TB patients within 6 months after start of TB treatments	
Ohkawa, 2002 [235]	To clarify risk factors associated with development of severe hepatoxicity during anti-TB chemotherapy in Japanse children	117 cases from a pediatric hospital in Japan (58 males and 59 females; age range, 0 to 16 years) during 1995-1999	In a retrospective analysis in a 350-bed referral children's hospital in a metropolitan area, the medical charts of all pediatric patients who received antituberculosis chemotherapy between January 1995 and	Of 8 pediatric patients in whom severe hepatotoxicity developed duringantituberculosis chemotherapy, 7 were male. Univariate analyses showed that children in whom hepatoxicity developed were predominantly male, younger, had EPTB,and were given pyrazinamide more often. Multivariate only age and pyrazinamide was associated with development of hepatotoxicity.	

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
			November 1999 were surveyed. Univariate and multivariate analyses were performed		
Ohmori, 2002 [215]	To observe the epidemiological trend of TB	Japan national TB statistics	The age- and sex-specific TB notification and mortality rates by 5-year intervals were analysed using the national TB statistics from 1910 to 2000.Descriptive analyses of tuberculosis notification rates and mortality rates by age, sex, year and birthcohort.	the cohort curves of mortality become flattened or even reversed after 1985 or 1990, especially in the younger male cohorts.	
Okanurak, 2008 [161]	To determine patient factors predicting successful TB treatment	1241 cases (819 (66.6) were male) from Thailand, Bangkok, Chest Clinic, Ministry of Public Health and health care centres, Bangkok Metropolitan Administration; 2004-2005.	A prospective cohort was conducted during May 2004 to November 2005. Newly diagnosed TB patients aged > or = 15 years were recruited after giving informed consent. Three sets of questionnaires were used to collect data from the patients three times. Data were also gathered from treatment cards.	355 (84.1) of females and 652 (79.6) males had successful treatment outcomes. Females more likely to have successful treatment than males (OR 1.9 1.2–2.9) in multivariate analysis. The finding that the treatment success rate was higher for females than males might refl ect the health behaviour of females, who may have paid more attention to their health than males.	
Ormerod, 1991 [263]	To report inter-relations between relapses, treatment regimen, and	1,009 notified TB patients in Blackburn (UK) between 1978 and 1987.	Multiple linear logistic regression using relapse as the dependent variable	Relapse occurred in 27 of 873 patients followed-up. Sex not associated with relapse, but compliance and age were determinants of relapse	

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
	compliance in treated TB patients		was used because of the complex relationships between treatment, compliance, age and calendar year of treatment.		
Ormerod, 1996 [242]	To assess the incidence and type of reactions to anti-TB drugs in an unselected series of patients	1317 cases in Blackburn Chest Clinic from United Kingdom during 1987-1992,	All patients treated for tuberculosis had details of drug treatment, durations and side-effects requiring alteration of treatment available. The data was compiled retrospectively for 1978-1980 patients and prospectively thereafter. Analysis of drug reactions was by drug, total months drug use, by age, sex and ethnic group, and reaction type.	Significant sex difference with females having a higher rate of rashes, Z 2 7.20 0.01 > P > 0.005, largely due to pyrazinamide, with the substantial majority occurring within 4 weeks of commencing treatment. Analysis of the age, sex and ethnic group of patients with hepatitis showed reaction rates increased with age, as has certainly been shown for H, 11'12 and that this age effect was only significant in males unlike the International Union Against Tuberculosis (1UAT) study, 11	
Pamra, 1976 [264]	To determine relapse rate in bacteriologically confirmed TB patients and to see whether any factors could predispose to relapse	543 consecutive newly diagnosed TB patients at the New Delhi TB Center in 1965, 1966 and 1967	patients with bacteriologically confirmed pulmonary tuberculosis who successfully completed treatment were followed for 5 years to determine relapse rates and to see whether any factors could be said to predispose to relapse.	The overall relapse rate among men (13.4%) was higher than among women (8.4%), this was not significant. Of the various factors included in the analysis,age, sex, initial extent of disease or cavitation did not influence relapse rate	

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
Pande, 1996 [236]	To assess the role of several factors (including gender) in the development of hepatoxicity in patients with PTB receiving anti-TB treatment	492 from India	A case-control study was undertaken to assess the role of age, sex, disease extent, nutritional status, past history of liver disease, infection with hepatitis viruses, acetylator status, and high alcohol intake as risk factors in the development of hepatotoxicity in patients with pulmonary tuberculosis receiving antituberculosis treatment. The cases comprised 86 consecutive patients who were diagnosed as having hepatitis induced by antituberculosis drugs and who were negative for any of the hepatitis markers (HAV-IgM, HBsAg, HBc-IgM, and anti-HCV). The control group comprised 406 consecutive patients attending the chest clinic who completed antituberculosis treatment without developing hepatitis. The variables analysed	Ratio of M:F in development of hepatoxicity during TB treatment was 1.26. Moreover, women appeared to develop hepatitis more commonly (44% compared with 34% in the non-hepatitis group), although this difference was not significant. Others'316 have also reported a female preponderance amongst those developing hepatitis.	It would be advantageous to identify this high risk group as toxic hepatitis complicates the management of tuberculosis.

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
			were age, sex, body mass index (BMI), history of high alcohol intake, radiological extent of the disease, acetylator status, and serum proteins.		
Pardeshi, 2009 [183]	To describe the survival pattern of patients on DOTS according to categories, age and sex of patients	716 patients were registered at the DTC in Tuberculosis unit (TU) at District Tuberculosis Centre (DTC), Yavatmal, India during the year 2004	Retrospective cohort study. Data of patients registered for DOTS in the year 2004 were collected from the tuberculosis register. Kaplan Meier plots and log rank tests to assess the survival pattern. Cox proportional hazards model for multivariate analysis.	There was no signiÞ cant difference in the survival curves between the male and female patients (log rank statistic= 0.05, d.f.= 1, P= 0.80). Survival rates at the end of intensive phase in males was 97%; and in females, 96%. The cumulative survival rate at the end of the treatment period was 92% in males and 93% in females. Gender was not a risk factor for mortality in Cox proportional hazard analysis of deaths in patients on DOTS (aOR 0.87 (0.46-1.67))	
Park, 2007 [268]	To determine the influence of disease severity and treatment modality on outcome of patients with spinal TB.	137 patients were diagnosed with spinal TB; 69 were men (50.4%), and 68 were women (49.6%), with a mean age of 44.07 years in 7 teaching hospitals in South Korea during the study period 1994–2003	A retrospective study (1994–2003), examining the clinical features, management, and treatment outcome of patients with spinal tuberculosis (TB). medical records and radiographic findings of patients with spinal TB were reviewed. The duration of triple chemotherapy with isoniazid, rifampin, and ethambutol, disease severity, operative procedures, and	Among patients with spinal TB, no relationship between sex and use of radical or nonradical surgery and outcomes at the end of TB treatment. Good outcome was favorable status: no symptoms, full physical activity at work, no evidence of central nervous system involvement, no remaining sinus or abscess that was clinically or radiologically detectable, and radiologic evidence of healing of the spinal lesion. An unfavorable status included at least 1 of the following conditions: not radiographically quiescent, limited physical activity, presence of a sinus or clinical abscess, myelopathy with functional impairment, or a need for	

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			outcome were analyzed. The outcome was assessed as both favorable and unfavorable according to predefined criteria.	additional chemotherapy for spinal disease.	
Pérez-Perdomo, 2000 [208]	To describe characteristics and survival experiences of AIDS patients with TB	1000 HIV positives Males constituted the majority of TB cases, 82.1% in Puerto Rico; 1981-1998,	A population based study using the AIDS Surveillance System, including survival analysis.	1000 AIDS cases were reported with TB (4.3% of total AIDS cases), males counted for 82.1% and 84% had PTB; Median survival time (months) was not significantly different between men and women following AIDS diagnosis among AIDS cases with active tuberculosis (definitive and presumptive diagnosis), Puerto Rico, 1981–1998	
Picon, 2007 [265]	To identify risk factors for recurrence of TB	610 patients who were sequentially enrolled in Brazil for treatment in the 1989-1994 period with a mean age of 36 ± 14 years during 1989-2000 (Of the 1559 new patients who were enrolled during the period evaluated, 610 met the inclusion criterion.)	historical cohort study. controlled, observational study comparing the incidence of recurrence in a group of individuals who had TB and were exposed to a series of potential risk factors with the incidence of recurrence in another group of individuals who also had TB but were not exposed to such factors. potential risk factors for recurrence were analyzed using the Cox proportional hazards model	In the multivariate analysis, sex was not independently associated with recurrence of TB	

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
Rajeswari, 2005 [261]	To assess the perceptions of patients of south India about their illness, their reactions to the initial diagnosis and the impact of the disease and the treatment, on their health (both physical and mental) and social life.	Of 980 patients registered for treatment in government health facilities of two tuberculosis units in Tamil Nadu, of south India, 610 (404 males; 206 females) were interviewed twice during July–December 2000	Patients who were cured or treatment completed were interviewed at two time points; Data on perceptions of their illness before the onset of illness and during the treatment period were collected, using a modified SF36 questionnaire.	Measures of physical, mental and social wellbeing increased from start to end of treatment for both men and women. E.g. 'Health status' was perceived to be good by5% of males and 7% of females before treatment, 34% of both males and females at the end of the intensive phase, and 78% of males and 82% of females bythe end of treatment (trend chi square po0:05). Prior to the start of treatment, 'bodypain' was perceived to be a factor moderately interfering with dailyactivities in 51% of males and 55% of females. At the end of treatment, only12% of males and 18% of females reported this problem. Prior to the start of treatment, daily activities were affected in both men and women, but theywere able to do these jobs bythe end of the intensive phase and more so at the end of treatment. At the end of treatment only 53% of patients were free from symptoms (Fig. 2): 52% of males and 38% of females continued to have symptoms such as cough (26% of males, 15% of females), breathlessness (13% of males, 8% of females), chest pain (6% of males, 6% of females), fever (3% of males, 4% of females), and others (3% of males, 5% of females).	.
Sacks, 1998 [206]	To examine clinical factors associated with in-hospital death in patients with active TB	160 hospitalized TB patients in Rietfontein Tropical Disease Hospital, a government hospital, used as a referral center for patients	A retrospective case-control study was performed on patients admitted. Clinical, demographic, and radiological characteristics of each	In-hospital fatalities were associated with female sex (p=0.01). When we addressed the question as to why women were more likely to die than men, HIV infection appeared not to be an important factor. Among the patients who died, 18 (62%) of 29 tested women	Whether there may be a biological reason for a higher short-term mortality in women requires further investigation, particularly with regard to the

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
		with TB, 80 who died compared to 80 who survived during hospitalization in South Africa, Johannesburg during August 1994 and March 1997	group were compared.	and 23 (56%) of 41 tested men were HIV positive (P = .60). Radiological presentations in women were not significantly more extensive than in men (data not shown). Proximate causes of death were diverse and in many instances, accurate clinical details immediately preceding death were not available. We found that patients who died were statistically more likely to be female. The preponderance of female deaths might be due to late presentation and poor access of women to health care, perhaps prejudiced by not being part of the labor force. Females in our study were perhaps less likely to present to the hospital because of the obligations of child care. We could not substantiate this since at least on entry parameters, women and men were equally matched for severity of disease. More women in our study were HIV positive than men, with lower mean CD4 lymphocyte counts on admission; hence, HIV disease may have contributed to excess female mortality.	duration of illness before presentation.
Samman, 2003 [146]	To study impact of resistance and other factors on treatment outcome	147 patients (1226 with f/up information) with culture proven diagnosis of TB seen at KKNGH hospital in Saudi Arabia, Jeddah from June 1993 to June 199	Studied all patients admitted to hospital. Treatment outcome was classified as success or failure based on the clinical assessment, improvement or deterioration of chest X-rays, and results of follow-up sputum	significantly higher prevalence of poor compliance among males (44%) than among females (15%). Treatment success was 86% for females and 53% for males ($p<0.010$). Among Saudi Nationals seen at the KKNGH in 1993-99 failed treatment was associated with male gender and poor compliance, and drug-resistant Mycobacterium tuberculosis.	Need additional studies exploring factors involved in non-compliance among Saudi males and females

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
			examination.		
Schaberg, 1996 [243]	To determine the current incidence of side-effects severe enough to cause intolerance of standard antituberculosis therapy with isoniazid, rifampin and pyrazinamide in patients hospitalized as a result of pulmonary tuberculosis	519 patients with proven pulmonary tuberculosis, who initially received standard antituberculosis therapy in Germany	Patients retrospectively studied in the department of infectious diseases in a teaching chest hospital. The incidence of severe side-effects related to the therapy, which led to the definitive termination of one of the three standard drugs, was measured and the risk factors for intolerance were analysed.	Sex not associated with intolerance of the standard therapy; % of females with severe side effects (all) was higher than males, but gender not significant in final model predicting side effects. Females 3 times more likely than males to have rash (sig).	
Shakya, 2004 [237]	To determine incidence of antitubercular drug-induced hepatotoxicity	50 patient with active TB and normal pretreatment liver function 22 (44%) female and 28 (56%) male patients; age range 15 and 57 years. in Nepal, Kathmandu.	Fifty patients diagnosed with active tuberculosis infection with normal pretreatment liver function were monitored clinically as well as biochemically in a prospective cohort analysis.	4/50 developed hepatotoxicity. females seemed to have higher risk of anti-TB drug–induced hepatotoxicity (OR 4.2, p=0.219). Authors discuss that the difference in the incidence of drug associated hepatotoxicity between males and females is mainly due to: 1. pharmacokinetic variations, probably slower biotransformation and subsequent clearance of exogenous molecules due to lower levels of microsomal enzymes; and 2. women probably being acetylators (slow acetylator enzymatic pattern shows male:female ratio of 4:1).28	
Shen, 2009 [196]	To identify risk factors for death during TB treatment	7,999 culture positive pulmonary cases reported in China, Shanghai during	Evaluated deaths among culture positive pulmonary TB cases. Demographic, clinical, mycobacteriological	male sex (adjusted OR = 1.7, 95% CI: 1.2–2.3) was a significant independent risk factor for death during treatment. Male sex was significantly associated with mortality in our study as well as in	Patients with advancing age, male sex, sputum smear positivity, and a comorbidity have the highest risk of death

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		2000-2006	information and treatment outcomes were routinely collected through a mandatory reporting system.	some previously studies [6,7,19]. A recent analysis of European surveillance data showed that male TB patients had approximately 50% higher risk of death [6]. However, other studies failed to detect a significant association between male gender and death among TB patients [4,5,20]. The higher risk in male patients was explained by some authors as the consequence of low compliance with anti-TB therapy, leading to repeated, short interruptions of treatment, or a greater occurrence of defaulting from treatment.	during anti-TB treatment.
Snider, 1975 [266]	To assess risk factors for reactivation	53 patients who had reactivation of tuberculosis with a median age 44 years in USA, Oklahoma; between 1970 and 1973	The central register cards of all cases of active tuberculosis reported to the Oklahoma State Department of Health from Jan 1, 1970 through Dec 31, 1973 were reviewed to identify patients with reactivated tuberculosis.	review of the medical records of the 53 patients who had reactivated tuberculosis between 1970 and 1973 in Oklahoma revealed no correlation between race and sex and risk of reactivation.	
Soares, 2006 [162]	To compare treatment success between patients treated under DOT(12%) with those who received self-administered therapy (SAT, 88%))	9929 new PTB cases in Brazil, Rio de Janeiro city	A longitudinal study in a cohort of tuberculosis (TB) patients. Of 9929 new pulmonary TB cases, 1190 (12%) were treated under DOT and 8739 (88%) under SAT. All patients received a three-drug regimen consisting of rifampicin (RMP),	Female sex was significantly associated with successful treatment (OR 1.46 (1.32–1.61)) when controlling for DOT alone (OR 1.6, 1.37-1.86), age, and positive smear or culture at enrollment (OR 1.56, 1.33-1.82)	

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			isoniazid (INH) and pyrazinamide for 2 months followed by 4 months of RMP and INH.		
Sterling, 2006 [186]	To report mortality rates through the 2-year follow-up phase of a TB treatment trial	1075 patients on TB treatment in the United States and Canada enrolled in the study between April 1995 and November 1998	We evaluated mortality in a large TB treatment trial conducted in the United States and Canada. Persons with culture-positive pulmonary TB were enrolled after 2 months of treatment, treated for 4 more months under direct observation, and followed for 2 years (total observation: 28 months). Cause of death was determined by death certificate, autopsy, and/or clinical observation. All study patients were combined for analyses that assessed predictors of mortality	Sex not associated with mortality in TBTC Study 22 in a multivariate Cox proportional hazards model.	
Tam, 2002 [267]	To evaluate adverse events (46 relapses and one failure) after 5 years and the prognostic influence of various factors	672 newly diagnosed pulmonary tuberculosis patients in Hong Kong	Clinical trial with Kaplan-Meier analysis of adverse events and Cox proportional hazards analysis of prognostic factors.	In the final multivariate analysis, adverse events (46 relapses and one failure) were related patients' sex (males more likely) and regimen, and pretreatment radiographic extent of disease. Elderly male patients were more at risk of an adverse event, as were those with more severe disease. adverse events were found in 41 (11.8%) of 346	

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				male patients but in only six (3.2%) of 188 female patients.	
Teleman, 2002 [239]	To determine the incidence, clinical course and outcome of TB drug-induced hepatitis (DH) and the risk factors associated with DH under general programme conditions.	Adult patients at the Singapore Tuberculosis Control Unit, a high volume national referral centre in 1998	A retrospective review of adult patients started on TB treatment in 1998.	55 cases of DH in the cohort of 1036 patients treated in 1998. Factors significantly associated with DH were female sex (OR 1.9, 95%CI 1.07–3.4, P 0.02), as well as abnormal baseline transaminases/ bilirubin, and age 60 years. All three patients with fatal DH had received pyrazinamide containing regimens.	
Thierfelder, 2008 [163]	To assess predictors for tuberculosis hospitalization and treatment outcome in Tajikistan.	1495 adult patients with pulmonary TB 45% of them women. Ages ranged from 18 to 84 years (median 32 years) in Kaijikistan during 2005-2006.	Stratified, single stage cluster sample survey of 1495 adult patients with pulmonary TB during 2 calendar years (2005-2006) from the registries of 10 TB centres chosen by simple random sampling. The primary outcome was referral to hospital. Logistic regression was conducted to test associations with the study outcome using linearization and a variance formula.	Independent predictors for hospitalization were male gender [OR 1.5 (95% CI 1.1-2.0)], smear status and age. Sex not associated with treatment success. There is no evidence from the literature and from clinical practice that tuberculosis is more severe in men. This suggests that there are social reasons inclining health care providers to hospitalize men: men are less self sustained when they are sick at home in the Tajik culture. It is also known that drugs and excessive alcohol consumption, which are risk factors for hospitalization in patients with TB (Bobak et al. 1999), are more common in males (Begum et al. 2001)	
Tollman, 1999 [216]	To examine changes in mortality in rural South Africa over the period 1992-1995 by age, sex and cause of death.	Community members in South Africa, Agincourt subdistrict, 1992-1995	Prospective community-based study involving annual update of a household census with enquiry into all birth, death and migration events. All reported deaths (n =	There is evidence for a reversal in the previously declining trend in mortality among women 20-44 years. A comparison of 1992-1993 with 1994-1995 shows that most of the increase in mortality is concentrated in the younger adult (20-49 year) age group. AIDS and related diseases, particularly	

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			1001) are the subject of a verbal autopsy.	tuberculosis, appear primarily responsible.	
Tsagaropoulou-Stinga, 1985 [238]	To be included	44 children (19 boys), ages between 4 months and 14 years (mean age, 4.5 years) treated for tuberculosis between March 1976 and April 1983.	prospective evaluation of incidence and degree of liver injury in children treated for tuberculosis with 15 to 20 mg isoniazid/kg/day and 15 mg rifampin/kg/day	The incidence of hepatotoxicity did not correlate with the patients' sex in in children treated for tuberculosis with 15 to 20 mg isoniazid/kg/day and 15 mg rifampin/kg/day	
van den Broek, 1998 [184]	To determine outcome of tuberculosis (TB) treatment and subsequent survival of human immunodeficiency virus (HIV) infected patients treated under routine programme conditions in a developing country.	561 newly diagnosed and relapse tuberculosis TB cases consecutively registered over a 6-month period in Tanzania, Mwanza, 505 patients alive at completion of treatment were eligible for assessment at 3 years.	Newly diagnosed and relapse tuberculosis cases consecutively registered over a 6-month period were enrolled into an epidemiological study of TB/HIV. Treatment outcome was based on information in tuberculosis treatment registers. Patients surviving treatment were assessed 3 years later by personal interview. Cause of death was determined by verbal autopsy.	At time of follow-up, the overall mortality was 19% and was associated with gemder, gender, or initial drug resistance or type of tuberculosis, but mortality was associated with HIV infection (hazard ratio [hr] 3.7, 95% confidence interval [CI] 2.6-5.2) and age 35 years and over (hr 1.5, 95% CI 1.02-2.1).	
van der Werf, 1990 [223]	To determine default and cure rates	1984-7 among 569 consecutive sputum-smear positive pulmonary tuberculosis (PTB) patients in Ghana, in the hills of Ashanti, in a rural ambulatory non-supervised	default and cure rates among consecutive sputum-smear positive pulmonary tuberculosis (PTB) patients registered between 1984 and 1987 in a rural ambulatory non-supervised service	79/198 (40%) of females and 194/371 (53%) males defaulted. Male gender, longer home-to-clinic distances and older age were significantly associated with higher default rates.	

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		service program	program were analysed.		
Vasankari, 2007 [197]	To determine risk factors for poor tuberculosis treatment outcome	of 629 cases, 386 (61.4%) were men and 243 (38.6%) women. The mean age was 62.9 years, all treated culture-verified PTB cases in Finland	: Medical records of all cases in 1995 - 1996 were abstracted to assess outcome of treatment. Outcome was divided into three groups: favourable, death and other unfavourable. Predictors of unfavourable outcome were assessed in univariate and multivariate analysis.	Significant independent risk factor for death were male sex (AOR 2.51 (1.42–4.45)) in 1995 - 1996 in Finland	
Voogt, 1996 [131]	To assess ototoxic effect of kanamycin, streptomycin and a standard anti-TB drug combination	92 TB patients (7-71 years old) undergoing treatment at a TB hospital in South Africa	ototoxic effect of kanamycin, streptomycin and a standard anti-TB drug combination, used in the treatment of 92 TB patients (7-71 years old), was examined by measuring the highest audible electric bone conduction frequency before and after treatment, using an Audimax 500 audiometer	Males and females equally affected by ototoxicity of kanamycin, streptomycin-no significant difference in South Africa	
Walpola, 2003 [204]	To review factors associated with TBrelated deaths in Queensland, Australia.	1003 tuberculosis cases notified between 1989 and 1998, in Queensland, Australia.	Review of data for TB patients dying before treatment completion; demographic and clinico-pathological comparison of TB-	Sixty-two males died of tuberculosis compared to 25 females, with crude CFRs of 10.6% and 5.9%, respectively.However, the difference in age-adjusted CFRs of respectively 9.7% (standard error [SE] 1.2) and 7.8% (SE	

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			related deaths with other notified patients after exclusion of losses to follow-up; matched case-control study of co-morbid conditions in patients under 75 years.	1.4) was not statistically significant, with the SE of the difference being 1.9.	
Wang, 2005 [185]	To investigate factors altering the manifestation and outcome of pulmonary tuberculosis (PTB).	July 2001-December 2002, 461 cases of culture-proven TB in northern Taiwan at a tertiary care referral centre	The medical records of culture-proven TB patients from July 2001 through December 2002 were reviewed**.**	Gender not a predictor of outcome (i.e. whether the patient was alive 6 months after the index mycobacterial culture was plated)	
Wang, 2008 [170]	To investigate the impact of age on the demographic, clinical, radiographic characteristics, and treatment outcomes of pulmonary TB patients in Taiwan.	August 2003- July 2006, PTB patients in Taiwan	We performed a retrospective analysis of the medical charts and chest radiographs of 83 elderly (> or =60 years old) and 74 young (< 60 years old) culture-proven pulmonary TB patients from 1 August 2003 to 31 July 2006.	Sex was not associated with treatment outcomes in pulmonary tuberculosis patients in Taiwan	
Weiss, 2006 [51]	To document sex differences in key aspects of TB control; to identify gender-specific barriers to early case detection, appropriate treatment, adherence, and cure; to compare and contrast findings from studies in Asia, Africa, and South America;	42 focus group discussions (5 to 11 participants each); 20394 patients registered at local TB control programs; clinical observation of 512 patients; outpatient survey of 2529 TB patients; EMIC interviews with 427 patients	A multi-methods approach guided plans for six components of the research at all four sites: situational analysis of health-services infrastructure and TB control programmes; focus group discussions to examine community views; examination of	Consistent cross-site findings from registry data showed that more women drop out during the course of diagnosis, while men who are diagnosed with TB are less likely to successfully complete treatment.	

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
	and to recommend policy and interventions for enhancing the gender sensitivity of TB control programmes.	currently in treatment. Bangladesh, India, Malawi and Colombia Time not specified	data from patients registered in local TB control programs; observation of patient-provider interaction; survey with TB out-patients; Explanatory Model Interview Catalogue.		
Yamasaki-Nakagawa, 2001 [22]	examine delays in tuberculosis (TB) diagnosis and compare health care seeking behaviour between men and women.	new patients assigned to DOTS mid-Dec 1997 - mid-June 1999 in Nepal, rural area	cohort, patient interviews	male:female ratio among interviewed subjects was higher than that among the study subjects because more women dropped out of treatment before being interviewed (2.4:1/2.1:1). In particular, more women than men died or defaulted soon after starting treatment. Although the causes of death among women were not clear, it is possible that their TB was very severe at the time of diagnosis. Those patients who were not interviewed may therefore have had a longer delay in case detection than those included in this study.	
Yee, 2003 [247]	To estimate the incidence, and risk factors, of major side effects from first-line anti-TB drugs. Side effects, resulting in modification or discontinuation of therapy, or hospitalization, were attributed on the basis of resolution after withdrawal, and/or recurrence with	430 patients treated for active TB in Montreal Chest Institute (Montreal, Canada) between 1990 and 1999	prospective study of TB patients	Time to a serious side effect was significantly more rapid in females and older patients. Occurrence of any major side effect was associated with female sex (adjusted hazard ratio, 2.5; 95% CI, 1.3 to 4.7), age over 60 years, birthplace in Asia, and HIV+ status.	Closer monitoring of female patients is warranted for side effects.

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
	rechallenge.				
Zwang, 2007 [217]	To investigate trends and age-and-sex patterns of mortality in pulmonary tuberculosis (PTB) and PTB/HIV co-infection in a rural population of South Africa.	a total of 2864 deaths were recorded PTB and PTB/HIV, South Africa, in a rural area, Agincourt county during 1992—2000 period,	Causes of death were assessed by VA, using a comprehensive questionnaire	The trends in crude death rate from PTB without HIV (Table 2) did not show any significant variation over the 1992—2000 period, either for men (P = 0.583) or for women (P = 0.877). In contrast, the crude death rate from PTB/HIV co-infection increased rapidly over the period for both sexes (P < 0.001 for males, and P = 0.020 for females). The average death rate over the period was significantly higher for men than for women (P = 0.001). There was a significantly higher increase in PTB mortality excess attributable to HIV in women than in men in the last 3 years (P = 0.001). the increase in HIV prevalence in young women has resulted in PTB/HIV mortality occurring in younger women than in men, and in a higher increase in mortality from PTB deaths in women in the last 3 years of the study period (P = 0.001).PTB/HIV death rate was higher in men than in women for all ages combined R(MH)=2.48, 95% CI 1.53-4.04, P<0.001). The median age at death from PTB/HIV in women (28 years) was lower than in men (38 years, P=0.002). While mortality from PTB without HIV remained constant over time, HIV/AIDS explained the rise in PTB mortality. In the last 3 years, the HIV/AIDS epidemic has caused the number of persons dying of PTB to increase by +117%, with the mortality excess being higher in women	Combined PTB and HIV programme activities need to be reinforced to respond to the increase in PTB mortality, particularly in women.

Reference	Objective(s)	Person, place, time	Design & methods	Main findings	Recommendations
				(+164%) than in men (+103%, P=0.001).	

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